APPENDIX A

Dioxin Workshop Report

NOTICE

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National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH

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Summary of U.S. EPA Dioxin Workshop

February 18–20, 2009

Cincinnati, Ohio

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

DISCLAIMER

This document summarizes the discussions presented at the Dioxin Workshop in February 2009, in Cincinnati, OH, as documented by the Session Co-Chairs. This document is not all inclusive or binding. Conclusions and recommendations to the U.S. EPA may not represent full consensus. The views expressed in this document are those of the Dioxin Workshop Panelists and do not necessarily reflect the views and policies of the U.S. Environmental Protection Agency. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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DIOXIN WORKSHOP TEAM

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INTRODUCTION

This document provides a summary of the Scientific Workshop to Inform EPA's Response to National Academy of Science Comments on the Health Effects of Dioxin in EPA's 2003 Dioxin Reassessment. The U.S. Environmental Protection Agency (U.S. EPA) and Argonne National Laboratories (ANL), through an inter-Agency agreement with the U.S. Department of Energy, convened this scientific workshop ("Dioxin Workshop") on February 18–20, 2009, in Cincinnati, Ohio. The goals of the Dioxin Workshop were to identify and address issues related to the dose-response assessment of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). This report summarizes the discussions and conclusions from this workshop. Previously, at the request of the U.S. EPA, the National Academy of Sciences (NAS) prepared a report, *Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment* (NAS, 2006), which made a number of recommendations to improve the U.S. EPA's risk assessment for TCDD (U.S. EPA, 2003). The 3-day Dioxin Workshop was convened specifically to ensure that the U.S. EPA's response to the NAS recommendations focuses on the key issues and reflects the most meaningful science.

The Dioxin Workshop included seven scientific sessions:

(1) Session 1: Quantitative Dose-Response Modeling Issues
(2) Session 2: Immunotoxicity
(3) Session 3A: Dose-Response for Neurotoxicity and Nonreproductive Endocrine Effects
(4) Session 3B: Dose-Response for Cardiovascular Toxicity and Hepatotoxicity
(5) Session 4A: Dose-Response for Cancer
(6) Session 4B: Dose-Response for Reproductive/Developmental Toxicity
(7) Session 5: Quantitative Uncertainty Analysis of Dose-Response

During each session, the U.S. EPA asked a panel of expert scientists to:

- identify and discuss the technical challenges involved in addressing the key NAS comments on the TCDD dose-response assessment in the U.S. EPA Reassessment (U.S. EPA, 2003);
- discuss approaches for addressing the key NAS comments; and
- identify important published, independently peer-reviewed literature, particularly studies describing epidemiologic and *in vivo* mammalian bioassays, which are expected to be most useful for informing the U.S. EPA's response.

The sessions were followed by open comment periods during which members of the audience were invited to address the Panels. At the conclusion of the open comment periods, the Panel Co-Chairs were asked to summarize and present the results of the panel discussions. The summaries could include minority opinions stated by panelists. The main points derived from the session summaries were used to prepare this document. Additionally, this document includes a list of the session panelists and their affiliations and three appendices. Appendix A presents the Dioxin Workshop Agenda. Appendix B identifies the charge questions presented to the Panel. Appendix C describes draft study selection criteria proposed by the Dioxin Workshop Team for consideration by the workshop panelists.

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NAS (National Academy of Sciences). 2006. Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment. National Academies Press, Washington, DC (July). Available at http://www.nap.edu/catalog.php?record_id=11688.

U.S. EPA (U.S. Environmental Protection Agency). 2003. Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds. NAS review draft, Volumes 1−3 (EPA/600/P-00/001Cb, Volume 1). U.S. Environmental Protection Agency, National Center for Environmental Assessment, Washington, DC (December). Available at http://www.epa.gov/nceawww1/pdfs/dioxin/nas-review/.

SCIENTIFIC WORKSHOP TO INFORM THE TECHNICAL WORK PLAN FOR U.S. EPA'S RESPONSE TO NAS COMMENTS ON THE HEALTH EFFECTS OF DIOXIN PRESENTED IN U.S. EPA'S DIOXIN REASSESSMENT

Dioxin Workshop Co-Chairs: Peter W. Preuss and Glenn Rice

The Dioxin Workshop session summaries were prepared by the session panel Co-Chairs with input from the panelists, as requested by the U.S. EPA prior to the workshop. The Co-Chairs subsequently presented these summaries to all of the workshop participants during designated periods at the workshop. In these summaries, the U.S. EPA asked that the Co-Chairs summarize the key issues from the panel discussions. Because the sessions were not designed to achieve consensus among the panelists, the summaries do not necessarily represent consensus opinions; rather, they reflect the essence of the panel discussions. Some of the specific points may represent the views of multiple panelists, while others only the views of a single panelist. Prior to the summarizations, there were opportunities for public comments on the discussion topics. Some Co-Chairs met with their sessions' panelists after their sessions ended to develop these summaries, while others developed reports based on their personal notes. Because Session 5 was the last session of the workshop—with little time provided to develop the summary—the Co-Chairs circulated a draft for comment by the Session 5 panelists after the workshop, prior to finalizing the session summary. The U.S. EPA collected the session summaries and then prepared this document. A draft of this document was distributed to all of the session Co-Chairs to provide them with a final opportunity to comment and make revisions. Finally, it should be noted that U.S. EPA was not prescriptive to the session Co-Chairs with respect to the format of the presentation materials and provided no specific instructions, resulting in unique formats among the session summaries.

SESSION 1: QUANTITATIVE DOSE-RESPONSE MODELING ISSUES

This session discussed the general dose-response modeling issues related to TCDD. Many of these issues were highlighted by NAS (2006). There was a general introductory presentation on TCDD kinetics, including information and uncertainties pertaining to the conversion of administered doses in animals to human body burden (BB) and additivity to background issues. This presentation was followed by a Panel discussion on the state of the science regarding dioxin dose-response modeling issues.

Session 1 Panelists (Session Co-Chairs are identified by asterisk)

- Bruce Allen, Bruce Allen Consulting
- Lesa Aylward, Summit Toxicology
- Roger Cooke, Resources for the Future
- Kenny Crump, Louisiana Tech University
- Mike DeVito, U.S. EPA
- Dale Hattis, Clark University
- Rick Hertzberg, Biomath Consulting
- Rob McDowell, U.S. Department of Agriculture
- Jim Olson, State University of New York, University at Buffalo

- *Lorenz Rhomberg, Gradient
- Woody Setzer, U.S. EPA
- *Jeff Swartout, U.S. EPA

Please note that the use of the term "concluded" or "recommended" in this summary does not mean that a consensus was reached. Session Summaries were written from the material prepared by the non-EPA/ANL Co-Chair and represent a synopsis of the panel discussions.

Key Study Selection Criteria

The Panel discussed the advantages and disadvantages of using key study criteria (Appendix C). They concluded that *a priori* criteria foster transparency and consistency, and could deflect *a posteriori* criticism. However, the Panel also acknowledged that having *a priori* criteria could introduce the potential for excluding useful data. Although the key study criteria provided by the U.S. EPA listed studies using TCDD only as a criterion, the Panel posed the possibility of using closely related dioxin-like compounds (DLCs) as surrogates for TCDD. The criterion for use of data from mammalian studies only was one criterion that received generalized support due to the lack of extrapolation protocols for nonmammalian species. The Panel also discussed the specific exposure-duration criterion and asked if there should be a preference for longer-term rather than acute studies. The Panel made three suggestions to modify U.S. EPA's key study selection criteria:

(1) Define more relevant exposure-level (i.e., dose) cut points using tissue concentrations.
(2) Reword statistical criteria to include do-it-yourself analysis.
(3) Reword the response criteria to clarify "outside of normal range."

Dose Metrics

The Panel discussed the relative merits of various measures of dose for modeling TCDD dose response. One general conclusion was that tissue concentration (TC) is the preferred metric, especially lipid-adjusted TC, because this measure more closely approximates exposures close to the target tissue when compared to administered doses. However, the Panel acknowledged that these data are often unavailable. They further noted that BB, which is defined as the concentration of TCDD in the body (ng/kg body weight) (U.S. EPA, 2003), might be useful as a surrogate for TC provided the two measures were proportional.

The Panel suggested that a linear approach to BB estimation, which was utilized by U.S. EPA (2003), is too simplistic because this approach does not take into account toxicokinetic issues related to TCDD—e.g., sequestration in the liver and fat, age-dependent elimination, and changing elimination rates over time. The Panel recommended the use of kinetic/mechanistic modeling to the extent possible to quantify tissue-based metrics.

The Panel raised the issue of whether the preferred dose metric would be different for different endpoints and exposure durations. This led to the Panel's comment that the peak exposure might be a more important metric than average BB for variable exposure scenarios. Given this discussion about different exposure durations being relevant to a specific endpoint, the Panel suggested that the U.S. EPA also consider peak measures in dose-response modeling.

The last point raised in this part of the discussion centered on the possibility of dose errors in experimental studies. The Panel highlighted the need for the U.S. EPA to consider dose error (i.e., uncertainty in the x-axis of the dose-response curve) when using dose surrogates.

Dose-Response Modeling of Mammalian Bioassays

The Panel considered several issues related to dose-response modeling of mammalian bioassay data for TCDD: supralinearity and incomplete response data ("anchoring"), defining the benchmark response (BMR) level with respect to establishing the point of departure (POD), and the use of threshold modeling—as further explained below.

The Panel discussed the specific issues of supralinearity and anchoring raised by the U.S. EPA with respect to modeling noncancer endpoints. The panel recognized that, for many of the most sensitive endpoints, the response at the lowest dose is high (e.g., quantal responses above 25% and continuous endpoints differ substantially from the mean, often implying 100% incidence in the treated animals). This lack of response anchoring at the low end of the dose-response curve (near the BMR) results in the higher responses determining the shape of the curve.

The Panel asked whether new tools might be needed or whether the current tools could be applied differently. In the context of developing new tools, the Panel emphasized the need for collaboration between biologists and mathematicians. When discussing application, the Panel suggested that the problem with supralinearity might be overcome by simply dropping the requirement for using the lower bound on the Benchmark Dose. In addition, the Panel posed several more approaches for further consideration in dose-response modeling by the U.S. EPA:

(1) Combine similar data sets to fill in data gaps.
(2) Use mechanistic approaches to model the data gaps.
(3) Dichotomize continuous data.

Finally, the Panel acknowledged that, in certain situations, there simply may not be enough information to provide meaningful answers.

The Panel discussed the BMR level for establishing a POD in the context of deriving a Reference Dose (RfD). The Panel generally agreed that, while the effective dose level (ED_{01}) used in the 2003 Reassessment may be useful for comparative analysis across endpoints, the ED_{01} estimates developed for all endpoints considered in the Reassessment were not appropriate for deriving an RfD because they were not based on the effect's adversity. The panel noted that ED_{01} also is much lower than typical EPA BMR levels. The Panel recommended that the U.S. EPA work to define endpoint-specific BMRs based on the consideration of adversity. Given that the same uncertainty factor framework is applied to all PODs, the Panel emphasized the need for consistency in BMRs; numerical consistency is needed for quantal BMRs and consistency in the choice of biological relevance should be applied for continuous BMRs.

The Panel generally discouraged threshold modeling by stating that thresholds are very difficult to pin down and suggested that the lower bound may always be zero.

Dose-Response Modeling of Epidemiological Studies

The Panel noted that many studies have been published with measured concentrations of TCDD that could be used for dose reconstruction. In this discussion, the Panel acknowledged that use of these data would entail dealing with toxicity equivalence (TEQ) issues and pharmacokinetic (PK) modeling. Pertaining to the use of these data for quantitative risk assessment by the U.S. EPA, the Panel posed the question, "At what point does indirect or confounded human data supersede controlled animal bioassay data?", or alternatively, "How much human data uncertainty can we tolerate?" The Panel suggested, at the least, that the epidemiologic data could be used to "ground-truth" the animal bioassay modeling results.

Supporting Information

The Panel acknowledged that Ah receptor (AhR) binding affinities are not necessarily tied to endpoint sensitivity, but they reiterated the need to consider mechanistic modeling to aid in developing appropriate dose metrics or filling in data gaps in the existing dose-response data.

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NAS (National Academy of Sciences). 2006. Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment. National Academies Press, Washington, DC (July). Available at http://www.nap.edu/catalog.php?record_id=11688.

U.S. EPA (U.S. Environmental Protection Agency). 2003. Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds. NAS Review Draft (EPA/600/P-00/001Cb). U.S. Environmental Protection Agency, National Center for Environmental Assessment, Washington, DC. Available at http://www.epa.gov/nceawww1/pdfs/dioxin/nas-review/.

SESSION 2: IMMUNOTOXICITY

The U.S. EPA plans to consider development of a quantitative dose-response assessment for the immunologic effects associated with TCDD exposure. Such an assessment would be based on information in U.S. EPA (2003), NAS (2006) and key studies identified in this workshop. The purpose of this session was to identify and discuss key issues pertaining to dose-response assessment for dioxin-induced immunologic effects.

Session 2 Panelists (Session Co-Chairs are identified by asterisk)

- Roger Cooke, Resources for the Future
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- Nancy Kerkvliet, Oregon State University
- Manolis Kogevinas, Centre for Research in Environmental Epidemiology
- Robert Luebke, U.S. EPA
- Paolo Mocarelli, University of Milan
- *Allen Silverstone, State University of New York, Upstate Medical University

- Courtney Sulentic, Wright State University
- Nigel Walker, National Institute of Environmental Health Sciences

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Key Study Selection Criteria

The Panel first addressed the Key Study Selection Criteria proposed by the U.S. EPA (Appendix C). The Panel raised the issue that the key study criteria do not apply to most studies designed to investigate immunotoxicity, including those used to calculate ED_{01}s (U.S. EPA, 2003). The Panel observed that most dioxin immunotoxicity studies are relatively high dose (>200 ng/kg-d) acute studies and/or use parenteral rather than oral administration.

The Panel discussed several studies often considered important for assessing the immunotoxic effects of TCDD exposure. The Oughton et al. (1995) mouse bioassay was discussed and, although the study does meet the proposed criteria, it could not be considered a key study; specifically, the Panel contended that since there were no functional alterations observed or measured in this bioassay, the changes in cellular phenotypes are only "suggestive" of immune alterations and cannot be regarded as having immunopathologic significance.

The Panel discussed two additional studies for further consideration by the U.S. EPA:

- Baccarelli et al. (2002). The Panel discussed this as a potentially key human epidemiological study that should be reviewed and considered further by the U.S. EPA. It measured the level of IgG, demonstrating a significant decline relative to dioxin body burdens.
- Smialowicz et al. (2008). The Panel noted that this study identified the antibody response to sheep red blood cells (SRBCs) as the critical effect, labeling this protocol as a functional assay. The Panel stated that if modeled, the U.S. EPA could calculate the BMR for this endpoint as 1 standard deviation from the control mean.

References

Baccarelli, A., P. Mocarelli, D.G. Patterson et al. 2002. Immunologic effects of dioxin: New results from Seveso and comparison with other studies. Environ. Health Perspect. 110(12):1169-1173.

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SESSION 3A: DOSE-RESPONSE FOR NEUROTOXICITY AND NONREPRODUCTIVE ENDOCRINE EFFECTS

The U.S. EPA plans to consider development of a quantitative dose-response assessment for neurological and/or nonreproductive endocrine effects associated with TCDD exposure. Such an assessment would be based on information in U.S. EPA (2003), NAS (2006) and key studies identified in this workshop. The purpose of this session was to identify and discuss key issues pertaining to dose-response assessment for dioxin-induced neurological and/or nonreproductive endocrine effects.

Session 3A Panelists (Session Co-Chairs are identified by asterisk)

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- Mike DeVito, U.S. EPA
- Mary Gilbert, U.S. EPA
- Rob Goble, Clark University
- Nancy Kerkvliet, Oregon State University
- Fumio Matsumura, University of California-Davis
- Paolo Mocarelli, University of Milan
- Chris Portier, National Institute of Environmental Health Sciences
- Lorenz Rhomberg, Gradient
- Allen Silverstone, State University of New York, Upstate Medical University
- Marie Sweeney, National Institute of Occupational Safety and Health
- *Bernie Weiss, University of Rochester

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What Are the Key Questions Regarding These Endpoints?

The Panel used the following question to initiate discussion: "*Are there identifiable indices of neurotoxicity and nonreproductive endocrine effects in animal studies and human populations?*" Under this discussion topic, the Panel discussed three endpoints: neurotoxicity (with focus on developmental exposures), thyroid dysfunction (e.g., thyroid hormone deficits), and diabetes. The Panel also addressed the relevance of windows of vulnerability to each

endpoint. The Panel acknowledged that, in some cases, the window of exposure may precede the window of expression of toxicity.

Epidemiological Study Selection

Developmental Neurotoxicity

The Panel recognized that an unusual feature for this endpoint is that there are sufficient human data for dose-response modeling (e.g., Dutch children [Huisman et al., 1995; Patandin et al., 1999] and U.S. children [Jacobson and Jacobson, 1996]) and there is an internal dose metric (serum concentrations). Additionally, the Panel discussed recent studies that address this endpoint in humans (from Japan [reference not provided] and Holland [e.g., Koopman-Esseboom et al., 1996; Vreugdenhil et al., 2002]). For continued investigation into this endpoint, the Panel raised two issues to the U.S. EPA:

- Conduct an evaluation of whether a modeled effect can be attributed to TCDD and not some other persistent organic pollutant (POP), although the Panel recognized that it is unlikely U.S. EPA will be able to distinguish among these exposures because other POPs are intrinsic confounders in the Dutch study.
- Allow animal data to inform the dose-response modeling of epidemiological data.

Thyroid Dysfunction

The Panel identified the availability of human data for this endpoint (e.g., Calvert et al., 1999; Koopman-Esseboom et al., 1994). Much of the thyroid dysfunction literature has been published since the 2003 Reassessment (e.g., Wang et al., 2005; Baccarelli et al., 2008). The Panel also noted the availability of an internal dose metric (serum concentrations). Additionally, the Panel discussed the mechanistic studies in animals that link TCDD to thyroid dysfunction. For continued investigation into this endpoint, the Panel raised three issues for the U.S. EPA to consider:

- Consider the newly available human data since the Reassessment.
- Investigate and clarify of the role of TCDD-induced thyroid dysfunction in developmental neurotoxicity.
- Evaluate and determine whether an effect can be attributed to TCDD or other contaminants.

Diabetes

The Panel discussed that data suggest that diabetes incidence in those under 55 years old may be associated with exposure to PCBs. They acknowledged that whether this is a dioxin-like compound (DLC) mediated effect or whether other POPs are responsible is still undetermined. The Panel also acknowledged that no animal model exists for the investigation of xenobiotic-induced diabetes, and that separating the injury dose level from the current body burdens would depend on good pharmacokinetics in humans. For continued investigation into this endpoint, the Panel listed two issues for the U.S. EPA to consider:

- Results from the Anniston study and the Great Lakes Fishermen study (references not provided) should be examined for dose metrics (both studies examine human PCB exposures).

- Changes of adipose tissue status need to be considered, given that dieting can cause release of lipid-soluble contaminants.

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Patandin, S., C.I. Lanting, P.G.H. Mulder, E.R. Boersma, P.J.J. Sauer and N. Weisglas-Kuperus. 1999. Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age. J. Pediatr. 134:33–41.

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Wang S.L., P.H. Su, S.B. Jong, Y.L. Guo, W.L. Chou and O. Päpke. 2005. *In utero* exposure to dioxins and polychlorinated biphenyls and its relations to thyroid function and growth hormone in newborns. Environ. Health Perspect. 113:1645–1650.

SESSION 3B: DOSE-RESPONSE FOR CARDIOVASCULAR TOXICITY AND HEPATOTOXICITY

The U.S. EPA plans to consider development of a quantitative dose-response assessment for cardiovascular and/or hepatic effects associated with TCDD exposure. Such an assessment would be based on information in U.S. EPA (2003), NAS (2006) and key studies identified in this workshop. The purpose of this session was to identify and discuss key issues pertaining to dose-response assessment for dioxin-induced cardiovascular and/or hepatic effects.

Session 3B Panelists (Session Co-Chairs are identified by asterisk)

- Bob Budinksy, Dow Chemical
- Manolis Kogevinas, Centre for Research in Environmental Epidemiology
- Rob McDowell, U.S. Department of Agriculture
- Jim Olson, State University of New York, University at Buffalo
- Marian Pavuk, Agency for Toxic Substances and Disease Registry
- *Jeff Swartout, U.S. EPA
- *Mary Walker, University of New Mexico
- Nigel Walker, National Institute of Environmental Health Sciences

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Key Study Selection Criteria

The Panel initially focused on the draft key study selection criteria offered by the U.S. EPA (Appendix C). The panel recommended that for cardiovascular effects, which are not usually observed in rodents, the use of knockout mouse models (ApoE KO and LDLR KO) be moved to the "primary" column because only these studies establish the cardiovascular toxicity model in mice.

The panel also was concerned that the gavage procedure can increase mouse blood pressure. Consequently, the panel recommended that gavage studies not be used for the blood pressure endpoint (i.e., only dietary dosing studies should be considered).

Human Health Endpoints

In relation to the hepatic endpoint, the Panel acknowledged the large body of dose response information on hepatic effects in rodents and that enzyme (mostly CYP1A1) induction was a sensitive effect. However, the Panel cited the lack of linkage of CYP1A1 to downstream events, which complicates the toxicological interpretation of this endpoint, and concluded that

the more important liver effects in rodents are probably on the "road to cancer." The Panel noted that hepatic effects were not seen in the epidemiological studies, but acknowledged that these studies were not designed to detect them.

In relation to the cardiovascular endpoint, the Panel identified hypertension and ischemic heart disease (IHD) as two key endpoints from the epidemiological studies. The Panel recommended that the U.S. EPA perform a meta-analysis of these data. The Panel also commented that recent animal studies support the observations linking TCDD exposure to IHD and hypertension. In particular, the National Toxicology Program (NTP) study shows inflammatory and structural effects on resistant vascular arterioles (NTP, 2006). Additional evidence from the study suggests that the vascular effects may be CYP1A1-dependent. The Panel suggested that the NTP study data might be used as a surrogate for dose-response modeling of hypertension and that such an approach would be supported by data on the role of AhR in vascular function and remodeling.

POD Issues

The Panel was not supportive of 1% of maximal response (ED_{01}), which was utilized in the 2003 Reassessment. The Panel concluded that the POD should depend on the specific endpoint and recommended the following to the U.S. EPA:

- For continuous measures, base the BMR on difference from control. Consider the adversity level—at what point does the endpoint become adverse?
- For incidence data, set the BMR to a fixed-risk level.

Supporting Information

The Panel posed several suggestions to the U.S. EPA for reducing uncertainty and improving the knowledge base for TCDD toxicity.

- Use in vitro data to define uncertainties, such as the relative sensitivity between rodents and humans and around the definition of a POD.
- Consider studies on dioxin-like compounds (DLCs).
- Use PK modeling to define the dose metric for hepatic effects.
- Use body burden or serum concentrations for cardiovascular endpoints.

Finally, the Panel recommended that U.S. EPA finish the reassessment quickly and establish a definitive plan to review and incorporate new data as they become available.

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SESSION 4A: DOSE-RESPONSE FOR CANCER

The U.S. EPA plans to consider development of a quantitative dose-response assessment for cancer associated with TCDD exposure. Such an assessment would be based on information in U.S. EPA (2003), NAS (2006) and key studies identified in this workshop. The purpose of this session was to identify and discuss key issues pertaining to dose-response assessment for dioxin-induced cancer.

Session 4A Panelists (Session Co-Chairs are identified by asterisk)

- Lesa Aylward, Summit Toxicology
- Kenny Crump, Louisiana Tech University
- Dale Hattis, Clark University
- *Janet Hess-Wilson, U.S. EPA
- Karen Hogan, U.S. EPA
- Manolis Kogevinas, Centre for Research in Environmental Epidemiology
- Marian Pavuk, Agency for Toxic Substances and Disease Registry
- Chris Portier, National Institute of Environmental Health Sciences
- Lorenz Rhomberg, Gradient
- Jay Silkworth, General Electric
- *Nigel Walker, National Institute of Environmental Health Sciences

Please note that the use of the term "concluded" or "recommended" in this summary does not mean that a consensus was reached. Session Summaries were written from the material prepared by the non-EPA/ANL Co-chair and represent a synopsis of the panel discussions.

Key Study Selection

The Panel discussed both human and rodent studies. In reviewing the epidemiological data, the Panel agreed the EPA should focus on four cohort studies (Dutch cohort, NIOSH cohort, BASF accident cohort, and Hamburg cohort) and pointed out that there are numerous updates and reevaluations of data now in the literature and others will be published soon. The Panel stated that it is appropriate for the U.S. EPA to consider the increase in total cancers for modeling human cancer data, however, Non-Hodgkin's lymphoma, and lung tumors are the main TCDD-related cancer types seen in humans exposed to TCDD. The Panel suggested the U.S. EPA focus the quantitative dose-response modeling on the human data.

In reviewing the rat data, the Panel identified four new NTP rodent cancer bioassays with liver and lungs as the main target organs. However, they suggested that dose-response modeling efforts should model "all cancers" from these NTP data sets as well and use tumor incidence—not individual rats as measures.

Key Study Selection Criteria

The Panel discussed whether data for TCDD only should be used or if PCB126 could be used to develop a dose-response curve. From this discussion, the Panel reached a general agreement that limiting the dose-response modeling and cancer assessment to TCDD only would be the best approach.

Regarding the oral dosing regimens, the Panel discussed the differences in results from different bioassays. They concluded that there were insufficient data to pick between oral feed (Kociba et al., 1978) and oral gavage (NTP, 2006) studies, but stated "If all aspects of studies were equal, an oral feed study is preferred." However, given that current data sets are not equal, they agreed that U.S. EPA should consider both feed and gavage studies.

The Panel put forth the recommendation that studies that include initiation-promotion model data and TgAC transgenic model data from oral exposure studies should be excluded from the primary category in the key study selection criteria (Appendix C lists the draft study selection criteria distributed prior to the meeting). Studies from both classifications should be moved to the second tier.

The Panel was also unsupportive of the "response magnitude outside the range of normal variability" criterion, as they did not believe it was applicable to a cancer endpoint.

Critical Endpoints to Consider

The Panel recognized that the MOA for TCDD includes cell growth/differentiation dysregulation, that different endpoints (tumor types) across species may be expected, and that there are differences in tumor sites across species. The Panel further acknowledged that there is insufficient information to determine if rodent tumor types observed are relevant to humans. Thus, the Panel suggests the following:

- U.S. EPA should consider all the observed cancer endpoints in its evaluation.

Nonlinear (aka threshold) Versus Linear Dose-Response Modeling

The Panel agreed that NTP bioassays appear to demonstrate nonlinear dose response, but they expressed concern about using animal data to infer slope and dose response for humans. The Panel pointed out that there are differences in slopes across different bioassays, and specifically, that some appear linear while others appear nonlinear. Given the observation of both nonlinear vs. linear, the Panel concluded that neither could be ruled out for extrapolation below the POD simply based on the available data. One panelist noted that U.S. EPA Cancer Guidelines (U.S. EPA, 2005) state that only if one can demonstrate that the MOA has a threshold dose-response shape, and can exclude all other potential linear MOAs, can one use a nonlinear model. Lastly, the Panel noted that there are data and rationales to support use of both linear and

nonlinear response below POD. From this discussion, the Panel raised one possibility to the U.S. EPA:

- Both linear and nonlinear model functions should be considered in the dose-response analysis.

Dose Metrics

In considering human data, the Panel expressed a preference for lipid-adjusted serum levels over body burden (BB), and they expressed concerns over the assumptions used in the back calculation of the BB in the epidemiologic cohorts. In considering the rat data, the Panel supported the use of BB—especially lipid-adjusted BB. The Panel, however, did express concern over the sequestering of TCDD in liver and then the use of liver levels in BB calculations.

Supporting Information—Biologically-Based Dose-Response (BBDR) Models and MOA

The Panel discussed BBDR. Though once considered an attractive proposition, BBDR models may mask uncertainty within the models, necessitating them to be used with greater caution. The Panel suggested two issues for the U.S. EPA to consider:

- If there is a published model, use it if it is valid—do not generate a new model.
- Focus on the actual experimental data to drive the analysis.

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SESSION 4B: DOSE-RESPONSE FOR REPRODUCTIVE/DEVELOPMENTAL TOXICITY

The U.S. EPA plans to consider development of a quantitative dose-response assessment for reproductive and developmental effects associated with TCDD exposure. Such an assessment would be based on information in U.S. EPA (2003), NAS (2006) and key studies identified in this workshop. The purpose of this session was to identify and discuss key issues pertaining to dose-response assessment for dioxin-induced reproductive and developmental effects.

Session 4B Panelists (Session Co-Chairs are identified by asterisk)

- Barbara Abbott, U.S. EPA
- Bruce Allen, Bruce Allen Consulting
- Roger Cooke, Resources for the Future
- George Daston, Procter & Gamble
- Mike DeVito, U.S. EPA
- Rob Goble, Clark University
- *Fumio Matsumura, University of California-Davis
- Paolo Mocarelli, University of Milan
- Brian Petroff, University of Kansas
- *Glenn Rice, U.S. EPA
- Marie Sweeney, National Institute of Occupational Safety and Health
- Mary Walker, University of New Mexico
- Bernie Weiss, University of Rochester

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A Major Question Posed During this Workshop Session was "Are Human Embryos and Infants Less Sensitive to Dioxin Exposures Than Some Experimental Animals?"

The Panel recognized that animal data show a wide range of species sensitivity to dioxin for a given developmental or reproductive endpoint. Presently, there are data for some endpoints that show that human sensitivity is comparable to experimental animals (e.g., semen quality), and for other endpoints the data demonstrate that humans are insensitive compared to other species (e.g., cleft palate). Lastly, the Panel recognized that there are some endpoints for which relative human sensitivity remains uncertain.

Key Study Selection

The Panel reviewed the charge questions (Appendix B), discussed them, and listed two issues for the U.S. EPA to consider:

- Concerning key study determination, use a stepwise approach that is dependent upon the information available and needed to address the question.

- Concerning the key studies informing the POD and the POD endpoint choice, use the POD to depart from what is certain and use a high-confidence study that has found effects at a low enough level at which other effects are protected.

The Panel also developed Table 1, based on the information presented in this session. Table 1 identifies specific reproductive and developmental effects of concern, listing whether an effect has been observed in test animals and epidemiologic cohorts. It also identifies the ED_{10} estimated by the U.S. EPA (2003) for health effects observed in rodent bioassays. If the U.S. EPA did not report an ED_{10} for an effect, the table identifies a study where the effect was reported and the lowest study dose where the effect was observed. Table 1 also identifies the epidemiologic cohort where the specific reproductive and developmental effects were observed.

Epidemiological Study Utility

The Panel reviewed the charge questions (Appendix B), discussed them, and made two suggestions to the U.S. EPA:

- Concerning the ability of epidemiological studies to inform critical effects, start with concordance across species (including humans) for the spectrum of effects.
- Concerning the ability of epidemiological studies to inform dose-response modeling, start with the epidemiology and then go to animal data if the dose response has not been well characterized for an endpoint of interest and compare to animal data as a reality check.

Animal Model Utility

The Panel reviewed and discussed the charge questions (Appendix B). Table 1, which identifies the effects that occur in animals and also have relevance to humans, summarizes much of this discussion. Regarding the influence of mode of action (MOA) on animal model choice, the Panel concluded that by evaluating concordance among health effects reported in epidemiologic and animal bioassay data, the U.S. EPA could identify a set of plausible reproductive and developmental effects to consider. Actual animal and human MOA information is helpful in that it creates comfort with the animal models and in defining the boundaries of possible effects.

TABLE 1

Reproductive/Developmental Effects of Concern for Human Health

Endpoint	Rodent (ED_{10} ng/kg-d)	Human	Notes
Sperm Count/Motility	Yes (6.2−28; 66−200)	Yes	ED_{10} bases Mabley et al. (1992a,b) caudal sperm count and daily sperm production range from 6.2−28; Gray et al. (1997) epididymal sperm count and total testis sperm counts range from 66−200.
Sex Ratio	No	Yes, Seveso	
Delayed Puberty Males	Yes (94)	Yu-cheng	ED_{10} basis rat male puberty delay Gray et al. (1997). Need to qualify epidemiology data because of cohort PCDD/PCDFs exposures.
Delayed Puberty in Females	Yes	No in Seveso	Gray and Ostby (2002) report delayed puberty in female offspring of pregnant rats receiving a single dose of 1 µg TCDD/kg on GD 15.
Cleft Palate	Yes (6300−6400)	No	ED_{10} basis Birnbaum et al. (1989).
Premature Senescence	Yes	No, Seveso	Franczak et al. (2006) report that rats prematurely entered reproductive senescence, after receiving cumulative TCDD doses as low as 1.7 µg TCDD/kg. They considered first occurrence of prolonged interestrous interval (>6 d) as evidence of onset of reproductive senescence.
Hormones E2	Yes	Yes, Males—Seveso	Li et al. (1995) report serum estradiol-17β (E2) concentrations induced by equine Chorionic Gonadotropin injection were significantly elevated in female rats orally administered 10 µg/kg TCDD on PND 22. While E2 decreased dramatically in control animals during the preovulatory LH surge, it did not in TCDD-treated rats.
Low Birth Weight	Yes (190)	Suggestive effect in Seveso in first 8 years after exposure	ED_{10} basis Gray et al. (1997).
Reproductive Cycling (prolongation)	Yes	Yes, Seveso Prepubertal exposure	Franczak et al. (2006) report loss of normal cyclicity in female rats at 8 months of age following a cumulative dose of 1.7 µg TCDD/kg.

Supporting Information

The Panel reviewed the charge questions (Appendix B), discussed them, and made two suggestions to the U.S. EPA:

- Concerning deviation from default approaches for noncancer endpoints, there needs to be a careful assessment of the POD and the application of uncertainty factors in light of PK/pharmacodynamics (PD), population characteristics and variability, and MOA information.
- Concerning the MOA's ability to clarify endpoint and the incorporation of a cascade of cellular event into dose-response for noncancer endpoint, any study that helps inform the dose response should be considered—including studies not specific to dioxins. Complicated mechanistic models need not be developed. Standard dose-response models can be applied. One can look at the cascade of events in a stepwise, simple way.

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SESSION 5: QUANTITATIVE UNCERTAINTY ANALYSIS OF DOSE-RESPONSE

This session addressed the uncertainty analysis to be considered for the dose-response assessments. The session opened with a presentation on current estimates of dioxin exposure levels. Then it focused on the factors to include in the scope of an uncertainty analysis including dioxin kinetics.

Session 5 Panelists (Session Co-Chairs are identified by asterisk)

- Bruce Allen, Bruce Allen Consulting
- Lesa Aylward, Summit Toxicology
- Roger Cooke, Resources for the Future
- Kenny Crump, Louisiana Tech University
- Mike DeVito, U.S. EPA
- Dale Hattis, Clark University
- *Rick Hertzberg, Biomath Consulting
- Nancy Kerkvliet, Oregon State University
- Leonid Kopylev, U.S. EPA
- Rob McDowell, U.S. Department of Agriculture
- Lorenz Rhomberg, Gradient
- Woody Setzer, U.S. EPA
- Marie Sweeney, National Institute of Occupational Safety and Health
- *Linda Teuschler, U.S. EPA

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The Panel summarized the NAS comments regarding uncertainty. Areas for improvement include:

- Ensure "transparency, thoroughness, and clarity in quantitative uncertainty analysis."
- Describe and define (quantitatively to the extent possible) the variability and uncertainty for key assumptions used for each key endpoint-specific risk assessment, including choices of data set, point of departure, dose-response model, and dose metric.
- Incorporate probabilistic models to represent the range of plausible values.

- Assess goodness-of-fit of dose-response models.
- Provide upper and lower bounds on central tendency estimates for all statistical estimates.
- When quantification is not possible, clearly state it, and explain what would be required to achieve quantification.

Identification of Important Uncertainties

The Panel reviewed the charge questions (Appendix B), discussed them, and listed eight issues for consideration by the U.S. EPA:

- Concerning species and strain differences in the U.S. EPA's Response to NAS, current U.S. EPA procedures do not take this into account when selecting one data set for risk assessment. Issues include "Where are humans in the distribution of potencies that can be generated? How likely is it that human response is similar to the selected data? Can we infer inter-individual variability from these differences?"
- Concerning the use of animal data for cross species extrapolation to humans (PK and PD uncertainties), issues to consider include differences in distribution and responses following bolus doses from those of subchronic and chronic protocols; uncertainty in liver doses due to sequestration; differences in receptor binding affinity among congeners; and age factors (e.g., assumption of a lifetime constant daily dose for a cancer extrapolation).
- Concerning the description of AhR response, biochemical changes occur at lower doses than toxicological changes. There should be an effort to identify the biochemical changes that would mark Ah receptor binding to inform the BMR, and, thus, prevent toxicity.
- Concerning model uncertainty, the mathematical model choice depends on endpoint. There should be an effort towards determining what is the most sensitive endpoint(s) for humans and conducting animal studies to model that endpoint(s).
- Concerning exposure and dose response in human studies, ensure enough similarity to current human exposure profiles (mixture composition) so that a dose-response assessment can be done. Incorporate new epidemiological studies. Evaluate concordance with animal data and consistency across studies. Panel-acknowledged uncertainties include exposure estimates from person to person, shape of human dose-response curve, healthy worker effect, and age dependence.
- Concerning POD determination, uncertainty factors are inherently mathematically inconsistent and that should be conveyed in the discussion of uncertainties when interpreting the POD.
- Concerning dose metric, tissue concentration is preferred. It should be evaluated against a background of variability in AhR-binding expression. There is uncertainty in what level of binding should be considered, in different cell types, tissues, life stage (development). The relationship between dose metric and causation of adverse effects should be examined.

Low-Dose Extrapolation

The Panel reviewed the charge questions and discussed them (Appendix B). The Panel concluded that curve-fitting uncertainty (for a given dataset, dose metric, and model) can be characterized and is useful, but, by itself, it is an incomplete characterization of uncertainty. The Panel acknowledged the difficulty of fully characterizing uncertainty, especially quantitatively. Some panelists argued that the problem is insurmountable and that no meaningful uncertainty analysis is likely to be performable. Other panelists contended that, the difficulties notwithstanding, "good-faith" efforts to do something practical and forthright to characterize uncertainty in low-dose extrapolation would be useful and important. The Panel clarified "good faith" as meaning a characterization that is useful and not misleading to decision makers and is inclusive of approaches that have meaningful support in the scientific community as a whole. Being in "good faith" is more important than being complete (i.e., addressing every uncertain element), especially since completeness is not a realistic goal. From this discussion, the Panel listed four issues for consideration by the U.S. EPA:

- Review alternative data sets, dose metrics, and models to see where consequential uncertainties and impacts on low-dose implications arise.
- Consider the impacts of choices among plausible alternative data sets, dose metrics, models, and other more qualitative choices—issues include how much difference the choices make and also how much relative credence should be put to each alternative as a way of gauging and describing the landscape of imperfect knowledge regarding possibilities for the true dose-response.
    - Hard to do quantitatively, since the factors are not readily expressed as statistical distributions, but can describe the rationale for believing/doubting each alternative in terms of available supporting evidence, contrary evidence, and needed assumptions.
    - Expert judgment methods may be helpful in characterizing the relative weights of scientific credibility among alternatives. The expert judgment process, when conducted systematically, can be thought of as adding data to the assessment of credibility of alternatives, rather than as just an opinion poll.
    - Information on plausibility of alternative low-dose extrapolation approaches can come from external considerations of mode of action, and not just from statistical success at fitting particular (high-dose) data sets.
- Characterizing uncertainty through a variety of approaches could be tried, and their relative merits and shortcomings discussed, as a way forward.
- Consider the sources of potential error, particularly in epidemiological data (e.g., TEF uncertainty and variation in congener mixtures) and if possible quantify their impact on the dose-response assessment.

Considerations for Conducting Uncertainty Analysis

Overall, the Panel was split on whether U.S. EPA should do quantitative uncertainty analyses. The Panel noted that if done on only some of the uncertainties, then results would be misleading and could be misused. Ultimately, the Panel listed seven issues for consideration by the U.S. EPA:

- The Panel recapped what some consider as being the first integrated risk assessment, with structured expert judgment and uncertainty analysis, i.e., the Rasmussen Report (WASH-1400; U.S. Nuclear Regulatory Commission, 1975). In their discussion of the report, the Panel noted that in addition to standard event tree/fault tree modeling, this report also tackled difficult model uncertainty issues involved in accident progression, dispersion of released pollutants in the atmosphere, environmental transport, exposure, health, and economic impacts. And though the Panel also recognized that this method was no longer state-of-the-art, the Panel contended that it represents a good example of a structured approach and methodology that could be built upon.

- The Panel also discussed TEQs used in epidemiological studies, based on intake, and recognized that the key uncertainty in what was measured was not just intake but also involved PK/PD issues. The Panel acknowledged that the TEQ system is regularly used on a concentration basis, but they expressed concern that the qualification becomes lost. TEQs ignore pharmacokinetics and the common practice of rounding to orders of magnitude introduces more error.
- Structure the risk assessment along MOA steps—identify key biochemical measures (~5−10) common across toxic endpoints and identify the degree of meaningful change in effect or effect variance. Make a table with all options for data set, model, etc.; make best estimates/choices and determine which of these choices matter the most to the answer.
- Use expert panels—expert judgment can be collected scientifically (procedures are published). But there are known biases; central tendency estimates work much better than extremes.
- Use supporting studies to fill in critical data gaps—Info filling methods do exist (e.g., PK modeling). Put short-term studies into the "supporting info" category (unless, of course, the risk assessment is for acute exposures, such as chemical spills).
- Be creative in the analysis of uncertainty. Intermediate steps between AhR binding and the end processes can be hypothesized based on data, experiences, and analogies related to other chemicals.
- The 2003 Reassessment presented potency estimates on wide variety of endpoints/models; needed to be more transparent in that discussion. Statistical graphics can be used to convey uncertainties.

Reference

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APPENDIX A: 2009 U.S. EPA DIOXIN WORKSHOP AGENDA

SCIENTIFIC WORKSHOP TO INFORM THE TECHNICAL WORK PLAN FOR U.S. EPA'S RESPONSE TO NAS COMMENTS ON THE HEALTH EFFECTS OF DIOXIN PRESENTED IN U.S. EPA'S DIOXIN REASSESSMENT

Cincinnati, OH

Date: February 18–20, 2009

BACKGROUND/WORKSHOP OBJECTIVE

At the request of the U.S. Environmental Protection Agency (U.S. EPA), the National Academy of Sciences (NAS) prepared a report, *Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment* (NAS, 2006), that made a number of recommendations to improve the U.S. EPA's risk assessment for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). In response, the U.S. EPA will prepare a technical report that addresses key comments on the dose-response assessment for TCDD. The U.S. EPA intends to develop its response through a transparent process that provides multiple opportunities for input.

To assist in this effort, a Workshop will be held to inform the U.S. EPA's evaluation of the NAS recommendations. The Workshop will be open to the public. At the Workshop, the U.S. EPA will solicit input from expert scientists and the public.

The goal of the Workshop is to ensure that the U.S. EPA's response to the NAS comments focuses on the key issues and reflects the most meaningful science. The three main objectives of the Workshop are to (1) identify and discuss the technical challenges involved in addressing the NAS key comments on the TCDD dose-response assessment in the U.S. EPA Reassessment (U.S. EPA, 2003), (2) discuss approaches for addressing these comments, and (3) identify key published, independently peer-reviewed literature, particularly studies describing epidemiologic and *in vivo* mammalian bioassays, which are expected to be most useful for informing the U.S. EPA response.

Workshop participants will be encouraged to think broadly about the body of scientific information that can be used to inform the U.S. EPA's response and to participate in open dialogue regarding ways in which the science can best be used to address the key dose-response issues. This Workshop is similar to scientific workshops being conducted under the new review process for the National Ambient Air Quality Standards (NAAQS)[1] that assess health-related information for criteria pollutants.

[1] Please see http://www.epa.gov/ttn/naaqs/ for more information on the new NAAQS review process.

The Workshop discussions are expected to build upon two prior publications:

1. *Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds* (U.S. EPA, 2003). This external review draft provides a comprehensive reassessment of dioxin exposure and human health effects. This "dioxin reassessment" was submitted in October 2004 to the National Academy of Sciences (NAS) for review.
2. *Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment* (NAS, 2006).

Workshop participants are encouraged to review both of these documents and other relevant materials (e.g., the National Toxicology Program report on TCDD [NTP, 2006]) before the meeting because they provide important insights into the key questions and challenges. There are a number of open comment periods that are intended to facilitate a broad discussion of the issues.

Scientists with significant expertise and experience relevant to the health effects of TCDD or dioxin-like compounds and associated topics will be asked to serve on "expert panels" for discussions throughout the Workshop. Workshop panelists will include a wide range of experts representing many scientific areas needed to assess TCDD dose-response (e.g., epidemiology, human and animal toxicology, nuclear receptor biology, dose-response modeling, risk assessment, and uncertainty analysis). The Workshop panelists will be asked to highlight significant and emerging research and to make recommendations to the U.S. EPA regarding the design and scope of the technical response to NAS comments on the dose-response analysis for TCDD—including, but not limited to, recommendations for evaluating associated uncertainty. Open comment periods will follow each panel discussion session. Public participation will be encouraged by way of these designated open comment periods and, also, by participation in the scientific poster session planned for the second evening (February 19).

U.S. EPA will use the input received during this Workshop as the foundation for its development of a technical work plan for responding to the NAS comments on the TCDD dose-response analysis. The work plan will outline the schedule, process, and approaches for evaluating the relevant scientific information and addressing the key issues. The work plan also will identify the key literature to be utilized in U.S. EPA's response.

As a follow-on activity to this Workshop, a panel is being established under the Federal Advisory Committee Act (FACA) to guide and review the U.S. EPA's response to NAS comments. The FACA panel will be asked to conduct a consultation with the Agency on the draft technical work plan. At the same time, the public will also have the opportunity to provide comments to the FACA panel on the work plan. The final technical work plan will guide the development of the technical report that will constitute the U.S. EPA's response to NAS comments. During the development of this response, the U.S. EPA will seek advice from the FACA panel and the public several times. Finally, the FACA panel will be asked to review the technical report in a public forum.

The preliminary Agenda presented on the following pages may be revised prior to the Workshop following review by the session Co-Chairs; the dates and general timing of the

sessions, however, will not change. A final Agenda and a set of charge questions, intended to provide general direction for the Workshop discussions, will be posted on the Workshop Internet site (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=199923) prior to the meeting.

A poster session will be held on the evening of the second day (February 19). The purpose of this poster session is to provide a forum for scientists to present recent studies relevant to TCDD dose-response assessment and to encourage open discussion about these presentations.

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NAS (National Academy of Sciences). 2006. Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment. National Academies Press, Washington, DC (July). Available at http://www.nap.edu/catalog.php?record_id=11688.

NTP (National Toxicology Program). 2006. Toxicology and Carcinogenesis Studies of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) (CAS No. 1746-01-6) in Female Harlan Sprague-Dawley Rats (Gavage Studies). U.S. Department of Health and Human Services. NTP TR 521. Research Triangle Park, NC (April).

U.S. EPA (U.S. Environmental Protection Agency). 2003. Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds, NAS review draft, Volumes 1-3 (EPA/600/P-00/001Cb, Volume 1). U.S. Environmental Protection Agency, National Center for Environmental Assessment, Washington, DC (December). Available at http://www.epa.gov/nceawww1/pdfs/dioxin/nas-review/.

WORKSHOP AGENDA

Day 1

8:00–9:00	**Registration**
9:00–9:30	**Welcome/Purpose of Meeting/Document Development Process**
9:30–9:45	**Panel Comments/Questions on Charge**

9:45–2:45 Session 1: Quantitative Dose-Response Modeling Issues (Hall of Mirrors)

9:45–10:10	**Background/Introductory Remarks**
10:10–10:35	**TCDD Kinetics: Converting Administered Doses in Animals to Human Body Burdens** Presenter: Michael Devito
10:35–11:30	**Panel Discussion**
11:30–1:00	**Lunch**
1:00–2:00	**Panel Discussion cont.**
2:00–2:45	**Open Comment Period**

2:45–3:05 Break

3:05–5:15 Session 2: Immunotoxicity (Hall of Mirrors)

3:05–3:15	**Background/Introductory Remarks**
3:15–4:45	**Panel Discussion**
4:45–5:15	**Open Comment Period**

Day 2

8:00–8:30 **Report-Outs for Sessions 1 and 2 (Hall of Mirrors)**

8:00–8:15 **Report-Out for 1: Quantitative Dose-Response Modeling Issues**

8:15–8:30 **Report-Out for 2: Immunotoxicity**

8:30–11:30 **Sessions 3A and 3B (concurrent sessions)**

8:30–11:30 **Session 3A: Dose-Response for Neurotoxicity and Nonreproductive Endocrine Effects (Hall of Mirrors)**

8:30–8:45 **Background/Introductory Remarks**

8:45–11:00 **Panel Discussion**

11:00–11:30 **Open Comment Period**

8:30–11:30 **Session 3B: Dose-Response for Cardiovascular Toxicity and Hepatotoxicity (Rookwood Room)**

8:30–8:45 **Background/Introductory Remarks**

8:45–11:00 **Panel Discussion**

11:00–11:30 **Open Comment Period**

11:30–1:00 **Lunch**

1:00–2:00 **Report-Outs for Sessions 3A and 3B (Hall of Mirrors)**

The structure of the session report-outs will include the following:

- Summary of session presentation including minority opinion
- Public comments
- Discussion

1:00–1:15 **Report-Out for 3A: Dose-Response for Neurotoxicity and Nonreproductive Endocrine Effects**

1:15–1:30 **Open Comment Period**

1:30–1:45 **Report-Out for 3B: Dose-Response for Cardiovascular Toxicity and Hepatotoxicity**

1:45–2:00 **Open Comment Period**

2:00–5:15 Sessions 4A and 4B (concurrent sessions)

2:00–5:15 Session 4A: Dose-Response for Cancer (Hall of Mirrors)

2:00–2:15 **Background/Introductory Remarks**

2:15–4:45 **Panel Discussion**

4:45–5:15 **Open Comment Period**

2:00–5:15 Session 4B: Dose-Response for Reproductive/Developmental Toxicity (Rookwood Room)

2:00–2:15 **Background/Introductory Remarks**

2:15–4:45 **Panel Discussion**

4:45–5:15 **Open Comment Period**

6:45–8:15 Poster Session (Rosewood Room)

Day 3

8:30–9:30 Report-Outs for Sessions 4A and 4B (Hall of Mirrors)

8:30–8:45 **Report-Out for 4A: Dose-Response for Cancer**

8:45–9:00 **Open Comment Period**

9:00–9:15 **Report-Out for 4B: Dose-Response for Reproductive/Developmental Toxicity**

9:15–9:30 **Open Comment Period**

9:30–3:30	**Session 5: Quantitative Uncertainty Analysis of Dose-Response (Hall of Mirrors)**
9:30–9:40	**Background/Introductory Remarks**
9:40–10:10	**Evidence of a Decline in Background Dioxin Exposures in Americans Between the 1990s and 2000s** Presenter: Matt Lorber
10:10–10:30	**Break**
10:30–11:30	**Panel Discussion**
11:30–1:00	**Lunch**
1:00–2:15	**Panel Discussion cont.**
2:15–2:30	Break
2:30–3:00	**Open Comment Period**
3:00–3:15	**Report-Out for 5: Quantitative Uncertainty Analysis of Dose-Response**
3:15–3:30	**Closing Remarks**
3:30	**Adjourn**

APPENDIX B: 2009 U.S. EPA DIOXIN WORKSHOP QUESTIONS TO GUIDE PANEL DISCUSSIONS

SESSION 1

Dose Metric

Considering all of the endpoints or target tissues, and species that U.S. Environmental Protection Agency (U.S. EPA)'s dose-response modeling might evaluate, what are the best measures of dose (e.g., ingested, tissue concentrations, body burden, receptor occupancy, other surrogate) and why?

Developing Dose-Response Models from Mammalian Bioassays

How best can the point of departure (POD) be determined when the response range is incompletely characterized (i.e., high response at the lowest dose or low response at the highest dose; observed in several key 2,3,7,8-Tetrachlorodibenzo-p-Dioxin [TCDD] studies)?

If considered to be biologically plausible, how can a threshold be incorporated into a dose-response function (e.g., for TCDD cancer data)?

How can nonmonotonic responses be incorporated into the dose-response function?

Developing Dose-Response Models from Epidemiological Studies

How can the epidemiological data be utilized best to inform the TCDD exposure-response modeling? Which epidemiological studies are most relevant?

Supporting Information

For those toxicological endpoints that are Ah receptor-mediated, how would the receptor kinetics influence the shape of the dose-response curve? How would downstream cellular events affect the shape of the dose-response curve? How can this cascade of cellular events be incorporated into a quantitative model of dose-response?

SESSIONS 2, 3A, 3B, 4A, AND 4B

Key Study Selection

For this endpoint, what refinements should be made to the draft criteria for selection of key studies?

What are the specific effects of concern for human health for this endpoint?

Based on the draft criteria for the selection of key studies, what are the key studies informing the shape of the dose-response curve above the POD and the choice of the POD for this endpoint?

Epidemiological Study Utility

How and to what extent do the epidemiological data inform the choice of critical effect?

How can the epidemiological data inform the quantitative dose-response modeling?

Animal Model Utility

Are there types of effects observed in animal models that are more relevant to humans than others? To what extent does information on mode of action (MOA) influence the choice of animal model (species, strain, sex)?

Supporting Information

Are there studies that establish a sufficient justification for departure from the default procedures that address the shape of the dose-response curve below the POD under the cancer guidelines?

Are there studies that establish a sufficient justification for departing from U.S. EPA's default approaches for noncancer endpoints?

To what extent can MOA information clarify the identification of endpoints of concern and dose-response metric for this endpoint? How can the cascade of cellular events for this endpoint be incorporated into a quantitative model of dose response?

SESSION 5

For cancer and noncancer TCDD dose-response assessments, U.S. EPA is interested in developing a quantitative uncertainty analysis addressing both parameter and model uncertainty, if feasible. Uncertainties will include, among others, choice of endpoint; underlying study uncertainties; choice of dose metric; interspecies extrapolations such as kinetic uncertainties; and choice of dose-response model, including threshold models. The U.S. EPA is currently examining techniques and tools for uncertainty analysis—including Bayesian and frequentist approaches.

Identification of Important Uncertainties

What are the major uncertainties pertaining to modeling the animal data?

Consider the dose metric (species or tissue specificity), vehicle of administration, exposure frequency, exposure duration, and POD determination (e.g., benchmark response selection or no-observed-adverse-effect level/lowest-observed-adverse-effect level identification).

What are the major uncertainties pertaining to dose-response modeling below the POD?

Consider how receptor kinetics and downstream cellular event information might be used to bound the uncertainties associated with dose-response modeling below the POD.

What are the major uncertainties in cross-species extrapolation (e.g., half-lives, tissue distribution, and toxicodynamics)?

Consider the primary species dosed with TCDD: mice, hamsters, rats, guinea pigs, and monkeys.

What are the major uncertainties pertaining to intrahuman variability?

Consider what data sets would be useful to represent sensitive subpopulations.

What are other significant sources of uncertainty for the cancer and noncancer assessments?

Considerations for Conducting Uncertainty Analysis

What data sets could be used to quantify uncertainties in cancer and noncancer TCDD dose-response assessments?

Consider dioxin-like compound dose-response data.

Consider MOA information.

What are the appropriate techniques for the TCDD dose-response uncertainty analysis, and what are their respective strengths and weaknesses of these approaches as applied to TCDD?

APPENDIX C: 2009 U.S. EPA DIOXIN WORKSHOP DRAFT SELECTION CRITERIA TO IDENTIFY KEY *IN VIVO* MAMMALIAN STUDIES THAT INFORM DOSE-RESPONSE MODELING FOR 2,3,7,8-TETRACHLORODIBENZO-*p*-DIOXIN (TCDD)[a]

Study Feature	Selection Rationale		
	Primary[b]	*Secondary*[c]	*Currently Excluded*
Chemical, purity, matrix/medium	TCDD-only doses included, purity specified, matrix in which TCDD is administered is identified	TCDD purity or matrix not clearly identified	Studies of dioxin-like compounds (DLCs) or mixtures
Peer review	Independently peer-reviewed, publicly available	Supplementary materials accompanying peer-reviewed publication	Not formally peer-reviewed; literature not publicly available
Study design, execution, and reporting	Clearly documented and consistent with standard toxicological principles, testing protocols, and practice (i.e., endpoint-appropriate, particularly for negative findings)	Testing protocol provides incomplete coverage of relevant endpoint-specific measures, particularly for negative findings	Studies not meeting standard principles and practices
Study subject: species, strain, and sensitivity for given endpoint; litter; life stage; gender	Mammalian species Strain and gender identified Animal age at beginning of treatment identified Litter confounders (within/between) accounted for	Mammalian species, *in vivo*, but only studying an artificially sensitive subject (e.g., knockout mouse)	Non-mammalian or not *in vivo*
Exposure route	Oral	Parenteral (e.g., intravenous, intramuscular, intraperitoneal, subcutaneous)	Inhalation, dermal, ocular
Dose level	Lowest dose ≤200 ng/kg-d for noncancer endpoints and ≤1 µg/kg-d for cancer	Lowest dose >200 ng/kg-d for noncancer endpoints, or >1.0 µg/kg-d for cancer	
Exposure frequency, duration, and timing	Dosing regimen characterized and explained		Characterization/explanation missing or cannot be determined
Controls	Appropriate and well characterized	Effect reported, but with no negative control	
Response	Effect relevant to human health Magnitude outside range of normal variability	Precursor effects, or adaptive responses potentially relevant to human health	Lethality
Statistical evaluation	Clearly described and appropriate to the endpoint and study design (e.g., per error variance, magnitude of effect)	Limited statistical context	

[a] NAS (2006) commented that the selection of data sets for quantitative dose-response modeling needed to be more transparent. These draft criteria are offered for consideration at the kickoff workshop. These criteria would be used to identify candidate studies of non-human mammals that would be used to define the point-of-departure (POD). These criteria are not designed for hazard identification or weight-of-evidence determinations. Studies addressing data other than direct TCDD dose-response in mammals (including toxicokinetic data on absorption, distribution, metabolism, or elimination; information on physiologically-based pharmacokinetic [PBPK] modeling, and mode of action data) will be evaluated separately.

[b] Presents preliminary draft criteria for evaluating a study being considered for estimating a POD in a TCDD dose-response model.

[c] Presents preliminary draft criteria that could qualify a study as primary with support from other lines of evidence (e.g., PBPK modeling), when no study for an endpoint meets the "primary" criteria.

This document is a draft for review purposes only and does not constitute Agency policy.

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APPENDIX B

Evaluation of Cancer and Noncancer Epidemiological Studies for Inclusion in TCDD Dose-Response Assessment

NOTICE

THIS DOCUMENT IS AN EXTERNAL REVIEW DRAFT. It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH

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APPENDIX B. EVALUATION OF CANCER AND NONCANCER EPIDEMIOLOGICAL STUDIES FOR INCLUSION IN TCDD DOSE-RESPONSE ASSESSMENT

B.1. EVALUATION OF CANCER STUDIES

B.1.1. NIOSH Cohort Studies

Table B-1. Fingerhut et al., 1991—All cancer sites, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. The data sources to ascertain vital status and cause of death information were the Social Security death files, the National Death Index, and the Internal Revenue Service. Vital status could be determined for 98% of the cohort.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration not satisfied. While the authors provide compelling arguments that suggest risks are not unduly biased by lack of cigarette smoking data, they acknowledge potential biases that could exist for other occupational exposure (e.g., asbestos) for which data were lacking.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration not satisfied. There was not a statistically significant linear trend of increasing mortality with increased duration of exposure.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration not satisfied. This study used duration of exposure, at an individual level, as a surrogate measure of TCDD. Duration of exposure determined by number of years workers were involved in processes involving TCDD contamination. Exposure was determined by reviewing, at each plant, operating conditions, job duties, records of TCDD levels in industrial hygiene samples, intermediate reactants, products, and wastes. Exposure assessment was limited and the uncertainty related to exposure measures not fully addressed.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. This is the largest of the occupational cohorts that has been exposed to TCDD. The cohort consisted of 5,172 workers and a total of 265 cancer deaths. Site-specific mortality analyses, including soft tissue sarcoma (n = 4), was limited by small numbers.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.

Response	Criteria satisfied. New England Journal of Medicine, 1991; 324:212–218. Authors address the possibility of bias from lack of control for potential confounders such as smoking and other occupational exposures. They address limitations of using death certificates for identifying certain causes of deaths, and limitations of using duration of employment as an exposure metric.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria not satisfied. Since this study used duration of exposure as the exposure metric, dose-response relationships cannot be quantified.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose-is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined.
Response	Criteria satisfied. Models incorporated period of latency, and a surrogate measure of cumulative TCDD exposure was modeled. The follow-up interval was sufficiently long (1942–1987).
Conclusion	Overall, quantitative exposure data are lacking on an individual-level basis. Further dose-response analysis should consider updated data for this cohort that includes serum-based measures of TCDD, in addition to an extension of the follow-up period. Given these limitations, this study is not further evaluated for TCDD dose-response assessment.

Table B-2. Steenland et al., 1999—All cancer sites combined, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. The study evaluated mortality from all cancer sites (combined). As described in the paper, the sources of vital status and cause of death information were received from the Social Security death files, the National Death Index, and the Internal Revenue Service. Vital status was known for 99.4% of the cohort members, cause of death information is available for 98% of the decedents.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. Occupational exposure to asbestos and 4-aminobiphenyl contributed to some excess cancer, but no evidence of confounding for the relationship between TCDD and all cancer mortality was detected following removal of workers who died of bladder cancer. No information is available for cigarette smoking, although dose-response patterns were stronger for nonsmoking related cancers. This finding suggests that smoking is not responsible for excess cancer risk that was observed in the cohort.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.

Response	Consideration satisfied. When a 15-year lag interval was incorporated into the exposure metric a statistically significant dose-response pattern was observed for all cancer sites combined with both a continuous measure of TCDD ($p = 0.05$) as well as one that was log-transformed ($p < 0.001$).
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. The study conducted detailed sensitivity analyses and evaluated different assumptions regarding latency, log-transformed TCDD exposures, and half-life values for TCDD.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. This is the largest of the occupational cohorts with exposures to TCDD. The cohort consisted of 5,132 male workers and a total of 377 cancer deaths. This permits characterization of risk for all cancer sites (combined).
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Journal of the National Cancer Institute, 1999; 91(9):779–786. The authors discussed the potential for bias from smoking, and other occupational exposures for which data for both were lacking at an individual basis.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. Exposure scores assigned on an individual level using a job-exposure matrix. The job-exposure matrix was based on estimated factor of contact with TCDD in each job, level of TCCD contamination of materials at each plant over time, and proportion of day worker could be in contact with materials. These factors were multiplied together to derive a daily exposure score, which was accumulated over the working history of each worker to obtain a cumulative measure of TCDD.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined.
Response	Criteria satisfied. The follow-up of the cohort extended from 1942 until the end of 1993. Greater than 25 years of follow-up have accrued in cohort allowing for latency to be examined. Different assumptions on the half-life of TCDD were evaluated and produced similar results. Latency intervals were incorporated, with strongest associations noted with an interval of 15 years.
Conclusion	This study meets the criteria and considerations noted above but has been superseded and updated by Steenland et al. (2001). Therefore, this study was not considered for further dose-response analyses.

Table B-3. Steenland et al., 2001—All cancer sites combined

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. The study evaluated mortality from all cancer sites (combined). As described by Steenland et al., (1999) the sources of vital status and cause of death information were received from the Social Security death files, the National Death Index, and the Internal Revenue Service. Vital status was known for 99.4% of the cohort members, cause of death information is available for 98% of the decedents.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. Occupational exposure to asbestos and 4-aminobiphenyl contributed to some excess cancer, but no evidence of confounding for the relationship between TCDD and all cancer mortality was detected following removal of workers who died of bladder cancer. No information is available for cigarette smoking, although dose-response patterns were similar between smoking and nonsmoking related cancers.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration satisfied. Increased risk estimates were observed in the higher cumulative exposure categories. The dose-response curve was not linear at higher doses.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. Exposure metrics considered included cumulative TCDD, log10TCDD, average exposure, and a cubic spline model was also evaluated. Exposure response relationships were also evaluated using TEQs. Exposure scores were assigned on an individual level using a job-exposure matrix. The job-exposure matrix was based on estimated factor of contact with TCDD in each job, level of TCCD contamination of materials at each plant over time, and proportion of day worker could be in contact with materials. Serum levels were measured in 199 workers at one of 8 plants in 1998. Different estimate of the half-life of TCDD were used, and similar results were produced. The paper presented a range in risk estimates thereby conveying the range of uncertainties in risk estimates derived using different measures of exposure.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. This is the largest of the occupational cohorts with exposures to TCDD. The cohort consisted of 3,538 male workers and a total of 256 cancer deaths.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied Am J Epidem, 2001, 154(5):451–458. However, additional details to assess uncertainties associated with characterizing serum data in a subset of workers to remainder of cohort are lacking.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.

Response	Criteria satisfied. The metrics considered included cumulative TCDD, log10TCDD, average exposure, and a cubic spline model was also evaluated. Exposure response relationships were also evaluated using TEQs. Serum lipid TCDD measurements from 170 workers whose TCDD levels were greater than 10 ppt (the upper ranges of a background level) were used along with JEM information, work histories, and a pharmacokinetic elimination model to estimate dose rates per unit exposure score. In this regression model, the estimated TCDD level at the time of last exposure was modeled as a function of exposure scores. The coefficient relating serum levels and exposure scores was then used to estimate serum TCDD levels over time from occupational exposure (minus the background level) for all 3,538 workers. Time-specific serum levels were then integrated over time to derive a cumulative serum lipid concentration due to occupational exposure for each worker.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined.
Response	Criteria satisfied. Greater than 25 years of follow-up have accrued in cohort allowing for latency to be examined. Different assumptions on the half-life of TCDD were evaluated producing similar results.
Conclusion	Overall, criteria have been satisfied. This study was modeled in the 2003 Reassessment and is considered for further dose-response evaluations herein.

Table B-4. Cheng et al., 2006—All cancer sites combined

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. The study evaluated cancer mortality. The vital status and the information regarding the cause of death were extracted from the Social Security death files, the National Death Index, and the Internal Revenue Service (Steenland et al., 1999). Vital status was known for 99.4% of the cohort members, while cause of death information is available for 98% of the decedents.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. This is the same data set used in the Steenland et al., (2001) paper. Occupational exposure to asbestos and 4-aminobiphenyl contributed to some excess cancer, but no evidence of confounding for the relationship between TCDD and all cancer mortality was detected following removal of workers who died of bladder cancer. No information is available for cigarette smoking, although dose-response patterns were similar between smoking and nonsmoking related cancers.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration satisfied. Slope coefficients are available for all cancers combined under a varying set of assumptions. Little evidence of an association was found when lag interval was not taken into account. Associations strengthened with incorporation of a 10 to 15 year lag interval. Dose-response was nonlinear at higher exposures, suggesting a nonlinear relationship or increased exposure misclassification at higher levels.

4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. Compared to the 1st order models, the concentration, and age dependent model (CADM) provided a better fit for the serum sampling data. CADM model exposure estimates are higher than those based on an age only, constant 8.7-year half-life model. As discussed by Aylward et al. (2005b), model exposure estimates are influenced not only by choice of elimination model, but also by choices in regression procedure (e.g., log transformation, use of intercept, and incorporation of background dose term). Other limitations or uncertainties in exposure assessment include the following • Job-exposure matrix based on limited sampling data, and subjective judgment on contact times and factors • Inability to take into account interindividual variability in TCDD elimination kinetics • Dose-rate regressions are based on a small sample of the cohort with serum measures; therefore, regression results may not be representative of remainder of the cohort.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. Largest cohort of TCDD exposed workers. The risk estimates are based on a total of 256 cancer deaths.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Risk Analysis, 2006; 4:1,059–1,071. Additional details to assess uncertainties associated with characterizing serum data can be found in Aylward et al. (2005b); Risk Anal. 25(4):945–956.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. Cumulative serum lipid concentrations were estimated for each worker. No other dioxin-like compounds were assessed in this analysis.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined.
Response	Criteria satisfied. Concentration and age-dependence of TCDD elimination and two compartments (hepatic and adipose tissue) were taken into account when estimating TCDD exposures. Nearly 50 years of follow-up were available permitting an evaluation of latency.
Conclusion	This study met the main criteria and considerations. The study is considered for further dose-response analyses.

Table B-5. Collins et al., 2009—All cancer sites combined, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.

Response	Consideration satisfied. Vital status complete for all but two workers.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. No information collected on smoking status, but no excess in lung cancer or nonmalignant respiratory diseases noted. Analyses took into account potential for exposure to pentachlorophenol.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration satisfied. No dose-response pattern was observed with all cancer sites combined, however, a dose-response pattern was observed with soft tissue sarcoma. The study found no association between TCDD and death from most types of cancer.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. The authors used these serum from 280 former TCP workers to estimate historical exposure levels of TCDD, furans, and polychlorinated biphenyls for all 1,615 workers. Exposure assessment included detailed work history, industrial hygiene monitoring, and the presence of chloracne cases among groups of workers. This data was integrated into a 1-compartment, first-order pharmacokinetic to determine the average TCDD dose associated with jobs in each group, after accounting for the presence of background exposures estimated from the residual serum TCDD concentration in the sampled individuals. The authors did not evaluate departures from linearity, or examine skewness at higher exposures. Exposure levels were not provided.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. Largest study of workers employed in one center, and a total of 177 deaths from cancer were observed. Limited precision in the relative risk estimate was noted for soft tissue sarcoma and TCDD exposures.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Published in Am J Epidemiol, 2009, 170(4):501–506. The authors discuss limitations of using death certificates for identifying deaths from soft tissue sarcoma for which a positive association was noted, assumptions in exposure characterization, and effects of cigarette smoking.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. This study has the largest number of serum samples obtained from a specific plant.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined.
Response	Criteria satisfied. Although specific analyses of latency were not reported, this cohort had a sufficient length of follow-up for cancer mortality outcomes.

Conclusion	The authors found a statistically significant dose-response trend for soft tissue sarcoma mortality and TCDD exposures. The all-tumor results are not amenable to dose-response analysis because they found no effect. Therefore, this study is considered for quantitative dose-response analysis for the soft tissue sarcoma mortality results, only.

B.1.2. BASF Cohort Studies

Table B-6. Zober et al., 1990—All cancer sites combined, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. A large component of the cohort (94 out of 247 workers) was assembled by actively seeking out workers who were alive in 1986 through the "Dioxin Investigation Programme." As a result, it is likely a number of deaths were missed due to the recruitment of survivors. This underascertainment is supported by much lower all cancer SMR one component of the cohort (SMR = 0.48, 95% CI: 0.13–1.23) relative to the general population.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. See above discussion of underascertainment in mortality for some of the cohort members. Although it is likely that other coexposures occurred (e.g., among firefighters), confounding could only occur if these coexposures were associated with both the endpoint and exposure (TCDD) being considered.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration not satisfied. Workers were not categorized on the basis of their exposure, but rather their mortality experience compared to control cohort and the general population. The design of the study does not allow for dose-response to be examined.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration not satisfied. Although years since first exposure was examined, exposure assessment was based on working in various occupational cohorts. Since there was no quantitative assignment of TCDD exposures, the associated uncertainties could not be evaluated.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration not satisfied. There were only 23 cancer deaths in the entire cohort. As such, this study lacked adequate statistical power to detect cancer mortality differences that were moderate in magnitude.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.

Response	Criteria satisfied. Int Arch Occup Envir Health, 1990, 62:139–157. The authors address issues related to the healthy worker effect, multiple comparisons, smoking, and small size of the cohort.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria not satisfied. Risks were derived by comparing mortality rates of the three cohort subsets relative to a control cohort and the general population by time since first exposure categories. Workers were not assigned exposures. There were no quantitative estimates of TCDD exposure.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined.
Response	Criteria not satisfied. While the study was able to indirectly look at variations in risk estimates related to latency by using time since exposure, there were no quantitative estimates of TCDD exposure.
Conclusion	This study is not suitable for dose-response analysis, as it failed the inclusion criteria. Most notably, the lack of exposure data does not permit the use of these data for a dose-response analysis.

Table B-7. Ott and Zober, 1996—All cancer sites combined

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Mortality ascertainment appeared to be fairly complete. The ascertainment of cancer incidence is more difficult to judge as geographical area not covered by a cancer registry.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. Information was collected on smoking status, body mass index, and other occupational exposures, however a large portion of the cohort was firefighters who may have been exposed to other occupational carcinogens. However, the recruitment of survivors may results in under-ascertainment of mortality.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration satisfied. Increased cancer incidence was observed in the highest TCDD cumulative exposure category. Risks were most pronounced when a period of 20 years since first exposure was incorporated into the model.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.

Response	Consideration satisfied. Cumulative measure of TCDD expressed was derived from serum measures. Exposure was also estimated by chloracne status of the cohort members. The authors have not addressed the potential implication of deriving TCDD exposure estimates for the whole cohort using sera data that were available for only about half of the cohort.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. For all cancer sites combined, there were 31 deaths. It is the smallest of the occupational cohorts, but the deaths can be grouped into quartiles to allow for evaluation of dose-response relationships.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Occupational and Environmental Medicine, 1996, 53:606–612. A large component of the cohort (94 out of 247 workers) was assembled by actively seeking out workers who were alive in 1986 through the "Dioxin Investigation Programme." As a result, it is likely a number of deaths were missed due to the recruitment of survivors. This underascertainment is supported by much lower all cancer SMR one component of the cohort (SMR = 0.48, 95% CI: 0.13–1.23) relative to the general population (Zober et al., 1990).
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. Serum samples, taken in 1989, were available for 138 surviving workers out of 254 and allowed for cumulative TCDD levels to be estimated using regression techniques in the remainder of the cohort.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined.
Response	Criteria satisfied. Exposure assignment took into the affect that body mass index had on TCDD half-lives. TCDD levels estimates through back-extrapolation of serum levels based on half-life estimates obtained from previous studies. Latency was considered with stronger association observed in external comparisons incorporating a latency of 20 years. The follow-up of the cohort was lengthy (>50 years).
Conclusion	Given a part of the cohort was based solely on survivors in the in the mid-1980s, the SMR statistic derived from this study underestimates excess mortality relative to the general population. The cohort also includes some firefighters who are recognized to be exposed to other carcinogenic agents—these exposures may be confounding the associations that were reported. However, exposure to TCDD was quantified and the effective dose and oral exposure estimable. Overall, criteria have been satisfied. This study was modeled in the 2003 Reassessment and is considered for further dose-response evaluations herein.

B.1.3. The Hamburg Cohort

Table B-8. Manz et al., 1991—All cancer sites combined, site-specific analyses

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Deaths were identified through medical records of the cohort members. A review of death certificates of the identified cancer deaths found a high degree of concordance (51/54). One of the 136 noncancer death certificates examined indicated an "occult" neoplasm.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. Smoking data were similar between exposed and nonexposed cohort based on independent samples. Occupational exposure for which individual data are lacking unlikely to explain dose-response with TCDD.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration satisfied. Dose-response patterns across three levels of exposure observed among those who started work before 1954, and among those who worked for 20 years or longer. Dose-response patterns not evident across whole cohort, among those with less than 20 years of employment, or among those who started after 1954.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. Categorical exposures were based on TCDD concentrations in precursor materials, products, waste, and soil from the plant grounds, measured after the plant closed in 1984. Exposure uncertainty examined using a separate group of 48 workers who provided adipose tissue samples. Other surrogate measures of exposure were considered in this study, including duration of exposure and year of first employment.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. For all cancer sites combined, there were 65 cancer deaths for the comparison to the comparison cohort of gas workers. The study is underpowered to look at site-specific cancers.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Lance,t 1991, 338:959–964. The authors discussed potential for misclassification using death certificates, healthy worker effect and their related use of a comparison cohort of gas supply workers, other occupational exposures present at the plant, potential impact and the lack of smoking data.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria not satisfied. Exposure consisted of a large DLC component that was not quantified. Given crude TCDD exposure categorization data, no quantitative exposure metric was derived.

3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined.
Response	Criteria satisfied. Exposure metrics were constructed that took into account duration of exposure, and periods when exposure was highest. However, exposure estimates did not consider lagged exposure.
Conclusion	This study is not amenable to further TCDD dose-response analysis and is not considered further here because it consisted of a large DLC component that was quantified and no quantitative exposure metric was derived. The dose-response patterns of risks observed across the three exposure groups provide compelling support for an association between TCDD and cancer mortality, particularly, given the associations observed when analyses restricted to those who were hired when TCDD exposures were known to be much higher, and among those who worked for at least 20 years. Subsequent studies improved the exposure assessment through the use of serum measures.

Table B-9. Flesch-Janys et al., 1995; Flesch-Janys et al., 1996 erratum—All cancer sites combined

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Medical records used to identify deaths over the period 1952–1992.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. Similarity in smoking rates between control cohort and the exposed workers was similar based on independent surveys. Occupational exposures to benzene, and dimethyl sulfate were unlikely to bias dose-response pattern observed as these exposures occurred in production departments with low-medium levels of exposure.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration satisfied. Dose-response relationship observed across 6 exposure categories, with the cohort of gas supply workers used as the referent.
4. Consideration	Consideration satisfied. Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	The exposure measure was an integrated TCDD concentration over time estimate that back calculated TCDD exposures to the end of the employment. Categorical and continuous TCDD exposures were examined in relation to the health outcome. These efforts improve the exposure assessment of earlier studies.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. For all cancer sites combined, there were 124 deaths in the exposed cohort, and 283 in the cohort of gas supply workers. No site-specific cancers were examined in this paper.

1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Am J Epidemiol, 1995, 1442:1165–1175. The authors discuss the potential role of other occupational exposures (i.e., dimethyl sulfate, solvents, and benzene), smoking, and suitability of the comparison cohort of gas supply workers.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. Serum and adipose tissues were used to estimate TCDD exposure in 190 workers. A one-compartment first-order kinetic model was used to estimate exposure at end of exposure for these workers. Regression methods were then used to estimates TCDD exposures for all workers.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined.
Response	Criteria not satisfied. Exposure was based on half-life estimates from individuals with repeated serum measures. Other dioxin-like compounds were considered with the TOTTEQ exposure metric. No consideration, however, was given to latency or lagged exposures.
Conclusion	The exposure data used within this study are well-suited to a dose-response analysis given the associations observed, the characterization of exposure using serum, and quality of ascertainment of cancer outcomes. However, subsequent methods have been applied to the cohort to derive different exposures to TCDD using area under the curve approaches, which updates the analysis herein. Therefore, subsequent studies (i.e., Becher et al., 1998) will supersede this evaluation.

Table B-10. Flesch-Janys et al., 1998—All cancer sites combined, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Mortality follow-up was extended until the end of 1992, an increase in 3 years from previous analyses of the cohort.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. Exposure was well characterized using sera data. While serum samples provided only from a subsample of surviving workers, these levels were consistent with expected levels in different production departments. The authors examined other potential occupational coexposures (e.g., β-hexachlorocyclohexane) and indirectly examined the potential effect of smoking on the associations that were detected.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.

Response	Consideration satisfied. A dose-response relationship across quartiles of TCDD was observed with cancer mortality based on the SMR statistic (SMRs = 1.24, 1.34, 1.34, 1.73), and a linear test for trend was statistically significant ($p = 0.01$).
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. The exposure measure was an integrated TCDD concentration over time estimate that back-calculated TCDD exposures to the end of the employment. Categorical and continuous TCDD exposures were examined in relation to the health outcome. These efforts improve the exposure assessment of earlier studies.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. For all cancer sites combined, there were 124 cancer deaths.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Environ Health Perspect, 1998, 106(2):655–662. The authors address uncertainties in the estimation of exposure, describe the potential for confounding from β-2,4,5-T, hexachlorocyclohexane, and cigarette smoking. In fact, they showed that blood levels of TCDD were not associated with smoking in a subsample suggesting little bias from lack of smoking data.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. Serum samples, taken from 190 workers were used to derive TCDD levels for the entire cohort. Methods used to estimate exposure took into account elimination of TCDD during employment periods when exposure took place, and the methods of the area under the curve was used as it takes into account variations in concentration over time, and reflects cumulative exposure.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined.
Response	Criteria satisfied. Exposure estimated based on half-lives observed in individuals with repeated samples. Area under the curve approach was used which is an improvement from past characterizations of exposure in this cohort.
Conclusion	The study provides data suitable for dose-response modeling. Derivation of exposure was done using current understanding of elimination of TCDD. Estimates of risks were derived from external comparisons to the general population that are unlikely to be biased by healthy worker effect, but risks generated using internal cohort comparisons would be preferable. Becher et al., (1998) assessed this same data taking cancer latency into account, therefore Flesch-Janys et al., (1998) will not be further considered for dose-response modeling.

Table B-11. Becher et al., 1998—All cancer sites combined

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Medical records used to identify deaths over the period 1952–1992. The follow-up interval was lengthy.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. Risks adjusted for exposures to TEQ, β-hexachlorbenzene, and employment characteristics. Smoking was shown to be similar to the comparison cohort of gas workers.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration satisfied. A variety of exposure measures for both TCDD and TEQs found positive associations with cancer mortality.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. The exposure measure was an integrated TCDD concentration over time estimate that back-calculated TCDD exposures to the end of the employment. Categorical and continuous TCDD exposures were examined in relation to the health outcome. Different models explored the shape of the dose-response curve. These efforts improve the exposure assessment of earlier studies.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. For all cancer sites combined, there were 124 cancer deaths.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Environ Health Perspect, 1998, 106(2):663–670. The authors discuss uncertainties associated with their use of exposure metrics, inability to evaluate effects for PCDD/Fs other than dioxin due to high correlations with β-HCH, and inability to characterize risks associated with exposures in children.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. The authors derived a measure of cumulative dose as a time-dependent variable ("area under curve") using serum measures available in a sample of 275 workers.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined.
Response	Criteria satisfied. TCDD levels estimates through back-extrapolation of serum levels based on half-life estimates obtained from previous studies. Latency was considered, and a variety of exposure metrics including nonlinear relationships were evaluated.

Conclusion	In this paper, a variety of exposure metrics were found to be positively associated with cancer mortality. The additional lifetime risk of cancer corresponded to a daily intake of 1pg ranged between .01 and 0.001. This study was modeled in the 2003 Reassessment and is considered for further dose-response evaluations herein.

B.1.4. The Seveso Cohort Studies

Table B-12. Bertazzi et al., 2001—All cancer sites combined, site-specific analyses

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Mortality appears to be well captured from the vital statistics registries in the region (99% complete). Vital status was ascertained using similar methods for both the exposed and reference populations. Both cancer and noncancer mortality outcomes were evaluated. Ideally, would have evaluated incident rather than decedent outcomes for cancer.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. Individual-level data on potential confounders (i.e., age, calendar period, and gender) were adjusted for. Information from other independent surveys suggests similarity between smoking behaviors across the regions. Comparison of cancer mortality rates before the time of the accident between the regions also revealed no differences.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration satisfied (for all cancers combined). No statistically significant excesses noted in Zone A, or Zone B relative to reference area. Evidence of an exposure-response relationship was detected for lymphatic and hematopoietic tissues by number of years since first exposure.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration not satisfied. Subjects were assigned to one of the zones (A, B, R, or reference) based on official residence on the day of the accident or at entry into the area. Exposure misclassification is likely and lack of individual-level data precludes an examination of this source of error.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. In total, 27, and 222, cancer deaths were found among residents of Zones A, and B, respectively. This allowed examined of gender-specific effects.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.

Response	Criteria satisfied. Am J Epidemiol, 2001 Jun 1; 153(11):1031–1044. Authors discuss completeness of mortality ascertainment, diagnostic accuracy of death certificates particularly with respect to diabetes, limited available of blood dioxin measures that did not permit estimation of TCDD dose on an individual-level basis.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria not satisfied. Individual-level exposure data are unavailable. Exposure based on place of residence at time of the explosion. Soil sampling performed indicated considerable variability in TCDD levels within each region. In addition, place of residency at time of explosion does not ensure individuals were at their home around the time of the accident.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined.
Response	Criteria not satisfied. An ecological measure of exposure (region of residency at time of accident) was used to categorize individuals according to their possible exposure. Latencies were considered. While such an approach has value for identifying wherever excesses occurred among highly exposed populations, it is not precise enough to conduct a quantitative dose-response analysis.
Conclusion	The lack of individual-level exposure data precludes quantitative dose-response modeling using these data.

Table B-13. Pesatori et al., 2003—All cancer sites combined, site-specific analyses

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Mortality was ascertained from 1977−1996, and, as reported in other related manuscripts, appears to be well captured from the vital statistics registries in the region (99% complete). Cancer incidence data was available from 1977−1991.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. Individual-level data on potential confounders (i.e., age, calendar period, and gender) were adjusted for.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration not satisfied. Although risk of all cancer mortality was not associated with zone of residence, increased risk of cancer incidence was observed in Zone A. Among men, excess lymphatic and hematopoietic cancer incidence was observed in Zone A (primarily to non-Hodgkin's lymphoma). Soft tissues sarcoma cancer incidence was also associated with residence in Zone R among males, but not the more highly exposed zones (A and B). Among females living in Zones A and B, higher rates were observed for multiple myeloma (RR = 4.9, 95% CI = 1.5−16.1), cancer of the vagina (RR = 5.5, 95% CI = 1.3−23.8), and cancer of the biliary tract (RR = 3.0, 95% CI = 1.1−8.2).

4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration not satisfied. Subjects were assigned to one of the zones (A, B, R, or reference) based on official residence on the day of the accident or at entry into the area. Exposure misclassification is likely and lack of individual-level data precludes an examination of this source of error.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied for some endpoints, although several of the cancer specific mortality results among women were based on very small number of deaths (i.e., <5).
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Occup Env Med, 1998; 55:126–131. Authors discuss limitations such as residency-based exposure assignment, absence of smoking, differential and death certification in exposed versus nonexposed areas.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria not satisfied. Individual-level exposure data are unavailable. Exposure based on place of residence at time of the explosion. Soil sampling performed indicated considerable variability in TCDD levels within each region. In addition, place of residency at time of explosion does not ensure individuals were at their home around the time of the accident.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined.
Response	Criteria not satisfied. An ecological measure of exposure (region of residency at time of accident) was used to categorize individuals according to their possible exposure. Latencies were considered. While such an approach has value for identifying wherever excesses occurred among highly exposed populations, it is not precise enough to conduct a quantitative dose-response analysis.
Conclusion	No dose-response patterns evident in the study, and the study lacked quantifiable measures of TCDD at an individual-level basis. The data are not well suited for dose-response analysis.

Table B-14. Consonni et al., 2008—All cancer sites combined, site-specific analyses

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Mortality appears to be well captured from the vital statistics registries in the region (99% complete). Both cancer and noncancer mortality evaluated, although diagnostic accuracy of death certificates is likely low. Ideally, would have evaluated incident rather than decedent outcomes for cancer.

2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. Individual-level data on potential confounders (i.e., age, calendar period, and gender) were adjusted for. Comparison of cancer mortality rates before the time of the accident between the regions also revealed no differences. Information from other independent surveys suggests similarity between smoking behaviors across the regions.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration satisfied for some outcomes. For all cancer sites combined, no evidence of dose-response was observed relative to general population across Zones A, B and R. Only statistically significant excess found in Zone A was for chronic rheumatic disease but based on only three deaths. Higher cancer excesses were found in Zone A after a latency period was incorporated; however, no dose-response relationship observed with this latency period. Evidence of an exposure-response relationship was detected for lymphatic and hematopoietic tissues by zone of residence.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration not satisfied. Subjects were assigned to one of the zones (A, B, R, or reference) based on official residence on the day of the accident or at entry into the area. Exposure misclassification is likely and lack of individual-level data precludes an examination of this source of error.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. In total, 42, 244, and 1,848 cancer deaths were found among residents of Zones A, B, and R respectively.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Am J Epidemiol, 2008, 167:847–858. Authors discuss potential for selection bias, limitation of residential based measure of exposure, similarities of mortality ascertainment in exposed and referent populations, and multiple testing.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria not satisfied. Individual-level exposure data are unavailable. Exposure based on place of residence at time of the explosion. Soil sampling performed indicated considerable variability in TCDD levels within each region. In addition, place of residency at time of explosion does not ensure individuals were at their home around the time of the accident.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined.
Response	Criteria not satisfied. An ecological measure of exposure (region of residency at time of accident) was used to categorize individuals according to their possible exposure. Latencies were considered. While such an approach has value for identifying wherever excesses occurred among highly exposed populations, it is not precise enough to conduct a quantitative dose-response analysis.

Conclusion	The lack of individual-level exposure data precludes quantitative dose-response modeling using these data.

Table B-15. Baccarelli et al., 2006—Site-specific analysis

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Polymerase chain reaction (PCR) methods were used to describe outcome measures. The prevalence of t(14; 18) was estimated as those individuals having a t(14; 18) positive blood sample divided by the t(14; 18) frequency (number of copies per million lymphocytes).
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. Questionnaire data were used to collect information on cigarette smoking. Other potential confounders (age, smoking status, and duration of smoking). In addition, both exposure and outcome were objectively and accurately measured.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration was not satisfied. Associations were detected between the frequency of t(14; 18) and plasma TCDD levels as well as zone of residence at the time of the explosion. No association was detected for these exposure measures and prevalence of t(14; 18). A dose-response trend was detected for TCDD and the mean number of t(14;18) translocations/10^6 lymphocytes, however the relevance of t(14; 18) in lymphocytes to non-Hodgkin's lymphoma is uncertain.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. The authors highlight that exposure metrics represent both past and current body burdens. They employ several different exposure metrics of TCDD: place of residence (Zone A, B, R or reference), categorical serum measures, a linear term, log (base 10) transformed TCDD, and individuals with chloracne diagnosed after the accident.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. Analyses are made using 72 highly exposed, and 72 low exposed individuals.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Carcinogenesis, 2006, 27(10):2001–2007. The authors discuss the limitation of using t(14; 18) translocations as an outcome measure, and the uncertain role it plays in the development of non-Hodgkin's lymphoma.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.

Response	Criteria satisfied. A total of 144 subjects were included in the study. This included 72 subjects who had low exposures, and 72 who had high exposures based on serum concentrations.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined.
Response	Criteria satisfied. A variety of measures were employed including current TCDD levels, as well as surrogates of exposure at the time of the accident.
Conclusion	While an association was observed with the frequency of t(14; 18) translocation, it is uncertain whether this translates into an increased risk of non-Hodgkin's lymphoma. Given the speculative nature of this endpoint and lack of demonstrated adverse effect, dose-response analyses for this outcome were not conducted.

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3 **Table B-16. Warner et al., 2002—Breast cancer incidence**
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1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Diagnoses of incident breast cancer were based on interview and information from medical records appears thorough. Of the 15 cases of breast cancer, 13 were confirmed by pathology and the remaining 2 by surgery report only. Three cases of breast cancer were excluded which represents a large proportion of the total cases identified. This would reduce sample size and could result in bias if the exclusion was association with TCDD exposure.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. Information was collected on an extensive series of risk factors by using an interviewer administered questionnaire. Participation rates for the survey were fairly good (80%).
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration satisfied. Limited evidence (not statistically significant) of a dose-response when TCDD was analyzed as a categorical variable; only one breast cancer case was in the referent exposure category. In the analysis of TCDD as a continuous measure ($\log_{10}$TCDD), the hazard ratio associated with a 10-fold increase in TCDD serum levels was 2.1 (95% CI: 1.0–4.6).
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. Different exposure metrics were considered in these analyses (categorical, continuous, measures on a log-scale). Exposure data are of high quality as they are based on serum samples taken among women near the time of the accident. As such, exposure assignment is not dependent on as many assumption as used in occupational cohorts were back-extrapolation for many years had to be performed.

5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration somewhat satisfied. Inadequate follow-up for cancer limited the number of cases available. Sample size also limited the conclusions draw from the categorical analysis based on very few cases for some exposure categories.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Paper published in Environ Health Perspect, 2002 Jul, 110(7):625–628. A major limitation of the study is the small number of incident cases of breast cancer (n = 15), important strengths of the study include characterization of TCDD using serum collected near the time of the accident.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. Serum was used to estimate TCDD levels in 981 of 1271 eligible women who had lived in either of the two contaminated sites in 1976. Data represent an objective measure of TCDD near the time of the exposure. Data obtained near the time of exposure which minimized the potential for exposure misclassification.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined.
Response	Criteria satisfied. Exposure characterized using serum measures obtained close to the time of the accident.
Conclusion	While characterization of exposure and availability of other risk factor data at an individual-level basis are important strengths of this study, small sample size (n = 15 cases) based on inadequate follow-up is a key limitation. Quantitative dose-response analyses were conducted using this study, but continued follow-up of the study population or consideration of all cancer outcomes would be valuable.

B.1.5. The Chapaevsk Study

Table B-17. Revich et al., 2001—All cancer sites combined, and site-specific analyses

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration cannot be evaluated. Insufficient details are provided in the paper to gauge the completeness and coverage of the cancer registry and mortality data. Health outcomes were studied on the basis of information in the official medical statistics.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration not satisfied. Given that this is an ecological study, bias may be present.

3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration cannot be evaluated. Dose-response was not evaluated as exposure was based on residency in the region vs. no residency.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration not satisfied. No individual-level exposure estimates were used.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. A total of 476 cancer deaths were observed among males, and 376 cancer deaths observed among females. The precision of the SMRs is demonstrated with fairly narrow confidence intervals for many causes of death.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria not satisfied. Published in Chemosphere, 2001, 43(4–7):951–966. Authors do not address the completeness of the mortality follow-up, and whether there are differences in death registrations between regions. The authors do acknowledge, however, that new investigations being undertaken would characterize exposure using serum-based measures.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria not satisfied. It is a cross-sectional study that compares mortality rates between regions. No individual-level exposure data available.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined.
Response	Criteria not satisfied. No individual-level exposure estimates were used in the study.
Conclusion	These cancer data are cross-sectional in nature and not appropriate for a dose-response analysis.

B.1.6. The Air Force Health ("Ranch Hands") Study

Table B-18. Akhtar et al., 2004—All cancer sites combined and site-specific analyses

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Cancer incidence and mortality based on information from repeated medical examinations, medical records and death certificate.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.

Response	Consideration not satisfied. The risk estimates were adjusted for a number of factors measured on an individual level including smoking. However, analyses are unable to distinguish between exposure to TCDD and 2,4-D as both were used in equal parts in the formulation of Agent Orange.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration satisfied. There is evidence of a dose-response for all cancers and for some site-specific cancers (i.e., malignant melanoma, and prostate cancer).
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. High quality exposure data for most veterans was collected, so extrapolation to other members of the cohort was not required. The serum dioxin measurements also correlated well with reported skin exposure to herbicide in Vietnam, but collection of the samples 25 years later required back-extrapolation.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. In total, 117 incidence cancers identified in the Ranch Hands cohort. For those sites with a dose-response association, malignant melanoma and prostate cancer, there were 16 and 34 incident cases, respectively.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Published in J Occup Environ Med, 2004, 46(2):123–136. Authors highlight that this is only cancer incidence study in US veterans, and the lengthy interval of follow-up (35–40 years)—both important strengths of the study. They addressed potential bias from healthy-worker effect, and uncertainties surrounding the estimation of TCDD exposure (extrapolation 30 years after exposure), as well as exposure to other chemical exposures. Study uses incident outcomes for cancer.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. Individual exposure estimates are based on measurements of dioxin serum lipid concentrations. They were available for 1,009 Ranch Hands and 1,429 in the comparison cohort.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined.
Response	Criteria satisfied. TCDD exposures at the end of duty were estimated by back-extrapolating 1987 serum values.
Conclusion	The major limitation of the study is the inability to isolate effects of TCDD from other chemicals used in the formulation of the herbicides. This limitation precludes dose-response modeling of the TCDD and cancer outcomes data.

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Table B-19. Michalek and Pavuk, 2008—All cancer sites combined

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Cancer incidence was ascertained through the use of medical records. Death certificate were used to identify some malignancies. Little data is provided on the number of individuals lost to follow-up, however the same mechanisms of case ascertainment were applied to both the comparison and Ranch Hand cohorts.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration not satisfied. Information collected from repeated physical examinations allowed for the adjustment of risk factors such as smoking. Agent Orange was a 50% mixture of 2,4-D and TCDD; therefore, potential for confounding by other coexposures is likely.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration satisfied for some comparisons. Statistically significant associations were noted with cancer incidence and TCDD when analyses were restricted to workers who served at most two years in Southeast Asia and those who sprayed more than 30 days before 1967.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. Initial TCDD dose were estimated at the end of the tour of duty for the Ranch Hands. Individual-level serum dioxin measurements correlated well with correlated with days of spraying and calendar period of service, but collection of the samples roughly 20 years later required back-extrapolation.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. A total of 347 incident cases of cancer were used in the analyses. For stratified analyses, statistical power is more limited. For example, only 67 incident cancer in the subset of workers who spent less than 2 years in Southeast Asia, and sprayed for at least 30 days before 1967.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied J Occup Environ Med 2008; 50:330–340. The authors discuss issues related to exposure misclassification error, and suggest approaches for improving characterization of days of spraying. Congener specific data were unavailable, thereby not allowing for congener specific risks or adjustments to be made.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. TCDD data was available for 986 veterans in the Ranch Hand cohort, and 1,597 members of the comparison cohort.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined.

Response	Criteria satisfied. TCDD exposures at the end of duty were estimated by back-extrapolating 1987 serum values.
Conclusion	Ranch Hand veterans were exposed to other contaminants in the herbicides that were mixed, thereby making it difficult to determine independent effects of TCDD on cancer. In particular, 2,4-D has been shown to be associated with some cancers, notable cancer of the prostate. This limitation precludes dose-response modeling of TCDD and cancer using data from this cohort.

B.1.7. Other Studies of Potential Relevance to Dose-Response Modeling

Table B-20. 't Mannetje et al., 2005—All cancer sites combined, site specific analyses

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. National records for death registrations through the New Zealand Health Information Service (NZHIS). Subjects not registered as having died during the study period were confirmed to be actually alive and resident in New Zealand using the New Zealand Electoral Roll, drivers' license, and social security records.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration not satisfied. Seventeen percent of workers were lost to follow up but it is unclear if bias resulted. The dichotomous exposure measure was based on exposure to TCDD, chlorinated dioxins and phenoxy herbicides, so confounding is a possibility by these coexposures.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration satisfied. Dose-response evidence for duration of employment and elevated mortality noted only in synthesis workers.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Exposure measures were limited to duration of employment and exposed/unexposed.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. For all cancer sites combined, there were 43 cancer deaths among the production workers, and 35 such deaths among the sprayers. Site-specific cancer analyses are limited by small sample sizes.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria not satisfied Occup Env Med, 2005; 62:34–40. A high percentage of the cohort was lost to follow-up (17%). The authors fail to mention this important limitation in this paper.

2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria not satisfied. This study used duration of exposure, at an individual level, as a surrogate measure of TCDD.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined.
Response	Criteria not satisfied. Exposure was defined according to duration, and not concentrations of TCDD. Latency intervals were not evaluated.
Conclusion	Overall, quantitative exposure data are lacking for TCDD and limited dose-response relationships were observed across duration of exposure categories. Furthermore, confounding by coexposures is a possibility. Taken together, these data are not suitable for inclusion in a dose-response analysis

Table B-21. McBride et al., 2009b—All cancer sites combined, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. The New Zealand Health Information Service Mortality Collection and the Registrar-General's Index to Deaths. Additional searches were based on the last known address from the work record; the electoral roll and the habitation index; the telephone book; the internet; and Terranet property information database. An additional search was carried out through the Births, Deaths, and Marriages office of the New Zealand Department of Internal Affairs. Lastly, automated personnel and pension records were also used to locate past New Plymouth workers and identify some deaths.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration not satisfied. Considerable amount of workers were lost to follow up (22%), but it is unclear if bias resulted. The dichotomous exposure measure was based on exposure to TCDD, chlorinated dioxins and phenoxy herbicides, so confounding is a possibility by these coexposures.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration not satisfied. There was no examination of dose-response effects.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. Dichotomous exposure (exposed/unexposed) and duration of employment were examined from job exposure classification assessed via occupational history records industrial hygienists/factory personnel knowledge and questionnaires. Authors discuss limitations in the assignment of exposure among cohort members.

5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration not satisfied. A low number of deaths (n = 76) may have limited ability to detect effects small in magnitude and exposure-response relationships.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Published in Occup Medicine, 2009; 59(4):255–263. The authors highlight cohort lost to follow-up, the limited size of the cohort, differences in cohort definitions between sprayers and producers, and the potential for other exposures during employment at the plant.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria not satisfied. TCDD exposures were not quantified.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined.
Response	Criteria not satisfied. Effective dose could not be estimated given the lack of individual-level exposure data.
Conclusion	The study lacks the quantification of exposures at an individual level, precluding dose-response analysis. This study is not considered further in the dose-response modeling analysis.

Table B-22. McBride et al., 2009a—All cancer sites combined, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. The New Zealand Health Information Service Mortality Collection and the Registrar-General's Index to Deaths were used to identify deaths. Additional searches were based on the last known address from the work record; the electoral roll and the habitation index; the telephone book; the internet; and several other public databases in New Zealand. An additional search was carried out through the Births, Deaths, and Marriages office of the New Zealand Department of Internal Affairs. Lastly, automated personnel and pension records were also used to locate past New Plymouth workers and identify some deaths.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. Workers lost to follow-up were an unlikely source of bias especially for internal analyses. Confounding by other coexposures (e.g., 2,4,6-TCP) unlikely to have resulted in bias, due to presumed poor correlation with TCDD.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.

Response	Consideration not satisfied. The linear test for trend for TCDD exposure was not statistically significant for all cancer sites (combined), as well as lung cancer mortality. Dose-response relationships were not apparent across quartiles of TCDD exposure for all cancer sites combined, digestive cancers, lung cancer, soft tissue sarcomas or non-Hodgkin's Lymphoma.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. Cumulative exposure to TCDD as a time-dependent metric was estimated for each worker from serum samples, but the authors did not examine a continuous measure of TCDD exposure (lagged or unlagged).
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Published in J Occup Environ Med 51:1049−1056. This paper discussed the 22% of the cohort lost to follow-up, differences in cohort definitions between sprayers and producers, and the potential for other exposures during employment at the plant.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. Serum measures available for 346 workers were used to derive TCDD exposures for the entire cohort using the area under the curve approach.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined.
Response	Criteria satisfied. Effective dose could be estimated from serum-derived cumulative exposure estimates.
Conclusion	Given that no dose-response associations were found, the data are not suited to dose-response analysis.

Table B-23. Hooiveld et al., 1998—All cancer sites combined, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Outcomes were mortality. Few deaths expected to be missed since only 5% of the cohort was lost to follow-up or had emigrated.

2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration not satisfied. Although dioxin-like compounds (PCDDs, PCDFs, and PCBs) were measured in the serum samples, these were not incorporated into the analysis. Therefore, confounding cannot be ruled out as an explanation of the reported association.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration satisfied. A dose-response pattern was observed for internal cohort comparison for all cancer mortality, with RRs of 5.0 and 5.6 for the medium and high exposure, respectively. Dose-response patterns evident for lung cancer as well.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. Detailed occupational histories to assign dichotomous exposures (exposed/unexposed) based on maximum exposure levels. Although serum data also collected for TCDD and other coexposures (PCDDs, PCDFs, and PCBs), study only presents data for TCDD exposure. TCDD exposures at time of maximum exposure were extrapolated from measured serum.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration not satisfied for internal cohort comparisons in either men or women. Among men, only 7 cancer deaths were observed among those in the unexposed part of the cohort, and 51 among exposed workers. For external cohort comparisons, a total of 20 deaths were observed.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Am J Epidemiol, 1998, 147:891–901. The authors address potential limitations of estimating TCDD exposure from a subsample of surviving workers, lack of smoking data, the healthy worker effect, and relevance of other occupational exposures.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. Serum samples were obtained from 94 of 144 subjects who were asked to participate in serum measurement study. Of these, a further 44 excluded due to absence due to holiday or work (n = 22), and nonexposed workers excluded because matching exposed worker not participating (n = 20). TCDD levels were extrapolated to the time of maximum exposure.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined.
Response	Criteria not satisfied. Exposures assigned based on levels at maximum exposure. Assignment of exposure based on nonrepresentative sample of 50 survivors among the occupational cohort.
Conclusion	The small number of identified cancer deaths, limitations in terms of the exposure assignment (based on nonrepresentative sample, and maximum exposure level) and concern over potential confounding by coexposures preclude using these data for a dose-response analysis.

B.2. EVALUATION OF NONCANCER STUDIES

B.2.1. NIOSH Cohort

Table B-24. Steenland et al., 1999—Mortality (noncancer)

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. The study evaluated mortality from all cancer sites (combined). As described in the paper, the sources of vital status and cause of death information were received from the Social Security death files, the National Death Index, and the Internal Revenue Service. Vital status was known for 99.4% of the cohort members, cause of death information is available for 98% of the decedents.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration not satisfied. External comparisons for all-cause and cardiovascular mortality do not appear to be affected by the "healthy worker effect" as similar patterns were observed with internal cohort comparisons. Nonetheless, internal cohort comparisons are unable to adjust for many of the individual-level risk factors for cardiovascular disease.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration satisfied. A dose-response relationship was observed with ischemic heart disease (linear test for trend $p = 0.05$), and with TCDD on a log-transformed scale the p-value was <0.001.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. The study conducted detailed sensitivity analyses and evaluated different assumptions regarding latency, log-transformed TCDD exposures, and half-life values for TCDD. Associations were stronger for log-transformed values, and latency intervals of 15 years.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. This is the largest of the occupational cohorts with exposures to TCDD. The cohort consisted of 5,132 male workers and a total of 456 deaths from ischemic heart disease. This permits characterization of risk for all cancer sites (combined).
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied Journal of the National Cancer Institute, 1999, 91(9):779–786. The authors discussed the potential for bias from smoking, and other occupational exposures for which data for both were lacking at an individual basis.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.

Response	Criteria not satisfied. Exposure scores assigned at an individual level based on job-exposure matrix (JEM). The JEM was based on estimated factor of contact with TCDD in each job, level of TCCD contamination of materials at each plant over time, and proportion of day worker could be in contact with materials. These factors were multiplied together to derive a daily exposure score, which was accumulated over the working history of each worker to obtain a cumulative measure of TCDD.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Criteria not satisfied. The follow-up of the cohort extended from 1942 until the end of 1993. Greater than 25 years of follow-up have accrued in cohort allowing for latency to be examined. Different assumptions on the half-life of TCDD were evaluated and produced similar results. Latency intervals were incorporated, with strongest associations noted no lag. Suggests mechanisms occur at the same time as exposure. However, noncancer mortality is not a viable endpoint to consider for further dose-response analysis.
Conclusion	TCDD exposures were quantified in this study, and a dose-response relationship was observed with ischemic heart disease mortality. The sample size was sufficient, and the follow-up interval was lengthy. However, no individual-level data were available for cardiovascular conditions, and the inability to adjust for these exposures introduces considerable uncertainty into the risk estimates. Furthermore, noncancer mortality is not considered a viable endpoint for dose-response analysis.

Table B-25. Collins et al., 2009—Mortality (noncancer)

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Vital status complete for all but two workers.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. No information collected on smoking status, but no excess in lung cancer or nonmalignant respiratory diseases noted. Analyses took into account potential for exposure to pentachlorophenol. External cohort comparisons should be interpreted cautiously due to healthy worker effect, but internal cohort comparisons should not be influence by this bias.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration not satisfied. No statistically significant mortality excess for any noncancer mortality outcome evaluated. This included ischemic heart disease, stroke, nonmalignant respiratory disease, ulcers, cirrhosis, and external causes of death (accidents). Modeling of continuous measure of TCDD was not related to diabetes, ischemic heart disease, or nonmalignant respiratory mortality.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.

Response	Consideration satisfied. The authors used these serum from 280 former TCP workers to estimate historical exposure levels of TCDD, furans, and polychlorinated biphenyls for all 1,615 workers. Exposure assessment included detailed work history, industrial hygiene monitoring, and the presence of chloracne cases among groups of workers. This data was integrated into a 1-compartment, first-order pharmacokinetic to determine the average TCDD dose associated with jobs in each group, after accounting for the presence of background exposures estimated from the residual serum TCDD concentration in the sampled individuals. The authors did not evaluate departures from linearity, or examine skewness at higher exposures. No presentation of exposure levels was provided.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. A total of 662 deaths were observed. Of these, 218 were from ischemic heart disease, and 16 from diabetes (two outcomes for which associations have been noted elsewhere).
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Published in Am J Epidemiol, 2009, 170(4):501–506. The authors discuss potential for exposure misclassification, large size of the cohort, lengthy follow-up interval, and large number of workers who provided serum from which TCDD exposures were estimated.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. This study has the greatest number of serum samples obtained from a specific plant.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Criteria not satisfied. Noncancer mortality is not a viable endpoint to consider for further dose-response analysis.
Conclusions	No dose-response associations were noted for noncancer mortality outcomes. The data are, therefore, not suited for dose-response modeling.

B.2.2. BASF Cohort

Table B-26. Ott and Zober, 1996—Mortality (noncancer)

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Mortality ascertainment appeared to be fairly complete.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.

Response	Consideration satisfied. Information was collected on smoking status, body mass index, and other occupational exposures, however a large portion of the cohort was firefighters who may have been exposed to other occupational carcinogens. However, the recruitment of survivors may results in under-ascertainment of mortality.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration not satisfied. For external cohort comparisons across the three TCDD exposure categories, there was no dose-response pattern observed for any of the noncancer causes of death. Cox regression risk estimates for all cause or circulatory disease mortality when TCDD was modeled as a continuous variable were not statistically significant.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. Cumulative measure of TCDD expressed was derived from serum measures. Exposure was also estimated by chloracne status of the cohort members. The authors have not addressed the potential implication of deriving TCDD exposure estimates for the whole cohort using sera data that were available for only about half of the cohort.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. For all causes of death, there were 92 deaths, while 37 circulatory deaths. Many of the cause-specific death had less than 5 deaths in the upper exposure category.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Occup Environ Med, 1996, 53:606–612. A large component of the cohort was assembled by actively seeking out workers who were alive in the mid 1980s. As a result, it is likely a number of deaths were missed. This is supported by much lower SMRs in this component of the cohort published in earlier studies of the cohort. This underascertainment of mortality results in biased SMR statistics (underestimated). The authors do highlight the value of the serum based measures to estimate TCDD exposure
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. Serum samples, taken in 1989, were available for 138 surviving workers out of 254 and allowed for cumulative TCDD levels to be estimated using regression techniques in the remainder of the cohort.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Criteria not satisfied. Exposure assignment took into the affect that body mass index had on TCDD half-lives. TCDD levels estimates through back-extrapolation of serum levels based on half-life estimates obtained from previous studies. Latency was considered with stronger association observed in external comparisons incorporating a latency of 20 years. The follow-up of the cohort was lengthy (>50 years). However, noncancer mortality is not a viable endpoint to consider for further dose-response analysis.

Conclusion	No associations noted with any noncancer deaths. External comparisons should be treated cautiously especially for cardiovascular mortality which is recognized to often be biased by the healthy-worker effect. In the absence of any outcome with an association with TCDD exposure, dose-response analyses of these data were not undertaken.

B.2.3. Hamburg Cohort

Table B-27. Flesch-Janys et al., 1995; Flesch-Janys et al., 1996 erratum—Mortality (noncancer)

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Medical records used to identify deaths over the period 1952−1992.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. Similarity in smoking rates between control cohort and the exposed workers was similar based on independent surveys. Occupational exposures to benzene, and dimethyl sulfate were unlikely to bias dose-response pattern observed as these exposures occurred in production departments with low to medium levels of TCDD exposure.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration satisfied. Dose-response relationship observed for all-cause mortality, cardiovascular mortality, and ischemic heart disease mortality across 6 exposure categories, with the cohort of gas supply workers used as the referent. The linear tests for trend for these three outcomes were all statistically significant ($p < 0.05$).
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. The exposure measures was an integrated TCDD concentration over time estimate that back-calculated TCDD exposures to the end of the employment. Categorical and continuous TCDD exposures were examined in relation to the health outcome. These efforts improve the exposure assessment of earlier studies.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. For all causes of death combined, there were 414 deaths in the exposed cohort, and 943 in the cohort of gas supply workers. A total of 157 and 76 deaths from cardiovascular disease, and ischemic heart disease were noted. The corresponding number in the cohort of gas supply workers was 459, and 205, respectively.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Am J Epidemiol, 1995, 1442:1165–1175. The authors discuss the potential role of other occupational exposures (i.e., dimethyl sulfate, solvents, benzene), smoking, and suitability of the comparison cohort of gas supply workers.

2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. Serum and adipose tissues were used to estimate TCDD exposure in 190 workers. A one-compartment first-order kinetic model was used to estimate exposure at end of exposure for these workers. Regression methods were then used to estimates TCDD exposures for all workers.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Criteria not satisfied. Exposure based on half-life estimates from individuals with repeated serum measures. Other dioxin-like compounds were considered with the TOTTEQ exposure metric. Noncancer mortality, however, is not a viable endpoint to consider for further dose-response analysis.
Conclusion	Although, the exposure data used within this study are well-suited to a dose-response analysis for all-cause and cardiovascular mortality given the associations observed, use of noncancer mortality endpoint is not amenable for further dose-response analysis.

B.2.4. The Seveso Women's Health Study

Table B-28. Eskenazi et al., 2002a—Menstrual cycle characteristics

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Information was also obtained from medical records for all obstetric and gynecologic conditions. Information on menstrual cycles was obtained from questionnaires. Women were asked about length of cycles, regularity, how many days flow lasted, and heaviness of menstrual flow (scanty, moderate, or heavy). Measurement error is likely for the subjective nature of self-reported menstrual parameters but specificity and sensitivity is difficult to ascertain due to lack of validation data for these measures.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. Detailed risk factor information was collected from questionnaire, allowing for the potential confounding influence of many risk factors to be controlled for. The length of cycle study findings may have been affected by the presence of a few outliers.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration satisfied. A positive dose-response relationship was found with TCDD among women who were premenarcheal at time of the explosion and longer menstrual cycle. Increased TCDD resulted in a reduced odds of scanty menstrual flow. No association was noted with these two outcomes among postmenarcheal women. A decreased risk of irregular cycles was observed with higher TCDD levels.

4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Criteria satisfied. Serum concentrations of TCDD offer improved exposure assessment, although delineating the critical exposure window is challenging given the nature of the very high initial exposure.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. Cohort was large enough as analyses were conducted on 301 women.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Am J Epidemiol, 2002; 156(4) 383−392. Limitations included an inability to assess affects on menstrual cycle at time body burdens were the highest (at time of the accident). Also, TCDD was estimated for 1976, not concurrent with their cycles in the previous year, and a large number of women were excluded due to intrauterine device or oral contraceptive use. Strengths included population-based nature of study, with characterization of exposure using serum, and levels of other polychlorinated dibenzo-*p*-dioxins and dibenzofurans were at background levels. Findings for length of menstrual cycle may be unduly influenced by the presence of some outliers.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. The study population was based on 301 women as those who were over the age of 44 were excluded, as well as women with surgical of natural menopause, women with Turner's syndrome, those who had been pregnant or breastfed in the past year, and those who had used an intrauterine device or oral contraceptives. For 272 women, TCDD levels were based on serum data provided in 1976; TCDD levels were back-extrapolated to 1976 levels for the other 29 women.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response had to be a nonfatal endpoint.
Response	Criteria satisfied. Ideally, TCDD exposures would be concurrent with reporting of cycle characteristics. Herein, TCDD exposures were based on levels in 1976; however, given the long half-life of TCDD and the same follow-up interval for all women, TCDD exposures in 1976 should correlate well with levels near the time of interview. Further, the critical window of exposure can be estimated for the women that were premenarcheal at the time of the accident (13 years).
Conclusion	This study meets all of the criteria and considerations for further dose-response analysis. The determination of the relevant time interval over which TCDD dose should be considered is uncertain .

Table B-29. Eskenazi et al., 2002b—Endometriosis

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration not satisfied. Results of a pilot study showed that ultrasounds had excellent specificity and sensitivity for ovarian endometriosis.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration not satisfied. More than half of the women were classified as 'uncertain' with respect to endometriosis disease status.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration not satisfied. While an increased risk of endometriosis was observed across the 3 TCDD categories, these risks were not statistically significant relative to the lowest exposure category. The test for trend based on a continuous measure (log_{10}TCDD) was also not statistically significant.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Criteria satisfied. Serum concentrations of TCDD offer improved exposure assessment, although delineating the critical exposure window is challenging given the nature of the very high initial exposure.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration not satisfied. Only a total of 19 cases of endometriosis were identified.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Environ Health Perspect 2002; 110(7) 629–634. Author's highlight that this is the first study to examine the relationship between TCDD and endometriosis, and the availability of sera data to estimate TCDD levels. Limitations included the small number of women with endometriosis, and inability to confirm disease status using laparoscopy. Finally, young women may have been underrepresented due to cultural difficulties in examining women who had never been sexually active.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. Eligible study subjects were women between 1 month and 40 years of age at time of accident. These analyses excluded virgins, those with Turner's syndrome, and women who refused the examination of ultrasound. Serum data were available for the 601 participants on which the analyses are based. Of these, 559 had serum measures taken in 1976/77, 25 between 1978 and 1981, and 17 women in 1996.

3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Criteria not satisfied. TCDD exposure was estimated at the time of "conception attempt" using serum measures, with extrapolation from 1976 levels using half-life assumptions. It is difficult to identify the relevant time interval over which TCDD dose should be considered for dose-response analysis. The critical window of exposure is unknown.
Conclusion	The lack of a statistically significant association coupled with a large number of women for which endometriosis disease status was "uncertain", precludes the use of these data to conduct dose-response analysis.

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3 **Table B-30. Eskenazi et al., 2003—Birth outcomes**
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1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration not satisfied. Outcomes were identified through self-reported questionnaires. Women were found to over-report birth weight, and have a tendency to underreport birth defects in children. As a large number of women in Seveso underwent voluntary abortion in the first year after the explosion, an awareness bias may have contributed to differential reporting of pregnancy histories.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration not satisfied. See above.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration not satisfied. There was no association between spontaneous abortions and $\log_{10}$TCDD, or with births small for gestational age. An inverse association with birth weight was noted in first eight years following the accident as were the number of births small for gestational age; however, none achieved statistical significance at $p < 0.05$.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Criteria satisfied. Serum concentrations of TCDD offer improved exposure assessment, although delineating the critical exposure window is challenging given the nature of the very high initial exposure.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. For spontaneous abortions there were 769 pregnancies. Fetal growth and gestational age analysis was carried out on 608 singleton births that occurred post-explosion.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.

Response	Criteria satisfied. Environ Health Perspect, 2003, 111(7):947–953. The authors highlight potential limitation of reliance on self-reported data to ascertain pregnancy outcomes. They also address the relevance of paternal exposures to TCDD on the developing fetus—such exposure data were not considered in this study.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. A total of 745 women in the SWHS had reported getting pregnant, of these 510 women were pregnant after the explosion (888 pregnancies). Analyses of spontaneous abortions based on 476 women (excludes those with voluntary abortion, ectopic pregnancy, or molar pregnancy). TCDD measured for 413 women in 1976/77, 12 women between 1978 and 1981, and 1996 for 19 women.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Criteria not satisfied. TCDD exposures were extrapolated to 1976 values. However, it is difficult to identify the relevant time interval over which TCDD dose should be considered for dose-response analysis.
Conclusion	The findings of the study are somewhat limited due to the reliance on self-reported information for pregnancy outcomes, and lack of paternal exposures. The findings were not statistically significant. Considered together, quantitative dose-response analyses for this study population were not undertaken.

Table B-31. Warner et al., 2004—Age at menarche

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. In this study age at menarche was based on retrospective recall 5 to 19 years before the interview. Previous work suggests moderate to high correlations between actual and recalled menarche, misclassification of outcome would bias risk estimates towards the null (assuming nondifferential misclassification).
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. Data collected from self-reported questionnaires allow for the potential confounding influence of many risk factors to be taken into account. Some misclassification of outcome may bias risk estimates towards the null.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration not satisfied. There was no association between TCDD levels and the age at menarche with either the continuous or categorical measures of TCDD.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.

Response	Criteria satisfied. Serum concentrations of TCDD offer improved exposure assessment, although delineating the critical exposure window is challenging given the nature of the very high initial exposure.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. Cohort was large enough as analyses were performed using 282 women who were premenarcheal at the time of the explosion.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Environ Health Perspect, 2004, 112:1289–1292. Authors discuss use of pooled serum from residents of the unexposed zone, and that those in lowest exposure group had high exposures relative with contemporary levels for the area. Strengths of study include use of serum to estimate TCDD exposure.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. The SWHS included women between 1 month and 40 years of age at time of accident who attempted to get pregnant after the explosion (n = 463). This study is restricted to those who were premenarcheal at the time of the explosion (n = 282). Serum was collected for these women, primarily in 1976–1977 (n = 257), between 1978 and 1981 for 23, and in 1996–1997 for the 2 remaining women.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Criteria not satisfied. TCDD exposures in 1976 were estimated by extrapolation serum levels obtained after this date using the Filser model. Both categorical and continuous measures of exposure were modeled. In utero measures of exposure are likely most relevant exposure based on findings from animal studies.
Conclusion	No association between TCDD levels and age at menarche was found. There may be some misclassification of age at menarche based on self-report, and biologically, the most relevant dose as suggested by animal studies occurs in utero. Additionally, it is difficult to identify the relevant time interval over which TCDD dose should be considered for dose-response analysis. For these reasons, these data are not suited to a dose-response analysis.

Table B-32. Eskenazi et al., 2005—Age at menopause

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Outcome measures were obtained based on self-reported data collected from questionnaires. Studies have shown that self-reports of age at menopause are reported with accuracy and reliability, and among women with surgical menopause, the self-reported age correlated well with that on the medical records.

2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. Data obtained from the questionnaire allow for the potential confounding influence of several potential confounders to be controlled for.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration not satisfied. Although risks of earlier menopause increased in the first four quintiles, with a statistically significant trend, no increased risk was noted in the highest exposure category (hazard ratio = 1.0 relative to lowest exposure group). Study authors suggest this is due to the "inverted U" dose response often seen with hormonally active compounds. Additionally, no statistically significant association was noted with $\log_{10}$TCDD for the individual quintiles.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Criteria satisfied. Serum concentrations of TCDD offer improved exposure assessment, although delineating the critical exposure window is challenging given the nature of the very high initial exposure.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. The study included 616 women. Of these, 260 were premenopausal, 169 classified as natural menopause, 83 as surgical menopause, 24 as impending menopause, 33 as premenopausal, and 58 in an "other" category.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Environ Health Perspect, 113:858–862 (2005). Authors highlight this is first study to look at relationship between dioxin and age at menopause. Other limitations of the study include lowest exposure group ($\leq$ 20.4 ppt) includes exposures level that are far higher than background, and age at menopause was based on retrospective recall. Strength of study is ability to characterize TCDD using serum measures.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. The Seveso Women's Health Study collected serum sample which allowed TCDD exposures to be characterized. Those women (n = 616) who had not reached natural menopause at the time of the accident were included in the study. Serum measures collected in 1976/77 were available for 564 women, for 28 women, sera was collected between 1978 and 1981, while for 24 women, sera was collected in 1996/97.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Criteria not satisfied. TCDD levels were estimated at the time of the explosion using available information on TCDD half-life. However, it is difficult to identify the relevant time interval over which TCDD dose should be considered for dose-response analysis. The critical window of exposure can be estimated but is large and highly uncertain.

Conclusion	The findings do not provide strong support for a dose-response relationship. As such, they are not well suited to a quantitative dose-response analysis.

Table B-33. Warner et al., 2007—Ovarian function

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Ovarian cyst analysis based on women who underwent ultrasound (n = 310). Ovarian follicle analysis based on self-report on menstrual cycle and done in women in preovulatory cycle (n = 96) at time of ultrasound. Hormonal analysis based on women in last 14 days of cycle (n = 129).
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. Data collected from self-reported questionnaires allow for the potential confounding influence of many risk factors to be taken into account. Some misclassification of outcome based on self-reports of menstrual cycle may bias risk estimates towards the null.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration not satisfied. There was no association between serum TCDD levels and the number or size of ovarian follicles. TCDD was also not associated wit the odds of ovulation.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Criteria satisfied. Serum concentrations of TCDD offer improved exposure assessment, although delineating the critical exposure window is challenging given the nature of the very high initial exposure.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. Cohort was large enough as analyses were performed using 129 women for ovulation outcome, and hormone analyses based on 87 women in luteal, and 55 in midluteal phases.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Environ Health Perspect, 2007,115:336–340. An important limitation cited by the authors was that women may not have been exposed at critical period (prenatally). Phases of the cycle may also have been misclassified as this was based on self-reported data. Strength, first study to have examined ovarian function and TCDD exposures.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. The SWHS included women between 1 month and 40 years of age at time of accident who were between 20–40 years of age and not using oral contraceptives at follow-up (n = 363).Of these, serum was collected for 330 women between 1976 and 1977, between 1978 and 1982 for 25 women, and between 1996 and 1997 for 8 women.

3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Criteria not satisfied. The women may not have been exposed at critical period (prenatally).
Conclusion	No association between TCDD levels and ovarian function was found. There may be some misclassification of period of the cycle based on self-report, and biologically, the most relevant dose as suggested by animal studies occurs in utero. For these reasons, these data are not suited to a dose-response analysis.

Table B-34. Eskenazi et al., 2007—Uterine leiomyoma

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Outcomes were determined using two definitions: current fibroids, or past diagnosis of fibroids. For past diagnosis of fibroids, self-reported data and medical records were used to determine whether women were previously diagnosed with fibroids, these were confirmed with medical records. A total of 25 women indicated they had never been diagnosed with fibroids. Medical records indicate a past diagnosis for these women, and they were classified as such. For current fibroids, this was determined at the time of the interview for 634 women using transvaginal ultrasound examinations.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. In the SWHS questionnaires were administered to the participants and detailed data for reproductive characteristics, smoking, body mass index, and alcohol use were collected so risks could readily be adjusted for these covariates.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration satisfied, but inversely. An inverse dose-response pattern with the percentage of women diagnosed (current and past history—combined) with fibroids across 3 categories of exposure. Namely, the percentages of women with fibroids in the ≤20, 20.1–75.0, and >75.0 ppt categories were 41.1%, 26.8%, and 20.0%, respectively.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. A variety of different exposure metrics were considered including linear, categorical, splines, and $\log_{10}$TCDD.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. A total of 251 women were found to have fibroids, and there were 62, 110, and 79 women with fibroids diagnosed in the 3 TCDD exposure categories.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.

Response	Criteria satisfied. Am J Epidemiol, 2007, 166:79–87. In this study, the authors found an inverse association between TCDD and uterine leiomyoma risk. The authors highlighted strengths of the study that included the longitudinal design, serum measures taken at an individual-level basis and most taken within 2 years of the accident, ability to include outcomes among those who did not take an ultrasound by using an adapted statistical approach. An important limitation that was the differences in risk by the stage of development could not be assessed as all women were exposed postnatally, and only 4 cases were observed among those who were premenarcheal at the time of exposure.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. Final sample consisted of 956 women in the Seveso Women's Health Study without a history of fibroids. For 872 of these women, serum was collected in 1976 and 1977. For 56 women, TCDD was measured in women between 1978 and 1981, and for 28 women the serum was collected in 1996.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Criteria not satisfied. TCDD exposures were back extrapolated to expected levels in 1976 (at the time of the accident). However, it is difficult to identify the relevant time interval over which TCDD dose should be considered for dose-response analysis. The critical window of exposure is unknown.
Conclusion	The data suggest an inverse (protective) effect between fibroids and exposure to TCDD. As such, these data are not suited to further dose-response analyses.

B.2.5. Other Seveso Noncancer Studies

Table B-35. Mocarelli et al., 2008—Semen quality

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Serum levels of TCDD were measured on an individual basis for men in exposed areas; pooled samples from men in uncontaminated areas were measured to assess background TCDD exposure levels.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. While compliance rates may have introduced some possible bias, this does not seem likely as different effects noted between the 22–31 and 32–39 year old age groups. Information collected for other risks factors, which have been used as adjustment factors in the models.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.

Response	Consideration satisfied. Figure 3 suggests dose-response relationship among those aged 1–9 at the time of the accident for sperm concentration and motility.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. Serum concentrations of TCDD offer improved exposure assessment, although delineating the critical exposure window is challenging.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. Analyses are based on 135 males exposed to TCDD.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Environmental Health Perspective s, 2008, 116(1):70–77. The authors describe strengths associated with characterization of exposure (using serum samples), and representativeness of study population. Limitation of study includes low compliance (but high for semen sample studies), namely, 60% among a group of healthy men. The compliance rate was higher among exposed group (69%).
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. Involved males, < 16 years old at time of accident.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Criteria satisfied. TCDD exposures were based on serum samples. Serum samples were drawn (in 1997/1998) from participants whose 1976 samples were above 15 ppt. Pooled samples obtained in 1997/98 were used to describe background TCDD levels in uncontaminated areas. The associated between TCDD exposure and semen quality was found statistically significant for the boys with 1 and 9 years of age at the time of the accident. This provides a critical window of exposure to estimate TCDD concentration.
Conclusion	Health outcomes are exposures are well characterized using serum data. However, the men exposed between the ages of 1 and 9 to elevated TCDD levels had reduced semen quality 22 years later. It is difficult to discern whether this effect is a consequence of the initial high exposure between 1 and 9 years of age or a function of the cumulative exposure for this entire exposure window beginning at the early age. Nonetheless, quantitative dose-response analyses for this outcome were conducted.

Table B-36. Mocarelli et al., 2000—Sex ratio

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Birth records examined for those who lived in parents who lived in the area and who provided serum samples.

2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration satisfied. Paternal TCDD exposures were associated with an increased probability of female births ($p = 0.008$).
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. Serum samples were used to estimate maternal and paternal TCDD levels. No discussion of exposure levels in reference population.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. Statistically significant findings achieved.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria not satisfied. The Lancet, 2000, 355:1858–1863. There is no discussion on the strengths and limitations of this study.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. Serum levels of TCDD were obtained from parents using samples provided in 1976/77. Serum measures available for 296 mothers and 239 fathers.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Criteria not satisfied. Serum based measures of TCDD were obtained shortly after the accident. TCDD levels were also extrapolated to the time of conception. However, it is difficult to identify the relevant time interval over which TCDD dose should be considered for dose-response analysis. The critical window of exposure is unknown.
Conclusion	The data from this study demonstrate a positive dose-response relationship with paternal TCDD levels at the time of the accident and increased likelihood for female births. However, It is difficult to identify the relevant time interval over which TCDD dose should be considered; specifically, it is difficult to discern whether this effect is a consequence of the initial high exposure during childhood or a function of the cumulative exposure for this entire exposure window beginning at the early age. Using the initial exposures in a dose-response model would yield LOAELs that are too high to be relevant to factor into the RfD calculation. Dose-response analysis for this outcome is, therefore, was not conducted.

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Table B-37. Baccarelli et al., 2008—Neonatal thyroid function

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Measures of b-TSH are taken using a standardized protocol 72 hours after birth. These b-TSH measures are taken on all newborns born in the region of Lombardy of which Seveso if a part of.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied for component of the study based on plasma dioxin measures. For the comparisons involving place of residence at the time of the accident, exposure misclassification is likely given variability in soil TCDD exposure levels within these areas.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration satisfied. Mean neonatal b-TSH was 0.98μU/ml [0.90–1.08] in the reference area, 1.35μU/ml [1.22–1.49] in zone B, and 1.66μU/ml [1.19–2.31] in zone A ($p < 0.001$). The plotted frequency distributions have similar shapes, but have shifted to the right for areas of higher exposures. Neonatal b-TSH was correlated with current maternal plasma TCDD (β-0.47, $p < 0.001$) in the 51 newborns for which individual maternal serum TCDD values were available.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. TEQs were measured among the 38 women for which serum samples were available and were defined for a mixture of dioxin-like compounds. Maternal mean total TEQs (PCDDs, PCDFs, coplanar PCBs, and noncoplanar PCBs) was 41.8 ppt. Two measures of exposure included place of residence at time of accident and plasma samples obtained from mothers at the time of delivery. Similarities in positive dose-response relationships give stronger weight to the findings.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied for exposure metric that was based on 'place of residence'. For plasma based estimate of maternal TCDD there were only 51 mother-child pairs. Only seven children in total were found to have b-TSH levels in excess of 5 uU/ml; this implies limited statistical power involving this health outcome.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. PLOS Medicine 2008; 5(7)1133–1142. The authors discuss the strength of the study related to characterization of exposure using serum sampling, and ability to adjust for factors related to b-TSH or TCDD levels (gender, birth weight, birth order, maternal age, hospital and type of delivery). They also highlight that a limitation of study was that the influence of mother-child dioxin transfer through colostrum could not be assessed because no information on breastfeeding before b-TSH measurement was available.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.

Response	Criteria satisfied. In the population-based study, eligible women who resided in zones A and B at the time of the accident (n = 1,772) were matched to nonexposed women. In the study based on plasma dioxin measurements, participants were the 51 children born to 38 women from zones A, B, R, or a reference zone for which plasma dioxin measurements were available.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Criteria satisfied. Maternal TCDD levels were estimated at the time of delivery based on plasma samples, and the critical window of exposure can be defined as the 9 month gestation period.
Conclusion	The data provide an opportunity for quantitative dose-response analyses.

Table B-38. Alaluusua et al., 2004—Oral hygiene

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Ascertainment of dental health was done blind to place of residence, used standard protocol for caries developed by the WHO, and the clinical examination supplemented by radiographic examination.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. Additional risk factor information was collected on questionnaires. These factors were considered as adjustment factors. Findings potentially susceptible to participation biases.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration satisfied. Increased prevalence of developmental enamel effects found with increased TCDD serum measures. Namely, prevalence in unexposed region was 26%, whereas in the low, middle, and high TCCD groups the prevalence was 10, 40, and 60%, respectively.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. TCDD exposure level based on serum lipids. No discussion of exposure levels in reference population.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Criteria satisfied. Despite small numbers, statistically significant findings were achieved.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.

Response	Criteria satisfied. Environmental Health Perspectives, 2004, 112(13)1313–1318. Authors mention two important strength of the study: characterization of TCDD exposure using serum collected shortly after the time of the accident, and the fact that developmental defects are permanent in nature. Therefore, they represent a health outcome can evaluated years later. Little discussion was made of the impact of differential compliance rates between the exposed (74%) and nonexposed (58%) groups. Authors mention two important strength of the study: characterization of TCDD exposure using serum collected shortly after the time of the accident, and the fact that developmental defects are permanent in nature. Therefore, they represent a health outcome can evaluated years later. Little discussion was made of the impact of differential compliance rates between the exposed (74%) and nonexposed (58%) groups.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. Serum levels of TCDD could be estimated for children in exposed areas. No serum levels were available for reference group of children, and assumption of zero exposure was made. This seems reasonable.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Criteria satisfied. It is difficult to discern whether this effect is a consequence of the initial high exposure during childhood or a function of the cumulative exposure of the entire exposure window beginning at early age. However, assumptions can be made regarding the critical window of exposure and the relevant dose can be calculated.
Conclusion	The considerations for conducting a dose-response analysis have been satisfied with the study population of only those subjects who lived in the ABR zone at the time of the accident; exposure data are unavailable for those in the referent area. While is difficult to identify the relevant time interval over which TCDD dose should be considered, quantitative dose-response analysis for this outcome was conducted.

Table B-39. Bertazzi et al., 2001—Mortality (noncancer)

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied for some causes of death, but not others. Mortality appears to be well captured from the vital statistics registries in the region (99% complete). Some health outcomes (e.g., diabetes) are subject to misclassification using death certificate data.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. Although individual-level data for individual risk factors are not available, the potential for confounding is likely minimal. For e.g., independent surveys suggests similarity between smoking behaviors across the regions. Exposure misclassification based on place of residency likely to bias risk estimates towards the null.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.

Response	Consideration not satisfied for most causes of death. An exception was the dose-response relationship was observed for chronic obstructive pulmonary disease across Zones A, and B.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration not satisfied. Exposure classification was based on the address of the residence on the date of the accident or when the person first entered the area. Although TCDD blood levels were also measured, these were not examined with respect to health outcomes. The lack of individual-level data also precluded an examination of these uncertainties.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. A total of 494 noncancer deaths were found among residents of Zones A, and B, respectively. This allowed examined of gender-specific effects.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Am J Epidemiol, 2001, 153:1031–1044. Authors discuss lack of individual-level exposure data and other risk factors (e.g., smoking), difficulties in extrapolating to background levels, diagnostic accuracy of using death certificates. Strengths included similarities between exposed and comparison population for several risk factors, completeness of follow-up, and consistent methods to identify mortality outcomes in the exposed and comparison populations.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria not satisfied. Individual-level exposure data are unavailable. Exposure based on place of residence at time of the explosion. Soil sampling performed indicated considerable variability in TCDD levels within each region. In addition, place of residency at time of explosion does not ensure individuals were at their home around the time of the accident.
3. Critieria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Criteria not satisfied. An ecological measure of exposure (region of residency at time of accident) was used to categorize individuals according to their possible exposure. Latencies were considered. While such an approach has value for identifying whether excesses occurred among highly exposed populations, it is not precise enough to conduct a quantitative dose-response analysis. Furthermore, noncancer mortality is not a viable endpoint to consider for further dose-response analysis.
Conclusion	Study is not suitable for dose-response analysis due to mortality as endpoint and lack of individual-level exposure data.

Table B-40. Consonni et al., 2008—Mortality (noncancer)

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied for some causes of death, but not others. Mortality appears to be well captured from the vital statistics registries in the region (99% complete). Some health outcomes (e.g., diabetes) are subject to misclassification using death certificate data.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. Although individual-level data for individual risk factors are not available, the potential for confounding is likely minimal. For e.g., information from other independent surveys suggests similarity between smoking behaviors across the regions. Exposure misclassification based on place of residency is likely to bias risk estimates towards the null.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration not satisfied. Statistically significant association noted in most highly exposed area for chronic rheumatic disease and chronic obstructive pulmonary disease. Dose-response pattern noted across Zones A, B and R for circulatory disease mortality 5–9 years after the accident.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration not satisfied. Lack of individual-level data precludes an examination of these uncertainties.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied for some causes of death but not others. For example, only three deaths from diabetes occurred among residents of Zone A. The limitation related to statistical power is exacerbated for stratified analyses carried out by number of years since the accident.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Am J Epidemiol, 2008, 167:847–858. Authors discuss potential for selection bias, limitation of residential based measure of exposure, similarities of mortality ascertainment in exposed and referent populations, and multiple testing.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria not satisfied. Individual-level exposure data are unavailable. Exposure based on place of residence at time of the explosion. Soil sampling performed indicated considerable variability in TCDD levels within each region. In addition, place of residency at time of explosion does not ensure individuals were at their home around the time of the accident.

3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Criteria not satisfied. An ecological measure of exposure (region of residency at time of accident) was used to categorize individuals according to their possible exposure. Latencies were considered. While such an approach has value for identifying whether excesses occurred among highly exposed populations, it is not precise enough to conduct a quantitative dose-response analysis. Furthermore, noncancer mortality is not a viable endpoint to consider for further dose-response analysis.
Conclusion	Study is not suitable further dose-response evaluation due to noncancer morality endpoint.

Table B-41. Baccarelli et al., 2005—Chloracne

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Chloracne cases identified using standardized criteria.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration satisfied. Plasma TCDD was associated with an increased risk of chloracne. The odds ratios increased in a dose-response pattern across zone of residence.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. Authors discussed implications of differential elimination rates by age and body growth.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. A total of 101 chloracne cases were identified, and 211 controls were selected. Statistically significant findings were observed in several comparisons.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. British Journal of Dermatology, 2005, 152, 459–465. The authors detail the limited statistical power they had available in the study. They also highlight a strength of the study that included uniqueness of age and sex distribution of chloracne cases, characterization of TCDD that could be done using sera samples, and availability of both clinical and epidemiological data.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.

Response	Criteria satisfied. TCDD was estimated in both chloracne cases and control using serum measures.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Criteria satisfied. Serum based measures of TCDD were obtained shortly after the accident. Chloracne is thought to be caused by the initial high exposure.
Conclusion	Exposure to TCDD at sufficiently high levels is recognized to cause chloracne. This study provides limited relevance to dose-response modeling of TCDD as exposure levels typically observed in the general population are much lower.

Table B-42. Baccarelli et al, 2002 and 2004—Immunological effects

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Common methods were used to describe blood levels of plasma immunoglobulins (IgA, IgG, and IgM) and complement components (C3 and C4).
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. Both exposure and outcome were objectively and accurately measured.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration satisfied. Plasma IgG levels were inversely related with TCDD.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. Both categorical (quintiles) and continuous measures of TCDD were examined in the dose-response analysis.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. Analyses are made using 72 highly exposed, and 72 low exposed individuals.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Toxicology letters, 2004, 149:287–293 and Environ Health Perspect, 2002, 110(12):1169–1173. The authors highlight that few studies have looked at immunological effects of TCDD in humans, that the current study was able to exclude those with concurrent medical conditions, and the ability to characterize exposure using serum measures. Limitations addressed were the uncertainty about the clinical relevance of the dose-response pattern found, and the relatively small size of the study population.

2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. A total of 120 subjects were included in the study. This included 62 randomly selected from the high exposed zone, and 58 selected from the reference area.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Criteria not satisfied. Dose-response relationships were examined using current TCDD levels. However, it is difficult to identify the relevant time interval over which TCDD dose should be considered for dose-response analysis.
Conclusion	An inverse dose-response association between IgG and TCDD was observed, however, because the relationship can not be described in terms of clinical relevance with respect to a specific health outcome, it is our view that these data are not suited to dose-response modeling.

B.2.6. Chapaevsk Study

Table B-43. Revich et al., 2001—Mortality (noncancer) and reproductive health

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration cannot be evaluated. Insufficient details are provided in the paper to gauge the completeness and coverage of the cancer registry and mortality data. Health outcomes were studied on the basis of information in the official medical statistics
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration not satisfied. It is an ecological study.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration cannot be evaluated. Dose-response was not evaluated as exposure was based on residency in the region vs. no residency.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration not satisfied. No individual-level exposure estimates were used.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. Population-based data over several years were used to make ecological comparisons.

1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Published in Chemosphere, 2001, 43(4–7):951–966.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria not satisfied. It is a cross-sectional study that compares mortality rates between regions. No individual-level exposure data available.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Criteria not satisfied. No exposure estimates were used in the study.
Conclusion	These cancer data are cross-sectional in nature and not appropriate for a dose-response analysis.

B.2.7. Air Force Health ("Ranch Hands") Study

Table B-44. Michalek and Pavuk, 2008—Diabetes

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Prevalent diabetes identified from medical records from repeated medical check-ups. Preferred method of ascertaining outcome relative to use of death certificates.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration not satisfied. Adjustment was made for a number of risk factors related to diabetes (e.g., BMI, family history, smoking). However, Agent Orange was a 50% mixture of 2,4-D and TCDD; therefore, potential for confounding by other coexposures is likely.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration satisfied. The RR for an increase in 10 units was 1.29 ($p < 0.001$), and the risks across the background, low and high exposure categories, relative to the unexposed were 0.86, 1.45, and 1.68.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. Initial TCDD dose were estimated at the end of the tour of duty for the Ranch Hands. Individual-level serum dioxin measurements correlated well with correlated with days of spraying and calendar period of service, but collection of the samples roughly 20 years later required back-extrapolation.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.

Response	Consideration satisfied. There were a total of 439 cases of diabetes identified.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. J Occup Environ Medicine, 2008, 50:330–340. The authors address strengths and limitations related to the accuracy of the one-compartment pharmacokinetic model, impact of the covariate time spent in Southeast Asia, and potential exposure misclassification on days sprayed.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria not satisfied. TCDD estimates were derived using serum samples. However, Ranch Hand veterans were exposed to other compounds in the herbicides, such as 2,4-D.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Criteria satisfied. TCDD levels at the end of service were estimated. Extrapolation was done using a half-life of 7.6 years. Exposures were grouped into comparison, background, low and high. This allows for a shape of the dose-response curve to be evaluated. A continuous measure of TCDD was also examined ($\log_{10}$TCDD).
Conclusion	Ranch Hand veterans were exposed to other contaminants in the herbicides that were mixed, thereby making it difficult to determine independent effects of TCDD on diabetes. In our view, this limitation precludes dose-response modeling of TCDD and diabetes using data from this cohort.

B.2.8. Other Noncancer Studies of Dioxin

Table B-45. McBride et al., 2009a—Mortality (noncancer)

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. The New Zealand Health Information Service Mortality Collection and the Registrar-General's Index to Deaths were used to identify deaths. Additional searches were based on the last known address from the work record; the electoral roll and the habitation index; the telephone book; the internet; and Terranet property information database. An additional search was carried out through the Births, Deaths, and Marriages office of the New Zealand Department of Internal Affairs. Lastly, automated personnel and pension records were also used to locate past New Plymouth workers and identify some deaths.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. Workers lost to follow-up were an unlikely source of bias especially for internal analyses. Confounding by other coexposures (e.g., 2,4,6-TCP) unlikely to have resulted in bias, due to presumed poor correlation with TCDD.

3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration not satisfied. There was no cause of death among those considered for which a dose-response trend was observed across four exposure categories of TCDD.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. Dichotomous exposure (exposed/unexposed) and duration of employment were examined from job exposure classification assessed via occupational history records industrial hygienists/factory personnel knowledge and questionnaires.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration not satisfied.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Published in J Occup Environ Med, 2009, 51:1049–1056. The other studies in the cohort highlight the 22% of the cohort lost to follow-up, the limited size of the cohort tissue sarcomas, differences in cohort definitions between sprayers and producers, and the potential for other exposures during employment at the plant.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. Serum measures available for 346 workers were used to derive TCDD exposures for the entire cohort using the area under the curve approach.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Criteria not satisfied. Dichotomous exposure assessment did not allow individual estimates of dose to be developed. However, noncancer mortality is not a viable endpoint to consider for further dose-response analysis.
Conclusion	A considerable portion of the cohort was lost to follow-up, and no dose-response associations noted. As a result, the data are not suited to dose-response analysis.

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Table B-46. McBride et al., 2009b—Mortality (noncancer)

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. The New Zealand Health Information Service Mortality Collection and the Registrar-General's Index to Deaths were used to identify deaths. Additional searches were based on the last known address from the work record; the electoral roll and the habitation index; the telephone book; the internet; and Terranet property information database. An additional search was carried out through the Births, Deaths, and Marriages office of the New Zealand Department of Internal Affairs. Lastly, automated personnel and pension records were also used to locate past New Plymouth workers and identify some deaths.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration not satisfied. Considerable amount of workers were lost to follow up (22%), but it is unclear if bias resulted. The dichotomous exposure measure was based on exposure to TCDD, chlorinated dioxins and phenoxy herbicides, so confounding is a possibility by these coexposures.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration not satisfied. Because no individual exposure estimates were available for these analyses, dose-response could not be evaluated.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. Consideration satisfied. Dichotomous exposure (exposed/unexposed) and duration of employment were examined from job exposure classification assessed via occupational history records industrial hygienists/factory personnel knowledge and questionnaires. Authors discuss limitations in the assignment of exposure among cohort members.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Published in Occup Medicine, 2009, 59(4):255–263. The authors highlight cohort lost to follow-up, the limited size of the cohort, differences in cohort definitions between sprayers and producers, and the potential for other exposures during employment at the plant.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria not satisfied. Exposures were not quantified. The dichotomous exposure measure was based on exposure to TCDD, chlorinated dioxins and phenoxy herbicides.

3. Critiera	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Effective dose could not be estimated given the lack of individual-level exposure data. Noncancer mortality is not a viable endpoint to consider for further dose-response analysis.
Conclusion	The study lacks the quantification of exposures at an individual level, and a considerable portion of the cohort was lost to follow-up. As a result, the data are not suited to dose-response analysis.

Table B-47. Ryan et al., 2002—Sex ratio

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration not satisfied. Company records were used to identify births, the date of birth, and the sex of the child. No information was provided on the expected completeness of identifying births in this manner. Moreover, the study was expanded to include workers who heard about the study in a public forum. Therefore, the study could be influenced by participation bias.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration not satisfied. See above.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration not satisfied. The study compared birth ratios among men and women employed at the plant to the general population. No categories of exposure were examined.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration not satisfied. This is not relevant as no analyses were done in relation to exposure levels.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. For the categories of exposure used (yes/no), and the stratified analyses by sex and subcohort, the study allows for the birth ratios to be estimated with sufficient precision.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.

Response	Criteria not satisfied. Published in Environ Health Perspect, 2002, 110(11):A699–A701. The authors discussed the limitations of using serum collected many years after they stopped working to estimate TCDD exposures when the preferred metric would be TCDD levels at the time of conception. They did not address issues about the representativeness of the study participants to the entire cohort of workers, nor did they address the limitation of not being able to conduct dose-response analyses using individual-level TCDD data.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria not satisfied. While serum measures were available for 84 of the 198 participants of the study, birth ratios were compared between the cohort of 2,4,5-T and 2,4,5-trichlorphgenol workers relative to the city of Ufa. There was no attempt to derive birth ratios in relation to exposure levels. The serum data were only used to demonstrate that these workers, on average, had TCDD levels 30 times higher than Ufa residents.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Criteria not satisfied. TCDD exposures were based on serum measures taken in some cases many years after children were born; no attempt was made to back-extrapolate to the time of conception.
Conclusion	The data are not suitable for dose-response modeling. Risk estimates have not been derived in relation to TCDD exposure levels. There exist uncertainties about the representativeness of the participants in relation to the cohort as a whole, and insufficient details are provided to evaluate the extent in which all births were identified. While these data should not be used for quantitative dose-response modeling, the much lower M/F birth ratio among exposed fathers is consistent with the finding by Mocarelli et al, and lends support to those findings.

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APPENDIX C

Kinetic Modeling

NOTICE

THIS DOCUMENT IS AN EXTERNAL REVIEW DRAFT. It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH

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APPENDIX C. KINETIC MODELING

C.1. LITERATURE SEARCH STRATEGY AND RESULTS—IDENTIFYING RECENT PUBLICATIONS FOR UPDATING TCDD TOXICOKINETIC MODEL INPUT PARAMETERS

The purpose of this literature search was to identify recent publications that address the input parameters for the physiologically based pharmacokinetic (PBPK) models Aylward and colleagues (described in articles published in 2005 and 2009) and Emond and colleagues (described in articles published in 2004, 2005, and 2006). This literature search was part of the U.S. Environmental Protection Agency (EPA)'s preparation of a response to the National Academy of Sciences' review (*Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment*, NAS, 2006]) of EPA *Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds* (U.S. EPA, 2003), herein called the "2003 Reassessment." English-only references from 2003 to May 2009 were searched using bibliographic data bases relevant to health effects and toxicology of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). The search focused on toxicokinetic data that could be used to update the dynamic disposition of 2,3,7,8-TCDD in mice, rats, guinea pigs, monkeys, and humans.

In the primary search, EPA identified 775 distinct citations based on the literature search criteria described below. EPA also performed an independent supplemental search to avoid missing key studies. EPA identified 28 papers for further analysis that appeared on first review to report data to update the input parameters of the Aylward and Emond PBPK models; considerations for selection are described in Section C.1.3.

C.1.1. Data Bases Searched

EPA used the following DIALOG bibliographic data bases in the primary search. Brief descriptions of the DIALOG data bases searched are provided in Section C.1.5.

1. File 6: NTIS
2. File 41: Pollution Abstracts
3. File 55: Biosis
4. File 153: IPA Toxicology

5. File 155: MedLine
6. File 156: ToxFile
7. File 157: Biosis Toxicology
8. File 159: CancerLit
9. File 336: RTECS

The PUBMED data base was used for the supplemental search.

C.1.2. Literature Search Strategy and Approach

The primary search used a tiered key-word approach, as documented below. The principal search term was the Chemical Abstract Service Registry Number (CASRN) or specific chemical name, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin or 2,3,7,8-TCDD. The next tier of search terms was species, and finally toxicokinetic keywords, as listed below. The period of the search was 2003 through May 2009, and articles were limited to English language.

The supplemental PUBMED search was limited to the most recent five years (2004 to present) and used four combinations of key words:

- TCDD + pharmacokinetic + humans,
- TCDD + toxicokinetic + humans,
- TCDD + pharmacokinetic + animals, and
- TCDD + toxicokinetic + animals.

C.1.2.1. *Chemical Search Terms—DIALOG Search*

- CASRN: 1746-01-6
- 2,3,7,8-tetrachlorodibenzo-*p*-dioxin
- 2,3,7,8-TCDD

C.1.2.2. *Primary Search Terms (Species)—DIALOG Search*

- Guinea pig(s)
- Human(s)
- Monkey(s)
- Mouse

- Mice
- Rodent(s)
- Rat(s)

C.1.2.3. *Secondary Search Terms (Toxicology)—DIALOG Search*

* = truncated
1w = terms are within 1 word of each other and in the order specified (see search term 32)

1. Absor*
2. ADME
3. Aryl hydrocarbon receptor
4. AhR
5. Bioavail*
6. Biliar*
7. Biotransform*
8. Cytochrome
9. CYP*
10. CYP1A1
11. CYP1A2
12. Diet, dietary, diets
13. Disposit*
14. Distrib*
15. Drink*
16. Elimin*
17. Excret*
18. Epidemiolog*
19. Feces
20. Feed*
21. First order kinetics
22. Food*
23. Gastro*
24. Gavage*
25. Half-life
26. Induct*
27. Ingest*
28. In silico
29. Kinetic*
30. Liver
31. Lymph*
32. Mechanism (1w) action
33. Metabo*
34. Oral*
35. P450
36. Partition coefficient
37. PBPK
38. Pharmacodynamic*
39. Pharmacokinetic*
40. Physiologically based
41. pharmacokinetic
42. Protein bind*
43. Toxicokinetic*
44. Urin*

ADME = absorption, distribution, metabolism, elimination; AhR = aryl hydrocarbon receptor; CYP = cytochrome P450.

C.1.3. Citation Screening Procedures and Results

Initial DIALOG searches resulted in a very large number of citation hits. Therefore, some title and key word restrictions were applied iteratively to screen out less relevant citations (e.g., requiring some search terms in title, requiring 2,3,7,8-TCDD rather than just TCDD). Then, using reference management software, pooled information obtained from the various DIALOG data bases was screened to remove duplicates. Citations then were numbered

sequentially (as a unique identifier). Information retrieved included the following (when available): author(s), publication year, title, source document name, volume, and page numbers.

The DIALOG search and duplicate removal procedure produced 775 unique citations. In the next step, all 775 citations were screened for potential applicability to updating parameters in the Aylward and Emond PBPK models. Of these 775 citations, 26 were selected for more detailed review to determine their potential applicability, and full publications were retrieved. Two citations were added from the supplemental search, giving a total of 28 articles identified for further review.

Bibliographic information for the 28 articles selected for full review is provided in the reference list at the end of this section. Table C-1 summarizes the model input parameters potentially addressed by the selected articles.

During 2003 to May 2009, the authors of the two kinetic models under consideration published several articles. For the Emond model, which was first published in 2004 (Emond et al., 2004), two subsequent papers have been published (Emond et al., 2005, 2006). The Aylward model, which originated from the 1995 papers by Carrier et al. (1995a, b), was later updated by the same group (Aylward et al., 2005a, b). The major change implemented in the last two papers was the description of a desorption process in the digestive tract. The transfer rate described is slow, but for a low body burden of TCDD, this process remains significant. This concept was reported in 2002 by Moser and McLachlan (2002). The major modifications expected to update the Emond model are (1) consideration of the desorption process in the gastrointestinal tract and (2) rearrangement of the elimination constant, which will have a negligible impact on the simulation. These changes are motivated by plausible observations reported in the literature.

Because of the body burden found in humans and the importance of selecting an appropriate dose metric in human risk assessment, the physiological model is an important tool for assessing the kinetics following exposure to TCDD (Kim et al., 2003). Based on the literature identified in this search, the major contributions that should be reviewed with respect to the Aylward and Emond kinetic models are not modes of action or pharmacokinetic mechanisms, but rather information for verifying or improving the accuracy of some model parameters.

Pharmacokinetics typically refers to four distinct steps including absorption, distribution, metabolism, and excretion. Physiologically-based models consider each step. In the model each

step is parameterized to reflect better predictions of the real observations. Occasionally, reviewing these models is essential to determine if any key processes or parameters might be described with better accuracy. This perspective underlies the review of the literature described here. The review indicates TCDD disposition has become recognized as relatively significant since the publication of the Emond and Aylward models. The literature that provides information related to improving these models, however, is limited. For the benefit of this exercise, EPA selected the literature that would likely contribute significantly to model response, or to clarify or confirm different key issues driving the model results. Regarding the two TCDD models, the two major issues that should be evaluated with respect to the recent literature identified are the elimination profile and the induction of CYP1A2.

Reviewing the elimination variation in different species and testing variable elimination with a data set appears to be appropriate. The literature reports that various factors might influence elimination rate. Recent publications report the influence of diverse predictors such age, body fat, or smoking habit on the elimination half-life (Milbrath et al., 2009; Kerger et al., 2006, 2007). Determining whether using the Milbrath et al. information would help account for intraspecies variability in elimination rate in the Emond and Aylward kinetic models would be useful. In 2006, Emond et al. reviewed the influence of body fat mass and CYP1A2 induction on the pharmacokinetics of TCDD. These two factors appear to contribute significantly to elimination and their influences seem to be driven by TCDD body burden. Mullerova and Kopecky (2007) discussed the influence of adipose tissue and the "yo-yo" effects on various diseases that might be influenced by persistent organic pollutant distribution. One group explored the importance of variable elimination and compared these predictions to first-order elimination using the Aylward and Emond models and supported these approaches for risk assessment (Heinzl et al., 2007). Two groups of authors considered a one-compartment model to derive the elimination half-life (Aylward et al., 2009; Nadal et al., 2008). Comparing the half-life they obtained using this approach for a range of body burden to the variable elimination half-life would be interesting.

The second important mechanism driving the distribution and elimination of TCDD is the induction of CYP1A2, identified as the major ligand protein in liver (Diliberto et al., 1997). For that process, authors suggested different aspects that should be investigated, including the importance of the dose metrics in the target tissue and the inducible level of CYP1A2 (Wilkes

et al., 2008; Staskal et al., 2005). Other papers address the intraspecies variability of lethal potency in mature species versus the developing fetus (Kransler et al., 2007; Korkalainen et al., 2004). Still others point out pronounced differences among species (namely, guinea pigs, hamsters, mice, and rats) (Bohonowych and Denison, 2007), as observed in studies of long-term effects of low TCDD dose in liver and in studies comparing hepatic accumulation and clearance of TCDD (Korenaga et al., 2007; Boverhof et al., 2005). The interspecies variation of the binding affinity constant of AhR also has been reported (Connor and Aylward, 2006; Nohara et al., 2006).

The articles identified in this literature review should be adequate to update the Aylward and Emond models, which need to be evaluated according to the same structure of compartments described in the literature by the two model authors.

C.1.4. References Selected for More Detailed Review for Updating the PBPK Models

Aylward, LL; Brunet, RC; Carrier, G; et al. (2004). Concentration-dependent TCDD elimination kinetics in humans: toxicokinetic modeling for moderately to highly exposed adults from Seveso, Italy, and Vienna, Austria, and impact on dose estimates for the NIOSH cohort. J Expo Anal Environ Epidemiol 15(1):51−65.

Aylward, LL; Brunet, RC; Starr, TB; et al. (2005). Exposure reconstruction for the TCDD-exposed NIOSH cohort using a concentration- and age-dependent model of elimination. Risk Anal 25(4):945−956.

Aylward, LL; Bodner, KM; Collins, JJ; et al. (2009). TCDD exposure estimation for workers at a New Zealand 2,4,5-T manufacturing facility based on serum sampling data. J Expo Sci Environ Epidemiol. doi: 10.1038/jes.2009.31.

Bohonowych, JE; Denison, MS. (2007). Persistent binding of ligands to the aryl hydrocarbon receptor. Toxicol Sci 98(1):99-109.

Boverhof, DR; Burgoon, LD; Tashiro, C; et al. (2005). Temporal and dose-dependent hepatic gene expression patterns in mice provide new insights into TCDD-mediated hepatotoxicity. Toxicol Sci 85(2):1048−1063.

Connor, KT; Aylward, LL. (2006). Human response to dioxin: aryl hydrocarbon receptor (AhR) molecular structure, function, and dose-response data for enzyme induction indicate an impaired human AhR. J Toxicol Environ Health B 9(2):147−171.

Heinzl, H; Mittlback, M; Edler, L. (2007). On the translation of uncertainty from toxicokinetic to toxicodynamic models - the TCDD example. Chemosphere 67(9):S365−S374.

Irigaray, P; Mejean, L; Laurent, F. (2005). Behaviour of dioxin in pig adipocytes. Food Chem Toxicol 43(3):457−460.

Kerger, BD; Leung, HW; Scott, P; et al. (2006). Age- and concentration-dependent elimination half-life of 2,3,7,8-tetrachlorodibenzo-p-dioxin in Seveso children. Environ Health Perspect 114(10):1596−1602.

Kerger, BD; Leung, HW; Scott, PK; et al. (2007). Refinements on the age-dependent half-life model for estimating child body burdens of polychlorodibenzodioxins and dibenzofurans. Chemosphere 67(9):S272−S278.

Kim, AH; Kohn, MC; Nyska, A; et al. (2003). Area under the curve as a dose metric for promotional responses following 2,3,7,8-tetrachlorodibenzo-p-dioxin exposure. Toxicol Appl Pharmacol 191(1):12−21.

Korenaga, T; Fukusato, T; Ohta, M; et al. (2007). Long-term effects of subcutaneously injected 2,3,7,8-tetrachlorodibenzo-p-dioxin on the liver of rhesus monkeys. Chemosphere 67(9):S399−S404.

Korkalainen, M; Tuomisto, J; Pohjanvirta, R. (2004). Primary structure and inducibility by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) of aryl hydrocarbon receptor repressor in a TCDD-sensitive and a TCDD-resistant rat strain. Biochem Biophys Res Communications 315(1):123−131.

Kransler, KM; McGarrigle, BP; Olson, JR. (2007). Comparative developmental toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the hamster, rat and guinea pig. Toxicology 229(3):214−225.

Maruyama, W; Yoshida, K; Tanaka, T; et al. (2002). Determination of tissue-blood partition coefficients for a physiological model for humans, and estimation of dioxin concentration in tissues. Chemosphere 46(7):975−985.

Maruyama, W; Yoshida, K; Tanaka, T; et al. (2003). Simulation of dioxin accumulation in human tissues and analysis of reproductive risk. Chemosphere 53(4):301-313.

Maruyama, W; Aoki, Y. (2006). Estimated cancer risk of dioxins to humans using a bioassay and physiologically based pharmacokinetic model. Toxicol Appl Pharmacol 214(2):188−198.

Milbrath, MO; Wenger, Y; Chang, C-W; et al. (2009). Apparent Half-Lives of Dioxins, Furans, and Polychlorinated Biphenyls as a Function of Age, Body Fat, Smoking Status, and Breast-Feeding. Environ Health Perspect 117(3):417−425.

Moser, GA; McLachlan, MS. (2002). Modeling digestive tract absorption and desorption of lipophilic organic contaminants in humans. Environ Sci Technol 36(15):3318−25.

Mullerova, D; Kopecky, J. (2007). White adipose tissue: storage and effector site for environmental pollutants. Physiol Res 56(4):375−381.

Nadal, M; Perello, G; Schuhmacher, M; et al. (2008). Concentrations of PCDD/PCDFs in plasma of subjects living in the vicinity of a hazardous waste incinerator: Follow-up and modeling validation. Chemosphere 73(6):901−906.

Nohara, K; Ao, K; Miyamoto, Y; et al. (2006). Comparison of the 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-induced CYP1A1 gene expression profile in lymphocytes from mice, rats, and humans: Most potent induction in humans. Toxicology 225(2-3):204−213.

Olsman, H; Engwall, M; Kammann, U; et al. (2007). Relative differences in aryl hydrocarbon receptor-mediated response for 18 polybrominated and mixed halogenated dibenzo-p-dioxins and -furans in cell lines from four different species. Environ Toxicol Chem 26(11):2448−2454.

Saghir, SA; Lebofsky, M; Pinson, DM; et al. (2005). Validation of Haber's Rule (doseX time=constant) in rats and mice for monochloroacetic acid and 2,3,7,8-tetrachlorodibenzo-p-dioxin under conditions of kinetic steady state. Toxicology 215(1−2):48−56.

Schecter, A; Pavuk, M; Popke, O; et al. (2003). Dioxin, dibenzofuran, and coplanar PCB Levels in Laotian blood and milk from Agent Orange-sprayed and nonsprayed areas, 2001. J Toxicol Environ Health A 66(21):2067−2075.

Staskal, DF; Diliberto, JJ; Devito, MJ; et al. (2005). Inhibition of human and rat CYP1A2 by TCDD and dioxin-like chemicals. Toxicol Sci 84(2):225−231.

Toyoshiba, H; Walker, NJ; Bailer, AJ; et al. (2004). Evaluation of toxic equivalency factors for induction of cytochromes P450 CYP1A1 and CYP1A2 enzyme activity by dioxin-like compounds. Toxicol Appl Pharmacol 194(2):156−168.

Wilkes, JG; Hass, BS; Buzatu, DA; et al. (2008) . Modeling and assaying dioxin-like biological effects for both dioxin-like and certain non-dioxin-like compounds. Toxicol Sci 102(1):187−195.

C.1.5. Brief Descriptions of DIALOG Bibliographic Data Bases Searched

The National Technical Information Service (NTIS) database comprises summaries of U.S. government-sponsored research, development, and engineering, plus analyses prepared by federal agencies, their contractors, or grantees. It is the means through which unclassified, publicly available, unlimited distribution reports are made available for sale from 240 agencies. Additionally, some state and local government agencies contribute summaries of their reports to the database. NTIS also provides access to the results of government-sponsored research and development from countries outside the United States. Organizations that currently contribute to the NTIS database include but are not limited to the following: the Japan Ministry of International Trade and Industry (MITI); laboratories administered by the United Kingdom

Department of Industry; the German Federal Ministry of Research and Technology (BMFT); and the French National Center for Scientific Research (CNRS).

Pollution Abstracts provides access to environmental information that combines information on scientific research and government policies in a single resource. Topics of growing concern are extensively covered from the standpoints of atmosphere, emissions, mathematical models, effects on people and animals, and environmental action in response to global pollution issues. This database also contains material from conference proceedings and hard-to-find summarized documents along with information from primary journals in the field of pollution.

BIOSIS Previews® contains citations from Biological Abstracts® (BA) and Biological Abstracts/Reports, Reviews, and Meetings® (BA/RRM) (formerly BioResearch Index®), the major publications of BIOSIS®. These publications constitute the major English-language service providing comprehensive worldwide coverage of research in the biological and biomedical sciences. Biological Abstracts includes approximately 350,000 accounts of original research yearly from nearly 5,000 primary journal and monograph titles. BA/RRM includes an additional 200,000+ citations a year from meeting abstracts, reviews, books, book chapters, notes, letters, and selected reports.

IPA Toxicology provides focused toxicology information on all phases of the development and use of drugs and on professional pharmaceutical practice. The scope of the database ranges from the clinical and practical to the theoretical aspects of toxicology literature. A unique feature of abstracts reporting clinical studies is the inclusion of the study design, number of patients, dosage, dosage forms, and dosage schedule.

Medical Literature, Analysis, and Retrieval System Online (MEDLINE®), produced by the U.S. National Library of Medicine (NLM), is NLM's premier bibliographic database. It contains more than 15 million references to journal articles in life sciences with a concentration on biomedicine. The broad coverage of the database includes basic biomedical research and the clinical sciences since 1950, including nursing, dentistry, veterinary medicine, pharmacy, allied health, and pre-clinical sciences. MEDLINE® also covers life sciences that are vital to biomedical practitioners, researchers, and educators, including some aspects of biology, environmental science, marine biology, and plant and animal science, as well as biophysics and chemistry. MEDLINE® is indexed using NLM's controlled vocabulary, Medical Subject

Headings (MeSH®). Approximately 400,000 records are added per year, of which more than 76 percent are in English. MEDLINE® contains AIDSLINE, HealthSTAR, Toxline, In Process (formerly known as Pre-MEDLINE®), In Data Review, and POPLINE.

ToxFile covers the toxicological, pharmacological, biochemical, and physiological effects of drugs and other chemicals. Adverse drug reactions, chemically induced diseases, carcinogenesis, mutagenesis, teratogenesis, environmental pollution, waste disposal, radiation, and food contamination are typical areas of coverage. The databases Environmental Mutagen Information Center (EMIC), Developmental and Reproductive Toxicology (DART), and Toxic Substances Control Act Test Submissions (TSCATS) are included in ToxFile. It is not clearly stated whether the Chemical Carcinogenesis Research Information System (CCRIS), Hazardous Substances Data Bank (HSDB), or Genetic Toxicology Data Bank (GENE-TOX) are included in ToxFile. Consequently, a separate, on-line search was conducted to ensure that these databases were searched.

BIOSIS® Toxicology contains citations from BA and BA/RRM (formerly BioResearch Index®), the major publications of BIOSIS®, that focus on toxicology and related topics. Records are drawn from journal articles, conference papers, monographs and book chapters, notes, letters, and reports, as well as original research. U.S. patent records are also included.

CANCERLIT® is produced by the International Cancer Research DataBank Branch (ICRDB) of the U.S. National Cancer Institute. The database consists of bibliographic records referencing cancer research publications dating from 1963 to 2002. Most records contain abstracts, and all records contain citation information and additional descriptive fields such as document type and language. Beginning with the June 1983 CANCERLIT update, records from the MEDLINE® database dealing with cancer topics have been added to CANCERLIT.

The Registry of Toxic Effects of Chemical Substances (RTECS®) is a comprehensive database of basic toxicity information for over 150,000 chemical substances including prescription and non-prescription drugs, food additives, pesticides, fungicides, herbicides, solvents, diluents, chemical wastes, reaction products of chemical waste, and substances used in both industrial and household situations. Reports of the toxic effects of each compound are cited. In addition to toxic effects and general toxicology reviews, data on skin and/or eye irritation, mutation, reproductive consequences and tumorigenicity are provided. Federal standards and regulations, National Institute for Occupational Safety and Health (NIOSH)

recommended exposure limits and information on the activities of EPA, NIOSH, National Toxicology Program (NTP), and Occupational Safety and Health Administration (OSHA) regarding the substance are also included. The toxic effects are linked to literature citations from both published and unpublished governmental reports, and published articles from the scientific literature. The database corresponds to the print version of the RTECS®, formerly known as the Toxic Substances List, which was started in 1971. Originally prepared by the NIOSH, the RTECS® database is now produced and distributed by Symyx Technologies, Inc.

C.2. TOXICOKINETIC MODELING CODE (EMOND ET AL., 2005)

C.2.1. Human Standard Model

C.2.1.1. *Model Code*

PROGRAM: 'Three Compartment PBPK Model for TCDD in Human: Standard Model (Non-Gestation)'

```
!HUM_NON_GEST_ICF_F083109.csl
!*************************************************

INITIAL  !INITIALIZATION OF PARAMETERS

     !SIMULATION PARAMETERS ====
CONSTANT EXP_TIME_ON       =     0.          ! TIME AT WHICH EXPOSURE BEGINS
(HOUR)
CONSTANT EXP_TIME_OFF      =     6.132e5   ! TIME AT WHICH EXPOSURE ENDS
(HOUR)
CONSTANT DAY_CYCLE         =     24.0      ! NUMBER OF HOURS BETWEEN DOSES
(HOUR)
CONSTANT BCK_TIME_ON       =     6.132e5      ! TIME AT WHICH BACKGROUND
EXPOSURE BEGINS (HOUR)
CONSTANT BCK_TIME_OFF      =     6.132e5      ! TIME AT WHICH BACKGROUND
EXPOSURE ENDS (HOUR)

     !EXPOSURE DOSES
CONSTANT  MSTOTBCKGR       =     0.0    ! ORAL BACKGROUND EXPOSURE DOSE
(NG/KG)
CONSTANT  MSTOT            =     1.0E-7       ! ORAL EXPOSURE DOSE (NG/KG)
CONSTANT  DOSEIV           =     0.0            ! INJECTED DOSE (NG/KG)
CONSTANT  MW             =     322.0        ! MOLECULAR WEIGHT (G/MOL)
 MSTOT_NM = MSTOT/MW                        ! CONVERTS THE DOSE TO NMOL/KG
 MSTOT_NMBCKGR = MSTOTBCKGR/MW  !CONVERTS THE BACKGROUND DOSE TO NMOL/KG
  DOSEIV_NM = DOSEIV/MW                     ! CONVERTS THE INJECTED DOSE TO
NMOL/KG

     !INITIAL GUESS OF THE FREE CONCENTRATION IN THE LIGAND (COMPARTMENT
INDICATED BELOW) ====
CONSTANT CFLLI0        =    0.0                  ! LIVER  (NMOL/L)
```

```
1
2       !BINDING CAPACITY (AhR) FOR NON LINEAR BINDING (COMPARTMENT INDICATED
3   BELOW) ===
4   CONSTANT LIBMAX         =    0.35            ! LIVER  (NMOL/L)
5
6       ! PROTEIN AFFINITY CONSTANTS (1A2 OR AhR, COMPARTMENT INDICATED BELOW)
7   ===
8   CONSTANT KDLI           =       0.1             ! LIVER (AhR) (NMOL/L) WANG
9   ET AL.. 1997
10  CONSTANT KDLI2          =       40.0          ! LIVER (1A2) (NMOL/L) EMOND ET
11  AL. 2004
12
13      !EXCRETION AND ABSORPTION CONSTANTS
14  CONSTANT KST            =       0.01            ! GASTRIC RATE CONSTANT (HR-
15  1), EMOND ET AL., 2005
16  CONSTANT KABS           =       0.06         ! INTESTINAL ABSORPTION CONSTANT
17  (HR-1), EMOND ET AL. 2005
18
19      !ELIMINATION CONSTANTS
20  CONSTANT CLURI          =      4.17D-8       ! URINARY CLEARANCE (L/HR), EMOND
21  ET AL., 2005
22  CONSTANT KELV           =     1.1e-3           ! INTERSPECIES VARIABLE
23  ELIMINATION CONSTANT (1/HOUR)
24
25      !CONSTANT TO DIVIDE THE ABSORPTION INTO LYMPHATIC AND PORTAL FRACTIONS
26  CONSTANT A              =       0.7                   ! LYMPHATIC FRACTION,
27  WANG ET AL. (1997)
28
29     !PARTITION COEFFICIENTS
30  CONSTANT PF             =       1.0e2               ! ADIPOSE TISSUE/BLOOD,
31  WANG ET AL. 1997
32  CONSTANT PRE            =       1.5                 ! REST OF THE BODY/BLOOD,
33  WANG ET AL. 1997
34  CONSTANT PLI            =       6.0                   ! LIVER/BLOOD, WANG ET
35  AL. 1997
36
37      !PARAMETERS FOR INDUCTION OF CYP1A2
38  CONSTANT PAS_INDUC      =       1.0           ! INCLUDE INDUCTION? (1 = YES, 0
39  = NO)
40  CONSTANT CYP1A2_1OUTZ   =   1.6e3       ! DEGRADATION CONCENTRATION CONSTANT
41  OF 1A2 (NMOL/L)
42  CONSTANT CYP1A2_1A1     =       1.6e3       ! BASAL CONCENTRATION OF 1A1
43  (NMOL/L)
44  CONSTANT CYP1A2_1EC50   =       1.3e2     ! DISSOCIATION CONSTANT TCDD-CYP1A2
45  (NMOL/L)
46  CONSTANT CYP1A2_1A2     =       1.6e3       ! BASAL CONCENTRATION OF 1A2
47  (NMOL/L)
48  CONSTANT CYP1A2_1KOUT   =       0.1       ! FIRST ORDER RATE OF DEGRADATION
49  (H-1)
50  CONSTANT CYP1A2_1TAU    =       0.25       ! HOLDING TIME (H)
51  CONSTANT CYP1A2_1EMAX   =       9.3e3   ! MAXIMUM INDUCTION OVER BASAL EFFECT
52  (UNITLESS)
53  CONSTANT HILL           =       0.6      !HILL CONSTANT; COOPERATIVELY LIGAND
54  BINDING EFFECT CONSTANT (UNITLESS)
55      ! DIFFUSIONAL PERMEABILITY FRACTION
56  CONSTANT PAFF           =      0.12                  ! ADIPOSE (UNITLESS)
```

```
CONSTANT PAREF          =      0.03                 ! REST OF BODY (UNITLESS)
CONSTANT PALIF          =      0.35                   ! LIVER (UNITLESS)

     !TISSUE BLOOD FLOW EXPRESSED AS A FRACTION OF CARDIAC OUTPUT  =========
CONSTANT QFF            =       0.05      ! ADIPOSE TISSUE BLOOD FLOW FRACTION
(UNITLESS), KRISHNAN 2008
CONSTANT QLIF           =       0.26      ! LIVER (UNITLESS), KRISHNAN 2008

     !COMPARTMENT TISSUE BLOOD EXPRESSED AS A FRACTION OF THE TOTAL
COMPARTMENT VOLUME =========
CONSTANT WFB0           =       0.050    ! ADIPOSE TISSUE, WANG ET AL. 1997
CONSTANT WREB0       =       0.030    ! REST OF THE BODY, WANG ET AL. 1997
CONSTANT WLIB0          =       0.266    ! LIVER, WANG ET AL. 1997

     !EXPOSURE SCENARIO FOR UNIQUE OR REPETITIVE WEEKLY OR MONTHLY EXPOSURE
     !NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LACK      =       0.0          ! DELAY BEFORE EXPOSURE ENDS
(WEEK)
CONSTANT WEEK_PERIOD    =       168.0     ! NUMBER OF HOURS IN THE WEEK
(HOURS)
CONSTANT WEEK_FINISH    =       168.0      ! TIME EXPOSURE ENDS (HOURS)
    !NUMBER OF EXPOSURES PER MONTH
CONSTANT MONTH_LACK     =       0.0        ! DELAY BEFORE EXPOSURE BEGINS
(MONTH)

     !SET FOR BACKGROUND EXPOSURE===========
     !TIME CONSTANT FOR BACKGROUND EXPOSURE==========
CONSTANT Day_LACK_BG      =    0.0          ! DELAY BEFORE EXPOSURE BEGINS
(HOUR)
CONSTANT Day_PERIOD_BG    =    24.0       ! LENGTH OF EXPOSURE (HOUR)

     !TIME CONSTANT FOR WEEKLY EXPOSURE
CONSTANT WEEK_LACK_BG     =    0.0       ! DELAY BEFORE BACKGROUND EXPOSURE
BEGINS (WEEK)
CONSTANT WEEK_PERIOD_BG   =    168.0     !  NUMBER OF HOURS IN THE WEEK
(HOURS)
CONSTANT WEEK_FINISH_BG   =    168.0       ! TIME EXPOSURE ENDS (HOURS)

     ! CONSTANT USED IN CARDIAC OUTPUT EQUATION
CONSTANT QCC            =    15.36                 ! (L/KG-H),  EMOND ET AL.
2004

     ! COMPARTMENT LIPID EXPRESSED AS THE FRACTION OF TOTAL LIPID
     !Data from Emonds Thesis 2001
CONSTANT F_TOTLIP         =    0.8000              ! ADIPOSE TISSUE
(UNITLESS)
CONSTANT B_TOTLIP         =    0.0057             ! BLOOD (UNITLESS)
CONSTANT RE_TOTLIP        =    0.0190            ! REST OF THE BODY
(UNITLESS)
CONSTANT LI_TOTLIP        =    0.0670              ! LIVER (UNITLESS)
CONSTANT MEANLIPID        =    974.0

END  ! END OF THE INITIAL SECTION


DYNAMIC ! DYNAMIC SIMULATION SECTION
```

```
   !
ALGORITHM  IALG          =      2         ! GEAR METHOD
CINTERVAL  CINT          =      10.0        ! COMMUNICATION INTERVAL
MAXTERVAL  MAXT          =    1.0e+10     !MAXIMUM INTERVAL CALCULATION
MINTERVAL  MINT          =    1.0E-10     !MINIMUM INTERVAL CALCULATION
VARIABLE   T             =      0.0
CONSTANT   TIMELIMIT     =     1.752e5  !SIMULATION LIMIT TIME (HOUR)
CONSTANT      Y0           =       0.0      ! AGE (YEARS) AT BEGINNING OF
SIMULATION
CONSTANT   GROWON        =        1.0    ! INCLUDE BODY WEIGHT AND HEIGHT
GROWTH? (1 = YES, 0 = NO)
  CINTXY  = CINT
  PFUNC   = CINT

  DAY=T/24.0                                    ! TIME IN DAYS
  WEEK =T/168.0                                ! TIME IN WEEKS
  MONTH =T/730.0                              ! TIME IN MONTHS
  YEAR=Y0+T/8760.0                          ! TIME IN YEARS
  GYR =Y0 + growon*T/8760.0        ! TIME FOR USE IN GROWTH EQUATION (YEARS)

DERIVATIVE ! PORTION OF CODE THAT SOLVES DIFFERENTIAL EQUATIONS

      ! CHRONIC OR SUBCHRONIC EXPOSURE SCENARIO =======
      ! NUMBER OF EXPOSURES PER DAY
 DAY_LACK     = EXP_TIME_ON        ! DELAY BEFORE EXPOSURE BEGINS (HOURS)
 DAY_PERIOD   = DAY_CYCLE          ! EXPOSURE PERIOD (HOURS)
 DAY_FINISH   = CINTXY             ! LENGTH OF EXPOSURE (HOURS)
 MONTH_PERIOD = TIMELIMIT          ! EXPOSURE PERIOD (MONTHS)
 MONTH_FINISH = EXP_TIME_OFF       ! LENGTH OF EXPOSURE (MONTHS)


      ! NUMBER OF EXPOSURES PER DAY AND MONTH
 DAY_FINISH_BG   = CINTXY
 MONTH_LACK_BG   = BCK_TIME_ON    !DELAY BEFORE BACKGROUD EXPOSURE BEGINS
(MONTHS)
 MONTH_PERIOD_BG = TIMELIMIT       ! BACKGROUND EXPOSURE PERIOD (MONTHS)
 MONTH_FINISH_BG = BCK_TIME_OFF    ! LENGTH OF BACKGROUND EXPOSURE (MONTHS)

 B = 1.0-A ! FRACTION OF DIOXIN ABSORBED IN THE PORTAL FRACTION OF THE LIVER

      !HUMAN BODY WEIGHT GROWTH EQUATION========
       ! POLYNOMIAL REGRESSION EXPRESSION WRITTEN
!APRIL 10 2008, OPTIMIZED WITH DATA OF PELEKIS ET AL. 2001
! POLYNOMIAL REGRESSION EXPRESSION WRITTEN WITH
!HUH AND BOLCH 2003 FOR BMI CALCULATION

  ! BODY WEIGHT CALCULATION
  WT0 = (0.0006*GYR**3 - 0.0912*GYR**2 + 4.32*GYR + 3.652)

   ! BODY MASS INDEX CALCULATION
     BH =  -2D-5*GYR**4+4.2D-3*GYR**3.0-0.315*GYR**2.0+9.7465*GYR+72.098

   !HEIGHT EQUATION FORMULATED FOR USE FROM 0 TO 70 YEARS
     BHM= (BH/100.0)               !HUMAN HEIGHT IN METERS (BHM)
     HBMI= WT0/(BHM**2.0) ! HUMAN BODY MASS INDEX (BMI)

```

```
    ! ADIPOSE TISSUE FRACTION
    WT0GR= WT0*1.0e3    ! BODY WEIGHT IN GRAMS
    WF0= -6.36D-20*WT0GR**4.0 +1.12D-14*WT0GR**3.0 -5.8D-10*WT0GR**2.0 +1.2D-
5*WT0GR+5.91D-2

    ! LIVER,VOLUME,
    ! APPROACH BASED ON LUECKE (2007)
    WLI0= (3.59D-2 -(4.76D-7*WT0GR)+(8.50D-12*WT0GR**2.0)-(5.45D-
17*WT0GR**3.0))

 WRE0 = (0.91 -(WLIB0*WLI0+WFB0*WF0+WLI0+WF0))/(1.0+WREB0)
                                    !REST OF THE BODY FRACTION; UPDATED FOR
EPA ASSESSMENT
 QREF = 1.0-(QFF+QLIF)                !REST OF BODY BLOOD FLOW
 QTTQF = QFF+QREF+QLIF               ! SUM MUST EQUAL 1

   !COMPARTMENT VOLUME (L OR KG) =========
 WF  =  WF0  * WT0                    ! ADIPOSE
 WRE =  WRE0 * WT0                    ! REST OF THE BODY
 WLI =  WLI0 * WT0                    ! LIVER
 WB=0.075*WT0                          ! BLOOD

   !COMPARTMENT TISSUE BLOOD (L OR KG) =========
 WFB  =  WFB0  * WF                    ! ADIPOSE
 WREB =  WREB0 * WRE                   ! REST OF THE BODY
 WLIB =  WLIB0 * WLI                   ! LIVER
   !CARDIAC OUTPUT FOR THE GIVEN BODY WEIGHT
QC= QCC*(WT0**0.75)                    ! [L BLOOD/HOUR]

QF  = QFF*QC                           ! ADIPOSE TISSUE BLOOD FLOW RATE
[L/HR]
QLI = QLIF*QC                          ! LIVER TISSUE BLOOD FLOW RATE [L/HR]
QRE = QREF*QC                         !REST OF THE BODY BLOOD FLOW RATE [L/HR]

QTTQ = QF+QRE+QLI                  ! TOTAL FLOW RATE [L/HR]

   !PERMEABILITY ORGAN FLOW [L/HR]=======
PAF  = PAFF*QF                          ! ADIPOSE
PARE = PAREF*QRE                        ! REST OF THE BODY
PALI = PALIF*QLI                        ! LIVER TISSUE

   ! ABSORPTION SECTION
   ! INTRAVENOUS
 IV        =    DOSEIV_NM * WT0          !AMOUNT IN NMOL
 MSTTBCKGR =    MSTOT_NMBCKGR *WT0       !AMOUNT IN (NMOL)
 MSTT      =    MSTOT_NM * WT0           !AMOUNT IN NMOL

     !REPETITIVE ORAL BACKGROUND EXPOSURE SCENARIOS
DAY_EXPOSURE_BG   = PULSE(DAY_LACK_BG,DAY_PERIOD_BG,DAY_FINISH_BG)
WEEK_EXPOSURE_BG  = PULSE(WEEK_LACK_BG,WEEK_PERIOD_BG,WEEK_FINISH_BG)
MONTH_EXPOSURE_BG = PULSE(MONTH_LACK_BG,MONTH_PERIOD_BG,MONTH_FINISH_BG)

MSTTCH_BG = (DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG)*MSTTBCKGR
MSTTFR_BG = MSTTBCKGR/CINT

CYCLE_BG =DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG
```

```
1
2
3       ! CONDITIONAL ORAL EXPOSURE (BACKGROUND EXPOSURE)
4   IF (MSTTCH_BG.EQ.MSTTBCKGR) THEN
5       ABSMSTT_GB= MSTTFR_BG
6   ELSE
7       ABSMSTT_GB = 0.0
8   END IF
9
10
11      !REPETITIVE ORAL MAIN EXPOSURE SCENARIO
12  DAY_EXPOSURE   = PULSE(DAY_LACK,DAY_PERIOD,DAY_FINISH)
13  WEEK_EXPOSURE  = PULSE(WEEK_LACK,WEEK_PERIOD,WEEK_FINISH)
14  MONTH_EXPOSURE = PULSE(MONTH_LACK,MONTH_PERIOD,MONTH_FINISH)
15
16  MSTTCH = (DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE)*MSTT
17  CYCLE = DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE
18  MSTTFR=MSTT/CINT
19
20      !CONDITIONAL ORAL EXPOSURE
21  IF (MSTTCH.EQ.MSTT) THEN
22     ABSMSTT= MSTTFR
23  ELSE
24     ABSMSTT = 0.
25  END IF
26
27   CYCLETOT=INTEG(CYCLE,0.0)
28
29        ! MASS Balance CHANGE IN THE LUMEN
30  RMSTT= -(KST+KABS)*MST+ABSMSTT +ABSMSTT_GB ! RATE OF CHANGE (NMOL/H)
31   MST = INTEG(RMSTT,0.)                      !AMOUNT REMAINING IN GI TRACT
32  (NMOL)
33
34        ! ABSORPTION IN LYMPH CIRCULATION
35  LYRMLUM = KABS*MST*A
36   LYMLUM = INTEG(LYRMLUM,0.0)
37
38        ! ABSORPTION IN PORTAL CIRCULATION
39  LIRMLUM = KABS*MST*B
40    LIMLUM = INTEG(LIRMLUM,0.0)
41
42        ! PERCENT OF DOSE REMAINING IN THE GI TRACT
43  PRCT_remain_GIT  = 100.0*MST/(MSTT+1E-30)
44
45        !IV ABSORTPION SCENARIO ---------
46   IVR= IV/PFUNC ! RATE FOR IV INFUSION IN BLOOD
47   EXPIV= IVR * (1.0-STEP(PFUNC))
48   IVDOSE = integ(EXPIV,0.0)
49
50        !SYSTEMIC BLOOD COMPARTMENT
51        ! MODIFICATION OCT 8 2009
52  CB=(QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM)/(QC+CLURI) !
53   CA = CB                                  !CONCENTRATION (NMOL/L)
54
55      !CB=(QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM-RAURI)/QC !
56      ! CA = CB                             ! CONCENTRATION (NMOL/L)
```

```
1
2          !URINARY EXCRETION BY KIDNEY
3          ! MODIFICATION OCT 8 2009
4   RAURI = CLURI *CB
5     AURI = INTEG(RAURI,0.0)
6
7
8          !CONCENTRATION UNIT
9     PRCT_B = 100.0*CB/(MSTT+1E-30)          ! PERCENT OF DOSE
10    CBSNGKGLIADJ = CB*MW/(0.55*B_TOTLIP) !serum concentration in lipid adjust
11  (PG/G LIPID=PPT)
12         CBPPT = CBSNGKGLIADJ
13    CBNGKG = CB*MW
14
15  CBpptRH = CB*MW*10000/(0.55*MEANLIPID) !SERUM CONCENTRATION IN LIPID ADJUST
16  (PG/G LIPID=PPT)
17
18      AUC_CBSNGKGLIADJ=INTEG(CBSNGKGLIADJ,0.0)
19
20         !ADIPOSE TISSUE COMPARTMENT
21  RAFB= QF*(CA-CFB)-PAF*(CFB-CF/PF)         !(NMOL/HR)
22   AFB = INTEG(RAFB,0.0)                     !(NMOL)
23   CFB = AFB/WFB                            !(NMOL/KG)
24         !TISSUE SUBCOMPARTMENT
25  RAF = PAF*(CFB-CF/PF)                     !(NMOL/HR)
26   AF = INTEG(RAF,0.0)                      !(NMOL)
27   CF  = AF/WF                              !(NMOL/KG)
28
29         !POST SIMULATION UNIT CONVERSION
30  CFTOTAL = (AF + AFB)/(WF + WFB) ! TOTAL CONCENTRATION NMOL/ML
31  PRCT_F = 100.0*CFTOTAL/(MSTT+1E-30)
32  CFNGKG =CFTOTAL*MW
33
34         !REST OF THE BODY COMPARTMENT========
35  RAREB= QRE*(CA-CREB)-PARE*(CREB-CRE/PRE) !(NMOL/HR)
36   AREB = INTEG(RAREB,0.0)                  !(NMOL)
37   CREB = AREB/WREB                         !(NMOL/KG)
38         !TISSUE SUBCOMPARTMENT
39  RARE = PARE*(CREB-CRE/PRE)                !(NMOL/HR)
40   ARE = INTEG(RARE,0.0)                   !(NMOL)
41   CRE  = ARE/WRE                           !(NMOL/KG)
42
43         !POST SIMULATION UNIT CONVERSION
44  CRETOTAL = (ARE + AREB)/(WRE + WREB) ! TOTAL CONCENTRATION IN NMOL/ML
45  PRCT_RE = 100.0*CRETOTAL/(MSTT+1E-30) ! PERCENT OF DOSE
46
47         !LIVER COMPARTMENT
48         !TISSUE BLOOD SUBCOMPARTMENT
49  RALIB = QLI*(CA-CLIB)-PALI*(CLIB-CFLLIR)+LIRMLUM          !(NMOL/HR)
50    ALIB = INTEG(RALIB,0.0)                                  !(NMOL)
51   CLIB = ALIB/WLIB
52         !TISSUE SUBCOMPARTMENT
53   RALI =  PALI*(CLIB-CFLLIR)-REXCLI                        !(NMOL/HR)
54    ALI = INTEG(RALI,0.0)                 !(NMOL)
55    CLI  = ALI/WLI                  !(NMOL/KG)
56
```

```
1
2         !FREE TCDD IN LIVER
3         ! MODIFICATION OCTOBER 8 2009
4   CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLIR)) &
5           +((CYP1A2_1O3*CFLLIR/(KDLI2+CFLLIR)*PAS_INDUC)))-CFLLI,CFLLI0) !
6   CONCENTRATION OF FREE TCDD IN LIVER
7       CFLLIR=DIM(CFLLI,0.0)
8
9   !MODIFIED FROM:
10        !PARAMETER (LIVER_1RMN = 1.0E-30)
11        ! CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLIR &       !
12  +LIVER_1RMN))+((CYP1A2_1O3*CFLLIR/(KDLI2+CFLLIR &
13        !         +LIVER_1RMN)*PAS_INDUC)))-CFLLI,CFLLI0)
14        !    CFLLIR=DIM(CFLLI,0.0)
15
16
17  CBNDLI= LIBMAX*CFLLIR/(KDLI+CFLLIR) !CONC OF TCDD BOUDN TO AhR
18
19  !CBNDLI= LIBMAX*CFLLIR/(KDLI+CFLLIR+LIVER_1RMN) !CONC BIND
20
21        !POST SIMULATION UNIT CONVERSION
22  CLITOTAL = (ALI + ALIB)/(WLI + WLIB)       ! TOTAL CONCENTRATION IN NMOL/ML
23  PRCT_LI = 100.0*CLITOTAL/(MSTT+1.0E-30)
24  rec_occ_AHR= 100.0*CFLLIR/(KDLI+CFLLIR+1.0)  ! PERCENT  BOUND TO AhR
25  OCCUPANCY
26  PROT_occ_1A2= 100.0*CFLLIR/(KDLI2+CFLLIR)    ! PERCENT  BOUND TO 1A2
27  OCCUPANCY
28  CLINGKG= CLITOTAL*MW                        ![NG TCDD/KG]
29  CBNDLINGKG = CBNDLI*MW
30
31      !FRACTION INCREASE OF INDUCTION OF CYP1A2
32  fold_ind=CYP1A2_1OUT/CYP1A2_1A2
33  VARIATIONOFAC =(CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2
34
35      !VARIABLE ELIMINATION BASED ON THE CYP1A2
36  KBILE_LI_T = Kelv*VARIATIONOFAC!
37
38   REXCLI = KBILE_LI_T*CFLLIR*WLI ! DOSE-DEPENDENT RATE OF BILLIARY EXCRETION
39  OF DIOXIN
40      EXCLI = INTEG(REXCLI,0.0)  !TOTAL AMOUNT OF DIOXIN EXCRETED
41
42      !CHEMICAL IN CYP450 (1A2) COMPARTMENT
43      !PARAMETER FOR INDUCTION OF CYP1A2
44
45  CYP1A2_1KINP = CYP1A2_1KOUT*CYP1A2_1OUTZ ! BASAL RATE OF CYP1A2 PRODUCTION
46  SET EQUAL TO BASAL RATE OF DEGRDATION AT STEADY STATE
47
48      ! MODIFICATION OCTOBER 8 2009
49  CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1.0 + CYP1A2_1EMAX *(CBNDLI+1.0e-30)**HILL
50  &
51       /(CYP1A2_1EC50**HILL + (CBNDLI+1.0e-30)**HILL)) &
52        - CYP1A2_1KOUT*CYP1A2_1OUT, CYP1A2_1OUTZ) ! LEVELS OF CYP1A2
53  ! MODEIFIED FROM:
54  !PARAMETER (CYP1A2_1RMN = 1e-30)
55  !CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1 + CYP1A2_1EMAX *(CBNDLI &
56  !     +CYP1A2_1RMN)**HILL/(CYP1A2_1EC50 + (CBNDLI + CYP1A2_1RMN)**HILL) &
```

```
!     +CYP1A2_1RMN) - CYP1A2_1KOUT*CYP1A2_1&
!     OUT, CYP1A2_1OUTZ)

! EQUATIONS INCORPORATING DELAY OF CYP1A2 PRODUCTION (NOT USED IN
SIMULATIONS)
CYP1A2_1RO2 = (CYP1A2_1OUT - CYP1A2_1O2)/ CYP1A2_1TAU
    CYP1A2_1O2 =INTEG(CYP1A2_1RO2, CYP1A2_1A1)
 CYP1A2_1RO3 = (CYP1A2_1O2 - CYP1A2_1O3)/ CYP1A2_1TAU
    CYP1A2_1O3 =INTEG(CYP1A2_1RO3, CYP1A2_1A2)

     !CHECK MASS BALANCE
  BDOSE= LYMLUM+LIMLUM+IVDOSE
  BMASSE = EXCLI+AURI+AFB+AF+AREB+ARE+ALIB+ALI
      BDIFF = BDOSE-BMASSE
     ! BODY BURDEN IN TERMS OF CONCENTRATION (NG/KG)
  BBNGKG = (AFB+AF+AREB+ARE+ALIB+ALI)*MW/WT0       !

     !COMMAND END OF THE SIMULATION
TERMT (T.GE. TIMELIMIT, 'Time limit has been reached.')

END   ! END OF THE DERIVATIVE SECTION
END   ! END OF THE DYTNAMIC SECTION
END   ! END OF THE PROGRAM
```

C.2.1.2. *Input File*

```
% base file name = "TESTJULY2009.m"
%clear @variable
output @clear
prepare @clear year T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG  CBNDLINGKG CBNGKG
%output @all
% PARAMETERS FOR SIMULATION
CINT = 1 %0.5
EXP_TIME_ON  =   0.       % TIME AT WHICH EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF = 613200     %324120     % HOUR/YEAR !TIME AT WHICH EXPOSURE
ENDS (HOUR)
DAY_CYCLE    = 24         % NUMBER OF HOURS BETWEEN DOSES (HOUR)
BCK_TIME_ON  = 613200     %324120     % TIME AT WHICH BACKGROUND EXPOSURE
BEGINS (HOUR)
BCK_TIME_OFF = 613200     %324120     % TIME AT WHICH BACKGROUND EXPOSURE
ENDS (HOUR)
TIMELIMIT    = 613200     %324120       %324120     % SIMULATION TIME LIMIT
(HOUR)
MSTOTBCKGR   =   0.       % ORAL BACKGROUND EXPOSURE DOSE (UG/KG)

% oral dose oral dose oral dose
MSTOT        = 9.97339283634997E-07       % ORAL DAILY EXPOSURE DOSE (NG/KG)
DOSEIV       =   0          %NG/KG
% oral dose oral dose oral dose

MEANLIPID    = 730        %
PAS_INDUC= 1          % INDUCTION INCLUDED? (1=YES, 0=NO)
```

C.2.2. Human Gestational Model

C.2.2.1. *Model Code*

PROGRAM: 'Three Compartment PBPK Model for TCDD in Human (Gestation)'

```
! Parameters were change may 16, 2002
! Come from {8MAI_CHR_PRE-EXP_GD}
! Come from {12_Mouse_GD}file
!*****************************************
!{{IMPORTANT-IMPORTANT-IMPORTANT-IMPORTANT}}
! REDUCTION OF MOTHER AND FETUS COMPARTMENT
! 2M_R_TCDD_JULY2002 ////(JULY 18,2002)////
!TCDD_RED_4Species_2003_4        ////(APR  8 ,2003)////
!TCDD_RED_4Species_2003_9        ////(APR  17 ,2003)////
!TCDD_RED_4Species_2003_12        ////(APR  17 ,2003)////
!************************************************
!APRIL 18 2003
!TCDD_4C_4SP_2003        ////(APR  18 ,2003)////
! was ''Gest 4 species 1.csl''   but update July 2009

!GEST_HUM_0_45Y_4_ICF_afterKKfix_v3_humangestational.csl
!HUM_GESTATIONAL_ICF_F083109.csl
!HUM_GESTATIONAL_ICF_F100709.csl
!************************************************

 !Legend/Legend/Legend/Legend/Legend/Legend/Legend/Legend/
 !Legend for this PBPK model
 !Mating: control the tenure of exchange between fetus and
    !Mother and also control imitated tissue growth
    !Control: WTFE, WPLA0, QPLAF
    !(for rat, mouse, human, and monkey)
 !Control transfer from mother to fetus and fetus to mother by TRANSTIME_ON
    !SWITCH_trans = 0 NO TRANSFER
    !SWITCH_trans = 1 TRANSFER OCCURS
 ! These switches are also controlled by mating parameters

INITIAL  !

     !SIMULATION PARAMETERS
CONSTANT PARA_ZERO          = 1e-30
CONSTANT EXP_TIME_ON     = 0.0       !TIME AT WHICH EXPOSURE BEGINS (HOURS)
CONSTANT EXP_TIME_OFF    = 530.0      !TIME AT WHICH EXPOSURE ENDS (HOURS)
CONSTANT DAY_CYCLE       =  24.0     !NUMBER OF HOURS BETWEEN DOSES (HOURS)
CONSTANT BCK_TIME_ON     = 0.0       !TIME AT WHICH BACKGROUND EXPOSURE
BEGINS (HOURS)
CONSTANT BCK_TIME_OFF    = 0.0       !TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOURS)
CONSTANT TRANSTIME_ON    = 0.0       !CONTROL TRANSFER FROM MOTHER TO FETUS
AT 9 WEEKS OR 1512 HOURS OF GESTATION

     ! INTRAVENOUS SEQUENCY
CONSTANT IV_LACK         = 0.0
CONSTANT IV_PERIOD       = 0.0

     !PREGNANCY PARAMETER
```

```
CONSTANT MATTING         = 0.0       !BEGINNING OF MATING (HOUR)
CONSTANT PFETUS          = 4.0       !PARTITION COEFFICIENT
CONSTANT CLPLA_FET       = 1.0e-3    !CLEARANCE TRANSFER FOR MOTHER TO FETUS
(L/HR)

     !CONSTANT EXPOSURE CONTROL
     !ACUTE, SUBCHRONIC, CHRONIC EXPOSURE =====
     !OR BACKGROUND EXPOSURE (IN THIS CASE 3 TIMES A DAY)===
CONSTANT MSTOTBCKGR      = 0.0       ! ORAL BACKGROUND EXPOSURE DOSE (NG/KG)
CONSTANT MSTOT           = 0.0       ! ORAL EXPOSURE DOSE (NG/KG)

     !ORAL ABSORPTION
     ! MSTT= MSTOT/1000 *WT0 *1/322*1000 !AMOUNT IN NMOL
  MSTOT_NM = MSTOT/MW              !CONVERTS THE DOSE TO NMOL/KG

     !INTRAVENOUS ABSORPTION
CONSTANT  DOSEIV         = 0.0       ! INJECTED DOSE (NG/KG)
  DOSEIV_NM = DOSEIV/MW            ! CONVERTS THE INJECTED DOSE TO NMOL/KG
CONSTANT DOSEIVLATE = 0.0            !INJECTED DOSE LATE (UG/KG)
  DOSEIVNMlate = DOSEIVLATE/MW     !AMOUNT IN NMOL/G

     !INITIAL GUESS OF THE FREE CONCENTRATION IN THE LIGAND (COMPARTMENT
INDICATED BELOW)====
CONSTANT CFLLI0          =  0.0      !LIVER    (NMOL/L)
CONSTANT CFLPLA0         =  0.0      !PLACENTA (NMOL/L)

     !BINDING CAPACITY (AhR) FOR NON LINEAR BINDING (COMPARTMENT INDICATED
BELOW) (NMOL/L) ===
CONSTANT LIBMAX          = 0.35     ! LIVER  (NMOL/L)
CONSTANT PLABMAX         = 0.2      !TEMPORARY PARAMETER

     !PROTEIN AFFINITY CONSTANTS (1A2 OR AhR, COMPARTMENT INDICATED BELOW)
(NMOL/ML)===
CONSTANT KDLI            = 0.1      !LIVER (AhR) (NMOL/L), WANG ET AL. 1997
CONSTANT KDLI2           = 40.0       !LIVER (1A2) (NMOL/L), EMOND ET AL.
2004
CONSTANT KDPLA           = 0.1      !ASSUME IDENTICAL TO KDLI (AhR)

     !EXCRETION AND ABSORPTION CONSTANT
CONSTANT KST             = 0.01     ! GASTRIC RATE CONSTANT (HR-1), EMOND ET
AL. 2005
CONSTANT KABS            = 0.06     ! INTESTINAL ABSORPTION CONSTANT (HR-1),
EMOND ET AL. (2005)

     !INTERSPECIES ELIMINATION CONSTANT
     !TEST ELIMINATION VARIABLE, EMOND ET AL. 2005
CONSTANT KELV          =     1.1e-3 !4.0D-3          ! INTERSPECIES VARIABLE
ELIMINATION CONSTANT (1/HOUR)

     ! ELIMINATION CONSTANTS
CONSTANT CLURI           =  4.17e-8 ! URINARY CLEARANCE (L/HR), EMOND ET AL.
2005

     ! CONSTANT TO DIVIDE THE ABSORPTION INTO LYMPHATIC AND PORTAL FRACTIONS
CONSTANT A               = 0.7        ! LYMPHATIC FRACTION, WANG ET AL. 1997
```

```
     !PARTITION COEFFICIENTS
CONSTANT PF              = 1.0e2     ! ADIPOSE TISSUE/BLOOD, WANG ET AL. 1997
CONSTANT PRE             = 1.5      ! REST OF THE BODY/BLOOD, WANG ET AL.
1997
CONSTANT PLI             = 6.0       ! LIVER/BLOOD, WANG ET AL. 1997
CONSTANT PPLA            = 1.5      ! TEMPORARY PARAMETER NOT CONFIGURED,
WANG ET AL. 1997

    !PARAMETER FOR INDUCTION OF CYP 1A2, WANG ET AL. 1997
CONSTANT PAS_INDUC       = 1.0        ! INCLUDE INDUCTION? (1 = YES, 0 = NO)
CONSTANT CYP1A2_1OUTZ    = 1.6e3     ! DEGRADATION CONCENTRATION CONSTANT OF
1A2 (NMOL/L)
CONSTANT CYP1A2_1A1      = 1.6e3     ! BASAL CONCENTRATION OF 1A1 (NMOL/L)
CONSTANT CYP1A2_1EC50    = 1.3e2    ! DISSOCIATION CONSTANT TCDD-CYP1A2
(NMOL/L)
CONSTANT CYP1A2_1A2      = 1.6e3     !BASAL CONCENTRATION OF 1A2 (NMOL/ML)
CONSTANT CYP1A2_1KOUT    = 0.1      ! FIRST ORDER RATE OF DEGRADATION (H-1)
CONSTANT CYP1A2_1TAU     = 0.25     !HOLDING TIME (H)
CONSTANT CYP1A2_1EMAX    = 9.3e3     ! MAXIMUM INDUCTION OVER BASAL EFFECT
(UNITLESS)
CONSTANT HILL            = 0.6      !HILL CONSTANT; COOPERATIVELY LIGAND
BINDING EFFECT CONSTANT (UNITLESS)

   !DIFFUSIONAL PERMEABILITY FRACTION, WANG ET AL (1997)
CONSTANT PAFF            = 0.12     ! ADIPOSE (UNITLESS)
CONSTANT PAREF           = 0.03     ! REST OF THE BODY (UNITLESS)
CONSTANT PALIF           = 0.35     ! LIVER (UNITLESS)
CONSTANT PAPLAF          = 0.3      ! OPTIMIZED PARAMETER

!TISSUE BLOOD FLOW EXPRESSED AS A FRACTION OF CARDIAC OUTPUT, KRISHNAN 2007
CONSTANT QFF             = 0.05     ! ADIPOSE TISSUE BLOOD FLOW FRACTION
(UNITLESS), KRISHNAN 2008
CONSTANT QLIF            = 0.26     ! LIVER (UNITLESS), KRISHNAN 2008

!===FRACTION OF TISSUE BLOOD WEIGHT Wang et al . (1997)
CONSTANT WFB0            = 0.050    !ADIPOSE TISSUE, WANG ET AL. 1997
CONSTANT WREB0           = 0.030    !REST OF THE BODY, WANG ET AL. 1997
CONSTANT WLIB0           = 0.266    !LIVER, WANG ET AL. 1997
CONSTANT WPLAB0          = 0.500    !ASSUME HIGHLY VASCULARIZED

! EXPOSURE SCENARIO FOR UNIQUE OR REPETITIVE WEEKLY OR MONTHLY EXPOSURE
! NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LACK       = 0.0       !DELAY BEFORE EXPOSURE ENDS (WEEK)
CONSTANT WEEK_PERIOD     = 168.0      ! NUMBER OF HOURS IN THE WEEK (HOURS)
CONSTANT WEEK_FINISH     = 168.0      ! TIME EXPOSURE ENDS (HOURS)

! NUMBER OF EXPOSURES PER MONTH
CONSTANT MONTH_LACK      = 0.0       !DELAY BEFORE EXPOSURE BEGINS (MONTHS)

!======= CONSTANT FOR BACKGROUND EXPOSURE===========
CONSTANT Day_LACK_BG     = 0.0       ! DELAY BEFORE EXPOSURE BEGINS (HOURS)
CONSTANT Day_PERIOD_BG   = 24.0       !LENGTH OF EXPOSURE (HOURS)

! NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LACK_BG    = 0.0      !DELAY BEFORE BACKGROUD EXPOSURE BEGINS
(WEEK)
```

```
CONSTANT WEEK_PERIOD_BG  = 168.0      ! NUMBER OF HOURS IN THE WEEK (HOURS)
CONSTANT WEEK_FINISH_BG  = 168.0      !TIME EXPOSURE ENDS (HOURS)


! CONSTANT USED IN CARDIAC OUTPUT EQUATION
CONSTANT QCC            =  15.36    ![L/KG-H], EMOND ET AL. 2004

! COMPARTMENT LIPID EXPRESSED AS THE FRACTION OF TOTAL LIPID
!Data from Emonds Thesis 2001
CONSTANT F_TOTLIP         =    0.8000       ! ADIPOSE TISSUE (UNITLESS)
CONSTANT B_TOTLIP         =    0.0057       ! BLOOD (UNITLESS)
CONSTANT RE_TOTLIP        =    0.0190       ! REST OF THE BODY (UNITLESS)
CONSTANT LI_TOTLIP        =    0.0670       ! LIVER (UNITLESS)
CONSTANT PLA_TOTLIP       =    0.019       ! PLACENTA (UNITLESS)
CONSTANT FETUS_TOTLIP     =    0.019     ! FETUS (UNITLESS)

CONSTANT MEANLIPID        =    974

END  ! END OF THE INITIAL SECTION

DYNAMIC ! DYNAMIC SIMULATION SECTION

ALGORITHM  IALG          =           2        ! GEAR METHOD
CINTERVAL  CINT          =         0.1        ! COMMUNICATION INTERVAL
MAXTERVAL  MAXT          =       1.0e+10      ! MAXIMUM CALCULATION INTERVAL
MINTERVAL  MINT          =       1.0E-10      ! MINIMUM CALCULATION INTERVAL
VARIABLE   T             =         0.0
CONSTANT   TIMELIMIT     =         100        !SIMULATION LIMIT TIME (HOUR)
CONSTANT      Y0           =          0.0      ! AGE (YEARS) AT BEGINNING OF
SIMULATION
CONSTANT   GROWON        =         1.0       ! INCLUDE BODY WEIGHT AND HEIGHT
GROWTH? (1=YES, 0=NO)

 CINTXY  = CINT
 PFUNC   = CINT

   !TIME TRANSFORMATION
 DAY= T/24.0
 WEEK  =T/168.0
 YEAR=Y0+T/8760.0                              ! TIME IN YEARS
  GYR =Y0 + growon*T/8760.0                    ! TIME FOR USE IN GROWTH
EQUATION

DERIVATIVE ! PORTION OF CODE THAT SOLVES DIFFERENTIAL EQUATIONS

!====== CHRONIC OR SUBCHRONIC EXPOSURE SCENARIO =======
! NUMBER OF EXPOSURES PER DAY

 DAY_LACK         = EXP_TIME_ON    ! DELAY BEFORE EXPOSURE BEGINS (HOURS)
 DAY_PERIOD       = DAY_CYCLE      ! EXPOSURE PERIOD (HOURS)
 DAY_FINISH       = CINTXY         ! LENGTH OF EXPOSURE (HOURS)
 MONTH_PERIOD     = TIMELIMIT      ! EXPOSURE PERIOD (MONTHS)
 MONTH_FINISH     = EXP_TIME_OFF   ! LENGTH OF EXPOSURE (MONTHS)


! NUMBER OF EXPOSURES PER DAY AND MONTH
```

```
 DAY_FINISH_BG    = CINTXY
 MONTH_LACK_BG    = BCK_TIME_ON    !DELAY BEFORE BACKGROUND EXPOSURE BEGINS
(MONTHS)
 MONTH_PERIOD_BG  = TIMELIMIT      !BACKGROUND EXPOSURE PERIOD (MONTHS)
 MONTH_FINISH_BG  = BCK_TIME_OFF   !LENGTH OF BACKGROUND EXPOSURE (MONTHS)

! INTRAVENOUS LATE
 IV_FINISH = CINTXY
 B = 1-A ! FRACTION OF DIOXIN ABSORBED IN THE PORTAL FRACTION OF THE LIVER

! MOTHER BODY WEIGHT GROWTH EQUATION
! MODIFICATION TO ADAPT THIS MODEL AT HUMAN MODEL
! BECAUSE LINEAR DESCRIPTION IS NOT GOOD ENOUGH FOR MOTHER GROWTH
! MOTHER BODY WEIGHT GROWTH
! HUMAN BODY WEIGHT (0 TO 45 YEARS)
! POLYNOMIAL REGRESSION EXPRESSION WRITTEN
!APRIL 10 2008, OPTIMIZED WITH DATA OF PELEKIS ET AL. 2001
! POLYNOMIAL REGRESSION EXPRESSION WRITTEN WITH
!HUH AND BOLCH 2003 FOR BMI CALCULATION

! BODY WEIGHT CALCULATION.  UNIT IN KG FOR GESTATIONAL PORTION

     WT0 = (0.0006*GYR**3 - 0.0912*GYR**2 + 4.32*GYR + 3.652)

 !BODY MASS INDEX CALCULATION

     BH =  -2D-5*GYR**4+4.2D-3*GYR**3.0-0.315*GYR**2.0+9.7465*GYR+72.098
!HEIGHT EQUATION FORMULATED FOR USE FROM 0 TO 70 YEARS
     BHM= (BH/100.0)!HUMAN HEIGHT IN METER (BHM)
     HBMI= WT0/(BHM**2.0) ! HUMAN BODY MASS INDEX (BMI)


!MODIFICATION IN KG
RTESTGEST= T-MATTING ! STARTING TIME FOR FETAL GROWTH
TESTGEST=DIM(RTESTGEST,0.0)
! GROWTH OF FETAL TISSUE
GESTATTION_FE=((4d-15*TESTGEST**4 -3d-11*TESTGEST**3 +1d-7*TESTGEST**2 -8d-
5*TESTGEST +0.0608))
   WTFER= DIM(GESTATTION_FE,0.0) ! FETAL COMPARTMENT WEIGHT
 WTFE= WTFER

!////////////////////////////////////////////////////////////////////
! FAT GROWTH EXPRESSION LINEAR DURING PREGNANCY
! FROM O'FLAHERTY_1992
!////////////////////////////////////////////////////////////////////

WT0GR= WT0*1.0e3    ! MOTHER BODY WEIGHT IN G

WF0 =(-6.36D-20*WT0GR**4.0 +1.12D-14*WT0GR**3.0 &
           -5.8D-10*WT0GR**2.0+1.2D-5*WT0GR+5.91D-2) ! MOTHER FAT COMPARTMENT
GROWTH

!////////////////////////////////////////////////////////////////////
! WPLA PLACENTA GROWTH EXPRESSION, SINGLE EXPONENTIAL WITH OFFSET
! FROM O'FLAHERTY_1992  ! FOR EACH PUP
!////////////////////////////////////////////////////////////////////
```

```
!SAME EQUATION THEN THE FORST MODEL. BODY WEIGHT KEPT IN G
!A CORRECTION FOR THE BODY WEIGHT (WTO(KG)*1000 = WTOGR)

WPLA0N_HUMAN= (850*exp(-9.434*(exp(-5.23d-4*(TESTGEST)))))
 WPLA0R = WPLA0N_HUMAN/WT0GR
 WPLA0W = DIM(WPLA0R,0.0) ! PLACENTA WEIGHT
  WPLA0=WPLA0W

!////////////////////////////////////////////////////////////////////
! QPLA PLACENTA GROWTH EXPRESSION, DOUBLE EXPONENTIAL WITH OFFSET
! FROM O'FLAHERTY_1992
!////////////////////////////////////////////////////////////////////

QPLAF_HUMAN= SWITCH_trans*((1d-10*TESTGEST**3.0 -5D-7*TESTGEST**2.0
+0.0017*TESTGEST+1.1937)/QC)
  GEST_QPLAF=DIM(QPLAF_HUMAN,0.0) ! PLACENTA BLOOD FLOW RATE
  QPLAF =GEST_QPLAF

! LIVER,VOLUME  (HUMAN 0 TO 70 YEARS)
! APPROACH BASED ON LUECKE (2007)
 WLI0= (3.59D-2 -(4.76D-7*WT0GR)+(8.50D-12*WT0GR**2.0)-(5.45D-17*WT0GR**3.0))
! LIVER VOLUME IN GROWING HUMAN

! VARIABILITY OF REST OF THE BODY DEPENDS ON OTHER ORGAN
 WRE0 = (0.91-(WLIB0*WLI0+WFB0*WF0+ WPLAB0*WPLA0 + WLI0 + WF0 +
WPLA0))/(1+WREB0)
 QREF = 1-(QFF+QLIF+QPLAF)            !REST BODY BLOOD FLOW (ML/HR)
 QTTQF = QFF+QREF+QLIF+QPLAF          ! SUM MUST EQUAL 1

! COMPARTMENT TISSUE BLOOD VOLUME (L) =========
 WF  =  WF0  * WT0                    ! ADIPOSE TISSUE
 WRE =  WRE0 * WT0                    ! REST OF THE BODY
 WLI =  WLI0 * WT0                    ! LIVER
 WPLA=  WPLA0* WT0                    ! PLACENTA

! COMPARTMENT TISSUE VOLUME (L) =========
 WFB  =  WFB0  * WF                   ! ADIPOSE TISSUE
 WREB =  WREB0 * WRE                  ! REST OF THE BODY
 WLIB =  WLIB0 * WLI                  ! LIVER
 WPLAB = WPLAB0* WPLA                 ! PLACANTA

! TOTAL VOLUME OF COMPARTMENT (L)======
WFT =   WF                            ! TOTAL ADIPOSE TISSUE
WRET =  WRE                           ! TOTAL REST OF THE BODY
WLIT =  WLI                           ! TOTAL LIVER TISSUE
WPLAT=  WPLAB                         ! TOTAL PLACENTA TISSUE

! CONSTANT USED IN CARDIAC OUTPUT EQUATION

! UNIT CHANGED ON JULY 14 2009  (L/HR)
QC= QCC*(WT0)**0.75

QF  = QFF*QC                         ! ADIPOSE TISSUE BLOOD FLOW RATE (L/HR)
QLI = QLIF*QC                        ! LIVER TISSUE BLOOD FLOW RATE (L/HR)
QRE = QREF*QC                        !REST OF THE BODY BLOOD FLOW RATE (L/HR)
QPLA = QPLAF*QC                      !PLACENTA TISSUE BLOOD FLOW RATE (L/HR)
```

```
QTTQ = QF+QRE+QLI+QPLA     !TOTAL FLOW RATE (L/HR)

! ========= DIFFUSIONAL PERMEABILITY FACTORS FRACTION ORGAN FLOW =========
PAF  = PAFF*QF                        ! ADIPOSE TISSUE BLOOD FLOW RATE (L/HR)
PARE = PAREF*QRE                      ! REST OF THE BODY BLOOD FLOW RATE
(L/HR)
PALI = PALIF*QLI                      ! LIVER TISSUE BLOOD FLOW RATE (L/HR)
PAPLA = PAPLAF*QPLA                   ! PLACENTA TISSUE BLOOD FLOW RATE (L/HR)

!************************************
! ABSORPTION SECTION
! ORAL
! INTRAPERITONEAL
! SUBCUTANEOUS
! INTRAVENOUS
!************************************

!BACKGROUND EXPOSURE
!EXPOSURE FOR STEADY STATE CONSIDERATION
!REPETITIVE EXPOSURE SCENARIO

MSTOT_NMBCKGR = MSTOTBCKGR/322       !AMOUNT IN NMOL/G
MSTTBCKGR =MSTOT_NMBCKGR *WT0

DAY_EXPOSURE_BG   = PULSE(DAY_LACK_BG,DAY_PERIOD_BG,DAY_FINISH_BG)
WEEK_EXPOSURE_BG  = PULSE(WEEK_LACK_BG,WEEK_PERIOD_BG,WEEK_FINISH_BG)
MONTH_EXPOSURE_BG = PULSE(MONTH_LACK_BG,MONTH_PERIOD_BG,MONTH_FINISH_BG)

MSTTCH_BG = (DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG)*MSTTBCKGR
MSTTFR_BG = MSTTBCKGR/CINT

CYCLE_BG =DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG

! CONDITIONAL ORAL EXPOSURE (BACKGROUND EXPOSURE)

IF (MSTTCH_BG.EQ.MSTTBCKGR) THEN
    ABSMSTT_GB= MSTTFR_BG
ELSE
    ABSMSTT_GB = 0.0
END IF

CYCLETOTBG=INTEG(CYCLE_BG,0.0)

!************************************
!MULTIROUTE  EXPOSURE
!REPETITIVE EXPOSURE SCENARIO
!************************************
MSTT= MSTOT_NM * WT0                   !AMOUNT IN NMOL
DAY_EXPOSURE   = PULSE(DAY_LACK,DAY_PERIOD,DAY_FINISH)
WEEK_EXPOSURE  = PULSE(WEEK_LACK,WEEK_PERIOD,WEEK_FINISH)
MONTH_EXPOSURE = PULSE(MONTH_LACK,MONTH_PERIOD,MONTH_FINISH)

MSTTCH = (DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE)*MSTT

MSTTFR = MSTT/CINT

```

```
CYCLE = DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE

SUMEXPEVENT= INTEG (CYCLE,0.0) !NUMBER OF CYCLES GENERATED DURING SIMULATION

! CONDITIONAL ORAL EXPOSURE
IF (MSTTCH.EQ.MSTT) THEN
   ABSMSTT= MSTTFR
ELSE
   ABSMSTT = 0.0
END IF


 CYCLETOT=INTEG(CYCLE,0.0)

! MASS CHANGE IN THE LUMEN
 RMSTT= -(KST+KABS)*MST +ABSMSTT +ABSMSTT_GB ! RATE OF CHANGE (NMOL/H)
  MST = INTEG(RMSTT,0.0)                      !AMOUNT REMAINING IN DUODENUM
(NMOL)

! ABSORPTION IN LYMPH CIRCULATION
 LYRMLUM = KABS*MST*A
  LYMLUM = INTEG(LYRMLUM,0.0)

! ABSORPTION IN PORTAL CIRCULATION
 LIRMLUM = KABS*MST*B
  LIMLUM = INTEG(LIRMLUM,0.0)


    !IV ABSORPTION SCENARIO---------
 IV= DOSEIV_NM * WT0 !AMOUNT IN NMOL
 IVR= IV/PFUNC ! RATE FOR IV INFUSION IN BLOOD
 EXPIV= IVR * (1-STEP(PFUNC))
 IVDOSE = integ(EXPIV,0.0)

   !IV LATE IN THE CYCLE
   !MODIFICATION JANUARY 13 2004
 IV_RlateR = DOSEIVNMlate*WT0
 IV_EXPOSURE=PULSE(IV_LACK,IV_PERIOD,IV_FINISH)

 IV_lateT = IV_EXPOSURE *IV_RlateR
 IV_late = IV_lateT/CINT

SUMEXPEVENTIV= integ(IV_EXPOSURE,0.0) !NUMBER OF CYCLE GENERATE DURING
SIMULATION

      !SYSTEMIC BLOOD COMPARTMENT
      ! MODIFICATION OCT 8 2009
CB=(QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM+QPLA*CPLAB+IV_late)/(QC+CLURI) !
 CA = CB                                  ! CONCENTRATION (NMOL/L)

     !CB=(QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM+QPLA*CPLAB+IV_late-RAURI)/QC
!(NMOL/L)

    !URINARY EXCRETION BY KIDNEY
    ! MODIFICATION OCT 8 2009
RAURI = CLURI *CB
```

```
  AURI = INTEG(RAURI,0.0)

    !RAURI = CLURI * CRE
    !AURI = INTEG(RAURI,0.0)

    !UNIT CONVERSION POST SIMULATION
CONSTANT MW=322 !MOLECULAR WEIGHT (NG/NMOL)
CONSTANT SERBLO = 0.55
CONSTANT UNITCORR = 1.0e3

 CBSNGKGLIADJ = CB*MW/(0.55*B_TOTLIP) !NG SERUM LIPID ADJUSTED/KG
   AUCBS_NGKGLIADJ=integ(CBSNGKGLIADJ,0.)
CBNGKG= CB*MW   !NG/KG
PRCT_B = 100.0*CB/(MSTT+1E-30)        !PERCENT OF ORAL DOSE IN BLOOD
PRCT_BIV = 100.0*CB/(IV_RlateR+1E-30) ! PERCENT OF IV DOSE IN BLOOD

    !ADIPOSE COMPARMTENT
    !TISSUE BLOOD SUBCOMPARTMENT
RAFB= QF*(CA-CFB)-PAF*(CFB-CF/PF)     !(NMOL/H)
 AFB = INTEG(RAFB,0.0)                 !(NMOL)
 CFB = AFB/WFB                        !(NMOL/L)
    !TISSUE SUBCOMPARTMENT
RAF = PAF*(CFB-CF/PF)                 !(NMOL/H)
 AF = INTEG(RAF,0.0)                  !(NMOL)
 CF  = AF/WF                          !(NMOL/L)

    !UNIT CONVERSION POST SIMULATION
CFTOTAL= (AF + AFB)/(WF + WFB) ! TOTAL CONCENTRATION IN NMOL/ML
PRCT_F = 100.0*CFTOTAL/(MSTT+1E-30) !PERCENT OF ORAL DOSE IN FAT
PRCT_FIV = 100.0*CFTOTAL/(IV_RlateR+1E-30) !PERCENT OF IV DOSE IN FAT
CFNGKG=CFTOTAL*MW ! FAT CONCENTRATION IN NG/KG
AUCF_NGKGH=integ(CFNGKG,0.)


    !REST OF THE BODY COMPARTMENT
    !TISSUE BLOOD SUBCOMPARTMENT
RAREB= QRE *(CA-CREB)-PARE*(CREB-CRE/PRE)      !(NMOL/H)
 AREB = INTEG(RAREB,0.0)                        !(NMOL)
 CREB = AREB/WREB                              !(NMOL/L)
    !TISSUE SUBCOMPARTMENT
RARE = PARE*(CREB - CRE/PRE)                   !(NMOL/H)
 ARE = INTEG(RARE,0.0)                         !(NMOL)
 CRE  = ARE/WRE                                 !(NMOL/L)
ARETOT = ARE +AREB

    !POST SIMULATION UNIT CONVERSION
CRETOTAL= (ARE + AREB)/(WRE + WREB)            ! TOTAL CONCENTRATION (NMOL/L)
PRCT_RE = 100.0*CRETOTAL/(MSTT+1E-30) ! PERCENT OF ORAL DOSE IN REST OF BODY
PRCT_REIV = 100.0*CRETOTAL/(IV_RlateR+1E-30)   ![ PERCENT OF IV DOSE IN REST
OF BODY
CRENGKG=CRETOTAL*MW                            ! REST OF THE BODY
CONCENTRATION (NG/KG)


    !LIVER COMPARTMENT
    !TISSUE BLOOD SUBCOMPARTMENT
```

```
 RALIB = QLI*(CA-CLIB)-PALI*(CLIB-CFLLIR)+LIRMLUM ! (NMOL/HR)
  ALIB = INTEG(RALIB,0.0)                          !(NMOL)
 CLIB = ALIB/WLIB                                 !(NMOL/L)
    !TISSUE SUBCOMPARMTENT
 RALI = PALI*(CLIB - CFLLIR)-REXCLI               ! (NMOL/HR)
  ALI = INTEG(RALI,0.0)                                !(NMOL)
 CLI  = ALI/WLI                                   !(NMOL/L)

    !FREE TCDD CONCENTRATION IN LIVER
      ! MODIFICATION OCTOBER 8 2009
 CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLIR)) &
        +((CYP1A2_1O3*CFLLIR/(KDLI2+CFLLIR)*PAS_INDUC)))-CFLLI,CFLLI0)
    CFLLIR=DIM(CFLLI,0.0) ! FREE TCDD CONCENTRATION IN LIVER
!MODIFIED FROM:
!PARAMETER (LIVER_1RMN = 1.0E-30)
! CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLIR &
!+LIVER_1RMN))+((CYP1A2_1O3*CFLLIR/(KDLI2 + CFLLIR &
!+LIVER_1RMN)*PAS_INDUC)))-CFLLI,CFLLI0)
!CFLLIR=DIM(CFLLI,0.0)

! MODIFICATION OCTOBER 8 2009
CBNDLI= LIBMAX*CFLLIR/(KDLI+CFLLIR) !BOUND CONCENTRATION (NMOL/L)

    !POST SIMULATION UNIT CONVERSION
CLITOTAL= (ALI + ALIB)/(WLI + WLIB) ! TOTAL CONCENTRATION (NMOL/L)
PRCT_LI = 100.0*CLITOTAL/(MSTT+1E-30) ! PERCENT OF ORAL DOSE IN LIVER
PRCT_LIIV = 100.0*CLITOTAL/(IV_RlateR+1E-30) ! PERCENT OF IV DOSE IN LIVER
Rec_occ= CFLLIR/(KDLI+CFLLIR)
CLINGKG=CLITOTAL*MW ! LIVER CONCENTRATION IN NG/KG
  AUCLI_NGKGH=integ(CLINGKG,0.0)
CBNDLINGKG = CBNDLI*MW ! BOUND CONCENTRATION IN NG/KG
  AUCBNDLI_NGKGH =INTEG(CBNDLINGKG,0.0)

    !FRACTION INCREASE OF INDUCTION OF CYP1A2
fold_ind=CYP1A2_1OUT/CYP1A2_1A2
VARIATIONOFAC =(CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2

!VARIABLE ELIMINATION BASED ON THE CYP1A2
! MODIFICATION OCTOBER 8 2009
KBILE_LI_T = Kelv*VARIATIONOFAC! ! DOSE-DEPENDENT EXCRETION RATE CONSTANT

 REXCLI = KBILE_LI_T*CFLLIR*WLI ! DOSE-DEPENDENT BILLIARY EXCRETION RATE
    EXCLI = INTEG(REXCLI,0.0)

!KBILE_LI_T =((CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2)*Kelv !


!CHEMICAL IN CYP450 (1A2) COMPARTMENT

CYP1A2_1KINP = CYP1A2_1KOUT* CYP1A2_1OUTZ ! BASAL PRODCUTION RATE OF CYP1A2
SET EQUAL TO BASAL DEGREDATION RATE

    ! MODIFICATION OCTOBER 8 2009
CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1.0 + CYP1A2_1EMAX *(CBNDLI+1.0e-30)**HILL
&
     /(CYP1A2_1EC50**HILL + (CBNDLI+1.0e-30)**HILL)) &
```

```
      - CYP1A2_1KOUT*CYP1A2_1OUT, CYP1A2_1OUTZ)
!MODIFIED FROM:
!PARAMETER (CYP1A2_1RMN = 1E-30)
!CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1 + CYP1A2_1EMAX *(CBND&
!LI +CYP1A2_1RMN)**HILL/(CYP1A2_1EC50 + (CBNDLI + CYP1A2_1&
!RMN)**HILL) +CYP1A2_1RMN) - CYP1A2_1KOUT*CYP1A2_1&
!OUT, CYP1A2_1OUTZ)

! EQUATIONS INCORPORATING DELAY OF CYP1A2 PRODUCTION (NOT USED IN
SIMULATIONS)
CYP1A2_1RO2 = (CYP1A2_1OUT - CYP1A2_1O2)/ CYP1A2_1TAU
  CYP1A2_1O2 =INTEG(CYP1A2_1RO2, CYP1A2_1A1)

CYP1A2_1RO3 = (CYP1A2_1O2 - CYP1A2_1O3)/ CYP1A2_1TAU
  CYP1A2_1O3 =INTEG(CYP1A2_1RO3, CYP1A2_1A2)

    !PLACENTA COMPARTMENT
    !TISSUE BLOOD SUBCOMPARTMENT
RAPLAB= QPLA*(CA - CPLAB)-PAPLA*(CPLAB -CFLPLAR)    ! NMOL/HR)
 APLAB = INTEG(RAPLAB,0.0)                           ! (NMOL)
 CPLAB = APLAB/(WPLAB+1E-30)                        ! (NMOL/ML)
    !TISSUE SUBCOMPARTMENT
RAPLA = PAPLA*(CPLAB-CFLPLAR)-RAMPF + RAFPM         ! (NMOL/HR)
 APLA = INTEG(RAPLA,0.0)                             ! (NMOL)
 CPLA  = APLA/(WPLA+1e-30)                          ! (NMOL/ML)

    ! NEW EQUATION AUGUST 28  2009
PARAMETER (PARA_ZERO = 1.0E-30)
CFLPLA= IMPLC(CPLA-(CFLPLAR*PPLA +(PLABMAX*CFLPLAR/(KDPLA&
    +CFLPLAR+PARA_ZERO)))-CFLPLA,CFLPLA0)
CFLPLAR=DIM(CFLPLA,0.0)

    !POST SIMULATION UNIT CONVERSION
CPLATOTAL = ((APLAB+APLA)/(WPLAB+WPLA))
PRCT_PLA = (CPLATOTAL/(MSTT+1E-30))*100
PRCT_PLAIV = (CPLATOTAL/(IV_RlateR+1E-30))*100

    !FETUS COMPARTMENT
RAFETUS= RAMPF-RAFPM
 AFETUS=INTEG(RAFETUS,0.0)
CFETUS=AFETUS/(WTFE+1.0e-30)
CFETOTAL= CFETUS
CFETUS_v = CFETUS/PFETUS

    !POST SIMULATION UNIT CONVERSION
 CFETUSNGKG = CFETUS*MW                    !(NG/KG)
 PRCT_FE = 100.0*CFETOTAL/(MSTT+1E-30)
 PRCT_FEIV = 100.0*CFETOTAL/(IV_RlateR+1E-30)

    !TRANSFER OF DIOXIN FROM PLACENTA TO FETUS
    !FETAL EXPOSURE ONLY DURING EXPOSURE

IF (T.LT.TRANSTIME_ON) THEN
 SWITCH_trans = 0.0
ELSE
 SWITCH_trans = 1
```

```
END IF

    !TRANSFER OF DIOXIN FROM PLACENTA TO FETUS
    ! MODIFICATION 26 SEPTEMBER 2003

RAMPF = (CLPLA_FET*CPLA)*SWITCH_trans
  AMPF=INTEG(RAMPF,0.0)

    !TRANSFER OF DIOXIN FROM FETUS TO PLACENTA
RAFPM = (CLPLA_FET*CFETUS_v)*SWITCH_trans!
 AFPM = INTEG(RAFPM,0.0)

    !CHECK MASS BALANCE ----------
BDOSE= IVDOSE +LYMLUM+LIMLUM
BMASSE = EXCLI+AURI+AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB+AFETUS !
BDIFF = BDOSE-BMASSE

    !BODY BURDEN (NMOL)
BODY_BURDEN = AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB

    !BODY BURDEN CONCENTRATION (NG/KG)
 BBNGKG =(AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB)*MW/WT0

! END SIMULATION COMMAND

TERMT (T.GE. TimeLimit, 'Time limit has been reached.')

END   ! END OF THE DERIVATIVE SECTION
END   ! END OF THE DYNAMIC SECTION
END   ! END OF THE PROGRAM
```

C.2.2.2. *Input File*

```
output @clear
prepare @clear T  year CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG  CBNDLINGKG CBNGKG

CINT = 1   %168 %100              %INTEGRATION TIME
   %EXPOSURE SCENARIO
EXP_TIME_ON       = 0          % TIME AT WHICH EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF      = 401190     %TIME AT WHICH EXPOSURE ENDS (HOUR)
DAY_CYCLE         = 24        %NUMBER OF HOURS BETWEEN DOSES (HOUR)
BCK_TIME_ON       = 401190     %TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
BCK_TIME_OFF      = 401190     %TIME AT WHICH BACKGROUND EXPOSURE ENDS (HOUR)
IV_LACK           = 401190
IV_PERIOD         = 401190
    %GESTATION CONTROL
MATTING           = 393120     % BEGINNING OF MATING (HOUR) AT 45 YEARS OLD
TIMELIMIT         = 399840     %SIMULATION TIME LIMIT (HOUR)
TRANSTIME_ON      = 394632     % TRANSFER FROM MOTHER TO FETUS AT 1512 HOURS
GESTATION
    %EXPOSURE DOSE
MSTOT             = 9.97339283634997E-07       % NG OF TCDD PER KG OF BW
MSTOTBCKGR        = 0.   %0.1      % ORAL BACKGROUND EXPOSURE DOSE (NG/KG)
DOSEIV            = 0.   %10
```

```
DOSEIVLATE        = 0.    %10

     % TRANFER MOTHER TO FETUS CLEARANCE
CLPLA_FET         = 0.001 % MOTHER TO FETUS TRANFER CLEARANCE (L/HR)
```

C.2.3. Rat Standard Model

C.2.3.1. *Model Code*

PROGRAM: 'Three Compartment PBPK Model in Rat: Standard Model (Non-Gestation)'

```
!Rat_Dioxin_3C June09_2clean_icf_afterKKfix_v3_ratnongest.csl
!RAT_NON_GEST_ICF_F083109.CSL
!RAT_NON_GEST_ICF_F100609.CSL
 !*************************************************

INITIAL  ! INITIALIZATION OF PARAMETERS

     !SIMULATION PARAMETERS
CONSTANT PARA_ZERO       =      1d-30
CONSTANT EXP_TIME_ON     =      0.0           ! TIME AT WHICH EXPOSURE BEGINS
(HOURS)
CONSTANT EXP_TIME_OFF    =     900.0           ! TIME AT WHICH EXPOSURE ENDS
(HOURS)
CONSTANT DAY_CYCLE       =     900.0            ! NUMBER OF HOURS BETWEEN
DOSES (HOURS)
CONSTANT BCK_TIME_ON     =      0.0           ! TIME AT WHICH BACKGROUND
EXPOSURE BEGINS (HOURS)
CONSTANT BCK_TIME_OFF    =      0.0           ! TIME AT WHICH BACKGROUND
EXPOSURE ENDS (HOURS)

CONSTANT MW=322 !MOLECULAR WEIGHT (NG/NMOL)
CONSTANT SERBLO = 0.55
CONSTANT UNITCORR = 1000


     !EXPOSURE DOSES
CONSTANT MSTOTBCKGR      =      0.0           !ORAL BACKGROUND EXPOSURE DOSE
(UG/KG)
CONSTANT MSTOT           =      10       !ORAL EXPOSURE DOSE (UG/KG)
CONSTANT MSTOTsc         =      0.0           !SUBCUTANEOUS EXPOSURE DOSE
(UG/KG)
CONSTANT DOSEIV          =      0.0           ! INJECTED DOSE (UG/KG)

     !ORAL DOSE
  MSTOT_NM               =   MSTOT/MW       !AMOUNT IN NMOL/G
  MSTOT_NMBCKGR          =   MSTOTBCKGR/MW  !AMOUNT IN NMOL/G

     !INTRAVENOUS DOSE
  DOSEIV_NM              =   DOSEIV/MW      !AMOUNT IN NMOL/G

     !INITIAL GUESS OF THE FREE CONCENTRATION IN THE LIGAND (COMPARTMENT
INDICATED BELOW)====
CONSTANT CFLLI0          =     0.0            !LIVER (NMOL/ML)
```

```
     !BINDING CAPACITY (AhR) FOR NON LINEAR BINDING (COMPARTMENT INDICATED
BELOW) (NMOL/ML) ===
CONSTANT LIBMAX          =    3.5e-4          ! LIVER (NMOL/ML), WANG ET AL.
1997

     ! PROTEIN AFFINITY CONSTANTS (1A2 OR AhR, COMPARTMENT INDICATED BELOW)
(NMOL/ML)===
CONSTANT KDLI            =    1.0e-4          ! LIVER (AhR) (NMOL/ML), WANG
ET AL. 1997
CONSTANT KDLI2           =    4.0e-2          !LIVER (1A2) (NMOL/ML), EMOND
ET AL. 2004

     !EXCRETION AND ABSORPTION CONSTANT [RAT]
CONSTANT KST             =    0.36            ! GASTRIC RATE CONSTANT (HR-1),
WANG ET AL. (1997)
CONSTANT KABS            =    0.48            !INTESTINAL ABSORPTION CONSTANT
(HR-1), WANG ET AL. 1997

     !URINARY ELIMINATION CLEARANCE (ML/HR)
CONSTANT CLURI           =     0.01           !URINARY CLEARANCE (ML/HR),
EMOND ET AL. 2004

     !INTERSPECIES VARIABLE ELIMINATION
CONSTANT KELV            =     0.15           ! INTERSPECIES VARIABLE
ELIMINATION CONSTANT (1/HOUR) (OPTIMIZED), EMOND ET AL. 2004

     ! CONSTANT TO DIVIDE THE ABSORPTION INTO LYMPHATIC AND PORTAL FRACTIONS
CONSTANT A               =     0.7            ! LYMPHATIC FRACTION, WANG ET
AL. 1997

     !PARTITION COEFFICIENTS
CONSTANT PF              =     100            ! ADIPOSE TISSUE/BLOOD, WANG ET
AL. 1997
CONSTANT PRE             =     1.5            ! REST OF THE BODY/BLOOD, WANG
ET AL. 1997
CONSTANT PLI             =     6.0              ! LIVER/BLOOD, WANG ET AL.
1997

     !PARAMETER FOR INDUCTION OF CYP 1A2 [MOUSE] ===
CONSTANT PAS_INDUC       =     1.0            ! INCLUDE INDUCTION? (1 = YES,
0 = NO)
CONSTANT CYP1A2_1OUTZ    =     1.6            ! DEGRADATION CONCENTRATION
CONSTANT OF 1A2 (NMOL/ML), WANG ET AL. 1997
CONSTANT CYP1A2_1A1      =     1.6            ! BASAL CONCENTRATION OF 1A1
(NMOL/ML), WANG ET AL. 1997
CONSTANT CYP1A2_1EC50    =     0.13           ! DISSOCIATION CONSTANT TCDD-
CYP1A2 (NMOL/ML) , WANG ET AL. 1997
CONSTANT CYP1A2_1A2      =     1.6            ! BASAL CONCENTRATION OF 1A2
(NMOL/ML) Wang et al (1997)
CONSTANT CYP1A2_1KOUT    =     0.1            ! FIRST ORDER RATE OF
DEGRADATION (H-1), WANG ET AL. 1997
CONSTANT CYP1A2_1TAU     =     0.25           ! HOLDING TIME (H), WANG ET AL.
1997
CONSTANT CYP1A2_1EMAX    =     600            ! MAXIMUM INDUCTION OVER BASAL
EFFECT (UNITLESS), WANG ET AL. 1997
```

```
CONSTANT HILL            =     0.6      !HILL CONSTANT; COOPERATIVELY LIGAND
BINDING EFFECT CONSTANT (UNITLESS)

   !TISSUE BLOOD FLOW EXPRESSED AS A FRACTION OF CARDIAC OUTPUT
CONSTANT QFF  = 0.069                          ! ADIPOSE TISSUE BLOOD FLOW
FRACTION (UNITLESS), WANG ET AL. 1997
CONSTANT QLIF = 0.183                          ! LIVER (UNITLESS), WANG ET AL.
1997

     !DIFFUSIONAL PERMEABILITY FRACTION
CONSTANT PAFF            = 0.0910              ! ADIPOSE (UNITLESS), WANG ET
AL. 1997
CONSTANT PAREF           = 0.0298              ! REST OF THE BODY (UNITLESS),
WANG ET AL. 1997
CONSTANT PALIF           = 0.35                ! LIVER (UNITLESS), WANG ET AL.
1997

     !FRACTION OF TISSUE VOLUME (UNITLESS)
CONSTANT WLI0            =  0.0360             ! LIVER, WANG ET AL. 1997
CONSTANT WF0             =  0.069              ! BLOOD, WANG ET AL. 1997

     !COMPARTMENT TISSUE BLOOD EXPRESSED AS A FRACTION OF THE TOTAL
COMPARTMENT VOLUME =========
CONSTANT WFB0            =  0.050              ! ADIPOSE TISSUE, WANG ET AL.
1997
CONSTANT WREB0           =  0.030              ! REST OF THE BODY, WANG ET AL.
1997
CONSTANT WLIB0           =  0.266              ! LIVER , WANG ET AL. 1997

     !EXPOSURE SCENARIO FOR UNIQUE OR REPETITIVE WEEKLY OR MONTHLY EXPOSURE
     ! NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LACK       = 0.0                  ! DELAY BEFORE EXPOSURE ENDS
(WEEK)
CONSTANT WEEK_PERIOD     = 168.0                ! NUMBER OF HOURS IN THE WEEK
(HOURS)
CONSTANT WEEK_FINISH     = 168.0                ! TIME EXPOSURE ENDS (HOURS)

     !NUMBER OF EXPOSURES PER MONTH
CONSTANT MONTH_LACK      = 0.0                  ! DELAY BEFORE EXPOSURE BEGINS
(MONTH)

     !SET FOR BACKGROUND EXPOSURE===========
     !CONSTANT FOR BACKGROUND EXPOSURE===========
CONSTANT Day_LACK_BG     = 0.0                  ! DELAY BEFORE EXPOSURE BEGINS
(HOURS)
CONSTANT Day_PERIOD_BG   = 24.0                 ! LENGTH OF EXPOSURE (HOURS)

     !NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LACK_BG    = 0.0                 ! DELAY BEFORE BACKGROUND
EXPOSURE (WEEK)
CONSTANT WEEK_PERIOD_BG  = 168.0                !NUMBER OF HOURS IN THE WEEK
(HOURS)
CONSTANT WEEK_FINISH_BG  = 168.0                ! TIME EXPOSURE ENDS (HOURS)

     !GROWTH CONSTANT FOR RAT
     !CONSTANT FOR MOTHER BODY WEIGHT GROWTH ======
```

```
CONSTANT BW_T0 = 250.0                          !CHANGED FOR SIMULATION

     ! CONSTANT USED IN CARDIAC OUTPUT EQUATION
CONSTANT QCCAR =311.4                          !CONSTANT (ML/MIN/KG), WANG ET
AL.

     ! COMPARTMENT LIPID EXPRESSED AS THE FRACTION OF TOTAL LIPID
CONSTANT F_TOTLIP        = 0.855               !ADIPOSE TISSUE (UNITLESS)
CONSTANT B_TOTLIP        = 0.0033              !BLOOD (UNITLESS)
CONSTANT RE_TOTLIP       = 0.019               !REST OF THE BODY (UNITLESS)
CONSTANT LI_TOTLIP       = 0.06                !LIVER (UNITLESS)

END      !END OF THE INITIAL SECTION

DYNAMIC  !DYNAMIC SIMULATION SECTION

ALGORITHM  IALG          =           2         ! GEAR METHOD
CINTERVAL  CINT          =         0.1         ! COMMUNICATION INTERVAL
MAXTERVAL  MAXT          =       1.0e+10       ! MAXIMUM CALCULATION INTERVAL
MINTERVAL  MINT          =       1.0E-10       ! MINIMUM CALCULATION INTERVAL
VARIABLE   T             =         0.0
CONSTANT   TIMELIMIT     =         900.0         !SIMULATION TIME LIMIT
(HOURS)
 CINTXY  = CINT
 PFUNC   = CINT

         !TIME CONVERSION
  DAY=T/24.0                                     ! TIME IN DAYS
  WEEK =T/168.0                                  ! TIME IN WEEKS
  MONTH =T/730.0                                 ! TIME IN MONTHS
  YEAR=T/8760.0                                  ! TIME IN YEARS


DERIVATIVE ! PORTION OF CODE THAT SOLVES DIFFERENTIAL EQUATIONS

        !CHRONIC OR SUBCHRONIC EXPOSURE SCENARIO =======
        !NUMBER OF EXPOSURES PER DAY
 DAY_LACK     = EXP_TIME_ON                  ! DELAY BEFORE EXPOSURE BEGINS
(HOURS)
 DAY_PERIOD   = DAY_CYCLE                    ! EXPOSURE PERIOD (HOURS)
 DAY_FINISH   = CINTXY                       ! LENGTH OF EXPOSURE (HOURS)
 MONTH_PERIOD = TIMELIMIT                    ! EXPOSURE PERIOD (MONTHS)
 MONTH_FINISH = EXP_TIME_OFF                 ! LENGTH OF EXPOSURE (MONTHS)

        !NUMBER OF EXPOSURES PER DAY AND MONTH
 DAY_FINISH_BG   = CINTXY                    ! LENGTH OF EXPOSURE (HOURS)
 MONTH_LACK_BG   = BCK_TIME_ON               ! DELAY BEFORE BACKGROUND
EXPOSURE BEGINS (MONTHS)
 MONTH_PERIOD_BG = TIMELIMIT                 ! BACKGROUND EXPOSURE PERIOD
(MONTHS)
 MONTH_FINISH_BG = BCK_TIME_OFF              ! LENGTH OF BACKGROUND EXPOSURE
(MONTHS)


  B = 1-A                                   ! FRACTION OF DIOXIN ABSORBED IN
THE PORTAL FRACTION OF THE LIVER
```

```
1
2           ! BODY WEIGHT GROWTH EQUATION========
3    PARAMETER (BW_RMN = 1.0E-30)
4    WT0= (BW_T0 *(1.0+(0.41*T)/(1402.5+T+BW_RMN)))
5
6           !VARIABILITY OF REST OF THE BODY DEPEND OTHERS ORGAN
7    WRE0 = (0.91 - (WLIB0*WLI0 + WFB0*WF0 + WLI0 + WF0))/(1.0+WREB0) !REST OF
8   THE BODY FRACTION; UPDATED FOR EPA ASSESSMENT
9    QREF = 1.0-(QFF+QLIF)                          !REST OF BODY BLOOD FLOW
10   QTTQF = QFF+QREF+QLIF                        ! SUM MUST EQUAL 1
11
12          !COMPARTMENT VOLUME (G) =========
13   WF  =  WF0  * WT0                            ! ADIPOSE
14   WRE =  WRE0 * WT0                            ! REST OF THE BODY
15   WLI =  WLI0 * WT0                            ! LIVER
16
17          !COMPARTMENT TISSUE BLOOD VOLUME (G) =========
18   WFB  =  WFB0  * WF                           ! ADIPOSE
19   WREB =  WREB0 * WRE                          ! REST OF THE BODY
20   WLIB =  WLIB0 * WLI                          ! LIVER
21
22          !CARDIAC OUTPUT FOR THE GIVEN BODY WEIGHT
23    QC= QCCAR*60.0*(WT0/UNITCORR)**0.75
24
25          ! COMPARTMENT BLOOD FLOW (ML/HR)
26    QF  = QFF*QC                                 ! ADIPOSE TISSUE BLOOD FLOW RATE
27    QLI = QLIF*QC                                ! LIVER TISSUE BLOOD FLOW RATE
28    QRE = QREF*QC                                ! REST OF THE BODY BLOOD FLOW
29   RATE
30    QTTQ = QF+QRE+QLI                    ! TOTAL FLOW RATE
31
32          !PERMEABILITY ORGAN FLOW (ML/HR)
33   PAF  = PAFF*QF                               ! ADIPOSE
34   PARE = PAREF*QRE                             ! REST OF THE BODY
35   PALI = PALIF*QLI                             ! LIVER TISSUE
36
37          !CONDITIONAL ORAL EXPOSURE (BACKGROUND EXPOSURE)
38          !EXPOSURE + !REPETITIVE EXPOSURE SCENARIO
39    IV= DOSEIV_NM * WT0  !AMOUNT IN NMOL
40    MSTT= MSTOT_NM * WT0 !AMOUNT IN NMOL
41    MSTTBCKGR =MSTOT_NMBCKGR *WT0
42
43          !REPETITIVE ORAL BACKGROUND EXPOSURE SCENARIOS
44    DAY_EXPOSURE_BG   = PULSE(DAY_LACK_BG,DAY_PERIOD_BG,DAY_FINISH_BG)
45    WEEK_EXPOSURE_BG  = PULSE(WEEK_LACK_BG,WEEK_PERIOD_BG,WEEK_FINISH_BG)
46    MONTH_EXPOSURE_BG = PULSE(MONTH_LACK_BG,MONTH_PERIOD_BG,MONTH_FINISH_BG)
47
48    MSTTCH_BG = (DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG)*MSTTBCKGR
49    MSTTFR_BG = MSTTBCKGR/CINT
50
51    CYCLE_BG =DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG
52
53   IF (MSTTCH_BG.EQ.MSTTBCKGR) THEN
54       ABSMSTT_GB= MSTTFR_BG
55   ELSE
56       ABSMSTT_GB = 0.0
```

```
END IF


        !REPETITIVE ORAL MAIN EXPOSURE SCENARIO
  DAY_EXPOSURE   = PULSE(DAY_LACK,DAY_PERIOD,DAY_FINISH)
  WEEK_EXPOSURE  = PULSE(WEEK_LACK,WEEK_PERIOD,WEEK_FINISH)
  MONTH_EXPOSURE = PULSE(MONTH_LACK,MONTH_PERIOD,MONTH_FINISH)

  MSTTCH = (DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE)*MSTT
  CYCLE = DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE
  MSTTFR = MSTT/CINT

  SUMEXPEVENT= integ (CYCLE,0.0) !NUMBER OF CYCLE GENERATE DURING SIMULATION


        !CONDITIONAL ORAL EXPOSURE
IF (MSTTCH.EQ.MSTT) THEN
   ABSMSTT= MSTTFR
ELSE
   ABSMSTT = 0.0
END IF

 CYCLETOT=INTEG(CYCLE,0.0)

        !MASS CHANGE IN THE LUMEN
 RMSTT  = -(KST+KABS)*MST+ABSMSTT +ABSMSTT_GB ! RATE OF CHANGE (NMOL/H)
   MST = INTEG(RMSTT,0.0)  !AMOUNT OF STAY IN DUODENUM (NMOL)

        !ABSORPTION IN LYMPH CIRCULATION
 LYRMLUM = KABS*MST*A
   LYMLUM = INTEG(LYRMLUM,0.0)

        !ABSORPTION IN PORTAL CIRCULATION
 LIRMLUM = KABS*MST*B
   LIMLUM = INTEG(LIRMLUM,0.0)

        !PERCENT OF DOSE REMAINING IN THE GI TRACT
 PRCT_remain_GIT  = (MST/(MSTT+PARA_ZERO))*100.0

        !ABSORPTION of Dioxin by IV route---------
 IVR= IV/PFUNC ! RATE FOR IV INFUSION IN BLOOD
 EXPIV= IVR * (1.0-STEP(PFUNC))
   IVDOSE = integ(EXPIV,0.0)

        !SYSTEMIC BLOOD COMPARTMENT
        ! MODIFICATION ON OCTOBER 6, 2009
CB=(QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM)/(QC+CLURI) !
   CA = CB

        !URINARY EXCRETION BY KIDNEY
        ! MODIFICATION ON OCTOBER 6, 2009
RAURI = CLURI *CB
  AURI = INTEG(RAURI,0.0)

        !CONVERSION EQUATION POST SIMULATION
 PRCT_B = (CB/(MSTT+PARA_ZERO))*100.0
```

```
 CBNGKG = CB*MW*UNITCORR ![NG/KG]


CBSNGKGLIADJ= (CB*MW*UNITCORR*(1.0/B_TOTLIP)*(1.0/SERBLO))![NG of TCDD
Serum/Kg OF LIPIP]

       !ADIPOSE TISSUE COMPARTMENT
       !TISSUE BLOOD SUBCOMPARTMENT
 RAFB = QF*(CA-CFB)-PAF*(CFB-CF/PF)                !(NMOL/HR)
   AFB = INTEG(RAFB,0.0)                            !(NMOL)
   CFB = AFB/WFB                                   !(NMOL/ML)
       !TISSUE SUBCOMPARTMENT
 RAF  = PAF*(CFB-CF/PF)                            !(NMOL/HR)
   AF  = INTEG(RAF,0.0)                             !(NMOL)
   CF  = AF/WF                                     !(NMOL/ML)

      !CONVERSION EQUATION POST SIMULATION
   CFTOTAL    = (AF + AFB)/(WF + WFB)       !TOTAL CONCENTRATION IN NMOL/ML
   PRCT_F  = (CFTOTAL/(MSTT+PARA_ZERO))*100.0 ! PRCENT OF DOSE IN FAT
   CFNGKG   = CFTOTAL*MW*UNITCORR           ! CONCENTRATION [NG/KG]

      !REST OF THE BODY COMPARTMENT
      ! TISSUE BLOOD SUBCOMPARTMENT
 RAREB= QRE*(CA-CREB)-PARE*(CREB-CRE/PRE)           !(NMOL/HR)
   AREB = INTEG(RAREB,0.0)                          !(NMOL)
   CREB = AREB/WREB                                !(NMOL/ML)
      ! TISSUE COMPARTMENT
 RARE = PARE*(CREB - CRE/PRE)                       !(NMOL/HR)
   ARE = INTEG(RARE,0.0)                               !(NMOL)
   CRE  = ARE/WRE                                  !(NMOL/ML)

   !CONVERSION EQUATION POST SIMULATION
   CRETOTAL= (ARE + AREB)/(WRE + WREB)              ! TOTAL CONCENTRATION IN
NMOL/ML
   PRCT_RE = (CRETOTAL/(MSTT+PARA_ZERO))*100.0
   CTREPGG= CRETOTAL*MW*UNITCORR !(PG/ML)
    AUC_REPPG = integ(CTREPGG,0.0)

   !LIVER COMPARTMENT
   !TISSUE BLOOD COMPARTMENT
 RALIB = QLI*(CA-CLIB)-PALI*(CLIB-CFLLIR)+LIRMLUM   !(NMOL/HR)
   ALIB = INTeg(RALIB,0.0)                          !(NMOL)
   CLIB = ALIB/WLIB
   !TISSUE COMPARTMENT
 RALI =  PALI*(CLIB-CFLLIR)-REXCLI                  !(NMOL/HR)
   ALI = integ(RALI,0.0)                               !(NMOL)
   CLI  = ALI/WLI                                  !(NMOL/ML)


PARAMETER (LIVER_1RMN = 1.0E-30)
CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLIR &
+LIVER_1RMN))+((CYP1A2_1O3*CFLLIR/(KDLI2+CFLLIR &
+LIVER_1RMN)*PAS_INDUC)))-CFLLIR,CFLLI0) ! FREE TCDD CONCENTRATION IN LIVER
CFLLIR=DIM(CFLLI,0.0)

  CBNDLI= LIBMAX*CFLLIR/(KDLI+CFLLIR+LIVER_1RMN) !BOUND CONCENTRATION
```

```
1
2         !CONVERSION EQUATION POST SIMULATION
3       CLITOTAL= (ALI + ALIB)/(WLI + WLIB)                ! TOTAL CONCENTRATION IN
4   NMOL/ML
5       PRCT_LI = (CLITOTAL/(MSTT+PARA_ZERO))*100.0
6       rec_occ_AHR= (CFLLIR/(KDLI+CFLLIR+1))*100.0          ! PERCENT OF AhR
7   OCCUPANCY
8       PROT_occ_1A2= (CFLLIR/(KDLI2+CFLLIR))*100.0          ! PERCENT OF 1A2
9   OCCUPANCY
10      CLINGKG =(CLITOTAL*MW*UNITCORR)
11      CBNDLINGKG = CBNDLI*MW*UNITCORR
12        AUCLI_NGKGH=INTEG(CLINGKG,0.0)
13      CLINGG=CLITOTAL*MW
14
15           !VARIABLE ELIMINATION HALF-LIFE BASED ON THE CONCENTRATION OF CYP1A2
16        KBILE_LI_T =((CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2)*Kelv ! INDUCED BILIARY
17  EXCRETION RATE CONSTANT
18
19    REXCLI= (KBILE_LI_T*CFLLIR*WLI) ! DOSE-DEPENDENT BILIARY EXCRETION RATE
20      EXCLI = INTEG(REXCLI,0.0)
21
22        !CHEMICAL IN CYP450 (1A2) COMPARTMENT
23      !===PARAMETER FOR INDUCTION OF CYP1A2
24
25    CYP1A2_1KINP = CYP1A2_1KOUT* CYP1A2_1OUTZ ! BASAL RATE OF CYP1A2 PRODUCTION
26  SET EQUAL TO BASAL RATE OF DEGREDATION
27
28
29        ! MODIFICATION ON OCTOBER 6, 2009
30    CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1.0 + CYP1A2_1EMAX *(CBNDLI+1.0e-
31  30)**HILL &
32        /(CYP1A2_1EC50**HILL + (CBNDLI+1.0e-30)**HILL)) &-
33         - CYP1A2_1KOUT*CYP1A2_1OUT, CYP1A2_1OUTZ)
34
35  ! EQUATIONS INCORPORATING DELAY OF CYP1A2 PRODUCTION (NOT USED IN
36  SIMULATIONS)
37
38    CYP1A2_1RO2 = (CYP1A2_1OUT - CYP1A2_1O2)/ CYP1A2_1TAU
39       CYP1A2_1O2 =INTEG(CYP1A2_1RO2, CYP1A2_1A1)
40    CYP1A2_1RO3 = (CYP1A2_1O2 - CYP1A2_1O3)/ CYP1A2_1TAU
41       CYP1A2_1O3 =INTEG(CYP1A2_1RO3, CYP1A2_1A2)
42
43  ! ------------CHECK MASS BALANCE ----------
44      BDOSE= LYMLUM+LIMLUM+IVDOSE
45      BMASSE = EXCLI+AURI+AFB+AF+AREB+ARE+ALIB+ALI
46          BDIFF = BDOSE-BMASSE
47
48  !---------------BODY BURDEN-----------------------
49      BBNGKG =(((AFB+AF+AREB+ARE+ALIB+ALI)*MW)/(WT0/UNITCORR)) !
50  ! ------------ END OF THE SIMULATION COMMAND ----------
51
52  TERMT (T.GE. TimeLimit, 'Time limit has been reached.')
53
54  END   ! END OF THE DERIVATIVE SECTION
55  END   ! END OF THE DYNAMIC SIMULATION SECTION
56  END   ! END OF THE PROGRAM.
```

C.2.3.2. *Input Files*

C.2.3.2.1. *Cantoni et al. (1981).*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

%Cantoni et al. 1981
%protocol:  oral exposure 1 dose/week for 45 weeks; female CD-COBS rats
%Rat_Dioxin_3C June09_2clean.csl
%RAT_NON_GEST_ICF_F083109.CSL  (now 09-11-09)
%dose levels: 0.01, 0.1, 1  ug/kg 1 dose/week for 45 weeks
%dose levels: 10, 100, 1000 ng/kg 1 dose/week for 45 weeks
%dose levels equivalent to: 1.43, 14.3 143 ng/kg 7 days/weeks for 45 weeks

MAXT              = 0.01
CINT              = 0.1
EXP_TIME_ON       = 0.              %delay before begin exposure (HOUR)
EXP_TIME_OFF      = 7560     %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE         = 168
BCK_TIME_ON       = 0.       %DELAY BEFORE BACGROUND EXPOSURE (HOUR)
BCK_TIME_OFF      = 0.       %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT         = 7560     %SIMULATION LIMIT TIME (HOUR)
BW_T0             = 125      % Body weight at the beginning of the simulation
(g)

%EXPOSURE DOSE SCENARIOS (UG/KG)
  %MSTOT          = 0.01     % exposure dose ug/kg
   %MSTOT        = 0.1      % exposure dose ug/kg
   MSTOT         = 1        % exposure dose ug/kg
```

C.2.3.2.2. *Chu et al. (2007).*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Chu et al. 2007
%protocol:  oral exposure daily for 28 days
%dose levels: 0.0025, 0.025, 0.250, 1.0 ug/kg every day for 28 days
% dose levels = 2.5, 25, 250, 1000 ng/kg every day for 28 days
MAXT            =  0.01
CINT            =  0.1
EXP_TIME_ON     =  0.            %delay before begin exposure (HOUR) 5 weeks
after start of experiment (age = 12 weeks)
EXP_TIME_OFF    =  672.            %TIME EXPOSURE STOP (HOUR); 30 doses, 1
every two weeks
DAY_CYCLE       =  24.            % once every two weeks
BCK_TIME_ON     =  0.              %DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
BCK_TIME_OFF    =  0.              %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT       =  672.           %SIMULATION LIMIT TIME (HOUR)
BW_T0           =  200.             % Body weight at the beginning of the
simulation (g); corresponds to 12 week old female

%EXPOSURE DOSE SCENARIOS (UG/KG)
```

```
  %MSTOT          = 0.0025        % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT          = 0.025         % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT          = 0.250          % ORAL EXPOSURE DOSE (UG/KG)
  MSTOT          = 1.0           % ORAL EXPOSURE DOSE (UG/KG)
```

C.2.3.2.3. *Crofton et al. (2005).*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Crofton et al. 2005
%protocol:  oral exposure daily for 4 days
%dose levels: 0.0001, 0.003, 0.01, 0.03, 0.1, 0.3, 1, 3, and 10 ug/kg every
day for four days
%dose levels: 0.1, 3, 10, 30, 100, 300, 1000, 3000, and 10000 ng/kg every day
for four days

MAXT            =  0.01
CINT            =  0.1
EXP_TIME_ON     =  0.            %delay before begin exposure (HOUR) 5 weeks
after start of experiment (age = 12 weeks)
EXP_TIME_OFF    =  96.            %TIME EXPOSURE STOP (HOUR); 30 doses, 1
every two weeks
DAY_CYCLE       =  24.            % once every two weeks
BCK_TIME_ON     =  0.              %DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
BCK_TIME_OFF    =  0.              %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT       =  96.            %SIMULATION LIMIT TIME (HOUR)
BW_T0           =  250             % Body weight at the beginning of the
simulation (g); corresponds to 12 week old female

%EXPOSURE DOSE SCENARIOS (UG/KG)
  MSTOT           = 0.0001        % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT          = 0.003         % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT          = 0.01          % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT          = 0.03          % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT          = 0.1          % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT          = 0.3          % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT          = 1.          % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT          = 3.          % ORAL EXPOSURE DOSE (UG/KG)
  MSTOT          = 10.          % ORAL EXPOSURE DOSE (UG/KG)


```

C.2.3.2.4. *Fattore et al. (2000).*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Fattore et al. 2000
%built and check in August 7 2009
%protocol:  oral exposure in diet for 13 weeks; SD rats
%dose levels:  0.02, 0.1, 0.2, 2 ug/kg 7 days/week for 13 weeks
%dose levels equivalent to: 20, 100, 200, 2000 ng/kg 7 days/week for 13 weeks

MAXT = 0.01
```

```
CINT  = 0.1
EXP_TIME_ON       = 0.              %TIME AT WHICH EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF      = 2184     %TIME AT WHICH EXPOSURE ENDS (HOUR)
DAY_CYCLE         = 24
BCK_TIME_ON       = 0.       %TIME AT WHICH BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF      = 0.       %TIME AT WHICH BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT         = 2184     %SIMULATION TIME LIMIT (HOUR)
BW_T0             = 150      % BODY WEIGHT AT THE BEGINNING OF THE SIMULATION
(G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
 %MSTOT            = 0.02              % EXPOSURE DOSE IN UG/KG
  %MSTOT          = 0.1               % EXPOSURE DOSE IN UG/KG
  %MSTOT          = 0.2               % EXPOSURE DOSE IN UG/KG
  MSTOT          = 2              % EXPOSURE DOSE IN UG/KG
```

C.2.3.2.5. *Franc et al. (2001). Sprague Dawley rats*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Franc et al. 2001
% Non-gestational rat model
% dose levels: 0.140, 0.420, and 1.400 ug/kg every 2 weeks for 22 weeks
% dose levels: 140, 420, and 1400 ng/kg every 2 weeks for 22 weeks
% dose levels equivalent to 10, 30, and 100 ng/kg/day

MAXT            =  0.01
CINT            =  0.1
EXP_TIME_ON     =  0.               %delay before begin exposure (HOUR)
EXP_TIME_OFF    =  3696.              %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE       =  336.
BCK_TIME_ON     =  0.                %DELAY BEFORE BACGROUND EXPOSURE (HOUR)
BCK_TIME_OFF    =  0.                %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT       =  3696.               %SIMULATION LIMIT TIME (HOUR)
BW_T0           =  200.              % Body weight at the beginning of the
simulation (g); corresponds to approximate weight of females 10 weeks old

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT         = 0.14     % ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT         = 0.42      % ORAL EXPOSURE DOSE (UG/KG)
   MSTOT         = 1.4      % ORAL EXPOSURE DOSE (UG/KG)
```

C.2.3.2.6. *Franc et al. (2001). Long-Evans rats*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Franc et al. 2001
% Non-gestational rat model
% dose levels: 0.140, 0.420, and 1.400 ug/kg every 2 weeks for 22 weeks
% dose levels: 140, 420, and 1400 ng/kg every 2 weeks for 22 weeks
% dose levels equivalent to 10, 30, and 100 ng/kg/day

```

```
MAXT            =  0.01
CINT            =  0.1
EXP_TIME_ON     =  0.               %delay before begin exposure (HOUR)
EXP_TIME_OFF    =  3696.              %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE       =  336.
BCK_TIME_ON     =  0.                %DELAY BEFORE BACGROUND EXPOSURE (HOUR)
BCK_TIME_OFF    =  0.                %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT       =  3696.              %SIMULATION LIMIT TIME (HOUR)
BW_T0           =  190.              % Body weight at the beginning of the
simulation (g); corresponds to approximate weight of females 10 weeks old

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT         = 0.14     % ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT         = 0.42      % ORAL EXPOSURE DOSE (UG/KG)
   MSTOT         = 1.4      % ORAL EXP
```

C.2.3.2.7. *Franc et al. (2001). Hans Wistar rats*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Franc et al. 2001
% Non-gestational rat model
% dose levels: 0.140, 0.420, and 1.400 ug/kg every 2 weeks for 22 weeks
% dose levels: 140, 420, and 1400 ng/kg every 2 weeks for 22 weeks
% dose levels equivalent to 10, 30, and 100 ng/kg/day

MAXT            =  0.01
CINT            =  0.1
EXP_TIME_ON     =  0.               %delay before begin exposure (HOUR)
EXP_TIME_OFF    =  3696.              %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE       =  336.
BCK_TIME_ON     =  0.                %DELAY BEFORE BACGROUND EXPOSURE (HOUR)
BCK_TIME_OFF    =  0.                %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT       =  3696.              %SIMULATION LIMIT TIME (HOUR)
BW_T0           =  205.              % Body weight at the beginning of the
simulation (g); corresponds to approximate weight of females 10 weeks old

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT         = 0.14     % ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT         = 0.42      % ORAL EXPOSURE DOSE (UG/KG)
   MSTOT         = 1.4      % ORAL EXP
```

C.2.3.2.8. *Hassoun et al. (2000).*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Hassoun et al. 2000
%protocol:  oral exposure for 13 weeks; SD rats
%dose levels:  0.003, 0.010, 0.022, 0.046 0.1 ug/kg 5 days/weeks for 13 weeks
%dose levels equivalent to: 3, 10, 22, 46 100 ng/kg 5 days/weeks for 13 weeks
%dose levels equivalent to: 2.14, 7.14, 15.7, 32.9 71.4 ng/kg 7 days/weeks
for 13 weeks
```

```
MAXT             = 0.01
CINT             = 0.1
EXP_TIME_ON      = 0.          %delay before begin exposure (HOUR)
EXP_TIME_OFF     = 2184.       %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE        =  24.
WEEK_PERIOD      = 168.
WEEK_FINISH      = 119.
BCK_TIME_ON      = 0.          %DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
BCK_TIME_OFF     = 0.          %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT        = 2184.       %SIMULATION LIMIT TIME (HOUR)
BW_T0            = 215.         % Body weight at the beginning of the
simulation (g)

%EXPOSURE DOSE SCENARIOS (UG/KG)
     %MSTOT        = 0.003      % exposure dose ug/kg
     %MSTOT      = 0.010             % exposure dose ug/kg
     %MSTOT      = 0.022             % exposure dose ug/kg
     %MSTOT      = 0.046                 % exposure dose ug/kg
     MSTOT      = 0.1             % exposure dose ug/kg
```

C.2.3.2.9. *Hutt et al. (2008).*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Hutt et al. 2008
% Non-gestational rat model
% dose levels: 0.050 ug/kg every week for 13 weeks
% dose levels: 50 ng/kg every week for 13 weeks
% dose levels equivalent to 7.14 ng/kg/day

MAXT             =  0.01
CINT             =  0.1
EXP_TIME_ON      =  0.               %delay before begin exposure (HOUR)
EXP_TIME_OFF     =  2184.               %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE        =  168.
BCK_TIME_ON      =  0.                %DELAY BEFORE BACGROUND EXPOSURE (HOUR)
BCK_TIME_OFF     =  0.                %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT        =  2184.               %SIMULATION LIMIT TIME (HOUR)
BW_T0            =  4.5             % Body weight at the beginning of the
simulation (g); corresponds to approximate weight of females 10 weeks old

%EXPOSURE DOSE SCENARIOS (UG/KG)
   MSTOT         = 0.05      % ORAL EXPOSURE DOSE (UG/KG)
```

C.2.3.2.10. *Kitchin and Woods (1979)*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Kitchen and Woods 1979
%protocol: single oral gavage
```

```
%dose levels:  0.0006, 0.002, 0.004, 0.020, 0.060, 0.200, 0.600, 2.000,
5.000, 20.000 ug/kg single oral gavage
% dose levels = 0.6, 2, 4, 20, 60, 200, 600, 2000, 5000, 20000 ng/kg single
oral gavage
MAXT            =  0.001
CINT            =  0.1
EXP_TIME_ON     =  0.           %delay before begin exposure (HOUR)
EXP_TIME_OFF    =  24.           %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE       =  24.           % daily
BCK_TIME_ON     =  0.              %DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
BCK_TIME_OFF    =  0.              %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT       =  24.           %SIMULATION LIMIT TIME (HOUR)
BW_T0           =  225.             % Body weight at the beginning of the
simulation (g)

%EXPOSURE DOSE SCENARIOS (UG/KG)
  %MSTOT         = 0.0006        % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 0.002         % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 0.004          % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 0.020          % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 0.060          % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 0.200        % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 0.600         % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 2.000          % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 5.000          % ORAL EXPOSURE DOSE (UG/KG)
  MSTOT         = 20.000          % ORAL EXPOSURE DOSE (UG/KG)
```

C.2.3.2.11. *Kociba et al. (1976) (13 weeks).*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Kociba et al. 1976.
%built and check in August 7 2009
%protocol:  5 days/week exposure for 13 weeks; SD rats
%Rat_Dioxin_3C June09_2clean.csl
%RAT_NON_GEST_ICF_F083109.CSL  (now 09-11-09)
%dose levels:  0.001, 0.01, 0.1, 1 ug/kg 5 days/weeks for 13 weeks
%dose levels: 1, 10, 100, 1000 ng/kg 5 days/weeks for 13 weeks
%dose levels equivalent to: 0.714, 7.14, 71.4, 714 ng/kg/d (adj) 7 days/weeks
for 13 weeks

MAXT             = 0.001
CINT             = 0.1
EXP_TIME_ON      = 0.        %delay before begin exposure (HOUR)
EXP_TIME_OFF     = 2184      %TIME EXPOSURE STOP (HOUR)
WEEK_PERIOD      = 168
WEEK_FINISH      = 119
DAY_CYCLE        =  24
BCK_TIME_ON      = 0.        %DELAY BEFORE BACGROUND EXPOSURE (HOUR)
BCK_TIME_OFF     = 0.        %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT        = 2184      %SIMULATION LIMIT TIME (HOUR)
BW_T0            = 180       % Body weight at the begeniong of the
simulation (g)
```

```
%EXPOSURE DOSE SCENARIOS (UG/KG)
%MSTOT           = 0.001
 %MSTOT          = 0.01
 %MSTOT          = 0.1
 MSTOT          = 1
```

C.2.3.2.12. *Kociba et al. (1978) (female) (104 weeks).*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Kociba et al, 1978.
%built and check in August 7 2009
%protocol:  daily dietary exposure for 104 weeks; SD rats
%dose levels:  0.001, 0.01, 0.1 ug/kg 7 days/week for 104 weeks
%dose levels: 1, 10, 100 ng/kg 7 days/week for 104 weeks

MAXT            =  0.01
CINT            =  0.1
EXP_TIME_ON     =  0.              %TIME AT WHICH EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF    =  17472           %TIME AT WHICH EXPOSURE ENDS (HOUR)
DAY_CYCLE       =  24
BCK_TIME_ON     =  0.              %TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
BCK_TIME_OFF    =  0.              %TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
TIMELIMIT       =  17472           %SIMULATION TIME LIMIT (HOUR)
BW_T0           =  180             % BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
 %MSTOT          = 0.001             % EXPOSURE DOSE IN UG/KG
 %MSTOT         = 0.01             % EXPOSURE DOSE IN UG/KG
 MSTOT         = 0.1             % EXPOSURE DOSE IN UG/KG
```

C.2.3.2.13. *Kociba et al. (1978) (male) (104 weeks).*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Kociba et al, 1978.
%built and check in August 7 2009
%protocol:  daily dietary exposure for 104 weeks; SD rats
%dose levels:  0.001, 0.01, 0.1 ug/kg 7 days/week for 104 weeks
%dose levels: 1, 10, 100 ng/kg 7 days/week for 104 weeks

MAXT            =  0.01
CINT            =  0.1
EXP_TIME_ON     =  0.              %TIME AT WHICH EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF    =  17472           %TIME AT WHICH EXPOSURE ENDS (HOUR)
DAY_CYCLE       =  24
BCK_TIME_ON     =  0.              %TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
```

```
BCK_TIME_OFF    =  0.              %TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
TIMELIMIT       =  17472           %SIMULATION TIME LIMIT (HOUR)
BW_T0           =  250             % BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
 %MSTOT          = 0.001             % EXPOSURE DOSE IN UG/KG
 %MSTOT         = 0.01             % EXPOSURE DOSE IN UG/KG
 MSTOT         = 0.1             % EXPOSURE DOSE IN UG/KG
```

C.2.3.2.14. *Latchoumycandane and Mathur (2002).*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Latchoumycandane and Mathur 2002.
%built and check in August 7 2009
%protocol:  1 time per day for 45 days oral gavage
%Rat_Dioxin_3C June09_2clean.csl
%RAT_NON_GEST_ICF_F083109.CSL  (now 09-11-09)
%dose levels:  0.001, 0.01, 0.1 ug/kg daily for 45 days
%dose levels:  1, 10, 100 ng/kg daily for 45 days

MAXT             = 0.01
CINT             = 0.1
EXP_TIME_ON      = 0.          % delay before begin exposure (HOUR)
EXP_TIME_OFF     = 1080        % TIME EXPOSURE STOP (HOUR)
DAY_CYCLE        = 24
BCK_TIME_ON      = 0.          % DELAY BEFORE BACGROUND EXPOSURE (HOUR)
BCK_TIME_OFF     = 0.          % TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT        = 1080        % SIMULATION LIMIT TIME (HOUR)
BW_T0            = 200         % Body weight at the beginning of the
simulation (g)

%EXPOSURE DOSE SCENARIOS (UG/KG)
  %MSTOT          = 0.001        % exposure dose ug/kg
  %MSTOT         = 0.01         % exposure dose ug/kg
  MSTOT         = 0.1          % exposure dose ug/kg
```

C.2.3.2.15. *Li et al. (1997).*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Li et al 1997
% created 1/10/10
% Non-gestational rat model
% dose levels: 3, 10, 30, 100, 300, 1000, 3000, 10000, 30000 nkd one dose via
gavage, sacrificed 24 hrs later

MAXT           =  0.1
CINT           =  0.1
```

```
EXP_TIME_ON     =  0.               %delay before begin exposure (HOUR)
EXP_TIME_OFF    =  24.               %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE       =  24.
BCK_TIME_ON     =  0.                %DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
BCK_TIME_OFF    =  0.                %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT       =  24.               %SIMULATION LIMIT TIME (HOUR)
BW_T0           =  56.5              % Body weight at the beginning of the
simulation (g)

%EXPOSURE DOSE SCENARIOS (UG/KG)
   MSTOT         = 0.003     % ORAL EXPOSURE DOSE (UG/KG)
    %MSTOT         = 0.01      % ORAL EXPOSURE DOSE (UG/KG)
    %MSTOT         = 0.03      % ORAL EXPOSURE DOSE (UG/KG)
    %MSTOT         = 0.1       % ORAL EXPOSURE DOSE (UG/KG)
    %MSTOT         = 0.3       % ORAL EXPOSURE DOSE (UG/KG)
    %MSTOT         = 1.        % ORAL EXPOSURE DOSE (UG/KG)
    %MSTOT         = 3.        % ORAL EXPOSURE DOSE (UG/KG)
    %MSTOT         = 10.       % ORAL EXPOSURE DOSE (UG/KG)
    %MSTOT         = 30.       % ORAL EXPOSURE DOSE (UG/KG)
```

C.2.3.2.16. *Murray et al. (1979).*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Murray et al 1979
%built and check in August 7 2009
%protocol:  dietary exposure for 3 generations (assume 120 day exposure for
each)
%dose levels: 0.001 0.01, 0.1 ug/kg/d
%dose levels: 1, 10, 100  ng/kg/d

MAXT            =  0.01
CINT            =  0.1
EXP_TIME_ON     =  0.               %TIME AT WHICH EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF    =  2880            %TIME AT WHICH EXPOSURE ENDS (HOUR);
CORRESPONDS TO 120 DAYS OF EXPOSURE
DAY_CYCLE       =  24.
BCK_TIME_ON     =  0.               %TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
BCK_TIME_OFF    =  0.               %TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
TIMELIMIT       =  2880            %SIMULATION TIME LIMIT (HOUR)
BW_T0           =  4.5              % BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
  %MSTOT           = 0.001        % ORAL EXPOSURE DOSE IN UG/KG
  %MSTOT         = 0.01         % ORAL EXPOSURE DOSE IN UG/KG
  MSTOT          = 0.1          % ORAL EXPOSURE DOSE IN UG/KG
```

C.2.3.2.17. *NTP (1982) (female) (chronic).*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

%NTP 1982
%built and check in August 7 2009
%protocol: twice weekly gavage for 104 weeks + 3 week observation period
%Rat_Dioxin_3C June09_2clean.csl
%RAT_NON_GEST_ICF_F083109.CSL  (now 09-11-09)
%dose levels:  0.005, 0.025, 0.25 ug/kg biweekly for 104 weeks + 3 week
observation period
%dose levels:  5, 25, 250 ng/kg biweekly for 104 weeks + 3 week observation
period
%dose levels equivalent to: 1.43, 7.14, 71.4 ng/kg/day (adj)

MAXT              = 0.01
CINT              = 0.1
EXP_TIME_ON       = 0.            %delay before begin exposure (HOUR)
EXP_TIME_OFF      = 17472         %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE         = 84
BCK_TIME_ON       = 0.            %DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
BCK_TIME_OFF      = 0.            %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT         = 17472         %SIMULATION LIMIT TIME (HOUR)
BW_T0             = 250           % Body weight at the beginning of the
simulation (g)

%EXPOSURE DOSE SCENARIOS (UG/KG)

  %MSTOT          = 0.005        % exposure dose ug/kg
  %MSTOT          = 0.025
  MSTOT          = 0.25
```

C.2.3.2.18. *NTP (1982) (male) (chronic).*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

%NTP 1982
%built and check in august 7 2009
%protocol: twice weekly gavage for 104 weeks + 3 week observation period
%Rat_Dioxin_3C June09_2clean.csl
%RAT_NON_GEST_ICF_F083109.CSL  (now 09-11-09)
%dose levels:  0.005, 0.025, 0.25 ug/kg biweekly for 104 weeks + 3 week
observation period
%dose levels:  5, 25, 250 ng/kg biweekly for 104 weeks + 3 week observation
period
%dose levels equivalent to: 1.43, 7.14, 71.4 ng/kg/day (adj)

MAXT              = 0.01
CINT              = 0.1
EXP_TIME_ON       = 0.            %delay before begin exposure (HOUR)
EXP_TIME_OFF      = 17472         %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE         = 84
```

```
BCK_TIME_ON        = 0.            %DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
BCK_TIME_OFF       = 0.            %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT          = 17472         %SIMULATION LIMIT TIME (HOUR)
BW_T0              = 350           % Body weight at the beginning of the
simulation (g)

%EXPOSURE DOSE SCENARIOS (UG/KG)

%MSTOT           = 0.005        % exposure dose ug/kg
%MSTOT           = 0.025
MSTOT           = 0.25
```

C.2.3.2.19. *NTP (2006) 14 weeks.*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% NTP 2006
%built and check in August 7 2009
%protocol:  oral exposure for 14 weeks; SD rats
%Rat_Dioxin_3C June09_2clean.csl
%RAT_NON_GEST_ICF_F083109.CSL  (now 09-11-09)
%dose levels:  0.003, 0.010, 0.022, 0.046 0.1 ug/kg 5 days/weeks for 14 weeks
%dose levels equivalent to: 3, 10, 22, 46 100 ng/kg 5 days/weeks for 14 weeks
%dose levels equivalent to: 2.14, 7.14, 15.7, 32.9 71.4 ng/kg 7 days/weeks for
14 weeks

MAXT             = 0.01
CINT             = 0.1
EXP_TIME_ON      = 0.          %delay before begin exposure (HOUR)
EXP_TIME_OFF     = 2352       %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE        =  24
WEEK_PERIOD      = 168
WEEK_FINISH      = 119
BCK_TIME_ON      = 0.          %DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
BCK_TIME_OFF     = 0.          %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT        = 2352       %SIMULATION LIMIT TIME (HOUR)
BW_T0            = 215         % Body weight at the beginning of the simulation
(g)

%EXPOSURE DOSE SCENARIOS (UG/KG)
     %MSTOT         = 0.003       % exposure dose ug/kg
     %MSTOT       = 0.010              % exposure dose ug/kg
     %MSTOT       = 0.022              % exposure dose ug/kg
     %MSTOT       = 0.046                  % exposure dose ug/kg
     MSTOT       = 0.1             % exposure dose ug/kg
```

C.2.3.2.20. *NTP (2006) 31 weeks.*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% NTP 2006
%built and check in August 7 2009
%protocol:  oral exposure for 31 weeks; SD rats
%Rat_Dioxin_3C June09_2clean.csl
%RAT_NON_GEST_ICF_F083109.CSL  (now 09-11-09)
%dose levels:  0.003, 0.010, 0.022, 0.046 0.1 ug/kg 5 days/weeks for 31 weeks
```

```
%dose levels equivalent to: 3, 10, 22, 46 100 ng/kg 5 days/weeks for 31 weeks
%dose levels equivalent to: 2.14, 7.14, 15.7, 32.9 71.4 ng/kg 7 days/weeks
for 31 weeks

MAXT             = 0.01
CINT             = 0.1
EXP_TIME_ON      = 0.          %delay before begin exposure (HOUR)
EXP_TIME_OFF     = 5208      %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE        =  24
WEEK_PERIOD      = 168
WEEK_FINISH      = 119
BCK_TIME_ON      = 0.          %DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
BCK_TIME_OFF     = 0.          %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT        = 5208      %SIMULATION LIMIT TIME (HOUR)
BW_T0            = 215         % Body weight at the beginning of the
simulation (g)

%EXPOSURE DOSE SCENARIOS (UG/KG)
     %MSTOT        = 0.003      % exposure dose ug/kg
     %MSTOT      = 0.010             % exposure dose ug/kg
     %MSTOT      = 0.022             % exposure dose ug/kg
     %MSTOT      = 0.046                 % exposure dose ug/kg
     MSTOT      = 0.1             % exposure dose ug/kg
```

C.2.3.2.21. *NTP (2006) 53 weeks.*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% NTP 2006
%built and check in August 7 2009
%protocol:  oral exposure for 53 weeks; SD rats
%Rat_Dioxin_3C June09_2clean.csl
%RAT_NON_GEST_ICF_F083109.CSL  (now 09-11-09)
%dose levels:  0.003, 0.010, 0.022, 0.046 0.1 ug/kg 5 days/weeks for 53 weeks
%dose levels equivalent to: 3, 10, 22, 46 100 ng/kg 5 days/weeks for 53 weeks
%dose levels equivalent to: 2.14, 7.14, 15.7, 32.9 71.4 ng/kg 7 days/weeks
for 53 weeks

MAXT             = 0.01
CINT             = 0.1
EXP_TIME_ON      = 0.          %delay before begin exposure (HOUR)
EXP_TIME_OFF     = 8904      %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE        =  24
WEEK_PERIOD      = 168
WEEK_FINISH      = 119
BCK_TIME_ON      = 0.          %DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
BCK_TIME_OFF     = 0.          %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT        = 8904      %SIMULATION LIMIT TIME (HOUR)
BW_T0            = 215         % Body weight at the beginning of the
simulation (g)

%EXPOSURE DOSE SCENARIOS (UG/KG)
     %MSTOT        = 0.003      % exposure dose ug/kg
     %MSTOT      = 0.010             % exposure dose ug/kg
```

```
      %MSTOT      = 0.022              % exposure dose ug/kg
      %MSTOT      = 0.046                  % exposure dose ug/kg
      MSTOT      = 0.1             % exposure dose ug/kg
```

C.2.3.2.22. *NTP (2006) 2 year.*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% NTP 2006
%built and check in August 7 2009
%protocol:  oral exposure for 105 weeks; SD rats
%dose levels:  0.003, 0.010, 0.022, 0.046, 0.1 ug/kg 5 days/week for 105
weeks
%dose levels equivalent to: 3, 10, 22, 46, 100 ng/kg 5 days/week for 105
weeks
%dose levels equivalent to: 2.14, 7.14, 15.7, 32.9, 71.4 ng/kg 7 days/week
for 105 weeks

MAXT             = 0.01
CINT             = 0.1
EXP_TIME_ON      = 0.         %TIME AT WHICH EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF     = 17640      %TIME AT WHICH EXPOSURE ENDS (HOUR)
DAY_CYCLE        =  24
WEEK_PERIOD      = 168
WEEK_FINISH      = 119
BCK_TIME_ON      = 0.         %TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
BCK_TIME_OFF     = 0.         %TIME AT WHICH BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT        = 17640      %SIMULATION TIME LIMIT (HOUR)
BW_T0            = 215        % BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
     %MSTOT        = 0.003      % EXPOSURE DOSE IN UG/KG
     %MSTOT      = 0.010             % EXPOSURE DOSE IN UG/KG
     %MSTOT      = 0.022             % EXPOSURE DOSE IN UG/KG
     %MSTOT      = 0.046                 % EXPOSURE DOSE IN UG/KG
     MSTOT      = 0.1             % EXPOSURE DOSE IN UG/KG
```

C.2.3.2.23. *Sewall et al. (1995).*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG
% Sewall et al. 1995
%Rat_Dioxin_3C June09_2clean.csl
%RAT_NON_GEST_ICF_F083109.CSL  (now 09-11-09)
%protocol: gavage every 2 weeks for 30 weeks
%dose levels: 0.049, 0.1498, 0.49, and 1.75 ug/kg every 2 weeks
%dose levels: 3.5, 10.7, 35, and 125 ng/kg/d or 49, 149.8, 490, and 1750
ng/kg every 2 weeks

MAXT             =  0.01
CINT             =  0.1
```

```
EXP_TIME_ON     =  0.            %delay before begin exposure (HOUR) 5 weeks
after start of experiment (age = 12 weeks)
EXP_TIME_OFF    =  5040            %TIME EXPOSURE STOP (HOUR); 30 doses, 1
every two weeks
DAY_CYCLE       =  336.            % once every two weeks
BCK_TIME_ON     =  0.               %DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
BCK_TIME_OFF    =  0.               %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT       =  5040            %SIMULATION LIMIT TIME (HOUR)
BW_T0           =  250              % Body weight at the beginning of the
simulation (g); corresponds to 12 week old female

%EXPOSURE DOSE SCENARIOS (UG/KG)
  %MSTOT           = 0.049        % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT          = 0.1498        % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT          = 0.49         % ORAL EXPOSURE DOSE (UG/KG)
  MSTOT          = 1.75         % ORAL EXPOSURE DOSE (UG/KG)
```

C.2.3.2.24. *Shi et al. (2007), adult portion.*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Shi et al 2007
%built and check in August 7 2009
%protocol:  gavage once per week for 322 days
%dose levels: 0.001, 0.005, 0.05 and 0.2 ug TCDD:kg body weight by gavage
once per week
%dose levels: 1, 5, 50 and 200 ng/kg ng TCDD:kg body weight by gavage once
per week
% dose equivalent adjusted 0.143, 0.714, 7.14 and 28.6 ng/kg/d

MAXT            =  0.0001
CINT            =  0.1
EXP_TIME_ON     =  504.             % TIME AT WHICH EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF    =  7728            %TIME AT WHICH EXPOSURE ENDS (HOUR);
CORRESPONDS TO 322 DAYS OF EXPOSURE
DAY_CYCLE       =  168.
BCK_TIME_ON     =  0.               % TIME AT WHICH BACKGROUND EXPOSURE
BEGINS (HOUR)
BCK_TIME_OFF    =  0.               % TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
TIMELIMIT       =  7728            %SIMULATION TIME LIMIT (HOUR)
BW_T0           =  4.5              % BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT          = 0.001     % ORAL EXPOSURE DOSE IN UG/KG
   %MSTOT         = 0.005     % ORAL EXPOSURE DOSE IN UG/KG
   %MSTOT         = 0.05      % ORAL EXPOSURE DOSE IN UG/KG
   MSTOT         = 0.2       % ORAL EXPOSURE DOSE IN UG/KG
```

C.2.3.2.25. *Van Birgelen et al. (1995).*

```
output @clear
prepare @clear
```

```
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Van Birgelen et al. (1995)
%protocol:  daily dietary exposure for 13 weeks
%dose levels: 0.0135, 0.0264, 0.0469, 0.320, 1.024 ug/kg every day for 13
weeks
% dose levels = 13.5, 26.4, 46.9, 320, 1024 ng/kg every day for 13 weeks
MAXT            =  0.01
CINT            =  0.1
EXP_TIME_ON     =  0.            %delay before begin exposure (HOUR)
EXP_TIME_OFF    =  2184.           %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE       =  24.            % once every two weeks
BCK_TIME_ON     =  0.              %DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
BCK_TIME_OFF    =  0.              %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT       =  2184.           %SIMULATION LIMIT TIME (HOUR)
BW_T0           =  150.             % Body weight at the beginning of the
simulation (g)

%EXPOSURE DOSE SCENARIOS (UG/KG)
  %MSTOT         = 0.0135        % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 0.0264         % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 0.0469          % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 0.320          % ORAL EXPOSURE DOSE (UG/KG)
  MSTOT         = 1.024          % ORAL EXPOSURE DOSE (UG/KG)
```

C.2.3.2.26. *Vanden Heuvel et al. (1994).*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Vanden Heuvel et al. 1994.
%built and check in August 7 2009
%protocol: single gavage
%Rat_Dioxin_3C June09_2clean.csl
%RAT_NON_GEST_ICF_F083109.CSL  (now 09-11-09)
%dose levels:0.00005, 0.0001, 0.001, 0.010, 0.1, 1, 10 ug/kg/d
%dose levels equivalent to: 0.05, 0.1, 1, 10, 100, 1000, 10000 ng/kg/d

MAXT              = 0.001
CINT              = 0.1
EXP_TIME_ON       = 0.            %delay before begin exposure (HOUR)
EXP_TIME_OFF      = 24          %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE         = 24
BCK_TIME_ON       = 0.            %DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
BCK_TIME_OFF      = 0.            %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT         = 24           %SIMULATION LIMIT TIME (HOUR)
BW_T0             = 250           % Body weight at the beginning of the
simulation (g)

%EXPOSURE DOSE SCENARIOS (UG/KG)

  %MSTOT            = 0.00005       % exposure dose ug/kg
  %MSTOT          = 0.0001        % exposure dose ug/kg
  %MSTOT          = 0.001         % exposure dose ug/kg
  %MSTOT          = 0.01          % exposure dose ug/kg
```

```
  %MSTOT           = 0.1           % exposure dose ug/kg
  %MSTOT           = 1             % exposure dose ug/kg
  MSTOT           = 10            % exposure dose ug/kg
```

C.2.4. Rat Gestational Model

C.2.4.1. *Model Code*

PROGRAM: 'Three Compartment PBPK Model for TCDD in Rat (Gestation)'

```
! Parameters were change May 16, 2002
! Come from {8MAI_CHR_PRE-EXP_GD}
! Come from {12_Mouse_GD}file
!*******************************************
!{{IMPORTANT-IMPORTANT-IMPORTANT-IMPORTANT}}
! REDUCTION OF MOTHER AND FETUS COMPARTMENT
! 2M_R_TCDD_JULY2002 ////(JULY 18,2002)////
!TCDD_RED_4Species_2003_4        ////(APR  8 ,2003)////
!TCDD_RED_4Species_2003_9        ////(APR  17 ,2003)////
!TCDD_RED_4Species_2003_12        ////(APR  17 ,2003)////
!*************************************************
!APRIL 18 2003
!TCDD_4C_4SP_2003        ////(APR  18 ,2003)////
! was ''Gest 4 species 1.csl''   but update July 2009

!DevTCDD4Species_ICF_afterKKfix_v3_ratgest.csl
!RAT_GESTATIONAL_ICF_F083109.csl
!RAT_GESTATIONAL_ICF_F100609.csl
!*************************************************

 !Legend/Legend/Legend/Legend/Legend/Legend/Legend/Legend/
 !Legend for this PBPK model
 !Mating: control the tenure of exchange between fetus and
    !Mother and also control imitated tissue growth
    !Control: WTFE, WFO, WPLA0, QPLAF,WT0
    !(for rat, mouse, human, and monkey)
 !Control transfer from mother to fetus or fetus to mother by TRANSTIME_ON
    !SWITCH_trans = 0 NO TRANSFER
    !SWITCH_trans = 1 TRANSFER OCCURS
    !Gest_off = 1
    !Gest_on=   0.0
 ! These switches are also controlled by mating parameters

INITIAL  !

     !SIMULATION PARAMETERS ====
CONSTANT PARA_ZERO          = 1E-30
CONSTANT EXP_TIME_ON     = 0.0       ! TIME AT WHICH EXPOSURE BEGINS (HOURS)
CONSTANT EXP_TIME_OFF    = 530       ! TIME AT WHICH EXPOSURE ENDS (HOURS)
CONSTANT DAY_CYCLE       = 24.0      ! NUMBER OF HOURS BETWEEN DOSES (HOURS)
CONSTANT BCK_TIME_ON     = 0.0       ! TIME AT WHICH BACKGROUND EXPOSURE
BEGINS (HOURS)
CONSTANT BCK_TIME_OFF    = 0.0       ! TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOURS)
CONSTANT TRANSTIME_ON    = 144.0     !CONTROL TRANSFER FROM MOTHER TO FETUS
AT GESTATIONAL DAY 6
```

```
 !UNIT CONVERSION
CONSTANT MW=322 ! MOLECULAR WEIGHT (NG/NMOL)
CONSTANT SERBLO = 0.55
CONSTANT UNITCORR = 1000


    !INTRAVENOUS SEQUENCE
constant IV_LACK         = 0.0
constant IV_PERIOD       = 0.0

    !PREGNANCY PARAMETER ====
CONSTANT MATTING         = 0.0       !BEGINNING OF MATING (HOUR)
CONSTANT N_FETUS         = 10.0       !NUMBER OF FETUS PRESENT

    !CONSTANT EXPOSURE CONTROL ===========
    !ACUTE, SUBCHRONIC, CHRONIC EXPOSURE =====
    !OR BACKGROUND EXPOSURE (IN THIS CASE 3 TIMES A DAY)===
CONSTANT MSTOTBCKGR      = 0.0       ! ORAL BACKGROUND EXPOSURE DOSE (UG/KG)
CONSTANT MSTOT           = 0.0       ! ORAL EXPOSURE DOSE (UG/KG)

    !ORAL ABSORPTION
  MSTOT_NM = MSTOT/MW              ! CONVERTS THE DOSE TO NMOL/G

    !INTRAVENOUS ABSORPTION
CONSTANT  DOSEIV         = 0.0       ! INJECTED DOSE (UG/KG)
  DOSEIV_NM = DOSEIV/MW            ! CONVERTS THE INJECTED DOSE TO NMOL/G
CONSTANT DOSEIVLATE = 0.0            ! INJECTED DOSE LATE (UG/KG)
  DOSEIVNMlate = DOSEIVLATE/MW     !AMOUNT IN NMOL/G

    !INITIAL GUESS OF THE FREE CONCENTRATION IN THE LIGAND (COMPARTMENT
INDICATED BELOW)====
CONSTANT CFLLI0          = 0.0  !LIVER    (NMOL/ML)
CONSTANT CFLPLA0         = 0.0  !PLACENTA (NMOL/ML)

    !BINDING CAPACITY (AhR) FOR NON LINEAR BINDING (COMPARTMENT INDICATED
BELOW) (NMOL/ML) ===
CONSTANT LIBMAX          = 3.5E-4   ! LIVER  (NMOL/ML), WANG ET AL. 1997
CONSTANT PLABMAX         = 2.0E-4   !TEMPORARY PARAMETER

    ! PROTEIN AFFINITY CONSTANTS (1A2 OR AhR, COMPARTMENT INDICATED BELOW)
(NMOL/ML)===
CONSTANT KDLI            = 1.0E-4   !LIVER (AhR) (NMOL/ML), WANG ET AL. 1997
CONSTANT KDLI2           = 4.0E-2   !LIVER (1A2) (NMOL/ML), EMOND ET AL. 2004
CONSTANT KDPLA           = 1.0E-4   !TEMPORARY PARAMETER; ASSUME IDENTICAL TO
KDLI (AhR)

    !EXCRETION AND ABSORPTION CONSTANT
CONSTANT KST             = 0.36     ! GASTRIC RATE CONSTANT (HR-1), WANG ET
AL. 1997
CONSTANT KABS            = 0.48     !INTESTINAL ABSORPTION CONSTANT (HR-1) ),
WANG ET AL. 1997

    ! ELIMINATION CONSTANTS
CONSTANT CLURI           = 0.01       ! URINARY CLEARANCE (ML/HR), EMOND ET
AL. 2004
```

```
1
2       !INTERSPECIES ELIMINATION VARIABLE
3   CONSTANT kelv            = 0.15     ! INTERSPECIES VARIABLE ELIMINATION
4   CONSTANT (1/HOUR)
5
6       ! CONSTANT TO DIVIDE THE ABSORPTION INTO LYMPHATIC AND PORTAL FRACTIONS
7   CONSTANT A               = 0.7        ! LYMPHATIC FRACTION, WANG ET AL. 1997
8
9       !PARTITION COEFFICIENTS
10  CONSTANT PF              = 100     ! ADIPOSE TISSUE/BLOOD, WANG ET AL. 1997
11  CONSTANT PRE             = 1.5      ! REST OF THE BODY/BLOOD, WANG ET AL.
12  1997
13  CONSTANT PLI             = 6.0       ! LIVER/BLOOD, WANG ET AL. 1997
14  CONSTANT PPLA            = 1.5      ! TEMPORARY PARAMETER NOT CONFIGURED,
15  WANG ET AL. 1997
16
17      !PARAMETER FOR INDUCTION OF CYP 1A2, WANG ET AL. 1997
18  CONSTANT PAS_INDUC       = 1.0        ! INCLUDE INDUCTION? (1 = YES, 0 = NO)
19  CONSTANT CYP1A2_1OUTZ    = 1.6      ! DEGRADATION CONCENTRATION CONSTANT OF
20  1A2 (NMOL/ML)
21  CONSTANT CYP1A2_1A1      = 1.6      ! BASAL CONCENTRATION OF 1A1 (NMOL/ML)
22  CONSTANT CYP1A2_1EC50    = 0.13      ! DISSOCIATION CONSTANT TCDD-CYP1A2
23  (NMOL/ML)
24  CONSTANT CYP1A2_1A2      = 1.6      !BASAL CONCENTRATION OF 1A2 (NMOL/ML)
25  CONSTANT CYP1A2_1KOUT    = 0.1      ! FIRST ORDER RATE OF DEGRADATION (H-1)
26  CONSTANT CYP1A2_1TAU     = 0.25     !HOLDING TIME (H)
27  CONSTANT CYP1A2_1EMAX    = 600      ! MAXIMUM INDUCTION OVER BASAL EFFECT
28  (UNITLESS)
29  CONSTANT HILL            = 0.6      !HILL CONSTANT; COOPERATIVELY LIGAND
30  BINDING EFFECT CONSTANT (UNITLESS)
31
32      !DIFFUSIONAL PERMEABILITY FRACTION
33  CONSTANT PAFF            = 0.0910   !ADIPOSE (UNITLESS), WANG ET AL. 1997
34  CONSTANT PAREF           = 0.0298   !REST OF THE BODY  (UNITLESS), WANG ET
35  AL. 1997
36  CONSTANT PALIF           = 0.3500   !LIVER (UNITLESS), WANG ET AL. 1997
37  CONSTANT PAPLAF          = 0.3      !TEMPORARY PARAMETER NOT CONFIGURED
38
39     !FRACTION OF TISSUE WEIGHT =========
40  CONSTANT WLI0            = 0.0360   !LIVER, WANG ET AL. 1997
41
42     !TISSUE BLOOD FLOW EXPRESSED AS A FRACTION OF CARDIAC OUTPUT
43  CONSTANT QFF             = 0.069    ! ADIPOSE TISSUE BLOOD FLOW FRACTION
44  (UNITLESS), WANG ET AL. 1997
45  CONSTANT QLIF            = 0.183    !LIVER (UNITLESS), WANG ET AL. 1997
46
47     !COMPARTMENT TISSUE BLOOD EXPRESSED AS A FRACTION OF THE TOTAL COMPARTMENT
48  VOLUME
49  CONSTANT WFB0            = 0.050    !ADIPOSE TISSUE, WANG ET AL. 1997
50  CONSTANT WREB0           = 0.030    !REST OF THE BODY, WANG ET AL. 1997
51  CONSTANT WLIB0           = 0.266    !LIVER, WANG ET AL. 1997
52  CONSTANT WPLAB0          = 0.500    !TEMPORARY PARAMETER NOT CONFIGURED
53
54     !EXPOSURE SCENARIO FOR UNIQUE OR REPETITIVE WEEKLY OR MONTHLY EXPOSURE
55     !NUMBER OF EXPOSURES PER WEEK
56  CONSTANT WEEK_LACK       = 0.0       !DELAY BEFORE EXPOSURE ENDS (WEEK)
```

```
CONSTANT WEEK_PERIOD     = 168      ! NUMBER OF HOURS IN THE WEEK (HOURS)
CONSTANT WEEK_FINISH     = 168      ! TIME EXPOSURE ENDS (HOURS)

   !NUMBER OF EXPOSURES PER MONTH
CONSTANT MONTH_LACK      = 0.0       !DELAY BEFORE EXPOSURE BEGINS (MONTHS)

   !CONSTANT FOR BACKGROUND EXPOSURE==========
CONSTANT Day_LACK_BG     = 0.0       !DELAY BEFORE EXPOSURE BEGINS (HOURS)
CONSTANT Day_PERIOD_BG   = 24       !LENGTH OF EXPOSURE (HOURS)

   !NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LACK_BG      = 0.0      !DELAY BEFORE BACKGROUD EXPOSURE BEGINS
(WEEKS)
CONSTANT WEEK_PERIOD_BG    = 168      !NUMBER OF HOURS IN THE WEEK (HOURS)
CONSTANT WEEK_FINISH_BG    = 168      !TIME EXPOSURE ENDS (HOURS)

   !INITIAL BODY WEIGHT
CONSTANT BW_T0             = 250      ! WANG ET AL. 1997
CONSTANT RATIO_RATF_MOUSEF = 1.0        !RATIO OF FETUS MOUSE/RAT AT
GESTATIONAL DAY 22

   ! COMPARTMENT LIPID EXPRESSED AS THE FRACTION OF TOTAL LIPID, POULIN ET AL
2000
CONSTANT F_TOTLIP          = 0.855              ! ADIPOSE TISSUE (UNITLESS)
CONSTANT B_TOTLIP          = 0.0023              ! BLOOD (UNITLESS)
CONSTANT RE_TOTLIP         = 0.019              ! REST OF THE BODY
(UNITLESS)
CONSTANT LI_TOTLIP         = 0.060              ! LIVER (UNITLESS)
CONSTANT PLA_TOTLIP        = 0.019
CONSTANT FETUS_TOTLIP      = 0.019

END     ! END OF THE INITIAL SECTION

DYNAMIC ! DYNAMIC SIMULATION SECTION
ALGORITHM  IALG          =           2        ! GEAR METHOD
CINTERVAL  CINT          =         0.1        ! COMMUNICATION INTERVAL
MAXTERVAL  MAXT          =        1.0e+10     ! MAXIMUM CALCULATION INTERVAL
MINTERVAL  MINT          =        1.0E-10     ! MINIMUM CALCULATION INTERVAL
VARIABLE   T             =         0.0
CONSTANT   TIMELIMIT     =         100        !SIMULATION LIMIT TIME (HOURS)
 CINTXY  = CINT
 PFUNC   = CINT

   !TIME CONVERSION
  DAY         = T/24           ! TIME IN DAYS
  WEEK        = T/168          ! TIME IN WEEKS
  MONTH       = T/730          ! TIME IN MONTHS
  YEAR        = T/8760         ! TIME IN YEARS

DERIVATIVE ! PORTION OF CODE THAT SOLVES DIFFERENTIAL EQUATIONS

   !CHRONIC OR SUBCHRONIC EXPOSURE SCENARIO =======
   !NUMBER OF EXPOSURES PER DAY
 DAY_LACK         = EXP_TIME_ON    ! DELAY BEFORE EXPOSURE BEGINS (HOURS)
 DAY_PERIOD       = DAY_CYCLE      ! EXPOSURE PERIOD (HOURS)
 DAY_FINISH       = CINTXY         ! LENGTH OF EXPOSURE (HOURS)
```

```
 MONTH_PERIOD     = TIMELIMIT      ! EXPOSURE PERIOD (MONTHS)
 MONTH_FINISH     = EXP_TIME_OFF   ! LENGTH OF EXPOSURE (MONTHS)

   !NUMBER OF EXPOSURES PER DAY AND MONTH
 DAY_FINISH_BG    = CINTXY
 MONTH_LACK_BG    = BCK_TIME_ON    !DELAY BEFORE BACKGROUD EXPOSURE BEGINS
(MONTHS)
 MONTH_PERIOD_BG  = TIMELIMIT      !BACKGROUND EXPOSURE (MONTHS)
 MONTH_FINISH_BG  = BCK_TIME_OFF   !LENGTH OF BACKGROUND EXPOSURE (MONTHS)

   !INTRAVENOUS LATE
 IV_FINISH = CINTXY
 B = 1-A ! FRACTION OF DIOXIN ABSORBED IN THE PORTAL FRACTION OF THE LIVER


!FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUM
E
  ! FROM OFLAHERTY_1992

RTESTGEST= T-MATTING
TESTGEST=DIM(RTESTGEST,0.0)

WTFER_RODENT= (2.3d-3*EXP(1.49d-2*(TESTGEST))+1.3d-2)*Gest_on
WTFER = (WTFER_RODENT*RATIO_RATF_MOUSEF*N_FETUS)
WTFE = DIM(WTFER,0.0)

  !
FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLUME
  ! FAT GROWTH EXPRESSION LINEAR DURING PREGNANCY
  ! FROM O'FLAHERTY_1992

WF0= (((9.66d-5*(TESTGEST))*gest_on)+0.069)

  ! PLACENTA,VOLUME, PLACENTA,VOLUME, PLACENTA,VOLUME, PLACENTA,VOLUME
  ! WPLA PLACENTA GROWTH  EXPRESSION, SINGLE EXPONENTIAL WITH OFFSET
  ! FROM O'FLAHERTY_1992  ! FOR EACH PUP

WPLA0N_RODENT = (0.6/(1+(5d+3*EXP(-0.0225*(TESTGEST)))))*N_FETUS
WPLA0R = (WPLA0N_RODENT/WT0)*Gest_on
WPLA0 = DIM(WPLA0R,0.0)

  ! PLACENTA,FLOW RATE, PLACENTA,FLOW RATE, PLACENTA,FLOW RATE, PLACENTA,FLOW
RATE
  ! QPLA PLACENTA GROWTH EXPRESSION, DOUBLE EXPONENTIAL WITH OFFSET
  ! FROM O'FLAHERTY_1992

 QPLARF = (1.67d-7 *exp(9.6d-3*(TESTGEST)) &
   +1.6d-3*exp(7.9d-3*(TESTGEST))+0.0)*Gest_on*SWITCH_trans
 QPLAF=DIM(QPLARF,0.0)              !FRACTION OF FLOW RATE IN PLACENTA

  ! GESTATION CONTROL
IF (T.LT.MATTING) THEN
    Gest_off = 1.0
    Gest_on=   0.0
ELSE
    Gest_off = 0.0
```

```
    Gest_on  = 1.0
END IF

  ! MOTHER BODY WEIGHT GROWTH EQUATION========
  ! MODIFICATION TO ADAPT THIS MODEL AT HUMAN MODEL
  ! BECAUSE LINEAR DESCRIPTION IS NOT GOOD ENOUGH FOR MOTHER GROWTH
  ! MOTHER BODY WEIGHT GROWTH

  PARAMETER (BW_RMN = 1.0E-30)
  WT0= BW_T0 *(1+(0.41*T)/(1402.5+T+BW_RMN))

  ! VARIABILITY OF REST OF THE BODY DEPENDS ON OTHER ORGANS
  WRE0 = (0.91 - (WLIB0*WLI0 + WFB0*WF0 +WPLAB0*WPLA0 + WLI0 + WF0 +
WPLA0))/(1+WREB0)  ! REST OF THE BODY FRACTION; UPDATED FOR EPA ASSESSMENT
  QREF = 1-(QFF+QLIF+QPLAF)            !REST OF BODY BLOOD FLOW RATE (ML/HR)
  QTTQF = QFF+QREF+QLIF+QPLAF          ! SUM MUST EQUAL 1

  ! COMPARTMENT VOLUME (ML OR G) =========
 WF  =  WF0  * WT0                    ! ADIPOSE TISSUE
 WRE =  WRE0 * WT0                    ! REST OF THE BODY
 WLI =  WLI0 * WT0                    ! LIVER
 WPLA=  WPLA0* WT0                    ! PLACENTA

   ! COMPARTMENT TISSUE BLOOD (ML OR G) =========
 WFB  =  WFB0  * WF                   ! ADIPOSE TISSUE
 WREB =  WREB0 * WRE                  ! REST OF THE BODY
 WLIB =  WLIB0 * WLI                  ! LIVER
 WPLAB = WPLAB0* WPLA                 ! PLACANTA

   ! CARDIAC OUTPUT FOR THE GIVEN BODY WEIGHT (ML/H) =========
   !QC= QCCAR*60*(WT0/1000.0)**0.75
CONSTANT QCC=18684.0                    ! EQUIVALENT TO 311.4 * 60
QC= QCC*(WT0/UNITCORR)**0.75

   !COMPARTMENT BLOOD FLOW RATE (ML/HR)
QF  = QFF*QC                          !ADIPOSE TISSUE BLOOD FLOW RATE
QLI = QLIF*QC                         !LIVER TISSUE BLOOD FLOW RATE
QRE = QREF*QC                         !REST OF THE BODY BLOOD FLOW RATE
QPLA = QPLAF*QC                       !PLACENTA TISSUE BLOOD FLOW RATE
QTTQ = QF+QRE+QLI+QPLA   !TOTAL FLOW RATE

    !PERMEABILITY ORGAN FLOW (ML/HR)=========
PAF  = PAFF*QF                       ! ADIPOSE TISSUE
PARE = PAREF*QRE                     ! REST OF THE BODY
PALI = PALIF*QLI                     ! LIVER TISSUE
PAPLA = PAPLAF*QPLA                  ! PLACENTA

    !************************************
    ! ABSORPTION SECTION
    ! ORAL
    ! INTRAPERITONEAL
    ! INTRAVENOUS
    !************************************

    !REPETITIVE ORAL BACKGROUND EXPOSURE SCENARIO

```

```
MSTOT_NMBCKGR = MSTOTBCKGR/MW       ! CONVERTS THE BACKGROUND DOSE TO NMOL/G
MSTTBCKGR =MSTOT_NMBCKGR *WT0

DAY_EXPOSURE_BG   = PULSE(DAY_LACK_BG,DAY_PERIOD_BG,DAY_FINISH_BG)
WEEK_EXPOSURE_BG  = PULSE(WEEK_LACK_BG,WEEK_PERIOD_BG,WEEK_FINISH_BG)
MONTH_EXPOSURE_BG = PULSE(MONTH_LACK_BG,MONTH_PERIOD_BG,MONTH_FINISH_BG)

MSTTCH_BG = (DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG)*MSTTBCKGR
MSTTFR_BG = MSTTBCKGR/CINT

CYCLE_BG =DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG

    ! CONDITIONAL ORAL EXPOSURE (BACKGROUND EXPOSURE)

IF (MSTTCH_BG.EQ.MSTTBCKGR) THEN
    ABSMSTT_GB= MSTTFR_BG
ELSE
    ABSMSTT_GB = 0.0
END IF

CYCLETOTBG=INTEG(CYCLE_BG,0.0)

   !REPETITIVE ORAL EXPOSURE SCENARIO

MSTT= MSTOT_NM * WT0                  !AMOUNT IN NMOL

DAY_EXPOSURE   = PULSE(DAY_LACK,DAY_PERIOD,DAY_FINISH)
WEEK_EXPOSURE  = PULSE(WEEK_LACK,WEEK_PERIOD,WEEK_FINISH)
MONTH_EXPOSURE = PULSE(MONTH_LACK,MONTH_PERIOD,MONTH_FINISH)

MSTTCH = (DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE)*MSTT
MSTTFR = MSTT/CINT

CYCLE = DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE
SUMEXPEVENT= INTEG (CYCLE,0.0) !NUMBER OF CYCLE GENERATE DURING SIMULATION

   ! CONDITIONAL ORAL EXPOSURE
IF (MSTTCH.EQ.MSTT) THEN
   ABSMSTT= MSTTFR
ELSE
   ABSMSTT = 0.0
END IF


 CYCLETOT=INTEG(CYCLE,0.0)

   ! MASS CHANGE IN THE LUMEN
 RMSTT= -(KST+KABS)*MST +ABSMSTT +ABSMSTT_GB ! RATE OF CHANGE (NMOL/H)
  MST = INTEG(RMSTT,0.0)                    !AMOUNT REMAINING IN DUODENUM
(NMOL)

   ! ABSORPTION IN LYMPH CIRCULATION
 LYRMLUM = KABS*MST*A
  LYMLUM = INTEG(LYRMLUM,0.0)

   ! ABSORPTION IN PORTAL CIRCULATION
```

```
 LIRMLUM = KABS*MST*B
  LIMLUM = INTEG(LIRMLUM,0.0)


! -----IV EXPOSURE ---------

 IV= DOSEIV_NM * WT0 !AMOUNT IN NMOL
 IVR= IV/PFUNC ! RATE FOR IV INFUSION IN BLOOD
 EXPIV= IVR * (1.0-STEP(PFUNC))
 IVDOSE = integ(EXPIV,0.0)

    !------IV LATE IN THE CYCLE
    ! MODIFICATION ON January 13 2004
 IV_RlateR = DOSEIVNMlate*WT0
 IV_EXPOSURE=PULSE(IV_LACK,IV_PERIOD,IV_FINISH)

 IV_lateT = IV_EXPOSURE *IV_RlateR
 IV_late = IV_lateT/CINT

SUMEXPEVENTIV= integ (IV_EXPOSURE,0.0) !NUMBER OF CYCLE GENERATE DURING
SIMULATION

    !SYSTEMIC CONCENTRATION OF TCDD

     ! MODIFICATION ON OCTOBER 6, 2009
 CB= (QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM+QPLA*CPLAB+IV_late)/(QC+CLURI) !
  CA = CB ! CONCENTRATION (NMOL/ML)


    !URINARY EXCRETION BY KIDNEY
    ! MODIFICATION ON OCTOBER 6, 2009
RAURI = CLURI *CB
  AURI = INTEG(RAURI,0.0)



  !UNIT CONVERSION POST SIMULATION
 CBSNGKGLIADJ=(CB*MW*UNITCORR*(1.0/B_TOTLIP)*(1.0/SERBLO))![NG of TCDD
Serum/Kg OF LIPIP]
   AUCBS_NGKGLIADJ=integ(CBSNGKGLIADJ,0.0)

  PRCT_B = (CB/(MSTT+1E-30))*100.0 !PERCENT OF ORAL DOSE IN BLOOD
  PRCT_BIV = (CB/(IV_RlateR+1E-30))*100.0 ! PERCENT OF IV DOSE IN BLOOD
  CBNGKG= CB*MW*UNITCORR


   !ADIPOSE COMPARTMENT
   !TISSUE BLOOD COMPARTMENT
RAFB= QF*(CA-CFB)-PAF*(CFB-CF/PF)     !(NMOL/H)
 AFB = INTEG(RAFB,0.0)                 !(NMOL)
  CFB = AFB/WFB                        !(NMOL/ML)
   !TISSUE COMPARTMENT
RAF = PAF*(CFB-CF/PF)                 !(NMOL/H)
 AF = INTEG(RAF,0.0)                   !(NMOL)
  CF  = AF/WF                          !(NM/ML)
```

```
    !UNIT CONVERSION POST SIMULATION
  CFTOTAL= (AF + AFB)/(WF + WFB) ! TOTAL CONCENTRATION IN NMOL/ML
  CFTFREE = CFB + CF !TOTAL FREE CONCENTRATION IN FAT  (NM/ML)
  PRCT_F = (CFTOTAL/(MSTT+1E-30))*100.0 ! PERCENT OF ORAL DOSE IN FAT
  PRCT_FIV = (CFTOTAL/(IV_RlateR+1E-30))*100.0 ! PERCENT OF IV DOSE IN FAT
  CFNGKG=CFTOTAL*MW*UNITCORR ! FAT CONCENTRATION NG/KG
    AUCF_NGKGH=integ(CFNGKG,0.0)

    !REST OF THE BODY COMPARTMENT
RAREB= QRE *(CA-CREB)-PARE*(CREB-CRE/PRE)  !(NMOL/H)
 AREB = INTEG(RAREB,0.0)                    !(NMOL)
  CREB = AREB/WREB                          !(NMOL/H)
   !TISSUE COMPARTMENT
RARE = PARE*(CREB - CRE/PRE)               !(NMOL/H)
 ARE = INTEG(RARE,0.0)                     !(NMOL)
  CRE  = ARE/WRE                            !(NMOL/ML)

    !UNIT CONVERSION POST SIMULATION
  CRETOTAL= (ARE + AREB)/(WRE + WREB)           ! TOTAL CONCENTRATION IN
NMOL/ML
  PRCT_RE = (CRETOTAL/(MSTT+1E-30))*100.0 ! PERCENT OF ORAL DOSE IN REST OF
THE BODY
  PRCT_REIV = (CRETOTAL/(IV_RlateR+1E-30))*100.0   !PERCENT OF IV DOSE IN
REST OF THE BODY
  CRENGKG=CRETOTAL*MW*UNITCORR ! REST OF THE BODY CONCENTRATION IN NG/KG


    !LIVER COMPARTMENT
    !TISSUE BLOOD COMPARTMENT
 RALIB = QLI*(CA-CLIB)-PALI*(CLIB-CFLLIR)+LIRMLUM !
  ALIB = INTEG(RALIB,0.0)                        !(NMOL)
   CLIB = ALIB/WLIB                             !(NMOL/ML)
   !TISSUE COMPARTMENT
 RALI = PALI*(CLIB - CFLLIR)-REXCLI             !  (NMOL/HR)
  ALI = INTEG(RALI,0.0)                           !(NMOL)
   CLI  = ALI/WLI                                !(NMOL/ML)

   !FREE TCDD CONCENTRATION IN LIVER COMPARTMENT
PARAMETER (LIVER_1RMN = 1.0E-30)
 CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLIR &
        +LIVER_1RMN))+((CYP1A2_1O3*CFLLIR/(KDLI2 + CFLLIR &
        +LIVER_1RMN)*PAS_INDUC)))-CFLLI,CFLLI0)
     CFLLIR=DIM(CFLLI,0.0) ! FREE CONCENTRATION IN LIVER

  CBNDLI= LIBMAX*CFLLIR/(KDLI+CFLLIR+LIVER_1RMN) !BOUND CONCENTRATION

  !VARIABLE ELIMINATION BASED ON THE CYP1A2
 KBILE_LI_T =((CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2)*Kelv ! INDUCED BILIARY
EXCRETION RATE CONSTANT IN LIVER
  REXCLI = KBILE_LI_T*CFLLIR*WLI ! DOSE-DEPENDENT BILIARY EXCRETION RATE
    EXCLI = INTEG(REXCLI,0.0)

  !UNIT CONVERSION POST SIMULATION
  CLITOTAL= (ALI + ALIB)/(WLI + WLIB) ! TOTAL CONCENTRATION IN NMOL/ML
  PRCT_LI = (CLITOTAL/(MSTT+1E-30))*100
  PRCT_LIIV = (CLITOTAL/(IV_RlateR+1E-30))*100.0
```

```
  Rec_occ= CFLLIR/(KDLI+CFLLIR)
  CLINGKG=CLITOTAL*MW*UNITCORR ! LIVER CONCENTRATION NG/KG
     AUCLI_NGKGH=INTEG(CLINGKG,0.0)
  CBNDLINGKG = CBNDLI*MW*UNITCORR
     AUCBNDLI_NGKGH =INTEG(CBNDLINGKG,0.0)


   !CHEMICAL IN CYP450 (1A2) COMPARTMENT
CYP1A2_1KINP = CYP1A2_1KOUT* CYP1A2_1OUTZ


    ! MODIFICATION ON OCTOBER 6, 2009
CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1.0 + CYP1A2_1EMAX *(CBNDLI+1.0e-30)**HILL
&
     /(CYP1A2_1EC50**HILL + (CBNDLI+1.0e-30)**HILL)) &
      - CYP1A2_1KOUT*CYP1A2_1OUT, CYP1A2_1OUTZ)

! EQUATIONS INCORPORATING DELAY OF CYP1A2 PRODUCTION (NOT USED IN
SIMULATIONS)

CYP1A2_1RO2 = (CYP1A2_1OUT - CYP1A2_1O2)/ CYP1A2_1TAU
  CYP1A2_1O2 =INTEG(CYP1A2_1RO2, CYP1A2_1A1)

CYP1A2_1RO3 = (CYP1A2_1O2 - CYP1A2_1O3)/ CYP1A2_1TAU
  CYP1A2_1O3 =INTEG(CYP1A2_1RO3, CYP1A2_1A2)

! TRANSFER OF DIOXIN FROM PLACENTA TO FETUS
! FETAL EXPOSURE ONLY DURING EXPOSURE

IF (T.LT.TRANSTIME_ON) THEN
 SWITCH_trans = 0.0
ELSE
 SWITCH_trans = 1.0
END IF

!TRANSFER OF DIOXIN FROM PLACENTA TO FETUS
! MODIFICATION 26 SEPTEMBER 2003

CONSTANT PFETUS= 4.0 !
CONSTANT CLPLA_FET = 0.17 !

RAMPF = (CLPLA_FET*CPLA) *SWITCH_trans
  AMPF=INTEG(RAMPF,0.0)

!TRANSFER OF DIOXIN FROM FETUS TO PLACENTA
RAFPM = (CLPLA_FET*CFETUS_v)*SWITCH_trans !
  AFPM = INTEG(RAFPM,0.0)

! TCDD IN PLACENTA (MOTHER) COMPARTMENT
RAPLAB= QPLA*(CA - CPLAB)-PAPLA*(CPLAB -CFLPLAR)    ! NMOL/H)
 APLAB = INTEG(RAPLAB,0.0)                           ! (NMOL)
 CPLAB = APLAB/(WPLAB+1E-30)                        ! (NMOL/ML)
RAPLA = PAPLA*(CPLAB-CFLPLAR)-RAMPF + RAFPM         ! (NMOL/H)
 APLA = INTEG(RAPLA,0.0)                             ! (NMOL)
 CPLA  = APLA/(WPLA+1e-30)                          ! (NMOL/ML)
```

```
PARAMETER (PARA_ZERO = 1.0E-30)
CFLPLA= IMPLC(CPLA-(CFLPLAR*PPLA +(PLABMAX*CFLPLAR/(KDPLA&
    +CFLPLAR+PARA_ZERO)))-CFLPLA,CFLPLA0)
CFLPLAR=DIM(CFLPLA,0.0)

   !UNIT CONVERSION POST SIMULATION
  CPLATOTAL= (APLA + APLAB)/((WPLA + WPLAB)+1e-30)! TOTAL CONCENTRATION IN
NMOL/ML
  PRCT_PLA = (CPLATOTAL/(MSTT+1E-30))*100
  PRCT_PLAIV = (CPLATOTAL/(IV_RlateR+1E-30))*100


   !FETUS COMPARTMENT
RAFETUS= RAMPF-RAFPM
 AFETUS=INTEG(RAFETUS,0.0)
CFETUS=AFETUS/(WTFE+1E-30)
CFETOTAL= CFETUS
CFETUS_v = CFETUS/PFETUS

  ! UNIT CONVERSION POST SIMULATION
CFETUSNGKG = CFETUS*MW*UNITCORR                    !(NG/KG)
AUC_FENGKGH = INTEG(CFETUSNGKG,0.0)
PRCT_FE = (CFETOTAL/(MSTT+1E-30))*100
PRCT_FEIV = (CFETOTAL/(IV_RlateR+1E-30))*100


! ------------CONTROL MASS BALANCE ----------
BDOSE= IVDOSE +LYMLUM+LIMLUM
BMASSE = EXCLI+AURI+AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB+AFETUS
BDIFF = BDOSE-BMASSE

      !BODY BURDEN (NG)
BODY_BURDEN = AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB !
BBFETUSNG     = AFETUS*MW*UNITCORR    ! UNIT (NG)
      ! BODY BURDEN IN TERMS OF CONCENTRATION (NG/KG)
 BBNGKG =(((AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB)/WT0)*MW*UNITCORR) !
  AUC_BBNGKGH=INTEG(BBNGKG,0.0)


! ------------COMMAND OF THE END OF SIMULATION ----------
TERMT (T.GE. TimeLimit, 'Time limit has been reached.')
END   ! END OF THE DERIVATIVE SECTION
END   ! END OF THE DYNAMIC SECTION
END   ! END OF THE PROGRAM
```

C.2.4.2. *Input Files*

C.2.4.2.1. *Bell et al. (2007).*

```
%clear variable
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH
```

```
%output @nciout=1 T BBFETUSNG %AJS turned off 9/21/09

%Bell et al. 2007 (rat species)
%protocol:  daily dietary dose for 12 weeks followed by a two-week mating
time and 21-day gestation period
%DevTCDD4Species.csl
%RAT_GESTATIONAL_ICF_F083109.csl (now 09-11-09)
%dose levels: 0.0024, 0.008, 0.046 ug/kg/d with 0.00003 ug/kg/d background
%dose levels: 2.4, 8, 46 ng/kg/d with 0.03 ng/kg/day background

   %EXPOSURES SCENARIOS
 MAXT             = 0.01
 CINT             = 0.1  %
 EXP_TIME_ON      = 0            % delay before begin exposure (HOUR)
 EXP_TIME_OFF     = 2856         % TIME EXPOSURE STOP (HOUR) 12 weeks
exposure + 2 weeks for mating + 21 days gestation with exposure
 DAY_CYCLE        = 24
 BCK_TIME_ON      = 0.           % DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
 BCK_TIME_OFF     = 2856.           % TIME OF BACKGROUND EXPOSURE STOP (HOUR)
 IV_LACK          = 505.
 IV_PERIOD        = 505.
 TIMELIMIT        = 2856         % SIMULATION LIMIT TIME (HOUR)
 BW_T0            = 85
 MATTING          = 2352         % BEGINNING MATING (HOUR)
 TRANSTIME_ON     = 2496         % SHOULD BE MATING TIME + 6 DAYS(144 HOURS)
 N_FETUS          = 10

%EXPOSURE DOSE SCENARIOS (UG/KG)
   MSTOT           = 0.00243        % ORAL EXPOSURE DOSE (UG/KG)

   %MSTOT           = 0.008         % ORAL EXPOSURE DOSE (UG/KG)

   %MSTOT = 0.0461          % ORAL EXPOSURE DOSE (UG/KG)
```

C.2.4.2.2. *Haavisto et al. (2006).*

```
%clear variable
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH

%Haavisto et al. 2006
%protocol:  single dose on GD 13
%dose levels: 0.04, 0.2, and 1.0 ug/kg on GD 13
%dose levels: 40, 200, and 1,000 ng/kg on GD 13

 MAXT = 0.001
 CINT = 0.1

   %EXPOSURES SCENARIOS
 EXP_TIME_ON         = 312           % TIME AT WHICH EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF        = 335           % TIME AT WHICH EXPOSURE ENDS (HOUR)
 DAY_CYCLE           = 24
```

```
 BCK_TIME_ON         = 0.             % TIME AT WHICH BACKGROUND EXPOSURE
BEGINS (HOUR)
 BCK_TIME_OFF        = 0.             % TIME AT WHICH BACKGROUND EXPOSURE
ENDS (HOUR)
 IV_LACK             = 505
 IV_PERIOD           = 505
 TIMELIMIT           = 336            % SIMULATION LIMIT TIME (HOUR)
 BW_T0               = 190
 MATTING             = 0.             % BEGINNING MATTING (HOUR)
 TRANSTIME_ON        = 144.           % SHOULD BE MATTING TIME + 6 DAYS(144
HOURS)
 N_FETUS             = 10

%EXPOSURE DOSE SCENARIOS (UG/KG)
  %MSTOT            = 0.04           % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT            = 0.2            % ORAL EXPOSURE DOSE (UG/KG)
  MSTOT            = 1.0            % ORAL EXPOSURE DOSE (UG/KG)
```

C.2.4.2.3. *Hojo et al. (2002).*

```
%clear variable
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH
%Hojo et al. 2002
%protocol:  single oral dose at GD8
%DevTCDD4Species.csl
%RAT_GESTATIONAL_ICF_F083109.csl (now 09-11-09)
%RAT_GESTATIONAL_ICF_F092009.csl (now 09-21-09
%dose levels: 0.02 0.06, 0.18 ug/kg  at GD8
%dose levels: 20, 60, 180  ng/kg at GD8
% author provided the body weight for each group at the beginning og
gestation (g)
    %20 ng/kg BW = 271g
    %60 ng/kg BW = 275g
    %180 ng/kg BW = 262g

%EXPOSURES SCENARIOS
 MAXT= 0.001
 CINT =0.1                          %
 EXP_TIME_ON     = 192           % delay before begin exposure (HOUR)
 EXP_TIME_OFF    = 216           % TIME EXPOSURE STOP (HOUR)
 DAY_CYCLE       = 24
 BCK_TIME_ON     = 0.            % DELAY BEFORE BACGROUND EXPOSURE (HOUR)
 BCK_TIME_OFF    = 0.            % TIME OF BACKGROUND EXPOSURE STOP (HOUR)
 IV_LACK         = 505
 IV_PERIOD       = 505
 TIMELIMIT       = 216            % SIMULATION LIMIT TIME (HOUR)
% BW_T0           = 190
 MATTING         = 0.             % BEGINNING MATTING (HOUR)
 TRANSTIME_ON    = 144.           % SHOULD BE MATTING TIME + 6 DAYS(144
HOURS)
 N_FETUS         = 10
```

```
%EXPOSURE DOSE SCENARIOS (UG/KG)

   %MSTOT          = 0.02     % ORAL EXPOSURE DOSE (UG/KG)
   %BW_T0          = 275      % 20 ng/kg BW = 271g

   %MSTOT         = 0.06     % ORAL EXPOSURE DOSE (UG/KG)
   %BW_T0         = 262      %60 ng/kg BW = 275g

   MSTOT         = 0.18     % ORAL EXPOSURE DOSE (UG/KG)
   BW_T0         = 278      %180 ng/kg BW = 262g
```

C.2.4.2.4. *Ikeda et al. (2005).*

```
%clear variable
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH

%Ikeda et al. 2005 (rat species)
%protocol:  loading dose of 400 ng/kg followed by weekly maintenance doses of
80 ng/kg for 6 weeks,
%dose levels: 0.4 ug/kg/day followed by weekly 0.08 ug/kg/day
%dose levels: 400 ng/kg/day followed by weekly 80 ng/kg/day

   %EXPOSURES SCENARIOS
 MAXT             =.1
 CINT             = 0.1  %
 EXP_TIME_ON      = 0            % TIME AT WHICH EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF     = 1008         % TIME AT WHICH EXPOSURE ENDS (HOUR); PRE-
MATING (2 WEEKS) + MATING (1 WEEK) + GESTATION (3 WEEKS)
 DAY_CYCLE        = 168          % WEEKLY CYCLE
 BCK_TIME_ON      = 0.           % TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
 BCK_TIME_OFF     = 167.         % TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
 IV_LACK          = 505.
 IV_PERIOD        = 505.
 TIMELIMIT        = 1008         % SIMULATION TIME LIMIT (HOUR)
 BW_T0            = 250
 MATTING          = 504         % BEGINNING OF MATING (HOUR)
 TRANSTIME_ON     = 648         % SHOULD BE MATING TIME + 6 DAYS (144 HOURS)
 N_FETUS          = 10

%EXPOSURE DOSE SCENARIOS (UG/KG)
   MSTOT           = 0.08        % ORAL EXPOSURE DOSE IN UG/KG
   MSTOTBCKGR      = 0.32       % BACKGROUND EXPOSURE IN UG/KG
```

C.2.4.2.5. *Kattainen et al. (2001).*

```
%clear variable
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH
```

```
%Kattainen et al. 2001
%protocol:  single gavage at GD15
%DevTCDD4Species.csl
%RAT_GESTATIONAL_ICF_F083109.csl (now 09-11-09)
%dose levels: 0.03 0.1, 0.3, 1 ug/kg  at GD15
%dose levels: 30, 100 300, 1000 ng/kg at GD15

 MAXT=0.001
 CINT =0.1

   %EXPOSURES SCENARIOS
 EXP_TIME_ON         = 336            % delay before begin exposure (HOUR)
 EXP_TIME_OFF        = 360            % TIME EXPOSURE STOP (HOUR)
 DAY_CYCLE           = 24
 BCK_TIME_ON         = 0.             % DELAY BEFORE BACKGROUND EXPOSURE
(HOUR)
 BCK_TIME_OFF        = 0.             % TIME OF BACKGROUND EXPOSURE STOP
(HOUR)
 IV_LACK             = 505
 IV_PERIOD           = 505
 TIMELIMIT           = 360            % SIMULATION LIMIT TIME (HOUR)
 BW_T0               = 190
 MATTING             = 0.             % BEGINNING MATTING (HOUR)
 TRANSTIME_ON        = 144.           % SHOULD BE MATTING TIME + 6 DAYS(144
HOURS)
 N_FETUS             = 10

%EXPOSURE DOSE SCENARIOS (UG/KG)
 %MSTOT            = 0.03           % ORAL EXPOSURE DOSE (UG/KG)
 %MSTOT            = 0.1            % ORAL EXPOSURE DOSE (UG/KG)
 %MSTOT            = 0.3            % ORAL EXPOSURE DOSE (UG/KG)
 MSTOT             = 1              % ORAL EXPOSURE DOSE (UG/KG
```

C.2.4.2.6. *Markowski et al. (2001).*

```
%clear variable
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH

%Markowski et al. 2001
%protocol:  single gavage at GD18
%DevTCDD4Species.csl
%RAT_GESTATIONAL_ICF_F083109.csl (now 09-11-09)
%dose levels: 0.02 0.06, 0.18 ug/kg at GD18
%dose levels: 20, 60, 180 ng/kg at GD18

%EXPOSURES SCENARIOS
 MAXT=0.0001
 CINT =0.1                          %
 EXP_TIME_ON     = 408           % delay before begin exposure (HOUR)
 EXP_TIME_OFF    = 432           % TIME EXPOSURE STOP (HOUR)
 DAY_CYCLE       = 24
 BCK_TIME_ON     = 0.            % DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
 BCK_TIME_OFF    = 0.            % TIME OF BACKGROUND EXPOSURE STOP (HOUR)
```

```
 IV_LACK         = 505
 IV_PERIOD       = 505
 TIMELIMIT       = 432            % SIMULATION LIMIT TIME (HOUR)
 BW_T0           = 190
 MATTING         = 0.             % BEGINNING MATING (HOUR)
 TRANSTIME_ON    = 144.           % SHOULD BE MATING TIME + 6 DAYS(144 HOURS)
 N_FETUS         = 10

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT         = 0.02  % ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT        = 0.06   % ORAL EXPOSURE DOSE (UG/KG)
   MSTOT        = 0.18   % ORAL EXPOSURE DOSE (UG/KG)
```

C.2.4.2.7. *Miettinen et al. (2006).*

```
%clear variable
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH

%Miettinen et al. 2006
%protocol:  single oral dose at GD15
%DevTCDD4Species.csl
%RAT_GESTATIONAL_ICF_F083109.csl (now 09-11-09)
%dose levels: 0.03 0.1, 0.3, 1 ug/kg at GD15
%dose levels: 30, 100, 300, 1000 ng/kg at GD15

 MAXT=0.01
 CINT =0.1                     %

   %EXPOSURES SCENARIOS
 EXP_TIME_ON   = 336          % delay before begin exposure (HOUR)
 EXP_TIME_OFF  = 360          % TIME EXPOSURE STOP (HOUR)
 DAY_CYCLE     = 24
 BCK_TIME_ON   = 0.           % DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
 BCK_TIME_OFF  = 0.           % TIME OF BACKGROUND EXPOSURE STOP (HOUR)
 IV_LACK       = 505
 IV_PERIOD     = 505
 TIMELIMIT     = 360          % SIMULATION LIMIT TIME (HOUR)
 BW_T0         = 180
 MATTING       = 0.           % BEGINNING MATING (HOUR)
 TRANSTIME_ON  = 144.         % SHOULD BE MATING TIME + 6 DAYS(144 HOURS)
 N_FETUS       = 10

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT        = 0.03        % ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT      = 0.1         % ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT      = 0.3         % ORAL EXPOSURE DOSE (UG/KG)
   MSTOT      = 1           % ORAL EXPOSURE DOSE (UG/KG)
```

C.2.4.2.8. *Nohara et al. (2000).*

```
%clear variable
output @clear
```

```
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH

%Nohara et al. 2000
%protocol:  single gavage at GD15
%DevTCDD4Species.csl
%RAT_GESTATIONAL_ICF_F083109.csl (now 09-11-09)
%dose levels: 0.0125, 0.050, 0.2, or 0.8 ug TCDD:kg body weight by gavage on
GD15.
%dose levels: 12.5, 50, 200, or 800 ng TCDD:kg body weight by gavage on GD15.

 MAXT=0.01
 CINT =0.1                      %

   %EXPOSURES SCENARIOS
 EXP_TIME_ON   = 336          % delay before begin exposure (HOUR)
 EXP_TIME_OFF  = 360          % TIME EXPOSURE STOP (HOUR)
 DAY_CYCLE     = 24
 BCK_TIME_ON   = 0.           % DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
 BCK_TIME_OFF  = 0.           % TIME OF BACKGROUND EXPOSURE STOP (HOUR)
 IV_LACK       = 505
 IV_PERIOD     = 505
 TIMELIMIT     = 360           % SIMULATION LIMIT TIME (HOUR)
 BW_T0         = 180
 MATTING       = 0.             % BEGINNING MATTING (HOUR)
 TRANSTIME_ON  = 144.     % SHOULD BE MATTING TIME + 6 DAYS(144 HOURS)
 N_FETUS       = 10

%EXPOSURE DOSE SCENARIOS (UG/KG)
  %MSTOT         = 0.0125     % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 0.050   % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 0.2     % ORAL EXPOSURE DOSE (UG/KG)
  MSTOT         = 0.8     % ORAL EXPOSURE DOSE (UG/KG)
```

C.2.4.2.9. *Ohsako et al. (2001).*

```
%clear variable
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH

%Ohsako et al. 2001
%protocol:  single oral dose at GD15
%DevTCDD4Species.csl
%RAT_GESTATIONAL_ICF_F083109.csl (now 09-11-09)
%RAT_GESTATIONAL_ICF_F092009.csl (now 09-21-09)
%dose levels: 0.0125, 0.05, 0.2, 0.8 ug/kg at GD15
%dose levels: 12.5, 50, 200, 800 ng/kg at GD15

%EXPOSURES SCENARIOS
 MAXT=0.01
 CINT =0.1                        %
 EXP_TIME_ON     = 360          % delay before begin exposure (HOUR)
 EXP_TIME_OFF    = 384          % TIME EXPOSURE STOP (HOUR)
```

```
 DAY_CYCLE       = 24
 BCK_TIME_ON     = 0.            % DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
 BCK_TIME_OFF    = 0.            % TIME OF BACKGROUND EXPOSURE STOP (HOUR)
 IV_LACK         = 505
 IV_PERIOD       = 505
 TIMELIMIT       = 384            % SIMULATION LIMIT TIME (HOUR)
 BW_T0           = 200
 MATTING         = 0.             % BEGINNING MATTING (HOUR)
 TRANSTIME_ON    = 144.           % SHOULD BE MATTING TIME + 6 DAYS(144
HOURS)
 N_FETUS         = 10

%EXPOSURE DOSE SCENARIOS (UG/KG)

 %MSTOT        = 0.0125    % ORAL EXPOSURE DOSE (UG/KG)
 %MSTOT        = 0.05      % ORAL EXPOSURE DOSE (UG/KG)
 %MSTOT        = 0.20      % ORAL EXPOSURE DOSE (UG/KG)
 MSTOT          = 0.80      % ORAL EXPOSURE DOSE (UG/KG)
```

C.2.4.2.10. *Schantz et al. (1996) and Amin et al. (2000).*

```
%clear variable
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH

%Amin et al. 2000 (rat species) and Schantz et al. 1996
%protocol:  daily doses on GDs 10 to 16
%DevTCDD4Species.csl
%RAT_GESTATIONAL_ICF_F083109.csl (now 09-11-09)
%dose levels: 25 and 100 ng/kg/day
%dose levels: 0.025 and 0.100 ug/kg/day

   %EXPOSURES SCENARIOS
 MAXT             = 0.001
 CINT             = 0.1  %
 EXP_TIME_ON      = 240.           % TIME AT WHICH EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF     = 384.         % TIME AT WHICH EXPOSURE ENDS (HOUR) GD 10
to 16
 DAY_CYCLE        = 24          % weekly cycle
 BCK_TIME_ON      = 1000.          % DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
 BCK_TIME_OFF     = 1000.         % TIME OF BACKGROUND EXPOSURE STOP (HOUR)
 IV_LACK          = 505.
 IV_PERIOD        = 505.
 TIMELIMIT        = 384.         % SIMULATION LIMIT TIME (HOUR)
 BW_T0            = 250.
 MATTING          = 0         % BEGINNING MATTING (HOUR)
 TRANSTIME_ON     = 144.         % SHOULD BE MATTING TIME + 6 DAYS(144 HOURS)
 N_FETUS          = 10

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT           = .025        % ORAL EXPOSURE DOSE (UG/KG)
   MSTOT           = .100
   MSTOTBCKGR      = 0    % Background Exposure (UG/KG)
```

C.2.4.2.11. *Seo et al. (1995).*

```
%clear variable
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH

%Seo et al. 1995
%protocol:  daily doses on GDs 10-16
%DevTCDD4Species.csl
%RAT_GESTATIONAL_ICF_F083109.csl (now 09-11-09)
%dose levels: 0.025 and 0.1 ug/kg on GDs 10-16
%dose levels: 25 and 100 ng/kg on GDs 10-16

 MAXT = 0.01
 CINT = 0.1

   %EXPOSURES SCENARIOS
 EXP_TIME_ON         = 240            % TIME AT WHICH EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF        = 384            % TIME AT WHICH EXPOSURE ENDS (HOUR)
 DAY_CYCLE           = 24
 BCK_TIME_ON         = 0.             % TIME AT WHICH BACKGROUND EXPOSURE
BEGINS (HOUR)
 BCK_TIME_OFF        = 0.             % TIME AT WHICH BACKGROUND EXPOSURE
ENDS (HOUR)
 IV_LACK             = 505
 IV_PERIOD           = 505
 TIMELIMIT           = 384            % SIMULATION LIMIT TIME (HOUR)
 BW_T0               = 190
 MATTING             = 0.             % BEGINNING MATTING (HOUR)
 TRANSTIME_ON        = 144.           % SHOULD BE MATTING TIME + 6 DAYS(144
HOURS)
 N_FETUS             = 10

%EXPOSURE DOSE SCENARIOS (UG/KG)
 %MSTOT            = 0.025            % ORAL EXPOSURE DOSE (UG/KG)
 MSTOT            = 0.1             % ORAL EXPOSURE DOSE (UG/KG)
```

C.2.5. Mouse Standard Model

C.2.5.1. *Model Code*

PROGRAM: 'Three Compartment PBPK Model for TCDD in Mice: Standard Model (Non-Gestation)'

```
!Mice_Dioxin_3C_June09_1_icf_afterKKfix_v3_mousenongest.csl
!MICE_NON_GESTAT_ICF_F083109.csl
!MICE_NON_GESTAT_ICF_F093009.csl
!MICE_NON_GESTAT_ICF_F100609.csl
!*************************************************

INITIAL  ! INITIALIZATION OF PARAMETERS

    !SIMULATION PARAMETERS ====
```

```
CONSTANT PARA_ZERO       =    1D-30
CONSTANT EXP_TIME_ON     =     0.0        ! TIME AT WHICH EXPOSURE BEGINS
(HOURS)
CONSTANT EXP_TIME_OFF    =    2832        ! TIME AT WHICH EXPOSURE ENDS
(HOURS)
CONSTANT DAY_CYCLE       =     24         ! NUMBER OF HOURS BETWEEN DOSES
(HOURS)
CONSTANT BCK_TIME_ON     =      0.0       ! TIME AT WHICH BACKGROUND EXPOSURE
BEGINS (HOURS)
CONSTANT BCK_TIME_OFF    =      0.0       ! TIME AT WHICH BACKGROUND EXPOSURE
ENDS (HOURS)

CONSTANT MW=322 ! MOLECULAR WEIGHT (NG/NMOL)
CONSTANT SERBLO = 0.55
CONSTANT UNITCORR = 1000

    !CONSTANT EXPOSURE CONTROL ===========
    !ACUTE, SUBCHRONIC, CHRONIC EXPOSURE =====
    !OR BACKGROUND EXPOSURE (IN THIS CASE 3 TIMES A DAY)===
CONSTANT MSTOTBCKGR     =       0.0       !ORAL BACKGROUND EXPOSURE DOSE
(UG/KG)
CONSTANT MSTOT          =       0.15     !ORAL EXPOSURE DOSE (UG/KG)
CONSTANT MSTOTsc        =       0.0       ! SUBCUTANEOUS EXPOSURE DOSE
(UG/KG)

    !ORAL ABSORPTION
  MSTOT_NM              =   MSTOT/MW    !AMOUNT IN NMOL/G

    ! INTRAVENOUS ABSORPTION
CONSTANT  DOSEIV   = 0.0                  !INJECTED DOSE (UG/KG)
  DOSEIV_NM = DOSEIV/MW   ! CONVERTS THE INJECTED DOSE TO NMOL/G

  !INITIAL GUESS OF THE FREE CONCENTRATION IN THE LIGAND (COMPARTMENT
INDICATED BELOW)====
CONSTANT CFLLI0          =       0.0       !LIVER (NMOL/ML)

  !BINDING CAPACITY (AhR) FOR NON LINEAR BINDING (COMPARTMENT INDICATED
BELOW) (NMOL/ML)
CONSTANT LIBMAX          =     3.5e-4     ! LIVER  (NMOL/ML), WANG ET AL.
1997

! PROTEIN AFFINITY CONSTANTS (1A2 OR AhR, COMPARTMENT INDICATED BELOW)
(NMOL/ML)===
CONSTANT KDLI            =     1.0e-4     !LIVER (AhR)(NMOL/ML), WANG ET AL.
1997
CONSTANT KDLI2           =     2.0e-2     !LIVER (1A2)(NMOL/ML), EMOND ET AL.
2004

!===EXCRETION AND ABSORPTION CONSTANT (OPTIMIZED)
CONSTANT KST             =    0.3   ! GASTRIC RATE CONSTANT (HR-1),
CONSTANT KABS            =    0.48  !INTESTINAL ABSORPTION CONSTANT (HR-1) ),
WANG ET AL. 1997

! ELIMINATION CONSTANTS
CONSTANT CLURI           =      0.09 ! URINARY CLEARANCE (ML/HR)

```

```
! ==test elimination variable
constant kelv            =     0.4        ! INTERSPECIES VARIABLE ELIMINATION
CONSTANT (1/HOUR)

! CONSTANT TO DIVIDE THE ABSORPTION INTO LYMPHATIC AND PORTAL FRACTIONS
CONSTANT A               =      0.7       ! LYMPHATIC FRACTION, WANG ET AL.
1997

!PARTITION COEFFICIENTS OPTIMIZED
CONSTANT PF              =   400          ! ADIPOSE TISSUE/BLOOD
CONSTANT PRE             =    3           ! REST OF THE BODY/BLOOD, WANG ET
AL. 2000
CONSTANT PLI             =    6           ! LIVER/BLOOD, WANG ET AL. 1997

!===PARAMETER FOR INDUCTION OF CYP 1A2
CONSTANT PAS_INDUC=     1.0      ! INCLUDE INDUCTION? (1 = YES, 0 = NO)
CONSTANT CYP1A2_1OUTZ = 1.6   ! DEGRADATION CONCENTRATION CONSTANT OF 1A2
(NMOL/ML)
CONSTANT CYP1A2_1A1 =   1.5   ! BASAL CONCENTRATION OF 1A1 (NMOL/ML)
CONSTANT CYP1A2_1EC50 = 0.13   ! DISSOCIATION CONSTANT TCDD-CYP1A2 (NMOL/ML)
CONSTANT CYP1A2_1A2 =   1.5   ! BASAL CONCENTRATION OF 1A2 (NMOL/ML)
CONSTANT CYP1A2_1KOUT = 0.1   ! FIRST ORDER RATE OF DEGRADATION (H-1)
CONSTANT CYP1A2_1TAU  = 1.5  ! HOLDING TIME (H)
CONSTANT CYP1A2_1EMAX = 600   ! MAXIMUM INDUCTION OVER BASAL EFFECT
(UNITLESS)
CONSTANT HILL         = 0.6      !HILL CONSTANT; COOPERATIVELY LIGAND BINDING
EFFECT CONSTANT (UNITLESS)
    !DIFFUSIONAL PERMEABILITY FRACTION
CONSTANT PAFF     = 0.12      ! ADIPOSE (UNITLESS), WANG ET AL. 2000
CONSTANT PAREF    = 0.03      ! REST OF THE BODY (UNITLESS)
CONSTANT PALIF    = 0.35      ! LIVER (UNITLESS)

    !COMPARTMENT TISSUE BLOOD VOLUME  =========
CONSTANT WLI0     =  0.0549   ! LIVER, ILSI 1994
CONSTANT WF0      =  0.069    ! ADIPOSE

    !TISSUE BLOOD FLOW EXPRESSED AS A FRACTION OF CARDIAC OUTPUT
CONSTANT QFF  = 0.070         ! ADIPOSE TISSUE BLOOD FLOW FRACTION
(UNITLESS), LEUNG ET AL. 1990
CONSTANT QLIF = 0.161         ! LIVER (UNITLESS)  ILSI ET AL. 1994

    !COMPARTMENT TISSUE BLOOD EXPRESSED AS A FRACTION OF THE TOTAL
COMPARTMENT VOLUME
CONSTANT WFB0 =    0.050      ! ADIPOSE TISSUE, WANG ET AL. 1997
CONSTANT WREB0 =   0.030      ! REST OF THE BODY, WANG ET AL. 1997
CONSTANT WLIB0 =   0.266      ! LIVER, WANG ET AL. 1997

    ! EXPOSURE SCENARIO FOR UNIQUE OR REPETITIVE WEEKLY OR MONTHLY EXPOSURE
    ! NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LACK   = 0.0     ! DELAY BEFORE EXPOSURE ENDS (WEEK)
CONSTANT WEEK_PERIOD = 168    ! NUMBER OF HOURS IN THE WEEK (HOURS)
CONSTANT WEEK_FINISH = 120    ! TIME EXPOSURE ENDS (HOURS)

    ! NUMBER OF EXPOSURES PER MONTH
CONSTANT MONTH_LACK   = 0.0    ! DELAY BEFORE EXPOSURE (MONTH)
```

```
    !SET FOR BACKGROUND EXPOSURE===========
    !CONSTANT FOR BACKGROUND EXPOSURE===========
CONSTANT Day_LACK_BG = 0.0     ! DELAY BEFORE EXPOSURE BEGINS (HOURS)
CONSTANT Day_PERIOD_BG = 24    ! LENGTH OF EXPOSURE (HOURS)

    ! NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LACK_BG   = 0.0 ! DELAY BEFORE BACKGROUD EXPOSURE (WEEK)
CONSTANT WEEK_PERIOD_BG = 168 !NUMBER OF HOURS IN THE WEEK (HOURS)
CONSTANT WEEK_FINISH_BG = 168 ! TIME EXPOSURE ENDS (HOURS)

    !GROWTH CONSTANT FOR RAT AND MOUSE
    !CONSTANT FOR MOTHER BODY WEIGHT GROWTH ======
CONSTANT BW_T0 = 20          !CHANGED FOR SIMULATION

    !CONSTANT USED IN CARDIAC OUTPUT EQUATION, HADDAD 2001
CONSTANT QCCAR =275         !CONSTANT (ML/MIN/KG)

    ! COMPARTMENT LIPID EXPRESSED AS THE FRACTION OF TOTAL LIPID
CONSTANT F_TOTLIP =  0.855    !ADIPOSE TISSUE (UNITLESS)
CONSTANT B_TOTLIP =  0.0033   !BLOOD (UNITLESS)
CONSTANT RE_TOTLIP = 0.019    !REST OF THE BODY (UNITLESS)
CONSTANT LI_TOTLIP = 0.06     !LIVER (UNITLESS)

END  ! END OF THE INITIAL SECTION

DYNAMIC ! DYNAMIC SIMULATION SECTION

ALGORITHM  IALG          =           2        !GEAR METHOD
CINTERVAL  CINT          =         1.0        !COMMUNICATION INTERVAL
MAXTERVAL  MAXT          =       1.0e+10      !MAXIMUM CALCULATION INTERVAL
MINTERVAL  MINT          =       1.0E-10      !MINIMUM CALCULATION INTERVAL
VARIABLE   T             =         0.0        !HOUR
CONSTANT   TIMELIMIT     =         2904.0       !SIMULATION TIME LIMIT
(HOURS)
 CINTXY  = CINT
 PFUNC   = CINT

    !TIME CONVERSION
  DAY         = T/24.0          ! TIME IN DAYS
  WEEK        = T/168.0         ! TIME IN WEEKS
  MONTH       = T/730.0         ! TIME IN MONTHS
  YEAR        = T/8760.0        ! TIME IN YEARS

    !NMAX =MAX(T,CTFNGKG)
nmax =max(T,CFNGKG)

DERIVATIVE ! PORTION OF CODE THAT SOLVES DIFFERENTIAL EQUATIONS

    !CHRONIC OR SUBCHRONIC EXPOSURE SCENARIO =======
    !NUMBER OF EXPOSURES PER DAY
 DAY_LACK     = EXP_TIME_ON       ! DELAY BEFORE EXPOSURE BEGINS (HOURS)
 DAY_PERIOD   = DAY_CYCLE         ! EXPOSURE PERIOD (HOURS)
 DAY_FINISH   = CINTXY            ! LENGTH OF EXPOSURE (HOURS)
 MONTH_PERIOD = TIMELIMIT         ! EXPOSURE PERIOD (MONTHS)
 MONTH_FINISH = EXP_TIME_OFF      ! LENGTH OF EXPOSURE (MONTHS)

```

```
      !NUMBER OF EXPOSURES PER DAY AND MONTH
 DAY_FINISH_BG   = CINTXY
 MONTH_LACK_BG   = BCK_TIME_ON    ! DELAY BEFORE BACKGROUD EXPOSURE BEGINS
(MONTHS)
 MONTH_PERIOD_BG = TIMELIMIT      ! BACKGROUND EXPOSURE PERIOD (MONTHS)
 MONTH_FINISH_BG = BCK_TIME_OFF   ! LENGTH OF BACKGROUND EXPOSURE (MONTHS)

      ! FRACTION OF DIOXIN ABSORBED IN THE PORTAL FRACTION OF THE LIVER
 B = 1.0-A


      !GROWTH UP EQUATION (G)

PARAMETER (BW_RMN = 1.0E-30)
WT0= (BW_T0 *(1.0+(0.41*T)/(1402.5+T+BW_RMN)))

      ! VARIABILITY OF REST OF THE BODY DEPENDS ON OTHER ORGANS
      !REST OF THE BODY FRACTION; UPDATED FOR EPA ASSESSMENT
 WRE0 = (0.91 - (WLIB0*WLI0 + WFB0*WF0 + WLI0 + WF0))/(1+WREB0)

      ! REST OF THE BODY BLOOD FLOW FRACTION
 QREF = 1.0-(QFF+QLIF)            !REST OF BODY BLOOD FLOW (ML/HR)
      !SUMMATION OF BLOOD FLOW FRACTION (SHOULD BE EQUAL TO 1)
 QTTQF = QFF+QREF+QLIF          ! SUM MUST EQUAL 1

      !COMPARTMENT VOLUME (G)
 WF  =  WF0  * WT0              ! ADIPOSE
 WRE =  WRE0 * WT0              ! REST OF THE BODY
 WLI =  WLI0 * WT0              ! LIVER

      !COMPARTMENT TISSUE BLOOD (G)
 WFB  =  WFB0  * WF             ! ADIPOSE
 WREB =  WREB0 * WRE            ! REST OF THE BODY
 WLIB =  WLIB0 * WLI            ! LIVER

      !CARDIAC OUTPUT FOR THE GIVEN BODY WEIGHT
  QC= QCCAR*60*(WT0/1000.0)**0.75

QF  = QFF*QC         ! ADIPOSE TISSUE BLOOD FLOW RATE (ML/HR)
QLI = QLIF*QC        ! LIVER TISSUE BLOOD FLOW RATE (ML/HR)
QRE = QREF*QC        ! REST OF THE BODY BLOOD FLOW RATE (ML/HR)

QTTQ = QF+QRE+QLI   !TOTAL FLOW RATE (ML/HR)

      !PERMEABILITY ORGAN FLOW (ML/HR) =======
PAF  = PAFF*QF       ! ADIPOSE TISSUE
PARE = PAREF*QRE     ! REST OF THE BODY
PALI = PALIF*QLI     ! LIVER TISSUE

      !ABSORPTION SECTION
      !ORAL
      !BACKGROUND EXPOSURE
      !EXPOSURE FOR STEADY STATE CONSIDERATION
      !REPETITIVE EXPOSURE SCENARIO

MSTOT_NMBCKGR = MSTOTBCKGR/322 !AMOUNT IN NMOL/G
```

```
MSTTBCKGR =MSTOT_NMBCKGR *WT0

     !REPETITIVE ORAL BACKGROUND EXPOSURE SCENARIOS
DAY_EXPOSURE_BG   = PULSE(DAY_LACK_BG,DAY_PERIOD_BG,DAY_FINISH_BG)
WEEK_EXPOSURE_BG  = PULSE(WEEK_LACK_BG,WEEK_PERIOD_BG,WEEK_FINISH_BG)
MONTH_EXPOSURE_BG = PULSE(MONTH_LACK_BG,MONTH_PERIOD_BG,MONTH_FINISH_BG)

MSTTCH_BG = (DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG)*MSTTBCKGR
MSTTFR_BG = MSTTBCKGR/CINT

totalBG= integ (MSTTCH_BG,0.0)
CYCLE_BG =DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG


     !CONDITIONAL ORAL EXPOSURE (BACKGROUND EXPOSURE)
IF (MSTTCH_BG.EQ.MSTTBCKGR) THEN
    ABSMSTT_GB= MSTTFR_BG
ELSE
    ABSMSTT_GB = 0.0
END IF

     !EXPOSURE + !REPETITIVE EXPOSURE SCENARIO
IV= DOSEIV_NM * WT0  !AMOUNT IN NMOL
MSTT= MSTOT_NM * WT0 !AMOUNT IN NMOL

DAY_EXPOSURE   = PULSE(DAY_LACK,DAY_PERIOD,DAY_FINISH)
WEEK_EXPOSURE  = PULSE(WEEK_LACK,WEEK_PERIOD,WEEK_FINISH)
MONTH_EXPOSURE = PULSE(MONTH_LACK,MONTH_PERIOD,MONTH_FINISH)

MSTTCH = (DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE)*MSTT
CYCLE = DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE

SUMEXPEVENT= integ (CYCLE,0.0)*cint !NUMBER OF CYCLE GENERATE DURING
SIMULATION

MSTTFR = MSTT/CINT

    ! CONDITIONAL ORAL EXPOSURE
IF (MSTTCH.EQ.MSTT) THEN
   ABSMSTT= MSTTFR
ELSE
   ABSMSTT = 0.0
END IF

 CYCLETOT=INTEG(CYCLE,0.0)


    !MASS CHANGE IN THE LUMEN
RMSTT= -(KST+KABS)*MST+ABSMSTT +ABSMSTT_GB ! RATE OF CHANGE (NMOL/H)
 MST = INTEG(RMSTT,0.0)  !AMOUNT OF STAY IN DUODENUM (NMOL)

    !ABSORPTION IN LYMPH CIRCULATION
LYRMLUM = KABS*MST*A
 LYMLUM = INTEG(LYRMLUM,0.0)

    !ABSORPTION IN PORTAL CIRCULATION
```

```
LIRMLUM = KABS*MST*B
  LIMLUM = INTEG(LIRMLUM,0.0)

    !PERCENT OF DOSE REMAINING IN THE GI TRACT
PRCT_remain_GIT  = (MST/(MSTT+1E-30))*100

RFECES = KST*MST + REXCLI
  FECES = INTEG(RFECES,0.0)
prctFECES = (FECES/(BDOSE_TOTAL+1E-30))*100


    !ABSORPTION OF DIOXIN BY IV ROUTE---------
 IVR= IV/PFUNC ! RATE FOR IV INFUSION IN BLOOD
 EXPIV= IVR * (1.0-STEP(PFUNC))
 IVDOSE = integ(EXPIV,0.0)

    !SYSTEMIC BLOOD CONCENTRATION (NMOL/ML)
    ! MODIFICATION ON OCTOBER 6, 2009
CB=(QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM)/(QC+CLURI) !
 CA = CB

    !URINARY EXCRETION BY KIDNEY
    ! MODIFICATION ON OCTOBER 6, 2009
RAURI = CLURI *CB
  AURI = INTEG(RAURI,0.0)

prctAURI = (AURI/(BDOSE_TOTAL+1E-30))*100


    !UNIT CONVERSION POST SIMULATION
PRCT_B = (CB/(MSTT+1E-30))*100  ! PERCENT OF DOSE/G TISSUE
CBNGKG=CB*MW*UNITCORR
CBSNGKGLIADJ= (CB*MW*UNITCORR*(1.0/B_TOTLIP)*(1.0/SERBLO))![NG of TCDD
Serum/Kg OF LIPIP]
CBPMOL_KG= CB*UNITCORR*UNITCORR       !CONCENTRATION IN PMOL/KG
CBNGG = CB*MW
    !ADIPOSE TISSUE COMPARTMENT
    !TISSUE BLOOD SUBCOMPARTMENT
RAFB = QF*(CA-CFB)-PAF*(CFB-CF/PF)       !(NMOL/HR)
 AFB = INTEG(RAFB,0.0)                    !(NMOL)
 CFB = AFB/WFB                           !(NMOL/ML)
    !TISSUE SUBCOMPARTMENT
RAF  = PAF*(CFB-CF/PF)                   !(NMOL/HR)
 AF  = INTEG(RAF,0.0)                     !(NMOL)
 CF  = AF/WF                             !(NMOL/ML)

    !POST SIMULATION UNIT CONVERSION
CFTOTAL    = (AF + AFB)/(WF + WFB) ! TOTAL CONCENTRATION IN FAT(NM/ML)
PRCT_F  = (CFTOTAL/(MSTT+1E-30))*100 ! PERCENT OF DOSE IN FAT
CFNGKG  = CFTOTAL*MW*UNITCORR
CFUGG=(CFTOTAL*MW)/UNITCORR
CFPMOL_KG= CFTOTAL*UNITCORR*UNITCORR       !CONCENTRATION IN PMOL/KG
CFNGG = CFTOTAL*MW

    !REST OF THE BODY COMPARTMENT
    !TISSUE BLOOD SUBCOMPARTMENT
```

```
RAREB= QRE*(CA-CREB)-PARE*(CREB-CRE/PRE)          !(NMOL/HR)
 AREB = INTEG(RAREB,0.0)                           !(NMOL)
 CREB = AREB/WREB                                 !(NMOL/ML)
    !TISSUE SUBCOMPARTMENT
RARE = PARE*(CREB - CRE/PRE)                      !(NMOL/HR)
 ARE = INTEG(RARE,0.0)                            !(NMOL)
 CRE  = ARE/WRE                                    !(NMOL/ML)

    !POST SIMULATION UNIT CONVERSION
CRETOTAL= (ARE + AREB)/(WRE + WREB)               ! CONCENTRATION AT STEADY
STATE
PRCT_RE = (CRETOTAL/(MSTT+1E-30))*100


    !LIVER COMPARTMENT
    !TISSUE BLOOD SUBCOMPARTMENT
RALIB = QLI*(CA-CLIB)-PALI*(CLIB-CFLLIR)+LIRMLUM   !(NMOL/HR)
  ALIB = INTeg(RALIB,0.0)                           !(NMOL)
 CLIB = ALIB/WLIB
    !TISSUE SUBCOMPARTMENT
 RALI =  PALI*(CLIB-CFLLIR)-REXCLI                 !(NMOL/HR)
  ALI = integ(RALI,0.0)                                    !(NMOL)
  CLI  = ALI/WLI                                    !(NMOL/ML)

    !FREE TCCD CONCENTRATION IN LIVER (NMOL/ML)
PARAMETER (LIVER_1RMN = 1.0E-30)
 CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLI &
       +LIVER_1RMN))+((CYP1A2_1O3*CFLLIR/(KDLI2+CFLLIR &
       +LIVER_1RMN)*PAS_INDUC)))-CFLLI,CFLLI0)
     CFLLIR=DIM(CFLLI,0.0) ! FREE CONCENTRATION IN LIVER

CBNDLI= LIBMAX*CFLLIR/(KDLI+CFLLIR+LIVER_1RMN) !BOUND CONCENTRATION

   !POST SIMULATION UNIT CONVERSION
CLITOTAL= (ALI + ALIB)/(WLI + WLIB)!
PRCT_LI = (CLITOTAL/(MSTT+1E-30))*100 ! PERCENT OF DOSE IN LIVER
rec_occ_AHR= (CFLLIR/(KDLI+CFLLIR+1E-30))*100.0  ! PERCENT OF AhR OCCUPANCY
PROT_occ_1A2= (CFLLIR/(KDLI2+CFLLIR))*100.0  ! PERCENT OF 1A2 OCCUPANCY
CLINGKG =(CLITOTAL*MW*UNITCORR)
CBNDLINGKG = CBNDLI*MW*UNITCORR
CLIUGG=(CLITOTAL*MW)/UNITCORR
CLIPMOL_KG= CLITOTAL*UNITCORR*UNITCORR       !CONCENTRATION IN PMOL/KG
CLINGG = CLITOTAL*MW

   !Fraction increase of induction of CYP1A2
fold_ind=(CYP1A2_1OUT/CYP1A2_1A2)
VARIATIONOfAC =(CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2

   !VARIABLE ELIMINATION BASED ON THE CYP1A2
KBILE_LI_T =((CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2)*Kelv !INDUCED BILIARY
EXCRETION RATE CONSTANT

REXCLI= (KBILE_LI_T*CFLLIR*WLI) !DOSE-DEPENDENT EXCRETION RATE
 EXCLI = INTEG(REXCLI,0.0)

   !CHEMICAL IN CYP450 (1A2) COMPARTMENT
```

```
   !EQUATION FOR INDUCTION OF CYP1A2

CYP1A2_1KINP = CYP1A2_1KOUT* CYP1A2_1OUTZ

   ! MODIFICATION ON OCTOBER 6, 2009
CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1.0 + CYP1A2_1EMAX *(CBNDLI+1.0e-30)**HILL
&
     /(CYP1A2_1EC50**HILL + (CBNDLI+1.0e-30)**HILL)) &
      - CYP1A2_1KOUT*CYP1A2_1OUT, CYP1A2_1OUTZ)
! EQUATIONS INCORPORATING DELAY OF CYP1A2 PRODUCTION (NOT USED IN
SIMULATIONS)

CYP1A2_1RO2 = (CYP1A2_1OUT - CYP1A2_1O2)/ CYP1A2_1TAU
  CYP1A2_1O2 =INTEG(CYP1A2_1RO2, CYP1A2_1A1)
CYP1A2_1RO3 = (CYP1A2_1O2 - CYP1A2_1O3)/ CYP1A2_1TAU
  CYP1A2_1O3 =INTEG(CYP1A2_1RO3, CYP1A2_1A2)

      ! MASS BALANCE CONTROL
 BDOSE= LYMLUM+LIMLUM+IVDOSE
 BMASSE = EXCLI+AURI+AFB+AF+AREB+ARE+ALIB+ALI
 BDIFF = BDOSE-BMASSE
      ! AMOUNT TOTAL PRESENT IN THE GI TRACT
BDOSE_TOTAL =LYMLUM+LIMLUM+FECES

      !BODY BURDEN IN NG
 Body_burden =(AFB+AF+AREB+ARE+ALIB+ALI)*MW

      !BODY BURDEN CONCENTRATION (NG/KG)
 BBNGKG =(((AFB+AF+AREB+ARE+ALIB+ALI)*MW)/(WT0/UNITCORR)) !

      !COMMAND FOR END OF SIMULATION
TERMT (T.GE. TimeLimit, 'Time limit has been reached.')

END   ! END OF THE DERIVATIVE SECTION
END   ! END OF THE DYNAMIC SECTION
END   ! END OF PROGRAM
```

C.2.5.2. *Input Files*

C.2.5.2.1. *Della Porta (1987) (female)*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Della Porta 1987 for female mice.
%dose levels:  2.5 and 5 ug/kg/week for 52 weeks
%dose levels:  2500 and 5000 ng/kg/week for 52 weeks
%dose levels equivalent to: 357 and 714 ng/kg/d

MAXT =  0.01
CINT  = 0.1
EXP_TIME_ON       = 0.       %delay before begin exposure (HOUR)
EXP_TIME_OFF      = 8736     %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE         = 168
BCK_TIME_ON       = 0.       %DELAY BEFORE BACGROUND EXPOSURE (HOUR)
```

```
BCK_TIME_OFF      = 0.       %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT         = 8736     %SIMULATION LIMIT TIME (HOUR)
BW_T0             = 20       % Body weight at the beginning of the simulation
(g); corresponds to 6 weeks of age and taken from Figure 3


%EXPOSURE DOSE SCENARIOS (UG/KG)
    %MSTOT          = 2.5      % exposure dose ug/kg
    MSTOT         = 5.0      % exposure dose ug/kg
```

C.2.5.2.2. *Della Porta (1987) (male)*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Della Porta 1987 for male mice.
%dose levels:  2.5 and 5 ug/kg/week for 52 weeks
%dose levels:  2500 and 5000 ng/kg/week for 52 weeks
%dose levels equivalent to: 357 and 714 ng/kg/d

MAXT =  0.01
CINT  = 0.1
EXP_TIME_ON       = 0.       %delay before begin exposure (HOUR)
EXP_TIME_OFF      = 8736     %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE         = 168
BCK_TIME_ON       = 0.       %DELAY BEFORE BACGROUND EXPOSURE (HOUR)
BCK_TIME_OFF      = 0.       %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT         = 8736     %SIMULATION LIMIT TIME (HOUR)
BW_T0             = 26       % Body weight at the beginning of the simulation
(g); corresponds to 6 weeks of age and taken from Figure 3


%EXPOSURE DOSE SCENARIOS (UG/KG)
    %MSTOT          = 2.5      % exposure dose ug/kg
    MSTOT         = 5.0      % exposure dose ug/kg
```

C.2.5.2.3. *NTP (1982) (female) (chronic)*

```
%RAT2.m
%clear variable
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG
%output @nciout=168 T SUMEXPEVENT

% NTP 1982.
%built and check in September 20, 2009
%protocol: twice weekly gavage for 104 weeks
%Rat_Dioxin_3C June09_2clean_2.csl
%MICE_NON_GESTAT_ICF_F083109.csl
%MICE_NON_GESTAT_ICF_F092009.csl (now 09-20-09)
%dose levels:  0.02, 0.1, 1 ug/kg/biweekly, ug/kg for 104 weeks
%dose levels:  20, 100, 1000 ng/kg/biweekly,ng/kg for 104 weeks
%dose levels equivalent to: 5.71, 28.57, 285.1 ng/kg/d
```

```
MAXT =  0.01
CINT  = 0.1
EXP_TIME_ON       = 0.       %delay before begin exposure (HOUR)
EXP_TIME_OFF      = 17472     %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE         = 84
BCK_TIME_ON       = 0.       %DELAY BEFORE BACGROUND EXPOSURE (HOUR)
BCK_TIME_OFF      = 0.       %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT         = 17472     %SIMULATION LIMIT TIME (HOUR)
BW_T0             = 23       % Body weight at the beginning of the simulation
(g)


%EXPOSURE DOSE SCENARIOS (UG/KG)
    %MSTOT          = 0.02      % exposure dose ug/kg
    %MSTOT         = 0.1       % exposure dose ug/kg
    MSTOT         = 1.0         % exposure dose ug/kg
```

C.2.5.2.4. *NTP (1982) (male) (chronic).*

```
%RAT2.m
%clear variable
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG
%output @nciout=168 T SUMEXPEVENT

% NTP 1982.
%built and check in September 20, 2009
%protocol: twice weekly gavage for 104 weeks
%Rat_Dioxin_3C June09_2clean_2.csl
%MICE_NON_GESTAT_ICF_F083109.csl
%MICE_NON_GESTAT_ICF_F092009.csl (now 09-20-09)
%dose levels:  0.005, 0.025, 0.25 ug/kg/biweekly, ug/kg for 104 weeks
%dose levels:  5, 25, 250 ng/kg/biweekly,ng/kg for 104 weeks
%dose levels equivalent to: 1.4, 7.1, 71 ng/kg/d

MAXT =  0.01
CINT  = 0.1
EXP_TIME_ON       = 0.       %delay before begin exposure (HOUR)
EXP_TIME_OFF      = 17472     %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE         = 84
BCK_TIME_ON       = 0.       %DELAY BEFORE BACGROUND EXPOSURE (HOUR)
BCK_TIME_OFF      = 0.       %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT         = 17472     %SIMULATION LIMIT TIME (HOUR)
BW_T0             = 25       % Body weight at the beginning of the simulation
(g)


%EXPOSURE DOSE SCENARIOS (UG/KG)
    %MSTOT          = 0.005      % exposure dose ug/kg
    %MSTOT         = 0.025       % exposure dose ug/kg
    MSTOT         = 0.25         % exposure dose ug/kg
```

C.2.5.2.5. *Smialowicz et al. (2008).*

```
output @clear
```

```
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Smialowicz et al. 2008.
%built and check in August 7 2009
%protocol:  oral gavage 5 days/week for 13 weeks
%Mice_Dioxin_3C_June09_1.csl
%MICE_NON_GESTAT_ICF_F083109.csl (now 09-11-09)
%dose levels:  0, 0.0015, 0.015, 0.15, 0.45 ug/kg
%dose levels:  0, 1.5, 15, 150, 450 nkd (0, 1.07, 10.7, 107, 321 nkd adj)

MAXT          = 0.01
CINT          = 0.1
TIMELIMIT     = 2184          %SIMULATION LIMIT TIME (HOUR)
EXP_TIME_ON   = 0.            %delay before begin exposure (HOUR)
EXP_TIME_OFF  = 2184          %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE     =  24
WEEK_PERIOD   = 168
WEEK_FINISH   = 119
BCK_TIME_ON   = 0.           %DELAY BEFORE BACGROUND EXPOSURE (HOUR)
BCK_TIME_OFF  = 0.           %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
BW_T0         = 28           % Body weight at the beginning of the simulation
(g)

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT      = 0.0015       % exposure dose (ug/kg)
   %MSTOT   = 0.015        % exposure dose (ug/kg)
   %MSTOT   = 0.150        % exposure dose (ug/kg)
   MSTOT   = 0.450        % exposure dose (ug/kg)
```

C.2.5.2.6. *Toth et al. (1979) (1 year).*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Toth et al. 1979
%built and check in August 7 2009
%protocol:  weekly gavage for 1 year
%Mice_Dioxin_3C_June09_1.csl
%MICE_NON_GESTAT_ICF_F083109.csl (now 09-11-09)
%dose levels:  7, 700, 7000 ng/kg 1/week for 52 weeks (1 year)
%dose levels:  0.007, 0.7, 7 ug/kg 1/week for 52 weeks (1 year)
%dose equivalent: 1, 100, 1000 ng/kg/day

MAXT          = 0.01
CINT          = 0.1
TIMELIMIT     = 8760
EXP_TIME_ON   = 0.          %delay before begin exposure (HOUR)
EXP_TIME_OFF  = 8760        %2208 %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE     =  168
WEEK_PERIOD   = 8760
WEEK_FINISH   = 8760
BCK_TIME_ON   = 0.          %DELAY BEFORE BACGROUND EXPOSURE (HOUR)
BCK_TIME_OFF  = 0.          %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
```

```
BW_T0        = 27          % Body weight at the beginning of the simulation
(g)


%EXPOSURE DOSE SCENARIOS (UG/KG)
    %MSTOT    = 0.007       % exposure dose (ug/kg)
    %MSTOT = 0.7          % exposure dose (ug/kg)
    MSTOT = 7           % exposure dose (ug/kg)
```

C.2.5.2.7. *White et al. (1986).*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% White et al 1986
%built and check in August 7 2009

%protocol:  oral exposure single dose
%dose levels:  0.714, 3.57, 7.14, 35.71, 71.43, 142.86 ng /kg/d ug/kg 1/day
for 14 consecutive days
%dose have been modified following Jeff email on Friday August 21 2009
%dose levels: 10, 50, 100, 500, 1000, 2000 ng /kg/d ug/kg 1/day for 14
consecutive days
%dose levels: 0.010, 0.050, 0.100, 0.500, 1.0, 2.0 ug /kg/d ug/kg 1/day for
14 consecutive days

MAXT         = 0.01
CINT         = 0.1
TIMELIMIT    = 336
EXP_TIME_ON  = 0.        %TIME AT WHICH EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF = 336       %TIME AT WHICH EXPOSURE ENDS (HOUR)
DAY_CYCLE    =  24
WEEK_PERIOD  = 336
WEEK_FINISH  = 336
BCK_TIME_ON  = 0.        %TIME AT WHICH BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF = 0.        %TIME AT WHICH BACKGROUND EXPOSURE ENDS (HOUR)
BW_T0        = 23        % BODY WEIGHT AT THE BEGINNING OF THE SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT = 0.010         % EXPOSURE DOSE IN UG/KG
   %MSTOT = 0.050       % EXPOSURE DOSE IN UG/KG
   %MSTOT = 0.100       % EXPOSURE DOSE IN UG/KG
   %MSTOT = 0.500       % EXPOSURE DOSE IN UG/KG
   %MSTOT =  1          % EXPOSURE DOSE IN UG/KG
   MSTOT =  2          % EXPOSURE DOSE IN UG/KG
```

C.2.6. Mouse Gestational Model

C.2.6.1. *Model Code*

PROGRAM: 'Three Compartment PBPK Model for TCDD in Mice (Gestation)'

```
! Parameters were change may 16, 2002
! Come from {8MAI_CHR_PRE-EXP_GD}
```

```
! Come from {12_Mouse_GD}file
!*****************************************
!{{IMPORTANT-IMPORTANT-IMPORTANT-IMPORTANT}}
! REDUCTION OF MOTHER AND FETUS COMPARTMENT
! 2M_R_TCDD_JULY2002 ////(JULY 18,2002)////
!TCDD_RED_4Species_2003_4        ////(APR  8 ,2003)////
!TCDD_RED_4Species_2003_9        ////(APR  17 ,2003)////
!TCDD_RED_4Species_2003_12        ////(APR  17 ,2003)////
!*************************************************
!APRIL 18 2003
!TCDD_4C_4SP_2003        ////(APR  18 ,2003)////
! was ''Gest 4 species 1.csl''   but update July 2009

!DevTCDD4Species_ICF_afterKKfix_v3_ratgest.csl
!MICE_GESTATIONAL_ICF_F092309.csl
!MICE_GESTATIONAL_ICF_F100609.csl
!*************************************************

 !Legend/Legend/Legend/Legend/Legend/Legend/Legend/Legend/
 !Legend for this PBPK model
 !Mating: control the tenure of exchange between fetus and
    !Mother and also control imitated tissue growth
    !Ctrl: WTFE, WFO, WPLA0, QPLAF,WT0
    !(for rat, mouse, human, and monkey)
 !Control transfer from mother to fetus and fetus to mother by TRANSTIME_ON
    !SWITCH_trans = 0 NO TRANSFER
    !SWITCH_trans = 1 TRANSFER OCCURS
    !Gest_off = 1
    !Gest_on=   0.
 ! These switches are also controlled by mating parameters

INITIAL  !

     !SIMULATION PARAMETERS ====
CONSTANT PARA_ZERO          = 1E-30
CONSTANT EXP_TIME_ON     = 288.       ! TIME AT WHICH EXPOSURE BEGINS (HOURS)
CONSTANT EXP_TIME_OFF    = 504      ! TIME AT WHICH EXPOSURE ENDS (HOURS)
CONSTANT DAY_CYCLE       =  504.     ! NUMBER OF HOURS BETWEEN DOSES (HOURS)
CONSTANT BCK_TIME_ON     = 0.0       ! TIME AT WHICH BACKGROUND EXPOSURE
BEGINS (HOURS)
CONSTANT BCK_TIME_OFF    = 0.0       ! TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOURS)
CONSTANT TRANSTIME_ON    = 144       !CONTROL TRANSFER FROM MOTHER TO FETUS
AT GESTATIONAL DAY 6

    !UNIT CONVERSION
CONSTANT MW=322 ! MOLECULAR WEIGHT (NG/NMOL)
CONSTANT SERBLO = 0.55
CONSTANT UNITCORR = 1000

    !INTRAVENOUS SEQUENCY
constant IV_LACK         = 0.0
constant IV_PERIOD       = 0.0

    !PREGNANCY PARAMETER ====
CONSTANT MATTING         = 0.0       !BEGINNING OF MATING (HOUR)
```

```
CONSTANT N_FETUS         = 10       !NUMBER OF FETUS PRESENT

    !CONSTANT EXPOSURE CONTROL ===========
    !ACUTE, SUBCHRONIC, CHRONIC EXPOSURE =====
    !OR BACKGROUND EXPOSURE (IN THIS CASE 3 TIMES A DAY)===
CONSTANT MSTOTBCKGR      = 0.0       ! ORAL BACKGROUND EXPOSURE DOSE (UG/KG)
CONSTANT MSTOT           = 0.0       ! ORAL EXPOSURE DOSE (UG/KG)

    !ORAL ABSORPTION
  MSTOT_NM = MSTOT/MW              !CONVERTS THE DOSE TO NMOL/G

    ! INTRAVENOUS ABSORPTION
CONSTANT  DOSEIV         = 0.0       ! INJECTED DOSE (UG/KG)
  DOSEIV_NM = DOSEIV/MW            ! CONVERTS THE INJECTED DOSE TO NMOL/G
CONSTANT DOSEIVLATE = 0.0            ! INJECTED DOSE LATE (UG/KG)
  DOSEIVNMlate = DOSEIVLATE/MW     !AMOUNT IN NMOL/G

    !INITIAL GUESS OF THE FREE CONCENTRATION IN THE LIGAND (COMPARTMENT
INDICATED BELOW)====
CONSTANT CFLLI0          = 0.0  !LIVER    (NMOL/ML)
CONSTANT CFLPLA0         = 0.0  !PLACENTA (NMOL/ML)

    !BINDING CAPACITY (AhR) FOR NON LINEAR BINDING (COMPARTMENT INDICATED
BELOW) (NMOL/ML) ===
CONSTANT LIBMAX          = 3.5E-4   ! LIVER  (NMOL/ML), WANG ET AL. 1997
CONSTANT PLABMAX         = 2.0E-4   !TEMPORARY PARAMETER

    ! PROTEIN AFFINITY CONSTANTS (1A2 OR AhR, COMPARTMENT INDICATED BELOW)
(NMOL/ML)===
CONSTANT KDLI            = 1.0E-4   !LIVER (AhR) (NMOL/ML), WANG ET AL. 1997
CONSTANT KDLI2           = 4.0E-2   !LIVER (1A2) (NMOL/ML), EMOND ET AL. 2004
CONSTANT KDPLA           = 1.0E-4   !TEMPORARY PARAMETER (AhR)

    !EXCRETION AND ABSORPTION CONSTANT
CONSTANT KST             =    0.3   ! GASTRIC RATE CONSTANT (HR-1)
CONSTANT KABS            =    0.48  !INTESTINAL ABSORPTION CONSTANT (HR-1) ),
WANG ET AL. 1997

! ELIMINATION CONSTANTS
CONSTANT CLURI           =      0.09 ! URINARY CLEARANCE (ML/HR)

   !TEST ELIMINATION VARIABLE
constant kelv            =     0.4        ! INTERSPECIES VARIABLE ELIMINATION
CONSTANT (1/HOUR)

    ! CONSTANT TO DIVIDE THE ABSORPTION INTO LYMPHATIC AND PORTAL FRACTIONS
CONSTANT A               = 0.7        ! LYMPHATIC FRACTION, WANG ET AL. 1997

    !PARTITION COEFFICIENTS
CONSTANT PF              = 400    ! ADIPOSE TISSUE/BLOOD
CONSTANT PRE             = 3      ! REST OF THE BODY/BLOOD, WANG ET AL. 2000
CONSTANT PLI             = 6     ! LIVER/BLOOD, WANG ET AL. 1997
CONSTANT PPLA            = 3      ! TEMPORARY PARAMETER NOT CONFIGURED

    !PARAMETER FOR INDUCTION OF CYP 1A2, WANG ET AL. 1997 OR OPTIMIZED
CONSTANT PAS_INDUC       = 1        ! INCLUDE INDUCTION? (1 = YES, 0 = NO)
```

```
CONSTANT CYP1A2_1OUTZ    = 1.6      ! DEGRADATION CONCENTRATION CONSTANT OF
1A2 (NMOL/ML) (OPTIMIZED)
CONSTANT CYP1A2_1A1      = 1.5      ! BASAL CONCENTRATION OF 1A1 (NMOL/ML),
WANG ET AL . (2000)
CONSTANT CYP1A2_1EC50    = 0.13      ! DISSOCIATION CONSTANT TCDD-CYP1A2
(NMOL/ML)
CONSTANT CYP1A2_1A2      = 1.5      !BASAL CONCENTRATION OF 1A2
(NMOL/ML),WANG ET AL. (2000)
CONSTANT CYP1A2_1KOUT    = 0.1      ! FIRST ORDER RATE OF DEGRADATION (H-1)
CONSTANT CYP1A2_1TAU     = 1.5      !HOLDING TIME (H) (OPTIMIZED), WANG ET AL
. (2000)
CONSTANT CYP1A2_1EMAX    = 600      ! MAXIMUM INDUCTION OVER BASAL EFFECT
(UNITLESS)
CONSTANT HILL            = 0.6      !HILL CONSTANT; COOPERATIVELY LIGAND
BINDING EFFECT CONSTANT (UNITLESS)

    !DIFFUSIONAL PERMEABILITY FRACTION, WANG ET AL. 1997
CONSTANT PAFF            = 0.12   !ADIPOSE (UNITLESS) OPTIMIZED, WANG ET AL.
2000
CONSTANT PAREF           = 0.03   !REST OF THE BODY (UNITLESS)
CONSTANT PALIF           = 0.35   !LIVER (UNITLESS)
CONSTANT PAPLAF          = 0.03   !TEMPORARY PARAMETER NOT CONFIGURED

   !FRACTION OF TISSUE WEIGHT =========
CONSTANT WLI0            = 0.0549   !LIVER  ILSI (1994)

   !TISSUE BLOOD FLOW EXPRESSED AS A FRACTION OF CARDIAC OUTPUT CONSTANT QFF
= 0.070    ! ADIPOSE TISSUE BLOOD FLOW FRACTION (UNITLESS), LEUNG ET AL. 1990
CONSTANT QLIF            = 0.161    !LIVER (UNITLESS), ILSI 1994

   !COMPARTMENT TISSUE BLOOD EXPRESSED AS A FRACTION OF THE TOTAL COMPARTMENT
VOLUME
CONSTANT WFB0            = 0.050    !ADIPOSE TISSUE, WANG ET AL. 1997
CONSTANT WREB0           = 0.030    !REST OF THE BODY, WANG ET AL. 1997
CONSTANT WLIB0           = 0.266    !LIVER, WANG ET AL. 1997
CONSTANT WPLAB0          = 0.500    !TEMPORARY PARAMETER NOT CONFIGURED

   !EXPOSURE SCENARIO FOR UNIQUE OR REPETITIVE WEEKLY OR MONTHLY EXPOSURE
   !NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LACK       = 0.0       !DELAY BEFORE EXPOSURE ENDS (WEEK)
CONSTANT WEEK_PERIOD     = 168      ! NUMBER OF HOURS IN THE WEEK (HOURS)
CONSTANT WEEK_FINISH     = 168      ! TIME EXPOSURE ENDS (HOURS)

   !NUMBER OF EXPOSURES PER MONTH
CONSTANT MONTH_LACK      = 0.0       !DELAY BEFORE EXPOSURE BEGINS (MONTH)

   !CONSTANT FOR BACKGROUND EXPOSURE===========
CONSTANT Day_LACK_BG     = 0.0       ! DELAY BEFORE EXPOSURE BEGINS (HOUR)
CONSTANT Day_PERIOD_BG   = 24       !LENGTH OF EXPOSURE (HOUR)

   !NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LACK_BG      = 0.0      !DELAY BEFORE BACKGROUD EXPOSURE (WEEK)
CONSTANT WEEK_PERIOD_BG    = 168      ! NUMBER OF HOURS IN THE WEEK (HOURS)
CONSTANT WEEK_FINISH_BG    = 168      !TIME EXPOSURE ENDS (HOURS)

   !INITIAL BODY WEIGHT
```

```
CONSTANT BW_T0              = 30      ! WANG ET AL. 1997
CONSTANT RATIO_RATF_MOUSEF = 0.2        !RATIO OF FETUS MOUSE/RAT AT
GESTATIONAL DAY 22
                                        ! FOR RAT (1) AND FOR MOUSE (0.2)

   !COMPARTMENT LIPID EXPRESSED AS THE FRACTION OF TOTAL LIPID, POULIN ET AL.
2000
CONSTANT F_TOTLIP          = 0.855              ! ADIPOSE TISSUE (UNITLESS)
CONSTANT B_TOTLIP          = 0.0033              ! BLOOD (UNITLESS)
CONSTANT RE_TOTLIP         = 0.019              ! REST OF THE BODY
(UNITLESS)
CONSTANT LI_TOTLIP         = 0.060              ! LIVER (UNITLESS)
CONSTANT PLA_TOTLIP        = 0.019              ! PLACENTA (UNITLESS)
CONSTANT FETUS_TOTLIP      = 0.019            ! FETUS (UNITLESS)

END     ! END OF THE INITIAL SECTION

DYNAMIC ! DYNAMIC SIMULATION SECTION
ALGORITHM  IALG          =           2        ! GEAR METHOD
CINTERVAL  CINT          =         0.1        ! COMMUNICATION INTERVAL
MAXTERVAL  MAXT          =       1.0e+10      ! MAXIMUM CALCULATION INTERVAL
MINTERVAL  MINT          =       1.0E-10      ! MINIMUM CALCULATION INTERVAL
VARIABLE   T             =         0.0
CONSTANT   TIMELIMIT     =         313        !SIMULATION LIMIT TIME (HOUR)
 CINTXY  = CINT
 PFUNC   = CINT

   !TIME CONVERSION
  DAY         = T/24           ! TIME IN DAYS
  WEEK        = T/168          ! TIME IN WEEKS
  MONTH       = T/730          ! TIME IN MONTHS
  YEAR        = T/8760         ! TIME IN YEARS

DERIVATIVE ! PORTION OF CODE THAT SOLVES DIFFERENTIAL EQUATIONS

   !CHRONIC OR SUBCHRONIC EXPOSURE SCENARIO =======
   !NUMBER OF EXPOSURES PER DAY
 DAY_LACK         = EXP_TIME_ON    ! DELAY BEFORE EXPOSURE BEGINS (HOURS)
 DAY_PERIOD       = DAY_CYCLE      ! EXPOSURE PERIOD (HOURS)
 DAY_FINISH       = CINTXY         ! LENGTH OF EXPOSURE (HOURS)
 MONTH_PERIOD     = TIMELIMIT      ! EXPOSURE PERIOD (MONTHS)
 MONTH_FINISH     = EXP_TIME_OFF   ! LENGTH OF EXPOSURE (MONTHS)

   !NUMBER OF EXPOSURES PER DAY AND MONTH
 DAY_FINISH_BG    = CINTXY
 MONTH_LACK_BG    = BCK_TIME_ON    !DELAY BEFORE BACKGROUD EXPOSURE BEGINS
(MONTHS)
 MONTH_PERIOD_BG  = TIMELIMIT      !BACKGROUND EXPOSURE PERIOD (MONTHS)
 MONTH_FINISH_BG  = BCK_TIME_OFF   !LENGTH OF BACKGROUND EXPOSURE (MONTHS)

   !INTRAVENOUS LATE
 IV_FINISH = CINTXY
 B = 1-A ! FRACTION OF DIOXIN ABSORBED IN THE PORTAL FRACTION OF THE LIVER
```

```
1
2   !FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUM
3   E
4     ! FROM OFLAHERTY_1992
5
6   RTESTGEST= T-MATTING
7   TESTGEST=DIM(RTESTGEST,0.0)
8
9   WTFER_RODENT= (2.3d-3*EXP(1.49d-2*(TESTGEST))+1.3d-2)*Gest_on
10  WTFER = (WTFER_RODENT*RATIO_RATF_MOUSEF*N_FETUS)
11  WTFE = DIM(WTFER,0.0)
12
13    !
14  FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLUME
15    ! FAT GROWTH EXPRESSION LINEAR DURING PREGNANCY
16    ! FROM O'FLAHERTY_1992
17
18  WF0= (((9.66d-5*(TESTGEST))*gest_on)+0.069)
19
20    ! PLACENTA,VOLUME, PLACENTA,VOLUME, PLACENTA,VOLUME, PLACENTA,VOLUME
21    ! WPLA PLACENTA GROWTH EXPRESSION, SINGLE EXPONENTIAL WITH OFFSET
22    ! FROM O'FLAHERTY_1992  ! FOR EACH PUP
23
24  WPLA0N_RODENT = (0.6/(1+(5d+3*EXP(-0.0225*(TESTGEST)))))*N_FETUS
25  WPLA0R = (WPLA0N_RODENT/WT0)*Gest_on
26  WPLA0 = DIM(WPLA0R,0.0)
27
28    ! PLACENTA,FLOW RATE, PLACENTA,FLOW RATE, PLACENTA,FLOW RATE, PLACENTA,FLOW
29  RATE
30    ! QPLA PLACENTA GROWTH EXPRESSION, DOUBLE EXPONENTIAL WITH OFFSET
31    ! FROM O'FLAHERTY_1992
32
33   QPLARF = (1.67d-7 *exp(9.6d-3*(TESTGEST)) &
34     +1.6d-3*exp(7.9d-3*(TESTGEST))+0.0)*Gest_on*SWITCH_trans
35   QPLAF=DIM(QPLARF,0.0)               !FRACTION OF FLOW RATE IN PLACENTA
36
37    ! GESTATION CONTROL
38  IF (T.LT.MATTING) THEN
39      Gest_off = 1
40      Gest_on=   0.0
41  ELSE
42      Gest_off = 0.0
43      Gest_on  = 1
44  END IF
45
46    ! MOTHER BODY WEIGHT GROWTH EQUATION========
47    ! MODIFICATION TO ADAPT THIS MODEL AT HUMAN MODEL
48    ! BECAUSE LINEAR DESCRIPTION IS NOT GOOD ENOUGH FOR MOTHER GROWTH
49    ! MOTHER BODY WEIGHT GROWTH
50
51    PARAMETER (BW_RMN = 1.0E-30)
52    WT0= BW_T0 *(1.0+(0.41*T)/(1402.5+T+BW_RMN))
53
54    ! VARIABILITY OF REST OF THE BODY DEPENDS ON OTHER ORGANS
55    WRE0 = (0.91 - (WLIB0*WLI0 + WFB0*WF0 +WPLAB0*WPLA0 + WLI0 + WF0 +
56  WPLA0))/(1.0+WREB0)  ! REST OF THE BODY FRACTION; UPDATED FOR EPA ASSESSMENT
```

```
  QREF = 1.0-(QFF+QLIF+QPLAF)            !REST OF BODY BLOOD FLOW RATE
(ML/HR)
  QTTQF = QFF+QREF+QLIF+QPLAF          ! SUM MUST EQUAL 1

  ! COMPARTMENT VOLUME (ML OR G) =========
 WF  =  WF0  * WT0                    ! ADIPOSE TISSUE
 WRE =  WRE0 * WT0                    ! REST OF THE BODY
 WLI =  WLI0 * WT0                    ! LIVER
 WPLA=  WPLA0* WT0                    ! PLACENTA

   ! COMPARTMENT TISSUE BLOOD (ML OR G) =========
 WFB  =  WFB0  * WF                   ! ADIPOSE TISSUE
 WREB =  WREB0 * WRE                  ! REST OF THE BODY
 WLIB =  WLIB0 * WLI                  ! LIVER
 WPLAB = WPLAB0* WPLA                 ! PLACANTA

   ! CARDIAC OUTPUT FOR THE GIVEN BODY WEIGHT
   !QC= QCCAR*60*(WT0/1000.0)**0.75
CONSTANT QCC=16500                    ! EQUIVALENT TO 275 * 60
QC= QCC*(WT0/UNITCORR)**0.75

   !COMPARTMENT BLOOD FLOW RATE (ML/HR)
QF  = QFF*QC                          !ADIPOSE TISSUE BLOOD FLOW RATE
QLI = QLIF*QC                         !LIVER TISSUE BLOOD FLOW RATE
QRE = QREF*QC                         !REST OF THE BODY BLOOD FLOW RATE
QPLA = QPLAF*QC                       !PLACENTA TISSUE BLOOD FLOW RATE
QTTQ = QF+QRE+QLI+QPLA   !TOTAL FLOW RATE

    !PERMEABILITY ORGAN FLOW (ML/HR)=========
PAF  = PAFF*QF                       ! ADIPOSE TISSUE
PARE = PAREF*QRE                     ! REST OF THE BODY
PALI = PALIF*QLI                     ! LIVER TISSUE
PAPLA = PAPLAF*QPLA                  ! PLACENTA

    !************************************
    ! ABSORPTION SECTION
    ! ORAL,
    ! INTRAPERITONEAL,
    ! INTRAVENOUS
    !************************************

    !REPETITIVE ORAL BACKGROUND EXPOSURE SCENARIO

MSTOT_NMBCKGR = MSTOTBCKGR/322       !AMOUNT IN NMOL/G
MSTTBCKGR =MSTOT_NMBCKGR *WT0

DAY_EXPOSURE_BG   = PULSE(DAY_LACK_BG,DAY_PERIOD_BG,DAY_FINISH_BG)
WEEK_EXPOSURE_BG  = PULSE(WEEK_LACK_BG,WEEK_PERIOD_BG,WEEK_FINISH_BG)
MONTH_EXPOSURE_BG = PULSE(MONTH_LACK_BG,MONTH_PERIOD_BG,MONTH_FINISH_BG)

MSTTCH_BG = (DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG)*MSTTBCKGR
MSTTFR_BG = MSTTBCKGR/CINT

CYCLE_BG =DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG

    ! CONDITIONAL ORAL EXPOSURE (BACKGROUND EXPOSURE)
```

```
1
2   IF (MSTTCH_BG.EQ.MSTTBCKGR) THEN
3       ABSMSTT_GB= MSTTFR_BG
4   ELSE
5       ABSMSTT_GB = 0.0
6   END IF
7
8   CYCLETOTBG=INTEG(CYCLE_BG,0.0)
9
10     !REPETITIVE ORAL EXPOSURE SCENARIO
11
12  MSTT= MSTOT_NM * WT0                    !AMOUNT IN NMOL
13
14  DAY_EXPOSURE   = PULSE(DAY_LACK,DAY_PERIOD,DAY_FINISH)
15  WEEK_EXPOSURE  = PULSE(WEEK_LACK,WEEK_PERIOD,WEEK_FINISH)
16  MONTH_EXPOSURE = PULSE(MONTH_LACK,MONTH_PERIOD,MONTH_FINISH)
17
18  MSTTCH = (DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE)*MSTT
19  MSTTFR = MSTT/CINT
20
21  CYCLE = DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE
22  SUMEXPEVENT= INTEG (CYCLE,0.0)/cint !NUMBER OF CYCLES GENERATED DURING
23  SIMULATION
24
25     ! CONDITIONAL ORAL EXPOSURE
26  IF (MSTTCH.EQ.MSTT) THEN
27     ABSMSTT= MSTTFR
28  ELSE
29     ABSMSTT = 0.0
30  END IF
31
32
33   CYCLETOT=INTEG(CYCLE,0.0)
34
35     ! MASS CHANGE IN THE LUMEN
36   RMSTT= -(KST+KABS)*MST +ABSMSTT +ABSMSTT_GB ! RATE OF CHANGE (NMOL/H)
37    MST = INTEG(RMSTT,0.0)                      !AMOUNT REMAINING IN DUODENUM
38  (NMOL)
39
40     ! ABSORPTION IN LYMPH CIRCULATION
41   LYRMLUM = KABS*MST*A
42    LYMLUM = INTEG(LYRMLUM,0.0)
43
44     ! ABSORPTION IN PORTAL CIRCULATION
45   LIRMLUM = KABS*MST*B
46    LIMLUM = INTEG(LIRMLUM,0.0)
47
48
49  ! -----IV EXPOSURE ---------
50
51   IV= DOSEIV_NM * WT0 !AMOUNT IN NMOL
52   IVR= IV/PFUNC ! RATE FOR IV INFUSION IN BLOOD
53   EXPIV= IVR * (1.0-STEP(PFUNC))
54   IVDOSE = integ(EXPIV,0.0)
55
56      !------IV late in the cycle
```

```
    ! MODIFICATION ON January 13 2004
 IV_RlateR = DOSEIVNMlate*WT0
 IV_EXPOSURE=PULSE(IV_LACK,IV_PERIOD,IV_FINISH)

 IV_lateT = IV_EXPOSURE *IV_RlateR
 IV_late = IV_lateT/CINT

SUMEXPEVENTIV= integ (IV_EXPOSURE,0.0) !NUMBER OF CYCLE GENERATE DURING
SIMULATION

    !SYSTEMIC CONCENTRATION OF TCDD
    ! MODIFICATION ON OCTOBER 6, 2009
 CB=(QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM+QPLA*CPLAB+IV_late)/(QC+CLURI) !
 CA = CB ! CONCENTRATION (NMOL/ML)

    !URINARY EXCRETION BY KIDNEY
    !MODIFICATION ON OCTOBER 6, 2009
RAURI = CLURI *CB
  AURI = INTEG(RAURI,0.0)

  !UNIT CONVERSION POST SIMULATION
 CBSNGKGLIADJ=(CB*MW*UNITCORR*(1/B_TOTLIP)*(1/SERBLO))![NG of TCDD Serum/Kg
OF LIPIP]
   AUCBS_NGKGLIADJ=integ(CBSNGKGLIADJ,0.0)

  PRCT_B = (CB/(MSTT+1E-30))*100 ! PERCENT OF ORAL DOSE IN BLOOD
  PRCT_BIV = (CB/(IV_RlateR+1E-30))*100 ! PERCENT OF IV DOSE IN BLOOD
  CBNGKG= CB*MW*UNITCORR
  CBNGG = CB*MW

   !ADIPOSE COMPARTMENT
   !TISSUE BLOOD COMPARTMENT
RAFB= QF*(CA-CFB)-PAF*(CFB-CF/PF)     !(NMOL/H)
 AFB = INTEG(RAFB,0.0)                 !(NMOL)
  CFB = AFB/WFB                        !(NMOL/ML)
   !TISSUE COMPARTMENT
RAF = PAF*(CFB-CF/PF)                 !(NMOL/H)
 AF = INTEG(RAF,0.0)                  !(NMOL)
  CF  = AF/WF                          !(NMOL/ML)

   !UNIT CONVERSION POST SIMULATION
  CFTOTAL= (AF + AFB)/(WF + WFB) ! TOTAL CONCENTRATION IN NMOL/ML
  CFTFREE = CFB + CF !TOTAL FREE CONCENTRATION IN FAT  (NM/ML)
  PRCT_F = (CFTOTAL/(MSTT+1E-30))*100 ! PERCENT OF ORAL DOSE IN FAT
  PRCT_FIV = (CFTOTAL/(IV_RlateR+1E-30))*100 ! PERCENT OF IV DOSE IN FAT
  CFNGKG=CFTOTAL*MW*UNITCORR ! FAT CONCENTRATION IN NG/KG
    AUCF_NGKGH=integ(CFNGKG,0.0)
  CFNGG = CFTOTAL*MW

   !REST OF THE BODY COMPARTMENT
RAREB= QRE *(CA-CREB)-PARE*(CREB-CRE/PRE)  !(NMOL/H)
 AREB = INTEG(RAREB,0.0)                    !(NMOL)
  CREB = AREB/WREB                          !(NMOL/H)
   !TISSUE COMPARTMENT
RARE = PARE*(CREB - CRE/PRE)               !(NMOL/H)
 ARE = INTEG(RARE,0.0)                     !(NMOL)
```

```
  CRE  = ARE/WRE                                !(NMOL/ML)

   !UNIT CONVERSION POST SIMULATION
  CRETOTAL= (ARE + AREB)/(WRE + WREB)           ! TOTAL CONCENTRATION IN
NMOL/ML
  PRCT_RE = (CRETOTAL/(MSTT+1E-30))*100 ! PERCENT OF ORAL DOSE IN REST OF
BODY
  PRCT_REIV = (CRETOTAL/(IV_RlateR+1E-30))*100   ![ PERCENT OF IV DOSE IN
REST OF THE BODY ]
  CRENGKG=CRETOTAL*MW*UNITCORR ! REST OF THE BODY CONCENTRATION IN NG/KG


   !LIVER COMPARTMENT
   !TISSUE BLOOD COMPARTMENT
 RALIB = QLI*(CA-CLIB)-PALI*(CLIB-CFLLIR)+LIRMLUM !
  ALIB = INTEG(RALIB,0.0)                        !(NMOL)
   CLIB = ALIB/WLIB                             !(NMOL/ML)
   !TISSUE COMPARTMENT
 RALI = PALI*(CLIB - CFLLIR)-REXCLI             !  (NMOL/HR)
  ALI = INTEG(RALI,0.0)                           !(NMOL)
   CLI  = ALI/WLI                                !(NMOL/ML)

   !FREE TCDD IN LIVER COMPARTMENT
PARAMETER (LIVER_1RMN = 1.0E-30)
 CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLIR &
        +LIVER_1RMN))+((CYP1A2_1O3*CFLLIR/(KDLI2 + CFLLIR &
        +LIVER_1RMN)*PAS_INDUC)))-CFLLI,CFLLI0)
     CFLLIR=DIM(CFLLI,0.0) ! FREE CONCENTRATION IN LIVER

  CBNDLI= LIBMAX*CFLLIR/(KDLI+CFLLIR+LIVER_1RMN) !BOUND CONCENTRATION

  !VARIABLE ELIMINATION BASED ON THE CYP1A2
 KBILE_LI_T =((CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2)*Kelv ! INDUCED BILIARY
EXCRETION RATE CONSTANT
  REXCLI = KBILE_LI_T*CFLLIR*WLI ! DOSE-DEPENDENT EXCRETION RATE
    EXCLI = INTEG(REXCLI,0.0)

  !UNIT CONVERSION POST SIMULATION
  CLITOTAL= (ALI + ALIB)/(WLI + WLIB) ! TOTAL CONCENTRATION IN NMOL/ML
  PRCT_LI = (CLITOTAL/(MSTT+1E-30))*100 ! PERCENT ORAL DOSE IN LIVER
  PRCT_LIIV = (CLITOTAL/(IV_RlateR+1E-30))*100 ! PERCENT IV DOSE IN LIVER
  Rec_occ= CFLLIR/(KDLI+CFLLIR)
  CLINGKG=CLITOTAL*MW*UNITCORR ! LIVER CONCENTRATION IN NG/KG
     AUCLI_NGKGH=INTEG(CLINGKG,0.0)
  CBNDLINGKG = CBNDLI*MW*UNITCORR
     AUCBNDLI_NGKGH =INTEG(CBNDLINGKG,0.0)
  CLINGG = CLITOTAL*MW

   !CHEMICAL IN CYP450 (1A2) COMPARTMENT
CYP1A2_1KINP = CYP1A2_1KOUT* CYP1A2_1OUTZ ! BASAL RATE OF CYP1A2 PRODUCTION
SET EQUAL TO BASAL RATE OF DEGREDATION

   ! MODIFICATION ON OCTOBER 6, 2009
CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1.0 + CYP1A2_1EMAX *(CBNDLI+1.0e-30)**HILL
&
     /(CYP1A2_1EC50**HILL + (CBNDLI+1.0e-30)**HILL)) &
```

```
      - CYP1A2_1KOUT*CYP1A2_1OUT, CYP1A2_1OUTZ)

! EQUATIONS INCORPORATING DELAY OF CYP1A2 PRODUCTION (NOT USED IN
SIMULATIONS)

      CYP1A2_1RO2 = (CYP1A2_1OUT - CYP1A2_1O2)/ CYP1A2_1TAU
  CYP1A2_1O2 =INTEG(CYP1A2_1RO2, CYP1A2_1A1)

CYP1A2_1RO3 = (CYP1A2_1O2 - CYP1A2_1O3)/ CYP1A2_1TAU
  CYP1A2_1O3 =INTEG(CYP1A2_1RO3, CYP1A2_1A2)

! TRANSFER OF DIOXIN FROM PLACENTA TO FETUS
! FETAL EXPOSURE ONLY DURING EXPOSURE

IF (T.LT.TRANSTIME_ON) THEN
 SWITCH_trans = 0.0
ELSE
 SWITCH_trans = 1
END IF

!TRANSFER OF DIOXIN FROM PLACENTA TO FETUS
! MODIFICATION 26 SEPTEMBER 2003

CONSTANT PFETUS= 4 !
CONSTANT CLPLA_FET = 0.17 !

RAMPF = (CLPLA_FET*CPLA) *SWITCH_trans
  AMPF=INTEG(RAMPF,0.0)

!TRANSFER OF DIOXIN FROM FETUS TO PLACENTA
RAFPM = (CLPLA_FET*CFETUS_v)*SWITCH_trans !
  AFPM = INTEG(RAFPM,0.0)

! TCDD IN PLACENTA MOTHER COMPARTMENT
RAPLAB= QPLA*(CA - CPLAB)-PAPLA*(CPLAB -CFLPLAR)    ! NMOL/H)
 APLAB = INTEG(RAPLAB,0.0)                           ! (NMOL)
 CPLAB = APLAB/(WPLAB+1E-30)                        ! (NMOL/ML)
RAPLA = PAPLA*(CPLAB-CFLPLAR)-RAMPF + RAFPM         ! (NMOL/H)
 APLA = INTEG(RAPLA,0.0)                             ! (NMOL)
 CPLA  = APLA/(WPLA+1e-30)                          ! (NMOL/ML)

PARAMETER (PARA_ZERO = 1.0E-30)
CFLPLA= IMPLC(CPLA-(CFLPLAR*PPLA +(PLABMAX*CFLPLAR/(KDPLA&
    +CFLPLAR+PARA_ZERO)))-CFLPLA,CFLPLA0)
CFLPLAR=DIM(CFLPLA,0.0)

   !UNIT CONVERSION POST SIMULATION
  CPLATOTAL= (APLA + APLAB)/((WPLA + WPLAB)+1e-30)! TOTAL CONCENTRATION IN
NMOL/ML
  PRCT_PLA = (CPLATOTAL/(MSTT+1E-30))*100
  PRCT_PLAIV = (CPLATOTAL/(IV_RlateR+1E-30))*100
  CPLANGG = CPLATOTAL*MW

   !FETUS COMPARTMENT
RAFETUS= RAMPF-RAFPM
 AFETUS=INTEG(RAFETUS,0.0)
```

```
CFETUS=AFETUS/(WTFE+1E-30)
CFETOTAL= CFETUS
CFETUS_v = CFETUS/PFETUS

  ! UNIT CONVERSION POST SIMULATION
CFETUSNGKG = CFETUS*MW*UNITCORR                    !(NG/KG)
AUC_FENGKGH = INTEG(CFETUSNGKG,0.0)
PRCT_FE = (CFETOTAL/(MSTT+1E-30))*100
PRCT_FEIV = (CFETOTAL/(IV_RlateR+1E-30))*100
CFETUSNGG = CFETOTAL*MW

! ------------CONTROL MASS BALANCE ----------
BDOSE= IVDOSE +LYMLUM+LIMLUM
BMASSE = EXCLI+AURI+AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB+AFETUS
BDIFF = BDOSE-BMASSE

      !BODY BURDEN (NG)
BODY_BURDEN = AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB !
BBFETUSNG     = AFETUS*MW*UNITCORR    ! NG
      ! BODY BURDEN IN TERMS OF CONCENTRATION (NG/KG)
 BBNGKG =(((AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB)/WT0)*MW*UNITCORR) !
  AUC_BBNGKGH=INTEG(BBNGKG,0.0)


! ------------COMMAND OF THE END OF SIMULATION ----------
TERMT (T.GE. TimeLimit, 'Time limit has been reached.')
END   ! END OF THE DERIVATIVE SECTION
END   ! END OF THE DYNAMIC SECTION
END   ! END OF THE PROGRAM
```

C.2.6.2. *Input Files*

C.2.6.2.1. *Keller et al. (2007).*

```
%clear variable
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH

%output @nciout=10 T SUMEXPEVENT wt0

%Keller et al. 2007
%protocol:  single oral dose at GD13
%DevTCDD4Species.csl
%MICE_GESTATIONAL_ICF_F092309.csl
%dose levels: 0.01, 0.100 1 ug/kg at GD13
%dose levels:   10, 100 1000 ng/kg at GD13

%EXPOSURES SCENARIOS
 MAXT=0.01
 CINT =0.1
 EXP_TIME_ON     = 312.          % delay before begin exposure (HOUR)
 EXP_TIME_OFF    = 336           % TIME EXPOSURE STOP (HOUR)
 DAY_CYCLE       = 24
 BCK_TIME_ON     = 0.            % DELAY BEFORE BACGROUND EXPOSURE (HOUR)
```

```
 BCK_TIME_OFF    = 0.            % TIME OF BACKGROUND EXPOSURE STOP (HOUR)
 IV_LACK         = 505
 IV_PERIOD       = 505
 TIMELIMIT       = 336            % SIMULATION LIMIT TIME (HOUR)
 BW_T0           = 24
 MATTING         = 0.             % BEGINNING MATTING (HOUR)
 TRANSTIME_ON    = 144.           % SHOULD BE MATTING TIME + 6 DAYS(144
HOURS)
 N_FETUS         = 10

%EXPOSURE DOSE SCENARIOS (UG/KG)

   %MSTOT         = 0.01           % ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT        = 0.1           % ORAL EXPOSURE DOSE (UG/KG)
   MSTOT        = 1           % ORAL EXPOSURE DOSE (UG/KG)
```

C.2.6.2.2. *Li et al. (2006).*

```
%TO BE USED AFTER THE
%clear variable
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH
%output @nciout=10 T SUMEXPEVENT
%Li et al.2006
%protocol:  daily oral dose from GD1 to GD3
%DevTCDD4Species.csl
%MICE_GESTATIONAL_ICF_F092309.csl
%dose levels: 0.002, 0.050, 0.10 ug/kg/day at GD1 to GD3
%dose levels: 2, 50, 100 ng/kg/day from GD1 to GD3

%EXPOSURES SCENARIOS
 MAXT=0.01
 CINT =0.1
 EXP_TIME_ON     = 0.            % delay before begin exposure (HOUR)
 EXP_TIME_OFF    = 72           % TIME EXPOSURE STOP (HOUR) 2 HOURS LESS THAN
GD3  put 70 to be sure 3 doses will be administrate
                                 % BECAUSE i STARTED TIME 0 FOR GD1
 DAY_CYCLE       = 24
 BCK_TIME_ON     = 0.            % DELAY BEFORE BACGROUND EXPOSURE (HOUR)
 BCK_TIME_OFF    = 0.            % TIME OF BACKGROUND EXPOSURE STOP (HOUR)
 IV_LACK         = 505
 IV_PERIOD       = 505
 TIMELIMIT       = 72.            % SIMULATION LIMIT TIME (HOUR) Run for 3
days
 BW_T0           = 27
 MATTING         = 0.             % BEGINNING MATTING (HOUR)
 TRANSTIME_ON    = 144.           % SHOULD BE MATTING TIME + 6 DAYS(144
HOURS)
 N_FETUS         = 10

%EXPOSURE DOSE SCENARIOS (UG/KG)

   %MSTOT         = 0.002           % ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT        = 0.05           % ORAL EXPOSURE DOSE (UG/KG)
```

```
MSTOT          = 0.10              % ORAL EXPOSURE DOSE (UG/KG)
```

C.3. TOXICOKINETIC MODELING RESULTS FOR KEY ANIMAL BIOASSAY STUDIES

The simulated TCDD serum-adjusted lipid concentrations reported in this appendix for the rodent bioassays were converted to TCDD concentrations in rodent whole blood. Initially, EPA multiplied the serum-adjusted lipid concentrations by 0.0033, the ratio of lipid content to total serum volume, then by 0.55, the value of the hematocrit. This product yields the TCDD concentration in whole rodent blood as predicted by the PBPK model. EPA assumed that the same whole blood TCDD concentration would result in the same effects in humans and rodents.

This conversion accomplishes the following:

1. Allows the human equivalent dose (HED) to be based on equivalent blood concentration (that represents serum plus erythrocyte TCDD), which is proportional to tissue exposure;
2. Avoids criticism that the total blood concentration is normalized to serum lipid alone in an unbalanced way (thus EPA does not contradict Centers for Disease Control and Prevention (CDC) data or methods);
3. Factors out any impact of the lipid content used in the PBPK model; and
4. TCDD concentration in whole blood is encouraged for use in the assessments by the NAS (NAS, 2006, p. 43); see additional information in Section 3.3.

C.3.1. Nongestational Studies

C.3.1.1. *Cantoni et al. (1981)*

Type:	Rat	**Dose:**	10, 100, 1000 ng/kg/week
Strain:	CD-COBS rats	**Route:**	Oral gavage exposure
Body weight:	BW set to 125g	**Regime:**	1 dose/week for 45 weeks
Sex:	Female	**Simulation time:**	7,560 hours (45 weeks)

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.43	Emond	1.85	3.70 (@ 7,392 hours)	1.82
	CADM	-	-	-
14.29	Emond	8.84	26.6 (@ 7,392 hours)	7.97

	CADM	-	-	-
142.86	Emond	50.0	227 (@ 7,392 hours)	41.9
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.43	Emond	247	328 (@ 7,398 hours)	242
	CADM	374	431	431
14.29	Emond	2,176	2,860 (@ 7,231 hours)	1,928
	CADM	3,884	4,330	4,330
142.86	Emond	20,500	26,978 (@ 7,399 hours)	17,255
	CADM	39,067	43,329	43,329
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.43	Emond	175	200 (@ 7,431 hours)	181
	CADM	250	280	244
14.29	Emond	837	937 (@ 7,427 hours)	807
	CADM	1,209	1,352	1,167
142.86	Emond	4,741	5,374 (@ 7,424 hours)	4,349
	CADM	10,050	11,224	9,734
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.43	Emond	26.1	31.7 (@ 7,398 hours)	26.3
	CADM	32.0	35.0	35.0
14.29	Emond	170	210 (@ 7,230 hours)	156
	CADM	225	243	243
142.86	Emond	1,337	1,695 (@ 7,398 hours)	1,151
	CADM	2,106	2,266	2,266

BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.43	Emond	6.04	7.76 (@ 7,396 hours)	6.01
	CADM	-	-	-
14.29	Emond	23.7	29.1 (@ 7,228 hours)	22.2
	CADM	-	-	-
142.86	Emond	66.8	80.0 (@ 1 hours)	63.4
	CADM	-	-	-

C.3.1.2. *Chu et al. (2007)*

Type:	Rat	**Dose:**	2.5, 25, 250, and 1,000 ng/kg-day
Strain:	Sprague-Dawley	**Route:**	Oral exposure
Body weight:	200 g	**Regime:**	1 dose per day for 28 days
Sex:	Female	**Simulation time:**	672 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.5	Emond	1.26	2.35 (@ 648 hours)	1.88
	CADM	-	-	-
25	Emond	7.66	15.3 (@ 648 hours)	10.4
	CADM	-	-	-
250	Emond	48.8	113 (@ 648 hours)	63.7
	CADM	-	-	-
1,000	Emond	169	418 (@ 648 hours)	222
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.5	Emond	148	268 (@ 652 hours)	255
	CADM	-	-	-
25	Emond	1,777	2,953 (@ 653 hours)	2,806
	CADM	-	-	-

250	Emond	19,232	30,262 (@ 653 hours)	28,668
	CADM	-	-	-
1,000	Emond	77,819	120,400 (@ 653 hours)	113,890
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.5	Emond	108	180 (@ 668 hours)	180
	CADM	-	-	-
25	Emond	660	1,020 (@ 659 hours)	1,015
	CADM	-	-	-
250	Emond	4,210	6,433 (@ 655 hours)	6,354
	CADM	-	-	-
1,000	Emond	14,576	22,610 (@ 655 hours)	22,280
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.5	Emond	16.1	27.5 (@ 652 hours)	26.9
	CADM	-	-	-
25	Emond	138	222 (@ 652 hours)	214
	CADM	-	-	-
250	Emond	1,239	1,935 (@ 652 hours)	1,842
	CADM	-	-	-
1,000	Emond	4,801	7,444 (@ 652 hours)	7,067
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.5	Emond	4.15	6.51 (@ 652 hours)	6.21
	CADM	-	-	-
25	Emond	20.5	28.5 (@ 652 hours)	27.4
	CADM	-	-	-
250	Emond	63.3	76.0 (@ 652 hours)	74.7
	CADM	-	-	-

1,000	Emond	90.2	99.0 (@ 653 hours)	98.3
	CADM	-	-	-

C.3.1.3. *Crofton et al. (2005)*

Type:	Rats	**Dose:**	0, 0.1, 3, 10, 30, 100, 300, 1000, 3000, and 10,000 ng/kg-day
Strain:	Long Evans	**Route:**	Oral exposure
Body weight:	4 weeks old BW set to 190 g	**Regime:**	One dose per day for four days
Sex:	Female	**Simulation time:**	96 hours

The CADM model was not run because the dosing duration is lower than the resolution of the model (1 week)

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.1	Emond	0.0202	0.041 (@ 72 hours)	0.0244
	CADM	-	-	-
3	Emond	0.488	1.10 (@ 72 hours)	0.582
	CADM	-	-	-
10	Emond	1.38	3.40 (@ 72 hours)	1.62
	CADM	-	-	-
30	Emond	3.46	9.44 (@ 72 hours)	3.93
	CADM	-	-	-
100	Emond	9.26	29.0 (@ 72 hours)	10.2
	CADM	-	-	-
300	Emond	23.1	81.8 (@ 72 hours)	24.5
	CADM	-	-	-
1000	Emond	65.7	260 (@ 72 hours)	68.2
	CADM	-	-	-
3000	Emond	181	764 (@ 72 hours)	187
	CADM	-	-	-
10,000	Emond	583	2,527 (@ 72 hours)	607
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.1	Emond	0.919	1.55 (@ 75 hours)	1.18
	CADM	-	-	-
3	Emond	37.4	62.6 (@ 76 hours)	53.3
	CADM	-	-	-
10	Emond	145	242 (@ 77 hours)	214
	CADM	-	-	-
30	Emond	494	818 (@ 78 hours)	742
	CADM	-	-	-
100	Emond	1,839	3,025 (@ 78 hours)	2,793
	CADM	-	-	-
300	Emond	5,925	9,692 (@ 78 hours)	9,028
	CADM	-	-	-
1000	Emond	20,717	33,738 (@ 79 hours)	31,564
	CADM	-	-	-
3000	Emond	63,511	103,140 (@ 79 hours)	96,545
	CADM	-	-	-
10,000	Emond	212,890	344,910 (@ 79 hours)	321,960
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.1	Emond	1.00	1.93 (@ 96 hours)	1.93
	CADM	-	-	-
3	Emond	24.6	45.9 (@ 96 hours)	45.9
	CADM	-	-	-
10	Emond	70.3	129 (@ 96 hours)	129
	CADM	-	-	-
30	Emond	177	317 (@ 96 hours)	317
	CADM	-	-	-
100	Emond	480	838 (@ 96 hours)	838
	CADM	-	-	-

300	Emond	1,206	2,065 (@ 96 hours)	2,065
	CADM	-	-	-
1000	Emond	3,452	5,836 (@ 96 hours)	5,836
	CADM	-	-	-
3000	Emond	9,522	16,050 (@ 96 hours)	16,050
	CADM	-	-	-
10,000	Emond	30,657	51,918 (@ 96 hours)	51,918
	CADM	-	-	-

BODY BURDEN (ng/kg)

Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.1	Emond	0.138	0.224 (@ 79 hours)	0.223
	CADM	-	-	-
3	Emond	4.04	6.56 (@ 78 hours)	6.44
	CADM	-	-	-
10	Emond	13.3	21.5 (@ 78 hours)	21.0
	CADM	-	-	-
30	Emond	39.3	63.5 (@ 78 hours)	61.5
	CADM	-	-	-
100	Emond	129	208 (@ 78 hours)	200
	CADM	-	-	-
300	Emond	384	618 (@ 77 hours)	590
	CADM	-	-	-
1000	Emond	1,270	2,041 (@ 77 hours)	1,942
	CADM	-	-	-
3000	Emond	3,793	6,094 (@ 77 hours)	5,784
	CADM	-	-	-
10,000	Emond	12,595	20,226 (@ 77 hours)	19,154
	CADM	-	-	-

BOUND LIVER (ng/kg)

Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.1	Emond	0	0.115 (@ 75 hours)	0
	CADM	-	-	-

3	Emond	2	2.47 (@ 76 hours)	2
	CADM	-	-	-
10	Emond	4	6.42 (@ 76 hours)	5
	CADM	-	-	-
30	Emond	10	14.1 (@ 76 hours)	12
	CADM	-	-	-
100	Emond	22	29.9 (@ 76 hours)	27
	CADM	-	-	-
300	Emond	41	51.9 (@ 77 hours)	49
	CADM	-	-	-
1000	Emond	68	80.2 (@ 1 hours)	77
	CADM	-	-	-
3000	Emond	90	98.6 (@ 1 hours)	96
	CADM	-	-	-
10,000	Emond	104	108 (@ 1 hours)	107
	CADM	-	-	-

C.3.1.4. *Della Porta et al. (2001) (female)*

Type:	Mouse	**Dose:**	2,500 and 5,000 ng/kg-week (equivalent to 357 and 714 ng/kg-day)
Strain:	B6C3	**Route:**	Gavage
Body weight:	6 weeks old (BW 20g)	**Regime:**	Once a week for 52 weeks
Sex:	Female	**Simulation time:**	8,736 hours

The CADM model was not run because the study duration is longer than the allowed model duration

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
357	Emond	67.0	741 (@ 8,568 hours)	46.8
	CADM	-	-	-
714	Emond	37.6	374 (@ 8,568 hours)	27.2
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
357	Emond	50,269	70,070 (@ 8,577 hours)	37,389
	CADM	-	-	-
714	Emond	25,422	35,352 (@ 8,577 hours)	19,105
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
357	Emond	25,235	28,559 (@ 8,589 hours)	22,498
	CADM	-	-	-
714	Emond	14,162	15,914 (@ 8,590 hours)	12,810
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
357	Emond	5,473	7,247 (@ 8,574 hours)	4,335
	CADM	-	-	-
714	Emond	2,878	3,774 (@ 8,574 hours)	2,318
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
357	Emond	71.5	99.1 (@ 2 hours)	65.4
	CADM	-	-	-
714	Emond	56.4	88.6 (@ 2 hours)	50.4
	CADM	-	-	-

C.3.1.5. *Della Porta et al. (2001) (male)*

Type:	Mouse	**Dose:**	2,500 and 5,000 ng/kg-week (equivalent to 357 and 714 ng/kg-day)
Strain:	B6C3	**Route:**	Gavage
Body weight:	6 weeks old (BW 26g)	**Regime:**	Once a week for 52 weeks
Sex:	Male	**Simulation time:**	8,736 hours

The CADM model was not run because the study duration is longer than the allowed model duration

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
357	Emond	67.8	787 (@ 8,568 hours)	47.0
	CADM	-	-	-
714	Emond	38.0	398 (@ 8,568 hours)	27.3
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
357	Emond	50,397	70,052 (@ 8,577 hours)	37,483
	CADM	-	-	-
714	Emond	25,493	35,347 (@ 8,577 hours)	19,155
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
357	Emond	25,516	28,851 (@ 8,589 hours)	22,861
	CADM	-	-	-
714	Emond	14,306	16,061 (@ 8,590 hours)	12,999
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
357	Emond	5,504	7,282 (@ 8,574 hours)	4,368
	CADM	-	-	-

714	Emond	2,894	3,791 (@ 8,574 hours)	2,335
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
357	Emond	71.6	99.2 (@ 2 hours)	65.4
	CADM	-	-	-
714	Emond	56.4	88.6 (@ 2 hours)	50.4
	CADM	-	-	-

C.3.1.6. *Fattore et al. (2000)*

Type:	Rat	**Dose:**	20, 200, 2,000 ng/kg-day
Strain:	Sprague Dawley	**Route:**	Oral in the diet
Body weight:	7 weeks old (BW 150g)	**Regime:**	Every day for 13 weeks
Sex:	Female and male	**Simulation time:**	2,184 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
20	Emond	9.59	15.0 (@ 2,160 hours)	11.1
	CADM	-	-	-
200	Emond	57.6	102 (@ 2,160 hours)	63.9
	CADM	-	-	-
2,000	Emond	476	903 (@ 2,160 hours)	522
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
20	Emond	2,448	3,228 (@ 2,164 hours)	3,078
	CADM	4,471	5,639	5,639
200	Emond	24,136	30,245 (@ 2,164 hours)	28,709
	CADM	45,337	56,499	56,499
2,000	Emond	234,170	288,020 (@ 2,164 hours)	272,590
	CADM	454,031	565,103	565,103
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
20	Emond	890	1,113 (@ 2,166 hours)	1,101
	CADM	1,545	1,796	1,756
200	Emond	5,355	6,542 (@ 2,165 hours)	6,430
	CADM	13,351	15,604	15,292
2,000	Emond	44,176	54,246 (@ 2,165 hours)	53,140
	CADM	131,259	153,534	150,516
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
20	Emond	187	242 (@ 2,164 hours)	233
	CADM	261	324	324
200	Emond	1,556	1,940 (@ 2,164 hours)	1,850
	CADM	2,496	3,084	3,084
2,000	Emond	14,432	17,797 (@ 2,164 hours)	16,891
	CADM	24,836	30,674	30,674
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
20	Emond	24.9	29.8 (@ 2,164 hours)	28.8
	CADM	-	-	-
200	Emond	69.4	76.0 (@ 2,164 hours)	74.7
	CADM	-	-	-

2,000	Emond	104	106 (@ 2,164 hours)	106
	CADM	-	-	-

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3 **C.3.1.7.** ***Franc et al. (2001) Sprague Dawley Rats***

Type:	Rats	**Dose:**	140, 420, and 1400 ng/kg every two weeks (equivalent to 10, 30, and 100 ng/kg-day)
Strain:	Sprague Dawley,	**Route:**	Oral gavage
Body weight:	200 g (10 weeks old)	**Regime:**	Once every two weeks for 22 weeks
Sex:	Female	**Simulation time:**	3,696 hours

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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
10	Emond	6.59	34.6 (@ 3,360 hours)	5.52
	CADM	-	-	-
30	Emond	14.5	98.1 (@ 3,360 hours)	11.3
	CADM	-	-	-
WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
100	Emond	36.4	315 (@ 3,360 hours)	26.4
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
10	Emond	1,447	2,458 (@ 3,368 hours)	1,150
	CADM	2,616	3,620	2,174
30	Emond	4,228	7,161 (@ 3,368 hours)	3,120
	CADM	7,936	10,899	6,510
100	Emond	13,821	23,417 (@ 3,368 hours)	9,658
	CADM	26,564	36,361	21,703

FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
10	Emond	619	787 (@ 3,417 hours)	560
	CADM	966	1,230	759
30	Emond	1,362	1,741 (@ 3,415 hours)	1,161
	CADM	2,448	3,203	1,849
100	Emond	3,430	4,464 (@ 3,412 hours)	2,755
	CADM	7,573	10,052	5,606
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
10	Emond	119	177 (@ 3,366 hours)	99.5
	CADM	159	212	133
30	Emond	308	472 (@ 3,366 hours)	240
	CADM	450	603	367
100	Emond	921	1,445 (@ 3,366 hours)	671
	CADM	1,462	1,969	1,181
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
10	Emond	18.6	32.9 (@ 1 hours)	16.4
	CADM	-	-	-
30	Emond	33.7	59.2 (@ 1 hours)	29.0
	CADM	-	-	-
100	Emond	57.5	86.9 (@ 1 hours)	50.4
	CADM	-	-	-

C.3.1.8. *Franc et al. (2001) Long-Evans Rats*

Type:	Rats	**Dose:**	140, 420, and 1400 ng/kg every two weeks (equivalent to 10, 30, and 100 ng/kg-day)
Strain:	Long-Evans	**Route:**	Oral gavage
Body weight:	190 g (10 weeks old)	**Regime:**	Once every two weeks for 22 weeks
Sex:	Female	**Simulation time:**	3,696 hours

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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
10	Emond	6.58	34.2 (@ 3,360 hours)	5.52
	CADM	-	-	-
30	Emond	14.5	97.0 (@ 3,360 hours)	11.3
	CADM	-	-	-
100	Emond	36.4	312 (@ 3,360 hours)	26.4
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
10	Emond	1,447	2,458 (@ 3,368 hours)	1,150
	CADM	2,616	3,620	2,174
30	Emond	4,228	7,161 (@ 3,368 hours)	3,121
	CADM	7,936	10,899	6,510
100	Emond	13,821	23,421 (@ 3,368 hours)	9,659
	CADM	26,564	36,361	21,703
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
10	Emond	619	788 (@ 3,417 hours)	560
	CADM	966	1,230	759
30	Emond	1,362	1,742 (@ 3,414 hours)	1,160
	CADM	2,448	3,203	1,849
100	Emond	3,429	4,466 (@ 3,412 hours)	2,752
	CADM	7,573	10,052	5,606
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
10	Emond	119	177 (@ 3,366 hours)	99.5
	CADM	159	212	133
30	Emond	308	472 (@ 3,366 hours)	240
	CADM	450	603	367
100	Emond	921	1,445 (@ 3,366 hours)	671
	CADM	1,462	1,969	1,181

BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
10	Emond	18.6	32.9 (@ 1 hours)	16.4
	CADM	-	-	-
30	Emond	33.7	59.2 (@ 1 hours)	29.0
	CADM	-	-	-
100	Emond	57.5	86.9 (@ 1 hours)	50.4
	CADM	-	-	-

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C.3.1.9. *Franc et al. (2001) Hans Wistar Rats*

Type:	Rats	**Dose:**	140, 420, and 1400 ng/kg every two weeks (equivalent to 10, 30, and 100 ng/kg-day)
Strain:	Hans Wistar	**Route:**	Oral gavage
Body weight:	205 g (10 weeks old)	**Regime:**	Once every two weeks for 22 weeks
Sex:	Female	**Simulation time:**	3,696 hours

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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
10	Emond	6.59	34.7 (@ 3,360 hours)	5.52
	CADM	-	-	-
30	Emond	14.5	98.7 (@ 3,360 hours)	11.3
	CADM	-	-	-
100	Emond	36.4	317 (@ 3,360 hours)	26.4
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
10	Emond	1,447	2,458 (@ 3,368 hours)	1,150
	CADM	2,616	3,620	2,174
30	Emond	4,228	7,160 (@ 3,368 hours)	3,120
	CADM	7,936	10,899	6,510

100	Emond	13,821	23,416 (@ 3,368 hours)	9,658
	CADM	26,564	36,361	21,703
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
10	Emond	619	787 (@ 3,418 hours)	560
	CADM	966	1,230	759
30	Emond	1,363	1,741 (@ 3,415 hours)	1,162
	CADM	2,448	3,203	1,849
100	Emond	3,431	4,463 (@ 3,412 hours)	2,757
	CADM	7,573	10,052	5,606
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
10	Emond	119	177 (@ 3,366 hours)	99.5
	CADM	159	212	133
30	Emond	308	472 (@ 3,366 hours)	240
	CADM	450	603	367
100	Emond	921	1,446 (@ 3,366 hours)	671
	CADM	1,462	1,969	1,181
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
10	Emond	18.6	32.9 (@ 1 hours)	16.4
	CADM	-	-	-
30	Emond	33.7	59.2 (@ 1 hours)	29.0
	CADM	-	-	-
100	Emond	57.5	86.9 (@ 1 hours)	50.4
	CADM	-	-	-

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C.3.1.10. *Hassoun et al. (2000)*

Type:	Rat	**Dose:**	0, 3, 10, 22, 46, 100 ng/kg/day (2.14, 7.14, 15.7, 32.9, and 71.4 ng/kg/day adjusted doses)
Strain:	Sprague Dawley	**Route:**	Oral gavage
Body weight:	8 weeks old (BW=215g)	**Regime:**	5 days/week for 13 weeks
Sex:	Female	**Simulation time:**	2184 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	1.94	3.12 (@ 2,112 hours)	1,303.17
	CADM	-	-	-
7.14	Emond	4.6136	7.71 (@ 2,112 hours)	2,901.26
	CADM	-	-	-
15.7	Emond	8.147	14.2 (@ 2,112 hours)	4,947.3
	CADM	-	-	-
32.9	Emond	14.009	25.8 (@ 2,112 hours)	8,277
	CADM	-	-	-
71.4	Emond	25.34	49.7 (@ 2,112 hours)	14,637
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	266.8	399 (@ 2,116 hours)	349
	CADM	-	-	-
7.14	Emond	888	1,259 (@ 2,117 hours)	1,079
	CADM	-	-	-
15.7	Emond	1,948.499	2,689 (@ 2,117 hours)	2,278.182
	CADM	-	-	-
32.9	Emond	4,055.031	5,484 (@ 2,117 hours)	4,607.265
	CADM	-	-	-
71.4	Emond	8,774.97	11,692 (@ 2,117 hours)	9,754.31
	CADM	-	-	-

FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	179.2	243 (@ 2,126 hours)	234.9
	CADM	-	-	-
7.14	Emond	427	553 (@ 2,124 hours)	528
	CADM	-	-	-
15.7	Emond	755	958 (@ 2,123 hours)	908
	CADM	-	-	-
32.9	Emond	1,299	1,627 (@ 2,122 hours)	1,529
	CADM	-	-	-
71.4	Emond	2,349.892	2,928 (@ 2,121 hours)	2,727.240
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	27.425	38.9 (@ 2,116 hours)	35.720
	CADM	-	-	-
7.14	Emond	76.87	105 (@ 2,116 hours)	93.67
	CADM	-	-	-
15.7	Emond	153.1	205 (@ 2,116 hours)	180.2
	CADM	-	-	-
32.9	Emond	295	390 (@ 2,116 hours)	339
	CADM	-	-	-
71.4	Emond	600	785 (@ 2,116 hours)	674
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	6	8.48 (@ 2,116 hours)	8
	CADM	-	-	-
7.14	Emond	13.7242	17.5 (@ 2,116 hours)	15.7348
	CADM	-	-	-
15.7	Emond	21.9703	27.1 (@ 2,116 hours)	24.4047
	CADM	-	-	-
32.9	Emond	32.817	39.2 (@ 2,116 hours)	35.608
	CADM	-	-	-

71.4	Emond	47.54	55.0 (@ 2,116 hours)	50.63
	CADM	-	-	-

C.3.1.11. *Hutt et al. (2008)*

Type:	Rat	**Dose:**	50 ng/kg-week
Strain:	Sprague-Dawley	**Route:**	Oral gavage
Body weight:	4.5 g	**Regime:**	1/week for 13 weeks
Sex:	Female	**Simulation time:**	2,184 hours (weekly exposure)

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
7.14	Emond	4.49	8.86 (@ 2,016 hours)	4.71
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
7.14	Emond	867.4	1,363 (@ 2,021 hours)	928.1
	CADM	1,678	2,007	2,007
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
7.14	Emond	423.6	555 (@ 2,040 hours)	459.9
	CADM	730	787.1	769
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
7.14	Emond	76	108 (@ 2,022 hours)	81
	CADM	108	126	126

BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
7.14	Emond	14	19.4 (@ 2,020 hours)	14
	CADM	-	-	-

C.3.1.12. *Kitchin and Woods (1979)*

Type:	Rats	**Dose:**	0, 0.6, 2, 4, 20, 60, 200, 600, 2000, 5000, 20,000 ng/kg/day
Strain:	Sprague-Dawley	**Route:**	Oral exposure
Body weight:	200 to 250 g (BW set to 225 g)	**Regime:**	Single dose
Sex:	Female	**Simulation time:**	24 hours*

* 1 week is the minimum that can be simulated with the CADM model, so the CADM model was not used.

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day)	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.6	Emond	0.0645	0.126 (@ 0 hours)	0.0441
	CADM	-	-	-
2	Emond	0.202	0.421 (@ 0 hours)	0.137
	CADM	-	-	-
4	Emond	0.384	0.841 (@ 0 hours)	0.258
	CADM	-	-	-
20	Emond	1.61	4.21 (@ 0 hours)	1.04
	CADM	-	-	-
60	Emond	4.15	12.6 (@ 0 hours)	2.55
	CADM	-	-	-
200	Emond	11.6	42.1 (@ 0 hours)	6.61
	CADM	-	-	-
600	Emond	30.3	126 (@ 0 hours)	15.8
	CADM	-	-	-
2000	Emond	90.9	422 (@ 0 hours)	42.8
	CADM	-	-	-

5000	Emond	218	1,056 (@ 0 hours)	96.9
	CADM	-	-	-
20000	Emond	863	4,233 (@ 0 hours)	365
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day)	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.6	Emond	2.95	3.81 (@ 4 hours)	2.31
	CADM	-	-	-
2	Emond	10.5	12.9 (@ 4 hours)	8.69
	CADM	-	-	-
4	Emond	22.2	26.3 (@ 4 hours)	18.9
	CADM	-	-	-
20	Emond	128	143 (@ 6 hours)	118
	CADM	-	-	-
60	Emond	420	463 (@ 8 hours)	406
	CADM	-	-	-
200	Emond	1,523	1,666 (@ 9 hours)	1,526
	CADM	-	-	-
600	Emond	4,821	5,258 (@ 10 hours)	4,932
	CADM	-	-	-
2000	Emond	16,603	18,080 (@ 11 hours)	17,226
	CADM	-	-	-
5000	Emond	41,971	45,674 (@ 11 hours)	43,803
	CADM	-	-	-
20000	Emond	167,820	182,580 (@ 11 hours)	175,890
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day)	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.6	Emond	1.60	2.47 (@ 24 hours)	2.47
	CADM	-	-	-
2	Emond	5.07	7.71 (@ 24 hours)	7.71
	CADM	-	-	-

4	Emond	9.68	14.6 (@ 24 hours)	14.6
	CADM	-	-	-
20	Emond	41.7	60.7 (@ 24 hours)	60.7
	CADM	-	-	-
60	Emond	110	155 (@ 24 hours)	155
	CADM	-	-	-
200	Emond	317	427 (@ 24 hours)	427
	CADM	-	-	-
600	Emond	851	1,102 (@ 24 hours)	1,102
	CADM	-	-	-
2000	Emond	2,620	3,276 (@ 24 hours)	3,276
	CADM	-	-	-
5000	Emond	6,361	7,816 (@ 24 hours)	7,816
	CADM	-	-	-
20000	Emond	25,401	30,827 (@ 24 hours)	30,827
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day)	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.6	Emond	0.322	0.341 (@ 9 hours)	0.338
	CADM	-	-	-
2	Emond	1.07	1.14 (@ 8 hours)	1.12
	CADM	-	-	-
4	Emond	2.14	2.27 (@ 8 hours)	2.23
	CADM	-	-	-
20	Emond	10.6	11.3 (@ 8 hours)	11.0
	CADM	-	-	-
60	Emond	31.7	33.8 (@ 7 hours)	32.8
	CADM	-	-	-
200	Emond	105	112 (@ 7 hours)	108
	CADM	-	-	-
600	Emond	315	337 (@ 7 hours)	324
	CADM	-	-	-
2000	Emond	1,049	1,123 (@ 7 hours)	1,074
	CADM	-	-	-

5000	Emond	2,621	2,806 (@ 7 hours)	2,680
	CADM	-	-	-
20000	Emond	10,468	11,215 (@ 7 hours)	10,693
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day)	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.6	Emond	0.216	0.309 (@ 3 hours)	0.159
	CADM	-	-	-
2	Emond	0.668	0.975 (@ 3 hours)	0.494
	CADM	-	-	-
4	Emond	1.25	1.86 (@ 3 hours)	0.927
	CADM	-	-	-
20	Emond	4.87	7.67 (@ 2 hours)	3.66
	CADM	-	-	-
60	Emond	11.2	18.3 (@ 2 hours)	8.55
	CADM	-	-	-
200	Emond	25.1	40.8 (@ 1 hours)	19.7
	CADM	-	-	-
600	Emond	45.8	68.2 (@ 1 hours)	37.6
	CADM	-	-	-
2000	Emond	73.3	93.1 (@ 1 hours)	64.7
	CADM	-	-	-
5000	Emond	90.9	104 (@ 1 hours)	84.7
	CADM	-	-	-
20000	Emond	106	110 (@ 1 hours)	104
	CADM	-	-	-

C.3.1.13. *Kociba et al. (1976)*

Type:	Rats	**Dose:**	1, 10, 100, 1000 ng/kg-day
Strain:	Sprague-Dawley (Spartan)	**Route:**	Diet exposure
Body weight:	170–190 g (bw=180g)	**Regime:**	5 days/week for 13 weeks
Sex:	Female	**Simulation time:**	2,184 hours (13wk exposed)

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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.714	Emond	0.859	1.38 (@ 2,112 hours)	1.13
	CADM	-	-	-
7.143	Emond	4.61	7.62 (@ 2,112 hours)	5.27
	CADM	-	-	-
WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
71.43	Emond	25.3	48.8 (@ 2,112 hours)	26.6
	CADM	-	-	-
714.3	Emond	181	403 (@ 2,112 hours)	184
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.714	Emond	88.3	140 (@ 2,116 hours)	126
	CADM	89.0	192	12.1
7.143	Emond	888	1,259 (@ 2,117 hours)	1,079
	CADM	970	2,007	29.0
71.43	Emond	8,776	11,693 (@ 2,117 hours)	9,756
	CADM	9,841	20,170	88.0
714.3	Emond	86,329	112,580 (@ 2,117 hours)	92,835
	CADM	98,617	201,814	455
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.714	Emond	79.4	114 (@ 2,129 hours)	111
	CADM	120	190	43.0
7.143	Emond	427	553 (@ 2,124 hours)	528
	CADM	456	787	67.0
71.43	Emond	2,348	2,925 (@ 2,121 hours)	2,720
	CADM	3,036	5,748	117

714.3	Emond	16,815	21,126 (@ 2,120 hours)	19,233
	CADM	28,382	55,013	274
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.714	Emond	10.8	16.1 (@ 2,116 hours)	15.1
	CADM	11.5	20.0	3.75
7.143	Emond	76.9	105 (@ 2,116 hours)	93.6
	CADM	65.3	126	6.22
71.43	Emond	600	785 (@ 2,116 hours)	673
	CADM	553	1,113	12.0
714.3	Emond	5,366	6,960 (@ 2,116 hours)	5,842
	CADM	5,401	10,967	37.0
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.714	Emond	2.89	4.17 (@ 2,116 hours)	3.81
	CADM	-	-	-
7.143	Emond	13.7	17.5 (@ 2,116 hours)	15.7
	CADM	-	-	-
71.43	Emond	47.5	55.0 (@ 2,116 hours)	50.6
	CADM	-	-	-
714.3	Emond	93.4	98.2 (@ 2,117 hours)	95.7
	CADM	-	-	-

C.3.1.14. *Kociba et al. (1978) Female*

Type:	Rats	**Dose:**	0, 1, 10, 100 ng/kg-day
Strain:	Sprague-Dawley (Spartan)	**Route:**	Diet exposure
Body weight:	170–190 g (bw=180)	**Regime:**	7 days/week for 104 weeks
Sex:	Female	**Simulation time:**	17,472 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	1.55	1.92 (@ 17,448 hours)	1.69
	CADM	-	-	-
10	Emond	7.15	9.25 (@ 17,448 hours)	7.16
	CADM	-	-	-
100	Emond	38.6	57.5 (@ 17,448 hours)	37.1
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	192	226 (@ 17,452 hours)	218
	CADM	292	333	333
10	Emond	1,618	1,742 (@ 17,452 hours)	1,665
	CADM	2,981	3,342	3,342
100	Emond	14,892	15,673 (@ 17,452 hours)	14,907
	CADM	29,917	33,432	33,432
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	147	165 (@ 17,457 hours)	164
	CADM	196	229	181
10	Emond	680	713 (@ 17,454 hours)	706
	CADM	861	1,015	789
100	Emond	3,663	3,788 (@ 17,454 hours)	3,731
	CADM	6,756	7,939	6,203
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	21.2	24.3 (@ 17,452 hours)	23.8
	CADM	26.0	27.0	27.0
10	Emond	131	140 (@ 17,452 hours)	136
	CADM	169	176	176

100	Emond	989	1,039 (@ 17,452 hours)	994
	CADM	1,546	1,601	1,601
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	5.11	5.77 (@ 17,452 hours)	5.59
	CADM	-	-	-
10	Emond	20.0	21.1 (@ 17,452 hours)	20.4
	CADM	-	-	-
100	Emond	59.9	61.5 (@ 17,452 hours)	60.1
	CADM	-	-	-

C.3.1.15. *Kociba et al. (1978) Male*

Type:	Rats	**Dose:**	0, 1, 10, 100 ng/kg-day
Strain:	Sprague-Dawley (Spartan)	**Route:**	Diet exposure
Body weight:	Body weight approximated to be 250 g	**Regime:**	7 days/week for 104 weeks
Sex:	Male	**Simulation time:**	17,472 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	1.56	1.96 (@ 17,448 hours)	1.70
	CADM	-	-	-
10	Emond	7.16	9.35 (@ 17,448 hours)	7.11
	CADM	-	-	-
100	Emond	38.7	59.3 (@ 17,448 hours)	37.1
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	194	229 (@ 17,452 hours)	221
	CADM	-	-	-

10	Emond	1,616	1,723 (@ 17,452 hours)	1,649
	CADM	-	-	-
100	Emond	14,898	15,671 (@ 17,452 hours)	14,912
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	148	167 (@ 17,456 hours)	166
	CADM	-	-	-
10	Emond	680	709 (@ 17,454 hours)	703
	CADM	-	-	-
100	Emond	3,677	3,803 (@ 17,453 hours)	3,747
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	21.4	24.6 (@ 17,452 hours)	24.1
	CADM	-	-	-
10	Emond	131	139 (@ 17,452 hours)	134
	CADM	-	-	-
100	Emond	991	1,041 (@ 17,452 hours)	995
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	5.15	5.83 (@ 17,452 hours)	5.64
	CADM	-	-	-
10	Emond	20.0	21.0 (@ 17,452 hours)	20.3
	CADM	-	-	-
100	Emond	60.0	61.5 (@ 17,452 hours)	60.1
	CADM	-	-	-

C.3.1.16. *Latchoumycandane and Mathur (2002)*

Type:	Rat	**Dose:**	0, 1, 10, 100 ng/kg-day
Strain:	Wistar	**Route:**	Oral gavage
Body weight:	45 days old (BW set to 200g)	**Regime:**	1/day for 45 days
Sex:	Male	**Simulation time:**	1,080 hours (daily exposure)

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	0.785	1.37 (@ 1,056 hours)	1.18
	CADM	-	-	-
10	Emond	4.65	8.18 (@ 1,056 hours)	6.18
	CADM	-	-	-
100	Emond	27.3	53.9 (@ 1,056 hours)	33.8
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	78.5	138 (@ 1,060 hours)	133
	CADM	116	217	217
10	Emond	902	1,423 (@ 1,060 hours)	1,358
	CADM	1,669	2,550	2,550
100	Emond	9,579	14,015 (@ 1,061 hours)	13,306
	CADM	17,681	25,915	25,915
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	69.8	113 (@ 1,072 hours)	113
	CADM	150	220	220
10	Emond	416	608 (@ 1,065 hours)	604
	CADM	744	1,009	1,009
100	Emond	2,448	3,425 (@ 1,062 hours)	3,380
	CADM	5,719	7,866	7,866

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	9.56	15.9 (@ 1,060 hours)	15.6
	CADM	14.0	22.2	22.2
10	Emond	76.7	117 (@ 1,060 hours)	113
	CADM	106	157	157
100	Emond	646	933 (@ 1,060 hours)	891
	CADM	988	1,439	1,439
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	2.64	4.12 (@ 1,060 hours)	3.96
	CADM	-	-	-
10	Emond	13.7	18.8 (@ 1,060 hours)	18.1
	CADM	-	-	-
100	Emond	48.6	59.0 (@ 1,060 hours)	57.5
	CADM	-	-	-

C.3.1.17. *Li et al. (1997)*

Type:	Rats	**Dose:**	0, 3, 10, 30, 100, 300, 1000, 3000, 10000, 30000 ng/kg/day
Strain:	Sprague-Dawley	**Route:**	Gastric intubation
Body weight:	22 day old, 55 to 58 g (BW set to 56.5 g)	**Regime:**	One dose for one day
Sex:	Female	**Simulation time:**	24 hours

The CADM model was not run because the dosing duration is lower than the resolution of the model (1 week)

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day)	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
3	Emond	0.266	0.470 (@ 1 hours)	0.180
	CADM	-	-	-
10	Emond	0.799	1.57 (@ 1 hours)	0.535
	CADM	-	-	-

30	Emond	2.10	4.68 (@ 1 hours)	1.37
	CADM	-	-	-
100	Emond	5.87	15.6 (@ 1 hours)	3.68
	CADM	-	-	-
300	Emond	15.0	46.8 (@ 0 hours)	8.83
	CADM	-	-	-
1,000	Emond	43.3	156 (@ 0 hours)	23.4
	CADM	-	-	-
3,000	Emond	120	469 (@ 0 hours)	59.9
	CADM	-	-	-
10,000	Emond	386	1,570 (@ 0 hours)	182
	CADM	-	-	-
30,000	Emond	1,172	4,762 (@ 0 hours)	535
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day)	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
3	Emond	14.7	18.6 (@ 4 hours)	11.9
	CADM	-	-	-
10	Emond	55.0	65.2 (@ 5 hours)	47.6
	CADM	-	-	-
30	Emond	185	210 (@ 6 hours)	170
	CADM	-	-	-
100	Emond	690	768 (@ 7 hours)	666
	CADM	-	-	-
300	Emond	2,248	2,473 (@ 8 hours)	2,240
	CADM	-	-	-
1,000	Emond	7,938	8,671 (@ 9 hours)	8,094
	CADM	-	-	-
3,000	Emond	24,474	26,639 (@ 9 hours)	25,267
	CADM	-	-	-
10,000	Emond	82,349	89,464 (@ 9 hours)	85,597
	CADM	-	-	-
30,000	Emond	245,610	265,670 (@ 10 hours)	255,390
	CADM	-	-	-

FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day)	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
3	Emond	8.75	12.7 (@ 24 hours)	12.7
	CADM	-	-	-
10	Emond	26.6	38.0 (@ 24 hours)	38.0
	CADM	-	-	-
30	Emond	70.8	98.9 (@ 24 hours)	98.9
	CADM	-	-	-
100	Emond	202	273 (@ 24 hours)	273
	CADM	-	-	-
300	Emond	530	689 (@ 24 hours)	689
	CADM	-	-	-
1,000	Emond	1,573	1,958 (@ 24 hours)	1,958
	CADM	-	-	-
3,000	Emond	4,433	5,358 (@ 24 hours)	5,358
	CADM	-	-	-
10,000	Emond	14,428	17,119 (@ 24 hours)	17,119
	CADM	-	-	-
30,000	Emond	44,361	51,948 (@ 22 hours)	51,898
	CADM	-	-	-

BODY BURDEN (ng/kg)				
Dose (ng/kg-day)	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
3	Emond	1.60	1.70 (@ 8 hours)	1.68
	CADM	-	-	-
10	Emond	5.33	5.66 (@ 8 hours)	5.56
	CADM	-	-	-
30	Emond	15.9	16.9 (@ 8 hours)	16.5
	CADM	-	-	-
100	Emond	52.8	56.2 (@ 7 hours)	54.5
	CADM	-	-	-
300	Emond	158	169 (@ 7 hours)	163
	CADM	-	-	-

1,000	Emond	525	561 (@ 7 hours)	539
	CADM	-	-	-
3,000	Emond	1,574	1,684 (@ 7 hours)	1,611
	CADM	-	-	-
10,000	Emond	5,240	5,610 (@ 7 hours)	5,360
	CADM	-	-	-
30,000	Emond	15,758	16,815 (@ 7 hours)	16,041
	CADM	-	-	-

BOUND LIVER (ng/kg)

Dose (ng/kg-day)	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
3	Emond	0.89	1.37 (@ 3 hours)	0.64
	CADM	-	-	-
10	Emond	2.58	4.10 (@ 2 hours)	1.88
	CADM	-	-	-
30	Emond	6.37	10.5 (@ 2 hours)	4.71
	CADM	-	-	-
100	Emond	15.54	25.9 (@ 2 hours)	11.77
	CADM	-	-	-
300	Emond	31.25	50.1 (@ 1 hours)	24.57
	CADM	-	-	-
1,000	Emond	56.75	79.8 (@ 1 hours)	47.62
	CADM	-	-	-
3,000	Emond	81.28	98.4 (@ 1 hours)	73.32
	CADM	-	-	-
10,000	Emond	99.77	108 (@ 1 hours)	95.68
	CADM	-	-	-
30,000	Emond	107.69	111 (@ 1 hours)	106.24
	CADM	-	-	-

C.3.1.18. *Murray et al. (1979) Adult Portion*

Type:	Rat	**Dose:**	1, 10, and 100 ng/kg-day
Strain:	Sprague Dawley	**Route:**	Diet oral dose
Body weight:	BW set to 4.5 g	**Regime:**	Once per day for 120 days
Sex:	Female	**Simulation time:**	2880 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	1.12	1.51 (@ 2,856 hours)	1.42
	CADM	-	-	-
10	Emond	5.88	7.59 (@ 2,856 hours)	6.75
	CADM	-	-	-
100	Emond	32.7	44.3 (@ 2,856 hours)	36.0
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	128	180 (@ 2,859 hours)	173
	CADM	-	-	-
10	Emond	1,273	1,618 (@ 2,860 hours)	1,540
	CADM	-	-	-
100	Emond	12,601	15,281 (@ 2,860 hours)	14,460
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	106	139 (@ 2,865 hours)	138
	CADM	-	-	-
10	Emond	556	665 (@ 2,864 hours)	657
	CADM	-	-	-
100	Emond	3,095	3,604 (@ 2,862 hours)	3,534
	CADM	-	-	-

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	14.8	20.0 (@ 2,860 hours)	19.6
	CADM	-	-	-
10	Emond	105	130 (@ 2,860 hours)	126
	CADM	-	-	-
100	Emond	837	1,003 (@ 2,860 hours)	957
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	3.77	4.95 (@ 2,859 hours)	4.77
	CADM	-	-	-
10	Emond	17.1	20.3 (@ 2,859 hours)	19.5
	CADM	-	-	-
100	Emond	55.3	60.9 (@ 2,860 hours)	59.4
	CADM	-	-	-

C.3.1.19. *NTP (1982)—Female Rats, Chronic*

Type:	Rat	**Dose:**	10, 50 and 500 ng/kg/wk, two doses per week
Strain:	Osborne-Mendel	**Route:**	Oral exposure
Body weight	6 weeks old (BW set to 250g)	**Regime:**	Biweekly (Simulation has been perform using female BW
Sex:	**Female**	**Simulation time**	17,472 hours (104 weeks of exposure)

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	1.96	3.11 (@ 17,220 hours)	1.94
	CADM	-	-	-
7.1	Emond	5.69	11.0 (@ 17,388 hours)	5.40
	CADM	-	-	-

71	Emond	29.8	82.2 (@ 17,388 hours)	26.9
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	265	308 (@ 17,226 hours)	265
	CADM	15,318	20,170	7,102
7.1	Emond	1,175	1,338 (@ 17,394 hours)	1,117
	CADM	30,700	40,353	14,200
71	Emond	10,734	12,182 (@ 17,395 hours)	9,882
	CADM	30,700	40,353	14,200
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	186	200 (@ 17,328 hours)	193
	CADM	4,655	5,748	2,107
7.1	Emond	541	569 (@ 17,409 hours)	544
	CADM	9,064	11,224	3,964
71	Emond	2,826	2,973 (@ 17,404 hours)	2,769
	CADM	17,879	22,172	7,671
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	27.9	31.1 (@ 17,225 hours)	28.4
	CADM	855	1,113	403
7.1	Emond	99.4	110 (@ 17,393 hours)	96.7
	CADM	1,695	2,208	787
71	Emond	729	814 (@ 17,393 hours)	683
	CADM	3,375	4,395	1,556
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	6.37	7.26 (@ 17,224 hours)	6.38
	CADM	-	-	-

7.1	Emond	16.6	18.5 (@ 17,392 hours)	16.1
	CADM	-	-	-
71	Emond	52.7	56.4 (@ 17,393 hours)	50.9
	CADM	-	-	-

C.3.1.20. *NTP (1982)—Male Rats, Chronic*

Type:	Rat	**Dose:**	10, 50 and 500 ng/kg/wk, two doses per week
Strain:	Osborne-Mendel	**Route:**	Oral exposure
Body weight	6 weeks old (BW set to 350g)	**Regime:**	Biweekly (Simulation has been perform using female BW
Sex:	**Male**	**Simulation time**	17,472 hours (104 weeks of exposure)

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	1.96	3.18 (@ 17,388 hours)	1.93
	CADM	-	-	-
7.1	Emond	5.70	11.4 (@ 17,388 hours)	5.39
	CADM	-	-	-
71	Emond	29.9	87.0 (@ 17,388 hours)	26.9
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	265	306 (@ 17,394 hours)	263
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
7.1	Emond	1,174	1,334 (@ 17,394 hours)	1,114
	CADM	-	-	-
71	Emond	10,736	12,170 (@ 17,395 hours)	9,881
	CADM	-	-	-

FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	186	199 (@ 17,412 hours)	193
	CADM	-	-	-
7.1	Emond	541	569 (@ 17,409 hours)	544
	CADM	-	-	-
71	Emond	2,836	2,983 (@ 17,404 hours)	2,784
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	27.8	30.9 (@ 17,393 hours)	28.2
	CADM	-	-	-
7.1	Emond	99.5	110 (@ 17,393 hours)	96.6
	CADM	-	-	-
71	Emond	730	816 (@ 17,393 hours)	684
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	6.36	7.22 (@ 17,392 hours)	6.35
	CADM	-	-	-
7.1	Emond	16.6	18.4 (@ 17,392 hours)	16.0
	CADM	-	-	-
71	Emond	52.7	56.3 (@ 17,393 hours)	50.9
	CADM	-	-	-

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C.3.1.21. *NTP (1982)—Female Mice, Chronic*

Type:	Mice	**Dose:**	40, 200 and 2000 ng/kg/wk, two doses during the week
Strain:	B6C3F1	**Route:**	Oral exposure
Body weight	6 weeks old (BW set to 23g)	**Regime:**	Biweekly (Simulation has been perform using female BW)
Sex:	Female	**Simulation time**	17,472 hours (104 weeks of exposure)

* The mice chronic exposure could not be simulated with the CADM model because this model simulates for only 123 days.

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
5.7	Emond	1.95	4.86 (@ 16,800 hours)	1.82
	CADM	-	-	-
28.6	Emond	5.84	19.8 (@ 17,388 hours)	5.17
	CADM	-	-	-
286	Emond	32.1	171 (@ 16,884 hours)	26.0
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
5.7	Emond	490	582 (@ 16,807 hours)	463
	CADM	-	-	-
28.6	Emond	2,236	2,629 (@ 17,395 hours)	2,025
	CADM	-	-	-
286	Emond	20,841	24,353 (@ 17,396 hours)	18,182
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
5.7	Emond	737	785 (@ 17,408 hours)	757
	CADM	-	-	-
28.6	Emond	2,213	2,337 (@ 17,404 hours)	2,216
	CADM	-	-	-
286	Emond	12,138	12,861 (@ 17,400 hours)	11,775
	CADM	-	-	-

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
5.7	Emond	91.9	103 (@ 17,393 hours)	91.2
	CADM	-	-	-
28.6	Emond	329	370 (@ 17,393 hours)	313
	CADM	-	-	-
286	Emond	2,400	2,740 (@ 17,393 hours)	2,176
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
5.7	Emond	6.18	7.29 (@ 16,805 hours)	5.93
	CADM	-	-	-
28.6	Emond	16.3	18.9 (@ 17,393 hours)	15.3
	CADM	-	-	-
286	Emond	52.3	67.8 (@ 2 hours)	49.3
	CADM	-	-	-

C.3.1.22. *NTP (1982)—Male Mice, Chronic*

Type:	Mice	**Dose:**	10, 50 and 500ng/kg/wk, two doses during the week
Strain:	B6C3F1	**Route:**	Oral exposure
Body weight	6 weeks old (BW set to 25g)	**Regime:**	Biweekly
Sex:	Male	**Simulation time**	17,472 hours (104 weeks of exposure)

* The mice chronic exposure could not be simulated with the CADM model because this model simulates for only 123 days.

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	0.767	1.53 (@ 17,304 hours)	0.749
	CADM	-	-	-
7.1	Emond	2.27	5.99 (@ 17,052 hours)	2.11
	CADM	-	-	-

71	Emond	11.2	46.7 (@ 17,388 hours)	9.59
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	138	165 (@ 17,310 hours)	136
	CADM	-	-	-
7.1	Emond	606	722 (@ 17,059 hours)	571
	CADM	-	-	-
71	Emond	5,409	6,328 (@ 17,395 hours)	4,805
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	290	314 (@ 17,411 hours)	306
	CADM	-	-	-
7.1	Emond	860	918 (@ 17,155 hours)	883
	CADM	-	-	-
71	Emond	4,257	4,490 (@ 17,402 hours)	4,204
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	32.3	36.2 (@ 17,309 hours)	33.3
	CADM	-	-	-
7.1	Emond	110	123 (@ 17,057 hours)	108
	CADM	-	-	-
71	Emond	710	802 (@ 17,393 hours)	660
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	2.56	3.03 (@ 17,309 hours)	2.53
	CADM	-	-	-

7.1	Emond	7.12	8.40 (@ 17,057 hours)	6.82
	CADM	-	-	-
71	Emond	27.1	32.4 (@ 2 hours)	25.3
	CADM	-	-	-

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3 **C.3.1.23.** ***NTP (2006) 14 Weeks***

Type:	Rat	**Dose:**	0, 3, 10, 22, 46, 100 ng/kg-day
Strain:	Sprague Dawley	**Route:**	Oral gavage
Body weight:	8 weeks old (BW=215g)	**Regime:**	5 days/weeks for 14 weeks
Sex:	Female and male	**Simulation time:**	2,352 hours (14 weeks)

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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	1.98	3.15 (@ 2,280 hours)	2.39
	CADM	-	-	-
7.14	Emond	4.69	7.75 (@ 2,280 hours)	5.30
	CADM	-	-	-
15.7	Emond	8.27	14.3 (@ 2,280 hours)	9.02
	CADM	-	-	-
32.9	Emond	14.2	25.9 (@ 2,280 hours)	15.1
	CADM	-	-	-
71.4	Emond	25.7	49.8 (@ 2,280 hours)	26.6
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	275	404 (@ 2,284 hours)	354
	CADM	-	-	-
7.14	Emond	909	1,270 (@ 2,285 hours)	1,089
	CADM	-	-	-
15.7	Emond	1,988	2,703 (@ 2,285 hours)	2,291
	CADM	-	-	-

32.9	Emond	4,129	5,508 (@ 2,285 hours)	4,628
	CADM	-	-	-
71.4	Emond	8,921	11,734 (@ 2,285 hours)	9,792
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	184	246 (@ 2,294 hours)	237
	CADM	-	-	-
7.14	Emond	436	557 (@ 2,292 hours)	532
	CADM	-	-	-
15.7	Emond	768	962 (@ 2,291 hours)	912
	CADM	-	-	-
32.9	Emond	1,319	1,633 (@ 2,289 hours)	1,535
	CADM	-	-	-
71.4	Emond	2,385	2,938 (@ 2,289 hours)	2,736
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	28.2	39.4 (@ 2,284 hours)	36.1
	CADM	-	-	-
7.14	Emond	78.5	106 (@ 2,284 hours)	94.4
	CADM	-	-	-
15.7	Emond	156	206 (@ 2,284 hours)	181
	CADM	-	-	-
32.9	Emond	300	391 (@ 2,284 hours)	340
	CADM	-	-	-
71.4	Emond	610	788 (@ 2,284 hours)	676
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	6.41	8.55 (@ 2,284 hours)	7.74
	CADM	-	-	-

7.14	Emond	13.9	17.6 (@ 2,284 hours)	15.8
	CADM	-	-	-
15.7	Emond	22.2	27.2 (@ 2,284 hours)	24.5
	CADM	-	-	-
32.9	Emond	33.2	39.3 (@ 2,284 hours)	35.7
	CADM	-	-	-
71.4	Emond	47.9	55.1 (@ 2,284 hours)	50.7
	CADM	-	-	-

C.3.1.24. *NTP (2006) 31 Weeks*

Type:	Rat	**Dose:**	0, 3, 10, 22, 46, 100 ng/kg-day
Strain:	Sprague Dawley	**Route:**	Oral gavage
Body weight:	8 weeks old (BW=215g)	**Regime:**	5 days/weeks for 31 weeks
Sex:	Female and male	**Simulation time:**	5,208 hours (31 weeks)

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	2.33	3.25 (@ 3,960 hours)	2.48
	CADM	-	-	-
7.14	Emond	5.32	7.89 (@ 3,960 hours)	5.40
	CADM	-	-	-
15.7	Emond	9.21	14.5 (@ 3,960 hours)	9.15
	CADM	-	-	-
32.9	Emond	15.7	26.2 (@ 5,136 hours)	15.3
	CADM	-	-	-
71.4	Emond	28.1	50.4 (@ 5,136 hours)	27.0
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	341	425 (@ 5,140 hours)	373
	CADM	-	-	-
7.14	Emond	1,075	1,308 (@ 3,965 hours)	1,117
	CADM	-	-	-

15.7	Emond	2,296	2,756 (@ 3,965 hours)	2,336
	CADM	-	-	-
32.9	Emond	4,696	5,597 (@ 5,141 hours)	4,712
	CADM	-	-	-
71.4	Emond	10,033	11,905 (@ 5,141 hours)	9,953
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	220	256 (@ 5,149 hours)	246
	CADM	-	-	-
7.14	Emond	501	570 (@ 4,139 hours)	542
	CADM	-	-	-
15.7	Emond	868	978 (@ 4,138 hours)	926
	CADM	-	-	-
32.9	Emond	1,476	1,657 (@ 5,145 hours)	1,558
	CADM	-	-	-
71.4	Emond	2,652	2,978 (@ 5,144 hours)	2,775
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	34.2	41.2 (@ 5,140 hours)	37.8
	CADM	-	-	-
7.14	Emond	91.6	108 (@ 3,964 hours)	96.6
	CADM	-	-	-
15.7	Emond	178	209 (@ 3,964 hours)	184
	CADM	-	-	-
32.9	Emond	339	398 (@ 5,140 hours)	346
	CADM	-	-	-
71.4	Emond	682	799 (@ 5,140 hours)	687
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	7.48	8.83 (@ 5,140 hours)	8.01
	CADM	-	-	-
7.14	Emond	15.6	17.9 (@ 3,964 hours)	16.1

	CADM	-	-	-
15.7	Emond	24.3	27.4 (@ 3,964 hours)	24.8
	CADM	-	-	-
32.9	Emond	35.7	39.6 (@ 5,140 hours)	36.0
	CADM	-	-	-
71.4	Emond	50.9	55.4 (@ 5,140 hours)	51.1
	CADM	-	-	-

C.3.1.25. *NTP (2006) 53 Weeks*

Type:	Rat	**Dose:**	0, 3, 10, 22, 46, 100 ng/kg-day
Strain:	Sprague Dawley	**Route:**	Oral gavage
Body weight:	8 weeks old (BW=215g)	**Regime:**	5 days/weeks for 105 weeks
Sex:	Female and male	**Simulation time:**	8,904 hours (53 weeks)

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	2.46	3.25 (@ 6,312 hours)	2.48
	CADM	-	-	-
7.14	Emond	5.53	7.89 (@ 3,960 hours)	5.41
	CADM	-	-	-
15.7	Emond	9.54	14.5 (@ 8,832 hours)	9.17
	CADM	-	-	-
32.9	Emond	16.2	26.3 (@ 8,832 hours)	15.3
	CADM	-	-	-
71.4	Emond	29.0	50.6 (@ 8,832 hours)	27.1
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	366	426 (@ 6,316 hours)	373
	CADM	-	-	-
7.14	Emond	1,134	1,308 (@ 3,965 hours)	1,121
	CADM	-	-	-
15.7	Emond	2,406	2,759 (@ 8,837 hours)	2,345
	CADM	-	-	-

32.9	Emond	4,902	5,612 (@ 8,837 hours)	4,727
	CADM	-	-	-
71.4	Emond	10,439	11,938 (@ 8,837 hours)	9,985
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	233	256 (@ 6,325 hours)	247
	CADM	-	-	-
7.14	Emond	524	570 (@ 4,139 hours)	544
	CADM	-	-	-
15.7	Emond	904	980 (@ 8,842 hours)	929
	CADM	-	-	-
32.9	Emond	1,533	1,661 (@ 8,841 hours)	1,562
	CADM	-	-	-
71.4	Emond	2,749	2,986 (@ 8,840 hours)	2,784
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	36.4	41.2 (@ 6,316 hours)	37.8
	CADM	-	-	-
7.14	Emond	96.1	108 (@ 3,964 hours)	96.9
	CADM	-	-	-
15.7	Emond	186	210 (@ 8,836 hours)	185
	CADM	-	-	-
32.9	Emond	353	399 (@ 8,836 hours)	347
	CADM	-	-	-
71.4	Emond	709	801 (@ 8,836 hours)	689
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	7.87	8.84 (@ 6,316 hours)	8.01
	CADM	-	-	-
7.14	Emond	16.2	17.9 (@ 3,964 hours)	16.1
	CADM	-	-	-
15.7	Emond	25.1	27.5 (@ 8,836 hours)	24.8

	CADM	-	-	-
32.9	Emond	36.6	39.7 (@ 8,836 hours)	36.1
	CADM	-	-	-
71.4	Emond	51.9	55.4 (@ 8,836 hours)	51.1
	CADM	-	-	-

C.3.1.26. *NTP (2006) 2 Years*

Type:	Rat	**Dose:**	0, 3, 10, 22, 46, 100 ng/kg-day
Strain:	Sprague Dawley	**Route:**	Oral gavage
Body weight:	8 weeks old (BW=215g)	**Regime:**	5 days/weeks for 105 weeks
Sex:	Female and male	**Simulation time:**	17,640 hours* (105 weeks)

*The CADM model simulates for 104 weeks only (17,472 hours). As a result, the terminal values from the CADM model may be underestimated compared to the Emond model, which considers the full 105 weeks of exposure.

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	2.56	3.47 (@ 17,568 hours)	2.62
	CADM	-	-	-
7.14	Emond	5.69	7.97 (@ 17,568 hours)	5.46
	CADM	-	-	-
15.7	Emond	9.79	14.6 (@ 17,568 hours)	9.22
	CADM	-	-	-
32.9	Emond	16.6	26.4 (@ 17,568 hours)	15.4
	CADM	-	-	-
71.4	Emond	29.7	50.8 (@ 17,568 hours)	27.1
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	385	460 (@ 17,572 hours)	403
	CADM	632	715	715
7.14	Emond	1,177	1,320 (@ 17,573 hours)	1,135
	CADM	2,127	2,387	2,387
15.7	Emond	2,487	2,779 (@ 17,573 hours)	2,361

	CADM	4,691	5,252	5,252
32.9	Emond	5,051	5,637 (@ 17,573 hours)	4,749
	CADM	9,822	10,984	10,984
71.4	Emond	10,734	11,976 (@ 17,573 hours)	10,018
	CADM	21,366	23,880	23,880
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	243	271 (@ 17,581 hours)	261
	CADM	302	355	277
7.14	Emond	541	575 (@ 17,579 hours)	549
	CADM	667	787	611
15.7	Emond	930	985 (@ 17,578 hours)	934
	CADM	1,242	1,463	1,138
32.9	Emond	1,574	1,667 (@ 17,577 hours)	1,568
	CADM	2,369	2,787	2,173
71.4	Emond	2,821	2,995 (@ 17,576 hours)	2,792
	CADM	4,890	5,748	4,489
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	38.1	44.0 (@ 17,572 hours)	40.4
	CADM	46.0	48.0	48.0
7.14	Emond	99.5	109 (@ 17,572 hours)	97.9
	CADM	125	130	130
15.7	Emond	192	211 (@ 17,572 hours)	186
	CADM	257	267	267
32.9	Emond	364	400 (@ 17,572 hours)	348
	CADM	520	538	538
71.4	Emond	729	804 (@ 17,572 hours)	691
	CADM	1,110	1,149	1,149
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	8.17	9.30 (@ 17,572 hours)	8.43

	CADM	-	-	-
7.14	Emond	16.6	18.0 (@ 17,572 hours)	16.2
	CADM	-	-	-
15.7	Emond	25.6	27.6 (@ 17,572 hours)	24.9
	CADM	-	-	-
32.9	Emond	37.3	39.7 (@ 17,572 hours)	36.2
	CADM	-	-	-
71.4	Emond	52.7	55.5 (@ 17,572 hours)	51.2
	CADM	-	-	-

C.3.1.27. *Sewall et al. (1995)*

Type:	Rat	**Dose:**	49, 149.8, 490, and 1750 ng/kg every two weeks or 3.5, 10.7, 35, and 125 ng/kg-day
Strain:	Sprauge-Dawley	**Route:**	Oral gavage
Body weight:	12 wk old (BW set to 250g)	**Regime:**	Once every 2 weeks for 30 weeks
Sex:	Female	**Simulation time:**	5040 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
3.5	Emond	3.29	13.7 (@ 4,704 hours)	2.88
	CADM	-	-	-
10.7	Emond	7.11	38.7 (@ 4,704 hours)	5.79
	CADM	-	-	-
35	Emond	16.6	120 (@ 4,704 hours)	12.6
	CADM	-	-	-
125	Emond	44.7	414 (@ 4,704 hours)	31.4
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
3.5	Emond	550	901 (@ 4,711 hours)	459
	CADM	-	-	-
10.7	Emond	1,605	2,632 (@ 4,712 hours)	1,229
	CADM	-	-	-
35	Emond	5,072	8,350 (@ 4,712 hours)	3,618

	CADM	-	-	-
125	Emond	17,683	29,256 (@ 4,713 hours)	12,011
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
3.5	Emond	310	383 (@ 4,765 hours)	290
	CADM	-	-	-
10.7	Emond	670	827 (@ 4,763 hours)	590
	CADM	-	-	-
35	Emond	1,569	1,957 (@ 4,760 hours)	1,304
	CADM	-	-	-
125	Emond	4,217	5,376 (@ 4,757 hours)	3,303
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
3.5	Emond	51.4	72.5 (@ 4,710 hours)	45.3
	CADM	-	-	-
10.7	Emond	130	189 (@ 4,710 hours)	106
	CADM	-	-	-
35	Emond	364	546 (@ 4,710 hours)	274
	CADM	-	-	-
125	Emond	1,164	1,793 (@ 4,710 hours)	824
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
3.5	Emond	10.2	15.8 (@ 2 hours)	9.18
	CADM	-	-	-
10.7	Emond	19.8	34.4 (@ 1 hours)	17.0
	CADM	-	-	-
35	Emond	37.0	63.2 (@ 1 hours)	31.4
	CADM	-	-	-
125	Emond	63.1	90.9 (@ 1 hours)	55.2
	CADM	-	-	-

C.3.1.28. *Shi et al. (2007) Adult Portion*

Type:	Rat	**Dose:**	1, 5, 50 and 200 ng/kg
Strain:	Sprague Dawley	**Route:**	Oral exposure
Body weight:	BW set to 4.5 g	**Regime:**	Weekly doses for 11 months
Sex:	Female	**Simulation time:**	8040 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.143	Emond	0.342	0.475 (@ 7,561 hours)	0.380
	CADM	-	-	-
0.714	Emond	1.07	1.53 (@ 7,560 hours)	1.09
	CADM	-	-	-
7.14	Emond	5.23	9.12 (@ 7,560 hours)	4.86
	CADM	-	-	-
28.6	Emond	13.9	29.2 (@ 7,560 hours)	12.4
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.143	Emond	26.1	36.5 (@ 7,564 hours)	29.6
	CADM	-	-	-
0.714	Emond	118	159 (@ 7,564 hours)	120
	CADM	-	-	-
7.14	Emond	1,068	1,415 (@ 7,565 hours)	970
	CADM	-	-	-
28.6	Emond	4,119	5,450 (@ 7,565 hours)	3,574
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.143	Emond	32.5	40.0 (@ 7,583 hours)	36.7
	CADM	-	-	-
0.714	Emond	102	120 (@ 7,584 hours)	106
	CADM	-	-	-

7.14	Emond	497	571 (@ 7,584 hours)	475
	CADM	-	-	-
28.6	Emond	1,322	1,527 (@ 7,584 hours)	1,217
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.143	Emond	3.94	4.99 (@ 7,566 hours)	4.45
	CADM	-	-	-
0.714	Emond	14.0	17.2 (@ 7,566 hours)	14.5
	CADM	-	-	-
7.14	Emond	90.8	112 (@ 7,566 hours)	84.4
	CADM	-	-	-
28.6	Emond	300	374 (@ 7,566 hours)	266
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.143	Emond	1.18	1.60 (@ 7,563 hours)	1.31
	CADM	-	-	-
0.714	Emond	3.62	4.75 (@ 7,563 hours)	3.70
	CADM	-	-	-
7.14	Emond	15.6	19.7 (@ 7,564 hours)	14.7
	CADM	-	-	-
28.6	Emond	33.5	40.7 (@ 7,564 hours)	31.2
	CADM	-	-	-

C.3.1.29. *Smialowicz et al. (2008)*

Type:	Mice	**Dose:**	0, 1.5, 15, 150, 450 ng/kg-day
Strain:	B6C3F1	**Route:**	Oral gavage
Body weight:	13 wk old (BW set to 28g)	**Regime:**	5 days/week for 13 weeks
Sex:	Female	**Simulation time:**	2184

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.07	Emond	0.438	0.815 (@ 2,112 hours)	0.557
	CADM	-	-	-
10.7	Emond	2.46	5.12 (@ 2,112 hours)	2.65
	CADM	-	-	-
107	Emond	13.4	36.4 (@ 2,112 hours)	12.7
	CADM	-	-	-
321	Emond	31.6	98.6 (@ 2,112 hours)	28.4
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.07	Emond	67.1	107 (@ 2,116 hours)	91.5
	CADM	59.0	92.0	88.0
10.7	Emond	683	971 (@ 2,117 hours)	787
	CADM	767	1,000	907
107	Emond	6,784	9,010 (@ 2,117 hours)	7,043
	CADM	8,349	10,306	8,998
321	Emond	20,218	26,379 (@ 2,117 hours)	20,405
	CADM	25,344	31,006	26,967
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.07	Emond	156	229 (@ 2,130 hours)	225
	CADM	151	210	204
10.7	Emond	885	1,155 (@ 2,124 hours)	1,111
	CADM	689	815	774
107	Emond	4,831	5,979 (@ 2,120 hours)	5,591
	CADM	2,771	3,224	2,937
321	Emond	11,420	14,037 (@ 2,119 hours)	12,920
	CADM	6,337	7,509	6,688

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.07	Emond	17.0	25.5 (@ 2,116 hours)	23.9
	CADM	21.0	29.0	29.0
10.7	Emond	117	159 (@ 2,116 hours)	141
	CADM	119	145	135
107	Emond	852	1,103 (@ 2,116 hours)	923
	CADM	727	875	778
321	Emond	2,304	2,958 (@ 2,116 hours)	2,419
	CADM	1,961	2,370	2,080
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.07	Emond	1.48	2.17 (@ 2,116 hours)	1.90
	CADM	-	-	-
10.7	Emond	7.60	9.86 (@ 2,116 hours)	8.42
	CADM	-	-	-
107	Emond	30.3	36.0 (@ 2,117 hours)	31.1
	CADM	-	-	-
321	Emond	51.1	58.1 (@ 2,117 hours)	51.8
	CADM	-	-	-

C.3.1.30. *Toth et al., 1 Year (1979)*

Type:	Mice	**Dose:**	7, 700, 7000 ng/kg/week
Strain:	Swiss/H/Riop	**Route:**	Oral gavage In gastric tube
Body weight:	10 weeks old (BW= 27g)	**Regime:**	1/week for 1 year (365 days)
Sex:	Female and male	**Simulation time:**	8,760 hours

We did not simulate the scenario using the CADM model because this model can only be run for a maximum of 123 days.

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	0.573	1.61 (@ 8,736 hours)	0.682
	CADM	-	-	-
100	Emond	14.2	116 (@ 8,736 hours)	15.7
	CADM	-	-	-
1,000	Emond	91.2	1,108 (@ 8,736 hours)	99.3
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	94.2	131 (@ 8,743 hours)	123
	CADM	-	-	-
100	Emond	7,343	10,134 (@ 8,745 hours)	9,604
	CADM	-	-	-
1,000	Emond	70,243	97,658 (@ 8,745 hours)	92,506
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	215	247 (@ 8,613 hours)	245
	CADM	-	-	-
100	Emond	5,339	5,914 (@ 8,760 hours)	5,914
	CADM	-	-	-
1,000	Emond	34,249	38,828 (@ 8,756 hours)	38,807
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	23.4	28.4 (@ 8,742 hours)	27.9
	CADM	-	-	-
100	Emond	929	1,189 (@ 8,742 hours)	1,132
	CADM	-	-	-

1,000	Emond	7,569	10,045 (@ 8,742 hours)	9,471
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	1.93	2.65 (@ 8,741 hours)	2.35
	CADM	-	-	-
100	Emond	31.8	58.4 (@ 2 hours)	36.7
	CADM	-	-	-
1,000	Emond	78.6	103 (@ 2 hours)	84.8
	CADM	-	-	-

C.3.1.31. *Van Birgelen et al. (1995)*

Type:	Rat	**Dose:**	0, 13.5, 26.4, 46.9, 320, 1024 ng/kg-day
Strain:	Sprague Dawley	**Route:**	Oral gavage
Body weight:	150 g	**Regime:**	Once per day for 13 weeks
Sex:	Female	**Simulation time:**	2184 hours (13 weeks)

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
13.5	Emond	7.20	11.1 (@ 2,160 hours)	8.47
	CADM	-	-	-
26.4	Emond	11.8	18.6 (@ 2,160 hours)	13.5
	CADM	-	-	-
46.9	Emond	18.1	29.6 (@ 2,160 hours)	20.5
	CADM	-	-	-
320	Emond	86.4	156 (@ 2,160 hours)	95.4
	CADM	-	-	-
1024	Emond	250	470 (@ 2,160 hours)	275
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
13.5	Emond	1,655	2,208 (@ 2,164 hours)	2,107
	CADM	-	-	-
26.4	Emond	3,228	4,216 (@ 2,164 hours)	4,017
	CADM	-	-	-
46.9	Emond	5,719	7,366 (@ 2,164 hours)	7,008
	CADM	-	-	-
320	Emond	38,484	47,999 (@ 2,164 hours)	45,537
	CADM	-	-	-
1024	Emond	121,640	150,410 (@ 2,164 hours)	142,510
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
13.5	Emond	669	843 (@ 2,167 hours)	835
	CADM	-	-	-
26.4	Emond	1,092	1,357 (@ 2,166 hours)	1,342
	CADM	-	-	-
46.9	Emond	1,680	2,071 (@ 2,166 hours)	2,045
	CADM	-	-	-
320	Emond	8,027	9,816 (@ 2,165 hours)	9,639
	CADM	-	-	-
1024	Emond	23,234	28,519 (@ 2,165 hours)	27,954
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
13.5	Emond	132	173 (@ 2,164 hours)	167
	CADM	-	-	-
26.4	Emond	240	308 (@ 2,164 hours)	296
	CADM	-	-	-
46.9	Emond	404	513 (@ 2,164 hours)	492
	CADM	-	-	-

320	Emond	2,437	3,031 (@ 2,164 hours)	2,887
	CADM	-	-	-
1024	Emond	7,521	9,310 (@ 2,164 hours)	8,846
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
13.5	Emond	19.9	24.2 (@ 2,164 hours)	23.4
	CADM	-	-	-
26.4	Emond	29.0	34.3 (@ 2,164 hours)	33.2
	CADM	-	-	-
46.9	Emond	38.8	45.0 (@ 2,164 hours)	43.7
	CADM	-	-	-
320	Emond	79.1	85.2 (@ 2,164 hours)	84.1
	CADM	-	-	-
1024	Emond	97.5	101 (@ 2,164 hours)	101
	CADM	-	-	-

C.3.1.32. *Vanden Heuvel et al. (1994)*

Type:	Rat	**Dose:**	0.05, 0.1, 1, 10, 100, 1000, 10000 ng/kg/d
Strain:	Sprague Dawley	**Route:**	Oral gavage
Body weight:	10 weeks old (BW 225 to 275g, set to 250g)	**Regime:**	Single dose
Sex:	Female	**Simulation time:**	24 hours *

* 1 week is the minimum that can be simulated with the CADM model, so the CADM model was not used.

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.05	Emond	0.01	0.011 (@ 0 hours)	0.0039
	CADM	-	-	-
0.1	Emond	0.0113	0.022 (@ 0 hours)	0.008
	CADM	-	-	-
1	Emond	0.106	0.215 (@ 0 hours)	0.0723
	CADM	-	-	-

10	Emond	0.883	2.15 (@ 0 hours)	0.583
	CADM	-	-	-
100	Emond	6.45	21.5 (@ 0 hours)	3.85
	CADM	-	-	-
1000	Emond	48.3	216 (@ 0 hours)	23.9
	CADM	-	-	-
10000	Emond	435	2,166 (@ 0 hours)	186
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.05	Emond	0.232	0.315 (@ 3 hours)	0.173
	CADM	-	-	0.0140
0.1	Emond	0.469	0.631 (@ 3 hours)	0.353
	CADM	-	-	0.0320
1	Emond	5.08	6.42 (@ 4 hours)	4.08
	CADM	-	-	0.950
10	Emond	60.2	68.7 (@ 5 hours)	54.1
	CADM	-	-	52.7
100	Emond	730	800 (@ 9 hours)	719
	CADM	-	-	1,342
1000	Emond	8,186	8,919 (@ 11 hours)	8,442
	CADM	-	-	15,967
10000	Emond	84,254	91,675 (@ 11 hours)	88,230
	CADM	-	-	162,773
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.05	Emond	0.138	0.215 (@ 24 hours)	0.215
	CADM	-	-	0.780
0.1	Emond	0.274	0.427 (@ 24 hours)	0.427
	CADM	-	-	1.57
1	Emond	2.58	3.97 (@ 24 hours)	3.97
	CADM	-	-	15.3

10	Emond	22.1	32.8 (@ 24 hours)	32.8
	CADM	-	-	125
100	Emond	170	235 (@ 24 hours)	235
	CADM	-	-	739
1000	Emond	1,348	1,720 (@ 24 hours)	1,720
	CADM	-	-	5,779
10000	Emond	12,500	15,265 (@ 24 hours)	15,265
	CADM	-	-	55,825
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.05	Emond	0.0269	0.028 (@ 9 hours)	0.0283
	CADM	-	-	0.0450
0.1	Emond	0.0538	0.057 (@ 9 hours)	0.0565
	CADM	-	-	0.0900
1	Emond	0.536	0.568 (@ 9 hours)	0.562
	CADM	-	-	0.900
10	Emond	5.32	5.65 (@ 8 hours)	5.55
	CADM	-	-	9.00
100	Emond	52.8	56.3 (@ 7 hours)	54.4
	CADM	-	-	90.0
1000	Emond	525	562 (@ 7 hours)	538
	CADM	-	-	900
10000	Emond	5,238	5,610 (@ 7 hours)	5,353
	CADM	-	-	9,000
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.05	Emond	0.0194	0.027 (@ 3 hours)	0.0142
	CADM	-	-	-
0.1	Emond	0.0383	0.054 (@ 3 hours)	0.0281
	CADM	-	-	-
1	Emond	0.353	0.506 (@ 3 hours)	0.261
	CADM	-	-	-

10	Emond	2.77	4.24 (@ 2 hours)	2.08
	CADM	-	-	-
100	Emond	16.1	26.4 (@ 2 hours)	12.4
	CADM	-	-	-
1000	Emond	57.4	80.2 (@ 1 hours)	48.5
	CADM	-	-	-
10000	Emond	100	108 (@ 1 hours)	96.1
	CADM	-	-	-

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3 **C.3.1.33.** ***White et al. (1986)***

Type:	Mice	**Dose:**	10, 50, 100, 500, 1000, 2000 ng/kg-day
Strain:	B6C3F1	**Route:**	Oral gavage
Body weight:	7 weeks old (BW set to 23g)	**Regime:**	1/day for 14 days
Sex:	Female	**Simulation time:**	336 hours

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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
10	Emond	1.09	2.73 (@ 312 hours)	1.42
	CADM	-	-	-
50	Emond	4.08	11.6 (@ 312 hours)	4.98
	CADM	-	-	-
100	Emond	7.14	21.7 (@ 312 hours)	8.44
	CADM	-	-	-
500	Emond	26.8	96.5 (@ 312 hours)	29.8
	CADM	-	-	-
1,000	Emond	48.7	187 (@ 312 hours)	53.1
	CADM	-	-	-
2,000	Emond	90.6	365 (@ 312 hours)	97.5
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
10	Emond	216	375 (@ 317 hours)	343
	CADM	217	468 (336h)	463
50	Emond	1,279	2,164 (@ 317 hours)	1,997
	CADM	1,775	3,261 (336h)	3,261
100	Emond	2,707	4,525 (@ 317 hours)	4,184
	CADM	3,999	6,923 (336h)	6,923
500	Emond	14,802	24,165 (@ 317 hours)	22,383
	CADM	22,705	36,362 (336h)	36,362
1,000	Emond	30,278	49,034 (@ 317 hours)	45,414
	CADM	46,309	73,145 (336h)	73,145
2,000	Emond	61,381	98,703 (@ 317 hours)	91,363
	CADM	93,577	146,695 (336h)	146,695
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
10	Emond	279	507 (@ 336 hours)	507
	CADM	316	537 (336h)	537
50	Emond	1,056	1,846 (@ 336 hours)	1,846
	CADM	1,029	1,564 (336h)	1,564
100	Emond	1,854	3,195 (@ 333 hours)	3,195
	CADM	1,662	2,470 (336h)	2,470
500	Emond	7,008	11,868 (@ 324 hours)	11,816
	CADM	5,711	8,594 (336h)	8,594
1,000	Emond	12,746	21,566 (@ 323 hours)	21,424
	CADM	10,498	15,993 (336h)	15,993
2,000	Emond	23,691	40,177 (@ 322 hours)	39,843
	CADM	19,990	30,726 (336h)	30,726

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
10	Emond	37.7	65.9 (@ 317 hours)	63.8
	CADM	47.9	85.9 (336h)	85.9
50	Emond	175	297 (@ 317 hours)	284
	CADM	207	342 (336h)	342
100	Emond	338	570 (@ 316 hours)	542
	CADM	388	624 (336h)	624
500	Emond	1,597	2,637 (@ 316 hours)	2,480
	CADM	1,761	2,754 (336h)	2,754
1,000	Emond	3,137	5,153 (@ 316 hours)	4,830
	CADM	3,455	5,387 (336h)	5,387
2,000	Emond	6,186	10,118 (@ 316 hours)	9,459
	CADM	6,836	10,643 (336h)	10,643
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
10	Emond	3.49	5.32 (@ 316 hours)	4.82
	CADM	-	-	-
50	Emond	11.4	16.4 (@ 317 hours)	15.1
	CADM	-	-	-
100	Emond	18.1	25.1 (@ 317 hours)	23.4
	CADM	-	-	-
500	Emond	44.2	56.2 (@ 317 hours)	53.8
	CADM	-	-	-
1,000	Emond	59.3	71.9 (@ 317 hours)	69.7
	CADM	-	-	-
2,000	Emond	74.4	86.1 (@ 317 hours)	84.3
	CADM	-	-	-

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C.3.2. Gestational Studies

C.3.2.1. *Bell et al. (2007)*

Type:	Rat	**Dose:**	2.4, 8, and 46 ng/kg-day with a 0.03 ng/kg-day background
Strain:	Han/Wistar	**Route:**	Diet oral dose
Body weight:	6 weeks (BW= 85g)	**Regime:**	Once per day for 12 weeks prior to mating, during the two week mating period, and during gestation
Sex:	Female	**Simulation time:**	2,352 hr (98 days) prior to gestation + 504 hr (21 days) during gestation for a total simulation of 2,856 hours

* Time averages are computed during the gestation period only.

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
2.43	2.20	6,295	3.10 (@ 2,352 hours)	2.20
8.03	5.14	14,674	7.31 (@ 2,352 hours)	5.08
46.03	18.4	52,584	28.1 (@ 2,352 hours)	18.1
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
2.43	320	914,290	437 (@ 2,356 hours)	321
8.03	1,040	2,969,800	1,349 (@ 2,356 hours)	1,042
46.03	5,892	16,829,000	7,289 (@ 2,356 hours)	6,007
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
2.43	205	585,530	263 (@ 2,336 hours)	211
8.03	478	1,365,100	589 (@ 2,335 hours)	486
46.03	1,713	4,891,500	2,045 (@ 2,334 hours)	1,745

BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
2.43	33.0	94,390	44.4 (@ 2,836 hours)	43.4
8.03	90.4	258,110	117 (@ 2,836 hours)	114
46.03	422	1,206,500	531 (@ 2,836 hours)	511
FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
2.43	3.03	8,648	39.6 (@ 2,530 hours)	6.48
8.03	6.65	18,999	86.7 (@ 2,529 hours)	14.4
46.03	20.9	59,794	272 (@ 2,527 hours)	46.0
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
2.43	7.10	20,289	8.98 (@ 2,356 hours)	7.23
8.03	15.1	43,242	18.2 (@ 2,356 hours)	15.4
46.03	39.6	113,070	44.8 (@ 2,356 hours)	40.6

C.3.2.2. *Haavisto et al. (2006)*

Type:	Rat	**Dose:**	20, 400, and 1,000 ng/kg
Strain:	Sprague Dawley	**Route:**	Oral exposure
Body weight	BW = 190 g	**Regime:**	Single dose on GD13
Sex:	Female	**Simulation time**	336 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	2.86	68.9	8.01 (@ 312 hours)	1.73
400	11.3	273	40.1 (@ 312 hours)	6.28
1000	46.9	1,129	202 (@ 312 hours)	22.8

LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	265	6,371	298 (@ 319 hours)	244
400	1,497	36,005	1,653 (@ 320 hours)	1,462
1000	8,061	193,860	8,832 (@ 321 hours)	8,147
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	56.3	1,354	81.9 (@ 336 hours)	81.9
400	232	5,584	321 (@ 336 hours)	321
1000	1,002	24,084	1,313 (@ 336 hours)	1,313
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	21.1	508	22.5 (@ 319 hours)	21.9
400	105	2,528	112 (@ 319 hours)	108
1000	524	12,612	561 (@ 319 hours)	538
FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	8.47	203	11.3 (@ 336 hours)	11.3
400	31.2	751	40.3 (@ 336 hours)	40.3
1000	112	2,689	139 (@ 336 hours)	139
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	8.20	197	13.5 (@ 314 hours)	6.03
400	24.9	598	40.8 (@ 313 hours)	19.1
1000	57.1	1,373	80.1 (@ 313 hours)	47.7

C.3.2.3. *Hojo et al. (2002)*

Type:	Rat	**Dose:**	20, 60 and 180 ng/kg
Strain:	Sprague Dawley	**Route:**	Oral exposure
Body weight	20 ng/kg BW = 271g 60 ng/kg BW = 275g 180 ng/kg BW = 262g	**Regime:**	Single dose on GD8
Sex:	Female	**Simulation time**	216 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	1.62	39.1	4.47 (@ 192 hours)	1.02
60	4.17	100	13.3 (@ 192 hours)	2.50
180	10.7	258	40.3 (@ 192 hours)	5.96
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	128	20,554	144 (@ 198 hours)	43.2
60	420	72,340	465 (@ 200 hours)	147
180	1,364	250,820	1,497 (@ 201 hours)	497
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	32.5	17,253	63.0 (@ 281 hours)	49.4
60	86.4	44,093	161 (@ 284 hours)	124
180	226	108,730	398 (@ 286 hours)	301
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	10.6	3,054	11.3 (@ 200 hours)	8.67
60	31.8	8,702	33.8 (@ 199 hours)	23.6
180	95.0	24,747	101 (@ 199 hours)	63.4

FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	15.9	2,334	18.4 (@ 206 hours)	1.64
60	39.8	5,829	45.7 (@ 205 hours)	4.10
180	96.3	13,866	110 (@ 203 hours)	9.72
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	4.88	759	7.74 (@ 194 hours)	1.75
60	11.2	1,848	18.5 (@ 194 hours)	4.26
180	23.6	4,157	38.5 (@ 193 hours)	9.65

C.3.2.4. *Ikeda et al. (2005)*

Type:	Rat	**Dose:**	400 ng/kg single dose and 80 ng/kg weekly maintenance dose
Strain:	Sprague Dawley	**Route:**	Oral gavage
Body weight:	10 weeks (BW= 250g)	**Regime:**	400 ng/kg single dose, two weekly maintenance doses prior to gestation and weekly maintenance doses during gestation
Sex:	Female	**Simulation time:**	504 hr (21 days) prior to gestation + 504 hr (21 days) during gestation for a total simulation of 1,008 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
16.5	22.9	23,086	101 (@ 144 hours)	10.1
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
16.5	7,755	7,817,300	17,016 (@ 150 hours)	2,698

FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
16.5	2,087	2,103,900	3,663 (@ 184 hours)	1,028
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
16.5	548	552,590	1,085 (@ 149 hours)	262
FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
16.5	45.9	46,290	245 (@ 679 hours)	30.2
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
16.5	44.0	44,361	63.8 (@ 149 hours)	26.8

C.3.2.5. *Kattainen et al. (2001)*

Type:	Rat	**Dose:**	30, 100, 300, and 1,000 ng/kg
Strain:	Han/Wistar (Kuopio) and Long/Evans (Turku/AB) crossing.	**Route:**	Oral exposure
Body weight:	BW no specify (BW set to 190g)*	**Regime:**	Single dose in the GD15
Sex:	Female	**Simulation time:**	360 hours

*Derelanko and Hollinger (1995).

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
30	2.23	53.7	5.95 (@ 336 hours)	1.36
100	6.25	150	19.8 (@ 336 hours)	3.62

300	16.1	387	59.8 (@ 336 hours)	8.62
1,000	46.9	1,128	200 (@ 336 hours)	22.7
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
30	193	4,648	219 (@ 342 hours)	175
100	713	17,141	793 (@ 344 hours)	680
300	2,298	55,266	2,533 (@ 345 hours)	2,267
1,000	8,055	193,720	8,831 (@ 345 hours)	8,134
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
30	42.8	1,027	62.8 (@ 360 hours)	62.8
100	123	2,964	175 (@ 360 hours)	175
300	327	7,853	446 (@ 360 hours)	446
1,000	981	23,588	1,289 (@ 360 hours)	1,289
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
30	15.9	382	16.9 (@ 343 hours)	16.4
100	52.7	1,266	56.2 (@ 343 hours)	54.3
300	158	3,791	168 (@ 343 hours)	162
1,000	524	12,612	561 (@ 343 hours)	538
FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
30	4.86	117	6.66 (@ 360 hours)	6.66
100	13.2	317	17.6 (@ 360 hours)	17.6
300	31.5	758	41.2 (@ 360 hours)	41.2
1,000	82.2	1,975	104 (@ 360 hours)	104

BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
30	6.57	158	10.7 (@ 338 hours)	4.80
100	15.8	381	26.3 (@ 338 hours)	11.9
300	31.6	760	50.6 (@ 337 hours)	24.7
1,000	57.1	1,373	80.1 (@ 337 hours)	47.7

C.3.2.6. *Keller et al. (2007)*

Type:	Mouse	**Dose:**	10, 100, and 1000 ng/kg
Strain:	CBA/J and C3H/HeJ	**Route:**	Oral
Body weight:	Not specified (24 g used in the simulation)	**Regime:**	Single dose at gestation day 13
Sex:	Female	**Simulation time:**	336 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
10	0.537	12.9	1.43 (@ 312 hours)	0.269
100	4.29	103	14.3 (@ 312 hours)	1.95
1,000	34.1	820	143 (@ 312 hours)	12.3
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
10	30.6	737	39.8 (@ 316 hours)	22.2
100	371	8,922	421 (@ 319 hours)	317
1,000	4,214	101,360	4,697 (@ 321 hours)	3,940
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
10	22.4	538	33.3 (@ 336 hours)	33.3
100	188	4,523	264 (@ 336 hours)	264
1,000	1,591	38,233	2,080 (@ 336 hours)	2,080

BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
10	5.57	134	5.99 (@ 319 hours)	5.72
100	54.3	1,306	59.0 (@ 318 hours)	54.7
1,000	530	12,747	581 (@ 318 hours)	524
FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
10	2.57	61.7	3.80 (@ 336 hours)	3.80
100	21.7	522	30.0 (@ 334 hours)	29.9
1,000	179	4,312	233 (@ 329 hours)	225
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
10	1.74	41.8	3.14 (@ 315 hours)	1.01
100	11.5	276	23.5 (@ 314 hours)	6.99
1,000	46.7	1,123	79.8 (@ 314 hours)	32.9

C.3.2.7. *Li et al. (2006) 3-Day*

Type:	Mouse	**Dose:**	2, 50, and 100 ng/kg-day
Strain:	NIH	**Route:**	Oral
Body weight:	25-28 g (used 27 g in the simulation)	**Regime:**	Daily exposure from gestation day 1 to gestation day 8
Sex:	Female	**Simulation time:**	72 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
2	0.159	11.4	0.392 (@ 48 hours)	0.136
50	2.84	205	8.90 (@ 48 hours)	2.38
100	5.12	369	17.3 (@ 48 hours)	4.20

LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
2	8.98	647	15.1 (@ 52 hours)	9.10
50	333	23,971	539 (@ 53 hours)	402
100	718	51,738	1,156 (@ 53 hours)	888
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
2	17.0	1,227	31.1 (@ 72 hours)	31.1
50	315	22,704	548 (@ 72 hours)	548
100	576	41,460	984 (@ 72 hours)	984
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
2	2.29	165	3.51 (@ 55 hours)	3.43
50	53.6	3,863	82.2 (@ 54 hours)	77.1
100	105	7,598	162 (@ 53 hours)	150
FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
2	0.00	0	0.000 (@ 72 hours)	0.00
50	0.0	0	0.000 (@ 72 hours)	0.00
100	0.0	0	0.000 (@ 72 hours)	0.00
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
2	0.538	38.8	0.864 (@ 51 hours)	0.498
50	8.24	594	13.5 (@ 2 hours)	8.16
100	13.6	981	23.7 (@ 2 hours)	13.6

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C.3.2.8. *Markowski et al. (2001)*

Type:	Rat	**Dose:**	20, 60 and 180 ng/kg
Strain:	Holtzman rats	**Route:**	Oral exposure
Body weight:	BW no specify (BW set to 190g)*	**Regime:**	Single dose in the GD18
Sex:	Female	**Simulation time:**	432 hours

*Derelanko and Hollinger (1995).

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	1.56	37.5	3.82 (@ 408 hours)	0.958
60	4.03	97.0	11.5 (@ 408 hours)	2.38
180	10.3	248	34.8 (@ 408 hours)	5.72
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	123	2,959	141 (@ 414 hours)	109
60	409	9,843	459 (@ 415 hours)	382
180	1,334	32,086	1,479 (@ 416 hours)	1,295
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	27.9	670	41.6 (@ 432 hours)	41.6
60	74.0	1,778	107 (@ 432 hours)	107
180	195	4,685	273 (@ 432 hours)	273
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	10.6	254	11.2 (@ 415 hours)	10.9
60	31.7	762	33.8 (@ 415 hours)	32.7
180	94.7	2,278	101 (@ 415 hours)	97.5

FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	1.26	30.2	1.80 (@ 432 hours)	1.80
60	3.21	77.2	4.49 (@ 432 hours)	4.49
180	7.81	188	10.7 (@ 432 hours)	10.7
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	4.74	114	7.59 (@ 410 hours)	3.43
60	11.0	265	18.2 (@ 410 hours)	8.16
180	23.2	559	38.1 (@ 409 hours)	17.7

C.3.2.9. *Mietinnen et al. (2006)*

Type:	Rat	**Dose:**	30, 100, 300 and 1000 ng/kg
Strain:	cross-breeding of Han/Wistar and Long-Evans rats	**Route:**	Oral exposure
Body weight:	BW 11 weeks (BW set to 180g)	**Regime:**	Single dose in the GD15
Sex:	Female	**Simulation time:**	360 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
30	2.22	53.4	5.87 (@ 336 hours)	1.36
100	6.23	150	19.6 (@ 336 hours)	3.61
300	16.0	386	59.0 (@ 336 hours)	8.61
1,000	46.6	1,123	198 (@ 336 hours)	22.7

LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
30	193	4,631	219 (@ 342 hours)	174
100	711	17,096	791 (@ 344 hours)	677
300	2,294	55,166	2,530 (@ 345 hours)	2,260
1,000	8,042	193,410	8,820 (@ 345 hours)	8,114
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
30	43.0	1,034	63.2 (@ 360 hours)	63.2
100	124	2,984	176 (@ 360 hours)	176
300	329	7,905	449 (@ 360 hours)	449
1,000	987	23,729	1,296 (@ 360 hours)	1,296
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
30	15.9	381	16.9 (@ 343 hours)	16.4
100	52.6	1,266	56.1 (@ 343 hours)	54.3
300	158	3,791	168 (@ 343 hours)	162
1,000	524	12,609	561 (@ 343 hours)	538
FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
30	4.83	116	6.62 (@ 360 hours)	6.62
100	13.1	315	17.5 (@ 360 hours)	17.5
300	31.3	753	41.0 (@ 360 hours)	41.0
1,000	81.7	1,963	104 (@ 360 hours)	104
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
30	6.56	158	10.7 (@ 338 hours)	4.78

100	15.8	381	26.3 (@ 338 hours)	11.9
300	31.6	760	50.5 (@ 337 hours)	24.6
1,000	57.0	1,372	80.1 (@ 337 hours)	47.6

C.3.2.10. *Nohara et al. (2000)*

Type:	Rat	**Dose:**	12.5, 50, 200 or 800 ng TCDD/kg
Strain:	Holtzman rats	**Route:**	Oral exposure
Body weight:	BW no specify (BW set to 190g)*	**Regime:**	Single dose in the GD15
Sex:	Female	**Simulation time:**	360 hours

*Derelanko and Hollinger (1995).

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
12.5	1.03	24.8	2.44 (@ 336 hours)	0.645
50	3.45	82.9	9.78 (@ 336 hours)	2.07
200	11.3	271	39.2 (@ 336 hours)	6.25
800	38.1	918	158 (@ 336 hours)	18.9
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
12.5	73.8	1,776	86.1 (@ 341 hours)	63.6
50	336	8,084	378 (@ 343 hours)	311
200	1,492	35,890	1,651 (@ 344 hours)	1,454
800	6,389	153,640	7,012 (@ 345 hours)	6,423
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
12.5	19.7	473	29.5 (@ 360 hours)	29.5
50	67.6	1,624	97.8 (@ 360 hours)	97.8
200	229	5,504	317 (@ 360 hours)	317
800	803	19,292	1,061 (@ 360 hours)	1,061

BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
12.5	6.62	159	7.04 (@ 343 hours)	6.88
50	26.4	635	28.1 (@ 343 hours)	27.3
200	105	2,528	112 (@ 343 hours)	108
800	420	10,092	449 (@ 343 hours)	430
FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
12.5	2.25	54.0	3.14 (@ 360 hours)	3.14
50	7.43	179	10.1 (@ 360 hours)	10.1
200	22.8	548	30.1 (@ 360 hours)	30.1
800	68.1	1,638	87.0 (@ 360 hours)	87.0
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
12.5	3.24	77.9	5.12 (@ 338 hours)	2.32
50	9.66	232	16.0 (@ 338 hours)	7.12
200	24.8	597	40.7 (@ 337 hours)	19.0
800	51.9	1,248	75.0 (@ 337 hours)	42.7

C.3.2.11. *Ohsako et al. (2001)*

Type:	Rat	**Dose:**	12.5, 50, 200, and 800 ng/kg-day
Strain:	Holtzmann	**Route:**	Oral exposure on GD15
Body weight	10 weeks (200g)	**Regime:**	Single dose
Sex:	Female	**Simulation time**	384 hours

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
12.5	1.04	25.0	2.48 (@ 360 hours)	0.649
50	3.47	83.6	9.93 (@ 360 hours)	2.07
200	11.4	273	39.9 (@ 360 hours)	6.26
800	38.4	925	161 (@ 360 hours)	18.9
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
12.5	74.3	1,788	86.5 (@ 365 hours)	64.2
50	338	8,126	379 (@ 367 hours)	314
200	1,497	36,006	1,655 (@ 368 hours)	1,461
800	6,402	153,960	7,025 (@ 369 hours)	6,443
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
12.5	19.0	457	28.6 (@ 384 hours)	28.6
50	65.3	1,569	94.7 (@ 384 hours)	94.7
200	221	5,321	307 (@ 384 hours)	307
800	777	18,671	1,029 (@ 384 hours)	1,029
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
12.5	6.63	159	7.05 (@ 367 hours)	6.89
50	26.4	635	28.2 (@ 367 hours)	27.3
200	105	2,529	112 (@ 367 hours)	108
800	420	10,093	449 (@ 367 hours)	430
FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
12.5	1.65	39.5	2.33 (@ 384 hours)	2.33

50	5.44	131	7.48 (@ 384 hours)	7.48
200	16.7	401	22.3 (@ 384 hours)	22.3
800	49.9	1,200	64.6 (@ 384 hours)	64.6
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
12.5	3.25	78.3	5.13 (@ 362 hours)	2.34
50	9.69	233	16.0 (@ 362 hours)	7.16
200	24.9	598	40.7 (@ 361 hours)	19.1
800	51.9	1,249	75.0 (@ 361 hours)	42.8

C.3.2.12. *Schantz et al. (1996) and Amin et al. (2000)*

Type:	Rat	**Dose:**	25 and 100 ng/kg-day
Strain:	Sprague Dawley	**Route:**	Oral exposure
Body weight:	BW not specified (BW set to 250g)	**Regime:**	Daily doses from GD 10 - 16
Sex:	Female	**Simulation time:**	384 hours; time averages are calculated from the beginning of the dosing

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
25	3.38	487	8.63 (@ 360 hours)	4.03
100	10.6	1,522	31.1 (@ 360 hours)	12.3
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
25	512	73,686	871 (@ 365 hours)	778
100	2,374	341,960	4,012 (@ 366 hours)	3,665
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
25	169	24,323	306 (@ 384 hours)	306

100	532	76,675	950 (@ 384 hours)	950
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
25	45.1	6,490	76.6 (@ 365 hours)	74.3
100	177	25,438	298 (@ 365 hours)	287
FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
25	25.2	3,627	30.4 (@ 343 hours)	27.3
100	74.1	10,672	88.1 (@ 342 hours)	77.9
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
25	9.99	1,439	14.4 (@ 364 hours)	12.8
100	25.2	3,632	34.2 (@ 364 hours)	31.6

C.3.2.13. *Seo et al. (1995)*

Type:	Rat	**Dose:**	25 and 100 ng/kg-day
Strain:	Sprague Dawley	**Route:**	Oral exposure
Body weight:	BW not specified (BW set to 190g)	**Regime:**	Daily doses from GD 10 - 16
Sex:	Female	**Simulation time:**	384 hours; time averages are calculated from the beginning of the dosing

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
25	3.33	479	8.25 (@ 360 hours)	4.00
100	10.4	1,498	29.6 (@ 360 hours)	12.2

LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
25	504	72,592	861 (@ 365 hours)	767
100	2,347	337,970	3,978 (@ 365 hours)	3,627
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
25	172	24,807	310 (@ 384 hours)	310
100	542	78,097	962 (@ 384 hours)	962
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
25	45.0	6,486	76.5 (@ 365 hours)	74.2
100	176	25,387	298 (@ 365 hours)	287
FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
25	24.7	3,551	29.8 (@ 343 hours)	26.8
100	72.6	10,456	86.6 (@ 342 hours)	76.8
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
25	9.90	1,426	14.3 (@ 364 hours)	12.7
100	25.0	3,607	34.1 (@ 364 hours)	31.4

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Table C-1. Model input parameters potentially addressed by selected articles

Articles	Model input parameters potentially addressed										
	Absorption	**Desorption**	**Distribution**	**Elimination**	**Kinetics**	**Induction CYP1A1**	**Interspecies differences**	**Age Differences**	**Aryl hydrocarbon receptor (AhR)**	**Mode of action**	**Partition coefficient**
Aylward et al., 2004	●	●	●	●	●						
Aylward et al., 2005a, b	●	●	●	●	●						
Aylward et al., 2009				●							
Bohonowych and Denison, 2007						●	●		●		
Boverhof et al., 2005						●	●				
Connor and Aylward, 2006							●	●	●		
Heinzl et al., 2007			●						●		
Irigaray et al., 2005			●				●				
Kerger et al., 2006			●		●			●			
Kerger et al., 2007								●			
Kim et al., 2003			●								
Korenaga et al., 2007						●	●				
Korkalainen et al., 2004							●	●			
Kransler et al., 2007							●	●			
Maruyama et al., 2002	●		●	●							
Maruyama et al., 2003	●		●	●							
Maruyama and Aoki, 2006	●		●	●							
Millbrath et al., 2009			●	●	●		●				
Moser and McLachlan, 2002		●		●							
Mullerova and Kopecky, 2007			●								
Nadal et al., 2009				●	●						
Nohara et al., 2006							●		●		
Olsman et al., 2007									●		
Saghir et al., 2005			●	●	●						
Schecter et al., 2003				●				●			
Staskal et al., 2005						●			●		
Toyoshiba et al., 2004			●			●			●		
Wilkes et al., 2008						●					

Partition coefficient estimates and CYP parameter value estimates were derived from Wang et al. (1997, 2000) and Santostefano et al. (1998).

C.4. RESPONSE SURFACE TABLES

In order to calculate human equivalent doses, the human model must be run with a daily intake which gives average blood concentrations which match the average concentrations in the rodent models. However, such calculation can require numerous human model runs with repeated intake adjustments in order to reach the target blood concentrations. To facilitate this process, a response surface was created for the human model. In the response surface, numerous intakes were run and the blood, fat, and body burden average concentrations were recorded. These tables can then be used to estimate the intake which would give a target blood concentration. The two closest intakes are found and the intake is estimated by linearly interpolating between the two doses. Then, this intake is run through the human model to confirm that the average blood concentration is within a specified tolerance of the target blood concentration.

For the current analysis, three different response surfaces were created: non-gestational lifetime to be used with long-term animal bioassays, nongestational five year average runs to be used with shorter term animal bioassays, and gestationsl to be used with gestational animal bioassays. All three response sufraces are shown in the following tables.

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C.4.1. Nongestational Lifetime

Nongestational Lifetime			
Intake (ng/kg/day)	**Fat (ng/kg)**	**Body Burden (ng/kg)**	**Blood (ng/kg)**
1.00E-09	2.39E-05	8.58E-06	2.52E-07
1.33E-09	3.18E-05	1.14E-05	3.35E-07
1.67E-09	3.98E-05	1.43E-05	4.19E-07
2.00E-09	4.77E-05	1.72E-05	5.03E-07
2.33E-09	5.57E-05	2.00E-05	5.87E-07
2.67E-09	6.36E-05	2.29E-05	6.70E-07
3.00E-09	7.16E-05	2.57E-05	7.54E-07
3.33E-09	7.95E-05	2.86E-05	8.38E-07
3.67E-09	8.74E-05	3.14E-05	9.22E-07
4.00E-09	9.54E-05	3.43E-05	1.01E-06
4.33E-09	1.03E-04	3.72E-05	1.09E-06
4.67E-09	1.11E-04	4.00E-05	1.17E-06
5.00E-09	1.19E-04	4.29E-05	1.26E-06
5.33E-09	1.27E-04	4.57E-05	1.34E-06
5.67E-09	1.35E-04	4.86E-05	1.42E-06
6.00E-09	1.43E-04	5.14E-05	1.51E-06
6.33E-09	1.51E-04	5.43E-05	1.59E-06
6.67E-09	1.59E-04	5.71E-05	1.68E-06
7.00E-09	1.67E-04	6.00E-05	1.76E-06
7.33E-09	1.75E-04	6.29E-05	1.84E-06
7.67E-09	1.83E-04	6.57E-05	1.93E-06
8.00E-09	1.91E-04	6.86E-05	2.01E-06
8.33E-09	1.99E-04	7.14E-05	2.09E-06
8.67E-09	2.07E-04	7.43E-05	2.18E-06
9.00E-09	2.14E-04	7.71E-05	2.26E-06
9.33E-09	2.22E-04	8.00E-05	2.34E-06
9.67E-09	2.30E-04	8.28E-05	2.43E-06
1.00E-08	2.38E-04	8.57E-05	2.51E-06

Nongestational Lifetime			
Intake (ng/kg/day)	**Fat (ng/kg)**	**Body Burden (ng/kg)**	**Blood (ng/kg)**
1.33E-08	3.17E-04	1.14E-04	3.34E-06
1.67E-08	3.96E-04	1.43E-04	4.18E-06
2.00E-08	4.75E-04	1.71E-04	5.01E-06
2.33E-08	5.54E-04	1.99E-04	5.84E-06
2.67E-08	6.33E-04	2.28E-04	6.67E-06
3.00E-08	7.12E-04	2.56E-04	7.50E-06
3.33E-08	7.91E-04	2.85E-04	8.34E-06
3.67E-08	8.70E-04	3.13E-04	9.17E-06
4.00E-08	9.49E-04	3.41E-04	1.00E-05
4.33E-08	1.03E-03	3.70E-04	1.08E-05
4.67E-08	1.11E-03	3.98E-04	1.17E-05
5.00E-08	1.19E-03	4.27E-04	1.25E-05
5.33E-08	1.26E-03	4.55E-04	1.33E-05
5.67E-08	1.34E-03	4.83E-04	1.41E-05
6.00E-08	1.42E-03	5.12E-04	1.50E-05
6.33E-08	1.50E-03	5.40E-04	1.58E-05
6.67E-08	1.58E-03	5.68E-04	1.66E-05
7.00E-08	1.66E-03	5.96E-04	1.75E-05
7.33E-08	1.73E-03	6.25E-04	1.83E-05
7.67E-08	1.81E-03	6.53E-04	1.91E-05
8.00E-08	1.89E-03	6.81E-04	1.99E-05
8.33E-08	1.97E-03	7.10E-04	2.08E-05
8.67E-08	2.05E-03	7.38E-04	2.16E-05
9.00E-08	2.13E-03	7.66E-04	2.24E-05
9.33E-08	2.21E-03	7.94E-04	2.32E-05
9.67E-08	2.28E-03	8.23E-04	2.41E-05
1.00E-07	2.36E-03	8.51E-04	2.49E-05
1.33E-07	3.14E-03	1.13E-03	3.31E-05
1.67E-07	3.92E-03	1.41E-03	4.13E-05

Nongestational Lifetime			
Intake (ng/kg/day)	**Fat (ng/kg)**	**Body Burden (ng/kg)**	**Blood (ng/kg)**
2.00E-07	4.70E-03	1.70E-03	4.96E-05
2.33E-07	5.48E-03	1.98E-03	5.78E-05
2.67E-07	6.26E-03	2.26E-03	6.60E-05
3.00E-07	7.04E-03	2.54E-03	7.42E-05
3.33E-07	7.82E-03	2.82E-03	8.24E-05
3.67E-07	8.60E-03	3.10E-03	9.06E-05
4.00E-07	9.38E-03	3.38E-03	9.89E-05
4.33E-07	1.02E-02	3.66E-03	1.07E-04
4.67E-07	1.09E-02	3.95E-03	1.15E-04
5.00E-07	1.17E-02	4.23E-03	1.24E-04
5.33E-07	1.25E-02	4.50E-03	1.31E-04
5.66E-07	1.32E-02	4.78E-03	1.39E-04
5.99E-07	1.40E-02	5.05E-03	1.47E-04
6.33E-07	1.47E-02	5.32E-03	1.55E-04
6.66E-07	1.55E-02	5.60E-03	1.63E-04
6.99E-07	1.63E-02	5.87E-03	1.71E-04
7.32E-07	1.70E-02	6.15E-03	1.79E-04
7.65E-07	1.78E-02	6.42E-03	1.87E-04
7.98E-07	1.85E-02	6.69E-03	1.95E-04
8.32E-07	1.93E-02	6.97E-03	2.03E-04
8.65E-07	2.00E-02	7.24E-03	2.11E-04
8.98E-07	2.08E-02	7.52E-03	2.19E-04
9.31E-07	2.16E-02	7.79E-03	2.27E-04
9.64E-07	2.23E-02	8.07E-03	2.35E-04
9.97E-07	2.31E-02	8.34E-03	2.43E-04
1.01E-06	2.34E-02	8.46E-03	2.47E-04
1.03E-06	2.37E-02	8.59E-03	2.50E-04
1.04E-06	2.41E-02	8.71E-03	2.54E-04
1.06E-06	2.44E-02	8.84E-03	2.58E-04

Nongestational Lifetime			
Intake (ng/kg/day)	**Fat (ng/kg)**	**Body Burden (ng/kg)**	**Blood (ng/kg)**
1.07E-06	2.48E-02	8.97E-03	2.61E-04
1.09E-06	2.52E-02	9.10E-03	2.65E-04
1.11E-06	2.55E-02	9.23E-03	2.69E-04
1.12E-06	2.59E-02	9.37E-03	2.73E-04
1.14E-06	2.63E-02	9.51E-03	2.77E-04
1.16E-06	2.67E-02	9.65E-03	2.81E-04
1.17E-06	2.70E-02	9.79E-03	2.85E-04
1.19E-06	2.74E-02	9.93E-03	2.89E-04
1.21E-06	2.78E-02	1.01E-02	2.93E-04
1.23E-06	2.82E-02	1.02E-02	2.98E-04
1.24E-06	2.87E-02	1.04E-02	3.02E-04
1.26E-06	2.91E-02	1.05E-02	3.06E-04
1.28E-06	2.95E-02	1.07E-02	3.11E-04
1.30E-06	2.99E-02	1.08E-02	3.15E-04
1.32E-06	3.04E-02	1.10E-02	3.20E-04
1.34E-06	3.08E-02	1.12E-02	3.25E-04
1.36E-06	3.13E-02	1.13E-02	3.29E-04
1.38E-06	3.17E-02	1.15E-02	3.34E-04
1.40E-06	3.22E-02	1.16E-02	3.39E-04
1.42E-06	3.26E-02	1.18E-02	3.44E-04
1.44E-06	3.31E-02	1.20E-02	3.49E-04
1.46E-06	3.36E-02	1.22E-02	3.54E-04
1.49E-06	3.41E-02	1.24E-02	3.59E-04
1.53E-06	3.51E-02	1.27E-02	3.70E-04
1.58E-06	3.61E-02	1.31E-02	3.81E-04
1.62E-06	3.72E-02	1.35E-02	3.92E-04
1.67E-06	3.83E-02	1.39E-02	4.03E-04
1.72E-06	3.94E-02	1.43E-02	4.15E-04
1.77E-06	4.05E-02	1.47E-02	4.27E-04

Nongestational Lifetime			
Intake (ng/kg/day)	**Fat (ng/kg)**	**Body Burden (ng/kg)**	**Blood (ng/kg)**
1.83E-06	4.17E-02	1.51E-02	4.39E-04
1.88E-06	4.29E-02	1.56E-02	4.52E-04
1.94E-06	4.41E-02	1.60E-02	4.65E-04
2.00E-06	4.54E-02	1.65E-02	4.79E-04
2.06E-06	4.67E-02	1.70E-02	4.93E-04
2.12E-06	4.81E-02	1.75E-02	5.07E-04
2.18E-06	4.95E-02	1.80E-02	5.22E-04
2.25E-06	5.09E-02	1.85E-02	5.37E-04
2.32E-06	5.24E-02	1.90E-02	5.52E-04
2.39E-06	5.39E-02	1.96E-02	5.68E-04
2.46E-06	5.55E-02	2.02E-02	5.85E-04
2.53E-06	5.71E-02	2.07E-02	6.02E-04
2.61E-06	5.87E-02	2.13E-02	6.19E-04
2.68E-06	6.04E-02	2.20E-02	6.37E-04
2.76E-06	6.22E-02	2.26E-02	6.55E-04
2.85E-06	6.40E-02	2.33E-02	6.74E-04
2.93E-06	6.58E-02	2.39E-02	6.93E-04
3.02E-06	6.77E-02	2.46E-02	7.13E-04
3.11E-06	6.96E-02	2.53E-02	7.34E-04
3.21E-06	7.16E-02	2.61E-02	7.55E-04
3.30E-06	7.37E-02	2.68E-02	7.76E-04
3.40E-06	7.58E-02	2.76E-02	7.99E-04
3.50E-06	7.80E-02	2.84E-02	8.22E-04
3.61E-06	8.02E-02	2.92E-02	8.45E-04
3.72E-06	8.25E-02	3.01E-02	8.69E-04
3.83E-06	8.48E-02	3.09E-02	8.94E-04
3.94E-06	8.73E-02	3.18E-02	9.20E-04
4.06E-06	8.98E-02	3.27E-02	9.46E-04
4.18E-06	9.23E-02	3.37E-02	9.73E-04

Nongestational Lifetime			
Intake (ng/kg/day)	**Fat (ng/kg)**	**Body Burden (ng/kg)**	**Blood (ng/kg)**
4.31E-06	9.49E-02	3.47E-02	1.00E-03
4.44E-06	9.76E-02	3.57E-02	1.03E-03
4.57E-06	1.00E-01	3.67E-02	1.06E-03
4.71E-06	1.03E-01	3.77E-02	1.09E-03
4.85E-06	1.06E-01	3.88E-02	1.12E-03
4.99E-06	1.09E-01	3.99E-02	1.15E-03
5.14E-06	1.12E-01	4.11E-02	1.18E-03
5.30E-06	1.15E-01	4.22E-02	1.22E-03
5.46E-06	1.19E-01	4.34E-02	1.25E-03
5.62E-06	1.22E-01	4.47E-02	1.29E-03
5.79E-06	1.25E-01	4.59E-02	1.32E-03
5.96E-06	1.29E-01	4.73E-02	1.36E-03
6.14E-06	1.33E-01	4.86E-02	1.40E-03
6.33E-06	1.36E-01	5.00E-02	1.44E-03
6.52E-06	1.40E-01	5.14E-02	1.48E-03
6.71E-06	1.44E-01	5.28E-02	1.52E-03
6.91E-06	1.48E-01	5.43E-02	1.56E-03
7.12E-06	1.52E-01	5.58E-02	1.60E-03
7.33E-06	1.56E-01	5.74E-02	1.65E-03
7.55E-06	1.61E-01	5.90E-02	1.69E-03
7.78E-06	1.65E-01	6.06E-02	1.74E-03
8.01E-06	1.70E-01	6.23E-02	1.79E-03
8.25E-06	1.74E-01	6.41E-02	1.84E-03
8.50E-06	1.79E-01	6.59E-02	1.89E-03
8.76E-06	1.84E-01	6.77E-02	1.94E-03
9.02E-06	1.89E-01	6.96E-02	1.99E-03
9.29E-06	1.94E-01	7.15E-02	2.05E-03
9.57E-06	2.00E-01	7.35E-02	2.10E-03
9.86E-06	2.05E-01	7.56E-02	2.16E-03

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Nongestational Lifetime			
Intake (ng/kg/day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.02E-05	2.11E-01	7.77E-02	2.22E-03
1.05E-05	2.16E-01	7.98E-02	2.28E-03
1.08E-05	2.22E-01	8.20E-02	2.34E-03
1.11E-05	2.28E-01	8.43E-02	2.41E-03
1.14E-05	2.34E-01	8.67E-02	2.47E-03
1.18E-05	2.41E-01	8.91E-02	2.54E-03
1.21E-05	2.47E-01	9.15E-02	2.61E-03
1.25E-05	2.54E-01	9.41E-02	2.68E-03
1.29E-05	2.61E-01	9.67E-02	2.75E-03
1.32E-05	2.68E-01	9.93E-02	2.82E-03
1.36E-05	2.75E-01	1.02E-01	2.90E-03
1.41E-05	2.83E-01	1.05E-01	2.98E-03
1.45E-05	2.90E-01	1.08E-01	3.06E-03
1.49E-05	2.98E-01	1.11E-01	3.14E-03
1.54E-05	3.06E-01	1.14E-01	3.22E-03
1.58E-05	3.14E-01	1.17E-01	3.31E-03
1.63E-05	3.23E-01	1.20E-01	3.40E-03
1.68E-05	3.31E-01	1.23E-01	3.49E-03
1.73E-05	3.40E-01	1.27E-01	3.58E-03
1.78E-05	3.49E-01	1.30E-01	3.68E-03
1.83E-05	3.58E-01	1.34E-01	3.78E-03
1.89E-05	3.68E-01	1.37E-01	3.88E-03
1.95E-05	3.78E-01	1.41E-01	3.98E-03
2.00E-05	3.88E-01	1.45E-01	4.09E-03
2.06E-05	3.98E-01	1.49E-01	4.20E-03
2.13E-05	4.09E-01	1.53E-01	4.31E-03
2.19E-05	4.20E-01	1.57E-01	4.42E-03
2.25E-05	4.31E-01	1.61E-01	4.54E-03
2.32E-05	4.42E-01	1.66E-01	4.66E-03

Nongestational Lifetime			
Intake (ng/kg/day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
2.39E-05	4.54E-01	1.70E-01	4.78E-03
2.46E-05	4.66E-01	1.75E-01	4.91E-03
2.54E-05	4.78E-01	1.80E-01	5.04E-03
2.61E-05	4.91E-01	1.84E-01	5.17E-03
2.69E-05	5.04E-01	1.89E-01	5.31E-03
2.77E-05	5.17E-01	1.95E-01	5.45E-03
2.86E-05	5.31E-01	2.00E-01	5.59E-03
2.94E-05	5.45E-01	2.05E-01	5.74E-03
3.03E-05	5.59E-01	2.11E-01	5.89E-03
3.12E-05	5.74E-01	2.16E-01	6.05E-03
3.21E-05	5.89E-01	2.22E-01	6.20E-03
3.31E-05	6.06E-01	2.29E-01	6.38E-03
3.41E-05	6.22E-01	2.35E-01	6.54E-03
3.51E-05	6.38E-01	2.41E-01	6.72E-03
3.62E-05	6.54E-01	2.48E-01	6.89E-03
3.73E-05	6.71E-01	2.54E-01	7.08E-03
3.84E-05	6.89E-01	2.61E-01	7.25E-03
3.95E-05	7.07E-01	2.68E-01	7.45E-03
4.07E-05	7.23E-01	2.74E-01	7.62E-03
4.19E-05	7.41E-01	2.82E-01	7.82E-03
4.32E-05	7.60E-01	2.89E-01	8.01E-03
4.45E-05	7.80E-01	2.97E-01	8.22E-03
4.58E-05	8.00E-01	3.05E-01	8.43E-03
4.72E-05	8.20E-01	3.13E-01	8.64E-03
4.86E-05	8.41E-01	3.21E-01	8.86E-03
5.01E-05	8.63E-01	3.29E-01	9.09E-03
5.16E-05	8.84E-01	3.38E-01	9.32E-03
5.31E-05	9.07E-01	3.47E-01	9.55E-03
5.47E-05	9.30E-01	3.56E-01	9.80E-03

Nongestational Lifetime			
Intake (ng/kg/day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
5.64E-05	9.53E-01	3.65E-01	1.00E-02
5.81E-05	9.77E-01	3.75E-01	1.03E-02
5.98E-05	1.00E+00	3.84E-01	1.06E-02
6.16E-05	1.03E+00	3.95E-01	1.08E-02
6.34E-05	1.05E+00	4.05E-01	1.11E-02
6.54E-05	1.08E+00	4.15E-01	1.14E-02
6.73E-05	1.11E+00	4.26E-01	1.17E-02
6.93E-05	1.13E+00	4.37E-01	1.19E-02
7.14E-05	1.16E+00	4.48E-01	1.22E-02
7.36E-05	1.19E+00	4.58E-01	1.25E-02
7.58E-05	1.22E+00	4.70E-01	1.28E-02
7.80E-05	1.25E+00	4.82E-01	1.31E-02
8.04E-05	1.28E+00	4.94E-01	1.34E-02
8.28E-05	1.31E+00	5.07E-01	1.38E-02
8.53E-05	1.34E+00	5.20E-01	1.41E-02
8.78E-05	1.37E+00	5.33E-01	1.45E-02
9.05E-05	1.41E+00	5.47E-01	1.48E-02
9.32E-05	1.44E+00	5.61E-01	1.52E-02
9.60E-05	1.48E+00	5.75E-01	1.55E-02
9.89E-05	1.51E+00	5.90E-01	1.59E-02
1.02E-04	1.55E+00	6.05E-01	1.63E-02
1.05E-04	1.59E+00	6.20E-01	1.67E-02
1.08E-04	1.62E+00	6.36E-01	1.71E-02
1.11E-04	1.66E+00	6.52E-01	1.75E-02
1.15E-04	1.70E+00	6.69E-01	1.79E-02
1.18E-04	1.75E+00	6.86E-01	1.84E-02
1.22E-04	1.79E+00	7.03E-01	1.88E-02
1.25E-04	1.83E+00	7.20E-01	1.93E-02
1.29E-04	1.87E+00	7.39E-01	1.97E-02

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Nongestational Lifetime			
Intake (ng/kg/day)	**Fat (ng/kg)**	**Body Burden (ng/kg)**	**Blood (ng/kg)**
1.33E-04	1.92E+00	7.57E-01	2.02E-02
1.37E-04	1.97E+00	7.76E-01	2.07E-02
1.41E-04	2.01E+00	7.96E-01	2.12E-02
1.45E-04	2.08E+00	8.23E-01	2.19E-02
1.50E-04	2.11E+00	8.36E-01	2.22E-02
1.54E-04	2.16E+00	8.57E-01	2.27E-02
1.59E-04	2.23E+00	8.88E-01	2.35E-02
1.63E-04	2.29E+00	9.10E-01	2.41E-02
1.68E-04	2.32E+00	9.24E-01	2.44E-02
1.73E-04	2.37E+00	9.47E-01	2.50E-02
1.79E-04	2.43E+00	9.71E-01	2.56E-02
1.84E-04	2.49E+00	9.96E-01	2.62E-02
1.89E-04	2.55E+00	1.02E+00	2.68E-02
1.95E-04	2.61E+00	1.05E+00	2.75E-02
2.01E-04	2.67E+00	1.07E+00	2.81E-02
2.07E-04	2.76E+00	1.11E+00	2.91E-02
2.13E-04	2.80E+00	1.13E+00	2.94E-02
2.20E-04	2.86E+00	1.16E+00	3.01E-02
2.26E-04	2.95E+00	1.19E+00	3.11E-02
2.33E-04	3.02E+00	1.22E+00	3.18E-02
2.40E-04	3.09E+00	1.25E+00	3.26E-02
2.47E-04	3.14E+00	1.27E+00	3.30E-02
2.55E-04	3.21E+00	1.31E+00	3.38E-02
2.62E-04	3.29E+00	1.34E+00	3.46E-02
2.70E-04	3.39E+00	1.38E+00	3.57E-02
2.78E-04	3.47E+00	1.42E+00	3.65E-02
2.86E-04	3.55E+00	1.45E+00	3.74E-02
2.95E-04	3.61E+00	1.48E+00	3.80E-02
3.04E-04	3.72E+00	1.53E+00	3.91E-02

Nongestational Lifetime			
Intake (ng/kg/day)	**Fat (ng/kg)**	**Body Burden (ng/kg)**	**Blood (ng/kg)**
3.13E-04	3.80E+00	1.56E+00	4.00E-02
3.22E-04	3.89E+00	1.60E+00	4.10E-02
3.32E-04	3.98E+00	1.64E+00	4.19E-02
3.42E-04	4.07E+00	1.68E+00	4.29E-02
3.52E-04	4.16E+00	1.72E+00	4.38E-02
3.63E-04	4.26E+00	1.77E+00	4.48E-02
3.74E-04	4.35E+00	1.81E+00	4.58E-02
3.85E-04	4.45E+00	1.85E+00	4.69E-02
3.97E-04	4.55E+00	1.90E+00	4.80E-02
4.08E-04	4.66E+00	1.94E+00	4.90E-02
4.21E-04	4.76E+00	1.99E+00	5.01E-02
4.33E-04	4.87E+00	2.04E+00	5.13E-02
4.46E-04	4.98E+00	2.09E+00	5.24E-02
4.60E-04	5.09E+00	2.14E+00	5.36E-02
4.74E-04	5.20E+00	2.19E+00	5.48E-02
4.88E-04	5.32E+00	2.24E+00	5.60E-02
5.02E-04	5.43E+00	2.30E+00	5.72E-02
5.17E-04	5.55E+00	2.35E+00	5.85E-02
5.33E-04	5.68E+00	2.41E+00	5.98E-02
5.49E-04	5.80E+00	2.47E+00	6.11E-02
5.65E-04	5.93E+00	2.53E+00	6.24E-02
5.82E-04	6.06E+00	2.59E+00	6.38E-02
6.00E-04	6.19E+00	2.65E+00	6.52E-02
6.18E-04	6.33E+00	2.71E+00	6.66E-02
6.36E-04	6.46E+00	2.78E+00	6.80E-02
6.55E-04	6.60E+00	2.84E+00	6.95E-02
6.75E-04	6.75E+00	2.91E+00	7.10E-02
6.95E-04	6.89E+00	2.98E+00	7.26E-02
7.16E-04	7.04E+00	3.05E+00	7.41E-02

Nongestational Lifetime			
Intake (ng/kg/day)	**Fat (ng/kg)**	**Body Burden (ng/kg)**	**Blood (ng/kg)**
7.38E-04	7.20E+00	3.13E+00	7.58E-02
7.60E-04	7.35E+00	3.20E+00	7.74E-02
7.83E-04	7.51E+00	3.28E+00	7.91E-02
8.06E-04	7.61E+00	3.33E+00	8.01E-02
8.30E-04	7.77E+00	3.41E+00	8.19E-02
8.55E-04	7.94E+00	3.49E+00	8.36E-02
8.81E-04	8.11E+00	3.58E+00	8.54E-02
9.07E-04	8.30E+00	3.67E+00	8.74E-02
9.21E-04	8.37E+00	3.70E+00	8.81E-02
9.35E-04	8.46E+00	3.75E+00	8.90E-02
9.49E-04	9.14E+00	4.12E+00	9.62E-02
9.63E-04	9.54E+00	4.33E+00	1.00E-01
9.69E-04	9.70E+00	4.42E+00	1.02E-01
9.77E-04	9.87E+00	4.51E+00	1.04E-01
1.17E-03	1.01E+01	4.58E+00	1.07E-01
1.18E-03	1.02E+01	4.63E+00	1.08E-01
1.20E-03	1.03E+01	4.68E+00	1.09E-01
1.22E-03	1.04E+01	4.73E+00	1.10E-01
1.24E-03	1.05E+01	4.75E+00	1.10E-01
1.26E-03	1.06E+01	4.81E+00	1.11E-01
1.27E-03	1.07E+01	4.86E+00	1.12E-01
1.29E-03	1.08E+01	4.92E+00	1.14E-01
1.31E-03	1.09E+01	4.97E+00	1.15E-01
1.33E-03	1.10E+01	5.03E+00	1.16E-01
1.35E-03	1.11E+01	5.08E+00	1.17E-01
1.37E-03	1.12E+01	5.13E+00	1.18E-01
1.39E-03	1.13E+01	5.18E+00	1.19E-01
1.41E-03	1.14E+01	5.23E+00	1.20E-01
1.43E-03	1.15E+01	5.29E+00	1.21E-01

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Nongestational Lifetime			
Intake (ng/kg/day)	**Fat (ng/kg)**	**Body Burden (ng/kg)**	**Blood (ng/kg)**
1.46E-03	1.16E+01	5.34E+00	1.22E-01
1.48E-03	1.17E+01	5.40E+00	1.23E-01
1.50E-03	1.18E+01	5.47E+00	1.25E-01
1.52E-03	1.20E+01	5.54E+00	1.26E-01
1.54E-03	1.21E+01	5.61E+00	1.28E-01
1.57E-03	1.22E+01	5.66E+00	1.29E-01
1.59E-03	1.24E+01	5.73E+00	1.30E-01
1.61E-03	1.25E+01	5.82E+00	1.32E-01
1.64E-03	1.27E+01	5.88E+00	1.33E-01
1.66E-03	1.28E+01	5.95E+00	1.35E-01
1.69E-03	1.29E+01	6.02E+00	1.36E-01
1.71E-03	1.31E+01	6.10E+00	1.37E-01
1.74E-03	1.32E+01	6.17E+00	1.39E-01
1.76E-03	1.33E+01	6.24E+00	1.40E-01
1.79E-03	1.35E+01	6.32E+00	1.42E-01
1.82E-03	1.36E+01	6.39E+00	1.43E-01
1.84E-03	1.38E+01	6.46E+00	1.45E-01
1.87E-03	1.40E+01	6.59E+00	1.47E-01
1.90E-03	1.46E+01	6.95E+00	1.54E-01
2.02E-03	1.50E+01	7.16E+00	1.58E-01
2.08E-03	1.51E+01	7.23E+00	1.59E-01
2.14E-03	1.53E+01	7.31E+00	1.61E-01
2.20E-03	1.56E+01	7.47E+00	1.64E-01
2.27E-03	1.59E+01	7.65E+00	1.68E-01
2.34E-03	1.62E+01	7.82E+00	1.71E-01
2.41E-03	1.66E+01	8.00E+00	1.74E-01
2.48E-03	1.69E+01	8.19E+00	1.78E-01
2.55E-03	1.72E+01	8.38E+00	1.81E-01
2.63E-03	1.76E+01	8.57E+00	1.85E-01

Nongestational Lifetime			
Intake (ng/kg/day)	**Fat (ng/kg)**	**Body Burden (ng/kg)**	**Blood (ng/kg)**
2.71E-03	1.79E+01	8.77E+00	1.89E-01
2.79E-03	1.83E+01	8.98E+00	1.92E-01
2.87E-03	1.87E+01	9.19E+00	1.96E-01
2.96E-03	1.90E+01	9.41E+00	2.00E-01
3.05E-03	1.94E+01	9.62E+00	2.04E-01
3.14E-03	1.98E+01	9.85E+00	2.08E-01
3.23E-03	2.02E+01	1.01E+01	2.13E-01
3.33E-03	2.06E+01	1.03E+01	2.17E-01
3.43E-03	2.10E+01	1.06E+01	2.21E-01
3.53E-03	2.14E+01	1.08E+01	2.25E-01
3.64E-03	2.18E+01	1.11E+01	2.30E-01
3.75E-03	2.25E+01	1.15E+01	2.37E-01
3.98E-03	2.29E+01	1.17E+01	2.41E-01
4.10E-03	2.32E+01	1.18E+01	2.44E-01
4.22E-03	2.35E+01	1.20E+01	2.48E-01
4.35E-03	2.40E+01	1.23E+01	2.52E-01
4.48E-03	2.44E+01	1.26E+01	2.57E-01
4.61E-03	2.49E+01	1.29E+01	2.63E-01
4.75E-03	2.55E+01	1.33E+01	2.69E-01
4.89E-03	2.61E+01	1.36E+01	2.74E-01
5.04E-03	2.69E+01	1.41E+01	2.83E-01
5.19E-03	2.75E+01	1.45E+01	2.90E-01
5.35E-03	2.83E+01	1.51E+01	2.98E-01
5.51E-03	2.91E+01	1.55E+01	3.06E-01
5.67E-03	2.97E+01	1.59E+01	3.13E-01
5.84E-03	3.03E+01	1.63E+01	3.19E-01
5.93E-03	3.04E+01	1.64E+01	3.20E-01
6.02E-03	3.07E+01	1.65E+01	3.23E-01
6.20E-03	3.15E+01	1.71E+01	3.31E-01

Nongestational Lifetime			
Intake (ng/kg/day)	**Fat (ng/kg)**	**Body Burden (ng/kg)**	**Blood (ng/kg)**
6.38E-03	3.22E+01	1.76E+01	3.39E-01
6.57E-03	3.28E+01	1.80E+01	3.46E-01
6.77E-03	3.35E+01	1.84E+01	3.53E-01
6.98E-03	3.42E+01	1.89E+01	3.60E-01
7.18E-03	3.50E+01	1.94E+01	3.68E-01
7.40E-03	3.57E+01	1.99E+01	3.76E-01
7.51E-03	3.61E+01	2.02E+01	3.80E-01
7.62E-03	3.63E+01	2.03E+01	3.82E-01
7.85E-03	3.67E+01	2.06E+01	3.87E-01
8.09E-03	3.70E+01	2.07E+01	3.89E-01
8.33E-03	3.75E+01	2.10E+01	3.94E-01
8.58E-03	3.89E+01	2.21E+01	4.09E-01
8.71E-03	3.93E+01	2.24E+01	4.14E-01
8.84E-03	3.97E+01	2.26E+01	4.18E-01
9.10E-03	4.04E+01	2.31E+01	4.25E-01
9.37E-03	4.13E+01	2.38E+01	4.35E-01
9.66E-03	4.21E+01	2.43E+01	4.44E-01
9.94E-03	4.31E+01	2.50E+01	4.53E-01
1.02E-02	4.39E+01	2.56E+01	4.62E-01
1.06E-02	4.47E+01	2.62E+01	4.71E-01
1.09E-02	4.56E+01	2.68E+01	4.80E-01
1.12E-02	4.66E+01	2.75E+01	4.90E-01
1.15E-02	4.75E+01	2.82E+01	5.00E-01
1.19E-02	4.82E+01	2.87E+01	5.07E-01
1.22E-02	4.91E+01	2.94E+01	5.17E-01
1.26E-02	5.00E+01	3.00E+01	5.26E-01
1.30E-02	5.12E+01	3.09E+01	5.39E-01
1.34E-02	5.24E+01	3.19E+01	5.52E-01
1.38E-02	5.36E+01	3.28E+01	5.65E-01

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Nongestational Lifetime			
Intake (ng/kg/day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.42E-02	5.48E+01	3.37E+01	5.77E-01
1.46E-02	5.57E+01	3.44E+01	5.87E-01
1.50E-02	5.68E+01	3.52E+01	5.97E-01
1.55E-02	5.78E+01	3.60E+01	6.08E-01
1.60E-02	5.88E+01	3.67E+01	6.19E-01
1.64E-02	5.97E+01	3.75E+01	6.29E-01
1.69E-02	6.10E+01	3.85E+01	6.42E-01
1.74E-02	6.22E+01	3.95E+01	6.55E-01
1.80E-02	6.34E+01	4.04E+01	6.68E-01
1.85E-02	6.47E+01	4.14E+01	6.81E-01
1.91E-02	6.60E+01	4.25E+01	6.94E-01
1.96E-02	6.73E+01	4.35E+01	7.08E-01
2.02E-02	6.86E+01	4.46E+01	7.22E-01
2.08E-02	7.00E+01	4.57E+01	7.36E-01
2.14E-02	7.13E+01	4.69E+01	7.51E-01
2.21E-02	7.28E+01	4.81E+01	7.66E-01
2.28E-02	7.42E+01	4.93E+01	7.81E-01
2.34E-02	7.57E+01	5.05E+01	7.97E-01
2.41E-02	7.71E+01	5.18E+01	8.12E-01
2.49E-02	7.87E+01	5.31E+01	8.28E-01
2.56E-02	8.02E+01	5.44E+01	8.44E-01
2.64E-02	8.18E+01	5.58E+01	8.61E-01
2.72E-02	8.33E+01	5.71E+01	8.77E-01
2.80E-02	8.50E+01	5.86E+01	8.95E-01
2.88E-02	8.67E+01	6.01E+01	9.12E-01
2.97E-02	8.83E+01	6.16E+01	9.30E-01
3.06E-02	9.03E+01	6.34E+01	9.50E-01
3.15E-02	9.21E+01	6.50E+01	9.69E-01
3.24E-02	9.40E+01	6.67E+01	9.89E-01

Nongestational Lifetime			
Intake (ng/kg/day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
3.34E-02	9.57E+01	6.83E+01	1.01E+00
3.44E-02	9.74E+01	6.99E+01	1.03E+00
3.54E-02	9.92E+01	7.15E+01	1.04E+00
3.65E-02	1.01E+02	7.32E+01	1.06E+00
3.76E-02	1.03E+02	7.51E+01	1.08E+00
3.87E-02	1.05E+02	7.69E+01	1.10E+00
3.99E-02	1.07E+02	7.89E+01	1.13E+00
4.11E-02	1.09E+02	8.09E+01	1.15E+00
4.23E-02	1.11E+02	8.30E+01	1.17E+00
4.36E-02	1.14E+02	8.53E+01	1.20E+00
4.49E-02	1.16E+02	8.76E+01	1.22E+00
4.63E-02	1.18E+02	8.99E+01	1.24E+00
4.76E-02	1.21E+02	9.22E+01	1.27E+00
4.91E-02	1.23E+02	9.46E+01	1.29E+00
5.05E-02	1.25E+02	9.70E+01	1.32E+00
5.21E-02	1.28E+02	9.95E+01	1.34E+00
5.36E-02	1.30E+02	1.02E+02	1.37E+00
5.52E-02	1.33E+02	1.05E+02	1.40E+00
5.69E-02	1.35E+02	1.07E+02	1.43E+00
5.86E-02	1.38E+02	1.10E+02	1.45E+00
6.03E-02	1.41E+02	1.13E+02	1.48E+00
6.22E-02	1.43E+02	1.16E+02	1.51E+00
6.40E-02	1.46E+02	1.19E+02	1.54E+00
6.59E-02	1.49E+02	1.22E+02	1.57E+00
6.79E-02	1.52E+02	1.25E+02	1.60E+00
7.00E-02	1.55E+02	1.28E+02	1.63E+00
7.21E-02	1.58E+02	1.31E+02	1.66E+00
7.42E-02	1.61E+02	1.35E+02	1.69E+00
7.64E-02	1.64E+02	1.38E+02	1.73E+00

Nongestational Lifetime			
Intake (ng/kg/day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
7.87E-02	1.67E+02	1.42E+02	1.76E+00
8.11E-02	1.71E+02	1.46E+02	1.80E+00
8.35E-02	1.74E+02	1.50E+02	1.83E+00
8.60E-02	1.78E+02	1.54E+02	1.87E+00
8.86E-02	1.81E+02	1.58E+02	1.90E+00
9.13E-02	1.85E+02	1.62E+02	1.94E+00
9.40E-02	1.88E+02	1.66E+02	1.98E+00
9.68E-02	1.92E+02	1.70E+02	2.02E+00
9.97E-02	1.96E+02	1.75E+02	2.06E+00
1.03E-01	1.99E+02	1.79E+02	2.10E+00
1.06E-01	2.03E+02	1.84E+02	2.14E+00
1.09E-01	2.07E+02	1.89E+02	2.18E+00
1.12E-01	2.11E+02	1.94E+02	2.22E+00
1.16E-01	2.15E+02	1.99E+02	2.27E+00
1.19E-01	2.20E+02	2.04E+02	2.31E+00
1.23E-01	2.24E+02	2.10E+02	2.36E+00
1.26E-01	2.28E+02	2.15E+02	2.40E+00
1.30E-01	2.33E+02	2.21E+02	2.45E+00
1.34E-01	2.38E+02	2.27E+02	2.50E+00
1.38E-01	2.42E+02	2.33E+02	2.55E+00
1.42E-01	2.47E+02	2.39E+02	2.60E+00
1.46E-01	2.52E+02	2.46E+02	2.65E+00
1.51E-01	2.57E+02	2.52E+02	2.70E+00
1.55E-01	2.62E+02	2.59E+02	2.75E+00
1.60E-01	2.67E+02	2.66E+02	2.81E+00
1.65E-01	2.72E+02	2.73E+02	2.86E+00
1.70E-01	2.78E+02	2.80E+02	2.92E+00
1.75E-01	2.83E+02	2.88E+02	2.98E+00
1.80E-01	2.89E+02	2.95E+02	3.04E+00

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Nongestational Lifetime			
Intake (ng/kg/day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.86E-01	2.94E+02	3.03E+02	3.10E+00
1.91E-01	3.00E+02	3.12E+02	3.16E+00
1.97E-01	3.06E+02	3.20E+02	3.22E+00
2.03E-01	3.12E+02	3.28E+02	3.28E+00
2.09E-01	3.18E+02	3.37E+02	3.35E+00
2.15E-01	3.25E+02	3.46E+02	3.42E+00
2.22E-01	3.31E+02	3.56E+02	3.48E+00
2.28E-01	3.38E+02	3.65E+02	3.55E+00
2.35E-01	3.44E+02	3.75E+02	3.62E+00
2.42E-01	3.51E+02	3.86E+02	3.70E+00
2.49E-01	3.58E+02	3.96E+02	3.77E+00
2.57E-01	3.65E+02	4.07E+02	3.85E+00
2.65E-01	3.73E+02	4.18E+02	3.92E+00
2.72E-01	3.80E+02	4.29E+02	4.00E+00
2.81E-01	3.88E+02	4.41E+02	4.08E+00
2.89E-01	3.95E+02	4.53E+02	4.16E+00
2.98E-01	4.03E+02	4.65E+02	4.24E+00
3.07E-01	4.11E+02	4.77E+02	4.33E+00
3.16E-01	4.19E+02	4.90E+02	4.41E+00
3.25E-01	4.28E+02	5.04E+02	4.50E+00
3.35E-01	4.36E+02	5.18E+02	4.59E+00
3.45E-01	4.45E+02	5.32E+02	4.68E+00
3.56E-01	4.54E+02	5.47E+02	4.78E+00
3.66E-01	4.63E+02	5.62E+02	4.87E+00
3.77E-01	4.72E+02	5.77E+02	4.97E+00
3.89E-01	4.82E+02	5.93E+02	5.07E+00
4.00E-01	4.91E+02	6.09E+02	5.17E+00
4.12E-01	5.01E+02	6.26E+02	5.28E+00
4.25E-01	5.11E+02	6.43E+02	5.38E+00

Nongestational Lifetime			
Intake (ng/kg/day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
4.37E-01	5.22E+02	6.61E+02	5.49E+00
4.50E-01	5.32E+02	6.79E+02	5.60E+00
4.64E-01	5.43E+02	6.98E+02	5.71E+00
4.92E-01	5.65E+02	7.37E+02	5.95E+00
5.07E-01	5.76E+02	7.57E+02	6.07E+00
5.22E-01	5.88E+02	7.78E+02	6.19E+00
5.54E-01	6.12E+02	8.22E+02	6.44E+00
5.71E-01	6.25E+02	8.44E+02	6.58E+00
5.88E-01	6.37E+02	8.68E+02	6.71E+00
6.05E-01	6.50E+02	8.92E+02	6.84E+00
6.23E-01	6.64E+02	9.17E+02	6.98E+00
6.61E-01	6.91E+02	9.68E+02	7.27E+00
6.81E-01	7.05E+02	9.95E+02	7.42E+00
7.02E-01	7.20E+02	1.02E+03	7.57E+00
7.23E-01	7.34E+02	1.05E+03	7.73E+00
7.44E-01	7.49E+02	1.08E+03	7.89E+00
7.67E-01	7.65E+02	1.11E+03	8.05E+00
7.90E-01	7.80E+02	1.14E+03	8.21E+00
8.13E-01	7.97E+02	1.17E+03	8.38E+00
8.38E-01	8.13E+02	1.21E+03	8.56E+00
8.63E-01	8.30E+02	1.24E+03	8.73E+00
8.89E-01	8.47E+02	1.28E+03	8.91E+00
9.16E-01	8.65E+02	1.31E+03	9.10E+00
9.43E-01	8.83E+02	1.35E+03	9.29E+00
9.71E-01	9.01E+02	1.39E+03	9.48E+00
1.00E+00	9.20E+02	1.43E+03	9.68E+00
1.06E+00	9.58E+02	1.51E+03	1.01E+01
1.09E+00	9.78E+02	1.55E+03	1.03E+01
1.13E+00	9.99E+02	1.59E+03	1.05E+01

Nongestational Lifetime			
Intake (ng/kg/day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.16E+00	1.02E+03	1.64E+03	1.07E+01
1.19E+00	1.04E+03	1.68E+03	1.10E+01
1.23E+00	1.06E+03	1.73E+03	1.12E+01
1.27E+00	1.09E+03	1.78E+03	1.14E+01
1.31E+00	1.11E+03	1.83E+03	1.17E+01
1.34E+00	1.13E+03	1.88E+03	1.19E+01
1.38E+00	1.16E+03	1.94E+03	1.22E+01
1.43E+00	1.18E+03	1.99E+03	1.24E+01
1.47E+00	1.21E+03	2.05E+03	1.27E+01
1.51E+00	1.23E+03	2.11E+03	1.30E+01
1.56E+00	1.26E+03	2.17E+03	1.32E+01
1.61E+00	1.28E+03	2.23E+03	1.35E+01
1.65E+00	1.31E+03	2.29E+03	1.38E+01
1.70E+00	1.34E+03	2.36E+03	1.41E+01
1.75E+00	1.37E+03	2.42E+03	1.44E+01
1.81E+00	1.40E+03	2.49E+03	1.47E+01
1.86E+00	1.43E+03	2.56E+03	1.50E+01
1.92E+00	1.46E+03	2.64E+03	1.54E+01
1.97E+00	1.49E+03	2.71E+03	1.57E+01
2.03E+00	1.52E+03	2.79E+03	1.60E+01
2.09E+00	1.56E+03	2.87E+03	1.64E+01
2.16E+00	1.59E+03	2.95E+03	1.67E+01
2.22E+00	1.62E+03	3.03E+03	1.71E+01
2.29E+00	1.66E+03	3.12E+03	1.75E+01
2.36E+00	1.70E+03	3.21E+03	1.79E+01
2.43E+00	1.73E+03	3.30E+03	1.82E+01
2.50E+00	1.77E+03	3.40E+03	1.86E+01
2.58E+00	1.81E+03	3.49E+03	1.91E+01
2.65E+00	1.85E+03	3.59E+03	1.95E+01

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Nongestational Lifetime			
Intake (ng/kg/day)	**Fat (ng/kg)**	**Body Burden (ng/kg)**	**Blood (ng/kg)**
2.73E+00	1.89E+03	3.70E+03	1.99E+01
2.82E+00	1.93E+03	3.80E+03	2.04E+01
2.90E+00	1.98E+03	3.91E+03	2.08E+01
2.99E+00	2.02E+03	4.03E+03	2.13E+01
3.08E+00	2.07E+03	4.14E+03	2.17E+01
3.17E+00	2.11E+03	4.26E+03	2.22E+01
3.26E+00	2.16E+03	4.38E+03	2.27E+01
3.36E+00	2.21E+03	4.51E+03	2.32E+01
3.46E+00	2.26E+03	4.64E+03	2.38E+01
3.57E+00	2.31E+03	4.77E+03	2.43E+01
3.67E+00	2.36E+03	4.91E+03	2.49E+01
3.78E+00	2.42E+03	5.05E+03	2.54E+01
3.90E+00	2.47E+03	5.20E+03	2.60E+01
4.01E+00	2.53E+03	5.35E+03	2.66E+01
4.13E+00	2.58E+03	5.50E+03	2.72E+01
4.26E+00	2.64E+03	5.66E+03	2.78E+01
4.39E+00	2.70E+03	5.83E+03	2.85E+01
4.52E+00	2.77E+03	6.00E+03	2.91E+01
4.65E+00	2.83E+03	6.17E+03	2.98E+01
4.79E+00	2.90E+03	6.35E+03	3.05E+01
4.94E+00	2.96E+03	6.53E+03	3.12E+01
5.08E+00	3.03E+03	6.72E+03	3.19E+01
5.24E+00	3.10E+03	6.92E+03	3.27E+01
5.39E+00	3.18E+03	7.12E+03	3.34E+01
5.56E+00	3.25E+03	7.33E+03	3.42E+01
5.72E+00	3.33E+03	7.54E+03	3.50E+01
5.89E+00	3.41E+03	7.76E+03	3.58E+01
6.07E+00	3.49E+03	7.98E+03	3.67E+01
6.25E+00	3.57E+03	8.22E+03	3.76E+01

Nongestational Lifetime			
Intake (ng/kg/day)	**Fat (ng/kg)**	**Body Burden (ng/kg)**	**Blood (ng/kg)**
6.44E+00	3.65E+03	8.45E+03	3.85E+01
6.63E+00	3.74E+03	8.70E+03	3.94E+01
6.83E+00	3.83E+03	8.95E+03	4.03E+01
7.04E+00	3.92E+03	9.21E+03	4.13E+01
7.25E+00	4.02E+03	9.48E+03	4.23E+01
7.47E+00	4.11E+03	9.76E+03	4.33E+01
7.69E+00	4.21E+03	1.00E+04	4.43E+01
7.92E+00	4.32E+03	1.03E+04	4.54E+01
8.16E+00	4.42E+03	1.06E+04	4.65E+01
8.40E+00	4.53E+03	1.10E+04	4.77E+01
8.66E+00	4.64E+03	1.13E+04	4.88E+01
8.92E+00	4.75E+03	1.16E+04	5.00E+01
9.18E+00	4.87E+03	1.19E+04	5.13E+01
9.46E+00	4.99E+03	1.23E+04	5.25E+01
9.74E+00	5.11E+03	1.26E+04	5.38E+01
1.00E+01	5.22E+03	1.30E+04	5.50E+01
1.00E+01	5.24E+03	1.30E+04	5.51E+01
1.34E+01	6.64E+03	1.72E+04	6.99E+01
1.67E+01	8.04E+03	2.14E+04	8.47E+01
2.00E+01	9.45E+03	2.56E+04	9.94E+01
2.33E+01	1.08E+04	2.97E+04	1.14E+02
2.67E+01	1.22E+04	3.39E+04	1.28E+02
3.00E+01	1.36E+04	3.81E+04	1.43E+02
3.33E+01	1.49E+04	4.22E+04	1.57E+02
3.67E+01	1.63E+04	4.63E+04	1.72E+02
4.00E+01	1.77E+04	5.05E+04	1.86E+02
4.33E+01	1.90E+04	5.46E+04	2.00E+02
4.67E+01	2.04E+04	5.87E+04	2.15E+02
5.00E+01	2.17E+04	6.28E+04	2.29E+02

Nongestational Lifetime			
Intake (ng/kg/day)	**Fat (ng/kg)**	**Body Burden (ng/kg)**	**Blood (ng/kg)**
5.33E+01	2.31E+04	6.69E+04	2.43E+02
5.67E+01	2.45E+04	7.10E+04	2.57E+02
6.00E+01	2.58E+04	7.51E+04	2.72E+02
6.33E+01	2.72E+04	7.92E+04	2.86E+02
6.67E+01	2.85E+04	8.32E+04	3.00E+02
7.00E+01	2.99E+04	8.73E+04	3.14E+02
7.33E+01	3.12E+04	9.13E+04	3.29E+02
7.67E+01	3.26E+04	9.54E+04	3.43E+02
8.00E+01	3.39E+04	9.94E+04	3.57E+02
8.33E+01	3.53E+04	1.03E+05	3.71E+02
8.67E+01	3.66E+04	1.07E+05	3.86E+02
9.00E+01	3.80E+04	1.12E+05	4.00E+02
9.33E+01	3.94E+04	1.16E+05	4.14E+02
9.67E+01	4.07E+04	1.20E+05	4.28E+02
1.00E+02	4.21E+04	1.24E+05	4.43E+02

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C.4.2. Nongestational 5-Year Average

Non-gestational 5-year Average			
Intake (ng/kg/day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.00E-09	5.18E-05	1.87E-05	5.45E-07
1.33E-09	6.90E-05	2.50E-05	7.26E-07
1.67E-09	8.62E-05	3.12E-05	9.07E-07
2.00E-09	1.03E-04	3.74E-05	1.09E-06
2.33E-09	1.21E-04	4.36E-05	1.27E-06
2.67E-09	1.38E-04	4.99E-05	1.45E-06
3.00E-09	1.55E-04	5.61E-05	1.63E-06
3.33E-09	1.72E-04	6.23E-05	1.81E-06
3.67E-09	1.90E-04	6.86E-05	1.99E-06
4.00E-09	2.07E-04	7.48E-05	2.17E-06
4.33E-09	2.24E-04	8.10E-05	2.36E-06
4.67E-09	2.41E-04	8.72E-05	2.54E-06
5.00E-09	2.58E-04	9.35E-05	2.72E-06
5.33E-09	2.76E-04	9.97E-05	2.90E-06
5.67E-09	2.93E-04	1.06E-04	3.08E-06
6.00E-09	3.10E-04	1.12E-04	3.26E-06
6.33E-09	3.27E-04	1.18E-04	3.44E-06
6.67E-09	3.44E-04	1.25E-04	3.62E-06
7.00E-09	3.61E-04	1.31E-04	3.80E-06
7.33E-09	3.79E-04	1.37E-04	3.98E-06
7.67E-09	3.96E-04	1.43E-04	4.16E-06
8.00E-09	4.13E-04	1.49E-04	4.34E-06
8.33E-09	4.30E-04	1.56E-04	4.52E-06
8.67E-09	4.47E-04	1.62E-04	4.70E-06
9.00E-09	4.65E-04	1.68E-04	4.89E-06
9.33E-09	4.82E-04	1.74E-04	5.07E-06
9.67E-09	4.99E-04	1.80E-04	5.25E-06
1.00E-08	5.16E-04	1.87E-04	5.43E-06
1.33E-08	6.87E-04	2.48E-04	7.22E-06
1.67E-08	8.57E-04	3.10E-04	9.01E-06
2.00E-08	1.03E-03	3.72E-04	1.08E-05
2.33E-08	1.20E-03	4.34E-04	1.26E-05
2.67E-08	1.37E-03	4.96E-04	1.44E-05
3.00E-08	1.54E-03	5.57E-04	1.62E-05
3.33E-08	1.71E-03	6.19E-04	1.80E-05

Non-gestational 5-year Average			
Intake (ng/kg/day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
3.67E-08	1.88E-03	6.81E-04	1.98E-05
4.00E-08	2.05E-03	7.43E-04	2.16E-05
4.33E-08	2.22E-03	8.04E-04	2.34E-05
4.67E-08	2.39E-03	8.66E-04	2.51E-05
5.00E-08	2.56E-03	9.28E-04	2.69E-05
5.33E-08	2.73E-03	9.89E-04	2.87E-05
5.67E-08	2.90E-03	1.05E-03	3.05E-05
6.00E-08	3.07E-03	1.11E-03	3.23E-05
6.33E-08	3.24E-03	1.17E-03	3.40E-05
6.67E-08	3.41E-03	1.23E-03	3.58E-05
7.00E-08	3.57E-03	1.30E-03	3.76E-05
7.33E-08	3.74E-03	1.36E-03	3.94E-05
7.67E-08	3.91E-03	1.42E-03	4.11E-05
8.00E-08	4.08E-03	1.48E-03	4.29E-05
8.33E-08	4.25E-03	1.54E-03	4.47E-05
8.67E-08	4.42E-03	1.60E-03	4.65E-05
9.00E-08	4.59E-03	1.66E-03	4.82E-05
9.33E-08	4.76E-03	1.72E-03	5.00E-05
9.67E-08	4.93E-03	1.79E-03	5.18E-05
1.00E-07	5.09E-03	1.85E-03	5.36E-05
1.33E-07	6.74E-03	2.45E-03	7.09E-05
1.67E-07	8.39E-03	3.05E-03	8.82E-05
2.00E-07	1.00E-02	3.65E-03	1.06E-04
2.33E-07	1.17E-02	4.25E-03	1.23E-04
2.67E-07	1.33E-02	4.85E-03	1.40E-04
3.00E-07	1.50E-02	5.45E-03	1.57E-04
3.33E-07	1.66E-02	6.05E-03	1.75E-04
3.67E-07	1.83E-02	6.65E-03	1.92E-04
4.00E-07	1.99E-02	7.25E-03	2.09E-04
4.33E-07	2.16E-02	7.85E-03	2.27E-04
4.67E-07	2.32E-02	8.45E-03	2.44E-04
5.00E-07	2.49E-02	9.05E-03	2.61E-04
5.33E-07	2.64E-02	9.63E-03	2.78E-04
5.66E-07	2.80E-02	1.02E-02	2.94E-04
5.99E-07	2.96E-02	1.08E-02	3.11E-04
6.33E-07	3.11E-02	1.14E-02	3.28E-04
6.66E-07	3.27E-02	1.19E-02	3.44E-04
6.99E-07	3.43E-02	1.25E-02	3.61E-04

Non-gestational 5-year Average			
Intake (ng/kg/day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
7.32E-07	3.59E-02	1.31E-02	3.77E-04
7.65E-07	3.74E-02	1.37E-02	3.94E-04
7.98E-07	3.90E-02	1.42E-02	4.10E-04
8.32E-07	4.06E-02	1.48E-02	4.27E-04
8.65E-07	4.22E-02	1.54E-02	4.43E-04
8.98E-07	4.37E-02	1.60E-02	4.60E-04
9.31E-07	4.53E-02	1.66E-02	4.77E-04
9.64E-07	4.69E-02	1.71E-02	4.93E-04
9.97E-07	4.85E-02	1.77E-02	5.10E-04
1.01E-06	4.92E-02	1.80E-02	5.17E-04
1.03E-06	4.99E-02	1.82E-02	5.24E-04
1.04E-06	5.06E-02	1.85E-02	5.32E-04
1.06E-06	5.13E-02	1.88E-02	5.40E-04
1.07E-06	5.20E-02	1.90E-02	5.47E-04
1.09E-06	5.28E-02	1.93E-02	5.55E-04
1.11E-06	5.35E-02	1.96E-02	5.63E-04
1.12E-06	5.43E-02	1.99E-02	5.71E-04
1.14E-06	5.51E-02	2.01E-02	5.79E-04
1.16E-06	5.59E-02	2.04E-02	5.88E-04
1.17E-06	5.67E-02	2.07E-02	5.96E-04
1.19E-06	5.75E-02	2.10E-02	6.05E-04
1.21E-06	5.83E-02	2.13E-02	6.13E-04
1.23E-06	5.92E-02	2.16E-02	6.22E-04
1.24E-06	6.00E-02	2.20E-02	6.31E-04
1.26E-06	6.09E-02	2.23E-02	6.40E-04
1.28E-06	6.17E-02	2.26E-02	6.49E-04
1.30E-06	6.26E-02	2.29E-02	6.58E-04
1.32E-06	6.35E-02	2.32E-02	6.68E-04
1.34E-06	6.44E-02	2.36E-02	6.77E-04
1.36E-06	6.53E-02	2.39E-02	6.87E-04
1.38E-06	6.63E-02	2.43E-02	6.97E-04
1.40E-06	6.72E-02	2.46E-02	7.07E-04
1.42E-06	6.82E-02	2.50E-02	7.17E-04
1.44E-06	6.91E-02	2.53E-02	7.27E-04
1.46E-06	7.02E-02	2.57E-02	7.38E-04
1.49E-06	7.12E-02	2.61E-02	7.48E-04
1.53E-06	7.32E-02	2.68E-02	7.70E-04
1.58E-06	7.53E-02	2.76E-02	7.92E-04

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Non-gestational 5-year Average			
Intake (ng/kg/ day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.62E-06	7.74E-02	2.84E-02	8.14E-04
1.67E-06	7.96E-02	2.92E-02	8.37E-04
1.72E-06	8.19E-02	3.00E-02	8.61E-04
1.77E-06	8.42E-02	3.09E-02	8.86E-04
1.83E-06	8.66E-02	3.18E-02	9.11E-04
1.88E-06	8.91E-02	3.27E-02	9.37E-04
1.94E-06	9.16E-02	3.36E-02	9.63E-04
2.00E-06	9.42E-02	3.46E-02	9.91E-04
2.06E-06	9.69E-02	3.56E-02	1.02E-03
2.12E-06	9.96E-02	3.66E-02	1.05E-03
2.18E-06	1.02E-01	3.77E-02	1.08E-03
2.25E-06	1.05E-01	3.87E-02	1.11E-03
2.32E-06	1.08E-01	3.98E-02	1.14E-03
2.39E-06	1.11E-01	4.10E-02	1.17E-03
2.46E-06	1.15E-01	4.21E-02	1.20E-03
2.53E-06	1.18E-01	4.33E-02	1.24E-03
2.61E-06	1.21E-01	4.46E-02	1.27E-03
2.68E-06	1.24E-01	4.58E-02	1.31E-03
2.76E-06	1.28E-01	4.71E-02	1.35E-03
2.85E-06	1.32E-01	4.85E-02	1.38E-03
2.93E-06	1.35E-01	4.98E-02	1.42E-03
3.02E-06	1.39E-01	5.13E-02	1.46E-03
3.11E-06	1.43E-01	5.27E-02	1.50E-03
3.21E-06	1.47E-01	5.42E-02	1.54E-03
3.30E-06	1.51E-01	5.57E-02	1.59E-03
3.40E-06	1.55E-01	5.73E-02	1.63E-03
3.50E-06	1.59E-01	5.89E-02	1.68E-03
3.61E-06	1.64E-01	6.05E-02	1.72E-03
3.72E-06	1.68E-01	6.22E-02	1.77E-03
3.83E-06	1.73E-01	6.40E-02	1.82E-03
3.94E-06	1.78E-01	6.58E-02	1.87E-03
4.06E-06	1.83E-01	6.76E-02	1.92E-03
4.18E-06	1.88E-01	6.95E-02	1.97E-03
4.31E-06	1.93E-01	7.15E-02	2.03E-03
4.44E-06	1.98E-01	7.34E-02	2.08E-03
4.57E-06	2.04E-01	7.55E-02	2.14E-03
4.71E-06	2.09E-01	7.76E-02	2.20E-03
4.85E-06	2.15E-01	7.98E-02	2.26E-03

Non-gestational 5-year Average			
Intake (ng/kg/ day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
4.99E-06	2.21E-01	8.20E-02	2.32E-03
5.14E-06	2.27E-01	8.42E-02	2.39E-03
5.30E-06	2.33E-01	8.66E-02	2.45E-03
5.46E-06	2.39E-01	8.90E-02	2.52E-03
5.62E-06	2.46E-01	9.14E-02	2.59E-03
5.79E-06	2.53E-01	9.39E-02	2.66E-03
5.96E-06	2.59E-01	9.65E-02	2.73E-03
6.14E-06	2.66E-01	9.92E-02	2.80E-03
6.33E-06	2.74E-01	1.02E-01	2.88E-03
6.52E-06	2.81E-01	1.05E-01	2.95E-03
6.71E-06	2.88E-01	1.07E-01	3.03E-03
6.91E-06	2.96E-01	1.10E-01	3.11E-03
7.12E-06	3.04E-01	1.13E-01	3.19E-03
7.33E-06	3.12E-01	1.16E-01	3.28E-03
7.55E-06	3.20E-01	1.19E-01	3.36E-03
7.78E-06	3.28E-01	1.23E-01	3.45E-03
8.01E-06	3.37E-01	1.26E-01	3.54E-03
8.25E-06	3.46E-01	1.29E-01	3.64E-03
8.50E-06	3.55E-01	1.33E-01	3.73E-03
8.76E-06	3.64E-01	1.36E-01	3.83E-03
9.02E-06	3.74E-01	1.40E-01	3.93E-03
9.29E-06	3.84E-01	1.44E-01	4.04E-03
9.57E-06	3.94E-01	1.48E-01	4.15E-03
9.86E-06	4.05E-01	1.52E-01	4.25E-03
1.02E-05	4.15E-01	1.56E-01	4.36E-03
1.05E-05	4.26E-01	1.60E-01	4.48E-03
1.08E-05	4.37E-01	1.64E-01	4.59E-03
1.11E-05	4.48E-01	1.68E-01	4.71E-03
1.14E-05	4.60E-01	1.73E-01	4.83E-03
1.18E-05	4.72E-01	1.78E-01	4.96E-03
1.21E-05	4.84E-01	1.82E-01	5.08E-03
1.25E-05	4.96E-01	1.87E-01	5.21E-03
1.29E-05	5.09E-01	1.92E-01	5.35E-03
1.32E-05	5.22E-01	1.97E-01	5.49E-03
1.36E-05	5.35E-01	2.02E-01	5.63E-03
1.41E-05	5.49E-01	2.08E-01	5.77E-03
1.45E-05	5.63E-01	2.13E-01	5.92E-03
1.49E-05	5.77E-01	2.18E-01	6.07E-03

Non-gestational 5-year Average			
Intake (ng/kg/ day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.54E-05	5.92E-01	2.24E-01	6.23E-03
1.58E-05	6.07E-01	2.30E-01	6.38E-03
1.63E-05	6.23E-01	2.36E-01	6.55E-03
1.68E-05	6.38E-01	2.42E-01	6.71E-03
1.73E-05	6.54E-01	2.49E-01	6.88E-03
1.78E-05	6.71E-01	2.55E-01	7.05E-03
1.83E-05	6.88E-01	2.62E-01	7.23E-03
1.89E-05	7.05E-01	2.69E-01	7.41E-03
1.95E-05	7.23E-01	2.75E-01	7.60E-03
2.00E-05	7.41E-01	2.83E-01	7.79E-03
2.06E-05	7.60E-01	2.90E-01	7.99E-03
2.13E-05	7.79E-01	2.97E-01	8.18E-03
2.19E-05	7.98E-01	3.05E-01	8.39E-03
2.25E-05	8.18E-01	3.13E-01	8.60E-03
2.32E-05	8.38E-01	3.21E-01	8.81E-03
2.39E-05	8.59E-01	3.29E-01	9.03E-03
2.46E-05	8.80E-01	3.38E-01	9.25E-03
2.54E-05	9.02E-01	3.46E-01	9.48E-03
2.61E-05	9.24E-01	3.55E-01	9.71E-03
2.69E-05	9.47E-01	3.64E-01	9.95E-03
2.77E-05	9.70E-01	3.73E-01	1.02E-02
2.86E-05	9.94E-01	3.83E-01	1.04E-02
2.94E-05	1.02E+00	3.92E-01	1.07E-02
3.03E-05	1.04E+00	4.02E-01	1.10E-02
3.12E-05	1.07E+00	4.12E-01	1.12E-02
3.21E-05	1.09E+00	4.23E-01	1.15E-02
3.31E-05	1.12E+00	4.35E-01	1.18E-02
3.41E-05	1.15E+00	4.46E-01	1.21E-02
3.51E-05	1.18E+00	4.57E-01	1.23E-02
3.62E-05	1.21E+00	4.68E-01	1.27E-02
3.73E-05	1.24E+00	4.80E-01	1.30E-02
3.84E-05	1.26E+00	4.92E-01	1.33E-02
3.95E-05	1.29E+00	5.04E-01	1.35E-02
4.07E-05	1.32E+00	5.14E-01	1.39E-02
4.19E-05	1.35E+00	5.26E-01	1.42E-02
4.32E-05	1.38E+00	5.39E-01	1.45E-02
4.45E-05	1.41E+00	5.52E-01	1.49E-02
4.58E-05	1.45E+00	5.66E-01	1.52E-02

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Non-gestational 5-year Average			
Intake (ng/kg/ day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
4.72E-05	1.48E+00	5.80E-01	1.56E-02
4.86E-05	1.52E+00	5.94E-01	1.59E-02
5.01E-05	1.55E+00	6.08E-01	1.63E-02
5.16E-05	1.59E+00	6.23E-01	1.67E-02
5.31E-05	1.62E+00	6.38E-01	1.71E-02
5.47E-05	1.66E+00	6.53E-01	1.75E-02
5.64E-05	1.70E+00	6.69E-01	1.79E-02
5.81E-05	1.74E+00	6.85E-01	1.83E-02
5.98E-05	1.78E+00	7.02E-01	1.87E-02
6.16E-05	1.82E+00	7.19E-01	1.91E-02
6.34E-05	1.86E+00	7.36E-01	1.96E-02
6.54E-05	1.90E+00	7.53E-01	2.00E-02
6.73E-05	1.95E+00	7.71E-01	2.05E-02
6.93E-05	1.99E+00	7.90E-01	2.09E-02
7.14E-05	2.04E+00	8.08E-01	2.14E-02
7.36E-05	2.06E+00	8.18E-01	2.16E-02
7.58E-05	2.11E+00	8.37E-01	2.21E-02
7.80E-05	2.15E+00	8.57E-01	2.26E-02
8.04E-05	2.20E+00	8.77E-01	2.31E-02
8.28E-05	2.25E+00	8.98E-01	2.36E-02
8.53E-05	2.30E+00	9.19E-01	2.42E-02
8.78E-05	2.35E+00	9.40E-01	2.47E-02
9.05E-05	2.40E+00	9.62E-01	2.52E-02
9.32E-05	2.46E+00	9.84E-01	2.58E-02
9.60E-05	2.51E+00	1.01E+00	2.64E-02
9.89E-05	2.57E+00	1.03E+00	2.69E-02
1.02E-04	2.62E+00	1.05E+00	2.75E-02
1.05E-04	2.68E+00	1.08E+00	2.81E-02
1.08E-04	2.74E+00	1.10E+00	2.88E-02
1.11E-04	2.80E+00	1.13E+00	2.94E-02
1.15E-04	2.86E+00	1.15E+00	3.00E-02
1.18E-04	2.92E+00	1.18E+00	3.07E-02
1.22E-04	2.98E+00	1.21E+00	3.13E-02
1.25E-04	3.05E+00	1.24E+00	3.20E-02
1.29E-04	3.11E+00	1.26E+00	3.27E-02
1.33E-04	3.18E+00	1.29E+00	3.34E-02
1.37E-04	3.25E+00	1.32E+00	3.41E-02
1.41E-04	3.32E+00	1.35E+00	3.48E-02

Non-gestational 5-year Average			
Intake (ng/kg/ day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.45E-04	3.45E+00	1.41E+00	3.62E-02
1.50E-04	3.46E+00	1.41E+00	3.63E-02
1.54E-04	3.53E+00	1.45E+00	3.71E-02
1.59E-04	3.67E+00	1.51E+00	3.86E-02
1.63E-04	3.75E+00	1.54E+00	3.94E-02
1.68E-04	3.77E+00	1.55E+00	3.96E-02
1.73E-04	3.86E+00	1.59E+00	4.06E-02
1.79E-04	3.95E+00	1.63E+00	4.15E-02
1.84E-04	4.04E+00	1.67E+00	4.24E-02
1.89E-04	4.13E+00	1.71E+00	4.33E-02
1.95E-04	4.22E+00	1.75E+00	4.43E-02
2.01E-04	4.31E+00	1.79E+00	4.52E-02
2.07E-04	4.44E+00	1.84E+00	4.66E-02
2.13E-04	4.49E+00	1.87E+00	4.72E-02
2.20E-04	4.59E+00	1.92E+00	4.82E-02
2.26E-04	4.72E+00	1.97E+00	4.95E-02
2.33E-04	4.81E+00	2.02E+00	5.05E-02
2.40E-04	4.91E+00	2.06E+00	5.16E-02
2.47E-04	5.00E+00	2.10E+00	5.24E-02
2.55E-04	5.10E+00	2.15E+00	5.35E-02
2.62E-04	5.21E+00	2.19E+00	5.47E-02
2.70E-04	5.33E+00	2.25E+00	5.60E-02
2.78E-04	5.44E+00	2.30E+00	5.71E-02
2.86E-04	5.55E+00	2.35E+00	5.83E-02
2.95E-04	5.66E+00	2.40E+00	5.94E-02
3.04E-04	5.78E+00	2.46E+00	6.07E-02
3.13E-04	5.90E+00	2.51E+00	6.19E-02
3.22E-04	6.02E+00	2.57E+00	6.32E-02
3.32E-04	6.14E+00	2.63E+00	6.44E-02
3.42E-04	6.26E+00	2.68E+00	6.57E-02
3.52E-04	6.39E+00	2.74E+00	6.71E-02
3.63E-04	6.52E+00	2.80E+00	6.84E-02
3.74E-04	6.65E+00	2.87E+00	6.98E-02
3.85E-04	6.78E+00	2.93E+00	7.12E-02
3.97E-04	6.92E+00	3.00E+00	7.26E-02
4.08E-04	7.06E+00	3.06E+00	7.41E-02
4.21E-04	7.20E+00	3.13E+00	7.56E-02
4.33E-04	7.34E+00	3.20E+00	7.71E-02

Non-gestational 5-year Average			
Intake (ng/kg/ day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
4.46E-04	7.49E+00	3.27E+00	7.86E-02
4.60E-04	7.64E+00	3.34E+00	8.02E-02
4.74E-04	7.79E+00	3.42E+00	8.18E-02
4.88E-04	7.95E+00	3.49E+00	8.34E-02
5.02E-04	8.10E+00	3.57E+00	8.50E-02
5.17E-04	8.26E+00	3.65E+00	8.67E-02
5.33E-04	8.43E+00	3.73E+00	8.84E-02
5.49E-04	8.59E+00	3.81E+00	9.02E-02
5.65E-04	8.76E+00	3.89E+00	9.19E-02
5.82E-04	8.93E+00	3.98E+00	9.37E-02
6.00E-04	9.11E+00	4.07E+00	9.56E-02
6.18E-04	9.29E+00	4.16E+00	9.74E-02
6.36E-04	9.47E+00	4.25E+00	9.94E-02
6.55E-04	9.65E+00	4.34E+00	1.01E-01
6.75E-04	9.84E+00	4.44E+00	1.03E-01
6.95E-04	1.00E+01	4.54E+00	1.05E-01
7.16E-04	1.02E+01	4.64E+00	1.07E-01
7.38E-04	1.04E+01	4.74E+00	1.09E-01
7.60E-04	1.06E+01	4.84E+00	1.12E-01
7.83E-04	1.08E+01	4.95E+00	1.14E-01
8.06E-04	1.10E+01	5.06E+00	1.16E-01
8.30E-04	1.13E+01	5.17E+00	1.18E-01
8.55E-04	1.15E+01	5.28E+00	1.20E-01
8.81E-04	1.17E+01	5.40E+00	1.23E-01
9.07E-04	1.19E+01	5.52E+00	1.25E-01
9.21E-04	1.20E+01	5.58E+00	1.26E-01
9.35E-04	1.22E+01	5.64E+00	1.27E-01
9.49E-04	1.30E+01	6.23E+00	1.37E-01
9.63E-04	1.38E+01	6.92E+00	1.45E-01
9.69E-04	1.43E+01	7.14E+00	1.50E-01
9.77E-04	1.48E+01	7.34E+00	1.55E-01
9.84E-04	1.52E+01	7.50E+00	1.59E-01
9.91E-04	1.55E+01	7.64E+00	1.63E-01
1.37E-03	1.56E+01	7.50E+00	1.63E-01
1.39E-03	1.57E+01	7.58E+00	1.65E-01
1.41E-03	1.59E+01	7.66E+00	1.66E-01
1.43E-03	1.60E+01	7.75E+00	1.68E-01
1.46E-03	1.62E+01	7.83E+00	1.69E-01

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Non-gestational 5-year Average			
Intake (ng/kg/ day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.48E-03	1.63E+01	7.92E+00	1.71E-01
1.50E-03	1.65E+01	8.00E+00	1.73E-01
1.52E-03	1.66E+01	8.09E+00	1.74E-01
1.54E-03	1.68E+01	8.18E+00	1.76E-01
1.57E-03	1.69E+01	8.27E+00	1.78E-01
1.59E-03	1.71E+01	8.36E+00	1.79E-01
1.61E-03	1.73E+01	8.46E+00	1.81E-01
1.64E-03	1.74E+01	8.55E+00	1.83E-01
1.66E-03	1.76E+01	8.64E+00	1.84E-01
1.69E-03	1.78E+01	8.74E+00	1.86E-01
1.71E-03	1.79E+01	8.83E+00	1.88E-01
1.74E-03	1.81E+01	8.93E+00	1.90E-01
1.76E-03	1.83E+01	9.03E+00	1.92E-01
1.79E-03	1.84E+01	9.13E+00	1.93E-01
1.82E-03	1.86E+01	9.23E+00	1.95E-01
1.84E-03	1.88E+01	9.33E+00	1.97E-01
1.87E-03	1.91E+01	9.53E+00	2.00E-01
1.90E-03	1.98E+01	1.01E+01	2.08E-01
1.93E-03	2.05E+01	1.08E+01	2.14E-01
1.96E-03	2.05E+01	1.05E+01	2.14E-01
2.27E-03	2.14E+01	1.09E+01	2.25E-01
2.34E-03	2.18E+01	1.11E+01	2.29E-01
2.41E-03	2.22E+01	1.14E+01	2.33E-01
2.48E-03	2.26E+01	1.16E+01	2.37E-01
2.55E-03	2.31E+01	1.19E+01	2.42E-01
2.63E-03	2.35E+01	1.22E+01	2.46E-01
2.71E-03	2.39E+01	1.24E+01	2.51E-01
2.79E-03	2.44E+01	1.27E+01	2.56E-01
2.87E-03	2.49E+01	1.30E+01	2.61E-01
2.96E-03	2.53E+01	1.33E+01	2.66E-01
3.05E-03	2.58E+01	1.36E+01	2.71E-01
3.14E-03	2.63E+01	1.39E+01	2.76E-01
3.23E-03	2.68E+01	1.42E+01	2.81E-01
3.33E-03	2.73E+01	1.45E+01	2.86E-01
3.43E-03	2.78E+01	1.49E+01	2.91E-01
3.53E-03	2.83E+01	1.52E+01	2.97E-01
3.64E-03	2.88E+01	1.55E+01	3.02E-01
3.75E-03	2.96E+01	1.61E+01	3.10E-01

Non-gestational 5-year Average			
Intake (ng/kg/ day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
3.81E-03	2.99E+01	1.63E+01	3.14E-01
3.86E-03	3.00E+01	1.63E+01	3.14E-01
4.22E-03	3.04E+01	1.66E+01	3.19E-01
4.35E-03	3.10E+01	1.69E+01	3.25E-01
4.48E-03	3.16E+01	1.73E+01	3.31E-01
4.61E-03	3.21E+01	1.77E+01	3.37E-01
4.75E-03	3.28E+01	1.81E+01	3.44E-01
4.89E-03	3.34E+01	1.86E+01	3.50E-01
5.04E-03	3.44E+01	1.94E+01	3.60E-01
5.19E-03	3.57E+01	2.06E+01	3.74E-01
5.35E-03	3.72E+01	2.12E+01	3.90E-01
5.51E-03	3.81E+01	2.17E+01	3.99E-01
5.67E-03	3.88E+01	2.23E+01	4.07E-01
5.84E-03	3.95E+01	2.28E+01	4.14E-01
5.93E-03	3.98E+01	2.30E+01	4.18E-01
6.02E-03	4.00E+01	2.33E+01	4.20E-01
6.20E-03	4.10E+01	2.38E+01	4.30E-01
6.38E-03	4.18E+01	2.44E+01	4.38E-01
6.57E-03	4.26E+01	2.49E+01	4.46E-01
6.77E-03	4.34E+01	2.55E+01	4.55E-01
6.98E-03	4.42E+01	2.61E+01	4.63E-01
7.18E-03	4.50E+01	2.67E+01	4.72E-01
7.40E-03	4.59E+01	2.73E+01	4.81E-01
7.51E-03	4.63E+01	2.77E+01	4.85E-01
7.62E-03	4.66E+01	2.78E+01	4.88E-01
7.85E-03	4.71E+01	2.81E+01	4.94E-01
8.09E-03	4.72E+01	2.79E+01	4.95E-01
8.33E-03	4.74E+01	2.83E+01	4.97E-01
8.58E-03	4.93E+01	2.99E+01	5.17E-01
8.71E-03	4.98E+01	3.03E+01	5.22E-01
8.84E-03	5.03E+01	3.06E+01	5.27E-01
9.10E-03	5.13E+01	3.15E+01	5.38E-01
9.37E-03	5.23E+01	3.22E+01	5.49E-01
9.66E-03	5.33E+01	3.29E+01	5.59E-01
9.94E-03	5.44E+01	3.38E+01	5.70E-01
1.02E-02	5.54E+01	3.46E+01	5.81E-01
1.06E-02	5.64E+01	3.54E+01	5.92E-01
1.09E-02	5.75E+01	3.62E+01	6.03E-01

Non-gestational 5-year Average			
Intake (ng/kg/ day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.12E-02	5.86E+01	3.71E+01	6.14E-01
1.15E-02	5.96E+01	3.79E+01	6.25E-01
1.19E-02	6.05E+01	3.85E+01	6.35E-01
1.22E-02	6.14E+01	3.92E+01	6.43E-01
1.26E-02	6.24E+01	4.01E+01	6.54E-01
1.30E-02	6.38E+01	4.15E+01	6.69E-01
1.34E-02	6.56E+01	4.31E+01	6.87E-01
1.38E-02	6.74E+01	4.42E+01	7.07E-01
1.42E-02	6.87E+01	4.53E+01	7.20E-01
1.46E-02	6.94E+01	4.59E+01	7.28E-01
1.50E-02	7.06E+01	4.69E+01	7.40E-01
1.55E-02	7.19E+01	4.78E+01	7.54E-01
1.60E-02	7.30E+01	4.87E+01	7.66E-01
1.64E-02	7.38E+01	4.96E+01	7.74E-01
1.69E-02	7.55E+01	5.11E+01	7.92E-01
1.74E-02	7.69E+01	5.23E+01	8.07E-01
1.80E-02	7.84E+01	5.36E+01	8.22E-01
1.85E-02	7.99E+01	5.49E+01	8.37E-01
1.91E-02	8.13E+01	5.62E+01	8.53E-01
1.96E-02	8.29E+01	5.75E+01	8.69E-01
2.02E-02	8.44E+01	5.89E+01	8.85E-01
2.08E-02	8.60E+01	6.03E+01	9.01E-01
2.14E-02	8.76E+01	6.18E+01	9.18E-01
2.21E-02	8.92E+01	6.32E+01	9.35E-01
2.28E-02	9.09E+01	6.48E+01	9.53E-01
2.34E-02	9.26E+01	6.63E+01	9.71E-01
2.41E-02	9.44E+01	6.80E+01	9.89E-01
2.49E-02	9.64E+01	6.98E+01	1.01E+00
2.56E-02	9.79E+01	7.13E+01	1.03E+00
2.64E-02	9.98E+01	7.30E+01	1.05E+00
2.72E-02	1.02E+02	7.48E+01	1.07E+00
2.80E-02	1.04E+02	7.66E+01	1.09E+00
2.88E-02	1.06E+02	7.85E+01	1.11E+00
2.97E-02	1.07E+02	8.04E+01	1.13E+00
3.06E-02	1.10E+02	8.28E+01	1.15E+00
3.15E-02	1.12E+02	8.51E+01	1.17E+00
3.24E-02	1.14E+02	8.69E+01	1.20E+00
3.34E-02	1.16E+02	8.88E+01	1.22E+00

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Non-gestational 5-year Average			
Intake (ng/kg/day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
3.44E-02	1.18E+02	9.08E+01	1.24E+00
3.54E-02	1.20E+02	9.28E+01	1.26E+00
3.65E-02	1.22E+02	9.47E+01	1.28E+00
3.76E-02	1.24E+02	9.73E+01	1.30E+00
3.87E-02	1.27E+02	9.96E+01	1.33E+00
3.99E-02	1.29E+02	1.02E+02	1.35E+00
4.11E-02	1.32E+02	1.04E+02	1.38E+00
4.23E-02	1.34E+02	1.07E+02	1.40E+00
4.36E-02	1.37E+02	1.10E+02	1.43E+00
4.49E-02	1.40E+02	1.13E+02	1.47E+00
4.63E-02	1.43E+02	1.16E+02	1.49E+00
4.76E-02	1.45E+02	1.19E+02	1.52E+00
4.91E-02	1.48E+02	1.22E+02	1.55E+00
5.05E-02	1.51E+02	1.25E+02	1.58E+00
5.21E-02	1.53E+02	1.28E+02	1.61E+00
5.36E-02	1.56E+02	1.31E+02	1.64E+00
5.52E-02	1.59E+02	1.34E+02	1.67E+00
5.69E-02	1.62E+02	1.38E+02	1.70E+00
5.86E-02	1.65E+02	1.41E+02	1.73E+00
6.03E-02	1.69E+02	1.45E+02	1.77E+00
6.22E-02	1.72E+02	1.48E+02	1.80E+00
6.40E-02	1.74E+02	1.52E+02	1.83E+00
6.59E-02	1.78E+02	1.55E+02	1.86E+00
6.79E-02	1.81E+02	1.59E+02	1.90E+00
7.00E-02	1.84E+02	1.63E+02	1.93E+00
7.21E-02	1.88E+02	1.67E+02	1.97E+00
7.42E-02	1.91E+02	1.71E+02	2.01E+00
7.64E-02	1.95E+02	1.76E+02	2.05E+00
7.87E-02	1.99E+02	1.81E+02	2.09E+00
8.11E-02	2.03E+02	1.86E+02	2.13E+00
8.35E-02	2.07E+02	1.90E+02	2.17E+00
8.60E-02	2.11E+02	1.95E+02	2.21E+00
8.86E-02	2.15E+02	2.00E+02	2.25E+00
9.13E-02	2.19E+02	2.05E+02	2.30E+00
9.40E-02	2.23E+02	2.10E+02	2.34E+00
9.68E-02	2.27E+02	2.16E+02	2.38E+00
9.97E-02	2.32E+02	2.22E+02	2.43E+00
1.03E-01	2.36E+02	2.27E+02	2.48E+00

Non-gestational 5-year Average			
Intake (ng/kg/day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.06E-01	2.41E+02	2.33E+02	2.52E+00
1.09E-01	2.45E+02	2.39E+02	2.57E+00
1.12E-01	2.50E+02	2.44E+02	2.62E+00
1.16E-01	2.55E+02	2.51E+02	2.67E+00
1.19E-01	2.60E+02	2.57E+02	2.72E+00
1.23E-01	2.65E+02	2.64E+02	2.77E+00
1.26E-01	2.70E+02	2.71E+02	2.83E+00
1.30E-01	2.75E+02	2.78E+02	2.88E+00
1.34E-01	2.80E+02	2.86E+02	2.94E+00
1.38E-01	2.86E+02	2.93E+02	3.00E+00
1.42E-01	2.92E+02	3.01E+02	3.06E+00
1.46E-01	2.97E+02	3.09E+02	3.11E+00
1.51E-01	3.03E+02	3.16E+02	3.17E+00
1.55E-01	3.08E+02	3.24E+02	3.23E+00
1.60E-01	3.14E+02	3.33E+02	3.29E+00
1.65E-01	3.20E+02	3.42E+02	3.36E+00
1.70E-01	3.27E+02	3.51E+02	3.42E+00
1.75E-01	3.33E+02	3.60E+02	3.49E+00
1.80E-01	3.39E+02	3.69E+02	3.56E+00
1.86E-01	3.46E+02	3.79E+02	3.63E+00
1.91E-01	3.53E+02	3.89E+02	3.70E+00
1.97E-01	3.60E+02	3.99E+02	3.77E+00
2.03E-01	3.66E+02	4.09E+02	3.84E+00
2.09E-01	3.73E+02	4.20E+02	3.91E+00
2.15E-01	3.81E+02	4.31E+02	3.99E+00
2.22E-01	3.88E+02	4.43E+02	4.07E+00
2.28E-01	3.96E+02	4.55E+02	4.15E+00
2.35E-01	4.03E+02	4.67E+02	4.23E+00
2.42E-01	4.11E+02	4.79E+02	4.31E+00
2.49E-01	4.20E+02	4.92E+02	4.40E+00
2.57E-01	4.28E+02	5.05E+02	4.48E+00
2.65E-01	4.36E+02	5.19E+02	4.57E+00
2.72E-01	4.45E+02	5.32E+02	4.66E+00
2.81E-01	4.53E+02	5.46E+02	4.75E+00
2.89E-01	4.62E+02	5.61E+02	4.84E+00
2.98E-01	4.71E+02	5.75E+02	4.93E+00
3.07E-01	4.80E+02	5.91E+02	5.03E+00
3.16E-01	4.90E+02	6.07E+02	5.13E+00

Non-gestational 5-year Average			
Intake (ng/kg/day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
3.25E-01	4.99E+02	6.23E+02	5.23E+00
3.35E-01	5.09E+02	6.40E+02	5.34E+00
3.45E-01	5.19E+02	6.57E+02	5.44E+00
3.56E-01	5.30E+02	6.75E+02	5.55E+00
3.66E-01	5.40E+02	6.93E+02	5.66E+00
3.77E-01	5.51E+02	7.12E+02	5.77E+00
3.89E-01	5.62E+02	7.31E+02	5.89E+00
4.00E-01	5.73E+02	7.51E+02	6.00E+00
4.12E-01	5.84E+02	7.71E+02	6.12E+00
4.25E-01	5.96E+02	7.92E+02	6.25E+00
4.37E-01	6.08E+02	8.13E+02	6.37E+00
4.50E-01	6.20E+02	8.35E+02	6.50E+00
4.64E-01	6.32E+02	8.58E+02	6.63E+00
4.92E-01	6.58E+02	9.05E+02	6.89E+00
5.07E-01	6.71E+02	9.29E+02	7.03E+00
5.22E-01	6.85E+02	9.55E+02	7.17E+00
5.54E-01	7.12E+02	1.01E+03	7.46E+00
5.71E-01	7.27E+02	1.04E+03	7.61E+00
5.88E-01	7.41E+02	1.06E+03	7.77E+00
6.05E-01	7.56E+02	1.09E+03	7.92E+00
6.23E-01	7.71E+02	1.12E+03	8.08E+00
6.61E-01	8.03E+02	1.18E+03	8.41E+00
6.81E-01	8.19E+02	1.22E+03	8.58E+00
7.02E-01	8.36E+02	1.25E+03	8.76E+00
7.23E-01	8.53E+02	1.28E+03	8.94E+00
7.44E-01	8.70E+02	1.32E+03	9.12E+00
7.67E-01	8.88E+02	1.36E+03	9.31E+00
7.90E-01	9.06E+02	1.39E+03	9.50E+00
8.13E-01	9.25E+02	1.43E+03	9.69E+00
8.38E-01	9.44E+02	1.47E+03	9.89E+00
8.63E-01	9.63E+02	1.51E+03	1.01E+01
8.89E-01	9.83E+02	1.55E+03	1.03E+01
9.16E-01	1.00E+03	1.60E+03	1.05E+01
9.43E-01	1.02E+03	1.64E+03	1.07E+01
9.71E-01	1.05E+03	1.69E+03	1.10E+01
1.00E+00	1.07E+03	1.73E+03	1.12E+01
1.06E+00	1.11E+03	1.83E+03	1.16E+01
1.09E+00	1.14E+03	1.88E+03	1.19E+01

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Non-gestational 5-year Average			
Intake (ng/kg/ day)	**Fat (ng/kg)**	**Body Burden (ng/kg)**	**Blood (ng/kg)**
1.13E+00	1.16E+03	1.94E+03	1.21E+01
1.16E+00	1.18E+03	1.99E+03	1.24E+01
1.19E+00	1.21E+03	2.04E+03	1.27E+01
1.23E+00	1.23E+03	2.10E+03	1.29E+01
1.27E+00	1.26E+03	2.16E+03	1.32E+01
1.31E+00	1.29E+03	2.22E+03	1.35E+01
1.34E+00	1.31E+03	2.28E+03	1.38E+01
1.38E+00	1.34E+03	2.35E+03	1.40E+01
1.43E+00	1.37E+03	2.41E+03	1.43E+01
1.47E+00	1.40E+03	2.48E+03	1.46E+01
1.51E+00	1.43E+03	2.55E+03	1.50E+01
1.56E+00	1.46E+03	2.62E+03	1.53E+01
1.61E+00	1.49E+03	2.69E+03	1.56E+01
1.65E+00	1.52E+03	2.77E+03	1.59E+01
1.70E+00	1.55E+03	2.85E+03	1.63E+01
1.75E+00	1.59E+03	2.93E+03	1.66E+01
1.81E+00	1.62E+03	3.01E+03	1.70E+01
1.86E+00	1.66E+03	3.10E+03	1.74E+01
1.92E+00	1.69E+03	3.18E+03	1.77E+01
1.97E+00	1.73E+03	3.27E+03	1.81E+01
2.03E+00	1.77E+03	3.37E+03	1.85E+01
2.09E+00	1.80E+03	3.46E+03	1.89E+01
2.16E+00	1.84E+03	3.56E+03	1.93E+01
2.22E+00	1.88E+03	3.66E+03	1.97E+01
2.29E+00	1.92E+03	3.76E+03	2.02E+01
2.36E+00	1.97E+03	3.87E+03	2.06E+01
2.43E+00	2.01E+03	3.98E+03	2.11E+01
2.50E+00	2.05E+03	4.09E+03	2.15E+01
2.58E+00	2.10E+03	4.21E+03	2.20E+01
2.65E+00	2.15E+03	4.33E+03	2.25E+01
2.73E+00	2.19E+03	4.45E+03	2.30E+01
2.82E+00	2.24E+03	4.58E+03	2.35E+01
2.90E+00	2.29E+03	4.71E+03	2.40E+01
2.99E+00	2.34E+03	4.85E+03	2.46E+01
3.08E+00	2.40E+03	4.98E+03	2.51E+01
3.17E+00	2.45E+03	5.13E+03	2.57E+01
3.26E+00	2.51E+03	5.27E+03	2.63E+01
3.36E+00	2.56E+03	5.42E+03	2.69E+01

Non-gestational 5-year Average			
Intake (ng/kg/ day)	**Fat (ng/kg)**	**Body Burden (ng/kg)**	**Blood (ng/kg)**
3.46E+00	2.62E+03	5.58E+03	2.75E+01
3.57E+00	2.68E+03	5.74E+03	2.81E+01
3.67E+00	2.74E+03	5.90E+03	2.87E+01
3.78E+00	2.80E+03	6.07E+03	2.94E+01
3.90E+00	2.87E+03	6.25E+03	3.01E+01
4.01E+00	2.93E+03	6.42E+03	3.07E+01
4.13E+00	3.00E+03	6.61E+03	3.15E+01
4.26E+00	3.07E+03	6.80E+03	3.22E+01
4.39E+00	3.14E+03	6.99E+03	3.29E+01
4.52E+00	3.22E+03	7.20E+03	3.37E+01
4.65E+00	3.29E+03	7.40E+03	3.45E+01
4.79E+00	3.37E+03	7.62E+03	3.53E+01
4.94E+00	3.45E+03	7.83E+03	3.61E+01
5.08E+00	3.53E+03	8.06E+03	3.69E+01
5.24E+00	3.61E+03	8.29E+03	3.78E+01
5.39E+00	3.69E+03	8.53E+03	3.87E+01
5.56E+00	3.78E+03	8.78E+03	3.96E+01
5.72E+00	3.87E+03	9.03E+03	4.06E+01
5.89E+00	3.96E+03	9.29E+03	4.15E+01
6.07E+00	4.06E+03	9.56E+03	4.25E+01
6.25E+00	4.15E+03	9.84E+03	4.35E+01
6.44E+00	4.25E+03	1.01E+04	4.46E+01
6.63E+00	4.36E+03	1.04E+04	4.56E+01
6.83E+00	4.46E+03	1.07E+04	4.67E+01
7.04E+00	4.57E+03	1.10E+04	4.79E+01
7.25E+00	4.68E+03	1.13E+04	4.90E+01
7.47E+00	4.79E+03	1.17E+04	5.02E+01
7.69E+00	4.91E+03	1.20E+04	5.15E+01
7.92E+00	5.03E+03	1.24E+04	5.27E+01
8.16E+00	5.15E+03	1.27E+04	5.40E+01
8.40E+00	5.28E+03	1.31E+04	5.53E+01
8.66E+00	5.41E+03	1.35E+04	5.67E+01
8.92E+00	5.54E+03	1.39E+04	5.81E+01
9.18E+00	5.68E+03	1.43E+04	5.95E+01
9.46E+00	5.82E+03	1.47E+04	6.10E+01
9.74E+00	5.97E+03	1.51E+04	6.25E+01
1.00E+01	6.10E+03	1.55E+04	6.39E+01
1.00E+01	6.12E+03	1.56E+04	6.41E+01

Non-gestational 5-year Average			
Intake (ng/kg/ day)	**Fat (ng/kg)**	**Body Burden (ng/kg)**	**Blood (ng/kg)**
1.34E+01	7.77E+03	2.05E+04	8.15E+01
1.67E+01	9.43E+03	2.55E+04	9.88E+01
2.00E+01	1.11E+04	3.05E+04	1.16E+02
2.33E+01	1.27E+04	3.54E+04	1.33E+02
2.67E+01	1.43E+04	4.03E+04	1.50E+02
3.00E+01	1.60E+04	4.53E+04	1.67E+02
3.33E+01	1.76E+04	5.02E+04	1.84E+02
3.67E+01	1.92E+04	5.51E+04	2.01E+02
4.00E+01	2.08E+04	6.00E+04	2.18E+02
4.33E+01	2.24E+04	6.49E+04	2.35E+02
4.67E+01	2.40E+04	6.97E+04	2.52E+02
5.00E+01	2.57E+04	7.46E+04	2.69E+02
5.33E+01	2.73E+04	7.94E+04	2.86E+02
5.67E+01	2.89E+04	8.43E+04	3.03E+02
6.00E+01	3.05E+04	8.91E+04	3.19E+02
6.33E+01	3.21E+04	9.39E+04	3.36E+02
6.67E+01	3.37E+04	9.87E+04	3.53E+02
7.00E+01	3.53E+04	1.04E+05	3.70E+02
7.33E+01	3.69E+04	1.08E+05	3.87E+02
7.67E+01	3.85E+04	1.13E+05	4.04E+02
8.00E+01	4.01E+04	1.18E+05	4.20E+02
8.33E+01	4.17E+04	1.23E+05	4.37E+02
8.67E+01	4.33E+04	1.27E+05	4.54E+02
9.00E+01	4.49E+04	1.32E+05	4.71E+02
9.33E+01	4.65E+04	1.37E+05	4.88E+02
9.67E+01	4.81E+04	1.41E+05	5.04E+02
1.00E+02	4.97E+04	1.46E+05	5.21E+02
1.10E+02	5.45E+04	1.60E+05	5.72E+02
1.20E+02	5.94E+04	1.74E+05	6.22E+02

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C.4.3. Gestational

Gestational			
Intake (ng/kg/ day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.00E-09	2.81E-05	1.11E-05	2.96E-07
1.33E-09	3.74E-05	1.47E-05	3.94E-07
1.67E-09	4.68E-05	1.84E-05	4.92E-07
2.00E-09	5.61E-05	2.21E-05	5.91E-07
2.33E-09	6.55E-05	2.58E-05	6.89E-07
2.67E-09	7.48E-05	2.95E-05	7.88E-07
3.00E-09	8.42E-05	3.32E-05	8.86E-07
3.33E-09	9.35E-05	3.69E-05	9.84E-07
3.67E-09	1.03E-04	4.05E-05	1.08E-06
4.00E-09	1.12E-04	4.42E-05	1.18E-06
4.33E-09	1.22E-04	4.79E-05	1.28E-06
4.67E-09	1.31E-04	5.16E-05	1.38E-06
5.00E-09	1.40E-04	5.53E-05	1.48E-06
5.33E-09	1.50E-04	5.90E-05	1.57E-06
5.67E-09	1.59E-04	6.26E-05	1.67E-06
6.00E-09	1.68E-04	6.63E-05	1.77E-06
6.33E-09	1.78E-04	7.00E-05	1.87E-06
6.67E-09	1.87E-04	7.37E-05	1.97E-06
7.00E-09	1.96E-04	7.74E-05	2.07E-06
7.33E-09	2.06E-04	8.11E-05	2.16E-06
7.67E-09	2.15E-04	8.47E-05	2.26E-06
8.00E-09	2.24E-04	8.84E-05	2.36E-06
8.33E-09	2.34E-04	9.21E-05	2.46E-06
8.67E-09	2.43E-04	9.58E-05	2.56E-06
9.00E-09	2.52E-04	9.95E-05	2.66E-06
9.33E-09	2.62E-04	1.03E-04	2.75E-06
9.67E-09	2.71E-04	1.07E-04	2.85E-06
1.00E-08	2.80E-04	1.11E-04	2.95E-06
1.33E-08	3.73E-04	1.47E-04	3.93E-06
1.67E-08	4.66E-04	1.84E-04	4.91E-06
2.00E-08	5.59E-04	2.21E-04	5.89E-06
2.33E-08	6.52E-04	2.57E-04	6.87E-06
2.67E-08	7.46E-04	2.94E-04	7.85E-06
3.00E-08	8.39E-04	3.31E-04	8.83E-06
3.33E-08	9.32E-04	3.67E-04	9.81E-06
3.67E-08	1.02E-03	4.04E-04	1.08E-05
4.00E-08	1.12E-03	4.41E-04	1.18E-05

Gestational			
Intake (ng/kg/ day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
4.33E-08	1.21E-03	4.78E-04	1.27E-05
4.67E-08	1.30E-03	5.14E-04	1.37E-05
5.00E-08	1.40E-03	5.51E-04	1.47E-05
5.33E-08	1.49E-03	5.88E-04	1.57E-05
5.67E-08	1.58E-03	6.24E-04	1.67E-05
6.00E-08	1.67E-03	6.61E-04	1.76E-05
6.33E-08	1.77E-03	6.97E-04	1.86E-05
6.67E-08	1.86E-03	7.34E-04	1.96E-05
7.00E-08	1.95E-03	7.70E-04	2.05E-05
7.33E-08	2.04E-03	8.07E-04	2.15E-05
7.67E-08	2.14E-03	8.43E-04	2.25E-05
8.00E-08	2.23E-03	8.80E-04	2.35E-05
8.33E-08	2.32E-03	9.17E-04	2.44E-05
8.67E-08	2.41E-03	9.53E-04	2.54E-05
9.00E-08	2.51E-03	9.90E-04	2.64E-05
9.33E-08	2.60E-03	1.03E-03	2.74E-05
9.67E-08	2.69E-03	1.06E-03	2.83E-05
1.00E-07	2.79E-03	1.10E-03	2.93E-05
1.33E-07	3.70E-03	1.46E-03	3.90E-05
1.67E-07	4.62E-03	1.83E-03	4.86E-05
2.00E-07	5.54E-03	2.19E-03	5.83E-05
2.33E-07	6.46E-03	2.55E-03	6.80E-05
2.67E-07	7.37E-03	2.92E-03	7.76E-05
3.00E-07	8.29E-03	3.28E-03	8.73E-05
3.33E-07	9.21E-03	3.64E-03	9.69E-05
3.67E-07	1.01E-02	4.01E-03	1.07E-04
4.00E-07	1.10E-02	4.37E-03	1.16E-04
4.33E-07	1.20E-02	4.74E-03	1.26E-04
4.67E-07	1.29E-02	5.10E-03	1.36E-04
5.00E-07	1.38E-02	5.46E-03	1.45E-04
5.33E-07	1.47E-02	5.82E-03	1.55E-04
5.66E-07	1.56E-02	6.17E-03	1.64E-04
5.99E-07	1.65E-02	6.53E-03	1.73E-04
6.33E-07	1.74E-02	6.88E-03	1.83E-04
6.66E-07	1.83E-02	7.24E-03	1.92E-04
6.99E-07	1.92E-02	7.59E-03	2.02E-04
7.32E-07	2.01E-02	7.95E-03	2.11E-04
7.65E-07	2.09E-02	8.30E-03	2.20E-04

Gestational			
Intake (ng/kg/ day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
7.98E-07	2.18E-02	8.66E-03	2.30E-04
8.32E-07	2.27E-02	9.01E-03	2.39E-04
8.65E-07	2.36E-02	9.37E-03	2.49E-04
8.98E-07	2.45E-02	9.72E-03	2.58E-04
9.31E-07	2.54E-02	1.01E-02	2.67E-04
9.64E-07	2.63E-02	1.04E-02	2.77E-04
9.97E-07	2.72E-02	1.08E-02	2.86E-04
1.01E-06	2.76E-02	1.09E-02	2.90E-04
1.03E-06	2.80E-02	1.11E-02	2.95E-04
1.04E-06	2.84E-02	1.13E-02	2.99E-04
1.06E-06	2.88E-02	1.14E-02	3.03E-04
1.07E-06	2.93E-02	1.16E-02	3.08E-04
1.09E-06	2.97E-02	1.18E-02	3.12E-04
1.11E-06	3.01E-02	1.20E-02	3.17E-04
1.12E-06	3.06E-02	1.21E-02	3.22E-04
1.14E-06	3.10E-02	1.23E-02	3.26E-04
1.16E-06	3.15E-02	1.25E-02	3.31E-04
1.17E-06	3.19E-02	1.27E-02	3.36E-04
1.19E-06	3.24E-02	1.29E-02	3.41E-04
1.21E-06	3.29E-02	1.31E-02	3.46E-04
1.23E-06	3.34E-02	1.32E-02	3.51E-04
1.24E-06	3.38E-02	1.34E-02	3.56E-04
1.26E-06	3.43E-02	1.36E-02	3.61E-04
1.28E-06	3.48E-02	1.38E-02	3.67E-04
1.30E-06	3.54E-02	1.40E-02	3.72E-04
1.32E-06	3.59E-02	1.42E-02	3.77E-04
1.34E-06	3.64E-02	1.45E-02	3.83E-04
1.36E-06	3.69E-02	1.47E-02	3.89E-04
1.38E-06	3.75E-02	1.49E-02	3.94E-04
1.40E-06	3.80E-02	1.51E-02	4.00E-04
1.42E-06	3.86E-02	1.53E-02	4.06E-04
1.44E-06	3.92E-02	1.56E-02	4.12E-04
1.46E-06	3.98E-02	1.58E-02	4.18E-04
1.49E-06	4.03E-02	1.60E-02	4.25E-04
1.53E-06	4.15E-02	1.65E-02	4.37E-04
1.58E-06	4.27E-02	1.70E-02	4.50E-04
1.62E-06	4.40E-02	1.75E-02	4.63E-04
1.67E-06	4.53E-02	1.80E-02	4.76E-04

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Gestational			
Intake (ng/kg/ day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.72E-06	4.66E-02	1.85E-02	4.90E-04
1.77E-06	4.80E-02	1.91E-02	5.05E-04
1.83E-06	4.94E-02	1.96E-02	5.20E-04
1.88E-06	5.08E-02	2.02E-02	5.35E-04
1.94E-06	5.23E-02	2.08E-02	5.50E-04
2.00E-06	5.38E-02	2.14E-02	5.66E-04
2.06E-06	5.54E-02	2.21E-02	5.83E-04
2.12E-06	5.70E-02	2.27E-02	6.00E-04
2.18E-06	5.87E-02	2.34E-02	6.17E-04
2.25E-06	6.04E-02	2.41E-02	6.35E-04
2.32E-06	6.22E-02	2.48E-02	6.54E-04
2.39E-06	6.40E-02	2.55E-02	6.73E-04
2.46E-06	6.58E-02	2.62E-02	6.93E-04
2.53E-06	6.77E-02	2.70E-02	7.13E-04
2.61E-06	6.97E-02	2.78E-02	7.33E-04
2.68E-06	7.17E-02	2.86E-02	7.55E-04
2.76E-06	7.38E-02	2.94E-02	7.77E-04
2.85E-06	7.60E-02	3.03E-02	8.00E-04
2.93E-06	7.82E-02	3.12E-02	8.22E-04
3.02E-06	8.04E-02	3.21E-02	8.46E-04
3.11E-06	8.27E-02	3.30E-02	8.71E-04
3.21E-06	8.51E-02	3.40E-02	8.96E-04
3.30E-06	8.76E-02	3.50E-02	9.22E-04
3.40E-06	9.01E-02	3.60E-02	9.48E-04
3.50E-06	9.27E-02	3.71E-02	9.76E-04
3.61E-06	9.54E-02	3.81E-02	1.00E-03
3.72E-06	9.82E-02	3.93E-02	1.03E-03
3.83E-06	1.01E-01	4.04E-02	1.06E-03
3.94E-06	1.04E-01	4.16E-02	1.09E-03
4.06E-06	1.07E-01	4.28E-02	1.12E-03
4.18E-06	1.10E-01	4.40E-02	1.16E-03
4.31E-06	1.13E-01	4.53E-02	1.19E-03
4.44E-06	1.16E-01	4.66E-02	1.22E-03
4.57E-06	1.20E-01	4.79E-02	1.26E-03
4.71E-06	1.23E-01	4.93E-02	1.30E-03
4.85E-06	1.27E-01	5.08E-02	1.33E-03
4.99E-06	1.30E-01	5.22E-02	1.37E-03
5.14E-06	1.34E-01	5.37E-02	1.41E-03

Gestational			
Intake (ng/kg/ day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
5.30E-06	1.38E-01	5.53E-02	1.45E-03
5.46E-06	1.42E-01	5.69E-02	1.49E-03
5.62E-06	1.46E-01	5.85E-02	1.53E-03
5.79E-06	1.50E-01	6.02E-02	1.58E-03
5.96E-06	1.54E-01	6.19E-02	1.62E-03
6.14E-06	1.59E-01	6.37E-02	1.67E-03
6.33E-06	1.63E-01	6.55E-02	1.72E-03
6.52E-06	1.68E-01	6.74E-02	1.76E-03
6.71E-06	1.72E-01	6.93E-02	1.81E-03
6.91E-06	1.77E-01	7.13E-02	1.86E-03
7.12E-06	1.82E-01	7.33E-02	1.92E-03
7.33E-06	1.87E-01	7.54E-02	1.97E-03
7.55E-06	1.93E-01	7.75E-02	2.03E-03
7.78E-06	1.98E-01	7.97E-02	2.08E-03
8.01E-06	2.03E-01	8.20E-02	2.14E-03
8.25E-06	2.09E-01	8.43E-02	2.20E-03
8.50E-06	2.15E-01	8.67E-02	2.26E-03
8.76E-06	2.21E-01	8.92E-02	2.33E-03
9.02E-06	2.27E-01	9.17E-02	2.39E-03
9.29E-06	2.34E-01	9.43E-02	2.46E-03
9.57E-06	2.40E-01	9.70E-02	2.53E-03
9.86E-06	2.47E-01	9.97E-02	2.60E-03
1.02E-05	2.54E-01	1.03E-01	2.67E-03
1.05E-05	2.61E-01	1.05E-01	2.74E-03
1.08E-05	2.68E-01	1.08E-01	2.82E-03
1.11E-05	2.75E-01	1.11E-01	2.90E-03
1.14E-05	2.83E-01	1.15E-01	2.98E-03
1.18E-05	2.91E-01	1.18E-01	3.06E-03
1.21E-05	2.99E-01	1.21E-01	3.14E-03
1.25E-05	3.07E-01	1.25E-01	3.23E-03
1.29E-05	3.16E-01	1.28E-01	3.32E-03
1.32E-05	3.24E-01	1.32E-01	3.41E-03
1.36E-05	3.33E-01	1.35E-01	3.51E-03
1.41E-05	3.42E-01	1.39E-01	3.60E-03
1.45E-05	3.52E-01	1.43E-01	3.70E-03
1.49E-05	3.61E-01	1.47E-01	3.80E-03
1.54E-05	3.71E-01	1.51E-01	3.90E-03
1.58E-05	3.81E-01	1.55E-01	4.01E-03

Gestational			
Intake (ng/kg/ day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.63E-05	3.92E-01	1.60E-01	4.12E-03
1.68E-05	4.03E-01	1.64E-01	4.23E-03
1.73E-05	4.13E-01	1.69E-01	4.35E-03
1.78E-05	4.25E-01	1.73E-01	4.47E-03
1.83E-05	4.36E-01	1.78E-01	4.59E-03
1.89E-05	4.48E-01	1.83E-01	4.71E-03
1.95E-05	4.60E-01	1.88E-01	4.84E-03
2.00E-05	4.72E-01	1.93E-01	4.97E-03
2.06E-05	4.85E-01	1.98E-01	5.10E-03
2.13E-05	4.98E-01	2.04E-01	5.24E-03
2.19E-05	5.12E-01	2.10E-01	5.38E-03
2.25E-05	5.25E-01	2.15E-01	5.53E-03
2.32E-05	5.40E-01	2.21E-01	5.68E-03
2.39E-05	5.54E-01	2.27E-01	5.83E-03
2.46E-05	5.69E-01	2.34E-01	5.98E-03
2.54E-05	5.84E-01	2.40E-01	6.14E-03
2.61E-05	6.00E-01	2.47E-01	6.31E-03
2.69E-05	6.16E-01	2.53E-01	6.48E-03
2.77E-05	6.32E-01	2.60E-01	6.65E-03
2.86E-05	6.49E-01	2.67E-01	6.82E-03
2.94E-05	6.66E-01	2.75E-01	7.01E-03
3.03E-05	6.84E-01	2.82E-01	7.19E-03
3.12E-05	7.02E-01	2.90E-01	7.38E-03
3.21E-05	7.20E-01	2.98E-01	7.58E-03
3.31E-05	7.42E-01	3.07E-01	7.80E-03
3.41E-05	7.62E-01	3.15E-01	8.01E-03
3.51E-05	7.82E-01	3.24E-01	8.22E-03
3.62E-05	8.03E-01	3.33E-01	8.44E-03
3.73E-05	8.24E-01	3.42E-01	8.68E-03
3.84E-05	8.45E-01	3.51E-01	8.89E-03
3.95E-05	8.68E-01	3.61E-01	9.12E-03
4.07E-05	8.88E-01	3.69E-01	9.34E-03
4.19E-05	9.11E-01	3.79E-01	9.59E-03
4.32E-05	9.35E-01	3.89E-01	9.83E-03
4.45E-05	9.59E-01	4.00E-01	1.01E-02
4.58E-05	9.83E-01	4.10E-01	1.03E-02
4.72E-05	1.01E+00	4.21E-01	1.06E-02
4.86E-05	1.04E+00	4.33E-01	1.09E-02

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Gestational			
Intake (ng/kg/ day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
5.01E-05	1.06E+00	4.44E-01	1.12E-02
5.16E-05	1.09E+00	4.56E-01	1.14E-02
5.31E-05	1.12E+00	4.68E-01	1.17E-02
5.47E-05	1.15E+00	4.81E-01	1.21E-02
5.64E-05	1.18E+00	4.93E-01	1.24E-02
5.81E-05	1.21E+00	5.06E-01	1.27E-02
5.98E-05	1.24E+00	5.20E-01	1.30E-02
6.16E-05	1.27E+00	5.34E-01	1.33E-02
6.34E-05	1.30E+00	5.48E-01	1.37E-02
6.54E-05	1.33E+00	5.62E-01	1.40E-02
6.73E-05	1.37E+00	5.77E-01	1.44E-02
6.93E-05	1.40E+00	5.92E-01	1.47E-02
7.14E-05	1.44E+00	6.08E-01	1.51E-02
7.36E-05	1.47E+00	6.24E-01	1.55E-02
7.58E-05	1.51E+00	6.40E-01	1.59E-02
7.80E-05	1.55E+00	6.57E-01	1.63E-02
8.04E-05	1.59E+00	6.74E-01	1.67E-02
8.28E-05	1.63E+00	6.92E-01	1.71E-02
8.53E-05	1.67E+00	7.10E-01	1.75E-02
8.78E-05	1.71E+00	7.28E-01	1.79E-02
9.05E-05	1.75E+00	7.47E-01	1.84E-02
9.32E-05	1.79E+00	7.66E-01	1.88E-02
9.60E-05	1.84E+00	7.86E-01	1.93E-02
9.89E-05	1.88E+00	8.07E-01	1.98E-02
1.02E-04	1.93E+00	8.28E-01	2.03E-02
1.05E-04	1.98E+00	8.49E-01	2.08E-02
1.08E-04	2.03E+00	8.71E-01	2.13E-02
1.11E-04	2.08E+00	8.93E-01	2.18E-02
1.15E-04	2.13E+00	9.16E-01	2.24E-02
1.18E-04	2.18E+00	9.39E-01	2.29E-02
1.22E-04	2.23E+00	9.63E-01	2.34E-02
1.25E-04	2.28E+00	9.87E-01	2.40E-02
1.29E-04	2.34E+00	1.01E+00	2.46E-02
1.33E-04	2.40E+00	1.04E+00	2.52E-02
1.37E-04	2.45E+00	1.06E+00	2.58E-02
1.41E-04	2.51E+00	1.09E+00	2.64E-02
1.45E-04	2.58E+00	1.12E+00	2.72E-02
1.50E-04	2.63E+00	1.15E+00	2.77E-02

Gestational			
Intake (ng/kg/ day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.54E-04	2.70E+00	1.18E+00	2.83E-02
1.59E-04	2.78E+00	1.21E+00	2.92E-02
1.63E-04	2.84E+00	1.24E+00	2.99E-02
1.68E-04	2.89E+00	1.27E+00	3.04E-02
1.73E-04	2.96E+00	1.30E+00	3.11E-02
1.79E-04	3.03E+00	1.33E+00	3.18E-02
1.84E-04	3.10E+00	1.36E+00	3.26E-02
1.89E-04	3.17E+00	1.40E+00	3.33E-02
1.95E-04	3.25E+00	1.43E+00	3.41E-02
2.01E-04	3.32E+00	1.47E+00	3.49E-02
2.07E-04	3.43E+00	1.52E+00	3.61E-02
2.13E-04	3.51E+00	1.56E+00	3.69E-02
2.20E-04	3.57E+00	1.59E+00	3.75E-02
2.26E-04	3.67E+00	1.63E+00	3.85E-02
2.33E-04	3.77E+00	1.68E+00	3.96E-02
2.40E-04	3.86E+00	1.72E+00	4.05E-02
2.47E-04	3.95E+00	1.76E+00	4.15E-02
2.55E-04	4.04E+00	1.81E+00	4.24E-02
2.62E-04	4.13E+00	1.85E+00	4.34E-02
2.70E-04	4.22E+00	1.90E+00	4.44E-02
2.78E-04	4.32E+00	1.94E+00	4.54E-02
2.86E-04	4.42E+00	1.99E+00	4.64E-02
2.95E-04	4.52E+00	2.04E+00	4.75E-02
3.04E-04	4.62E+00	2.09E+00	4.86E-02
3.13E-04	4.73E+00	2.14E+00	4.97E-02
3.22E-04	4.84E+00	2.20E+00	5.08E-02
3.32E-04	4.95E+00	2.25E+00	5.20E-02
3.42E-04	5.06E+00	2.30E+00	5.31E-02
3.52E-04	5.17E+00	2.36E+00	5.43E-02
3.63E-04	5.29E+00	2.42E+00	5.56E-02
3.74E-04	5.41E+00	2.48E+00	5.68E-02
3.85E-04	5.53E+00	2.54E+00	5.81E-02
3.97E-04	5.65E+00	2.60E+00	5.94E-02
4.08E-04	5.78E+00	2.66E+00	6.07E-02
4.21E-04	5.91E+00	2.73E+00	6.20E-02
4.33E-04	6.04E+00	2.79E+00	6.34E-02
4.46E-04	6.17E+00	2.86E+00	6.48E-02
4.60E-04	6.31E+00	2.93E+00	6.63E-02

Gestational			
Intake (ng/kg/ day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
4.74E-04	6.45E+00	3.00E+00	6.77E-02
4.88E-04	6.59E+00	3.07E+00	6.92E-02
5.02E-04	6.74E+00	3.15E+00	7.07E-02
5.17E-04	6.88E+00	3.22E+00	7.23E-02
5.33E-04	7.03E+00	3.30E+00	7.39E-02
5.49E-04	7.19E+00	3.38E+00	7.55E-02
5.65E-04	7.34E+00	3.46E+00	7.71E-02
5.82E-04	7.50E+00	3.54E+00	7.88E-02
6.00E-04	7.67E+00	3.63E+00	8.05E-02
6.18E-04	7.83E+00	3.71E+00	8.22E-02
6.36E-04	8.00E+00	3.80E+00	8.40E-02
6.55E-04	8.17E+00	3.89E+00	8.58E-02
6.75E-04	8.35E+00	3.98E+00	8.77E-02
6.95E-04	8.53E+00	4.08E+00	8.95E-02
7.16E-04	8.70E+00	4.17E+00	9.14E-02
7.38E-04	8.89E+00	4.27E+00	9.33E-02
7.60E-04	9.08E+00	4.37E+00	9.53E-02
7.83E-04	9.27E+00	4.47E+00	9.74E-02
8.06E-04	9.47E+00	4.58E+00	9.94E-02
8.30E-04	9.67E+00	4.69E+00	1.02E-01
8.55E-04	9.88E+00	4.80E+00	1.04E-01
8.81E-04	1.01E+01	4.91E+00	1.06E-01
9.07E-04	1.03E+01	5.03E+00	1.08E-01
9.21E-04	1.04E+01	5.09E+00	1.09E-01
9.35E-04	1.05E+01	5.14E+00	1.10E-01
9.49E-04	1.26E+01	6.31E+00	1.32E-01
1.37E-03	1.38E+01	6.99E+00	1.45E-01
1.39E-03	1.40E+01	7.07E+00	1.46E-01
1.41E-03	1.41E+01	7.15E+00	1.48E-01
1.43E-03	1.42E+01	7.23E+00	1.49E-01
1.46E-03	1.44E+01	7.31E+00	1.51E-01
1.48E-03	1.45E+01	7.39E+00	1.52E-01
1.50E-03	1.46E+01	7.47E+00	1.54E-01
1.52E-03	1.48E+01	7.55E+00	1.55E-01
1.54E-03	1.49E+01	7.64E+00	1.57E-01
1.57E-03	1.51E+01	7.73E+00	1.58E-01
1.59E-03	1.52E+01	7.82E+00	1.60E-01
1.61E-03	1.54E+01	7.91E+00	1.62E-01

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Gestational			
Intake (ng/kg/ day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.64E-03	1.56E+01	8.00E+00	1.63E-01
1.69E-03	1.59E+01	8.19E+00	1.67E-01
1.71E-03	1.60E+01	8.28E+00	1.68E-01
1.74E-03	1.62E+01	8.38E+00	1.70E-01
1.76E-03	1.64E+01	8.47E+00	1.72E-01
1.79E-03	1.65E+01	8.57E+00	1.73E-01
1.82E-03	1.67E+01	8.67E+00	1.75E-01
1.84E-03	1.69E+01	8.77E+00	1.77E-01
1.87E-03	1.74E+01	9.10E+00	1.83E-01
2.34E-03	1.98E+01	1.06E+01	2.08E-01
2.41E-03	2.02E+01	1.08E+01	2.12E-01
2.48E-03	2.06E+01	1.11E+01	2.16E-01
2.55E-03	2.10E+01	1.13E+01	2.21E-01
2.63E-03	2.14E+01	1.16E+01	2.25E-01
2.71E-03	2.19E+01	1.18E+01	2.30E-01
2.79E-03	2.23E+01	1.21E+01	2.34E-01
2.87E-03	2.28E+01	1.24E+01	2.39E-01
2.96E-03	2.32E+01	1.27E+01	2.44E-01
3.05E-03	2.37E+01	1.30E+01	2.48E-01
3.14E-03	2.41E+01	1.33E+01	2.53E-01
3.23E-03	2.46E+01	1.36E+01	2.58E-01
3.33E-03	2.51E+01	1.39E+01	2.63E-01
3.43E-03	2.56E+01	1.42E+01	2.69E-01
3.53E-03	2.61E+01	1.46E+01	2.74E-01
3.64E-03	2.66E+01	1.49E+01	2.79E-01
4.22E-03	2.83E+01	1.60E+01	2.96E-01
4.35E-03	2.88E+01	1.63E+01	3.02E-01
4.48E-03	2.93E+01	1.67E+01	3.08E-01
4.61E-03	2.99E+01	1.71E+01	3.14E-01
4.75E-03	3.05E+01	1.75E+01	3.20E-01
4.89E-03	3.11E+01	1.79E+01	3.26E-01
5.04E-03	3.30E+01	1.92E+01	3.46E-01
5.19E-03	3.41E+01	2.00E+01	3.58E-01
5.35E-03	3.49E+01	2.05E+01	3.66E-01
5.51E-03	3.55E+01	2.10E+01	3.73E-01
5.67E-03	3.62E+01	2.14E+01	3.80E-01
5.84E-03	3.69E+01	2.19E+01	3.87E-01
5.93E-03	3.73E+01	2.22E+01	3.91E-01

Gestational			
Intake (ng/kg/ day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
6.02E-03	3.77E+01	2.25E+01	3.95E-01
6.20E-03	3.84E+01	2.30E+01	4.03E-01
6.38E-03	3.92E+01	2.36E+01	4.12E-01
6.57E-03	4.00E+01	2.42E+01	4.20E-01
6.77E-03	4.08E+01	2.48E+01	4.28E-01
6.98E-03	4.16E+01	2.54E+01	4.37E-01
7.18E-03	4.25E+01	2.60E+01	4.45E-01
7.40E-03	4.33E+01	2.66E+01	4.54E-01
7.51E-03	4.37E+01	2.69E+01	4.58E-01
8.33E-03	4.46E+01	2.76E+01	4.68E-01
8.58E-03	4.66E+01	2.91E+01	4.89E-01
8.71E-03	4.74E+01	2.97E+01	4.97E-01
8.84E-03	4.79E+01	3.00E+01	5.02E-01
9.10E-03	4.86E+01	3.06E+01	5.10E-01
9.37E-03	4.95E+01	3.13E+01	5.19E-01
9.66E-03	5.07E+01	3.22E+01	5.32E-01
9.94E-03	5.17E+01	3.30E+01	5.42E-01
1.02E-02	5.27E+01	3.38E+01	5.53E-01
1.06E-02	5.37E+01	3.46E+01	5.63E-01
1.09E-02	5.46E+01	3.53E+01	5.73E-01
1.12E-02	5.58E+01	3.63E+01	5.85E-01
1.15E-02	5.67E+01	3.69E+01	5.94E-01
1.19E-02	5.74E+01	3.75E+01	6.02E-01
1.22E-02	5.85E+01	3.84E+01	6.13E-01
1.26E-02	5.96E+01	3.93E+01	6.25E-01
1.30E-02	6.19E+01	4.12E+01	6.49E-01
1.34E-02	6.32E+01	4.23E+01	6.63E-01
1.38E-02	6.45E+01	4.33E+01	6.76E-01
1.42E-02	6.57E+01	4.44E+01	6.89E-01
1.46E-02	6.64E+01	4.49E+01	6.96E-01
1.50E-02	6.78E+01	4.61E+01	7.11E-01
1.55E-02	6.83E+01	4.66E+01	7.16E-01
1.60E-02	6.96E+01	4.76E+01	7.29E-01
1.64E-02	7.09E+01	4.88E+01	7.43E-01
1.69E-02	7.26E+01	5.02E+01	7.61E-01
1.74E-02	7.40E+01	5.14E+01	7.76E-01
1.80E-02	7.54E+01	5.27E+01	7.90E-01
1.85E-02	7.68E+01	5.39E+01	8.06E-01

Gestational			
Intake (ng/kg/ day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.91E-02	7.83E+01	5.52E+01	8.21E-01
1.96E-02	7.98E+01	5.66E+01	8.37E-01
2.02E-02	8.13E+01	5.79E+01	8.53E-01
2.08E-02	8.29E+01	5.94E+01	8.69E-01
2.14E-02	8.45E+01	6.08E+01	8.86E-01
2.21E-02	8.61E+01	6.23E+01	9.03E-01
2.28E-02	8.78E+01	6.38E+01	9.20E-01
2.34E-02	8.95E+01	6.54E+01	9.38E-01
2.41E-02	9.12E+01	6.70E+01	9.56E-01
2.49E-02	9.29E+01	6.86E+01	9.75E-01
2.56E-02	9.47E+01	7.03E+01	9.93E-01
2.64E-02	9.65E+01	7.20E+01	1.01E+00
2.72E-02	9.84E+01	7.37E+01	1.03E+00
2.80E-02	1.00E+02	7.55E+01	1.05E+00
2.88E-02	1.02E+02	7.74E+01	1.07E+00
2.97E-02	1.04E+02	7.93E+01	1.09E+00
3.06E-02	1.07E+02	8.20E+01	1.12E+00
3.15E-02	1.09E+02	8.38E+01	1.14E+00
3.24E-02	1.11E+02	8.57E+01	1.16E+00
3.34E-02	1.13E+02	8.76E+01	1.18E+00
3.44E-02	1.15E+02	8.96E+01	1.20E+00
3.54E-02	1.16E+02	9.15E+01	1.22E+00
3.65E-02	1.18E+02	9.35E+01	1.24E+00
3.76E-02	1.21E+02	9.61E+01	1.27E+00
3.87E-02	1.23E+02	9.84E+01	1.29E+00
3.99E-02	1.26E+02	1.01E+02	1.32E+00
4.11E-02	1.28E+02	1.03E+02	1.34E+00
4.23E-02	1.31E+02	1.06E+02	1.37E+00
4.36E-02	1.34E+02	1.09E+02	1.40E+00
4.49E-02	1.36E+02	1.12E+02	1.43E+00
4.63E-02	1.39E+02	1.15E+02	1.45E+00
4.76E-02	1.42E+02	1.18E+02	1.48E+00
4.91E-02	1.44E+02	1.21E+02	1.51E+00
5.05E-02	1.47E+02	1.24E+02	1.54E+00
5.21E-02	1.50E+02	1.27E+02	1.57E+00
5.36E-02	1.52E+02	1.30E+02	1.60E+00
5.52E-02	1.55E+02	1.33E+02	1.63E+00
5.69E-02	1.59E+02	1.37E+02	1.66E+00

Gestational			
Intake (ng/kg/ day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
5.86E-02	1.62E+02	1.40E+02	1.69E+00
6.03E-02	1.64E+02	1.43E+02	1.72E+00
6.22E-02	1.67E+02	1.46E+02	1.75E+00
6.40E-02	1.70E+02	1.50E+02	1.79E+00
6.59E-02	1.74E+02	1.54E+02	1.82E+00
6.79E-02	1.77E+02	1.58E+02	1.86E+00
7.00E-02	1.80E+02	1.62E+02	1.89E+00
7.21E-02	1.84E+02	1.66E+02	1.93E+00
7.42E-02	1.87E+02	1.70E+02	1.96E+00
7.64E-02	1.91E+02	1.75E+02	2.00E+00
7.87E-02	1.95E+02	1.79E+02	2.05E+00
8.11E-02	1.99E+02	1.84E+02	2.09E+00
8.35E-02	2.03E+02	1.89E+02	2.13E+00
8.60E-02	2.07E+02	1.93E+02	2.17E+00
8.86E-02	2.11E+02	1.98E+02	2.21E+00
9.13E-02	2.15E+02	2.03E+02	2.25E+00
9.40E-02	2.19E+02	2.08E+02	2.29E+00
9.68E-02	2.23E+02	2.14E+02	2.34E+00
9.97E-02	2.28E+02	2.20E+02	2.39E+00
1.03E-01	2.32E+02	2.25E+02	2.43E+00
1.06E-01	2.36E+02	2.31E+02	2.48E+00
1.09E-01	2.40E+02	2.36E+02	2.52E+00
1.12E-01	2.45E+02	2.42E+02	2.57E+00
1.16E-01	2.50E+02	2.49E+02	2.62E+00
1.19E-01	2.55E+02	2.55E+02	2.67E+00
1.23E-01	2.60E+02	2.62E+02	2.72E+00
1.26E-01	2.65E+02	2.69E+02	2.78E+00
1.30E-01	2.70E+02	2.76E+02	2.83E+00
1.34E-01	2.75E+02	2.83E+02	2.89E+00
1.38E-01	2.81E+02	2.91E+02	2.95E+00
1.42E-01	2.87E+02	2.99E+02	3.00E+00
1.46E-01	2.92E+02	3.06E+02	3.06E+00
1.51E-01	2.97E+02	3.14E+02	3.12E+00
1.55E-01	3.03E+02	3.22E+02	3.18E+00
1.60E-01	3.09E+02	3.30E+02	3.24E+00
1.65E-01	3.15E+02	3.39E+02	3.30E+00
1.70E-01	3.21E+02	3.48E+02	3.37E+00
1.75E-01	3.27E+02	3.57E+02	3.43E+00

Gestational			
Intake (ng/kg/ day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.80E-01	3.34E+02	3.67E+02	3.50E+00
1.86E-01	3.40E+02	3.76E+02	3.57E+00
1.91E-01	3.47E+02	3.86E+02	3.64E+00
1.97E-01	3.54E+02	3.96E+02	3.71E+00
2.03E-01	3.60E+02	4.06E+02	3.78E+00
2.09E-01	3.68E+02	4.17E+02	3.85E+00
2.15E-01	3.75E+02	4.28E+02	3.93E+00
2.22E-01	3.82E+02	4.40E+02	4.01E+00
2.28E-01	3.90E+02	4.52E+02	4.09E+00
2.35E-01	3.98E+02	4.64E+02	4.17E+00
2.42E-01	4.05E+02	4.76E+02	4.25E+00
2.49E-01	4.13E+02	4.89E+02	4.33E+00
2.57E-01	4.22E+02	5.02E+02	4.42E+00
2.65E-01	4.30E+02	5.15E+02	4.51E+00
2.72E-01	4.38E+02	5.29E+02	4.60E+00
2.81E-01	4.47E+02	5.42E+02	4.68E+00
2.89E-01	4.55E+02	5.56E+02	4.77E+00
2.98E-01	4.64E+02	5.71E+02	4.87E+00
3.07E-01	4.73E+02	5.86E+02	4.96E+00
3.16E-01	4.83E+02	6.03E+02	5.06E+00
3.25E-01	4.92E+02	6.19E+02	5.16E+00
3.35E-01	5.02E+02	6.35E+02	5.26E+00
3.45E-01	5.13E+02	6.53E+02	5.37E+00
3.56E-01	5.23E+02	6.70E+02	5.48E+00
3.66E-01	5.33E+02	6.88E+02	5.59E+00
3.77E-01	5.44E+02	7.07E+02	5.70E+00
3.89E-01	5.55E+02	7.26E+02	5.81E+00
4.00E-01	5.66E+02	7.46E+02	5.93E+00
4.12E-01	5.77E+02	7.66E+02	6.05E+00
4.25E-01	5.88E+02	7.86E+02	6.17E+00
4.37E-01	6.00E+02	8.08E+02	6.29E+00
4.50E-01	6.12E+02	8.30E+02	6.42E+00
4.64E-01	6.24E+02	8.52E+02	6.54E+00
4.92E-01	6.50E+02	8.99E+02	6.81E+00
5.07E-01	6.63E+02	9.23E+02	6.95E+00
5.22E-01	6.76E+02	9.49E+02	7.09E+00
5.54E-01	7.04E+02	1.00E+03	7.38E+00
5.71E-01	7.18E+02	1.03E+03	7.53E+00

Gestational			
Intake (ng/kg/ day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
5.88E-01	7.32E+02	1.06E+03	7.68E+00
6.05E-01	7.47E+02	1.08E+03	7.83E+00
6.23E-01	7.62E+02	1.11E+03	7.99E+00
6.61E-01	7.94E+02	1.18E+03	8.32E+00
6.81E-01	8.10E+02	1.21E+03	8.49E+00
7.02E-01	8.27E+02	1.24E+03	8.67E+00
7.23E-01	8.43E+02	1.28E+03	8.84E+00
7.44E-01	8.61E+02	1.31E+03	9.02E+00
7.67E-01	8.78E+02	1.35E+03	9.21E+00
7.90E-01	8.96E+02	1.38E+03	9.40E+00
8.13E-01	9.15E+02	1.42E+03	9.59E+00
8.38E-01	9.33E+02	1.46E+03	9.78E+00
8.63E-01	9.53E+02	1.50E+03	9.99E+00
9.16E-01	9.93E+02	1.59E+03	1.04E+01
9.43E-01	1.01E+03	1.63E+03	1.06E+01
9.71E-01	1.03E+03	1.68E+03	1.08E+01
1.00E+00	1.06E+03	1.72E+03	1.11E+01
1.06E+00	1.10E+03	1.82E+03	1.15E+01
1.09E+00	1.12E+03	1.87E+03	1.18E+01
1.13E+00	1.15E+03	1.92E+03	1.20E+01
1.16E+00	1.17E+03	1.98E+03	1.23E+01
1.19E+00	1.20E+03	2.03E+03	1.25E+01
1.23E+00	1.22E+03	2.09E+03	1.28E+01
1.27E+00	1.25E+03	2.15E+03	1.31E+01
1.31E+00	1.27E+03	2.21E+03	1.33E+01
1.34E+00	1.30E+03	2.27E+03	1.36E+01
1.38E+00	1.33E+03	2.33E+03	1.39E+01
1.43E+00	1.35E+03	2.40E+03	1.42E+01
1.47E+00	1.38E+03	2.46E+03	1.45E+01
1.51E+00	1.41E+03	2.53E+03	1.48E+01
1.56E+00	1.44E+03	2.60E+03	1.51E+01
1.61E+00	1.47E+03	2.68E+03	1.55E+01
1.65E+00	1.51E+03	2.75E+03	1.58E+01
1.70E+00	1.54E+03	2.83E+03	1.61E+01
1.75E+00	1.57E+03	2.91E+03	1.65E+01
1.81E+00	1.61E+03	2.99E+03	1.68E+01
1.86E+00	1.64E+03	3.08E+03	1.72E+01
1.92E+00	1.68E+03	3.16E+03	1.76E+01

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Gestational			
Intake (ng/kg/ day)	**Fat (ng/kg)**	**Body Burden (ng/kg)**	**Blood (ng/kg)**
1.97E+00	1.71E+03	3.25E+03	1.79E+01
2.03E+00	1.75E+03	3.34E+03	1.83E+01
2.09E+00	1.79E+03	3.44E+03	1.87E+01
2.16E+00	1.83E+03	3.54E+03	1.91E+01
2.22E+00	1.87E+03	3.64E+03	1.96E+01
2.29E+00	1.91E+03	3.74E+03	2.00E+01
2.36E+00	1.95E+03	3.85E+03	2.04E+01
2.43E+00	1.99E+03	3.95E+03	2.09E+01
2.50E+00	2.04E+03	4.07E+03	2.13E+01
2.58E+00	2.08E+03	4.18E+03	2.18E+01
2.65E+00	2.13E+03	4.30E+03	2.23E+01
2.73E+00	2.17E+03	4.42E+03	2.28E+01
2.82E+00	2.22E+03	4.55E+03	2.33E+01
2.90E+00	2.27E+03	4.68E+03	2.38E+01
2.99E+00	2.32E+03	4.81E+03	2.44E+01
3.08E+00	2.38E+03	4.95E+03	2.49E+01
3.17E+00	2.43E+03	5.09E+03	2.55E+01
3.26E+00	2.48E+03	5.24E+03	2.60E+01
3.36E+00	2.54E+03	5.39E+03	2.66E+01
3.46E+00	2.60E+03	5.54E+03	2.72E+01
3.57E+00	2.66E+03	5.70E+03	2.79E+01
3.67E+00	2.72E+03	5.86E+03	2.85E+01
3.78E+00	2.78E+03	6.03E+03	2.91E+01
3.90E+00	2.84E+03	6.20E+03	2.98E+01
4.01E+00	2.91E+03	6.38E+03	3.05E+01
4.13E+00	2.98E+03	6.56E+03	3.12E+01
4.26E+00	3.04E+03	6.75E+03	3.19E+01
4.39E+00	3.12E+03	6.95E+03	3.27E+01
4.52E+00	3.19E+03	7.15E+03	3.34E+01
4.65E+00	3.26E+03	7.35E+03	3.42E+01
4.79E+00	3.34E+03	7.56E+03	3.50E+01
4.94E+00	3.42E+03	7.78E+03	3.58E+01
5.08E+00	3.50E+03	8.01E+03	3.66E+01
5.24E+00	3.58E+03	8.24E+03	3.75E+01
5.39E+00	3.66E+03	8.47E+03	3.84E+01
5.56E+00	3.75E+03	8.72E+03	3.93E+01
5.72E+00	3.84E+03	8.97E+03	4.02E+01
5.89E+00	3.93E+03	9.23E+03	4.12E+01

Gestational			
Intake (ng/kg/ day)	**Fat (ng/kg)**	**Body Burden (ng/kg)**	**Blood (ng/kg)**
6.07E+00	4.02E+03	9.50E+03	4.22E+01
6.25E+00	4.12E+03	9.77E+03	4.32E+01
6.44E+00	4.22E+03	1.01E+04	4.42E+01
6.63E+00	4.32E+03	1.03E+04	4.53E+01
6.83E+00	4.42E+03	1.06E+04	4.64E+01
7.04E+00	4.53E+03	1.10E+04	4.75E+01
7.25E+00	4.64E+03	1.13E+04	4.86E+01
7.47E+00	4.75E+03	1.16E+04	4.98E+01
7.69E+00	4.87E+03	1.19E+04	5.10E+01
7.92E+00	4.99E+03	1.23E+04	5.23E+01
8.16E+00	5.11E+03	1.26E+04	5.36E+01
8.40E+00	5.24E+03	1.30E+04	5.49E+01
8.66E+00	5.37E+03	1.34E+04	5.62E+01
8.92E+00	5.50E+03	1.38E+04	5.76E+01
9.18E+00	5.63E+03	1.42E+04	5.91E+01
9.46E+00	5.77E+03	1.46E+04	6.05E+01
9.74E+00	5.92E+03	1.50E+04	6.20E+01
1.00E+01	6.05E+03	1.54E+04	6.34E+01
1.00E+01	6.07E+03	1.54E+04	6.36E+01
1.34E+01	7.71E+03	2.04E+04	8.08E+01
1.67E+01	9.35E+03	2.53E+04	9.80E+01
2.00E+01	1.10E+04	3.02E+04	1.15E+02
2.33E+01	1.26E+04	3.52E+04	1.32E+02
2.67E+01	1.42E+04	4.01E+04	1.49E+02
3.00E+01	1.58E+04	4.50E+04	1.66E+02
3.33E+01	1.74E+04	4.98E+04	1.83E+02
3.67E+01	1.90E+04	5.47E+04	2.00E+02
4.00E+01	2.07E+04	5.96E+04	2.17E+02
4.33E+01	2.23E+04	6.44E+04	2.33E+02
4.67E+01	2.39E+04	6.93E+04	2.50E+02
5.00E+01	2.54E+04	7.41E+04	2.67E+02

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APPENDIX D

Epidemiological Kinetic Modeling

NOTICE

THIS DOCUMENT IS AN EXTERNAL REVIEW DRAFT. It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH

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APPENDIX D. EPIDEMIOLOGICAL KINETIC MODELING

D.1. BACCARELLI ET AL. (2008) MODELING

D.1.1. Input File for Exposure During Pregnancy

```
CINT = 1   %168 %100            %integration time
  %Exposure scenario
EXP_TIME_ON      = 0        % delay before begin exposure (HOUR)
EXP_TIME_OFF     = 401190    %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE        = 24       %TIME
BCK_TIME_ON      = 401190    %DELAY BEFORE BACKGROUND EXP (HOUR)
BCK_TIME_OFF     = 401190    %TIME OF BACKGROUND EXP STOP (HOUR)
IV_LACK          = 401190
IV_PERIOD        = 401190
  %GESTATION CONTROL
MATTING          = 262800    % BEGINNING MATTING (HOUR)at 30 years old
TIMELIMIT        = 269184    %SIMULATION LIMIT TIME (HOUR)
TRANSTIME_ON     = 264312    % EXCHANGE MOTHER FETUS 1512 HOUR POST
MATTING
  %Exposure dose
MSTOT            = 0.021     % ng of TCDD /kg of BW
MSTOTBCKGR       = 0.  %0.1     % ORAL BACKGROUND EXPOSURE DOSE (nG/KG)
DOSEIV           = 0.  %10
DOSEIVLATE       = 0.  %10

   % TRANFER MOTHER TO FETUS CLEARANCE
CLPLA_FET        = 0.001 % MOTHER TO FETUS TRANFERT CLEARANCE(L/HR)
```

D.1.2. Table of Results for Baccarelli et al. (2008)

Table D-1. Estimated continuous intake corresponding to maternal serum concentration in Figure 2A

Variable	Value	Notes
Infant b-TSH	5 uU/mL	BMR
Maternal lipid adjusted serum	270 ng/kg	From Figure 2A
Intake	0.024 ng/kg-day	From Emond model, pregnancy at 30 years

Table D-2. Estimated maximum intake corresponding to maternal serum concentration in Figure 2A

Variable	Value	Notes
Infant b-TSH	--	--
Maternal lipid adjusted serum	309.5 ng/kg	Maximum from Figure 2A
Intake	0.030 ng/kg-day	From Emond model, pregnancy at 30 years

D.2. MOCARELLI ET AL. (2008) MODELING

D.2.1. Input File for Exposure for Pulse to Measurement 0.5 Years After the Seveso Pulse Dose

```
CINT = 1. %
EXP_TIME_ON  = 54312.      % Delay before begin exposure (HOUR) 6.2 years
EXP_TIME_OFF = 54335.    %324120    % HOUR/YEAR !TIME EXPOSURE STOP
(HOUR) 6.2 years + 23 hours
DAY_CYCLE    = 24.       % TIME
BCK_TIME_ON  = 0.        % DELAY BEFORE BACKGROUND EXP (HOUR)
BCK_TIME_OFF = 613200    % TIME OF BACKGROUND EXP STOP (HOUR)
TIMELIMIT    = 58692.    % half a year (July 1976 until January 1977) past 6.2 years
MSTOTBCKGR   = 3.7E-4     % ORAL BACKGROUND EXPOSURE DOSE (UG/KG)

% oral dose oral dose oral dose
MSTOT       = 232.4   % Seveso, ORAL DAILY EXPOSURE DOSE (NG/KG)
DOSEIV      =  0        % 40  %50 %5 %0.5 %0.3 %0.2 %0.1%0.05%0.3 %NG/KG
% oral dose oral dose oral dose

MEANLIPID    = 731       % 711 %664 %778 %468 %671 %730 %662 %592%615%730%
PAS_INDUC= 1         % NON INDUCTION (0) CONTROLE DE L'INDUCTION

%human variable parameter
MALE = 1.
FEMALE = 0.
Y0 = 0.              % 0 years old at the beginning of the simulation
```

D.2.2. Input File for Exposure from Pulse to the End of the Critical Window 3.8 Years After the Seveso Pulse Dose

```
CINT = 1. %
EXP_TIME_ON  = 54312.      % Delay before begin exposure (HOUR) 6.2 years
EXP_TIME_OFF = 54335.    %324120    % HOUR/YEAR !TIME EXPOSURE STOP
(HOUR) 6.2 years + 23 hours
DAY_CYCLE    = 24.       % TIME
```

```
BCK_TIME_ON  = 0.       % DELAY BEFORE BACKGROUND EXP (HOUR)
BCK_TIME_OFF = 613200.    % TIME OF BACKGROUND EXP STOP (HOUR)
TIMELIMIT    = 87600.     % 10 years
MSTOTBCKGR   = 3.7e-4      % ORAL BACKGROUND EXPOSURE DOSE (UG/KG)

% oral dose oral dose oral dose
MSTOT       = 232.5   % Serveso, ORAL DAILY EXPOSURE DOSE (NG/KG)
DOSEIV      =  0        % 40  %50 %5 %0.5 %0.3 %0.2 %0.1%0.05%0.3 %NG/KG
% oral dose oral dose oral dose

MEANLIPID    = 730       % 711 %664 %778 %468 %671 %730 %662 %592%615%730%
PAS_INDUC= 1         % NON INDUCTION (0) CONTROLE DE L'INDUCTION

%human variable parameter
MALE = 1.
FEMALE = 0.
Y0 = 0.             % 0 years old at the beginning of the simulation
```

D.2.3. Input File for Continuous Exposure for 10 Years

```
CINT = 1. %
EXP_TIME_ON  = 0.      % Delay before begin exposure (HOUR)
EXP_TIME_OFF = 87600.    % HOUR/YEAR !TIME EXPOSURE STOP (HOUR)
DAY_CYCLE    = 24.       % TIME
BCK_TIME_ON  = 0.       %324120     % DELAY BEFORE BACKGROUND EXP (HOUR)
BCK_TIME_OFF = 613200    %324120     % TIME OF BACKGROUND EXP STOP (HOUR)
TIMELIMIT    = 87600.     % 10 years
MSTOTBCKGR   = 0. %3.35E-4      % ORAL BACKGROUND EXPOSURE DOSE (UG/KG)

% oral dose oral dose oral dose
MSTOT       = 3.903   % Seveso, ORAL DAILY EXPOSURE DOSE (NG/KG)
DOSEIV      =  0        % 40  %50 %5 %0.5 %0.3 %0.2 %0.1%0.05%0.3 %NG/KG
% oral dose oral dose oral dose

MEANLIPID    = 730       % 711 %664 %778 %468 %671 %730 %662 %592%615%730%
PAS_INDUC= 1         % NON INDUCTION (0) CONTROLE DE L'INDUCTION

%human variable parameter
MALE = 1.
FEMALE = 0.
Y0 = 0.             % 0 years old at the beginning of the simulation
```

D.2.4. Tables of Results for Mocarelli et al. (2008)

Table D-3. Matching critical window average after pulse to critical window average for continuous intake run

Person modeled, beginning at age 0	Lipid adjusted serum (1976) ng/kg from Figure 3E	Pulse dose, 0.5 year lag time (ng/kg)	Average lipid adjusted serum 3.8 years after incident (ng/kg)	Continuous intake for 10 years (ng/kg-day)
Boy, 1st quartile	68	8.135	57.72	0.008024
Boy, 4th quartile	733	232.5	580.5	0.2128

Table D-4. Matching critical window peak after pulse to peak critical window concentration for continuous intake run

Person modeled, beginning at age 0	Lipid adjusted serum (1976) ng/kg from Figure 3E	Pulse dose, 0.5 year lag time (ng/kg)	Peak lipid adjusted serum after incident (ng/kg)	Continuous intake for 10 years (ng/kg-day)
Boy, 1st quartile	68	8.135	248.0	0.03194
Boy, 4th quartile	733	232.5	6674	3.904

D.3. ALALUUSUA ET AL. (2004) MODELING

D.3.1. Input File for Exposure for Pulse to Measurement 0.5 Years After the Seveso Pulse Dose

```
CINT = 1. %
EXP_TIME_ON  = 21900.    % Delay before begin exposure (HOUR) 2.5 years
EXP_TIME_OFF = 21923.    % 21900+23     % HOUR/YEAR !TIME EXPOSURE STOP
(HOUR) 2.5 years and 23 hours
DAY_CYCLE    = 24.       % TIME
BCK_TIME_ON  = 0.        % DELAY BEFORE BACKGROUND EXP (HOUR)
BCK_TIME_OFF = 613200.   % TIME OF BACKGROUND EXP STOP (HOUR)
TIMELIMIT    = 26280.    % half a year (July 1976 until January 1977) past 2.5 years
MSTOTBCKGR   = 3.7e-4    % ORAL BACKGROUND EXPOSURE DOSE (UG/KG)

% oral dose oral dose oral dose
MSTOT        = 24.22     % Seveso, ORAL DAILY EXPOSURE DOSE (NG/KG)
DOSEIV       =  0        % 40  %50 %5 %0.5 %0.3 %0.2 %0.1%0.05%0.3 %NG/KG
% oral dose oral dose oral dose
```

```
MEANLIPID    = 730       % 711 %664 %778 %468 %671 %730 %662 %592%615%730%
PAS_INDUC= 1         % NON INDUCTION (0) CONTROLE DE L'INDUCTION

%human variable parameter
MALE = 1.
FEMALE = 0.
Y0 = 0.              % 0 years old at the beginning of the simulation
```

D.3.2. Input File for Exposure from Pulse to the End of the Critical Window 2.5 Years After the Seveso Pulse Dose

```
CINT = 1. %
EXP_TIME_ON  = 21900.    % Delay before begin exposure (HOUR) 2.5 years
EXP_TIME_OFF = 21923.    % 324120     % HOUR/YEAR !TIME EXPOSURE STOP
(HOUR) 2.5 years and 23 hours
DAY_CYCLE    = 24.       % TIME
BCK_TIME_ON  = 0.        % 324120     % DELAY BEFORE BACKGROUND EXP (HOUR)
BCK_TIME_OFF = 613200.   % 324120     % TIME OF BACKGROUND EXP STOP (HOUR)
TIMELIMIT    = 43800.    % 5 years
MSTOTBCKGR   = 3.7e-4    % ORAL BACKGROUND EXPOSURE DOSE (UG/KG)

% oral dose oral dose oral dose
MSTOT        = 24.22   % Seveso, ORAL DAILY EXPOSURE DOSE (NG/KG)
DOSEIV       =   0         % 40  %50 %5 %0.5 %0.3 %0.2 %0.1%0.05%0.3 %NG/KG
% oral dose oral dose oral dose

MEANLIPID    = 730       % 711 %664 %778 %468 %671 %730 %662 %592%615%730%
PAS_INDUC= 1         % NON INDUCTION (0) CONTROLE DE L'INDUCTION

%human variable parameter
MALE = 1.
FEMALE = 0.
Y0 = 0.              % 0 years old at the beginning of the simulation
```

D.3.3. Input File for Continuous Exposure for 5 Years

```
CINT = 1. %
EXP_TIME_ON  = 0.        % Delay before begin exposure (HOUR)
EXP_TIME_OFF = 43800.    % 324120     % HOUR/YEAR !TIME EXPOSURE STOP (HOUR)
DAY_CYCLE    = 24.       % TIME
BCK_TIME_ON  = 0.        % 324120     % DELAY BEFORE BACKGROUND EXP (HOUR)
BCK_TIME_OFF = 613200.   % 324120     % TIME OF BACKGROUND EXP STOP (HOUR)
TIMELIMIT    = 43800.    % End of critical window (5 years)
MSTOTBCKGR   = 0.        % ORAL BACKGROUND EXPOSURE DOSE (UG/KG)

% oral dose oral dose oral dose
MSTOT        = 0.03486   % Seveso, ORAL DAILY EXPOSURE DOSE (NG/KG)
```

```
DOSEIV      =  0        % 40  %50 %5 %0.5 %0.3 %0.2 %0.1%0.05%0.3 %NG/KG
% oral dose oral dose oral dose

MEANLIPID   = 730      % 711 %664 %778 %468 %671 %730 %662 %592%615%730%
PAS_INDUC= 1        % NON INDUCTION (0) CONTROLE DE L'INDUCTION

%human variable parameter
MALE = 1.
FEMALE = 0.
Y0 = 0.             % 0 years old at the beginning of the simulation
```

D.3.4. Tables of Results for Alaluusua et al. (2004)

Table D-5. Matching critical window average after pulse to critical window average for continuous intake run

Person modeled, beginning at age 0	Lipid adjusted serum (1976) ng/kg estimated from tertile bins[a]	Pulse dose, 0.5 year lag time (ng/kg)	Average lipid adjusted serum 2.5 years after incident (ng/kg)	Continuous intake for 5 years (ng/kg-day)
Boy, 1st tertile	130	24.22	110.8	0.03486
Boy, 2nd tertile	383	108.9	322.7	0.1578
Boy, 3rd tertile	1830	1041	1538	1.511
Girl, 1st tertile	130	23.03	110.8	0.03211
Girl, 2nd tertile	383	105.3	324.4	0.1481
Girl, 3rd tertile	1830	1015	1546	1.427
Boy and girl, averaged, 1st tertile	130	-	-	0.03349
Boy and girl, averaged, 2nd tertile	383	-	-	0.1530
Boy and girl, averaged, 3rd tertile	1830	-	-	1.469

[a]Mean of tertile bin assuming a lognormal distribution of serum concentrations.

Table D-6. Matching critical window peak after pulse to peak critical window concentration for continuous intake run

Person modeled, beginning at age 0	Lipid adjusted serum (1976) ng/kg estimated from tertile bins	Pulse dose, 0.5 year lag time (ng/kg)	Peak lipid adjusted serum after incident (ng/kg)	Continuous intake for 5 years (ng/kg-day)
Boy, 1st tertile	130	24.22	618.8	0.2113
Boy, 2nd tertile	383	108.9	2700	1.783
Boy, 3rd tertile	1830	1041	24706	31.35
Girl, 1st tertile	130	23.02	588.0	0.1882
Girl, 2nd tertile	383	105.3	2610	1.642
Girl, 3rd tertile	1830	1015	24113	29.52
Boy and girl, averaged, 1st tertile	130	-	-	0.1998
Boy and girl, averaged, 2nd tertile	383	-	-	1.713
Boy and girl, averaged, 3rd tertile	1830	-	-	30.44

[a]Mean of tertile bin assuming a lognormal distribution of serum concentrations.

D.4. ESKANAZI ET AL. (2002) MODELING

D.4.1. Input File for Exposure for Pulse to Measurement 0.5 Years After the Seveso Pulse Dose

```
CINT = 1. %
EXP_TIME_ON  = 58692.      % Delay before begin exposure (HOUR) 6.7 years
EXP_TIME_OFF = 58715.    % HOUR/YEAR !TIME EXPOSURE STOP (HOUR) 6.7 years +
23 hours
DAY_CYCLE    = 24.       % TIME
BCK_TIME_ON  = 0.        %324120    % DELAY BEFORE BACKGROUND EXP (HOUR)
BCK_TIME_OFF = 613200.   %324120    % TIME OF BACKGROUND EXP STOP (HOUR)
TIMELIMIT    = 63072.    % half a year (July 1976 until January 1977) past 6.7 years
MSTOTBCKGR   = 3.7e-4    % ORAL BACKGROUND EXPOSURE DOSE (UG/KG)

% oral dose oral dose oral dose
MSTOT        = 7193   % Seveso, ORAL DAILY EXPOSURE DOSE (NG/KG)
DOSEIV       =  0        % 40  %50 %5 %0.5 %0.3 %0.2 %0.1%0.05%0.3 %NG/KG
% oral dose oral dose oral dose

MEANLIPID    = 730       % 711 %664 %778 %468 %671 %730 %662 %592%615%730%
```

```
PAS_INDUC= 1        % NON INDUCTION (0) CONTROLE DE L'INDUCTION

%human variable parameter
MALE = 0.
FEMALE = 1.
Y0 = 0.             % 0 years old at the beginning of the simulation
```

D.4.2. Input File for Exposure from Pulse to the End of the Critical Window 6.7 Years After the Seveso Pulse Dose

```
CINT = 1. %
EXP_TIME_ON  = 58692.      % Delay before begin exposure (HOUR) 6.7 years
EXP_TIME_OFF = 58715.    %324120    % HOUR/YEAR !TIME EXPOSURE STOP
(HOUR) 6.7 years + 23 hours
DAY_CYCLE    = 24.       % TIME
BCK_TIME_ON  = 0.        %324120    % DELAY BEFORE BACKGROUND EXP (HOUR)
BCK_TIME_OFF = 613200    %324120    % TIME OF BACKGROUND EXP STOP (HOUR)
TIMELIMIT    = 113880.   % 13 years
MSTOTBCKGR   = 3.7e-4    % ORAL BACKGROUND EXPOSURE DOSE (UG/KG)

% oral dose oral dose oral dose
MSTOT        = 7193   % Seveso, ORAL DAILY EXPOSURE DOSE (NG/KG)
DOSEIV       =  0        % 40  %50 %5 %0.5 %0.3 %0.2 %0.1%0.05%0.3 %NG/KG
% oral dose oral dose oral dose

MEANLIPID    = 730       % 711 %664 %778 %468 %671 %730 %662 %592%615%730%
PAS_INDUC= 1        % NON INDUCTION (0) CONTROLE DE L'INDUCTION

%human variable parameter
MALE = 0.
FEMALE = 1.
Y0 = 0.             % 0 years old at the beginning of the simulation
```

D.4.3. Input File for Continuous Exposure for 13 Years

```
CINT = 1. %
EXP_TIME_ON  = 0.       % Delay before begin exposure (HOUR)
EXP_TIME_OFF = 113880.    %324120    % HOUR/YEAR !TIME EXPOSURE STOP
(HOUR) 13 years
DAY_CYCLE    = 24.       % TIME
BCK_TIME_ON  = 0.        %324120    % DELAY BEFORE BACKGROUND EXP (HOUR)
BCK_TIME_OFF = 613200.    %324120    % TIME OF BACKGROUND EXP STOP (HOUR)
TIMELIMIT    = 113880.   % 13 years
MSTOTBCKGR   = 0. %3.35E-4      % ORAL BACKGROUND EXPOSURE DOSE (UG/KG)

% oral dose oral dose oral dose
MSTOT        = 166   % Seveso, ORAL DAILY EXPOSURE DOSE (NG/KG)
```

```
DOSEIV      =  0          % 40  %50 %5 %0.5 %0.3 %0.2 %0.1%0.05%0.3 %NG/KG
% oral dose oral dose oral dose

MEANLIPID   = 730        % 711 %664 %778 %468 %671 %730 %662 %592%615%730%
PAS_INDUC= 1          % NON INDUCTION (0) CONTROLE DE L'INDUCTION

%human variable parameter
MALE = 0.
FEMALE = 1.
Y0 = 0.               % 0 years old at the beginning of the simulation
```

D.4.4. Tables of Results for Eskanazi et al. (2002)

Table D-7. Matching critical window average after pulse to critical window average for continuous intake run

Person modeled, beginning at age 0	Lipid adjusted serum (adjusted to 1976-1977 levels) ng/kg from Figure 1A	Pulse dose, 0.5 year lag time (ng/kg)	Average lipid adjusted serum 6.7 years after incident (ng/kg)	Continuous intake for 13 years (ng/kg-day)
Girl, estrous cycle 28.5 days	166	28.40	114.0	0.01660
Girl, estrous cycle 29 days	693	215.5	455.1	0.1224
Girl, estrous cycle 29.5 days	2020	1008	1295	0.5693
Girl, estrous cycle 30 days	8450	7193	5179	4.054

Table D-8. Matching critical window peak after pulse to peak critical window concentration for continuous intake run

Person modeled, beginning at age 0	Lipid adjusted serum (adjusted to 1976-1977 levels) ng/kg from Figure 1A	Pulse dose, 0.5 year lag time (ng/kg)	Peak lipid adjusted serum after incident (ng/kg)	Continuous intake for 13 years (ng/kg-day)
Girl, estrous cycle 28.5 days	166	28.40	838.2	0.1800
Girl, estrous cycle 29 days	693	215.5	6183	3.148
Girl, estrous cycle 29.5 days	2020	1008	28316	20.86
Girl, estrous cycle 30 days	8450	7193	198240	166.6

D.5. REFERENCES

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APPENDIX E

Noncancer Benchmark Dose Modeling

NOTICE

THIS DOCUMENT IS AN EXTERNAL REVIEW DRAFT. It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH

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APPENDIX E. NONCANCER BENCHMARK DOSE MODELING

E.1. BMDS INPUT TABLES

E.1.1. Amin et al. (2000)

Endpoint [c]	Administered Dose (ng/kg-day)		
	0	25 [a]	100
	Internal Dose (ng/kg blood) [b]		
	0	3.38	10.57
	(n = 10)	(n = 10)	(n = 10)
Saccharin consumed, female rats (0.25%) (ml saccharin solution/100 g body weight) [c]	31.67 ± 6.53	24.60 ± 3.79	10.70 ± 1.68
Saccharin consumed, female rats (0.50%) (ml saccharin solution/100 g body weight) [c]	22.40 ± 5.05	11.38 ± 2.42	4.54 ± 1.05
Saccharin preference ratio, female rats (0.25%) (ratio of saccharin solution consumed to total fluid consumed) [d]	82.14 ± 4.22	58.12 ± 10.71	54.87 ± 6.17
Saccharin preference ratio, female rats (0.50%) (ratio of saccharin solution consumed to total fluid consumed) [d]	72.73 ± 7.79	44.48 ± 10.39	33.77 ± 7.79

[a] LOAEL identified.
[b] From the Emond PBPK model described in 3.3.
[c] Values are the mean ± SE. Data obtained from Figure 2 in Amin et al. 2000.
[d] Values are the ratio ± SE. Data obtained from Figure 3 in Amin et al. 2000.

E.1.2. Bell et al. (2007)

Endpoint	Administered Dose (ng/kg-day)			
	0	2.4 [a]	8	46
	Internal Dose (ng/kg blood) [b]			
	0	2.20	5.14	18.41
	(n = 30)	(n = 30)	(n = 30)	(n = 30)
Proportion of male rat pups that had not undergone balano-preputial separation on PND 49 [c]	1/30 (3%)	5/30 (17%)	6/30 (20%)	15/30 (50%)

[a] LOAEL identified.
[b] From the Emond PBPK model described in 3.3.
[c] Data obtained from Figure 2 in Bell et al. 2007.

E.1.3. Cantoni et al. (1981)

Endpoint	Administered Dose (ng/kg-day)			
	0	1.43 [a]	14.3	143
	Internal Dose (ng/kg blood) [b]			
	0	1.85	8.84	50.05
	(n = 4)	(n = 4)	(n = 3)	(n = 3)
Urinary coproporphyrins in female rats (µg coproporphyrin methyl ester/24 hr) at 3 months [c]	0.74 ± 0.17	1.81 ± 0.42 [d]	2.73 ± 0.75 [e]	3.00 ± 1.30 [e]
Urinary porphyrins in rats (nmol/24 hr) after 45 weeks [c]	2.27 ± 0.49	5.55 ± 0.85 [d]	7.62 ± 1.79 [d]	196.89 ± 63.14 [e]

[a] LOAEL identifed.
[b] From the Emond PBPK model described in 3.3.
[c] Values are the mean ± SE. Data for urinary coproporphyrins and urinary porphyrins obtained from Figure 1 and Table 1, respectively, in Cantoni et al. 1981.
[d] Statistically significant as compared to control ($p < 0.05$).
[e] Statistically significant as compared to control ($p < 0.01$).

E.1.4. Crofton et al. (2005)

Endpoint	Administered Dose (ng/kg-day)									
	0	0.1	3	10	30 [a]	100 [b]	300	1,000	3,000	10,000
	Internal Dose (ng/kg blood) [c]									
	0	0.02	0.49	1.38	3.46	9.26	23.07	65.65	180.90	583.48
	(n = 14)	(n = 6)	(n = 12)	(n = 6)	(n = 6)	(n = 6)	(n = 6)	(n = 6)	(n = 6)	(n = 4)
Serum T4 in female rats (% control) [d]	100.00 ± 15.44	96.27 ± 14.98	98.57 ± 18.11	99.76 ± 19.04	93.32 ± 12.11	70.94 ± 12.74	62.52 ± 14.75	52.68 ± 22.73	54.66 ± 19.71	49.15 ± 11.15

[a] NOAEL identifed.
[b] LOAEL identifed.
[c] From the Emond PBPK model described in 3.3.
[d] Values are the mean ± SD. Data were obtained from a Crofton et al. supplemental file, available at http://ehp.niehs.nih.gov/docs/2005/8195/supplemental.pdf.

E.1.5. DeCaprio et al. (1986)

Endpoint	Administered Dose (ng/kg-day)				
	0	0.12	0.61 [a]	4.9 [b]	26
	Internal Dose (ng/kg blood) [c]				
	n/a	n/a	n/a	n/a	n/a
	(n = 10)	(n = 10)	(n = 11)	(n = 10)	(n = 4)
Absolute kidney weight (g), males [d]	5.49 ± 0.17	5.14 ± 0.12	4.71 ± 0.12	4.3 ± 0.15 [f]	-
Absolute thymus weight (g), males [d]	0.56 ± 0.050	0.45 ± 0.022	0.44 ± 0.034	0.35 ± 0.167 [g]	-
Body weight (g), males [e]	713 ± 15	682 ± 16	651 ± 19	603 ± 20 [f]	433 ± 38 [h]
Relative brain weight, males [d]	0.54 ± 0.015	0.56 ± 0.016	0.6 ± 0.016	0.65 ± 0.016 [f]	-
Relative liver weight, males [d]	4.54 ± 0.23	4.1 ± 0.14	5.36 ± 0.61	5.63±0.29 [f]	-
Relative thymus weight, males [d]	0.078 ± 0.006	0.066 ± 0.003	0.068 ± 0.004	0.06±0.003 [f]	-
Endpoint	**Administered Dose (ng/kg-day)**				
	0	**0.12**	**0.68**	**4.86**	**31**
	Internal Dose (ng/kg blood) [c]				
	0	**n/a**	**n/a**	**n/a**	**n/a**
	(n = 8)	**(n = 10)**	**(n = 9)**	**(n = 10)**	**(n = 4)**
Body weight (g), females [e]	602 ± 12	583 ± 22	570 ± 22	531 ± 14 [f]	351 ± 49 [h]
Relative liver weight, females [d]	4.3 ± 0.26	4.49 ± 0.35	4.27 ± 0.16	5.54 ± 0.43 [f]	-

[a] NOAEL identified.
[b] LOAEL identified.
[c] Internal dose not calculated using the Emond PBPK (guinea pigs).
[d] Organ weight data in guinea pigs obtained from Table 2 of DeCaprio et al. 1986. Values are the mean ± SE. Relative organs weights were calculated as organ weight (g) / body weight (g) X 100.
[e] Body weight data in guinea pigs obtained from Table 1 of DeCaprio et al. 1986. Values are the mean ± SE.
[f] Statistically significant as compared to control ($p < 0.05$).
[g] Statistically significant as compared to control ($p < 0.01$).
[h] Statistically significant as compared to control ($p < 0.001$).

E.1.6. Franc et al. (2001)

Endpoint	Administered Dose (ng/kg-day)			
	0	10 [a]	30 [b]	100
	Internal Dose (ng/kg blood) [c]			
	0	6.59	14.48	36.43
	(n = 8)	(n = 8)	(n = 8)	(n = 8)
S-D rats, relative liver weight [d]	100.0 ± 5.0	108.1 ± 6.0 [e]	116.8 ± 9.2 [e]	155.3 ± 10.9 [e]
L-E rats, relative liver weight [d]	100.0 ± 3.5	106.3 ± 6.3	116.8 ± 3.2 [e]	122.2 ± 7.0 [e]
S-D rats, relative thymus weight [d]	100.2 ± 29.4	91.2 ± 17.0	51.4 ± 15.4 [e]	22.8 ± 10.6 [e]
L-E rats, relative thymus weight [d]	103.4 ± 19.3	95.4 ± 24.9	38.7 ± 17.0 [e]	35.0 ± 27.6 [e]
H/W rats, relative thymus weight [d]	101.2 ± 12.7	97.5 ± 11.7.0	71.0 ± 8.5 [e]	49.3 ± 15.4 [e]

[a] NOAEL identified.
[b] LOAEL identified.
[c] From the Emond PBPK model described in 3.3.
[d] Values are the mean ± SE. Data obtained from Figure 5 in Franc et al. 2001.
[e] Statistically significant as compared to control ($p < 0.05$).

E.1.7. Hojo et al. (2002)

Endpoint	Administered Dose (ng/kg-day)			
	0	20 [a]	60	180
	Internal Dose (ng/kg blood) [b]			
	0	1.62	4.17	10.70
	(n = 5)	(n = 5)	(n = 6)	(n = 5)
DRL reinforcements/min, rat litters [c]	-0.814 ± 0.45	-0.364 ± 0.82	0.374 ± 0.54	-0.163 ± 0.44
DRL responses/min, rat litters [c]	18.44 ± 7.99	-0.99 ± 10.96	-4.52 ± 7.19	-0.41 ± 15.23

[a] LOAEL identified.
[b] From the Emond PBPK model described in 3.3.
[c] DRL = differential reinforcement of low rate. Values are the mean ± SD. Data obtained from Table 5 in Hojo et al. 2002.

E.1.8. Kattainen et al. (2001)

Endpoint	Administered Dose (ng/kg-day)				
	0	30 [a]	100	300	1,000
	Internal Dose (ng/kg blood) [b]				
	0	2.23	6.25	16.08	46.86
	(n = 16)	(n = 17)	(n = 15)	(n = 12)	(n = 19)
3rd molar mesio-distal length in female rat offspring (molar development) (mm) [c]	1.86 ± 0.017	1.58 ± 0.045 [e]	1.6 ± 0.069 [e]	1.5 ± 0.064 [e]	1.35 ± 0.118 [e]
Proportion of female rat offspring without 3rd molar eruption on PND 35 [d]	1/16 (10%)	3/17 (20%)	4/15 (30%)	6/12 (50%) [e]	13/19 (70%) [e]

[a] LOAEL identified.
[b] From the Emond PBPK model described in 3.3.
[c] Values are the mean ± SE. Data were obtained from Figure 3 in Kattainen et al. 2001.
[d] Data were obtained from Figure 2 in Kattainen et al. 2001.
[e] Statistically significant as compared to control ($p < 0.05$).

E.1.9. Keller et al. (2007, 2008a, b)

Endpoint	Administered Dose (ng/kg-day)			
	0	10 [a]	100	1,000
	Internal Dose (ng/kg blood) [b]			
	0	0.54	4.29	34.06
Frequency of missing 3rd mandibular molars in CBA J mice [c]	0/29 (0%)	2/23 (10%)	6/29 (20%)	30/30 (100%)

[a] LOAEL identified.
[b] From the Emond PBPK model described in 3.3.
[c] Data obtained from Table 1 in Keller et al. 2007.

E.1.10. Kociba et al. (1978)

Endpoint	Administered Dose (ng/kg-day)			
	0	1 [a]	10 [b]	100
	Internal Dose (ng/kg blood) [c]			
	0	1.55	7.15	38.56
	(n = 5)	(n = 5)	(n = 5)	(n = 5)
Urinary coproporphyrin (µg/48 h), female rats [d]	9.8 ± 1.3	8.6 ± 2	16.4 ± 4.7 [e]	17.4 ± 4 [e]
µg uroporphyrin per mg creatinine, female rats [d]	0.157 ± 0.05	0.143 ± 0.037	0.181 ± 0.053	0.296 ± 0.074 [e]

[a] NOAEL identified.
[b] LOAEL identified.
[c] From the Emond PBPK model described in 3.3.
[d] Values are the mean ± SD. Data obtained from Table 2 in Kociba et al. 1978.
[e] Statistically significant as compared to control ($p < 0.05$).

E.1.11. Latchoumycandane and Mathur (2002)

Endpoint	Administered Dose (ng/kg-day)			
	0	1 [a]	10	100
	Internal Dose (ng/kg blood) [b]			
	0	0.78	4.65	27.27
	(n = 6)	(n = 6)	(n = 6)	(n = 6)
Daily sperm production ($\times 10^6$) in adult male rats (mg) [c]	22.19 ± 2.67	15.67 ± 2.65 [d]	13.65 ± 2.19 [d]	13.1 ± 3.16 [d]

[a] LOAEL identified.
[b] From the Emond PBPK model described in 3.3.
[c] Values are the mean ± SD. Data obtained from Table 1 in Latchoumycandane and Mathur 2002.
[d] Statistically significant as compared to control ($p < 0.05$).

E.1.12. Li et al. (1997)

Endpoint	Administered Dose (ng/kg-day)									
	0	3 [a]	10 [b]	30	100	300	1,000	3,000	10,000	30,000
	Internal Dose (ng/kg blood) [c]									
	0	0.27	0.80	2.1	5.87	15	43.33	119.94	385.96	1171.90
	(n = 10)	(n =10)	(n = 10)	(n = 10)	(n = 10)	(n = 10)	(n = 10)	(n = 10)	(n = 10)	(n = 10)
Serum FSH (ng/ml) in female rats [d]	23.86 ± 9.38	22.16 ± 15.34	85.23 ± 29.83	73.30 ± 15.34	126.14 ± 50.28	132.10 ± 36.65	116.76 ± 16.19	304.26 ± 48.58	346.88 ± 47.73	455.11 ± 90.34

[a] NOAEL identified.
[b] LOAEL identified.
[c] From the Emond PBPK model described in 3.3.
[d] Values are the mean ± SE. Data obtained from Figure 3 in Li et al. 1997.

E.1.13. Li et al. (2006)

Endpoint	Administered Dose (ng/kg-day)			
	0	2 [a]	50	100
	Internal Dose (ng/kg blood) [b]			
	0	0.16	2.84	5.12
	(n = 10)	(n = 10)	(n = 10)	(n = 10)
Serum estradiol/(pg·ml)$^{-1}$ in female mice (1~3d) [c]	10.17 ± 3.85	19.91 ± 6.31	24.72 ± 4.60	18.09 ± 5.57
Serum progesterone (ng·ml)$^{-1}$ in female mice (1~3d) [c]	61.74 ± 3.51	30.56 ± 12.80 [d]	16.93 ± 10.53	11.36 ± 13.83

[a] LOAEL identified.
[b] From the Emond PBPK model described in 3.3.
[c] Values are the mean ± SE. Data obtained from Figures 3 (estradiol) and 4 (progesterone) in Li et al. 2006.
[d] Statistically significant as compared to control ($p < 0.01$).

E.1.14. Markowski et al. (2001)

Endpoint	Administered Dose (ng/kg-day)			
	0	20 [a]	60	180
	Internal Dose (ng/kg blood) [b]			
	0	1.56	4.03	10.32
	(n = 7)	(n = 4)	(n = 6)	(n = 7)
FR10 earned run opportunities, adult female offspring [c]	13.29 ± 8.65	11.25 ± 5.56	5.75 ± 3.53	7 ± 6.01
FR2 total revolutions, adult female offspring [c]	119.29 ± 69.9	108.5 ± 61	56.5 ± 31.21	68.14 ± 33.23
FR5 earned run opportunities, adult female offspring [c]	26.14 ± 12.28	23.5 ± 7.04	12.8 ± 6.17	13.14 ± 7.14

[a] LOAEL identified.
[b] From the Emond PBPK model described in 3.3.
[c] Values are the mean ± SD. Data obtained from Table 3 in Markowski et al. 2001.

E.1.15. Miettinen et al. (2006)

Endpoint	Administered Dose (ng/kg-day)				
	0	30 [a]	100	300	1,000
	Internal Dose (ng/kg blood) [b]				
	0	2.22	6.23	16.01	46.64
	(n = 42)	(n = 29)	(n = 15)	(n = 24)	(n = 32)
Cariogenic lesions in rat pups [c]	25/42 (60%)	23/29 (79%) [d]	19/25 (76%)	20/24 (83%) [d]	29/32 (91%) [d]

[a] LOAEL identified.
[b] From the Emond PBPK model described in 3.3.
[c] Data obtained from Table 2 in Miettinen et al. 2006.
[d] Statistically significant as compared to control ($p < 0.05$).

E.1.16. National Toxicology Program (1982)

Endpoint	Administered Dose (ng/kg-day)			
	0	1.43 [a]	7.14	71.4
	Internal Dose (ng/kg blood) [b]			
	0	0.77	2.27	11.24
	(n = 73)	(n = 49)	(n = 49)	(n = 50)
Numbers of male mice with toxic hepatitis [c]	1/73 (1.4%)	5/49 (10%)	3/49 (6.1%)	44/50 (88%)

[a] LOAEL identified.
[b] From the Emond PBPK model described in 3.3.
[c] Data obtained from Table 11 in NTP 1982.

E.1.17. National Toxicology Program (2006)

Endpoint [e]	Administered Dose (ng/kg-day)					
	0	2.14 [a]	7.14	15.7	32.9	71.4
	Internal Dose (ng/kg blood) [b]					
	0	2.56	5.69	9.79	16.57	29.70
	(n = 10)	(n = 10)	(n = 10)	(n = 10)	(n = 10)	(n = 10)
Gingival squamous hyperplasia	1/53 (2%)	7/54 (13%)[d]	14/53 (26%)[c]	13/53 (25%)[c]	15/53 (28%)[c]	16/53 (30%)[c]
Liver, hepatocyte hypertrophy	0/53 (0%)	19/54 (40%)[c,]	19/53 (40%)[c]	42/53 (80%)[c]	41/53 (80%)[c]	52/53 (100%)[c]
Heart, cardiomyopathy	10/53 (19%)	12/54 (22%)	22/53[c] (42%)	25/52[c] (48%)	32/53[c] (60%)	36/52[c] (69%)
Liver, eosinophilic focus, multiple	3/53 (6%)	8/54 (15%)	14/53 (26%)	17/53 (32%)	22/53 (42%)	42/53 (79%)
Liver, fatty change, diffuse	0/53 (0%)	2/54 (4%)	12/53[c] (23%)	17/53[c] (32%)	30/53[c] (57%)	48/53[c] (91%)
Liver, necrosis	1/53 (2%)	4/54 (7%)	4/53 (8%)	8/53[d] (15%)	10/53[c] (19%)	17/53[c] (32%)
Liver, pigmentation	4/53 (8%)	9/54 (17%)	34/53[c] (64%)	48/53[c] (91%)	52/53[c] (98%)	53/53[c] (100%)
Liver, toxic hepatopathy	0/53 (0%)	2/54 (4%)	8/53 (15%)	30/53 (57%)	45/50 (85%)	53/53 (100%)
Oval cell hyperplasia	0/53 (0%)	4/54 (10%)[d]	3/53 (10%)	20/53 (40%)[c]	38/53 (70%)[d]	53/53 (100%)[c]
Lung, alveolar to bronchiolar epithelial metaplasia (Alveolar epithelium, metaplasia, bronchiolar)	2/53 (4%)	19/54 [c] (35%)	33/53[c] (62%)	35/52[c] (67%)	45/53[c] (85%)	46/52[c] (89%)

[a] LOAEL identified.
[b] From the Emond PBPK model described in 3.3.
[c] Statistically significant as compared to control ($p < 0.01$).
[d] Statistically significant as compared to control ($p < 0.05$).
[e] Data are for female rats in 2-year gavage study. Data for all endpoints obtained from Table A5b in NTP 2006.

E.1.18. Ohsako et al. (2001)

Endpoint	Administered Dose (ng/kg-day)				
	0	12.5 [a]	50 [b]	200	800
	Internal Dose (ng/kg blood) [c]				
	0	1.04	3.47	11.36	38.42
	(n = 12)	(n = 10)	(n = 10)	(n = 10)	(n = 12)
Anogenital distance (mm) in male rat offspring, PND120 [d]	28.91 ± 0.90	27.94 ± 0.79	25.17 ± 1.02 [e]	26.01 ± 0.90 [f]	23.80 ± 0.45 [e]

[a] NOAEL for selected endpoint.
[b] LOAEL for selected endpoint.
[c] From the Emond PBPK model described in 3.3.
[d] Values are the mean ± SE. Data obtained from Figure 7 in Ohsako et al. 2001.
[e] Statistically significant as compared to control ($p < 0.01$).
[f] Statistically significant as compared to control ($p < 0.05$).

E.1.19. Shi et al. (2007)

Endpoint	Administered Dose (ng/kg-day)				
	0	0.143 [a]	0.714 [b]	7.14	28.6
	Internal Dose (ng/kg blood) [c]				
	0	0.34	1.07	5.23	13.91
	(n = 10)	(n = 10)	(n = 10)	(n = 10)	(n = 10)
Serum estradiol – 17β at proestrus 9 in female rats at 9 mo.of age (pg/ml) [d]	102.86 ± 13.10	86.19 ± 6.19	63.33 ± 9.29 [e]	48.1 ± 5.95 [e]	38.57 ± 7.14 [e]

[a] NOAEL identified.
[b] LOAEL identified.
[c] From the Emond PBPK model described in 3.3.
[d] Values are the mean ± SE. Data obtained from Figure 4 in Shi et al. 2007.
[e] Statistically significant as compared to control ($p < 0.05$).

E.1.20. Smialowicz et al. (2008)

Endpoint	Administered Dose (ng/kg-day)				
	0	1.07 [a]	10.7	107	321
	Internal Dose (ng/kg blood) [b]				
	0	0.44	2.46	13.40	31.65
	(n = 15)	(n = 14)	(n = 15)	(n = 15)	(n = 8)
PFC per 10^6 cells in female mice [c]	1491 ± 716	1129 ± 171 [d]	945 ± 516 [d]	677 ± 465 [d]	161 ± 117 [d]
PFC x 10^4 per spleen in female mice [c]	27.8 ± 13.4	21 ± 13.6 [d]	17.6 ± 9.4 [d]	12.6 ± 8.7 [d]	3.0 ± 3.1 [d]

[a] LOAEL identified.
[b] From the Emond PBPK model described in 3.3.
[c] Values are the mean ± SD. Data obtained from Table 4 in Smialowicz et al. 2008.
[d] Statistically significant as compared to control ($p < 0.05$).

E.1.21. Toth et al. (1979)

Endpoint	Administered Dose (ng/kg-day)			
	0	1 [a]	100	1,000
	Internal Dose (ng/kg blood) [b]			
	0	0.57	14.21	91.21
	(n =38)	(n = 44)	(n = 44)	(n = 43)
Number with amyloidosis plus skin lesions in mice [c]	0/38 (0%)	5/44 (11%)	10/44 (23%)	17/43 (40%)
Number with skin lesions in mice [c]	0/38 (0%)	5/44 (11%)	13/44 (30%)	25/43 (58%)

[a] LOAEL identified.
[b] From the Emond PBPK model described in 3.3.
[c] Data obtained from Table 2 in Toth et al. 1979.

E.1.22. Van Birgelen et al. (1995)

Endpoint	Administered Dose (ng/kg-day)					
	0	14 [a]	26	47	320	1,024
	Internal Dose (ng/kg blood) [b]					
	0	7.20	11.76	18.09	86.41	250.16
	n = 8	n = 8	n = 8	n = 8	n = 8	n = 8
Hepatic retinol (mg/g liver) in female rats [c]	14.9 ± 3.1	8.4 ± 1.2 [d]	8.2 ± 0.8 [d]	5.1 ± 0.3 [d]	2.2 ± 0.3 [d]	0.6 ± 0.2 [d]
Hepatic retinol palmitate (mg/g liver) in female rats [c]	472 ± 96	94 ± 24 [d]	107 ± 27 [d]	74 ± 14 [d]	22 ± 8 [d]	3 ± 1 [d]
Plasma FT4 (pmol/liter) in female rats [c]	23.4 ± 1.1	24.5 ± 2.0	22.4 ± 1.0	19.3 ± 3.3	16.3 ± 1.5 [d]	10.3 ± 1.7 [d]
Plasma TT4 (nmol/liter) in female rats [c]	40.9 ± 2.4	41.4 ± 1.9	41.4 ± 2.3	32.3 ± 2.6 [d]	33.6 ± 2.2 [d]	25.5 ± 2.7 [d]

[a] LOAEL identified.
[b] From the Emond PBPK model described in 3.3.
[c] Values are the mean ± SE. Data obtained from Table 3 in Van Birgelen et al. 1995.
[d] Statistically significant as compared to control ($p < 0.05$).

E.1.23. White et al. (1986)

Endpoint	Administered Dose (ng/kg-day)						
	0	10 [a]	50	100	500	1,000	2,000
	Internal Dose (ng/kg blood) [b]						
	0	1.09	4.08	7.14	26.81	48.72	90.56
	(n = 8)	(n = 8)	(n = 8)	(n = 8)	(n = 8)	(n = 8)	(n = 8)
CH50 (U/ml) in female mice [c]	91 ± 5	54 ± 3 [d]	63 ± 4 [d]	56 ± 9 [d]	41 ± 6 [d]	32 ± 6 [d]	17 ± 6 [d]

[a] LOAEL identified.
[b] From the Emond PBPK model described in 3.3.
[c] Values are the mean ± SE. Data obtained from Table 1 in White et al. 1986.
[d] Statistically significant as compared to control ($p < 0.05$).

E.2. ALTERNATE DOSE: WHOLE BLOOD BMDS RESULTS

E.2.1. Amin et al., 2000: 0.25% Saccharin Consumed, Female

E.2.1.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
linear [b]	**1**	**0.551**	**179.214**	**9.147E+00**	**6.094E+00**	
polynomial, 2-degree	1	0.551	179.214	9.147E+00	6.094E+00	
power	1	0.551	179.214	9.147E+00	6.094E+00	power bound hit (power = 1)
power, unrestricted [c]	0	N/A	180.858	8.367E+00	3.419E+00	unrestricted (power = 0.736)

[a] Non-constant variance model selected ($p = 0.0005$)
[b] Best-fitting model, BMDS output presented in this appendix
[c] Alternate model, BMDS output also presented in this appendix

E.2.1.2. *Output for Selected Model: Linear*

Amin et al., 2000: 0.25% Saccharin Consumed, Female

```
 ================================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\1\Blood\1_Amin_2000_25_SC_Linear_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\1_Amin_2000_25_SC_Linear_1.plt
                                                    Mon Feb 08 10:44:22 2010
 ================================================================================

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   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   Signs of the polynomial coefficients are not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                        lalpha =      5.29482
                           rho =            0
                        beta_0 =      31.5112
                        beta_1 =     -1.97726
```

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	beta_0	beta_1
lalpha	1	-0.99	-0.029	0.044
rho	-0.99	1	0.026	-0.04
beta_0	-0.029	0.026	1	-0.94
beta_1	0.044	-0.04	-0.94	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-2.54215	1.65048	-5.77702	0.692726
rho	2.40985	0.541771	1.34799	3.4717
beta_0	31.2644	4.1929	23.0464	39.4823
beta_1	-1.9414	0.436071	-2.79609	-1.08672

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	31.7	31.3	20.6	17.8	0.0727
3.378	10	24.6	24.7	12	13.4	-0.0264
10.57	10	10.7	10.8	5.33	4.91	-0.0362

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-92.841935	4	193.683870
A2	-85.255316	6	182.510632
A3	-85.429148	5	180.858295
fitted	-85.606998	4	179.213995
R	-98.136607	2	200.273213

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)

```
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              25.7626          4          <.0001
   Test 2              15.1732          2       0.0005072
   Test 3             0.347663          1          0.5554
   Test 4               0.3557          1          0.5509

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


             Benchmark Dose Computation

Specified effect =             1

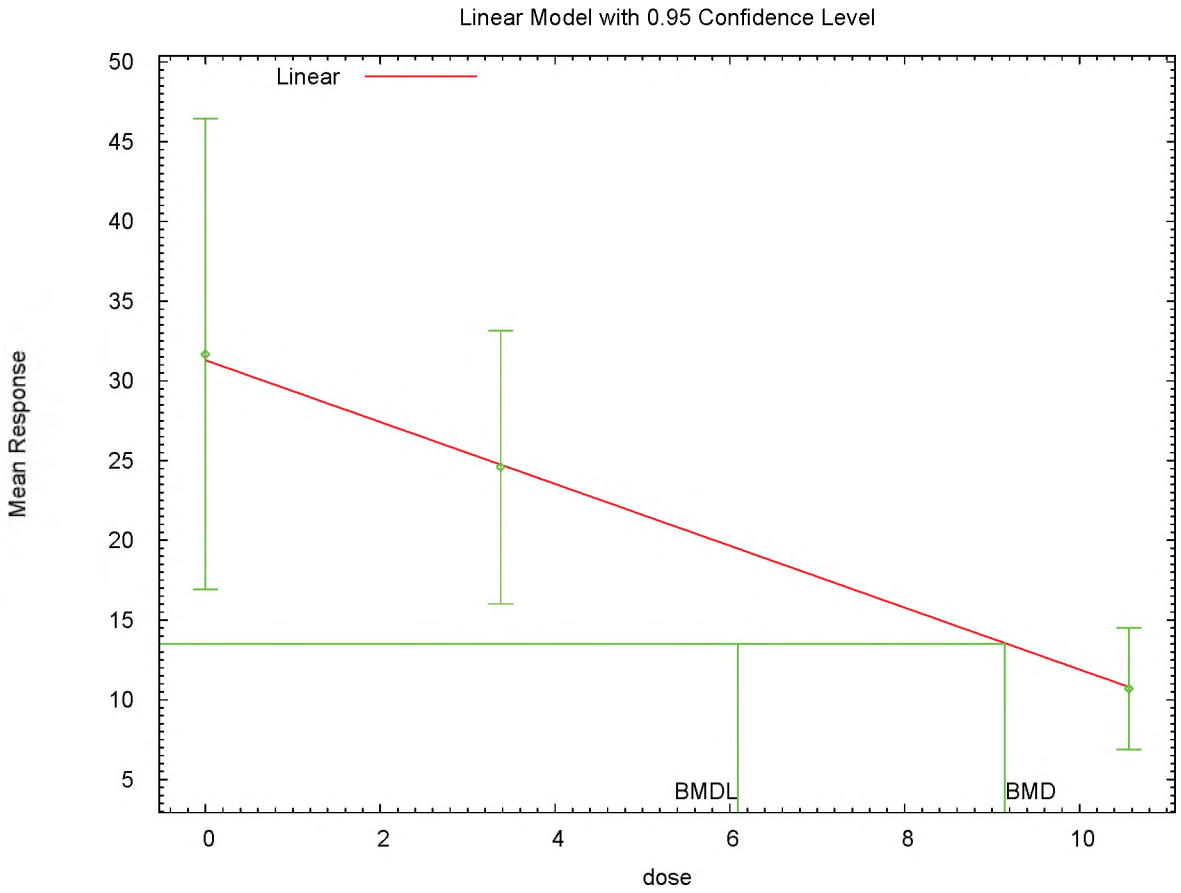
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

              BMD =        9.14709


             BMDL =        6.09414
```

E.2.1.3. *Figure for Selected Model: Linear*



E.2.1.4. *Output for Additional Model Presented: Power, Unrestricted*

Amin et al., 2000: 0.25% Saccharin Consumed, Female

```
 ================================================================
          Power Model. (Version: 2.15;  Date: 04/07/2008)
          Input Data File: C:\1\Blood\1_Amin_2000_25_SC_Pwr_U_1.(d)
          Gnuplot Plotting File:  C:\1\Blood\1_Amin_2000_25_SC_Pwr_U_1.plt
                                              Mon Feb 08 10:44:22 2010
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    The form of the response function is:

    Y[dose] = control + slope * dose^power


    Dependent variable = Mean
    Independent variable = Dose
    The power is not restricted
    The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)
```

```
   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                         lalpha =      5.29482
                            rho =            0
                        control =      31.6727
                          slope =      -2.2195
                          power =     0.952715


           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho      control        slope        power

    lalpha            1        -0.99         0.34        -0.17       -0.061

       rho        -0.99            1        -0.42         0.19        0.068

   control         0.34        -0.42            1        -0.72        -0.56

     slope        -0.17         0.19        -0.72            1         0.97

     power       -0.061        0.068        -0.56         0.97            1


                                Parameter Estimates

                                                      95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha         -2.48291          2.08669           -6.57274             1.60693
            rho          2.38455         0.692047            1.02817             3.74094
        control            32.99          5.40754            22.3914             43.5886
          slope         -3.91099          3.83883            -11.435             3.61299
          power         0.735877         0.350669          0.0485775             1.42318


      Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0    10       31.7           33         20.6         18.7         -0.223
3.378    10       24.6         23.4           12         12.4          0.302
10.57    10       10.7         10.8         5.33         4.94          -0.08

 Warning: Likelihood for fitted model larger than the Likelihood for model A3.


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user
```

```
Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                      Likelihoods of Interest

           Model      Log(likelihood)   # Param's      AIC
            A1          -92.841935           4     193.683870
            A2          -85.255316           6     182.510632
            A3          -85.429148           5     180.858295
         fitted         -85.429148           5     180.858295
             R          -98.136607           2     200.273213


                  Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              25.7626          4          <.0001
   Test 2              15.1732          2        0.0005072
   Test 3             0.347663          1           0.5554
   Test 4         -8.2423e-013          0              NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-Square
     test for fit is not valid


               Benchmark Dose Computation

Specified effect =            1

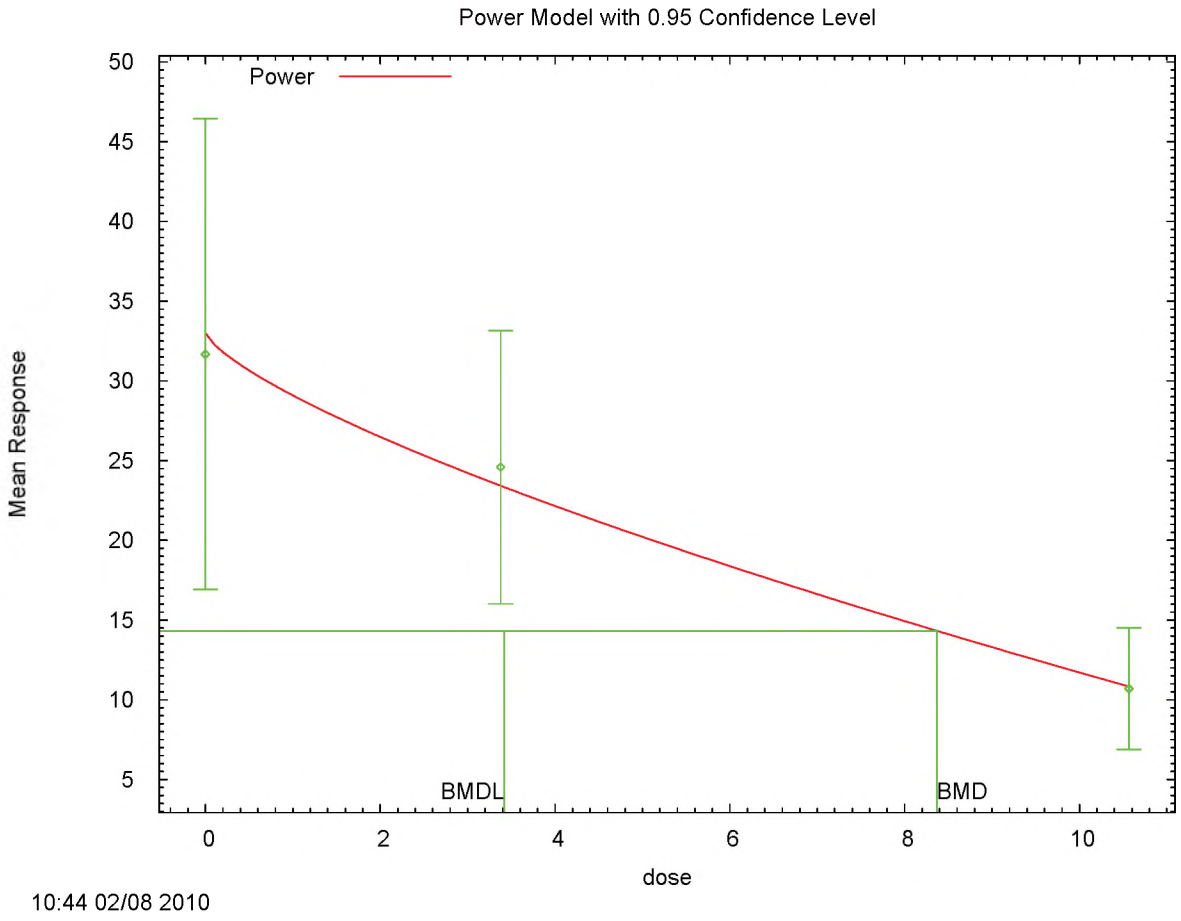
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 8.36678


            BMDL = 3.41906
```

E.2.1.5. *Figure for Additional Model Presented: Power, Unrestricted*



E.2.2. Amin et al., 2000: 0.25% Saccharin Preference Ratio, Female

E.2.2.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
linear [b]	**1**	**0.002**	**227.807**	**1.162E+01**	**5.572E+00**	
polynomial, 2-degree	1	0.002	227.807	1.162E+01	5.572E+00	
power	1	0.002	227.807	1.162E+01	5.572E+00	power bound hit (power = 1)

[a] Non-constant variance model selected ($p = 0.0135$)
[b] Best-fitting model, BMDS output presented in this appendix

E.2.2.2. *Output for Selected Model: Linear*

Amin et al., 2000: 0.25% Saccharin Preference Ratio, Female

```
 ================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\1\Blood\2_Amin_2000_25_SP_Linear_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\2_Amin_2000_25_SP_Linear_1.plt
                                                Mon Feb 08 10:44:49 2010
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   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   Signs of the polynomial coefficients are not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                        lalpha =      6.34368
                           rho =            0
                        beta_0 =      75.4888
                        beta_1 =     -2.24733


           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho       beta_0       beta_1

    lalpha            1           -1         0.22        -0.31

       rho           -1            1        -0.22         0.31

    beta_0         0.22        -0.22            1        -0.77

    beta_1        -0.31         0.31        -0.77            1


                              Parameter Estimates

                                                    95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha          3.00523           9.2122           -15.0503            21.0608
            rho         0.797764          2.21138           -3.53646            5.13199
         beta_0          75.1087          6.74312            61.8924            88.3249
         beta_1         -2.16469          1.00825           -4.14082          -0.188553


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------
```

```
    0    10       82.1         75.1         13.3         25.2          0.884
3.378    10       58.1         67.8         33.9         24.2          -1.27
10.57    10       54.9         52.2         19.5         21.8          0.383


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
      Model A3 uses any fixed variance parameters that
      were specified by the user

 Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                       Likelihoods of Interest

             Model      Log(likelihood)   # Param's      AIC
              A1         -108.574798            4     225.149597
              A2         -104.269377            6     220.538754
              A3         -105.147952            5     220.295903
          fitted         -109.903705            4     227.807410
               R         -112.382522            2     228.765045


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              16.2263          4         0.00273
   Test 2              8.61084          2          0.0135
   Test 3              1.75715          1           0.185
   Test 4              9.51151          1        0.002042

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1.  You may want to try a different
model


             Benchmark Dose Computation

Specified effect =            1
```

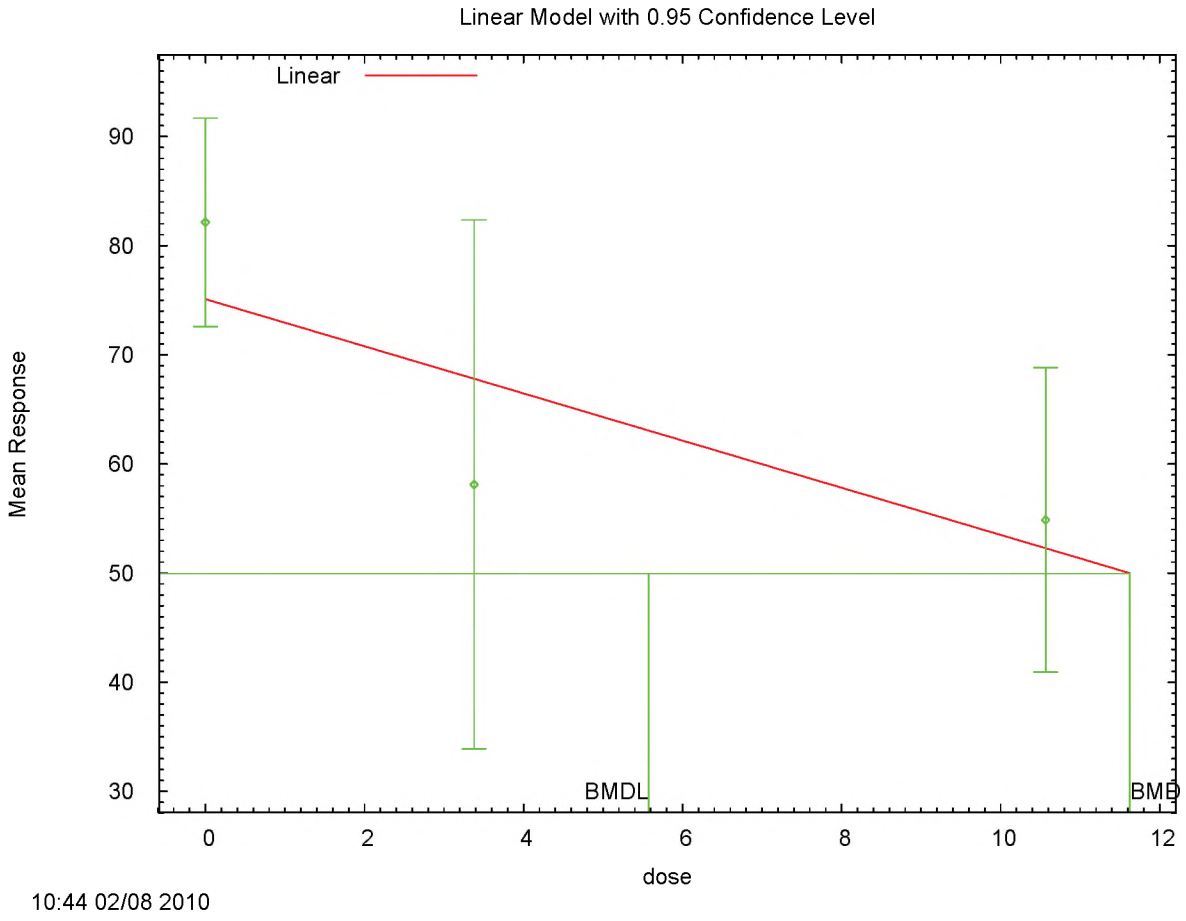
```
Risk Type          =     Estimated standard deviations from the control mean

Confidence level =          0.95

              BMD =        11.6241


             BMDL =        5.57215
```

E.2.2.3. *Figure for Selected Model: Linear*



E.2.3. Amin et al., 2000: 0.50% Saccharin Consumed, Female

E.2.3.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
linear [b]	**1**	**0.060**	**158.591**	**1.016E+01**	**6.567E+00**	
polynomial, 2-degree	1	0.060	158.591	1.016E+01	6.567E+00	
power	1	0.060	158.591	1.016E+01	6.567E+00	power bound hit (power = 1)
power, unrestricted [c]	0	N/A	157.060	6.567E+00	1.155E+00	unrestricted (power = 0.396)

[a] Non-constant variance model selected (p = <0.0001)
[b] Best-fitting model, BMDS output presented in this appendix
[c] Alternate model, BMDS output also presented in this appendix

E.2.3.2. *Output for Selected Model: Linear*

Amin et al., 2000: 0.50% Saccharin Consumed, Female

```
 ================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\1\Blood\3_Amin_2000_50_SC_Linear_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\3_Amin_2000_50_SC_Linear_1.plt
                                                Mon Feb 08 10:45:20 2010
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   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   Signs of the polynomial coefficients are not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                        lalpha =      4.68512
                           rho =            0
                        beta_0 =      20.0631
                        beta_1 =     -1.57142


          Asymptotic Correlation Matrix of Parameter Estimates
```

	lalpha	rho	beta_0	beta_1
lalpha	1	-0.96	0.019	-0.0016
rho	-0.96	1	-0.031	0.015
beta_0	0.019	-0.031	1	-0.96
beta_1	-0.0016	0.015	-0.96	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-0.982115	0.982262	-2.90731	0.943084
rho	2.11808	0.401166	1.33181	2.90435
beta_0	18.6171	3.1782	12.3879	24.8462
beta_1	-1.33226	0.322037	-1.96344	-0.70108

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	22.4	18.6	16	13.5	0.873
3.378	10	11.4	14.1	7.66	10.1	-0.856
10.57	10	4.54	4.54	3.33	3.04	-0.00339

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-83.696404	4	175.392808
A2	-73.511830	6	159.023660
A3	-73.530233	5	157.060467
fitted	-75.295363	4	158.590726
R	-90.294746	2	184.589492

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	33.5658	4	<.0001
Test 2	20.3691	2	<.0001
Test 3	0.0368066	1	0.8479
Test 4	3.53026	1	0.06026

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

Specified effect = 1

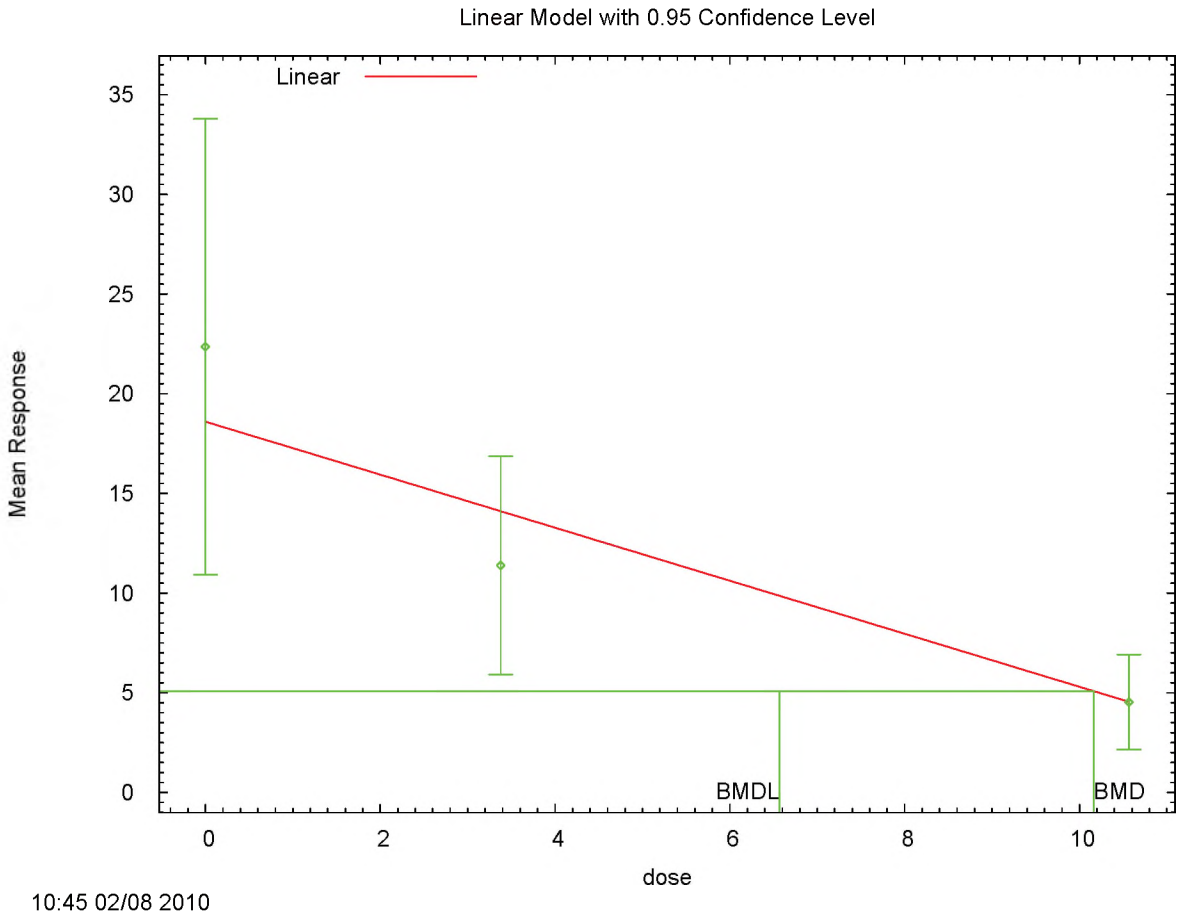
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 10.1633

BMDL = 6.56742

E.2.3.3. *Figure for Selected Model: Linear*



E.2.3.4. *Output for Additional Model Presented: Power, Unrestricted*

Amin et al., 2000: 0.50% Saccharin Consumed, Female

```
================================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\Blood\3_Amin_2000_50_SC_Pwr_U_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\3_Amin_2000_50_SC_Pwr_U_1.plt
                                                Mon Feb 08 10:45:20 2010
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  The form of the response function is:

  Y[dose] = control + slope * dose^power


  Dependent variable = Mean
  Independent variable = Dose
  The power is not restricted
  The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)
```

```
   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                         lalpha =      4.68512
                            rho =            0
                        control =      22.3564
                          slope =     -6.53901
                          power =     0.425213


           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho      control        slope        power

    lalpha            1        -0.96         0.34        -0.31        -0.15

       rho        -0.96            1        -0.47         0.36         0.15

   control         0.34        -0.47            1        -0.81        -0.52

     slope        -0.31         0.36        -0.81            1         0.92

     power        -0.15         0.15        -0.52         0.92            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha        -0.708629            1.298          -3.25267             1.83541
            rho          1.96142         0.529653           0.923323             2.99953
        control          22.6293          4.48416            13.8405             31.4181
          slope         -7.10123          4.04394           -15.0272            0.824743
          power         0.395571         0.168677          0.0649698            0.726173


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0    10       22.4         22.6           16           15        -0.0577
3.378    10       11.4         11.1         7.66         7.46          0.105
10.57    10       4.54         4.58         3.33         3.12        -0.0475

Degrees of freedom for Test A3 vs fitted <= 0


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
      Model A3 uses any fixed variance parameters that
      were specified by the user
```

```
Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                       Likelihoods of Interest

           Model      Log(likelihood)   # Param's      AIC
            A1          -83.696404           4     175.392808
            A2          -73.511830           6     159.023660
            A3          -73.530233           5     157.060467
         fitted         -73.530233           5     157.060467
             R          -90.294746           2     184.589492


                  Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              33.5658          4          <.0001
   Test 2              20.3691          2          <.0001
   Test 3            0.0368066          1          0.8479
   Test 4                    0          0             NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-Square
     test for fit is not valid


               Benchmark Dose Computation

Specified effect =            1

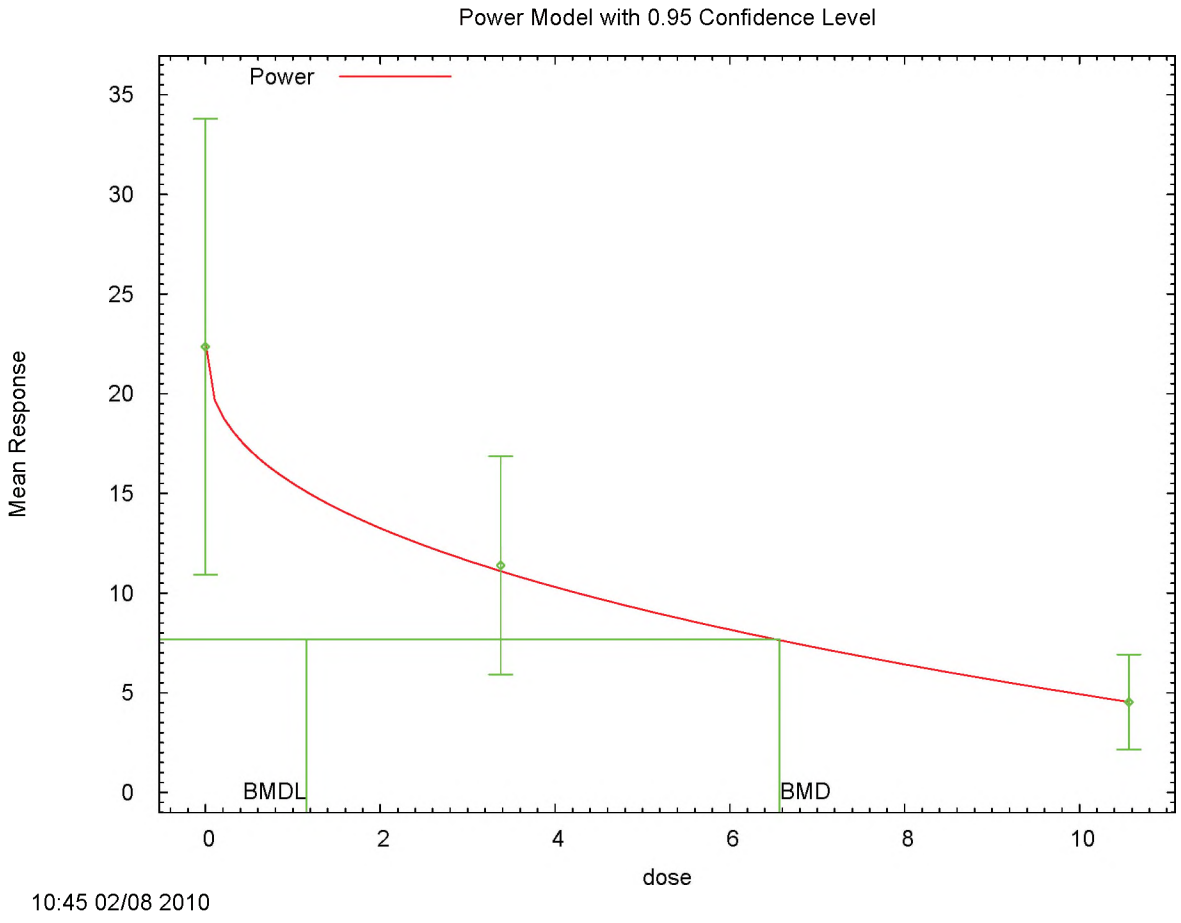
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 6.56719


            BMDL = 1.15476
```

E.2.3.5. *Figure for Additional Model Presented: Power, Unrestricted*



E.2.4. Amin et al., 2000: 0.50% Saccharin Preference Ratio, Female

E.2.4.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
linear [b]	**1**	**0.135**	**234.250**	**8.144E+00**	**5.105E+00**	
polynomial, 2-degree	1	0.135	234.250	8.144E+00	5.105E+00	
power	1	0.135	234.250	8.144E+00	5.105E+00	power bound hit (power = 1)
power, unrestricted [c]	0	N/A	234.020	2.598E+00	1.057E-14	unrestricted (power = 0.282)

[a] Constant variance model selected ($p = 0.5593$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.2.4.2. *Output for Selected Model: Linear*

Amin et al., 2000: 0.50% Saccharin Preference Ratio, Female

```
 ================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\1\Blood\4_Amin_2000_50_SP_LinearCV_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\4_Amin_2000_50_SP_LinearCV_1.plt
                                                  Mon Feb 08 10:45:50 2010
 ================================================================

 -
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                         alpha =      764.602
                           rho =            0   Specified
                        beta_0 =      65.8627
                        beta_1 =     -3.34297
```

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	beta_0	beta_1
alpha	1	2.6e-008	2.1e-009
beta_0	2.6e-008	1	-0.73
beta_1	2.1e-009	-0.73	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval	
			Lower Conf. Limit	Upper Conf. Limit
alpha	741.255	191.391	366.135	1116.38
beta_0	65.8627	7.22524	51.7015	80.0239
beta_1	-3.34297	1.12815	-5.55412	-1.13183

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	72.7	65.9	24.6	27.2	0.797
3.378	10	44.5	54.6	32.9	27.2	-1.17
10.57	10	33.8	30.5	24.6	27.2	0.375

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that
were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.009921	4	234.019841
A2	-112.428886	6	236.857773
A3	-113.009921	4	234.019841
fitted	-114.125184	3	234.250368
R	-117.976057	2	239.952114

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)

```
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              11.0943          4         0.02552
   Test 2              1.16207          2          0.5593
   Test 3              1.16207          2          0.5593
   Test 4              2.23053          1          0.1353

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


             Benchmark Dose Computation

Specified effect =             1

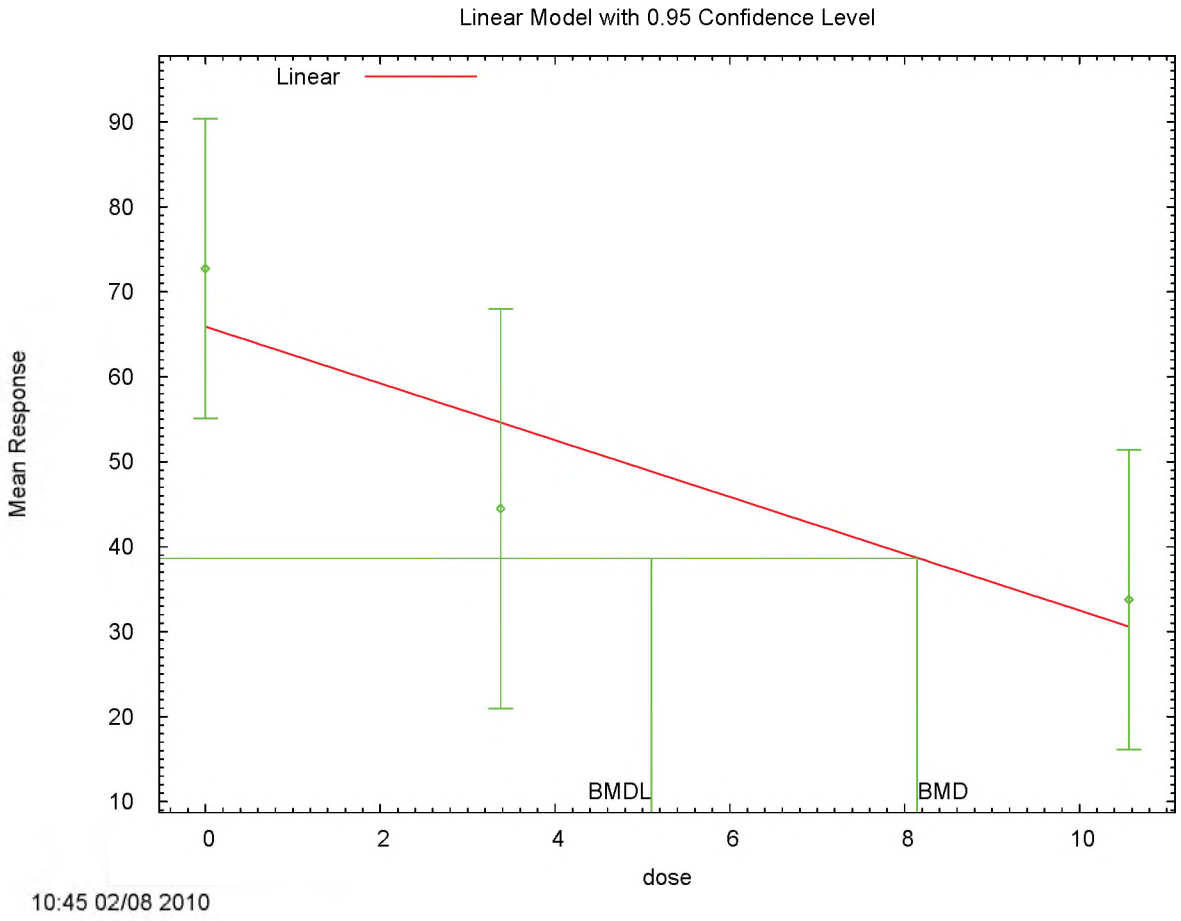
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

              BMD =        8.14425


             BMDL =        5.10523
```

E.2.4.3. *Figure for Selected Model: Linear*



E.2.4.4. *Output for Additional Model Presented: Power, Unrestricted*

Amin et al., 2000: 0.50% Saccharin Preference Ratio, Female

```
================================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\Blood\4_Amin_2000_50_SP_PwrCV_U_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\4_Amin_2000_50_SP_PwrCV_U_1.plt
                                                 Mon Feb 08 10:45:50 2010
================================================================================

-
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the response function is:

  Y[dose] = control + slope * dose^power


  Dependent variable = Mean
  Independent variable = Dose
  rho is set to 0
  The power is not restricted
  A constant variance model is fit
```

```
   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                         alpha =      764.602
                           rho =            0   Specified
                       control =      72.7273
                         slope =     -20.0402
                         power =     0.281985


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been specified by the user,
                and do not appear in the correlation matrix )

                  alpha      control        slope        power

    alpha             1    -1.2e-009    -1.2e-009    -2.2e-010

  control    -1.2e-009            1        -0.51        -0.22

    slope    -1.2e-009        -0.51            1         0.92

    power    -2.2e-010        -0.22         0.92            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         alpha          688.142          177.677              339.9             1036.38
       control          72.7273          8.29543             56.4686              88.986
         slope         -20.0402          15.0576            -49.5526             9.47219
         power         0.281985         0.325861            -0.35669            0.920661


      Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0    10       72.7         72.7         24.6         26.2      4.67e-009
3.378    10       44.5         44.5         32.9         26.2      1.52e-008
10.57    10       33.8         33.8         24.6         26.2      1.77e-008

 Warning: Likelihood for fitted model larger than the Likelihood for model A3.


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = Sigma^2
```

```
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                       Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
              A1         -113.009921            4     234.019841
              A2         -112.428886            6     236.857773
              A3         -113.009921            4     234.019841
          fitted         -113.009921            4     234.019841
               R         -117.976057            2     239.952114


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              11.0943          4         0.02552
   Test 2              1.16207          2          0.5593
   Test 3              1.16207          2          0.5593
   Test 4        -2.84217e-014          0              NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-Square
     test for fit is not valid


               Benchmark Dose Computation

Specified effect =             1

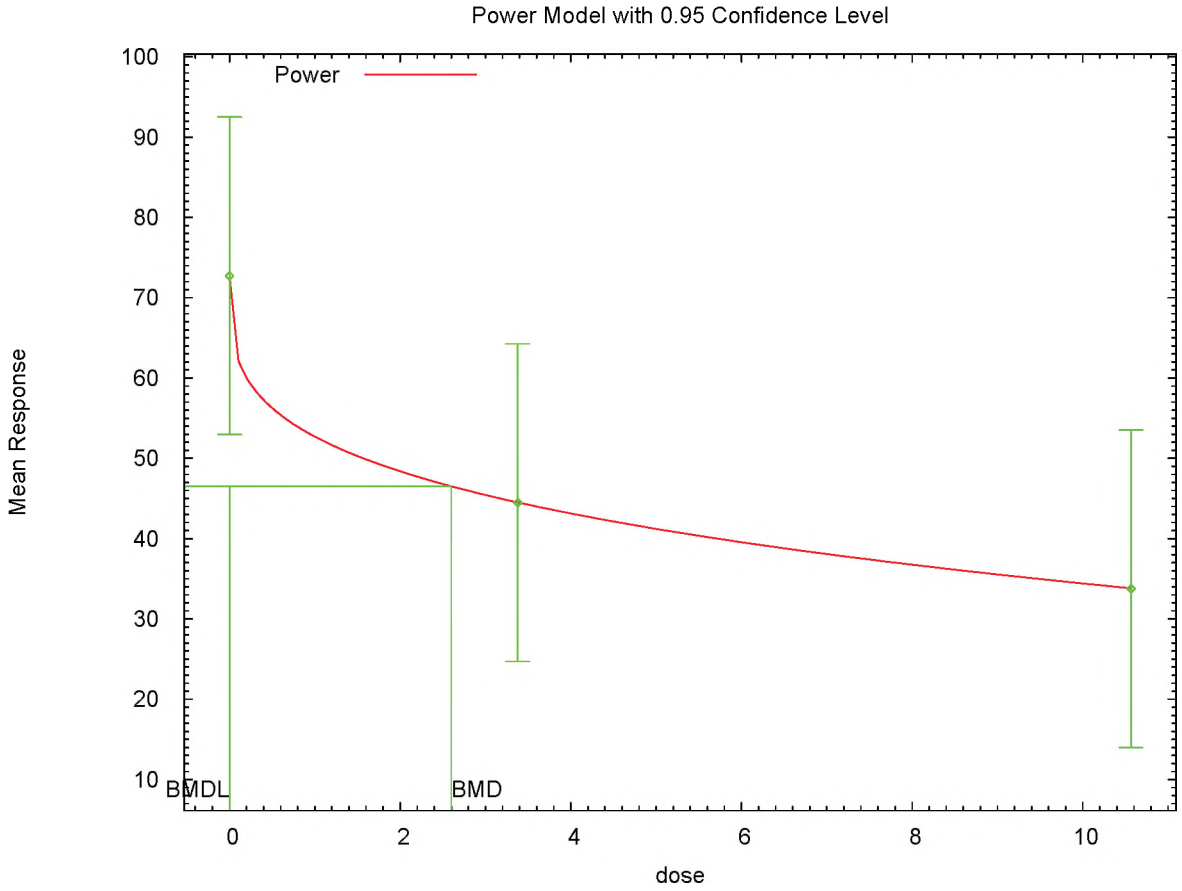
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 2.59831


            BMDL = 1.05661e-014
```

E.2.4.5. *Figure for Additional Model Presented: Power, Unrestricted*



E.2.5. Bell et al., 2007a: Balano-Preputial Separation, Postnatal Day 49

E.2.5.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
gamma	2	0.684	112.136	2.867E+00	1.943E+00	power bound hit (power = 1)
logistic	2	0.342	113.915	6.159E+00	4.746E+00	negative intercept (intercept = -2.246)
log-logistic [a]	**2**	**0.777**	**111.908**	**2.246E+00**	**1.394E+00**	**slope bound hit (slope = 1)**
log-probit	2	0.269	114.254	5.322E+00	3.512E+00	slope bound hit (slope = 1)
multistage, 3-degree	2	0.684	112.136	2.867E+00	1.943E+00	final ß = 0
probit	2	0.367	113.713	5.715E+00	4.422E+00	
Weibull	2	0.684	112.136	2.867E+00	1.943E+00	power bound hit (power = 1)
gamma, unrestricted	1	0.566	113.746	1.862E+00	1.829E-01	unrestricted (power = 0.741)
log-logistic, unrestricted [b]	1	0.501	113.871	1.998E+00	2.795E-01	unrestricted (slope = 0.93)
log-probit, unrestricted	1	0.456	113.977	2.038E+00	3.250E-01	unrestricted (slope = 0.54)
Weibull, unrestricted	1	0.551	113.771	1.914E+00	2.346E-01	unrestricted (power = 0.795)

[a] Best-fitting model, BMDS output presented in this appendix

[b] Alternate model, BMDS output also presented in this appendix

E.2.5.2. *Output for Selected Model: Log-Logistic*

Bell et al., 2007a: Balano-Preputial Separation, Postnatal Day 49

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\1\Blood\5_Bell_2007_BPS_LogLogistic_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\5_Bell_2007_BPS_LogLogistic_1.plt
                                                Mon Feb 08 10:46:18 2010
 ================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
```

```
   Slope parameter is restricted as slope >= 1

   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =    0.0333333
                     intercept =     -2.99896
                         slope =            1


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -slope
                have been estimated at a boundary point, or have been specified by the user,
                and do not appear in the correlation matrix )

            background    intercept

background            1        -0.49

 intercept        -0.49            1



                                Parameter Estimates

                                                      95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background         0.038005            *               *                   *
      intercept         -3.00658            *               *                   *
          slope                1            *               *                   *

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -53.7077         4
   Fitted model          -53.954         2     0.492596      2         0.7817
  Reduced model         -63.9797         1       20.544      3        0.0001309

           AIC:          111.908


                                 Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size        Residual
   ---------------------------------------------------------------------
    0.0000     0.0380         1.140     1.000          30        -0.134
    2.2040     0.1326         3.977     5.000          30         0.551
    5.1378     0.2329         6.988     6.000          30        -0.427
   18.4110     0.4965        14.895    15.000          30         0.038

 Chi^2 = 0.50      d.f. = 2        P-value = 0.7769


   Benchmark Dose Computation

Specified effect =           0.1
```

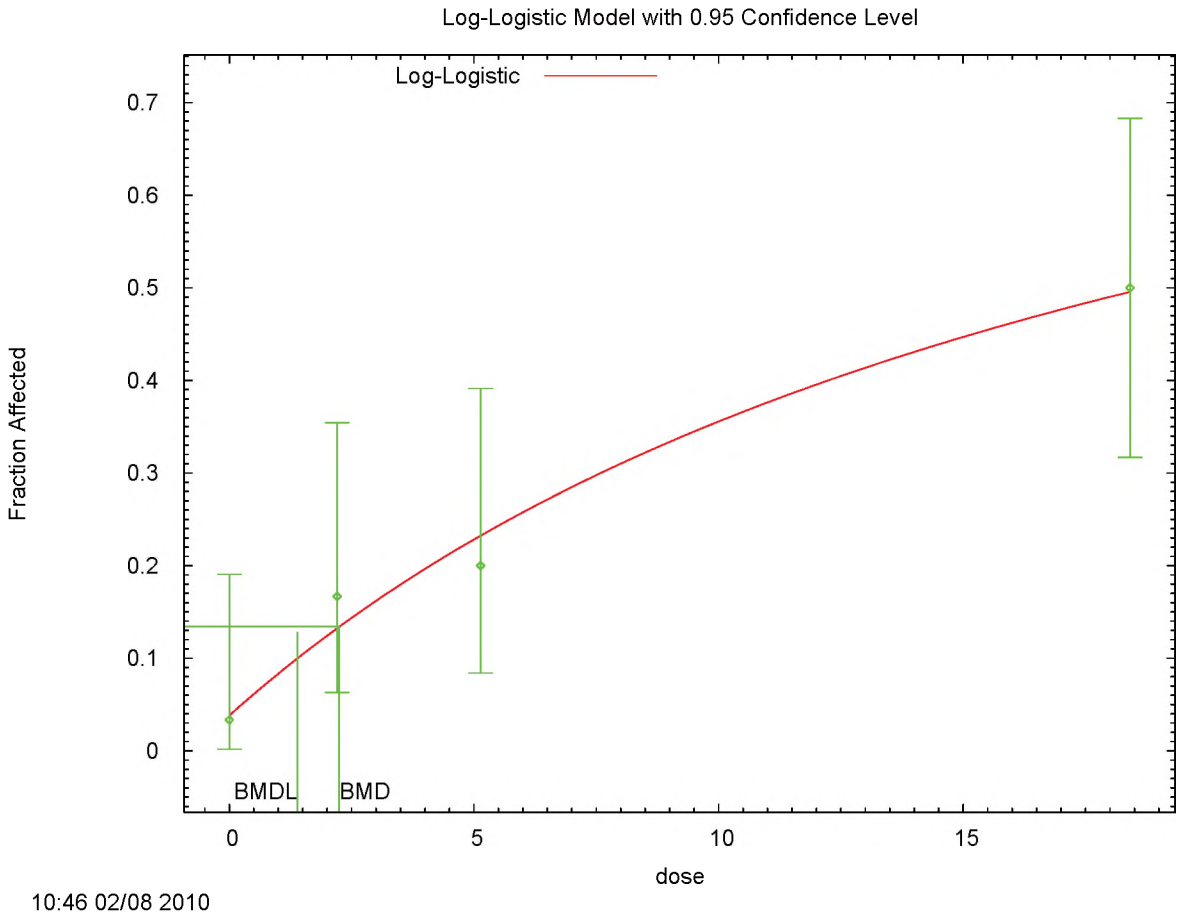
```
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        2.24647

            BMDL =        1.39385
```

E.2.5.3. *Figure for Selected Model: Log-Logistic*



E.2.5.4. *Output for Additional Model Presented: Log-Logistic, Unrestricted*

Bell et al., 2007a: Balano-Preputial Separation, Postnatal Day 49

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\1\Blood\5_Bell_2007_BPS_LogLogistic_U_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\5_Bell_2007_BPS_LogLogistic_U_1.plt
                                                Mon Feb 08 10:46:18 2010
 ================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =    0.0333333
                     intercept =     -2.68464
                         slope =     0.858398


           Asymptotic Correlation Matrix of Parameter Estimates

             background    intercept        slope

background            1        -0.48         0.35

 intercept        -0.48            1        -0.94

     slope         0.35        -0.94            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
    background        0.0353402            *                *                   *
     intercept         -2.84051            *                *                   *
         slope         0.929645            *                *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -53.7077         4
```

Fitted model	-53.9354	3	0.455534	1	0.4997
Reduced model	-63.9797	1	20.544	3	0.0001309

AIC: 113.871

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0353	1.060	1.000	30	-0.060
2.2040	0.1400	4.201	5.000	30	0.420
5.1378	0.2389	7.166	6.000	30	-0.499
18.4110	0.4858	14.573	15.000	30	0.156

Chi^2 = 0.45 d.f. = 1 P-value = 0.5005

Benchmark Dose Computation

Specified effect = 0.1

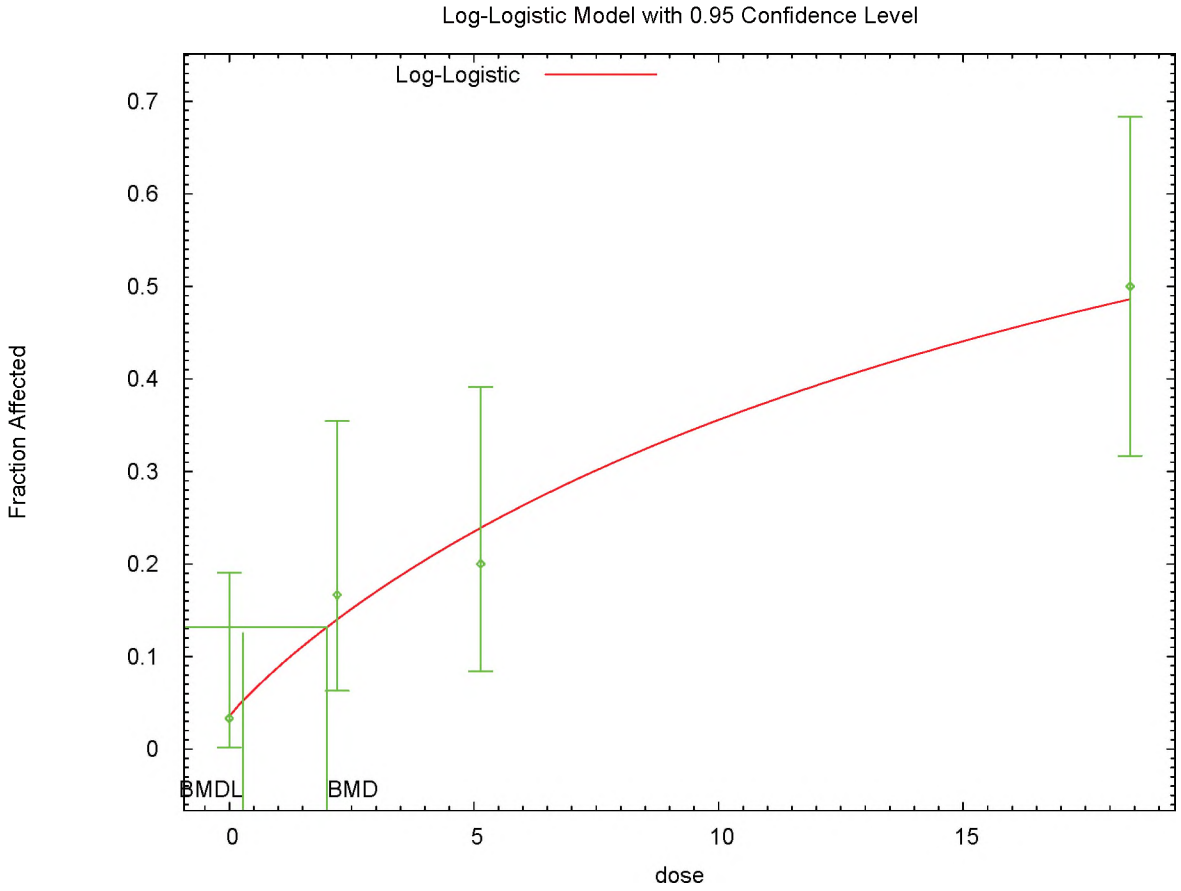
Risk Type = Extra risk

Confidence level = 0.95

BMD = 1.99765

BMDL = 0.279534

E.2.5.5. *Figure for Additional Model Presented: Log-Logistic, Unrestricted*



E.2.6. Cantoni et al., 1981: Urinary Coproporhyrins, 3 Months

E.2.6.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	2	0.003	32.882	3.209E+01	1.567E+01	
exponential (M3)	2	0.003	32.882	3.209E+01	1.567E+01	power hit bound (d = 1)
exponential (M4) [b]	**1**	**0.486**	**23.459**	**5.339E-01**	**1.803E-01**	
exponential (M5)	1	0.486	23.459	5.339E-01	1.803E-01	power hit bound (d = 1)
Hill	1	0.788	23.047	4.333E-01	error	n lower bound hit (n = 1)
linear	2	0.005	31.595	1.464E+01	2.753E+00	
polynomial, 3-degree	2	0.005	31.595	1.464E+01	2.753E+00	
power	2	0.005	31.595	1.464E+01	2.753E+00	power bound hit (power = 1)
power, unrestricted [c]	1	0.610	23.235	2.766E-02	2.031E-05	unrestricted (power = 0.304)
Hill, unrestricted	0	N/A	24.974	2.602E-01	error	unrestricted (n = 0.739)

[a] Non-constant variance model selected ($p = 0.0039$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.2.6.2. *Output for Selected Model: Exponential (M4)*

Cantoni et al., 1981: Urinary Coproporhyrins, 3 Months

```
 ================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\1\Blood\6_Cantoni_1981_UriCopro_Exp_1.(d)
         Gnuplot Plotting File:
                                                Mon Feb 08 10:46:46 2010
 ================================================================

 Figure1-UrinaryCoproporphyrin_3months
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
```

```
      sign = -1 for decreasing trend.

   Model 2 is nested within Models 3 and 4.
   Model 3 is nested within Model 5.
   Model 4 is nested within Model 5.


Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


              Initial Parameter Values

              Variable          Model 4
              --------          --------
                lnalpha             -1.50063
                    rho              2.60979
                      a             0.704303
                      b            0.0604961
                      c              4.47268
                      d                    1



                Parameter Estimates

               Variable          Model 4
               --------          -------
                lnalpha            -1.75302
                    rho              2.6322
                      a            0.761218
                      b            0.241561
                      c             4.15597
                      d                   1


        Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0      4       0.7414       0.3475
  1.847      4        1.807       0.8341
  8.839      4        2.734        1.506
  50.05      4            3          2.6


              Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
      0        0.7612       0.2907          -0.1366
  1.847         1.626       0.7892           0.4588
  8.839          2.88        1.674          -0.1743
  50.05         3.164        1.895          -0.1725


Other models for which likelihoods are calculated:
```

```
  Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
           Var{e(ij)} = Sigma^2


                            Likelihoods of Interest

                 Model      Log(likelihood)      DF         AIC
                -------    -----------------    ----   ------------
                    A1       -12.90166           5      35.80333
                    A2       -6.203643           8      28.40729
                    A3       -6.487204           6      24.97441
                     R       -15.73713           2      35.47427
                     4       -6.729737           5      23.45947


Additive constant for all log-likelihoods =      -14.7.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.


                             Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)


                          Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                        19.07           6            0.004052
  Test 2                         13.4           3            0.003854
  Test 3                       0.5671           2              0.7531
 Test 6a                       0.4851           1              0.4861


  The p-value for Test 1 is less than .05.  There appears to be a
  difference between response and/or variances among the dose
  levels, it seems appropriate to model the data.

  The p-value for Test 2 is less than .1.  A non-homogeneous
  variance model appears to be appropriate.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 6a is greater than .1.  Model 4 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 1.000000

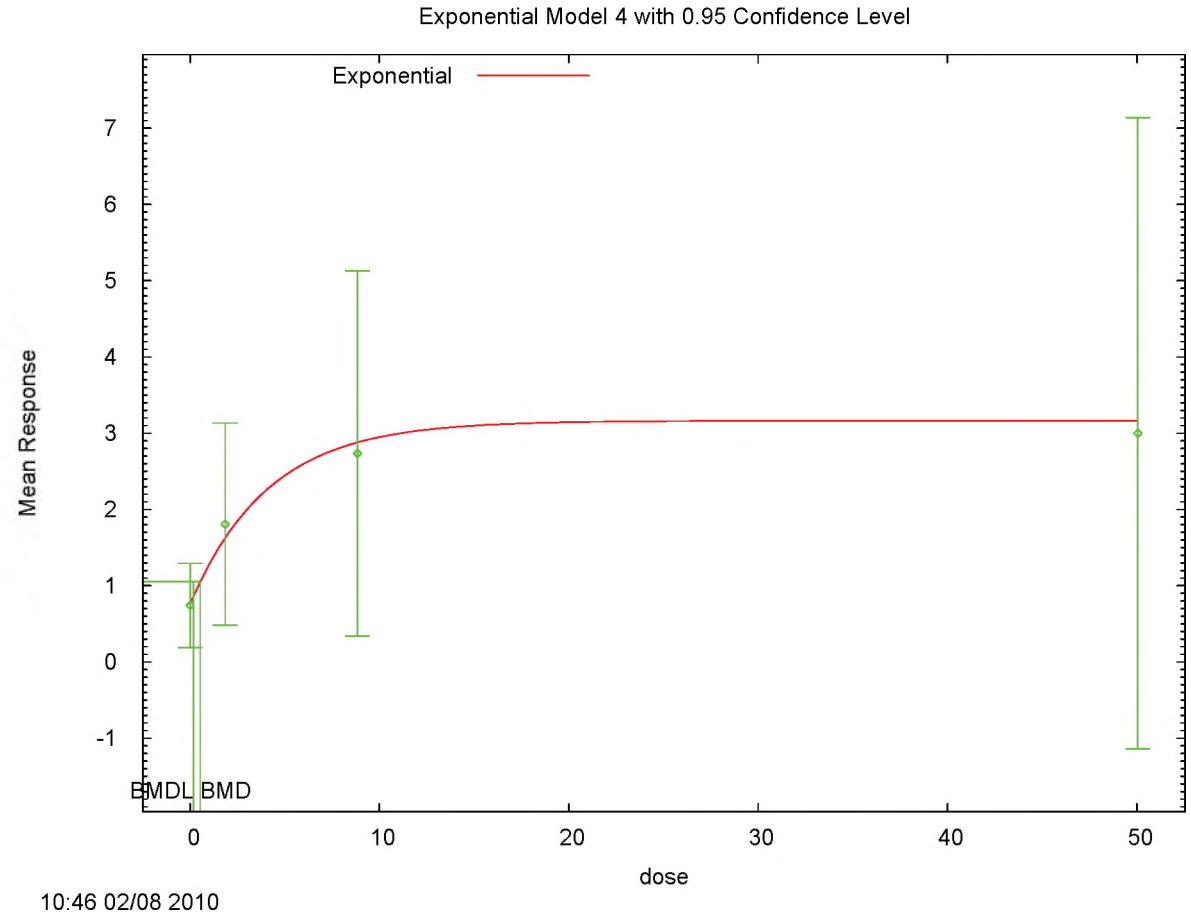
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000
```

```
BMD =      0.533855

BMDL =     0.180293
```

E.2.6.3. *Figure for Selected Model: Exponential (M4)*



E.2.6.4. *Output for Additional Model Presented: Power, Unrestricted*

Cantoni et al., 1981: Urinary Coproporhyrins, 3 Months

```
================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\Blood\6_Cantoni_1981_UriCopro_Pwr_U_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\6_Cantoni_1981_UriCopro_Pwr_U_1.plt
                                          Mon Feb 08 10:46:47 2010
================================================================

Figure1-UrinaryCoproporphyrin_3months
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the response function is:

  Y[dose] = control + slope * dose^power
```

Dependent variable = Mean
Independent variable = Dose
The power is not restricted
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	0.90039
rho =	0
control =	0.741372
slope =	0.93685
power =	0.224904

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	control	slope	power
lalpha	1	-0.62	-0.53	-0.036	0.024
rho	-0.62	1	0.43	-0.2	-0.16
control	-0.53	0.43	1	-0.28	0.086
slope	-0.036	-0.2	-0.28	1	-0.77
power	0.024	-0.16	0.086	-0.77	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-1.78125	0.617807	-2.99213	-0.570373
rho	2.64332	0.744946	1.18325	4.10338
control	0.75678	0.139979	0.482426	1.03113
slope	0.845767	0.324854	0.209065	1.48247
power	0.304211	0.135053	0.0395119	0.568909

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	4	0.741	0.757	0.348	0.284	-0.109
1.847	4	1.81	1.78	0.834	0.877	0.0705
8.839	4	2.73	2.4	1.51	1.3	0.515
50.05	4	3	3.54	2.6	2.18	-0.493

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

```
Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                       Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1          -12.901663            5      35.803325
             A2           -6.203643            8      28.407287
             A3           -6.487204            6      24.974409
         fitted           -6.617347            5      23.234694
              R          -15.737135            2      35.474269


                   Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value

  Test 1               19.067          6        0.004052
  Test 2               13.396          3        0.003854
  Test 3             0.567122          2          0.7531
  Test 4             0.260285          1          0.6099

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


               Benchmark Dose Computation

Specified effect =             1

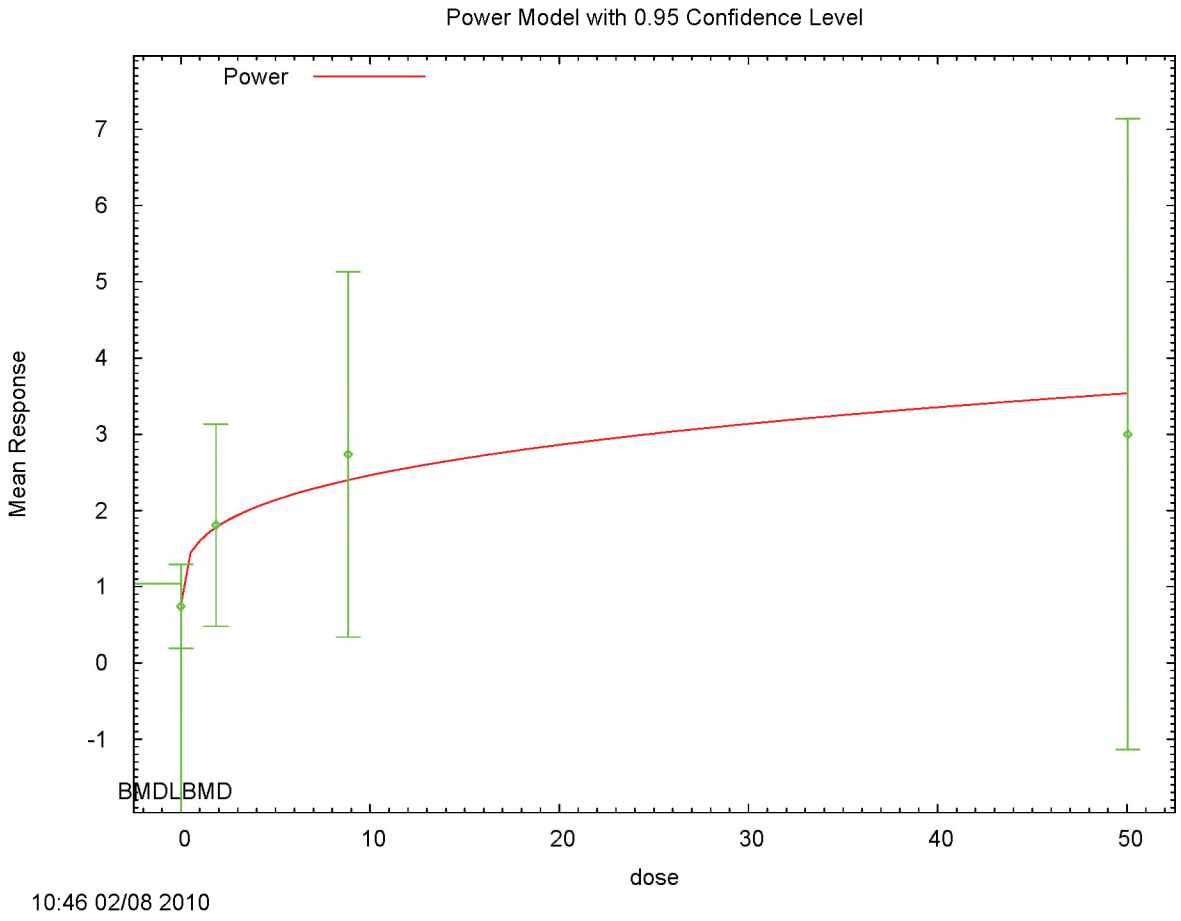
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 0.0276599


             BMDL = 2.03143e-005
```

E.2.6.5. *Figure for Additional Model Presented: Power, Unrestricted*



E.2.7. Cantoni et al., 1981: Urinary Porphyrins

E.2.7.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2) [b]	2	<0.001	55.465	3.760E+00	2.762E+00	
exponential (M3)	2	<0.001	55.465	3.760E+00	2.762E+00	power hit bound (d = 1)
exponential (M4)	1	<0.0001	59.187	2.484E-01	1.448E-01	
exponential (M5)	0	N/A	61.084	2.878E-01	1.461E-01	
Hill	0	N/A	62.199	6.233E+00	3.341E+00	
linear	2	<0.001	57.187	2.484E-01	1.448E-01	
polynomial, 3-degree	1	<0.0001	10.000	error	error	
power	1	<0.0001	59.084	2.878E-01	1.461E-01	

[a] Non-constant variance model selected (p = <0.0001)

[b] Best-fitting model, BMDS output presented in this appendix

E.2.7.2. *Output for Selected Model: Exponential (M2)*

Cantoni et al., 1981: Urinary Porphyrins

```
 ================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\1\Blood\7_Cantoni_1981_UriPor_Exp_1.(d)
         Gnuplot Plotting File:
                                                  Mon Feb 08 10:47:24 2010
 ================================================================

 Table 1, dose converted to ng per kg per day
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
```

```
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


                Initial Parameter Values

                Variable          Model 2
                --------          --------
                  lnalpha          -3.57509
                      rho           2.23456
                        a           3.36453
                        b         0.0819801
                        c                 0
                        d                 1



                  Parameter Estimates

                 Variable          Model 2
                 --------          -------
                  lnalpha          -1.85879
                      rho           1.82273
                        a           3.57896
                        b         0.0803347
                        c                 0
                        d                 1


          Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0      4          2.27          0.49
  1.847      4          5.55          0.85
  8.839      3          7.62          1.79
  50.05      3         196.9         63.14


                Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
      0         3.579        1.262           -2.074
  1.847         4.152        1.445            1.936
  8.839          7.28         2.41           0.2441
  50.05         199.5        49.25         -0.09069


Other models for which likelihoods are calculated:

  Model A1:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)
```

```
  Model  R:        Yij = Mu + e(i)
            Var{e(ij)} = Sigma^2


                              Likelihoods of Interest

                   Model      Log(likelihood)      DF         AIC
                  -------    -----------------    ----   ------------
                      A1       -51.42175           5      112.8435
                      A2       -15.31211           8      46.62422
                      A3       -15.66963           6      43.33925
                       R       -68.75058           2      141.5012
                       2       -23.73254           4      55.46509


Additive constant for all log-likelihoods =     -12.87.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.


                               Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does Model 2 fit the data? (A3 vs. 2)


                          Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                        106.9            6           < 0.0001
  Test 2                        72.22            3           < 0.0001
  Test 3                        0.715            2             0.6994
  Test 4                        16.13            2           0.000315


  The p-value for Test 1 is less than .05.  There appears to be a
  difference between response and/or variances among the dose
  levels, it seems appropriate to model the data.

  The p-value for Test 2 is less than .1.  A non-homogeneous
  variance model appears to be appropriate.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 4 is less than .1.  Model 2 may not adequately
  describe the data; you may want to consider another model.


Benchmark Dose Computations:

  Specified Effect = 1.000000

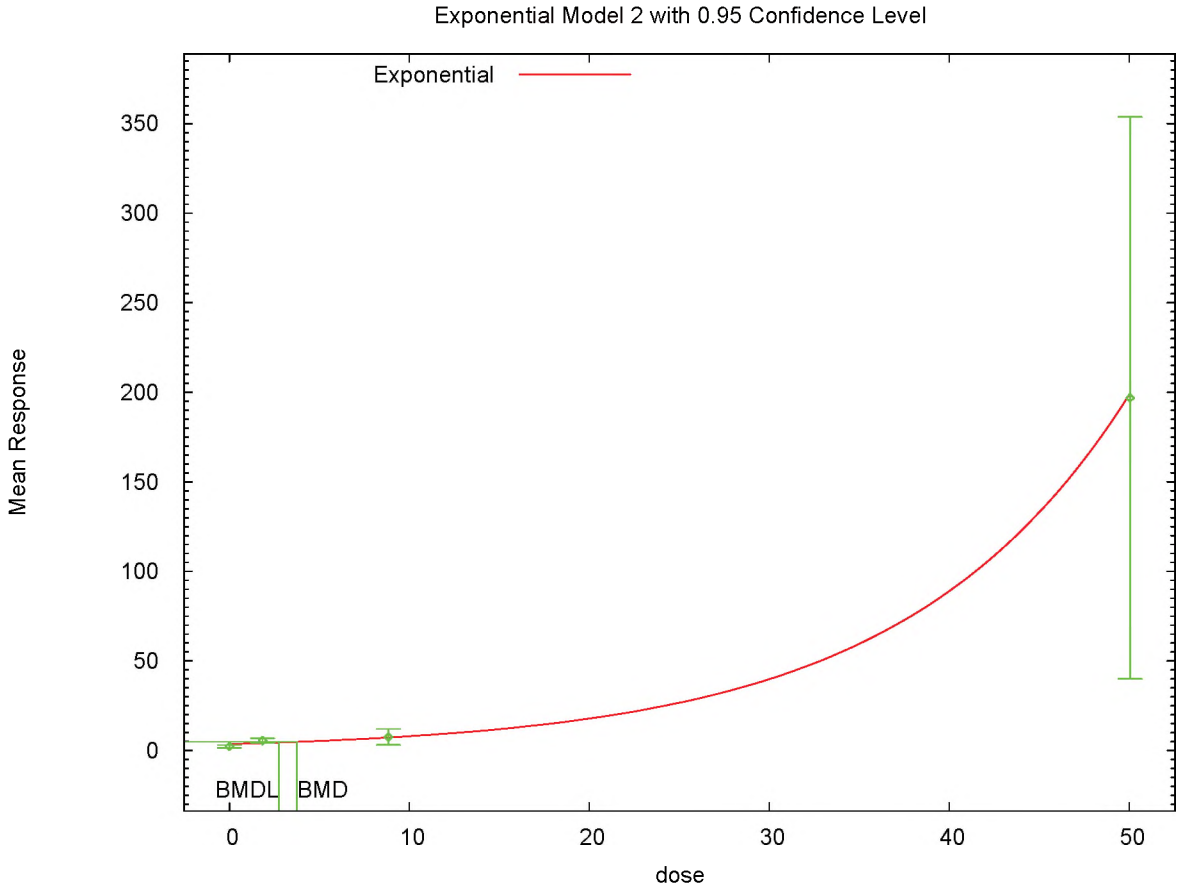
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD =      3.75968

              BMDL =      2.76247
```

E.2.7.3. *Figure for Selected Model: Exponential (M2)*



E.2.8. Crofton et al., 2005: Serum, T4

E.2.8.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	8	<0.0001	516.356	1.144E+02	6.239E+01	
exponential (M3)	8	<0.0001	516.356	1.144E+02	6.239E+01	power hit bound (d = 1)
exponential (M4) [b]	7	**0.942**	**476.449**	**5.190E+00**	**3.029E+00**	
exponential (M5)	6	0.912	478.234	5.757E+00	3.094E+00	
Hill	6	0.972	477.450	5.724E+00	3.024E+00	
linear	8	<0.0001	522.460	2.406E+02	1.761E+02	
polynomial, 8-degree	8	<0.0001	522.460	2.406E+02	1.761E+02	
power	8	<0.0001	522.460	2.406E+02	1.761E+02	power bound hit (power = 1)
power, unrestricted	7	0.018	491.101	2.449E+00	3.307E-01	unrestricted (power = 0.243)

[a] Constant variance model selected ($p = 0.7647$)

[b] Best-fitting model, BMDS output presented in this appendix

E.2.8.2. *Output for Selected Model: Exponential (M4)*

Crofton et al., 2005: Serum, T4

```
 ================================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\1\Blood\8_Crofton_2005_T4_ExpCV_1.(d)
         Gnuplot Plotting File:
                                                    Mon Feb 08 10:48:04 2010
 ================================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.
```

Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 10
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	5.47437
rho(S)	0
a	104.999
b	0.00641895
c	0.445764
d	1

(S) = Specified

Parameter Estimates

Variable	Model 4
lnalpha	5.50623
rho	0
a	100.332
b	0.076678
c	0.523626
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	14	100	15.44
0.0202	6	96.27	14.98
0.4882	12	98.57	18.11
1.384	6	99.76	19.04
3.455	6	93.32	12.11
9.257	6	70.94	12.74
23.07	6	62.52	14.75
65.65	6	52.68	22.73
180.9	6	54.66	19.71
583.5	4	49.15	11.15

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	100.3	15.69	-0.07952
0.0202	100.3	15.69	-0.6231
0.4882	98.58	15.69	-0.000744
1.384	95.52	15.69	0.6614
3.455	89.21	15.69	0.6422

```
   9.257         76.04         15.69          -0.7962
   23.07         60.69         15.69           0.2854
   65.65         52.85         15.69         -0.02621
   180.9         52.54         15.69           0.3319
   583.5         52.54         15.69          -0.4323


Other models for which likelihoods are calculated:

  Model A1:        Yij = Mu(i) + e(ij)
                Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
                Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
                Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
                Var{e(ij)} = Sigma^2


                            Likelihoods of Interest

                  Model      Log(likelihood)      DF         AIC
                 -------    -----------------    ----   ------------
                     A1       -233.0774           11      488.1549
                     A2       -230.2028           20      500.4056
                     A3       -233.0774           11      488.1549
                      R       -268.4038            2      540.8076
                      4       -234.2243            4      476.4486


Additive constant for all log-likelihoods =     -66.16.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.


                              Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)


                          Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                        76.4            18            < 0.0001
  Test 2                       5.749             9              0.7647
  Test 3                       5.749             9              0.7647
 Test 6a                       2.294             7              0.9418


  The p-value for Test 1 is less than .05.  There appears to be a
  difference between response and/or variances among the dose
  levels, it seems appropriate to model the data.

  The p-value for Test 2 is greater than .1.  A homogeneous
  variance model appears to be appropriate here.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 6a is greater than .1.  Model 4 seems
  to adequately describe the data.
```

```
Benchmark Dose Computations:

  Specified Effect = 1.000000

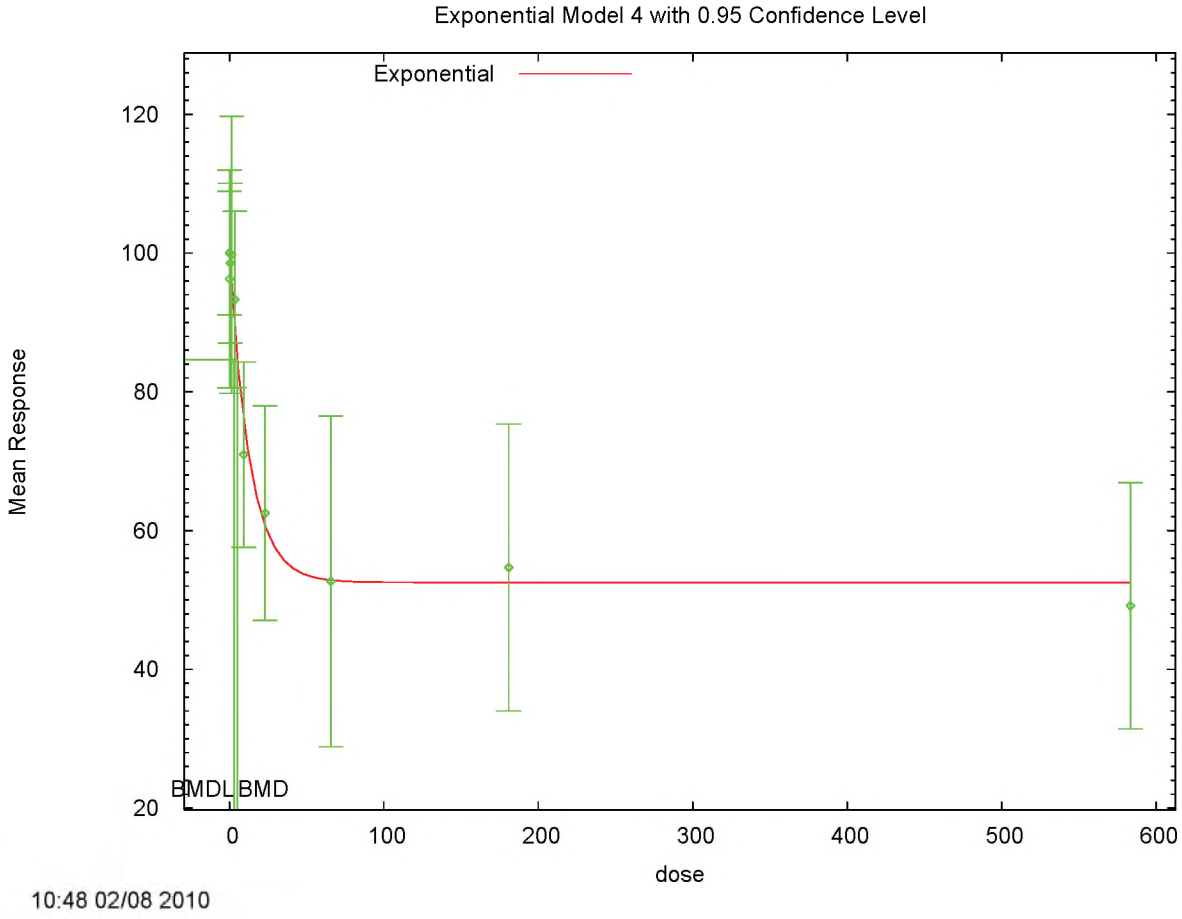
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD =      5.18983

              BMDL =      3.02894
```

E.2.8.3. *Figure for Selected Model: Exponential (M4)*



E.2.9. Franc et al., 2001: S-D Rats, Relative Liver Weight

E.2.9.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	2	0.968	234.369	7.800E+00	6.040E+00	
exponential (M3)	1	0.880	236.327	9.201E+00	6.051E+00	
exponential (M4)	1	0.580	236.610	6.365E+00	4.512E+00	
exponential (M5)	0	N/A	238.346	9.474E+00	4.425E+00	
Hill	0	N/A	238.346	9.479E+00	3.004E+00	
linear	2	0.858	234.610	6.365E+00	4.512E+00	
polynomial, 3-degree	1	0.935	236.311	8.946E+00	4.598E+00	
power [b]	1	0.839	236.346	9.474E+00	4.587E+00	

[a] Constant variance model selected ($p = 0.107$)

[b] Best-fitting model, BMDS output presented in this appendix

E.2.9.2. *Output for Selected Model: Power*

Franc et al., 2001: S-D Rats, Relative Liver Weight

```
 ======================================================================
          Power Model. (Version: 2.15;  Date: 04/07/2008)
          Input Data File: C:\1\Blood\88_Franc_2001_SD_RelLivWt_PowerCV_1.(d)
          Gnuplot Plotting File:  C:\1\Blood\88_Franc_2001_SD_RelLivWt_PowerCV_1.plt
                                                Thu Apr 15 11:46:32 2010
 ======================================================================

 Figure 5, SD rats, relative liver weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   The power is restricted to be greater than or equal to 1
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values

alpha =	527.447	
rho =	0	Specified
control =	100	
slope =	0.947018	
power =	1.13144	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	control	slope	power
alpha	1	-6.3e-009	5.4e-009	-4.7e-009
control	-6.3e-009	1	-0.74	0.71
slope	5.4e-009	-0.74	1	-1
power	-4.7e-009	0.71	-1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	462.113	115.528	235.682	688.544
control	100.494	7.31114	86.1645	114.824
slope	0.593276	1.31535	-1.98476	3.17131
power	1.25841	0.597816	0.086712	2.43011

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	100	100	14	21.5	-0.065
6.587	8	108	107	16.9	21.5	0.158
14.48	8	117	118	25.9	21.5	-0.109
36.43	8	155	155	30.9	21.5	0.0157

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that
were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-114.152281	5	238.304562
A2	-111.103649	8	238.207299
A3	-114.152281	5	238.304562
fitted	-114.172940	4	236.345880
R	-125.052064	2	254.104127

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	27.8968	6	<.0001
Test 2	6.09726	3	0.107
Test 3	6.09726	3	0.107
Test 4	0.0413179	1	0.8389

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

Benchmark Dose Computation

Specified effect = 0.1

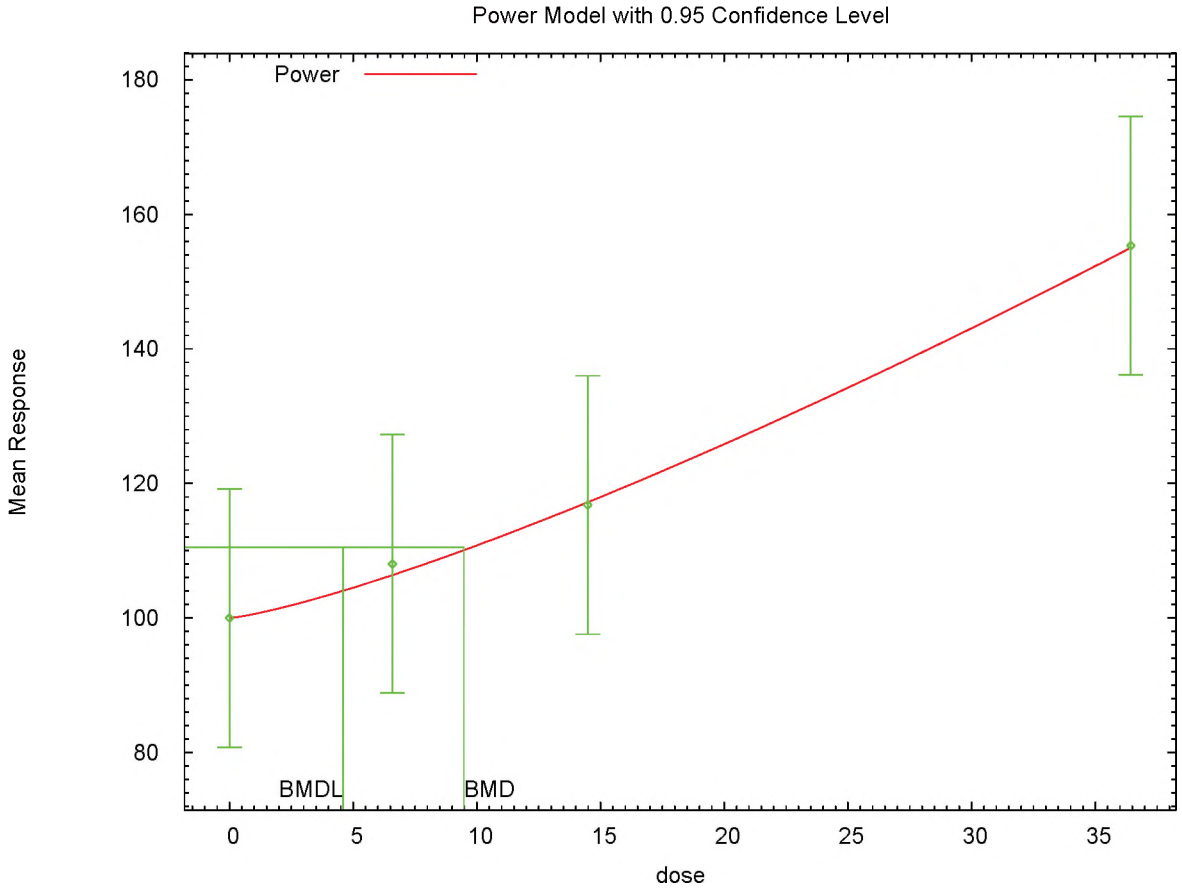
Risk Type = Relative risk

Confidence level = 0.95

BMD = 9.47408

BMDL = 4.5873

E.2.9.3. *Figure for Selected Model: Power*



E.2.10. Franc et al., 2001: L-E Rats, Relative Liver Weight

E.2.10.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	2	0.441	208.974	1.708E+01	1.098E+01	
exponential (M3)	2	0.441	208.974	1.708E+01	1.098E+01	power hit bound (d = 1)
exponential (M4)	1	0.785	209.408	7.997E+00	2.601E+00	
exponential (M5)	1	0.785	209.408	7.997E+00	2.601E+00	power hit bound (d = 1)
Hill [b]	1	0.829	209.381	7.725E+00	1.225E+00	n lower bound hit (n = 1)
linear	2	0.499	208.725	1.570E+01	9.619E+00	
polynomial, 3-degree	1	<0.0001	10.000	8.604E+00	error	
power	2	0.499	208.725	1.570E+01	9.619E+00	power bound hit (power = 1)
Hill, unrestricted [c]	0	N/A	211.337	7.217E+00	1.147E+00	unrestricted (n = 0.545)
power, unrestricted	1	0.965	209.336	7.193E+00	error	unrestricted (power = 0.524)

[a] Non-constant variance model selected ($p = 0.0632$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.2.10.2. *Output for Selected Model: Hill*

Franc et al., 2001: L-E Rats, Relative Liver Weight

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\1\Blood\89_Franc_2001_LE_RelLivWt_Hill_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\89_Franc_2001_LE_RelLivWt_Hill_1.plt
                                                Thu Apr 15 11:48:44 2010
 ================================================================

 Figure 5, L-E rats, relative liver weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   Power parameter restricted to be greater than 1
```

```
   The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                       lalpha =      5.41581
                          rho =            0
                    intercept =          100
                            v =       22.225
                            n =     0.443155
                            k =       18.746


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -n
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

                 lalpha          rho    intercept            v            k

    lalpha            1           -1        -0.21         0.33         0.18

       rho           -1            1         0.21        -0.33        -0.18

 intercept        -0.21         0.21            1        0.028         0.35

         v         0.33        -0.33        0.028            1         0.91

         k         0.18        -0.18         0.35         0.91            1


                                 Parameter Estimates

                                                      95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha         -17.2754          17.3066           -51.1957             16.6449
            rho          4.77884          3.67625           -2.42648             11.9842
      intercept          99.5348          3.61286            92.4538             106.616
              v          36.3963          24.1862           -11.0079             83.8004
              n                1               NA
              k          20.5223          28.2566           -34.8596             75.9042

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     8        100         99.5           10         10.5          0.125
6.584     8        106          108         17.9         12.9         -0.455
14.47     8        117          115         8.97         14.8          0.426
36.41     8        122          123         19.9         17.4        -0.0954


 Model Descriptions for likelihoods calculated
```

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                     Likelihoods of Interest

           Model      Log(likelihood)   # Param's      AIC
             A1         -100.516456           5     211.032912
             A2          -96.870820           8     209.741641
             A3          -99.666984           6     211.333969
         fitted          -99.690373           5     209.380746
              R         -105.717087           2     215.434174


                  Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value

  Test 1              17.6925          6        0.007048
  Test 2              7.29127          3         0.06317
  Test 3              5.59233          2         0.06104
  Test 4            0.0467774          1          0.8288

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =           0.1

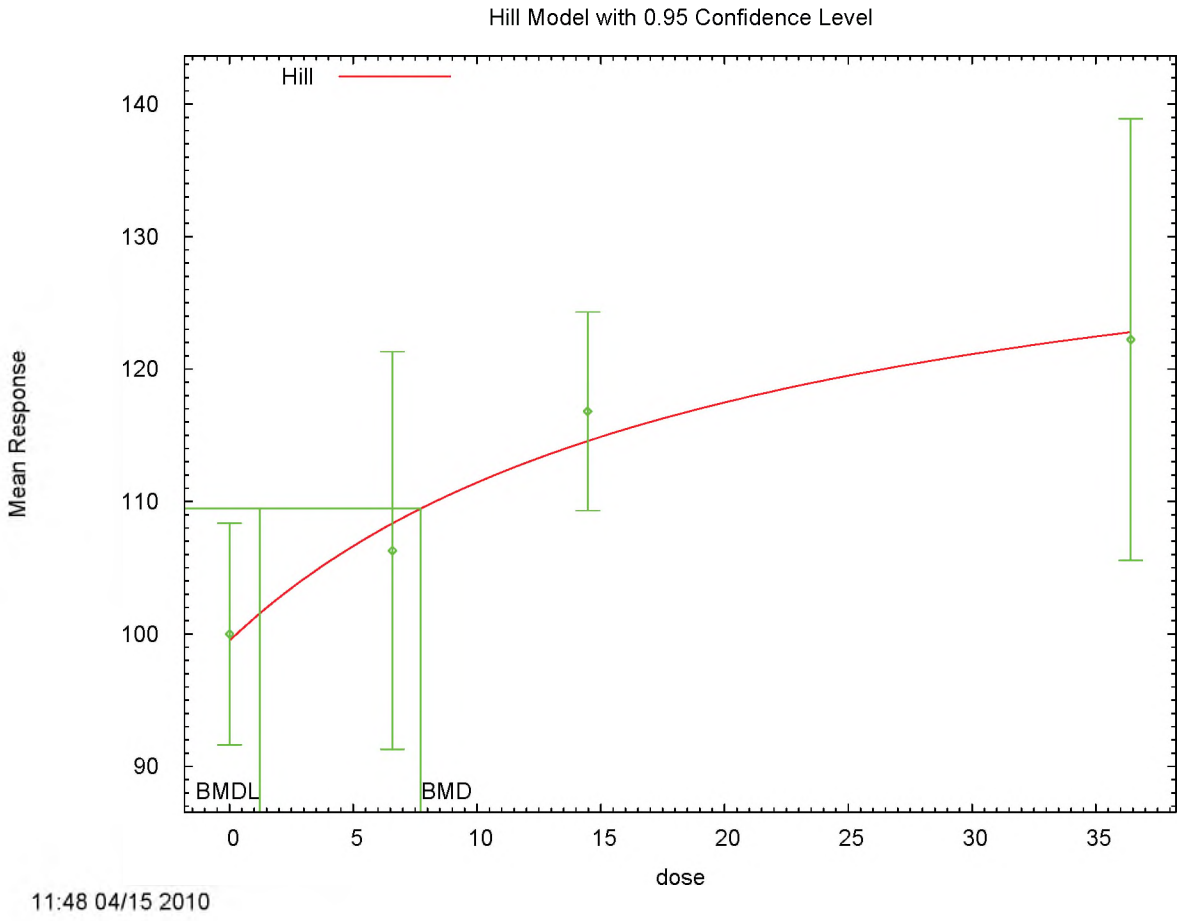
Risk Type        =     Relative risk

Confidence level =           0.95

             BMD =        7.72492

            BMDL =       1.22451
```

E.2.10.3. *Figure for Selected Model: Hill*



E.2.10.4. *Output for Additional Model Presented: Hill, Unrestricted*

Franc et al., 2001: L-E Rats, Relative Liver Weight

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\1\Blood\89_Franc_2001_LE_RelLivWt_Hill_U_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\89_Franc_2001_LE_RelLivWt_Hill_U_1.plt
                                              Thu Apr 15 11:48:50 2010
 ================================================================

 Figure 5, L-E rats, relative liver weight
------------------------------------------------------------------------

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   Power parameter is not restricted
   The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

   Total number of dose groups = 4
```

```
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                         lalpha =      5.41581
                            rho =            0
                      intercept =          100
                              v =       22.225
                              n =     0.443155
                              k =       18.746


           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho    intercept            v            n            k

    lalpha            1           -1        -0.22        -0.14         0.24        -0.15

       rho           -1            1         0.22         0.14        -0.24         0.15

 intercept        -0.22         0.22            1        0.022         0.11        0.013

         v        -0.14         0.14        0.022            1        -0.9            1

         n         0.24        -0.24         0.11         -0.9            1        -0.92

         k        -0.15         0.15        0.013            1        -0.92            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha         -19.2405           18.21          -54.9315             16.4505
            rho          5.19575         3.86861          -2.38657             12.7781
      intercept          99.5348         3.51796           92.6398              106.43
              v          440.285         13708.5          -26427.9             27308.5
              n         0.544741        0.730981         -0.887956             1.97744
              k          7266.27          485402            -944104              958637


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     8        100         99.5           10         10.3          0.128
6.584     8        106          109         17.9           13         -0.589
14.47     8        117          114         8.97         14.6          0.558
36.41     8        122          123         19.9         17.8        -0.0957

Degrees of freedom for Test A3 vs fitted <= 0


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2
```

```
Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1         -100.516456            5     211.032912
             A2          -96.870820            8     209.741641
             A3          -99.666984            6     211.333969
         fitted          -99.668321            6     211.336641
              R         -105.717087            2     215.434174


                   Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value

  Test 1              17.6925          6        0.007048
  Test 2              7.29127          3         0.06317
  Test 3              5.59233          2         0.06104
  Test 4           0.00267242          0              NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-Square
     test for fit is not valid


        Benchmark Dose Computation

Specified effect =           0.1

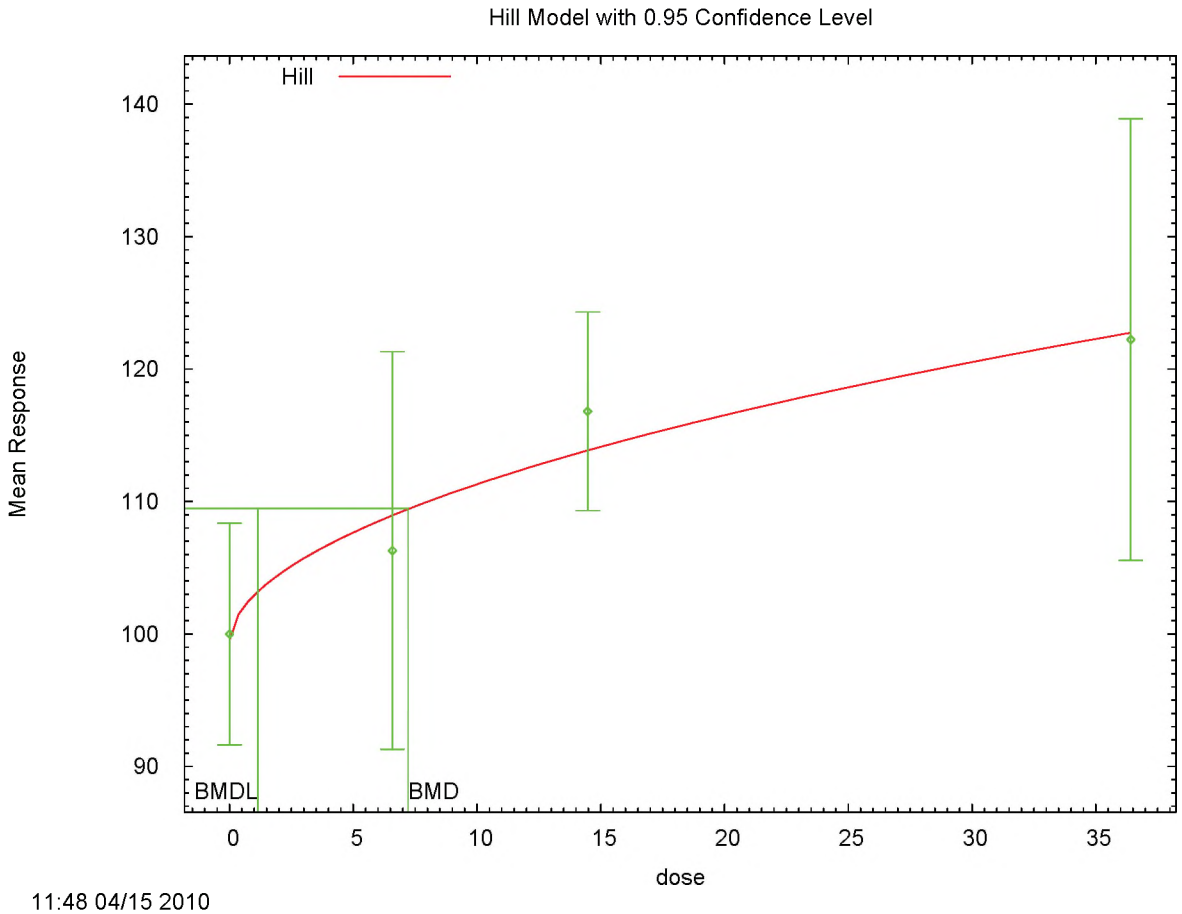
Risk Type        =     Relative risk

Confidence level =           0.95

             BMD =        7.21718

            BMDL =       1.14742
```

E.2.10.5. *Figure for Additional Model Presented: Hill, Unrestricted*



E.2.11. Franc et al., 2001: S-D Rats, Relative Thymus Weight

E.2.11.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	2	0.814	285.107	2.478E+00	1.535E+00	
exponential (M3)	1	0.016	292.452	3.173E+01	1.007E+00	
exponential (M4) [b]	1	0.720	286.825	1.878E+00	9.221E-01	
exponential (M5)	0	N/A	288.696	3.296E+00	9.365E-01	
Hill	0	N/A	288.696	3.625E+00	6.199E-01	
linear	2	0.404	286.508	4.783E+00	3.893E+00	
polynomial, 3-degree [c]	2	0.404	286.508	4.783E+00	3.893E+00	
power	2	0.404	286.508	4.783E+00	3.893E+00	power bound hit (power = 1)
power, unrestricted	1	0.483	287.189	6.795E-01	3.271E-03	unrestricted (power = 0.515)

[a] Non-constant variance model selected ($p = 0.0320$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.2.11.2. *Output for Selected Model: Exponential (M4)*

Franc et al., 2001: S-D Rats, Relative Thymus Weight

```
 ================================================================
          Exponential Model. (Version: 1.61;  Date: 7/24/2009)
          Input Data File: C:\1\Blood\91_Franc_2001_SD_RelThyWt_Exp_1.(d)
          Gnuplot Plotting File:
                                                  Thu Apr 15 11:51:19 2010
 ================================================================

 Figure 5, SD rats, relative thymus weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
```

```
   Model 3 is nested within Model 5.
   Model 4 is nested within Model 5.


Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


                Initial Parameter Values

                Variable          Model 4
                --------          --------
                  lnalpha             3.35464
                      rho             1.08199
                        a                 105
                        b           0.0569979
                        c            0.108531
                        d                   1



                  Parameter Estimates

                 Variable          Model 4
                 --------          -------
                  lnalpha             2.4312
                      rho            1.28672
                        a            110.959
                        b          0.0663498
                        c           0.146486
                        d                  1


         Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0      8          100          83.2
  6.587      8         91.17         47.97
  14.48      8         51.41         43.48
  36.43      8         22.79         29.98


                Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
      0           111         69.78          -0.4442
  6.587         77.43         55.36           0.7019
  14.48         52.49         43.11          -0.0709
  36.43          24.7         26.54          -0.2031


Other models for which likelihoods are calculated:

  Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
```

```
  Model A2:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
              Var{e(ij)} = Sigma^2


                              Likelihoods of Interest

                   Model      Log(likelihood)      DF         AIC
                  -------    ------------------    ----   ------------
                      A1       -141.9834            5      293.9669
                      A2       -137.5818            8      291.1637
                      A3       -138.3482            6      288.6964
                       R       -146.9973            2      297.9946
                       4       -138.4123            5      286.8245


Additive constant for all log-likelihoods =     -29.41.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.


                               Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)


                           Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                        18.83            6           0.004459
  Test 2                        8.803            3            0.03203
  Test 3                        1.533            2             0.4647
 Test 6a                       0.1282            1             0.7203


  The p-value for Test 1 is less than .05.  There appears to be a
  difference between response and/or variances among the dose
  levels, it seems appropriate to model the data.

  The p-value for Test 2 is less than .1.  A non-homogeneous
  variance model appears to be appropriate.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 6a is greater than .1.  Model 4 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 0.100000

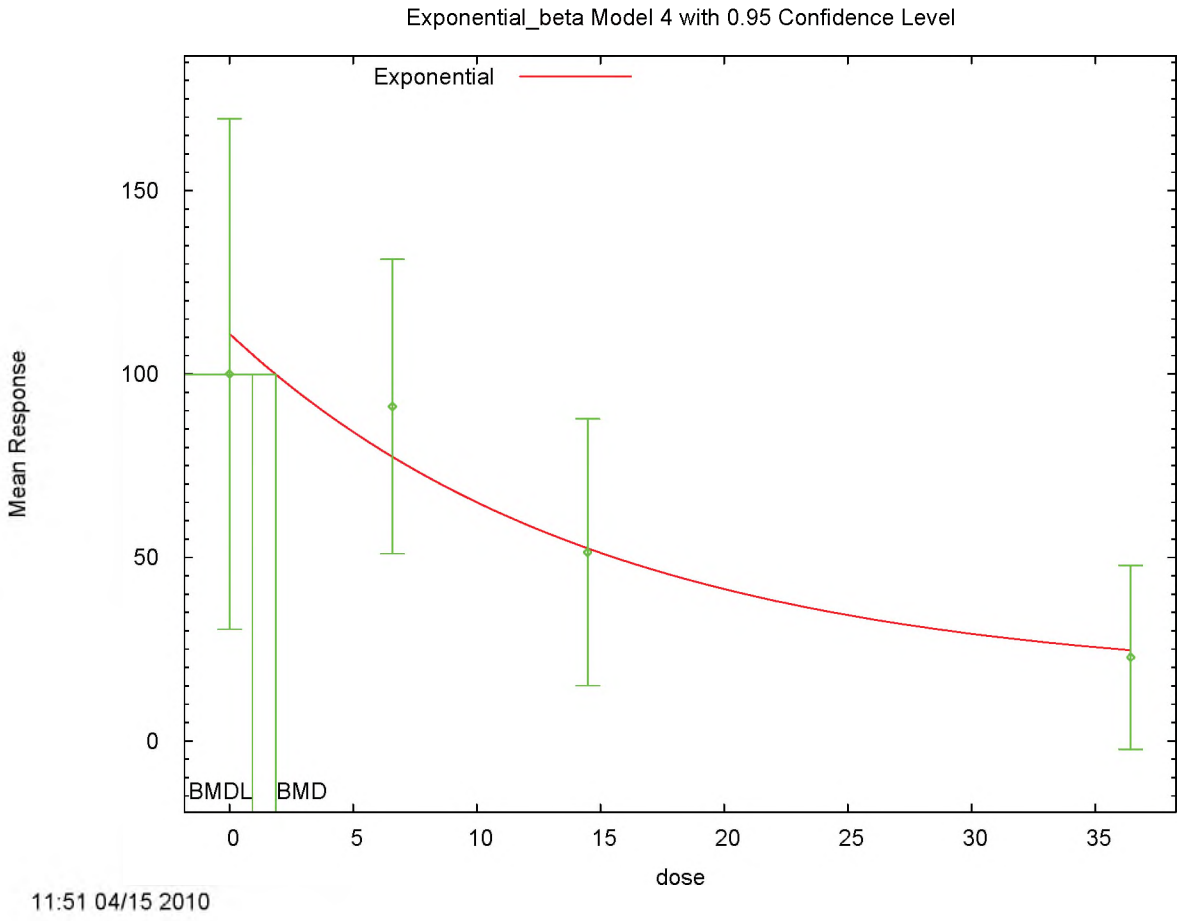
         Risk Type = Relative deviation

  Confidence Level = 0.950000

               BMD =      1.87814

              BMDL =     0.922136
```

E.2.11.3. *Figure for Selected Model: Exponential (M4)*



E.2.11.4. *Output for Additional Model Presented: Polynomial, 3-degree*

Franc et al., 2001: S-D Rats, Relative Thymus Weight

```
 ================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\1\Blood\91_Franc_2001_SD_RelThyWt_Poly_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\91_Franc_2001_SD_RelThyWt_Poly_1.plt
                                                 Thu Apr 15 11:51:20 2010
 ================================================================

 Figure 5, SD rats, relative thymus weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   The polynomial coefficients are restricted to be negative
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 4
```

```
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                         lalpha =       8.0075
                            rho =            0
                         beta_0 =          100
                         beta_1 =            0
                         beta_2 =    -0.475283
                         beta_3 =            0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -beta_2    -beta_3
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

                 lalpha          rho       beta_0       beta_1

    lalpha            1        -0.99        0.018       0.0095

       rho        -0.99            1       -0.022      -0.0024

    beta_0         0.018       -0.022            1        -0.87

    beta_1        0.0095      -0.0024        -0.87            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha           2.8315          1.71297          -0.525852             6.18885
            rho          1.19884         0.416889           0.381756             2.01593
         beta_0          94.5944          14.6685            65.8446             123.344
         beta_1         -1.97776         0.509904           -2.97715           -0.978362
         beta_2                0               NA
         beta_3                0               NA

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     8        100          94.6         83.2           63          0.243
6.587     8       91.2          81.6           48         57.6          0.471
14.48     8       51.4            66         43.5         50.7         -0.811
36.43     8       22.8          22.5           30         26.7         0.0269


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
```

```
            Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
      Model A3 uses any fixed variance parameters that
      were specified by the user

 Model  R:         Yi = Mu + e(i)
             Var{e(i)} = Sigma^2


                        Likelihoods of Interest

             Model      Log(likelihood)   # Param's      AIC
              A1         -141.983433            5     293.966865
              A2         -137.581833            8     291.163667
              A3         -138.348184            6     288.696368
          fitted         -139.254163            4     286.508326
               R         -146.997301            2     297.994602


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                      Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              18.8309          6        0.004459
   Test 2               8.8032          3         0.03203
   Test 3               1.5327          2          0.4647
   Test 4              1.81196          2          0.4041

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


             Benchmark Dose Computation

Specified effect =           0.1

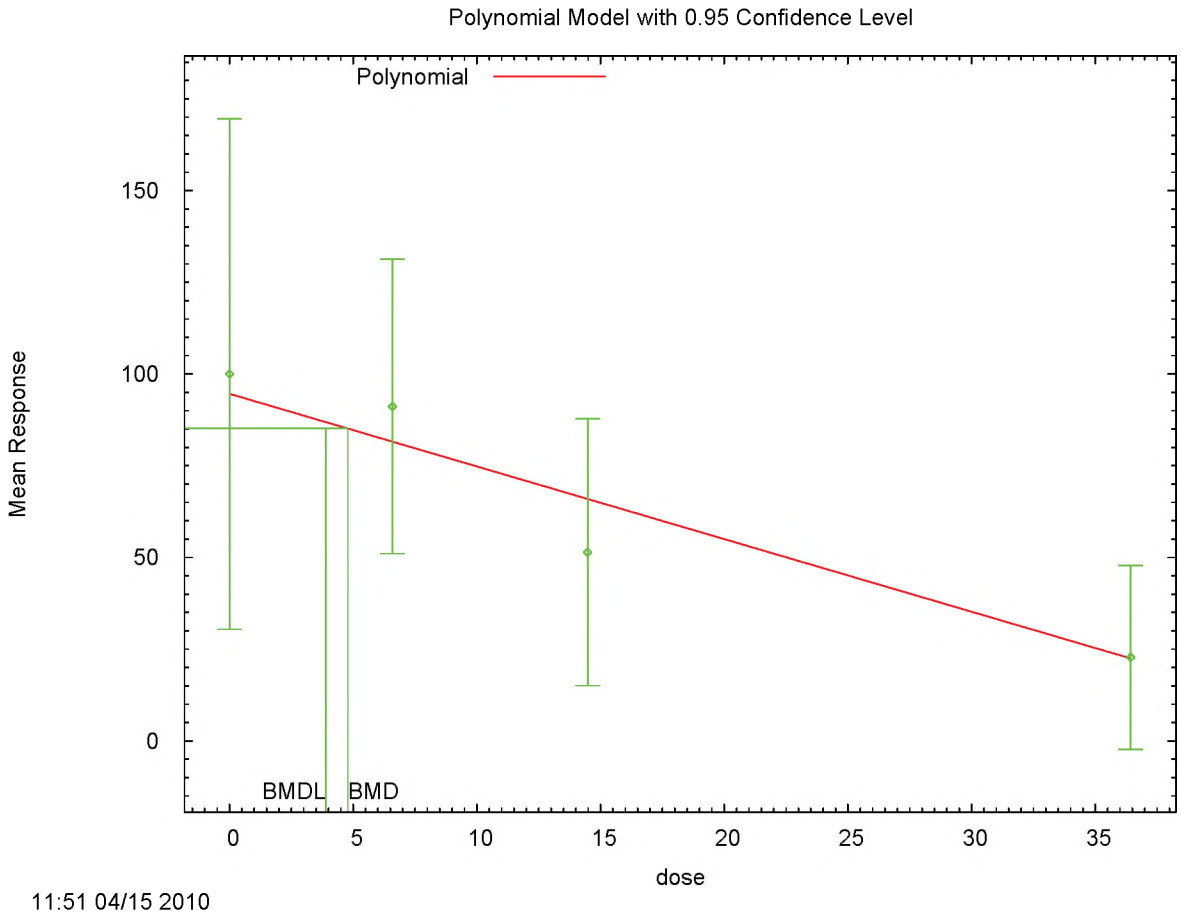
Risk Type        =     Relative risk

Confidence level =          0.95

             BMD =        4.78292


             BMDL =         3.8932
```

E.2.11.5. *Figure for Additional Model Presented: Polynomial, 3-degree*



E.2.12. Franc et al., 2001: L-E Rats, Relative Thymus Weight

E.2.12.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	2	0.440	301.449	2.726E+00	1.212E+00	
exponential (M3)	2	0.440	301.449	2.726E+00	1.212E+00	power hit bound (d = 1)
exponential (M4) [b]	1	0.227	303.266	2.084E+00	5.926E-01	
exponential (M5)	0	N/A	303.805	7.859E+00	9.801E-01	
Hill	0	N/A	303.805	7.480E+00	7.512E-01	
linear	2	0.304	302.186	5.045E+00	3.349E+00	
polynomial, 3-degree	2	0.304	302.186	5.045E+00	3.349E+00	
power	2	0.304	302.186	5.045E+00	3.349E+00	power bound hit (power = 1)
power, unrestricted	1	0.168	303.710	1.374E+00	9.032E-09	unrestricted (power = 0.601)

[a] Constant variance model selected ($p = 0.5063$)

[b] Best-fitting model, BMDS output presented in this appendix

E.2.12.2. *Output for Selected Model: Exponential (M4)*

Franc et al., 2001: L-E Rats, Relative Thymus Weight

```
 ================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\1\Blood\92_Franc_2001_LE_RelThyWt_ExpCV_1.(d)
         Gnuplot Plotting File:
                                                Thu Apr 15 11:53:37 2010
 ================================================================

 Figure 5, L-E rats, relative thymus weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.
```

Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	8.1814
rho(S)	0
a	105
b	0.0506168
c	0.166582
d	1

(S) = Specified

Parameter Estimates

Variable	Model 4
lnalpha	8.22706
rho	0
a	105.977
b	0.0660042
c	0.221786
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	8	100	54.72
6.584	8	95.41	70.46
14.47	8	38.69	47.97
36.41	8	34.98	77.96

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	106	61.16	-0.2764
6.584	76.91	61.16	0.8555
14.47	55.24	61.16	-0.765
36.41	30.96	61.16	0.186

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

```
  Model A2:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
              Var{e(ij)} = Sigma^2


                            Likelihoods of Interest

                 Model      Log(likelihood)      DF         AIC
                -------    -----------------    ----   ------------
                   A1       -146.9024            5      303.8049
                   A2       -145.7361            8      307.4723
                   A3       -146.9024            5      303.8049
                    R       -150.6049            2      305.2098
                    4       -147.6329            4      303.2658


Additive constant for all log-likelihoods =     -29.41.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.


                             Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)


                         Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                       9.738            6             0.1362
  Test 2                       2.333            3             0.5063
  Test 3                       2.333            3             0.5063
 Test 6a                       1.461            1             0.2268


  The p-value for Test 1 is greater than .05.  There may not be a
  diffence between responses and/or variances among the dose levels
  Modelling the data with a dose/response curve may not be appropriate.

  The p-value for Test 2 is greater than .1.  A homogeneous
  variance model appears to be appropriate here.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 6a is greater than .1.  Model 4 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 0.100000

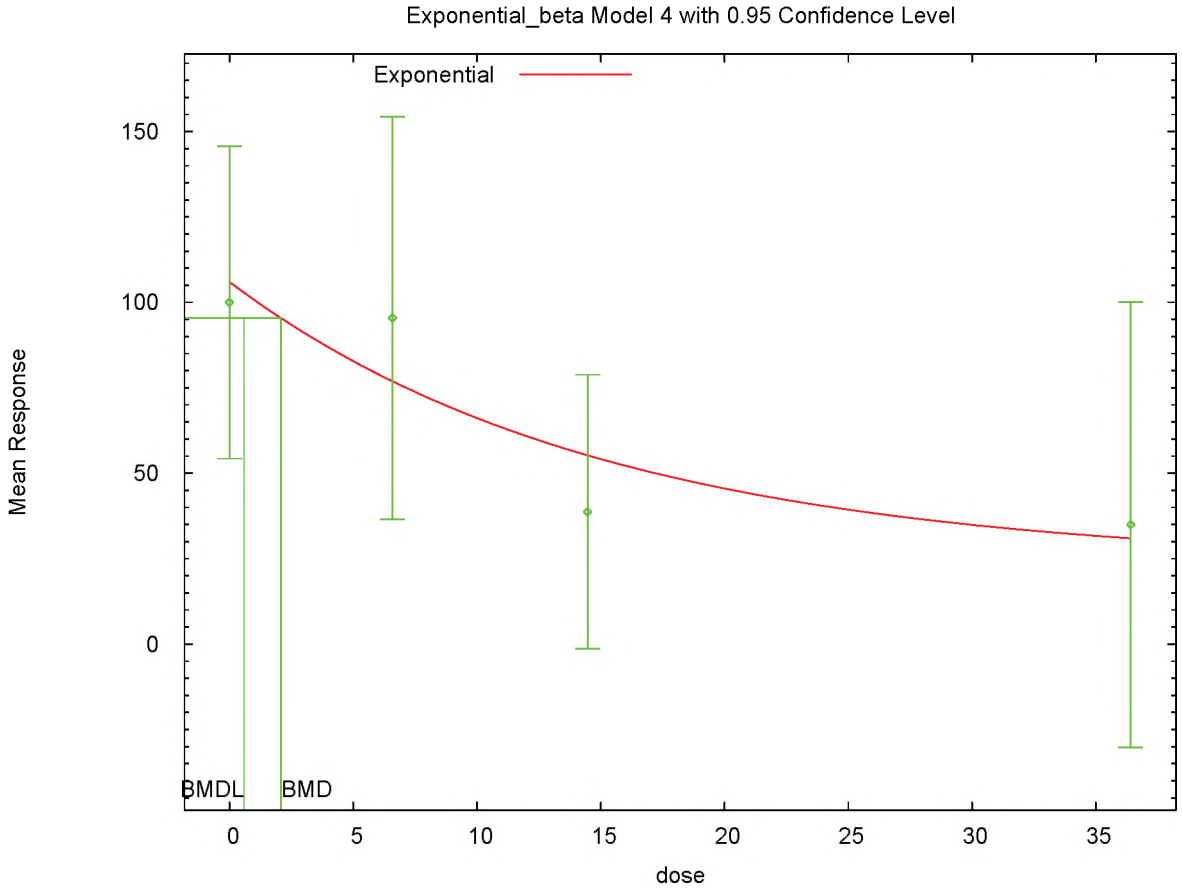
         Risk Type = Relative deviation

  Confidence Level = 0.950000

               BMD =      2.08379

              BMDL =     0.592601
```

E.2.12.3. *Figure for Selected Model: Exponential (M4)*



E.2.13. Franc et al., 2001: H/W Rats, Relative Thymus Weight

E.2.13.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2) [b]	2	0.698	261.646	5.094E+00	3.132E+00	
exponential (M3)	1	0.407	263.616	5.944E+00	3.140E+00	
exponential (M4)	1	0.396	263.646	5.063E+00	1.864E+00	
exponential (M5)	0	N/A	264.927	9.945E+00	2.127E+00	
Hill	0	N/A	264.927	9.638E+00	1.853E+00	
linear	2	0.645	261.804	6.874E+00	5.006E+00	
polynomial, 3-degree	2	0.645	261.804	6.874E+00	5.006E+00	
power	2	0.645	261.804	6.874E+00	5.006E+00	power bound hit (power = 1)
power, unrestricted	1	0.363	263.755	5.487E+00	2.573E-01	unrestricted (power = 0.881)

[a] Constant variance model selected ($p = 0.4331$)

[b] Best-fitting model, BMDS output presented in this appendix

E.2.13.2. *Output for Selected Model: Exponential (M2)*

Franc et al., 2001: H/W Rats, Relative Thymus Weight

```
 ================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\1\Blood\93_Franc_2001_HW_RelThyWt_ExpCV_1.(d)
         Gnuplot Plotting File:
                                                Thu Apr 15 11:55:55 2010
 ================================================================

 Figure 5, H/W rats, relative thymus weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.
```

```
Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact
```

Initial Parameter Values

Variable	Model 2
lnalpha	6.96647
rho(S)	0
a	56.9433
b	0.0204806
c	0
d	1

(S) = Specified

Parameter Estimates

Variable	Model 2
lnalpha	6.98895
rho	0
a	103.047
b	0.0206828
c	0
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	8	100	35.98
6.588	8	97.53	32.98
14.48	8	71.02	23.99
36.44	8	49.29	43.48

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	103	32.93	-0.2617
6.588	89.92	32.93	0.6532
14.48	76.38	32.93	-0.4596
36.44	48.49	32.93	0.06871

```
Other models for which likelihoods are calculated:

  Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
```

```
  Model A2:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
              Var{e(ij)} = Sigma^2


                              Likelihoods of Interest

                   Model      Log(likelihood)      DF         AIC
                  -------    ------------------    ----   ------------
                      A1       -127.4636            5      264.9271
                      A2       -126.0925            8       268.185
                      A3       -127.4636            5      264.9271
                       R        -132.935            2        269.87
                       2       -127.8231            3      261.6463


Additive constant for all log-likelihoods =     -29.41.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.


                                Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does Model 2 fit the data? (A3 vs. 2)


                            Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                         13.69           6             0.03336
  Test 2                         2.742           3              0.4331
  Test 3                         2.742           3              0.4331
  Test 4                        0.7192           2               0.698


  The p-value for Test 1 is less than .05.  There appears to be a
  difference between response and/or variances among the dose
  levels, it seems appropriate to model the data.

  The p-value for Test 2 is greater than .1.  A homogeneous
  variance model appears to be appropriate here.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 4 is greater than .1.  Model 2 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 0.100000

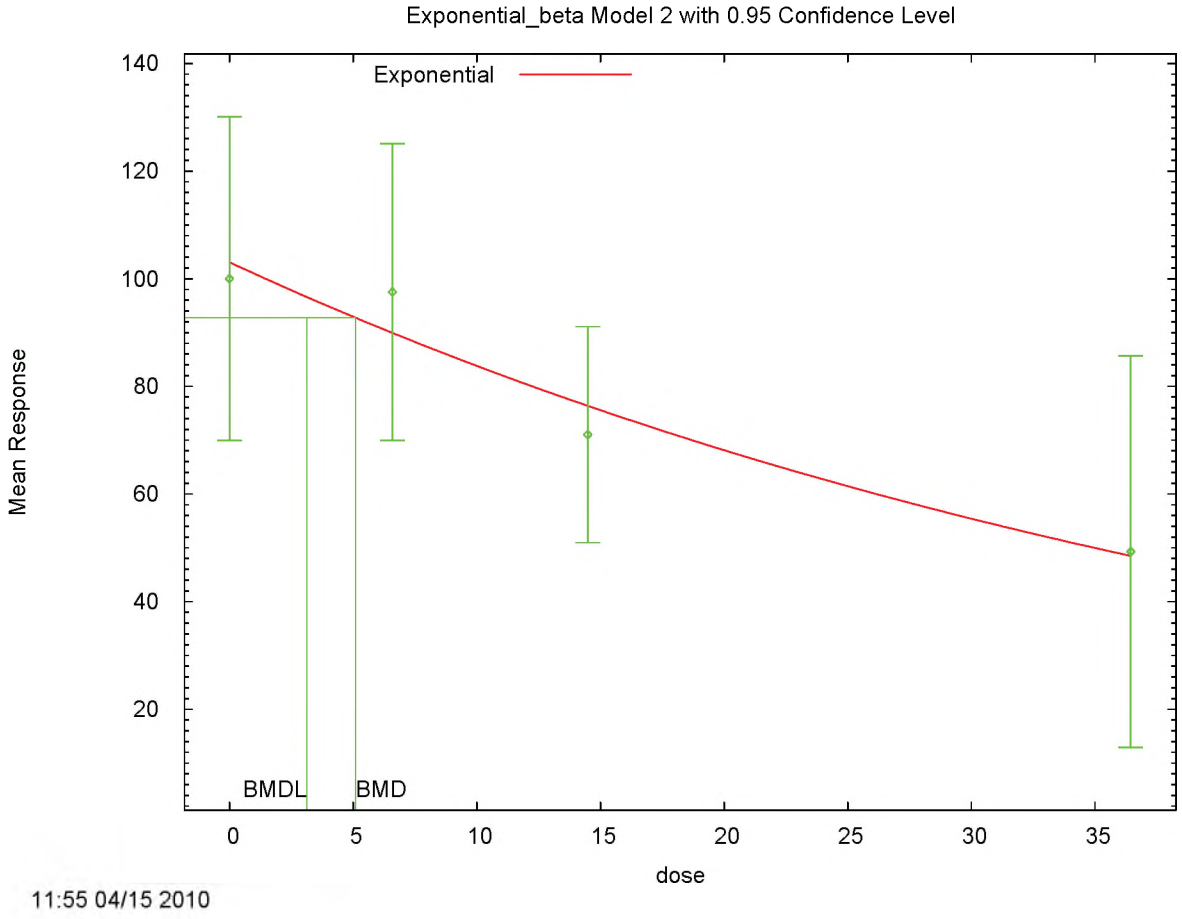
         Risk Type = Relative deviation

  Confidence Level = 0.950000

               BMD =      5.09411

              BMDL =      3.13214
```

E.2.13.3. *Figure for Selected Model: Exponential (M2)*



E.2.14. Hojo et al., 2002: DRL Reinforce Per Minute

E.2.14.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Hill	1	0.101	4.465	1.667E+00	6.209E-08	n upper bound hit (n = 18)
linear	2	0.009	9.124	1.352E+01	6.020E+00	
polynomial, 3-degree	2	0.009	9.124	1.352E+01	6.020E+00	
power	2	0.009	9.124	1.352E+01	6.020E+00	power bound hit (power = 1)
power, unrestricted	1	0.025	6.780	2.428E-01	1.070E-14	unrestricted (power = 0.103)
exponential (M2)	2	0.007	9.612	1.623E+01	8.673E+00	
exponential (M3)	2	0.007	9.612	1.623E+01	8.673E+00	power hit bound (d = 1)
exponential (M4) [b]	**1**	**0.054**	**5.488**	**1.316E+00**	**2.367E-03**	
exponential (M5)	0	N/A	6.465	1.728E+00	9.452E-03	

[a] Constant variance model selected ($p = 0.4321$)

[b] Best-fitting model, BMDS output presented in this appendix

E.2.14.2. *Output for Selected Model: Exponential (M4)*

Hojo et al., 2002: DRL Reinforce Per Minute

```
 ========================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\1\Blood\21_Hojo_2002_DRLrein_ExpCV_1.(d)
         Gnuplot Plotting File:
                                                  Mon Feb 08 10:49:08 2010
 ========================================================================

 Table 5, values adjusted by a constant to allow exponential model
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.
```

Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	-1.29672
rho(S)	0
a	0.0817
b	0.15642
c	16.3733
d	1

(S) = Specified

Parameter Estimates

Variable	Model 4
lnalpha	-1.11961
rho	0
a	0.0547452
b	0.708154
c	18.214
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	5	0.086	0.448
1.625	5	0.536	0.821
4.169	6	1.274	0.54
10.7	5	0.737	0.443

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.05475	0.5713	0.1223
1.625	0.6989	0.5713	-0.6375
4.169	0.9479	0.5713	1.398
10.7	0.9966	0.5713	-1.016

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

```
  Model A2:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
              Var{e(ij)} = Sigma^2


                            Likelihoods of Interest

                 Model      Log(likelihood)      DF         AIC
                -------    -----------------    ----   ------------
                    A1          3.11555           5        3.7689
                    A2          4.489557          8       7.020886
                    A3           3.11555          5        3.7689
                     R          -2.435087         2       8.870174
                     4           1.255891         4       5.488219


Additive constant for all log-likelihoods =      -19.3.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.


                             Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)


                         Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                      13.85             6             0.03137
  Test 2                      2.748             3              0.4321
  Test 3                      2.748             3              0.4321
 Test 6a                      3.719             1             0.05379


  The p-value for Test 1 is less than .05.  There appears to be a
  difference between response and/or variances among the dose
  levels, it seems appropriate to model the data.

  The p-value for Test 2 is greater than .1.  A homogeneous
  variance model appears to be appropriate here.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 6a is less than .1.  Model 4 may not adequately
  describe the data; you may want to consider another model.


Benchmark Dose Computations:

  Specified Effect = 1.000000

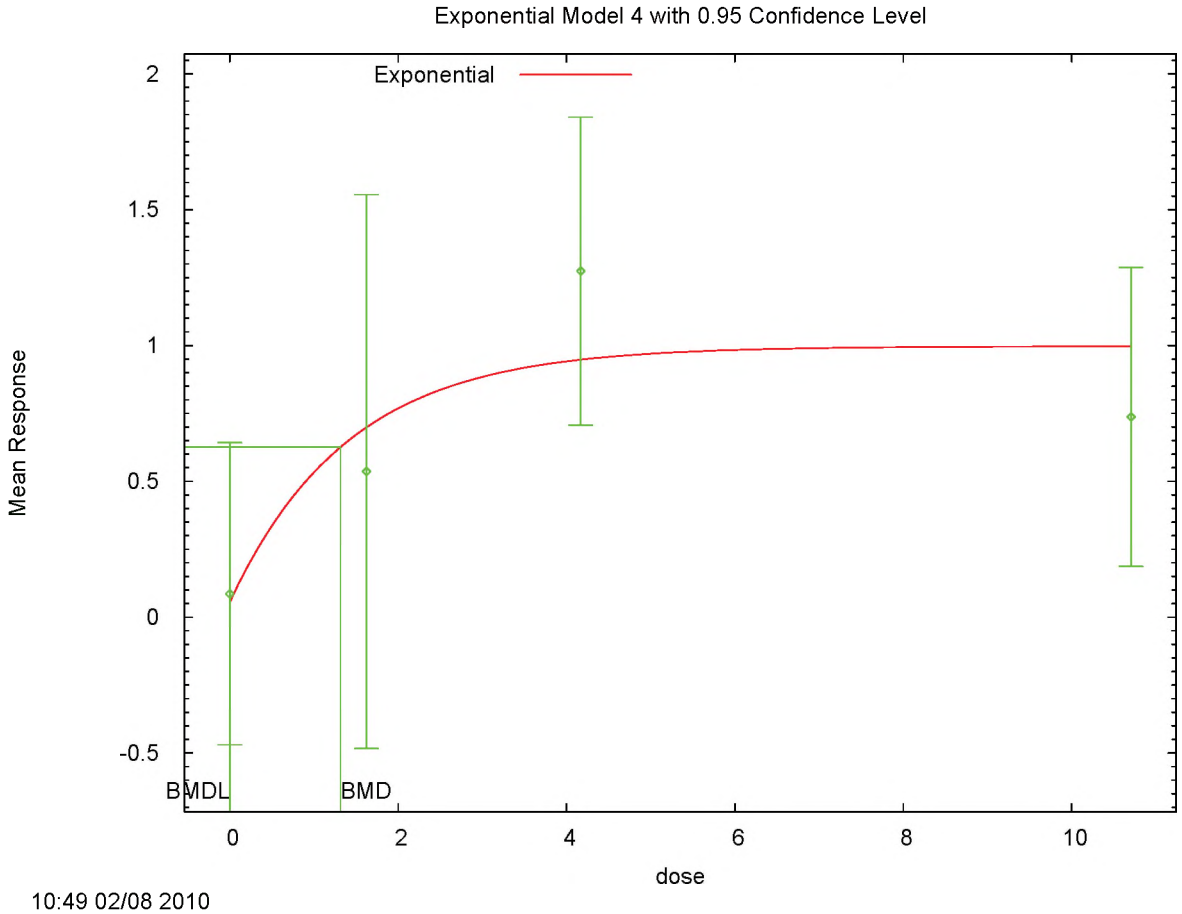
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

              BMD =      1.31616
```

BMDL = 0.00236664

E.2.14.3. *Figure for Selected Model: Exponential (M4)*



10:49 02/08 2010

E.2.15. Hojo et al., 2002: DRL Response Per Minute

E.2.15.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Hill	0	N/A	126.353	1.373E+00	1.070E-14	
linear	2	0.006	132.243	1.064E+01	5.340E+00	
polynomial, 3-degree	2	0.006	132.243	1.064E+01	5.340E+00	
power	2	0.006	132.243	1.064E+01	5.340E+00	power bound hit (power = 1)
power, unrestricted	2	0.741	122.455	1.070E+03	error	unrestricted (power = 0)
exponential (M2)	2	0.570	122.980	5.027E-01	error	
exponential (M3)	2	0.570	122.980	5.027E-01	error	power hit bound (d = 1)
exponential (M4) [b]	**1**	**0.477**	**124.360**	**3.813E-01**	**1.553E-02**	
exponential (M5)	0	N/A	126.353	8.430E-01	2.221E-02	

[a] Constant variance model selected ($p = 0.3004$)

[b] Best-fitting model, BMDS output presented in this appendix

E.2.15.2. *Output for Selected Model: Exponential (M4)*

Hojo et al., 2002: DRL Response Per Minute

```
 ================================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\1\Blood\23_Hojo_2002_DRLresp_ExpCV_1.(d)
         Gnuplot Plotting File:
                                                  Mon Feb 08 10:50:10 2010
 ================================================================================

 Table 5, values adjusted by a constant to allow exponential model
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.
```

Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	4.51689
rho(S)	0
a	24.6362
b	0.379327
c	0.0184785
d	1

(S) = Specified

Parameter Estimates

Variable	Model 4
lnalpha	4.54096
rho	0
a	23.4674
b	1.61185
c	0.101317
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	5	23.46	7.986
1.625	5	4.013	10.96
4.169	6	0.478	7.194
10.7	5	4.594	15.23

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	23.47	9.684	-0.001008
1.625	3.915	9.684	0.02265
4.169	2.403	9.684	-0.4869
10.7	2.378	9.684	0.5118

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

```
  Model A2:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
              Var{e(ij)} = Sigma^2


                              Likelihoods of Interest

                   Model      Log(likelihood)      DF         AIC
                  -------    -----------------    ----   ------------
                      A1       -57.92733            5      125.8547
                      A2       -56.09669            8      128.1934
                      A3       -57.92733            5      125.8547
                       R       -64.49611            2      132.9922
                       4        -58.1801            4      124.3602


Additive constant for all log-likelihoods =      -19.3.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.


                               Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)


                           Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                         16.8           6             0.01005
  Test 2                        3.661           3              0.3004
  Test 3                        3.661           3              0.3004
 Test 6a                       0.5056           1              0.4771


  The p-value for Test 1 is less than .05.  There appears to be a
  difference between response and/or variances among the dose
  levels, it seems appropriate to model the data.

  The p-value for Test 2 is greater than .1.  A homogeneous
  variance model appears to be appropriate here.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 6a is greater than .1.  Model 4 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 1.000000

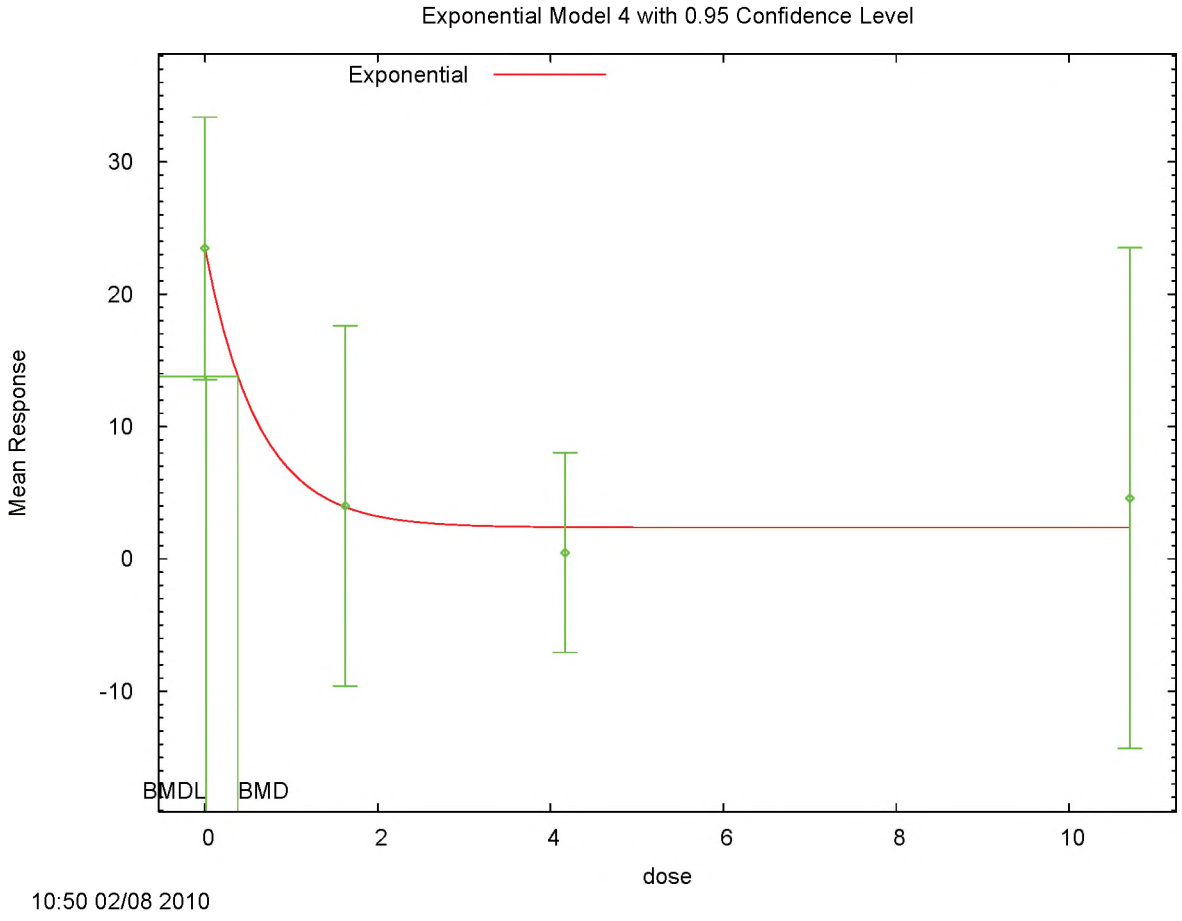
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD =     0.381347
```

BMDL = 0.0155267

E.2.15.3. *Figure for Selected Model: Exponential (M4)*



E.2.16. Kattainen et al., 2001: 3rd Molar Eruption, Female

E.2.16.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
logistic	3	0.360	88.508	9.223E+00	6.671E+00	negative intercept (intercept = -1.586)
log-logistic [a]	**3**	**0.982**	**85.227**	**2.399E+00**	**1.328E+00**	**slope bound hit (slope = 1)**
log-probit	3	0.522	87.424	7.346E+00	4.561E+00	slope bound hit (slope = 1)
probit	3	0.379	88.352	8.802E+00	6.549E+00	negative intercept (intercept = -0.975)
multistage, 4-degree	3	0.781	86.155	4.042E+00	2.626E+00	final ß = 0
log-logistic, unrestricted [b]	2	0.949	87.162	1.931E+00	1.840E-01	unrestricted (slope = 0.91)
log-probit, unrestricted	2	0.941	87.181	2.075E+00	2.395E-01	unrestricted (slope = 0.549)

[a] Best-fitting model, BMDS output presented in this appendix

[b] Alternate model, BMDS output also presented in this appendix

E.2.16.2. *Output for Selected Model: Log-Logistic*

Kattainen et al., 2001: 3rd Molar Eruption, Female

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\1\Blood\24_Katt_2001_Erup_LogLogistic_BMR1.(d)
         Gnuplot Plotting File:  C:\1\Blood\24_Katt_2001_Erup_LogLogistic_BMR1.plt
                                              Mon Feb 08 10:50:39 2010
 ================================================================

 Figure 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model
```

Default Initial Parameter Values
background = 0.0625
intercept = -3.07535
slope = 1

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -slope
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	background	intercept
background	1	-0.53
intercept	-0.53	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0699339	*	*	*
intercept	-3.07219	*	*	*
slope	1	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-40.5286	5			
Fitted model	-40.6137	2	0.170195	3	0.9823
Reduced model	-50.7341	1	20.411	4	0.0004142

AIC: 85.2274

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0699	1.119	1.000	16	-0.117
2.2297	0.1570	2.669	3.000	17	0.221
6.2523	0.2788	4.182	4.000	15	-0.105
16.0824	0.4670	5.604	6.000	12	0.229
46.8576	0.7066	13.426	13.000	19	-0.215

Chi^2 = 0.17 d.f. = 3 P-value = 0.9820

Benchmark Dose Computation

Specified effect = 0.1

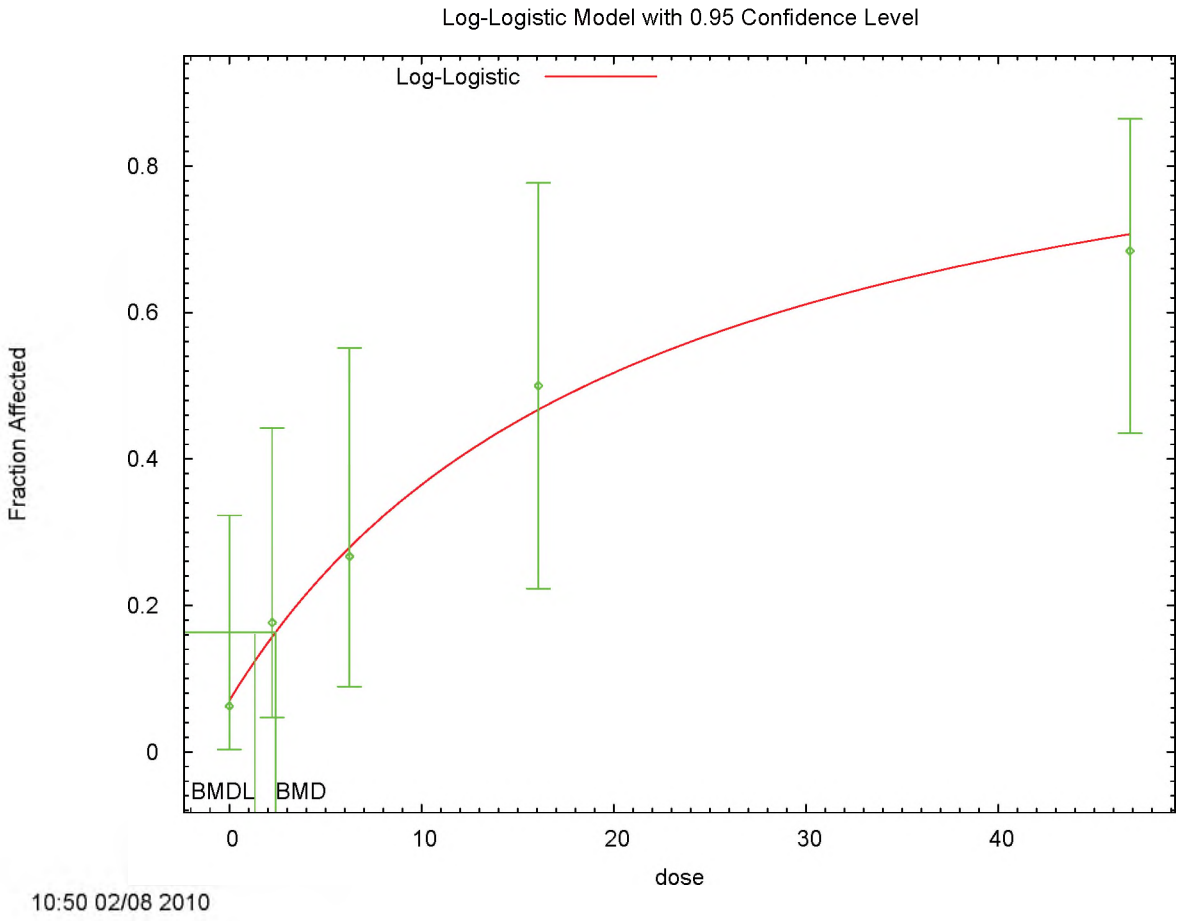
Risk Type = Extra risk

Confidence level = 0.95

BMD = 2.39879

BMDL = 1.32815

E.2.16.3. *Figure for Selected Model: Log-Logistic*



E.2.16.4. *Output for Additional Model Presented: Log-Logistic, Unrestricted*

Kattainen et al., 2001: 3rd Molar Eruption, Female

```
 ========================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\1\Blood\24_Katt_2001_Erup_LogLogistic_U_BMR1.(d)
         Gnuplot Plotting File:  C:\1\Blood\24_Katt_2001_Erup_LogLogistic_U_BMR1.plt
                                                Mon Feb 08 10:50:40 2010
 ========================================================================

 Figure 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 5
```

```
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =       0.0625
                     intercept =      -2.7659
                         slope =     0.901885


           Asymptotic Correlation Matrix of Parameter Estimates

             background    intercept        slope

background            1        -0.52         0.38

 intercept        -0.52            1        -0.94

     slope         0.38        -0.94            1


                                Parameter Estimates

                                                                95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background        0.0630045            *               *                   *
      intercept         -2.79616            *               *                   *
          slope         0.910333            *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -40.5286         5
   Fitted model        -40.5811         3      0.105049      2          0.9488
  Reduced model        -50.7341         1        20.411      4        0.0004142

           AIC:         87.1622


                                Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size        Residual
   ---------------------------------------------------------------------------
    0.0000     0.0630         1.008     1.000          16        -0.008
    2.2297     0.1683         2.862     3.000          17         0.090
    6.2523     0.2922         4.383     4.000          15        -0.217
   16.0824     0.4692         5.631     6.000          12         0.214
   46.8576     0.6903        13.116    13.000          19        -0.058

 Chi^2 = 0.10      d.f. = 2        P-value = 0.9491


   Benchmark Dose Computation

Specified effect =            0.1

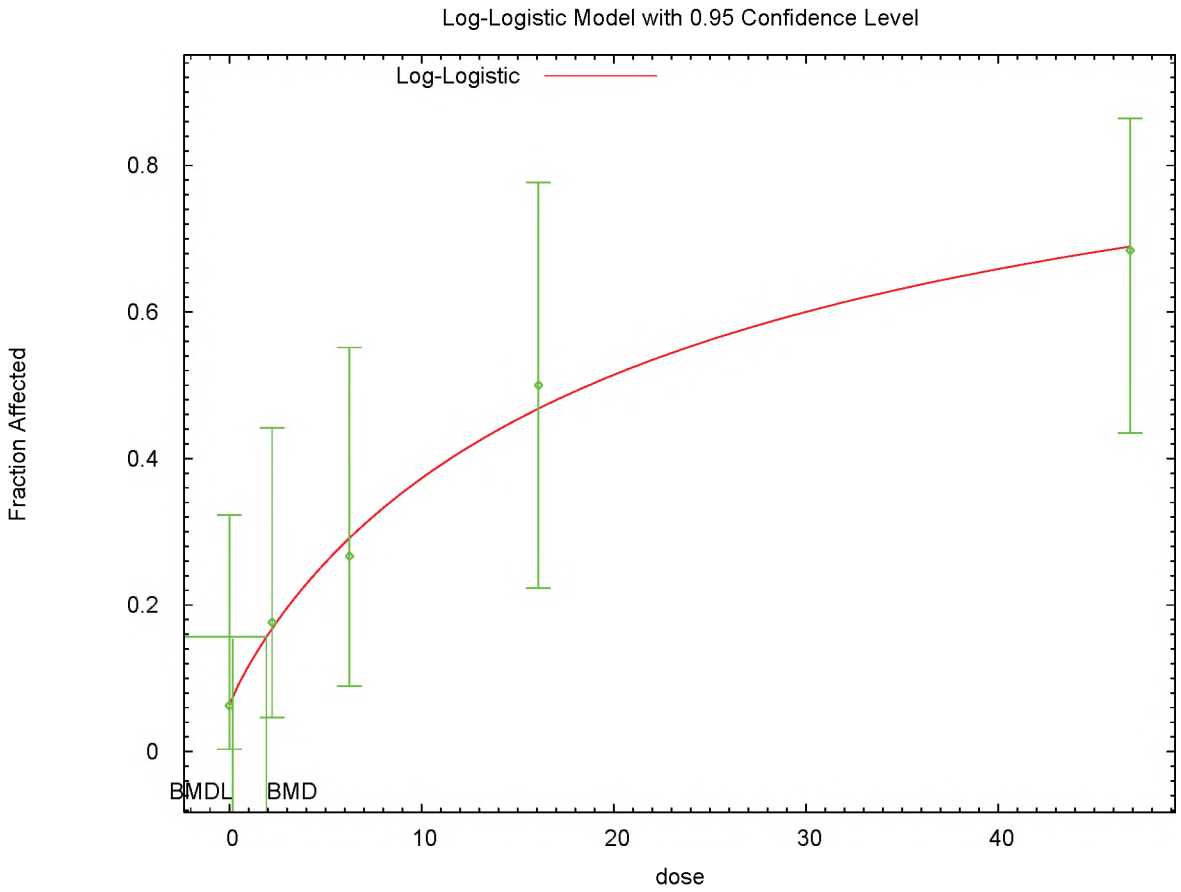
Risk Type        =      Extra risk

Confidence level =           0.95
```

```
BMD =         1.93079

BMDL =        0.18403
```

E.2.16.5. *Figure for Additional Model Presented: Log-Logistic, Unrestricted*



E.2.17. Kattainen et al., 2001: 3rd Molar Length, Female

E.2.17.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	3	<0.0001	-124.866	1.669E+01	9.933E+00	
exponential (M3)	3	<0.0001	-124.866	1.669E+01	9.933E+00	power hit bound (d = 1)
exponential (M4)	2	0.002	-147.120	4.237E-01	2.530E-01	
exponential (M5)	2	0.002	-147.120	4.237E-01	2.530E-01	power hit bound (d = 1)
Hill [b]	**2**	**0.022**	**-152.239**	**3.132E-01**	**1.679E-01**	**n lower bound hit (n = 1)**
linear	3	<0.0001	-124.024	1.982E+01	1.277E+01	
polynomial, 4-degree	3	<0.0001	-124.024	1.982E+01	1.277E+01	
power	3	<0.0001	-124.024	1.982E+01	1.277E+01	power bound hit (power = 1)
Hill, unrestricted [c]	1	<0.0001	-130.856	1.215E-02	error	unrestricted (n = 13.042)
power, unrestricted	2	0.263	-157.201	1.964E-03	8.002E-06	unrestricted (power = 0.195)

[a] Non-constant variance model selected (p = <0.0001)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.2.17.2. *Output for Selected Model: Hill*

Kattainen et al., 2001: 3rd Molar Length, Female

```
 ======================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\1\Blood\25_Katt_2001_Length_Hill_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\25_Katt_2001_Length_Hill_1.plt
                                                Mon Feb 08 10:51:09 2010
 ======================================================================

 Figure 3 female only
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   Power parameter restricted to be greater than 1
```

The variance is to be modeled as Var(i) = exp(lalpha + rho * ln(mean(i)))

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	-2.37155
rho =	0
intercept =	1.85591
v =	-0.507874
n =	0.845932
k =	2.03129

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -n
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	lalpha	rho	intercept	v	k
lalpha	1	-0.98	-0.16	0.84	-0.38
rho	-0.98	1	0.2	-0.79	0.4
intercept	-0.16	0.2	1	-0.3	-0.11
v	0.84	-0.79	-0.3	1	-0.52
k	-0.38	0.4	-0.11	-0.52	1

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
lalpha	3.31084	1.404	0.559057	6.06262
rho	-14.2657	2.62739	-19.4153	-9.11612
intercept	1.85483	0.0159477	1.82357	1.88609
v	-0.453667	0.0620227	-0.575229	-0.332105
n	1	NA		
k	1.91219	0.624785	0.687636	3.13675

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	16	1.86	1.85	0.0661	0.0639	0.0674
2.23	17	1.58	1.61	0.185	0.175	-0.789
6.252	15	1.6	1.51	0.265	0.28	1.22
16.08	12	1.5	1.45	0.221	0.371	0.51
46.86	19	1.35	1.42	0.515	0.431	-0.716

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
              A1           56.758717           6    -101.517434
              A2           85.856450          10    -151.712901
              A3           84.934314           7    -155.868628
          fitted           81.119648           5    -152.239295
               R           45.373551           2     -86.747101


                  Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value

  Test 1              80.9658          8          <.0001
  Test 2              58.1955          4          <.0001
  Test 3              1.84427          3          0.6053
  Test 4              7.62933          2         0.02205

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1.  You may want to try a different
model


        Benchmark Dose Computation

Specified effect =            1

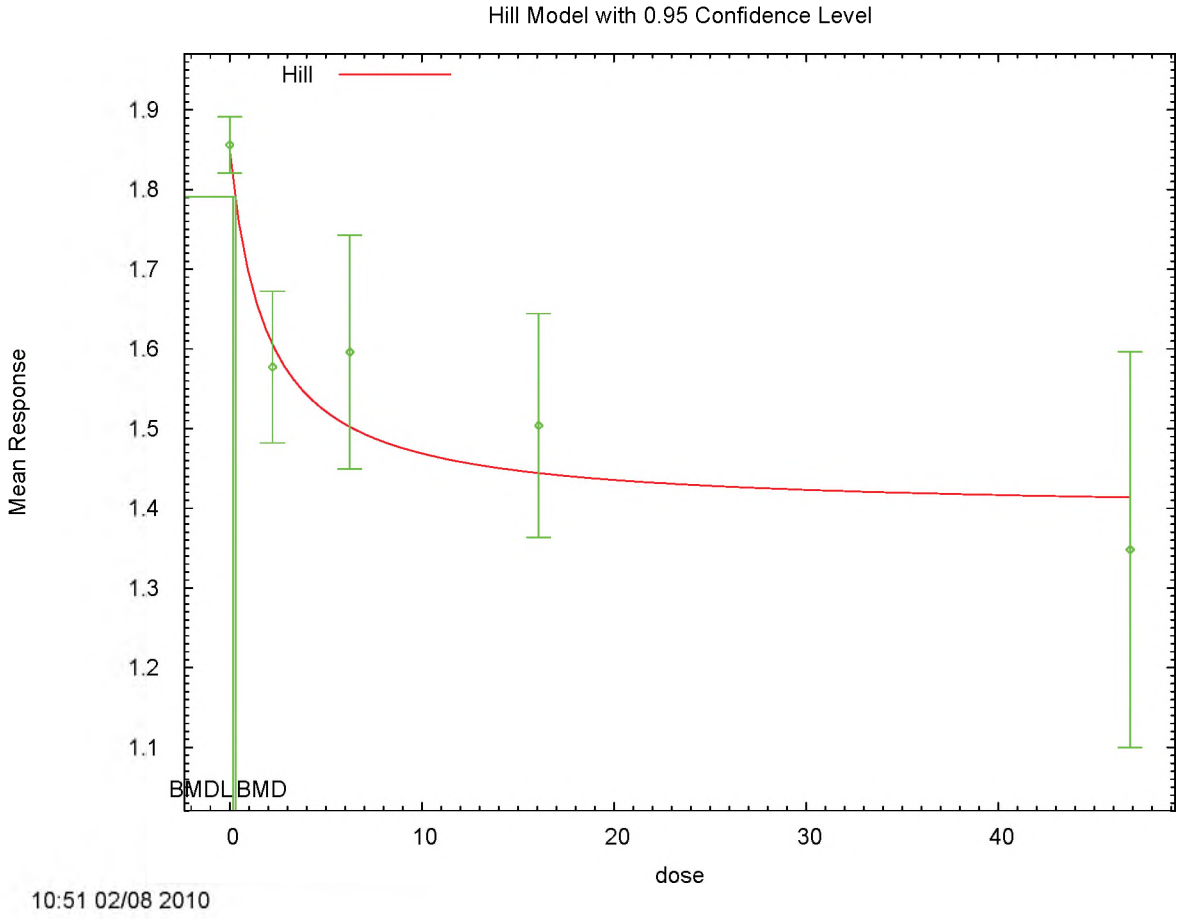
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =       0.313211

            BMDL =      0.167922
```

E.2.17.3. *Figure for Selected Model: Hill*



E.2.17.4. *Output for Additional Model Presented: Hill, Unrestricted*

Kattainen et al., 2001: 3rd Molar Length, Female

```
 ================================================================================
          Hill Model. (Version: 2.14;  Date: 06/26/2008)
          Input Data File: C:\1\Blood\25_Katt_2001_Length_Hill_U_1.(d)
          Gnuplot Plotting File:  C:\1\Blood\25_Katt_2001_Length_Hill_U_1.plt
                                                  Mon Feb 08 10:51:09 2010
 ================================================================================

 Figure 3 female only
 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   Power parameter is not restricted
   The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))
```

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	-2.37155
rho =	0
intercept =	1.85591
v =	-0.507874
n =	0.845932
k =	2.03129

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	intercept	v	n	k
lalpha	1	-0.98	-0.16	0.84	1.4e-016	3.3e-017
rho	-0.98	1	0.22	-0.77	-2.2e-016	-5.1e-017
intercept	-0.16	0.22	1	-0.35	6e-017	1.4e-017
v	0.84	-0.77	-0.35	1	-2.6e-016	-6.2e-017
n	1.4e-016	-2.2e-016	6e-017	-2.6e-016	1	1
k	3.3e-017	-5.1e-017	1.4e-017	-6.2e-017	1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	4.25154	1.5913	1.13265	7.37044
rho	-15.7639	2.90127	-21.4503	-10.0776
intercept	1.85591	0.0160104	1.82453	1.88729
v	-0.357293	0.0463784	-0.448193	-0.266393
n	13.0417	4.64308e+013	-9.10027e+013	9.10027e+013
k	0.0136512	2.57737e+011	-5.05155e+011	5.05155e+011

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	16	1.86	1.86	0.0661	0.064	2.09e-009
2.23	17	1.58	1.5	0.185	0.345	0.937
6.252	15	1.6	1.5	0.265	0.345	1.09
16.08	12	1.5	1.5	0.221	0.345	0.0534
46.86	19	1.35	1.5	0.515	0.345	-1.9

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

```
Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1           56.758717            6    -101.517434
             A2           85.856450           10    -151.712901
             A3           84.934314            7    -155.868628
         fitted           71.427978            6    -130.855955
              R           45.373551            2     -86.747101


                   Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value

  Test 1              80.9658          8          <.0001
  Test 2              58.1955          4          <.0001
  Test 3              1.84427          3          0.6053
  Test 4              27.0127          1          <.0001

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1.  You may want to try a different
model


        Benchmark Dose Computation

Specified effect =             1

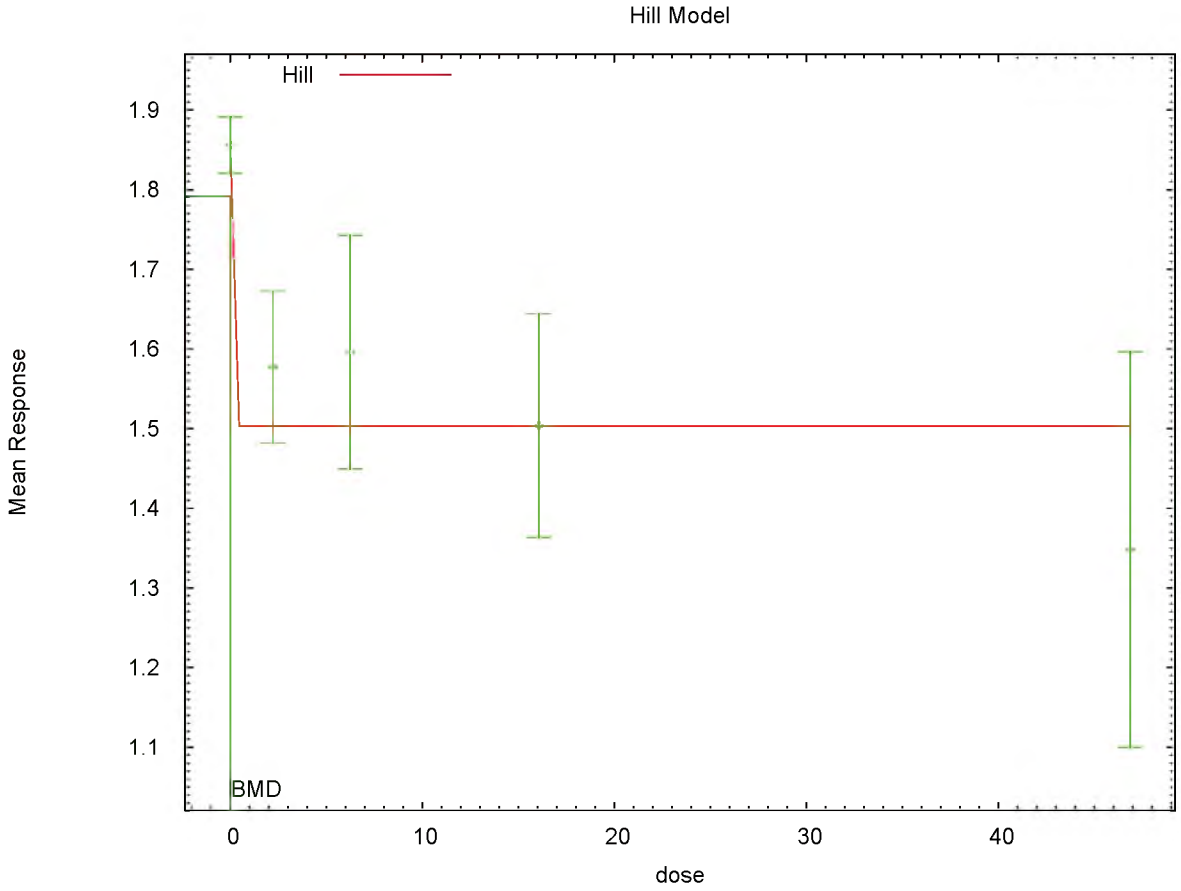
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =       0.012148


BMDL computation failed.
```

E.2.17.5. *Figure for Additional Model Presented: Hill, Unrestricted*



E.2.18. Keller et al., 2007: Missing Mandibular Molars, CBA J

E.2.18.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
gamma	1	0.105	52.510	3.342E+00	8.986E-01	
logistic	2	0.335	49.984	3.069E+00	2.212E+00	negative intercept (intercept = -3.414)
log-logistic	1	0.105	52.524	4.009E+00	2.411E+00	
log-probit	1	0.105	52.524	3.845E+00	2.421E+00	
multistage, 1-degree [a]	**3**	**0.255**	**50.425**	**1.091E+00**	**7.624E-01**	
multistage, 2-degree	1	0.122	51.391	1.916E+00	9.654E-01	
multistage, 3-degree	1	0.150	50.853	1.713E+00	9.584E-01	
probit	2	0.342	49.904	2.927E+00	2.053E+00	negative intercept (intercept = -1.873)
Weibull	1	0.108	52.219	2.744E+00	9.350E-01	

[a] Best-fitting model, BMDS output presented in this appendix

E.2.18.2. *Output for Selected Model: Multistage, 1-Degree*

Keller et al., 2007: Missing Mandibular Molars, CBA J

```
 ================================================================
         Multistage Model. (Version: 3.0;  Date: 05/16/2008)
         Input Data File: C:\1\Blood\26_Keller_2007_Molars_Multi1_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\26_Keller_2007_Molars_Multi1_1.plt
                                              Mon Feb 08 10:51:47 2010
 ================================================================

 Table 1 using mandibular molars only
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
```

```
Degree of polynomial = 1


Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                    Background =           0
                       Beta(1) = 3.03988e+018


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)

  Beta(1)            1



                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background                0            *               *                   *
        Beta(1)         0.096571            *               *                   *

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -21.5798         4
   Fitted model         -24.2126         1       5.26564      3          0.1533
  Reduced model          -71.326         1       99.4926      3         <.0001

           AIC:         50.4251


                                 Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000          29        0.000
    0.5374     0.0506         1.163     2.000          23        0.796
    4.2881     0.3391         9.833     6.000          29       -1.504
   34.0560     0.9627        28.881    30.000          30        1.078

 Chi^2 = 4.06      d.f. = 3        P-value = 0.2554


   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

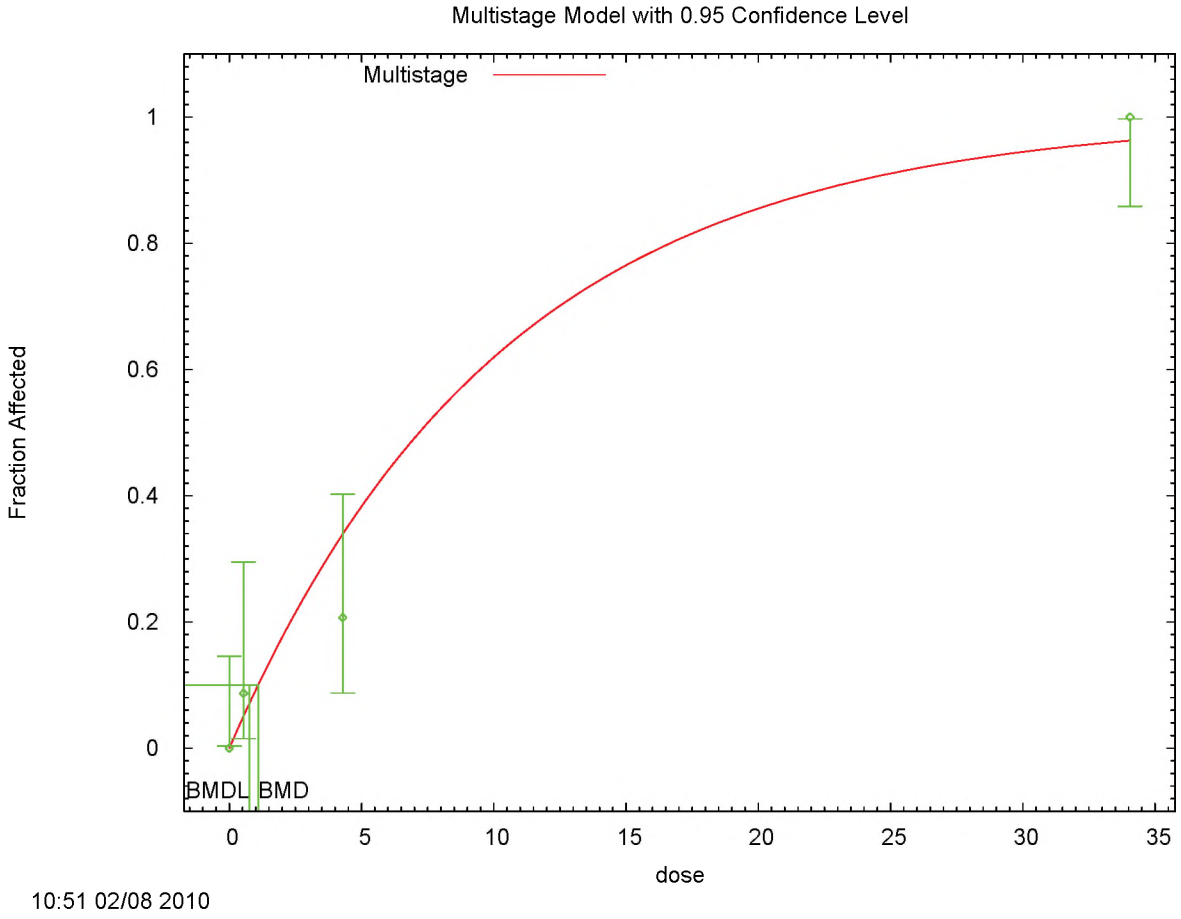
             BMD =       1.09102

            BMDL =      0.762404
```

```
            BMDU =        1.56496

Taken together, (0.762404, 1.56496) is a 90      % two-sided confidence
interval for the BMD
```

E.2.18.3. *Figure for Selected Model: Multistage, 1-Degree*



E.2.19. Kociba et al., 1978: Urinary Coproporphyrin, Females

E.2.19.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	2	<0.0001	82.975	2.378E+01	1.340E+01	
exponential (M3)	2	<0.0001	82.975	2.378E+01	1.340E+01	power hit bound (d = 1)
exponential (M4) [b]	**1**	**0.006**	**73.823**	**1.566E+00**	**7.180E-01**	
exponential (M5)	0	N/A	69.047	6.225E+00	1.586E+00	
Hill	0	N/A	69.047	5.473E+00	error	
linear	2	<0.001	82.233	1.790E+01	3.862E+00	
polynomial, 3-degree	2	<0.001	82.233	1.790E+01	3.862E+00	
power	2	<0.001	82.233	1.790E+01	3.862E+00	power bound hit (power = 1)
power, unrestricted	1	<0.001	78.691	1.148E+00	8.984E-09	unrestricted (power = 0.416)

[a] Non-constant variance model selected ($p = 0.0298$)

[b] Best-fitting model, BMDS output presented in this appendix

E.2.19.2. *Output for Selected Model: Exponential (M4)*

Kociba et al., 1978: Urinary Coproporphyrin, Females

```
 ======================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\1\Blood\29_Kociba_1978_Copro_Exp_1.(d)
         Gnuplot Plotting File:
                                                 Mon Feb 08 10:52:47 2010
 ======================================================================

 Table2-UrinaryCoproporphyrin
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.
```

Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	-5.58269
rho	2.98472
a	8.17
b	0.0692478
c	2.23623
d	1

Parameter Estimates

Variable	Model 4
lnalpha	-4.90852
rho	2.80743
a	8.91071
b	0.15304
c	1.97526
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	5	9.8	1.3
1.547	5	8.6	2
7.155	5	16.4	4.7
38.56	5	17.4	4

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	8.911	1.852	1.074
1.547	10.74	2.407	-1.991
7.155	14.69	3.736	1.021
38.56	17.58	4.805	-0.08246

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

```
  Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
           Var{e(ij)} = Sigma^2


                            Likelihoods of Interest

                 Model      Log(likelihood)      DF         AIC
                -------    -----------------    ----   ------------
                    A1       -31.69739            5      73.39478
                    A2       -27.21541            8      70.43081
                    A3       -28.16434            6      68.32868
                     R       -41.73188            2      87.46376
                     4       -31.91136            5      73.82272


Additive constant for all log-likelihoods =     -18.38.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.


                              Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)


                         Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                      29.03             6           < 0.0001
  Test 2                      8.964             3            0.02977
  Test 3                      1.898             2             0.3872
 Test 6a                      7.494             1            0.00619


  The p-value for Test 1 is less than .05.  There appears to be a
  difference between response and/or variances among the dose
  levels, it seems appropriate to model the data.

  The p-value for Test 2 is less than .1.  A non-homogeneous
  variance model appears to be appropriate.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 6a is less than .1.  Model 4 may not adequately
  describe the data; you may want to consider another model.


Benchmark Dose Computations:

  Specified Effect = 1.000000

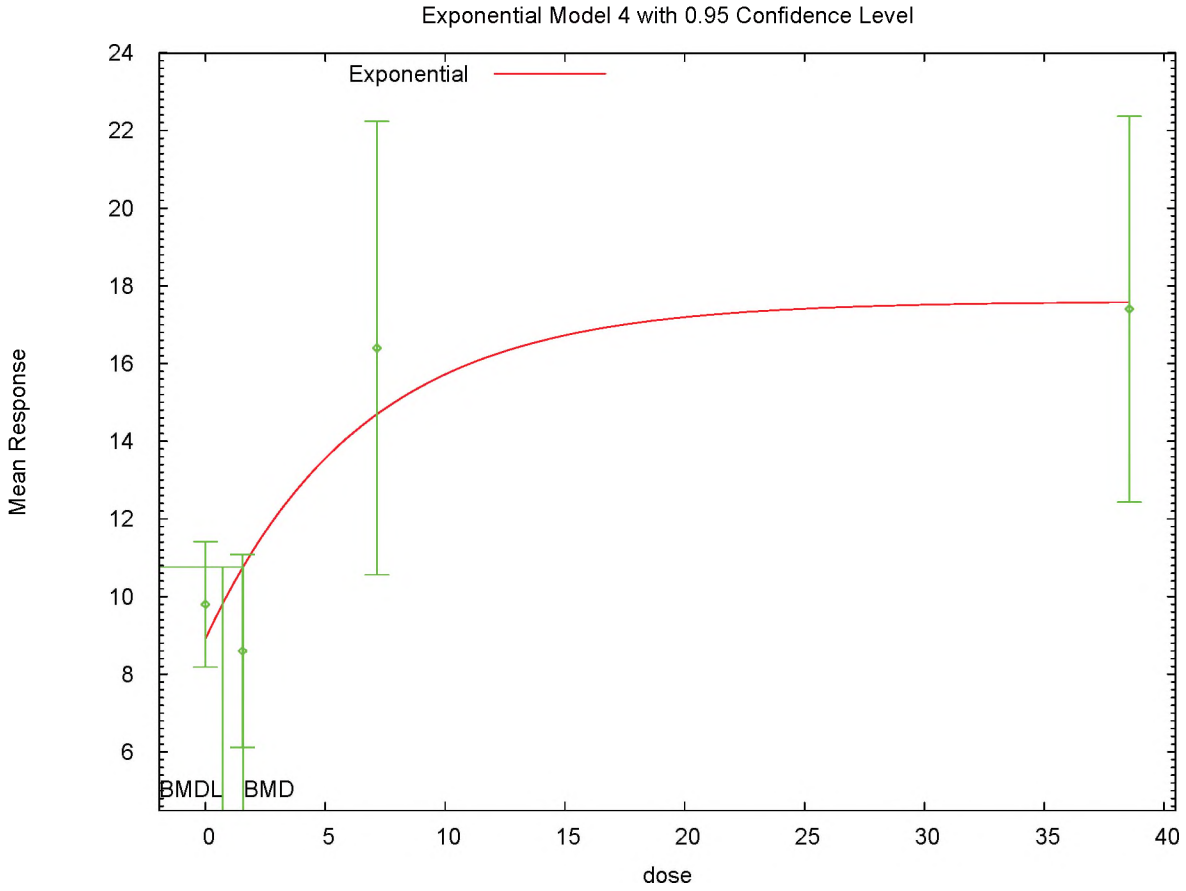
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD =      1.56562

              BMDL =     0.718033
```

E.2.19.3. *Figure for Selected Model: Exponential (M4)*



E.2.20. Kociba et al., 1978: Uroporphyrin per Creatinine, Female

E.2.20.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	2	0.755	-93.828	1.641E+01	1.259E+01	
exponential (M3)	2	0.755	-93.828	1.641E+01	1.259E+01	power hit bound (d = 1)
exponential (M4)	1	0.499	-91.935	1.216E+01	3.958E+00	
exponential (M5)	0	N/A	-90.190	7.542E+00	4.128E+00	
Hill	0	N/A	-90.190	7.607E+00	3.966E+00	
linear [b]	**2**	**0.793**	**-93.928**	**1.306E+01**	**9.287E+00**	
polynomial, 3-degree	2	0.793	-93.928	1.306E+01	9.287E+00	
power	1	0.497	-91.928	1.326E+01	9.287E+00	

[a] Constant variance model selected ($p = 0.4919$)

[b] Best-fitting model, BMDS output presented in this appendix

E.2.20.2. *Output for Selected Model: Linear*

Kociba et al., 1978: Uroporphyrin per Creatinine, Female

```
 ========================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\1\Blood\28_Kociba_1978_Uropor_LinearCV_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\28_Kociba_1978_Uropor_LinearCV_1.plt
                                              Mon Feb 08 10:52:17 2010
 ========================================================================

 Table 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values

alpha =	0.0030385	
rho =	0	Specified
beta_0 =	0.149139	
beta_1 =	0.00381789	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	beta_0	beta_1
alpha	1	1.9e-009	-2.6e-009
beta_0	1.9e-009	1	-0.6
beta_1	-2.6e-009	-0.6	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval	
			Lower Conf. Limit	Upper Conf. Limit
alpha	0.00248773	0.000786688	0.000945846	0.00402961
beta_0	0.149139	0.0139684	0.121761	0.176517
beta_1	0.00381789	0.000711776	0.00242284	0.00521295

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	5	0.157	0.149	0.05	0.0499	0.352
1.547	5	0.143	0.155	0.037	0.0499	-0.54
7.155	5	0.181	0.176	0.053	0.0499	0.204
38.56	5	0.296	0.296	0.074	0.0499	-0.0161

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that
were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	50.195349	5	-90.390697

```
              A2           51.400051            8     -86.800103
              A3           50.195349            5     -90.390697
          fitted           49.963863            3     -93.927727
               R           41.049755            2     -78.099510


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              20.7006          6        0.002076
   Test 2              2.40941          3          0.4919
   Test 3              2.40941          3          0.4919
   Test 4              0.46297          2          0.7934

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


             Benchmark Dose Computation

Specified effect =             1

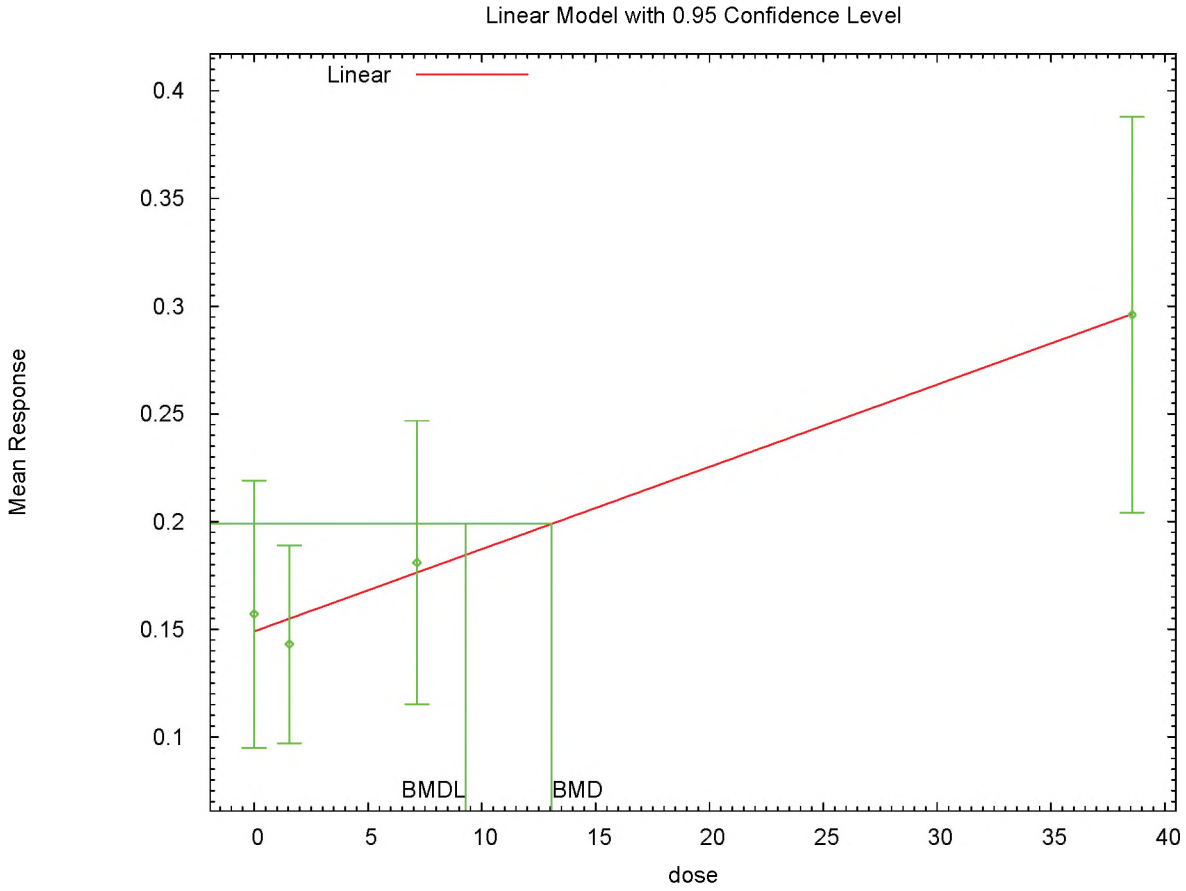
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

              BMD =         13.064


             BMDL =        9.28715
```

E.2.20.3. *Figure for Selected Model: Linear*



E.2.21. Latchoumycandane and Mathur, 2002: Sperm Production

E.2.21.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	2	<0.0001	93.831	1.739E+01	9.432E+00	
exponential (M3)	2	<0.0001	93.831	1.739E+01	9.432E+00	power hit bound (d = 1)
exponential (M4)	1	0.700	75.261	1.912E-01	7.976E-02	
exponential (M5)	0	N/A	77.263	2.925E-01	7.970E-02	
Hill [b]	**1**	**0.962**	**75.115**	**1.171E-01**	**1.324E-02**	**n lower bound hit (n = 1)**
linear	2	<0.0001	94.250	1.995E+01	1.212E+01	
polynomial, 3-degree	2	<0.0001	94.250	1.995E+01	1.212E+01	
power	2	<0.0001	94.250	1.995E+01	1.212E+01	power bound hit (power = 1)
Hill, unrestricted [c]	0	N/A	77.113	9.955E-02	1.228E-09	unrestricted (n = 0.916)
power, unrestricted	1	0.501	75.566	6.921E-06	6.921E-06	unrestricted (power = 0.087)

[a] Constant variance model selected ($p = 0.8506$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.2.21.2. *Output for Selected Model: Hill*

Latchoumycandane and Mathur, 2002: Sperm Production

```
 ======================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\1\Blood\30_Latch_2002_Sperm_HillCV_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\30_Latch_2002_Sperm_HillCV_1.plt
                                                 Mon Feb 08 10:53:26 2010
 ======================================================================

 (x10^6) Table 1 without Vitamin E
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
```

```
   Power parameter restricted to be greater than 1
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


                 Default Initial Parameter Values
                        alpha =      7.23328
                          rho =            0   Specified
                    intercept =        22.19
                            v =        -9.09
                            n =      1.93059
                            k =     0.546864


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -rho    -n
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

                  alpha    intercept            v            k

      alpha           1    -2.2e-009    -3.7e-008    -5.9e-009

  intercept    -2.2e-009            1        -0.76        -0.23

          v    -3.7e-008        -0.76            1        -0.24

          k    -5.9e-009        -0.23        -0.24            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
           alpha           6.0283          1.74022             2.61753             9.43907
       intercept          22.1894          1.00236             20.2248              24.154
               v         -9.16715          1.30966             -11.734            -6.60026
               n                1                NA
               k         0.320198         0.220443          -0.111862            0.752259

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     6       22.2         22.2         2.67         2.46       0.000631
0.7845     6       15.7         15.7         2.65         2.46       -0.00931
4.651      6       13.7         13.6         2.19         2.46         0.0372
27.27      6       13.1         13.1         3.16         2.46        -0.0285


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
```

```
           Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
       Model A3 uses any fixed variance parameters that
       were specified by the user

 Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1          -33.556444            5      77.112888
             A2          -33.158811            8      82.317623
             A3          -33.556444            5      77.112888
          fitted         -33.557588            4      75.115176
              R          -47.392394            2      98.784788


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              28.4672          6          <.0001
   Test 2             0.795266          3          0.8506
   Test 3             0.795266          3          0.8506
   Test 4           0.00228746          1          0.9619

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =             1

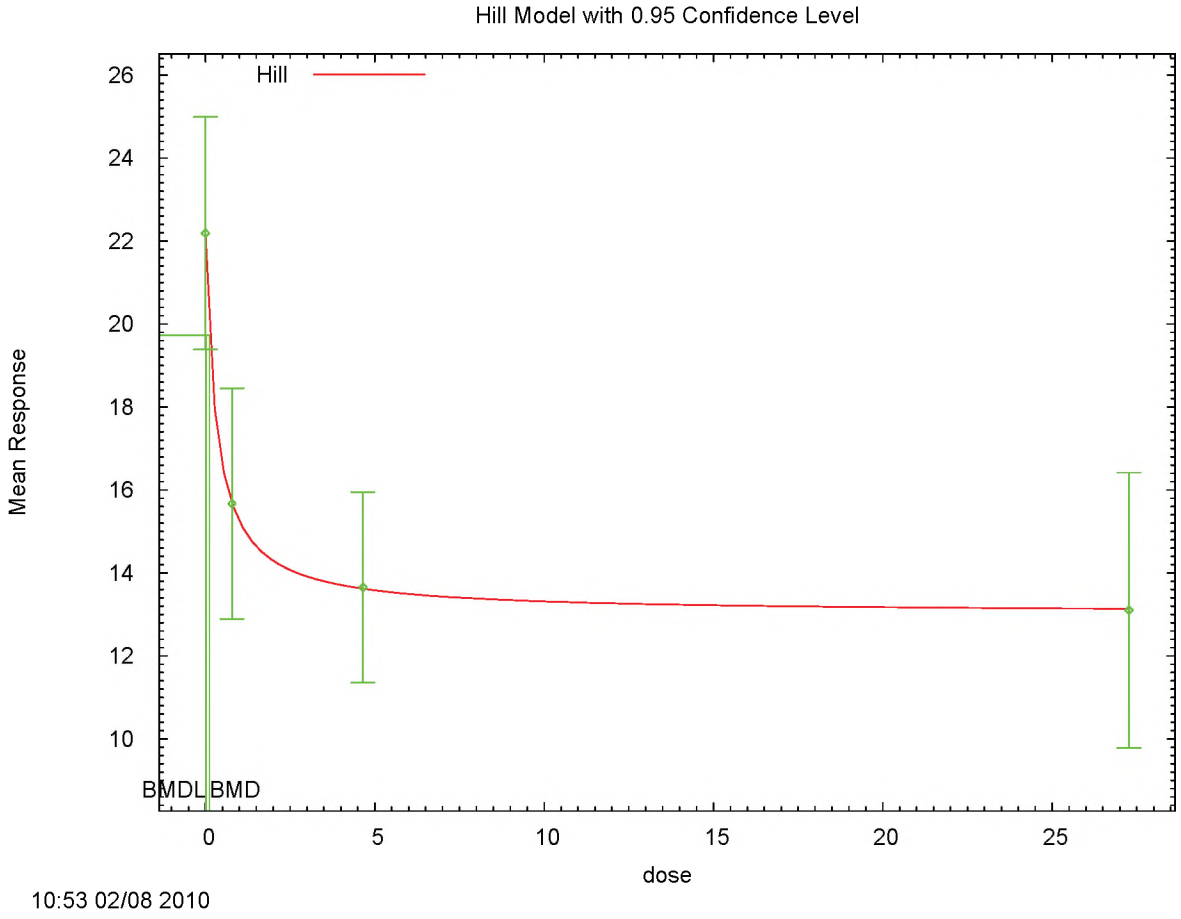
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =       0.117131

            BMDL =     0.0132353
```

E.2.21.3. *Figure for Selected Model: Hill*



E.2.21.4. *Output for Additional Model Presented: Hill, Unrestricted*

Latchoumycandane and Mathur, 2002: Sperm Production

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\1\Blood\30_Latch_2002_Sperm_HillCV_U_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\30_Latch_2002_Sperm_HillCV_U_1.plt
                                              Mon Feb 08 10:53:26 2010
 ================================================================

 (x10^6) Table 1 without Vitamin E
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter is not restricted
   A constant variance model is fit
```

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

alpha =	7.23328	
rho =	0	Specified
intercept =	22.19	
v =	-9.09	
n =	1.93059	
k =	0.546864	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	intercept	v	n	k
alpha	1	-9.8e-009	1.6e-007	1.6e-007	1.2e-007
intercept	-9.8e-009	1	-0.5	-0.015	-0.13
v	1.6e-007	-0.5	1	0.76	0.56
n	1.6e-007	-0.015	0.76	1	0.86
k	1.2e-007	-0.13	0.56	0.86	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	6.02773	1.74006	2.61728	9.43818
intercept	22.19	1.00231	20.2255	24.1545
v	-9.23667	2.03204	-13.2194	-5.25394
n	0.916265	1.66287	-2.34291	4.17544
k	0.301742	0.440535	-0.561692	1.16518

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	6	22.2	22.2	2.67	2.46	3.4e-008
0.7845	6	15.7	15.7	2.65	2.46	-1.51e-007
4.651	6	13.7	13.6	2.19	2.46	2.62e-007
27.27	6	13.1	13.1	3.16	2.46	-5.45e-007

Degrees of freedom for Test A3 vs fitted <= 0

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

```
Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                       Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1          -33.556444            5      77.112888
             A2          -33.158811            8      82.317623
             A3          -33.556444            5      77.112888
          fitted         -33.556444            5      77.112888
              R          -47.392394            2      98.784788


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              28.4672          6          <.0001
   Test 2             0.795266          3          0.8506
   Test 3             0.795266          3          0.8506
   Test 4          6.96332e-013         0              NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-Square
     test for fit is not valid


        Benchmark Dose Computation

Specified effect =             1

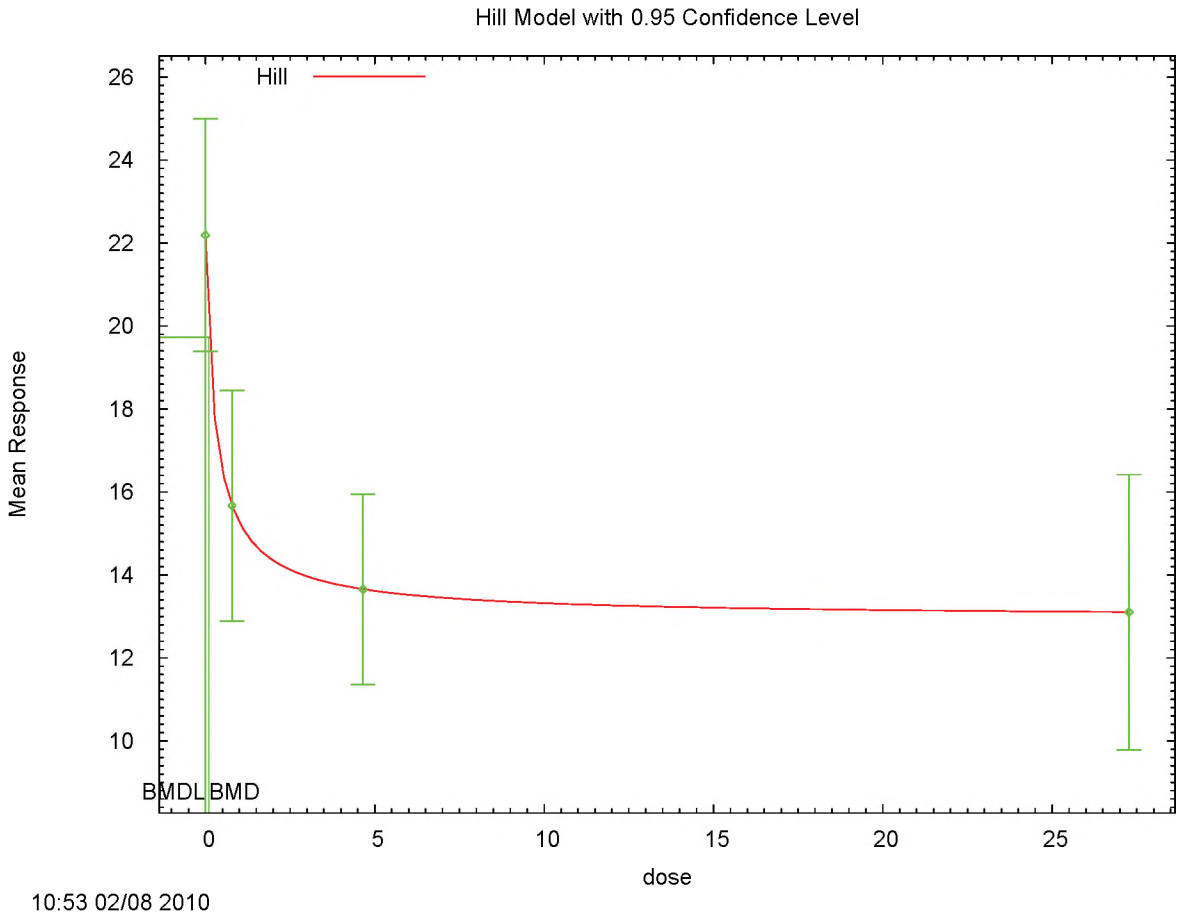
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =      0.0995543

            BMDL =  1.22818e-009
```

E.2.21.5. *Figure for Additional Model Presented: Hill, Unrestricted*



E.2.22. Li et al., 1997: FSH

E.2.22.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	8	<0.0001	1095.292	5.222E+02	4.121E+02	
exponential (M3)	8	<0.0001	1095.292	5.222E+02	4.121E+02	power hit bound (d = 1)
exponential (M4)	7	<0.0001	1059.480	3.432E+01	9.930E+00	
exponential (M5)	6	<0.0001	1066.195	1.019E+02	8.583E-01	
Hill	7	<0.0001	1056.459	5.423E+00	error	n lower bound hit (n = 1)
linear	8	<0.0001	1077.695	2.003E+02	1.357E+02	
polynomial, 8-degree	9	<0.0001	1155.670	error	1.916E+02	
power [b]	**8**	**<0.0001**	**1077.695**	**2.003E+02**	**1.357E+02**	**power bound hit (power = 1)**
Hill, unrestricted	6	0.001	1039.481	2.204E-01	error	unrestricted (n = 0.32)
power, unrestricted [c]	7	0.002	1037.474	1.963E-01	2.484E-02	unrestricted (power = 0.305)

[a] Non-constant variance model selected (p = <0.0001)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.2.22.2. *Output for Selected Model: Power*

Li et al., 1997: FSH

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\1\Blood\72_Li_1997_FSH_Pwr_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\72_Li_1997_FSH_Pwr_1.plt
                                              Mon Feb 08 13:36:35 2010
 ================================================================

 Figure 3: FSH in female S-D rats 24hr after dosing, 22 day old rats
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   The power is restricted to be greater than or equal to 1
```

The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 10
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	9.8191
rho =	0
control =	22.1591
slope =	52.284
power =	0.294106

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -power
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	lalpha	rho	control	slope
lalpha	1	-0.99	-0.29	-0.033
rho	-0.99	1	0.2	0.033
control	-0.29	0.2	1	-0.36
slope	-0.033	0.033	-0.36	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	3.50054	1.225	1.09958	5.9015
rho	1.27087	0.241869	0.796814	1.74492
control	87.4348	12.9347	62.0833	112.786
slope	0.492306	0.0919718	0.312044	0.672567
power	1	NA		

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	23.9	87.4	29.6	98.6	-2.04
0.266	10	22.2	87.6	48.5	98.7	-2.1
0.7988	10	85.2	87.8	94.3	98.9	-0.0832
2.097	10	73.3	88.5	48.5	99.4	-0.483
5.867	10	126	90.3	159	101	1.12
15	10	132	94.8	116	104	1.14
43.33	10	117	109	51.2	113	0.223
119.9	10	304	146	154	137	3.65
386	10	347	277	151	205	1.07
1172	10	455	664	286	358	-1.85

```
Model Descriptions for likelihoods calculated


Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
              A1         -535.687163          11    1093.374327
              A2         -496.367061          20    1032.734122
              A3         -502.709623          12    1029.419246
          fitted         -534.847518           4    1077.695035
               R         -574.835246           2    1153.670492


                   Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value

  Test 1              156.936         18          <.0001
  Test 2              78.6402          9          <.0001
  Test 3              12.6851          8          0.1232
  Test 4              64.2758          8          <.0001

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1.  You may want to try a different
model


               Benchmark Dose Computation

Specified effect =             1

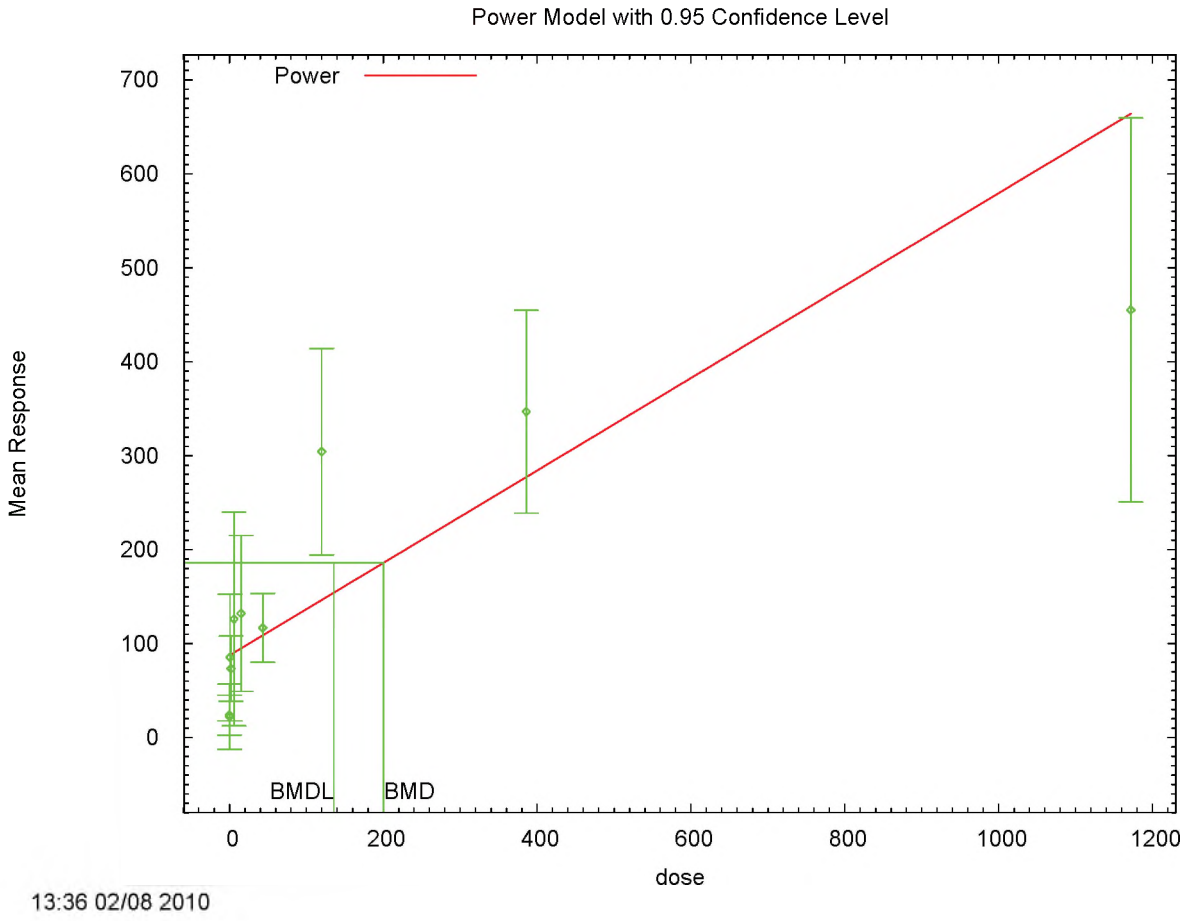
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 200.314
```

```
BMDL = 135.673
```

E.2.22.3. *Figure for Selected Model: Power*



E.2.22.4. *Output for Additional Model Presented: Power, Unrestricted*

Li et al., 1997: FSH

```
================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\Blood\72_Li_1997_FSH_Pwr_U_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\72_Li_1997_FSH_Pwr_U_1.plt
                                          Mon Feb 08 13:36:46 2010
================================================================

Figure 3: FSH in female S-D rats 24hr after dosing, 22 day old rats

  The form of the response function is:

  Y[dose] = control + slope * dose^power


  Dependent variable = Mean
```

Independent variable = Dose
The power is not restricted
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 10
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	9.8191
rho =	0
control =	22.1591
slope =	52.284
power =	0.294106

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	control	slope	power
lalpha	1	-0.99	-0.69	-0.06	0.26
rho	-0.99	1	0.65	0.0089	-0.23
control	-0.69	0.65	1	-0.23	0.029
slope	-0.06	0.0089	-0.23	1	-0.85
power	0.26	-0.23	0.029	-0.85	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	3.67487	1.12134	1.47708	5.87265
rho	1.17882	0.221526	0.744632	1.613
control	15.8201	6.87715	2.34113	29.299
slope	52.528	9.46821	33.9706	71.0853
power	0.304867	0.0336805	0.238855	0.37088

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	23.9	15.8	29.6	32	0.795
0.266	10	22.2	50.9	48.5	63.7	-1.43
0.7988	10	85.2	64.9	94.3	73.5	0.876
2.097	10	73.3	81.7	48.5	84.1	-0.314
5.867	10	126	106	159	98.1	0.652
15	10	132	136	116	114	-0.102
43.33	10	117	182	51.2	135	-1.52
119.9	10	304	242	154	160	1.24
386	10	347	339	151	195	0.134
1172	10	455	469	286	236	-0.182

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)

```
            Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
        Model A3 uses any fixed variance parameters that
        were specified by the user

 Model  R:         Yi = Mu + e(i)
             Var{e(i)} = Sigma^2


                       Likelihoods of Interest

             Model      Log(likelihood)   # Param's      AIC
              A1         -535.687163          11    1093.374327
              A2         -496.367061          20    1032.734122
              A3         -502.709623          12    1029.419246
           fitted        -513.737215           5    1037.474431
               R         -574.835246           2    1153.670492


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              156.936         18          <.0001
   Test 2              78.6402          9          <.0001
   Test 3              12.6851          8          0.1232
   Test 4              22.0552          7        0.002485

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1.  You may want to try a different
model


                Benchmark Dose Computation

Specified effect =             1

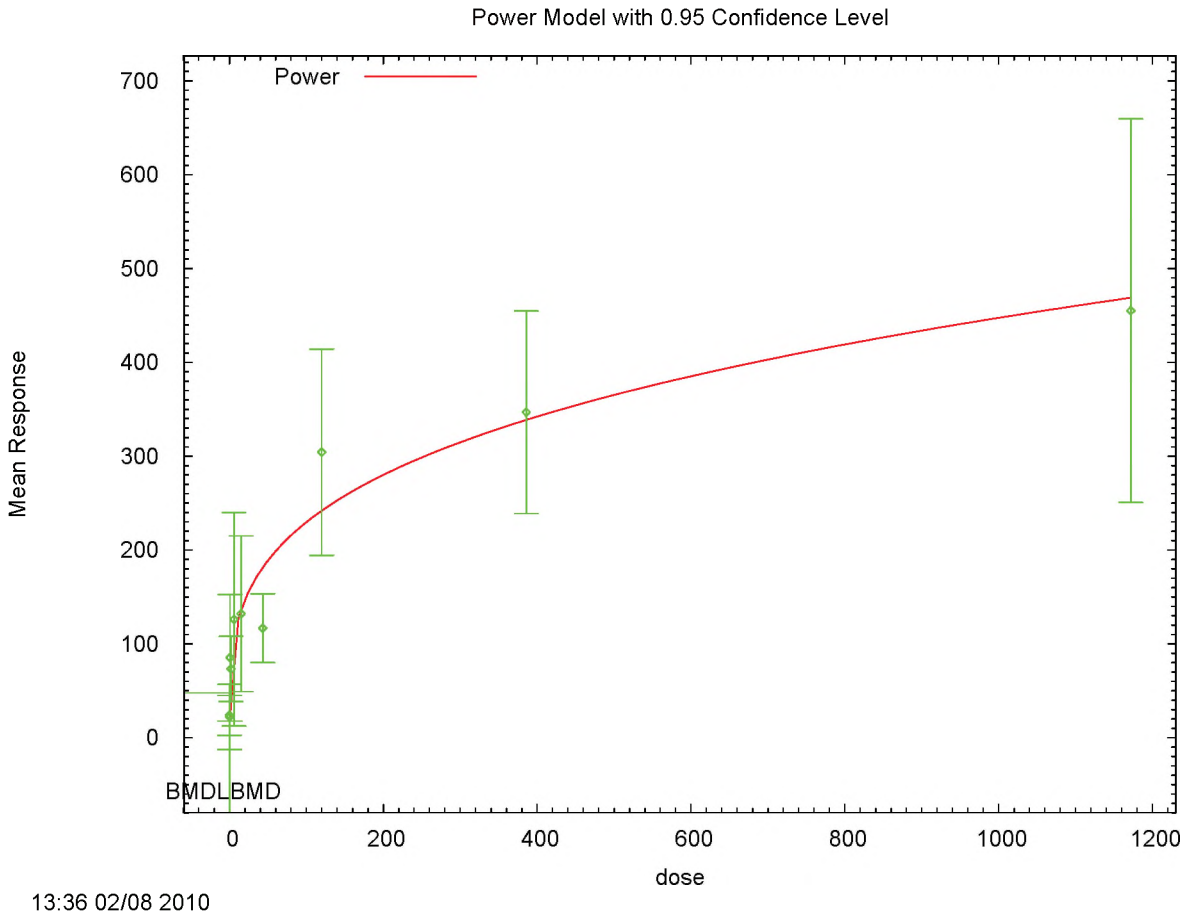
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

              BMD = 0.196278


             BMDL = 0.0248364
```

E.2.22.5. *Figure for Additional Model Presented: Power, Unrestricted*



E.2.23. Li et al., 2006: Estradiol, 3-Day

E.2.23.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	2	0.156	269.027	1.416E+01	5.544E+00	
exponential (M3)	2	0.156	269.027	1.416E+01	5.544E+00	power hit bound (d = 1)
exponential (M4)	1	0.341	268.212	error	error	
exponential (M5)	0	N/A	270.212	error	error	
Hill	0	N/A	270.212	error	error	
linear [b]	**2**	**0.162**	**268.952**	**1.606E+01**	**5.379E+00**	
polynomial, 3-degree	2	0.162	268.952	1.606E+01	5.379E+00	
power	2	0.162	268.952	1.606E+01	5.379E+00	power bound hit (power = 1)
Hill, unrestricted	0	N/A	270.265	9.273E+12	9.273E+12	unrestricted (n = 0.03)
power, unrestricted	1	0.328	268.265	9.455E+10	error	unrestricted (power = 0.015)

[a] Constant variance model selected ($p = 0.4372$)

[b] Best-fitting model, BMDS output presented in this appendix

E.2.23.2. *Output for Selected Model: Linear*

Li et al., 2006: Estradiol, 3-Day

```
 ================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\1\Blood\31_Li_2006_Estra_LinearCV_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\31_Li_2006_Estra_LinearCV_1.plt
                                          Mon Feb 08 10:54:00 2010
 ================================================================

 Figure 3, 3-day estradiol
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit
```

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

alpha =	267.211	
rho =	0	Specified
beta_0 =	16.1705	
beta_1 =	1.0106	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	beta_0	beta_1
alpha	1	2.1e-012	5e-014
beta_0	2.1e-012	1	-0.69
beta_1	5e-014	-0.69	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval	
			Lower Conf. Limit	Upper Conf. Limit
alpha	263.435	58.9057	147.981	378.888
beta_0	16.1705	3.55949	9.19407	23.147
beta_1	1.0106	1.2148	-1.37037	3.39156

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	10.2	16.2	12.2	16.2	-1.17
0.1588	10	19.9	16.3	20	16.2	0.697
2.839	10	24.7	19	14.6	16.2	1.11
5.124	10	18.1	21.3	17.6	16.2	-0.635

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that
were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-129.653527	5	269.307054
A2	-128.294657	8	272.589314
A3	-129.653527	5	269.307054
fitted	-131.476097	3	268.952193
R	-131.819169	2	267.638338

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	7.04902	6	0.3163
Test 2	2.71774	3	0.4372
Test 3	2.71774	3	0.4372
Test 4	3.64514	2	0.1616

The p-value for Test 1 is greater than .05. There may not be a
diffence between responses and/or variances among the dose levels
Modelling the data with a dose/response curve may not be appropriate

The p-value for Test 2 is greater than .1. A homogeneous variance
model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears
to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems
to adequately describe the data

Benchmark Dose Computation

Specified effect = 1

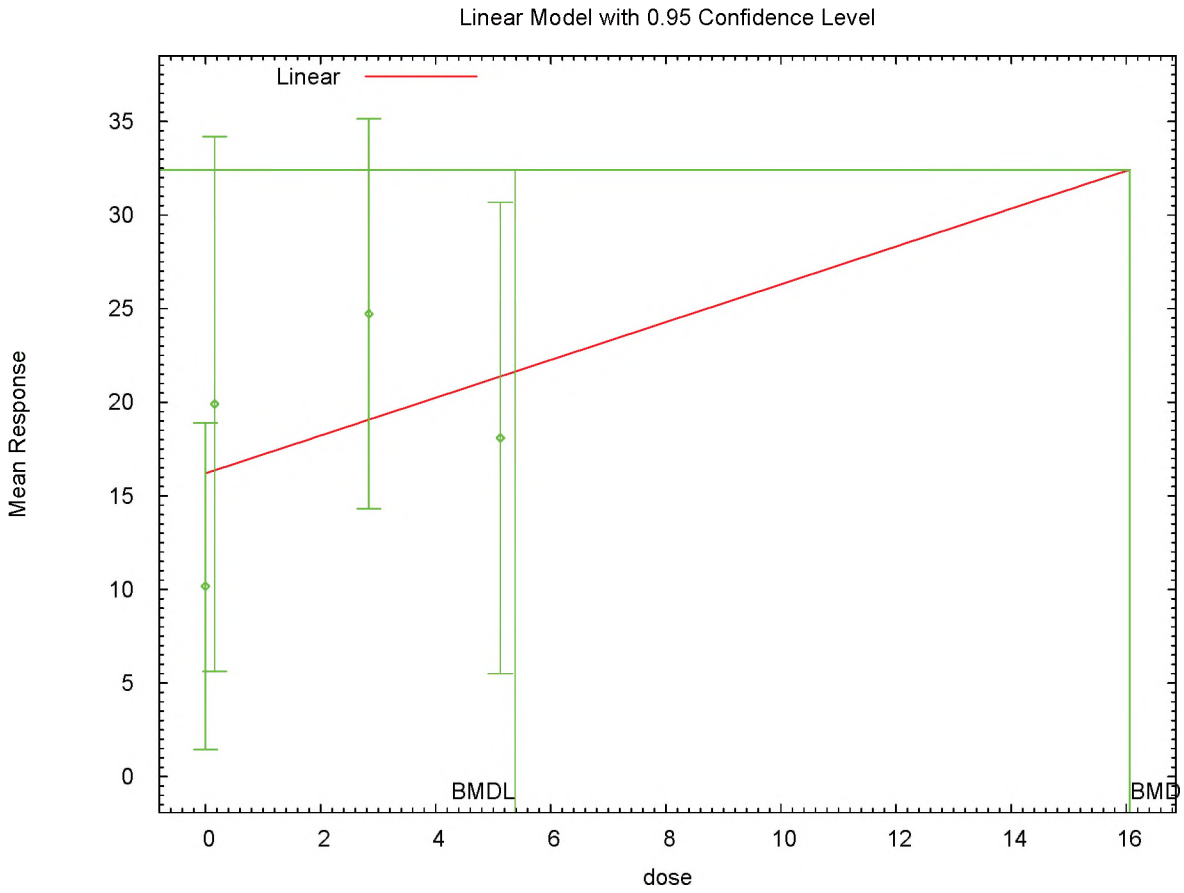
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 16.0605

BMDL = 5.37895

E.2.23.3. *Figure for Selected Model: Linear*



E.2.24. Li et al., 2006: Progesterone, 3-Day

E.2.24.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	2	<0.001	329.928	2.619E+00	error	
exponential (M3)	2	0.001	328.101	1.340E-01	error	power hit bound (d = 1)
exponential (M4)	1	0.384	315.734	1.074E-02	6.633E-03	
exponential (M5)	0	N/A	317.734	4.301E-02	4.272E-03	
Hill [b]	**1**	**0.386**	**315.728**	**9.461E-04**	**8.006E-11**	**n lower bound hit (n = 1)**
linear	2	<0.001	330.729	3.891E+00	2.626E+00	
polynomial, 3-degree	2	<0.001	330.729	3.891E+00	2.626E+00	
power	2	<0.001	330.729	3.891E+00	2.626E+00	power bound hit (power = 1)
power, unrestricted	1	0.404	315.673	2.812E-59	2.812E-59	unrestricted (power = 0.01)

[a] Non-constant variance model selected ($p = 0.0013$)

[b] Best-fitting model, BMDS output presented in this appendix

E.2.24.2. *Output for Selected Model: Hill*

Li et al., 2006: Progesterone, 3-Day

```
 ======================================================================
          Hill Model. (Version: 2.14;  Date: 06/26/2008)
          Input Data File: C:\1\Blood\32_Li_2006_Progest_Hill_1.(d)
          Gnuplot Plotting File:  C:\1\Blood\32_Li_2006_Progest_Hill_1.plt
                                                 Wed Feb 10 10:57:14 2010
 ======================================================================

 Figure 4, 3-day progesterone
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   Power parameter restricted to be greater than 1
   The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
```

```
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                        lalpha =      7.08699
                           rho =            0
                     intercept =      61.7404
                             v =     -50.3835
                             n =      1.47286
                             k =     0.128302


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -n
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

                 lalpha          rho    intercept            v            k

    lalpha            1        -0.99       -0.093         0.82         0.22

       rho        -0.99            1         0.12        -0.79         -0.2

 intercept       -0.093         0.12            1        -0.43        0.014

         v         0.82        -0.79        -0.43            1        0.035

         k         0.22         -0.2        0.014        0.035            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha          14.0902          3.36095             7.50284             20.6775
            rho         -2.27438         0.861553              -3.963            -0.585772
      intercept          61.7488           3.3373             55.2078             68.2898
              v         -42.1007          7.70852            -57.2091            -26.9922
              n                1               NA
              k       0.00282851         0.020619           -0.037584           0.0432411

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0    10       61.7         61.7         11.1         10.6       -0.00251
0.1588    10       30.6         20.4         40.5         37.2          0.865
2.839     10       16.9         19.7         33.3         38.7         -0.225
5.124     10       11.4         19.7         43.7         38.8         -0.678


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
```

```
            Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
      Model A3 uses any fixed variance parameters that
      were specified by the user

 Model  R:         Yi = Mu + e(i)
             Var{e(i)} = Sigma^2


                        Likelihoods of Interest

             Model      Log(likelihood)   # Param's      AIC
              A1         -159.632675            5     329.265349
              A2         -151.812765            8     319.625529
              A3         -152.488175            6     316.976349
           fitted        -152.863841            5     315.727683
               R         -165.698875            2     335.397750


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                      Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              27.7722          6       0.0001037
   Test 2              15.6398          3        0.001344
   Test 3              1.35082          2          0.5089
   Test 4             0.751333          1          0.3861

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =            1

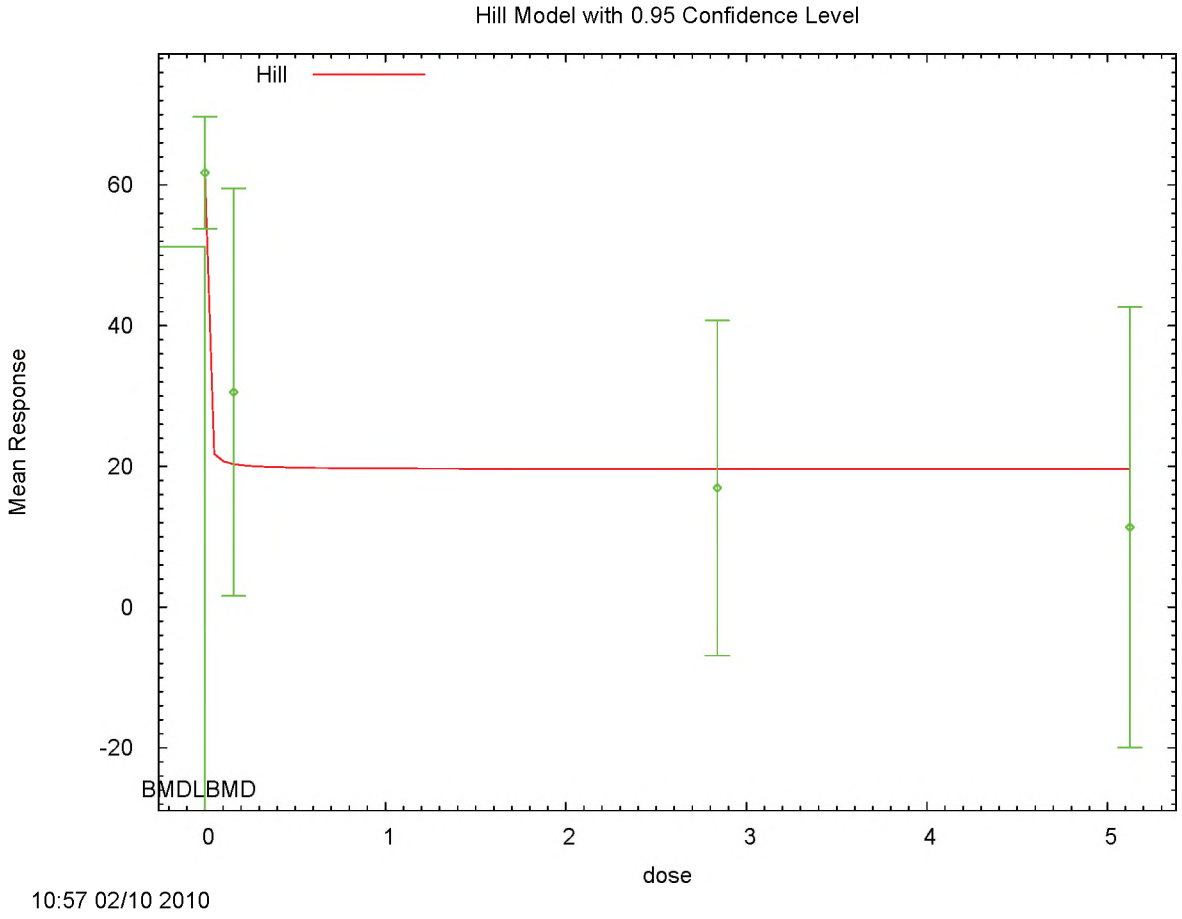
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =    0.000946102

            BMDL =  8.00639e-011
```

E.2.24.3. *Figure for Selected Model: Hill*



E.2.25. Markowski et al., 2001: FR10 Run Opportunities

E.2.25.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2) [b]	**2**	**0.304**	**117.150**	**8.570E+00**	**2.887E+00**	
exponential (M3)	2	0.304	117.150	8.570E+00	2.887E+00	power hit bound (d = 1)
exponential (M4)	1	0.371	117.570	3.452E+00	1.299E-02	
exponential (M5)	0	N/A	118.918	2.315E+00	1.391E-02	
Hill	0	N/A	118.918	1.801E+00	1.274E-09	
linear	2	0.226	117.744	1.106E+01	5.741E+00	
polynomial, 3-degree	2	0.226	117.744	1.106E+01	5.741E+00	
power	2	0.226	117.744	1.106E+01	5.741E+00	power bound hit (power = 1)
power, unrestricted	1	0.239	118.158	5.768E+00	1.032E-14	unrestricted (power = 0.276)

[a] Constant variance model selected ($p = 0.1719$)

[b] Best-fitting model, BMDS output presented in this appendix

E.2.25.2. *Output for Selected Model: Exponential (M2)*

Markowski et al., 2001: FR10 Run Opportunities

```
 ================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\1\Blood\33_Mark_2001_FR10opp_ExpCV_1.(d)
         Gnuplot Plotting File:
                                                 Mon Feb 08 10:55:13 2010
 ================================================================

 Table 3
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.
```

```
Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact
```

Initial Parameter Values

Variable	Model 2
lnalpha	3.5321
rho(S)	0
a	6.77975
b	0.0581937
c	0
d	1

(S) = Specified

Parameter Estimates

Variable	Model 2
lnalpha	3.63127
rho	0
a	12.2901
b	0.0808832
c	0
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	7	13.29	8.65
1.557	4	11.25	5.56
4.03	6	5.75	3.53
10.32	7	7	6.01

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	12.29	6.145	0.4305
1.557	10.84	6.145	0.1347
4.03	8.871	6.145	-1.244
10.32	5.335	6.145	0.717

```
Other models for which likelihoods are calculated:

  Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
```

```
  Model A2:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
              Var{e(ij)} = Sigma^2


                            Likelihoods of Interest

                  Model      Log(likelihood)      DF         AIC
                 -------    -----------------    ----   ------------
                     A1       -54.38526           5      118.7705
                     A2       -51.88568           8      119.7714
                     A3       -54.38526           5      118.7705
                      R       -57.45429           2      118.9086
                      2       -55.57522           3      117.1504


Additive constant for all log-likelihoods =     -22.05.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.


                             Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does Model 2 fit the data? (A3 vs. 2)


                         Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                       11.14             6            0.08423
  Test 2                       4.999             3             0.1719
  Test 3                       4.999             3             0.1719
  Test 4                        2.38             2             0.3042


  The p-value for Test 1 is greater than .05.  There may not be a
  diffence between responses and/or variances among the dose levels
  Modelling the data with a dose/response curve may not be appropriate.

  The p-value for Test 2 is greater than .1.  A homogeneous
  variance model appears to be appropriate here.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 4 is greater than .1.  Model 2 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 1.000000

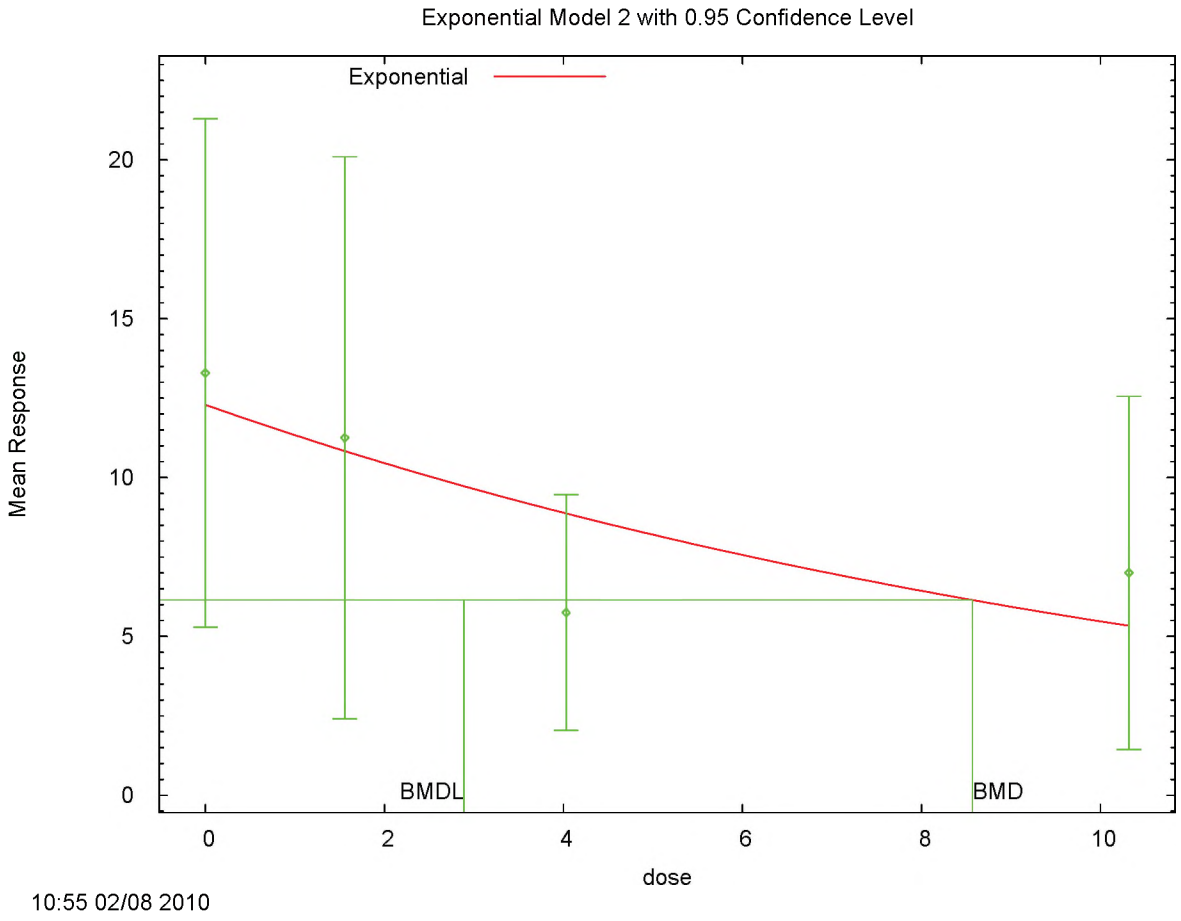
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD =      8.56961

              BMDL =      2.88708
```

E.2.25.3. *Figure for Selected Model: Exponential (M2)*



E.2.26. Markowski et al., 2001: FR2 Revolutions

E.2.26.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	2	0.236	217.219	8.486E+00	3.232E+00	
exponential (M3)	2	0.236	217.219	8.486E+00	3.232E+00	power hit bound (d = 1)
exponential (M4)	1	0.263	217.583	3.413E+00	1.766E-02	
exponential (M5)	0	N/A	218.532	2.415E+00	9.313E-01	
Hill [b]	**1**	**0.654**	**216.532**	**1.840E+00**	**5.992E-01**	**n upper bound hit (n = 18)**
linear	2	0.180	217.764	1.058E+01	5.602E+00	
polynomial, 3-degree	2	0.180	217.764	1.058E+01	5.602E+00	
power	2	0.180	217.764	1.058E+01	5.602E+00	power bound hit (power = 1)
power, unrestricted [c]	1	0.161	218.294	5.739E+00	1.032E-14	unrestricted (power = 0.318)

[a] Constant variance model selected ($p = 0.1092$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.2.26.2. *Output for Selected Model: Hill*

Markowski et al., 2001: FR2 Revolutions

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\1\Blood\34_Mark_2001_FR2rev_HillCV_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\34_Mark_2001_FR2rev_HillCV_1.plt
                                          Mon Feb 08 10:55:47 2010
 ================================================================

 Table 3
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter restricted to be greater than 1
   A constant variance model is fit
```

```
   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                          alpha =      2598.74
                            rho =            0   Specified
                      intercept =       119.29
                              v =       -62.79
                              n =      2.13752
                              k =      2.53662


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -rho    -n
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

                    alpha    intercept            v            k

      alpha             1     1.2e-008       1e-009     3.5e-008

  intercept     1.2e-008            1        -0.81        -0.52

          v       1e-009        -0.81            1         0.37

          k     3.5e-008        -0.52         0.37            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
           alpha          2183.85          630.425             948.245             3419.46
       intercept           119.29          17.6629             84.6713             153.909
               v         -56.5223          21.9082            -99.4615            -13.5831
               n               18               NA
               k          1.68653         0.295154             1.10804             2.26502

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     7        119          119         69.9         46.7     -2.41e-007
1.557     4        109          108           61         46.7      2.29e-007
 4.03     6       56.5         62.8         31.2         46.7         -0.329
10.32     7       68.1         62.8         33.2         46.7          0.304


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
```

```
           Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
      Model A3 uses any fixed variance parameters that
      were specified by the user

 Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1         -104.165520            5     218.331040
             A2         -101.140174            8     218.280349
             A3         -104.165520            5     218.331040
          fitted        -104.266162            4     216.532324
              R         -107.599268            2     219.198536


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              12.9182          6         0.04435
   Test 2              6.05069          3          0.1092
   Test 3              6.05069          3          0.1092
   Test 4             0.201284          1          0.6537

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =            1

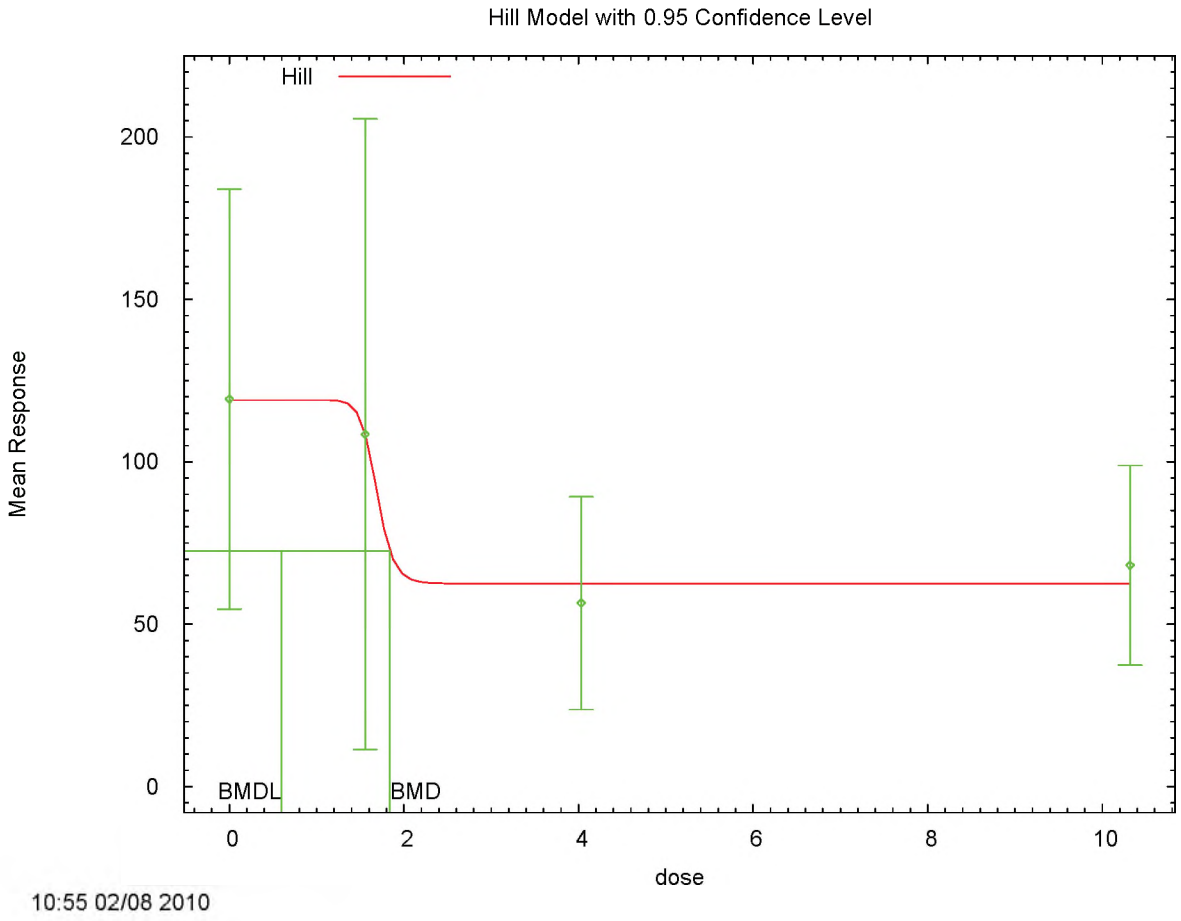
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =       1.83952

            BMDL =      0.599228
```

E.2.26.3. *Figure for Selected Model: Hill*



E.2.26.4. *Output for Additional Model Presented: Power, Unrestricted*

Markowski et al., 2001: FR2 Revolutions

```
 ================================================================
          Power Model. (Version: 2.15;  Date: 04/07/2008)
          Input Data File: C:\1\Blood\34_Mark_2001_FR2rev_PowerCV_U_1.(d)
          Gnuplot Plotting File:  C:\1\Blood\34_Mark_2001_FR2rev_PowerCV_U_1.plt
                                                Mon Feb 08 10:55:49 2010
 ================================================================

 Table 3
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   The power is not restricted
   A constant variance model is fit
```

```
   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                         alpha =      2598.74
                           rho =            0   Specified
                       control =       119.29
                         slope =     -10.3599
                         power =     0.824761


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been specified by the user,
                and do not appear in the correlation matrix )

                  alpha      control        slope        power

     alpha            1      -3e-010     6.9e-010     9.9e-010

   control      -3e-010            1        -0.63        -0.28

     slope     6.9e-010        -0.63            1         0.87

     power     9.9e-010        -0.28         0.87            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
          alpha          2350.22          678.449            1020.48             3679.95
        control          120.082          18.0782            84.6491             155.514
          slope         -27.8164          24.2447           -75.3352             19.7023
          power         0.317923         0.350841          -0.369713             1.00556


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     7        119          120         69.9         48.5        -0.0432
1.557     4        109         88.1           61         48.5          0.843
 4.03     6       56.5         76.8         31.2         48.5          -1.02
10.32     7       68.1         61.7         33.2         48.5          0.353


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
```

were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-104.165520	5	218.331040
A2	-101.140174	8	218.280349
A3	-104.165520	5	218.331040
fitted	-105.147159	4	218.294317
R	-107.599268	2	219.198536

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	12.9182	6	0.04435
Test 2	6.05069	3	0.1092
Test 3	6.05069	3	0.1092
Test 4	1.96328	1	0.1612

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance
model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears
to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems
to adequately describe the data

Benchmark Dose Computation

Specified effect = 1

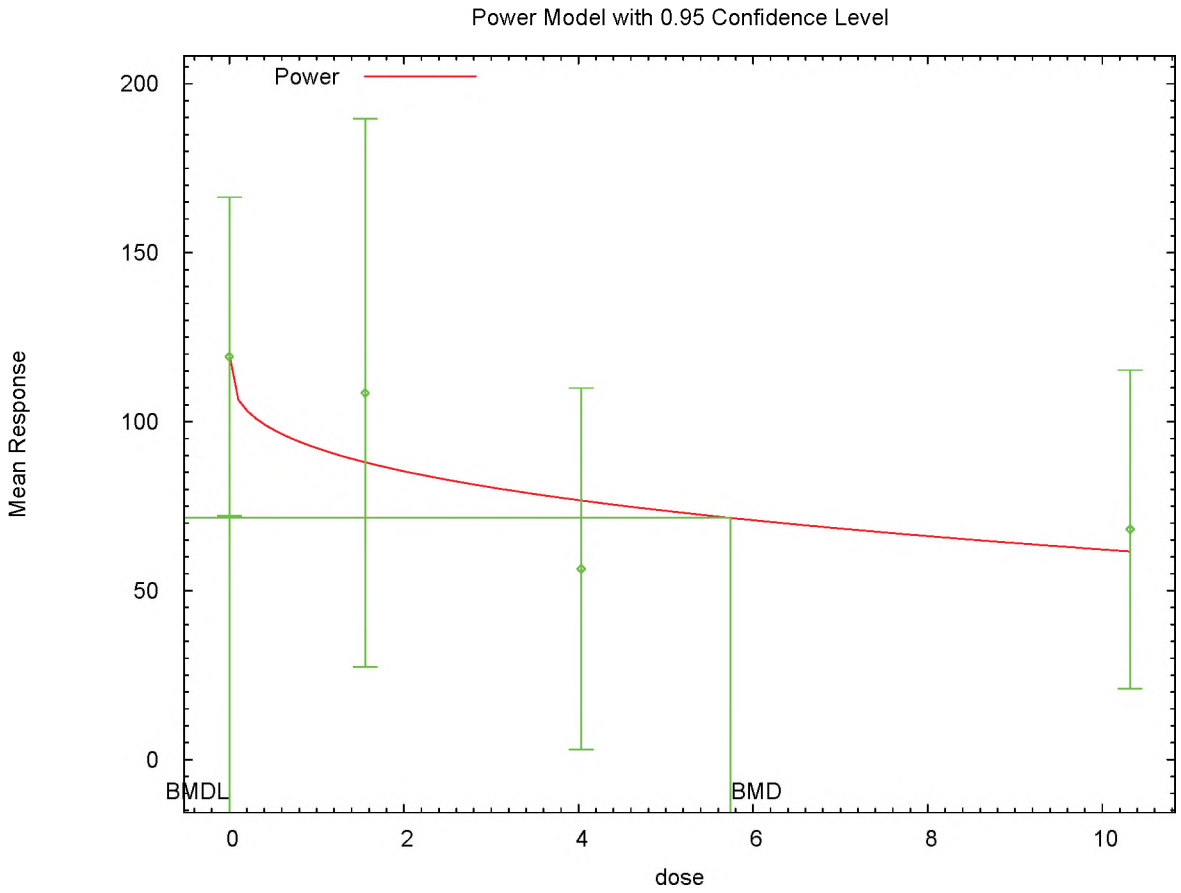
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 5.73906

BMDL = 1.03181e-014

E.2.26.5. *Figure for Additional Model Presented: Power, Unrestricted*



E.2.27. Markowski et al., 2001: FR5 Run Opportunities

E.2.27.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	2	0.205	133.193	5.078E+00	2.439E+00	
exponential (M3)	2	0.205	133.193	5.078E+00	2.439E+00	power hit bound (d = 1)
exponential (M4)	1	0.254	133.328	2.160E+00	6.854E-01	
exponential (M5)	0	N/A	134.032	2.124E+00	9.667E-01	
Hill [b]	**1**	**0.939**	**132.032**	**1.723E+00**	**9.085E-01**	**n upper bound hit (n = 18)**
linear	2	0.122	134.229	7.234E+00	4.430E+00	
polynomial, 3-degree	2	0.122	134.229	7.234E+00	4.430E+00	
power	2	0.122	134.229	7.234E+00	4.430E+00	power bound hit (power = 1)
power, unrestricted [c]	1	0.134	134.268	2.666E+00	1.032E-14	unrestricted (power = 0.392)

[a] Constant variance model selected ($p = 0.2262$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.2.27.2. *Output for Selected Model: Hill*

Markowski et al., 2001: FR5 Run Opportunities

```
 ================================================================
          Hill Model. (Version: 2.14;  Date: 06/26/2008)
          Input Data File: C:\1\Blood\35_Mark_2001_FR5opp_HillCV_1.(d)
          Gnuplot Plotting File:  C:\1\Blood\35_Mark_2001_FR5opp_HillCV_1.plt
                                                Mon Feb 08 10:56:24 2010
 ================================================================

 Table 3
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter restricted to be greater than 1
   A constant variance model is fit
```

```
   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                          alpha =      77.4849
                            rho =            0   Specified
                      intercept =        26.14
                              v =       -13.34
                              n =      2.77257
                              k =      2.48811


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -rho    -n
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

                    alpha    intercept            v            k

      alpha             1    -3.2e-009     1.9e-008     6.2e-008

  intercept    -3.2e-009            1        -0.81        -0.51

          v     1.9e-008        -0.81            1         0.36

          k     6.2e-008        -0.51         0.36            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
           alpha          64.5863          18.6445             28.0438             101.129
       intercept            26.14          3.03753             20.1865             32.0935
               v         -13.1569           3.7676            -20.5413            -5.77257
               n               18               NA
               k          1.68073         0.208677             1.27173             2.08973

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     7       26.1         26.1         12.3         8.04      -1.9e-008
1.557     4       23.5         23.5         7.04         8.04     -1.94e-007
 4.03     6       12.8           13         6.17         8.04        -0.0558
10.32     7       13.1           13         7.14         8.04         0.0517


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
```

```
           Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
      Model A3 uses any fixed variance parameters that
      were specified by the user

 Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                        Likelihoods of Interest

             Model      Log(likelihood)   # Param's      AIC
              A1          -62.013133            5     134.026266
              A2          -59.839035            8     135.678070
              A3          -62.013133            5     134.026266
           fitted         -62.016025            4     132.032049
               R          -67.530040            2     139.060081


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                      Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1               15.382          6         0.01748
   Test 2               4.3482          3          0.2262
   Test 3               4.3482          3          0.2262
   Test 4           0.00578335          1          0.9394

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =             1

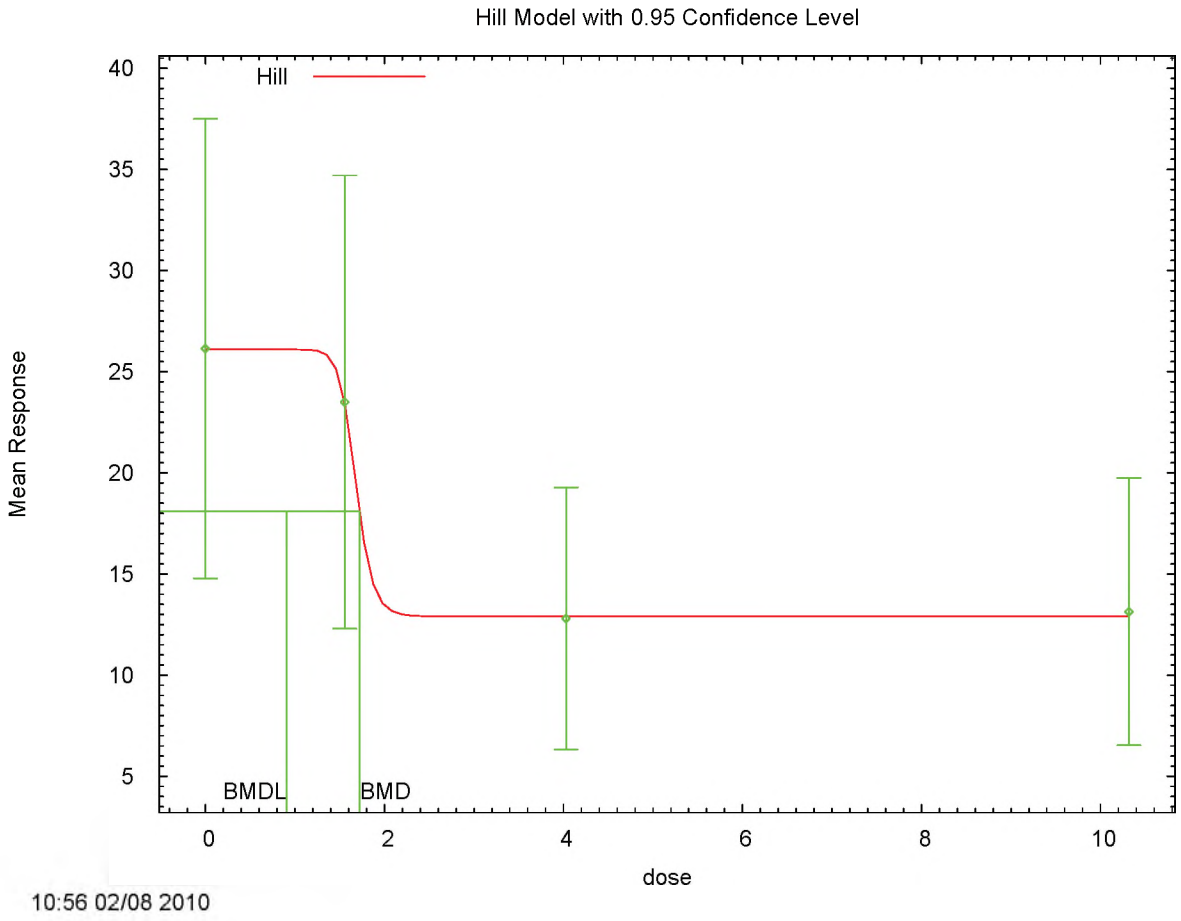
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =       1.72335

            BMDL =      0.908491
```

E.2.27.3. *Figure for Selected Model: Hill*



E.2.27.4. *Output for Additional Model Presented: Power, Unrestricted*

Markowski et al., 2001: FR5 Run Opportunities

```
 ================================================================
          Power Model. (Version: 2.15;  Date: 04/07/2008)
          Input Data File: C:\1\Blood\35_Mark_2001_FR5opp_PwrCV_U_1.(d)
          Gnuplot Plotting File:  C:\1\Blood\35_Mark_2001_FR5opp_PwrCV_U_1.plt
                                                Mon Feb 08 10:56:24 2010
 ================================================================

 Table 3
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   The power is not restricted
   A constant variance model is fit
```

```
   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                Default Initial Parameter Values
                        alpha =      77.4849
                          rho =            0   Specified
                      control =        26.14
                        slope =      -2.3827
                        power =     0.844532


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been specified by the user,
                and do not appear in the correlation matrix )

                  alpha      control        slope        power

     alpha            1    -9.3e-009     1.4e-008     9.3e-009

   control    -9.3e-009            1        -0.64        -0.34

     slope     1.4e-008        -0.64            1          0.9

     power     9.3e-009        -0.34          0.9            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
          alpha          70.8926          20.4649            30.7821             111.003
        control          26.3582          3.12902            20.2254             32.4909
          slope         -5.73309          4.02937           -13.6305             2.16433
          power         0.391903         0.281862          -0.160536            0.944342


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     7       26.1         26.4         12.3         8.42        -0.0686
1.557     4       23.5         19.5         7.04         8.42          0.941
 4.03     6       12.8         16.5         6.17         8.42          -1.06
10.32     7       13.1           12         7.14         8.42          0.343


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
      Model A3 uses any fixed variance parameters that
```

were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-62.013133	5	134.026266
A2	-59.839035	8	135.678070
A3	-62.013133	5	134.026266
fitted	-63.134001	4	134.268002
R	-67.530040	2	139.060081

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	15.382	6	0.01748
Test 2	4.3482	3	0.2262
Test 3	4.3482	3	0.2262
Test 4	2.24174	1	0.1343

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance
model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears
to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems
to adequately describe the data

Benchmark Dose Computation

Specified effect = 1

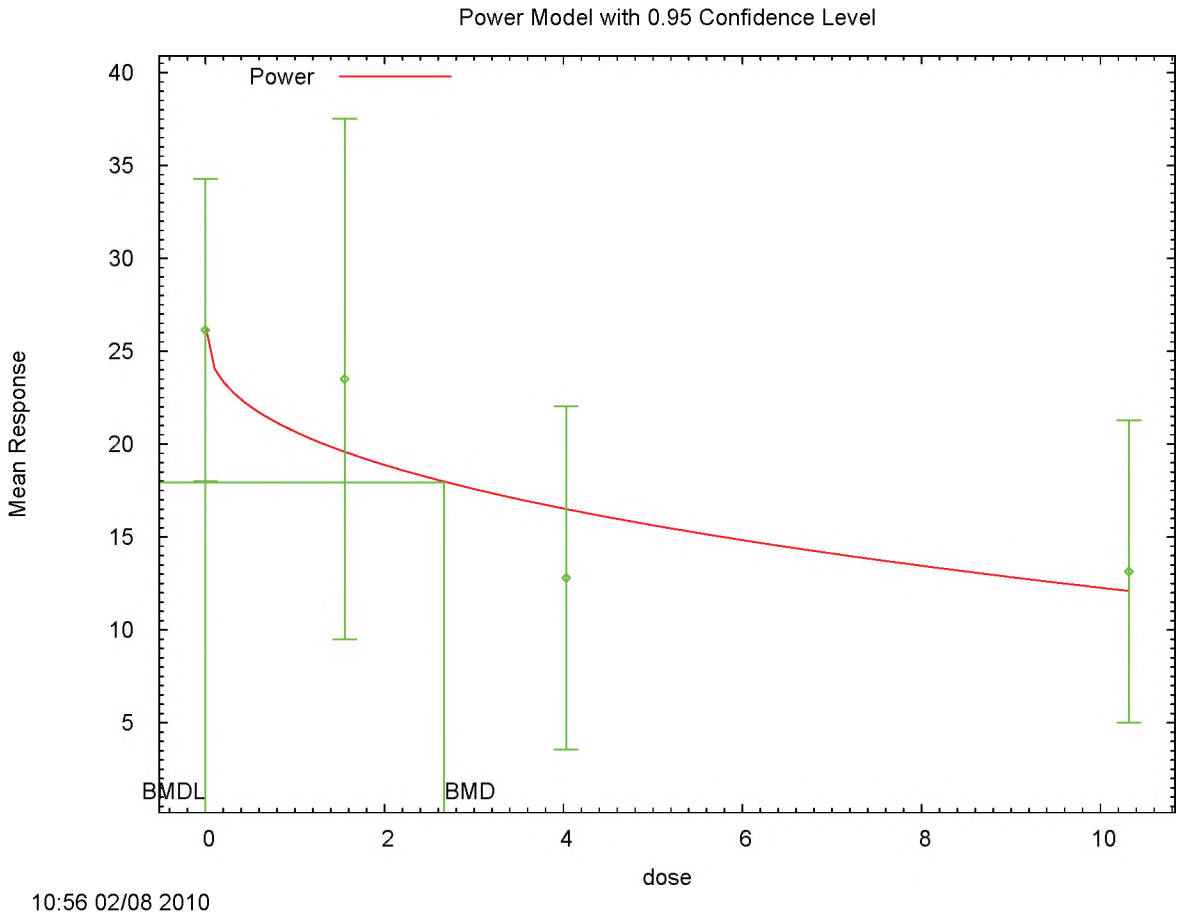
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 2.66625

BMDL = 1.03181e-014

E.2.27.5. *Figure for Additional Model Presented: Power, Unrestricted*



E.2.28. Miettinen et al., 2006: Cariogenic Lesions, Pups

E.2.28.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
gamma	3	0.410	162.280	3.401E+00	1.889E+00	power bound hit (power = 1)
logistic	3	0.371	162.518	4.108E+00	2.450E+00	
log-logistic [a]	**3**	**0.602**	**161.292**	**1.428E+00**	**5.175E-01**	**slope bound hit (slope = 1)**
log-probit	3	0.300	163.040	6.321E+00	3.127E+00	slope bound hit (slope = 1)
multistage, 4-degree	3	0.410	162.280	3.401E+00	1.889E+00	final ß = 0
probit	3	0.350	162.656	4.548E+00	2.889E+00	
Weibull	3	0.410	162.280	3.401E+00	1.889E+00	power bound hit (power = 1)
gamma, unrestricted	2	0.798	161.801	3.374E-03	8.884E-242	unrestricted (power = 0.215)
log-logistic, unrestricted [b]	2	0.728	161.983	4.942E-02	error	unrestricted (slope = 0.465)
log-probit, unrestricted	2	0.732	161.972	6.495E-02	error	unrestricted (slope = 0.289)
Weibull, unrestricted	2	0.766	161.884	1.792E-02	error	unrestricted (power = 0.324)

[a] Best-fitting model, BMDS output presented in this appendix

[b] Alternate model, BMDS output also presented in this appendix

E.2.28.2. *Output for Selected Model: Log-Logistic*

Miettinen et al., 2006: Cariogenic Lesions, Pups

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\1\Blood\36_Miet_2006_Cariogenic_LogLogistic_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\36_Miet_2006_Cariogenic_LogLogistic_1.plt
                                              Mon Feb 08 10:56:59 2010
 ================================================================

 Table 2 converting the percentage into the number of animals, and control is Control II from the
study. Dose is in ng per kg and is from Table 1
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = DichEff
```

```
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                  Default Initial Parameter Values
                     background =     0.595238
                      intercept =       -2.494
                          slope =            1


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -slope
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

             background    intercept

background            1        -0.66

 intercept        -0.66            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background         0.644165            *                *                   *
      intercept         -2.55354            *                *                   *
          slope                1            *                *                   *

* - Indicates that this value is not calculated.



                         Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -77.6769         5
   Fitted model          -78.646         2       1.93832      3          0.5853
  Reduced model         -83.2067         1       11.0597      4          0.0259

           AIC:         161.292


                                Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------
    0.0000     0.6442        27.055    25.000          42       -0.662
    2.2195     0.6966        20.200    23.000          29        1.131
    6.2259     0.7603        19.007    19.000          25       -0.003
   16.0142     0.8416        20.198    20.000          24       -0.111
   46.6355     0.9231        29.540    29.000          32       -0.358

 Chi^2 = 1.86      d.f. = 3        P-value = 0.6024


   Benchmark Dose Computation
```

```
Specified effect =           0.1

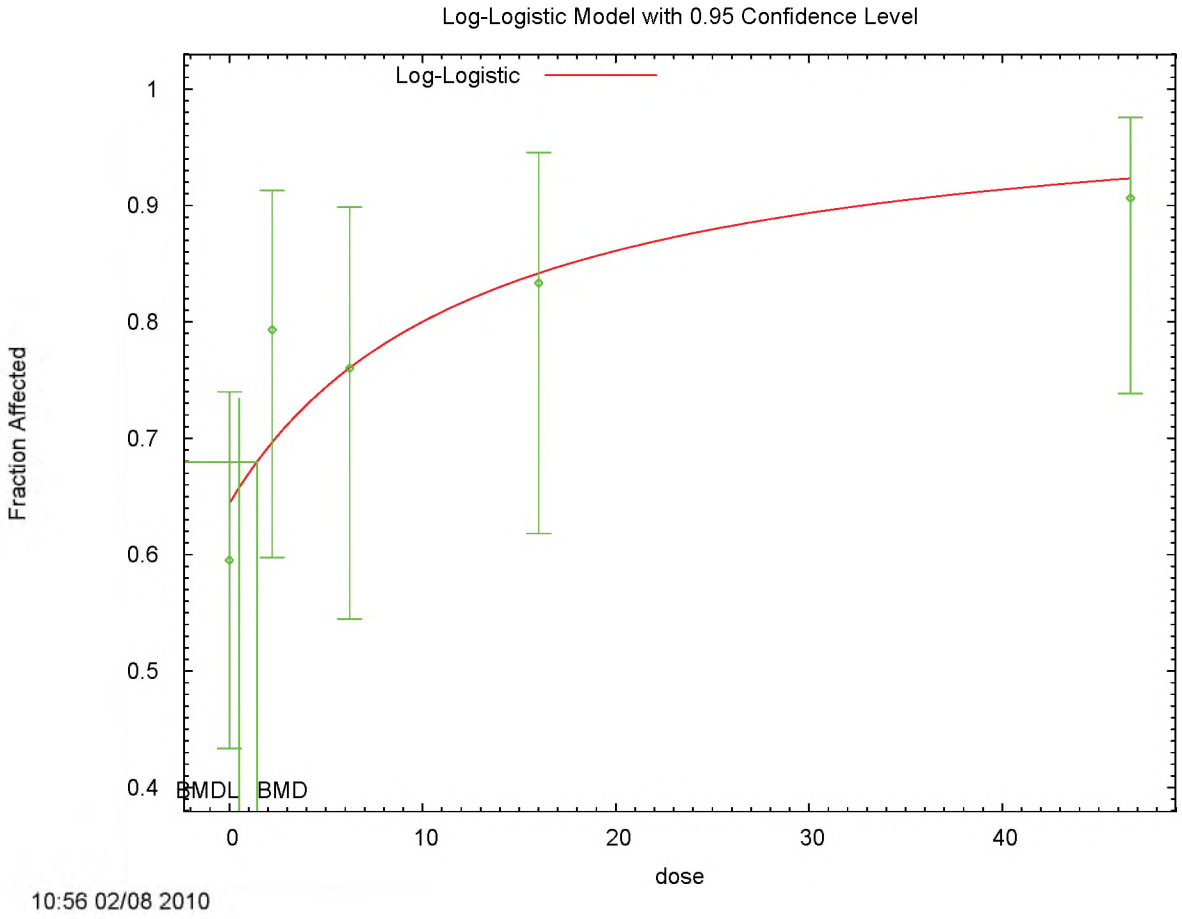
Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =       1.42805

            BMDL =      0.517495
```

E.2.28.3. *Figure for Selected Model: Log-Logistic*



E.2.28.4. *Output for Additional Model Presented: Log-Logistic, Unrestricted*

Miettinen et al., 2006: Cariogenic Lesions, Pups

```
================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\Blood\36_Miet_2006_Cariogenic_LogLogistic_U_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\36_Miet_2006_Cariogenic_LogLogistic_U_1.plt
                                          Mon Feb 08 10:56:59 2010
================================================================
```

```
 Table 2 converting the percentage into the number of animals, and control is Control II from the
study. Dose is in ng per kg and is from Table 1
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =     0.595238
                     intercept =    -0.739403
                         slope =     0.442847


           Asymptotic Correlation Matrix of Parameter Estimates

             background    intercept        slope

background            1        -0.51         0.24

 intercept        -0.51            1        -0.89

     slope         0.24        -0.89            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background         0.597745            *               *                   *
      intercept        -0.798024            *               *                   *
          slope         0.465259            *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -77.6769         5
   Fitted model        -77.9915         3      0.629204      2          0.7301
  Reduced model        -83.2067         1       11.0597      4          0.0259

           AIC:         161.983


                                Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size        Residual
   ----------------------------------------------------------------------
    0.0000     0.5977        25.105    25.000          42        -0.033
    2.2195     0.7566        21.940    23.000          29         0.458
```

```
     6.2259      0.8042        20.105     19.000          25        -0.557
    16.0142      0.8474        20.338     20.000          24        -0.192
    46.6355      0.8910        28.512     29.000          32         0.277

 Chi^2 = 0.63      d.f. = 2        P-value = 0.7281


   Benchmark Dose Computation

Specified effect =            0.1

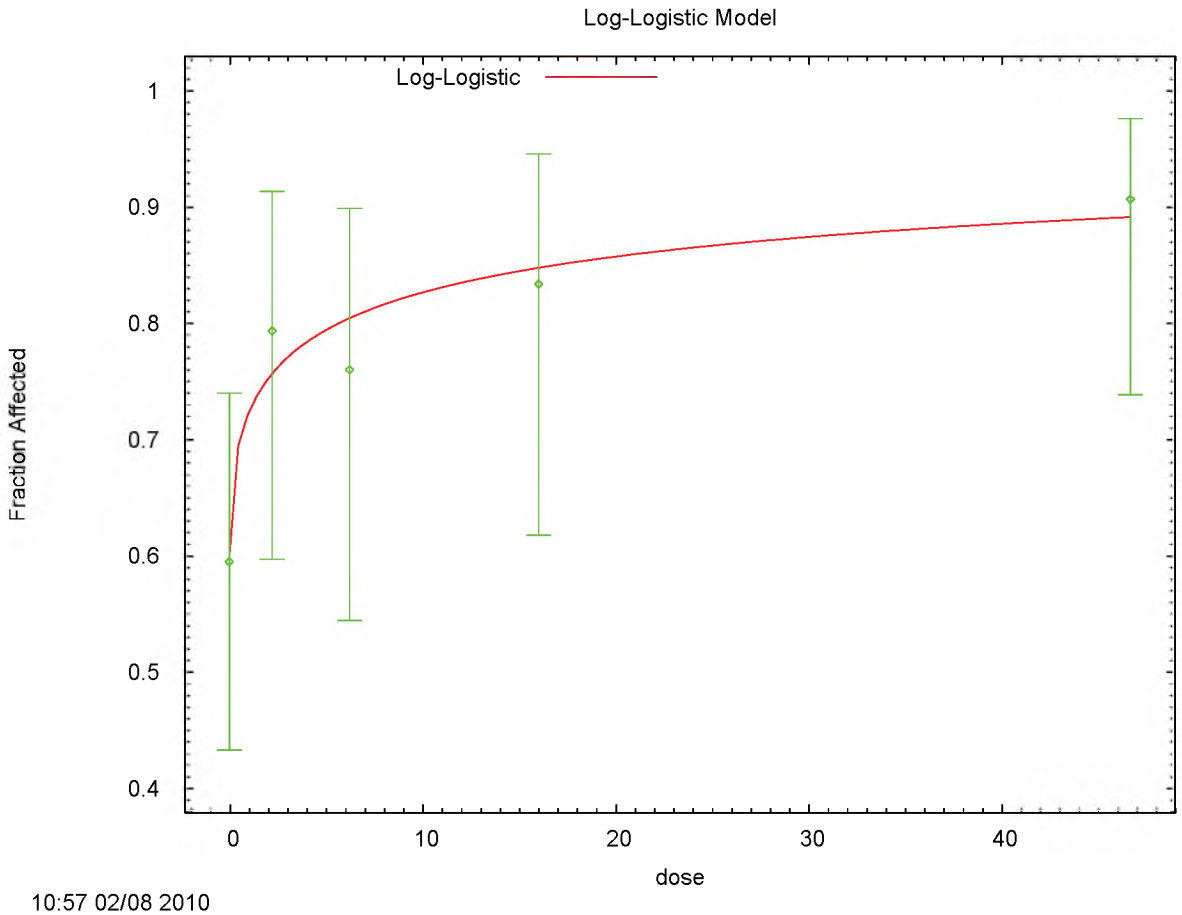
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.049422

           Benchmark dose computation failed.  Lower limit includes zero.
```

E.2.28.5. *Figure for Additional Model Presented: Log-Logistic, Unrestricted*



E.2.29. Murray et al., 1979: Fertility in F2 Generation

E.2.29.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
gamma	0	N/A	61.729	4.481E+00	1.590E+00	
logistic	1	0.051	61.318	2.420E+00	1.722E+00	negative intercept (intercept = -2.567)
log-logistic	0	N/A	61.729	4.971E+00	1.565E+00	
multistage, 1-degree	1	0.031	63.154	1.598E+00	8.747E-01	
multistage, 2-degree [a]	**1**	**0.079**	**60.464**	**2.733E+00**	**1.366E+00**	
probit	1	0.048	61.544	2.250E+00	1.590E+00	negative intercept (intercept = -1.459)
Weibull	0	N/A	61.729	5.042E+00	1.604E+00	
log-probit, unrestricted	0	N/A	61.729	4.244E+00	1.506E+00	unrestricted (slope = 3.182)

[a] Best-fitting model, BMDS output presented in this appendix

E.2.29.2. *Output for Selected Model: Multistage, 2-Degree*

Murray et al., 1979: Fertility in F2 Generation

```
 ======================================================================
         Multistage Model. (Version: 3.0;  Date: 05/16/2008)
         Input Data File: C:\1\Blood\Murray_1979_fert_index_f2_Multi2_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\Murray_1979_fert_index_f2_Multi2_1.plt
                                                 Wed Feb 10 16:06:28 2010
 ======================================================================

 Table 1 but expressed as number of dams who do not produce offspring
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2
```

```
 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                     Background =    0.0567204
                        Beta(1) =            0
                        Beta(2) =    0.0155037


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Beta(1)
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

             Background      Beta(2)

Background            1        -0.45

   Beta(2)        -0.45            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background        0.0780188           *               *                   *
        Beta(1)                0           *               *                   *
        Beta(2)        0.0141051           *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
      Full model        -25.8194         3
    Fitted model        -28.2318         2       4.82474      1         0.02805
   Reduced model        -34.0009         1        16.363      2       0.0002798

           AIC:         60.4636


                                Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size        Residual
   ---------------------------------------------------------------------
    0.0000     0.0780         2.497     4.000          32         0.991
    1.1242     0.0943         1.886     0.000          20        -1.443
    5.8831     0.4341         8.683     9.000          20         0.143

 Chi^2 = 3.08      d.f. = 1        P-value = 0.0790


   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

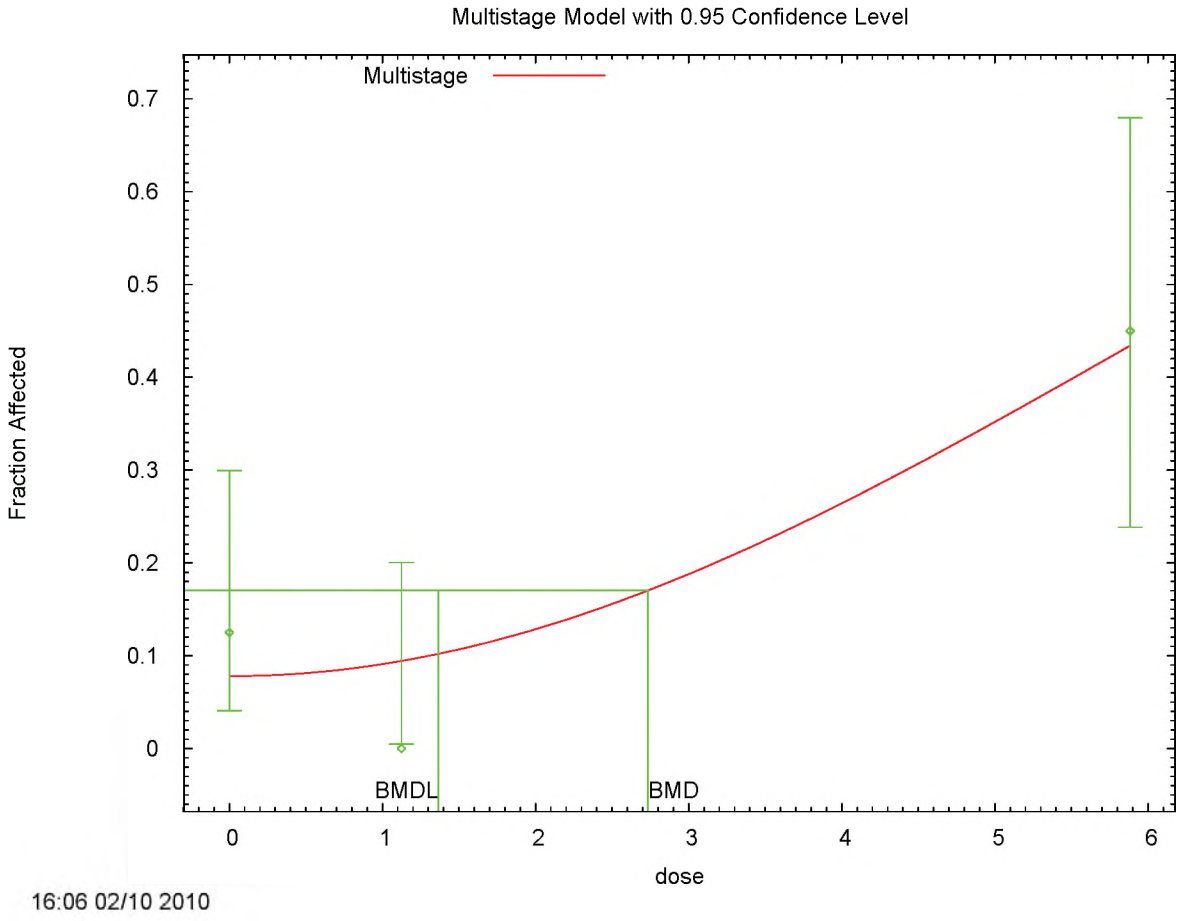
             BMD =        2.73307
```

```
                BMDL =        1.36619

                BMDU =        4.10938

Taken together, (1.36619, 4.10938) is a 90      % two-sided confidence
interval for the BMD
```

E.2.29.3. *Figure for Selected Model: Multistage, 2-Degree*



E.2.30. National Toxicology Program, 1982: Toxic Hepatitis, Male Mice

E.2.30.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
gamma	1	0.027	113.103	3.823E+00	2.005E+00	
logistic	2	0.092	110.352	3.108E+00	2.465E+00	negative intercept (intercept = -3.388)
log-logistic	1	0.026	113.089	3.797E+00	2.141E+00	
log-probit	1	0.027	113.111	3.565E+00	2.294E+00	
multistage, 3-degree [a]	**1**	**0.036**	**112.045**	**2.782E+00**	**1.343E+00**	
probit	2	0.082	110.512	2.763E+00	2.241E+00	negative intercept (intercept = -1.894)
Weibull	1	0.025	113.044	3.967E+00	1.704E+00	

[a] Best-fitting model, BMDS output presented in this appendix

E.2.30.2. *Output for Selected Model: Multistage, 3-Degree*

National Toxicology Program, 1982: Toxic Hepatitis, Male Mice

```
 ================================================================
         Multistage Model. (Version: 3.0;  Date: 05/16/2008)
         Input Data File: C:\1\Blood\37_NTP_1982_ToxHep_Multi3_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\37_NTP_1982_ToxHep_Multi3_1.plt
                                          Mon Feb 08 10:57:32 2010
 ================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 4
 Total number of specified parameters = 0
 Degree of polynomial = 3


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
```

Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values
Background = 0.0471757
Beta(1) = 0.00749116
Beta(2) = 0
Beta(3) = 0.00139828

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Beta(2)
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Background	Beta(1)	Beta(3)
Background	1	-0.77	0.69
Beta(1)	-0.77	1	-0.95
Beta(3)	0.69	-0.95	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0267933	*	*	*
Beta(1)	0.0283198	*	*	*
Beta(2)	0	*	*	*
Beta(3)	0.0012342	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-51.0633	4			
Fitted model	-53.0224	3	3.91812	1	0.04777
Reduced model	-121.743	1	141.358	3	<.0001

AIC: 112.045

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0268	1.956	1.000	73	-0.693
0.7665	0.0482	2.363	5.000	49	1.759
2.2711	0.1005	4.925	3.000	49	-0.915
11.2437	0.8775	43.877	44.000	50	0.053

Chi^2 = 4.41 d.f. = 1 P-value = 0.0357

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

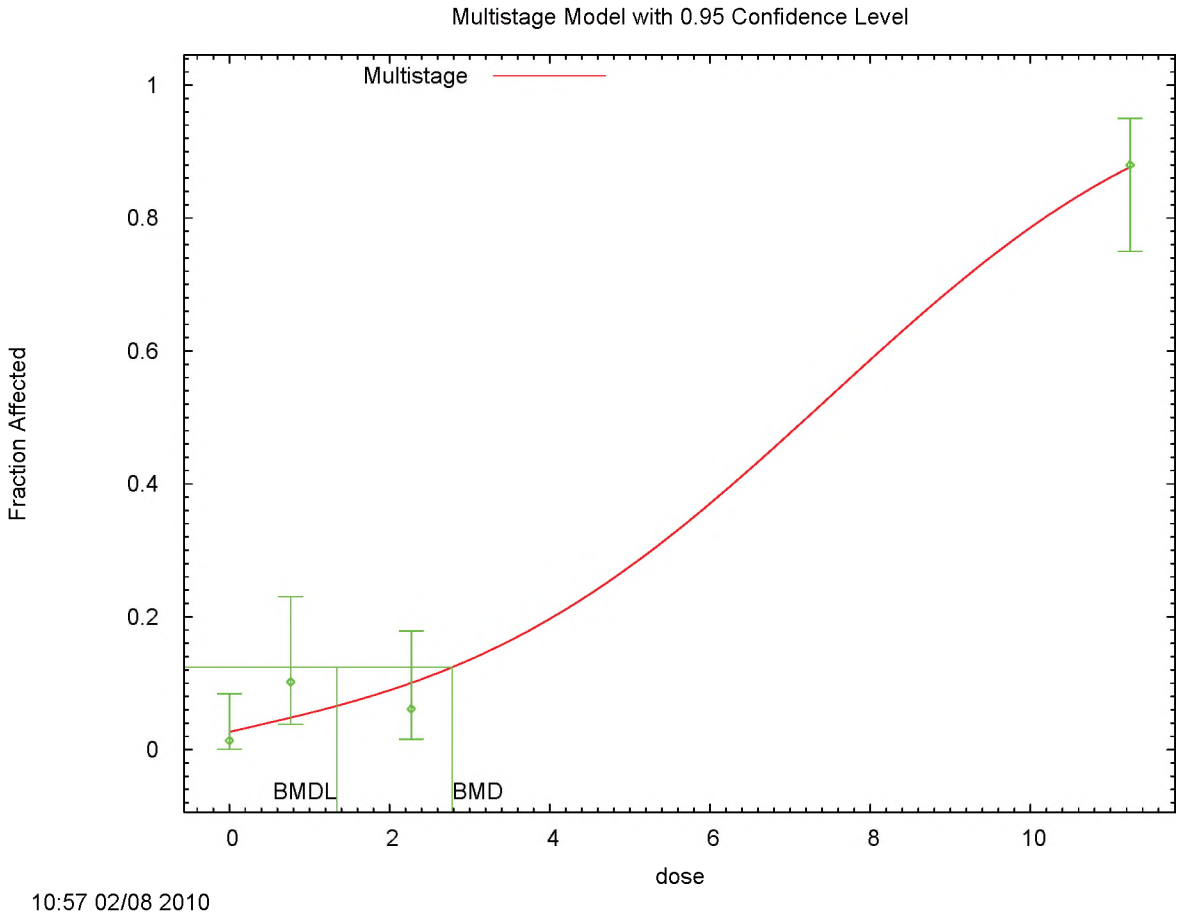
```
                BMD =        2.78201

               BMDL =        1.34308

               BMDU =         4.5214

Taken together, (1.34308, 4.5214 ) is a 90     % two-sided confidence
interval for the BMD
```

E.2.30.3. *Figure for Selected Model: Multistage, 3-Degree*



E.2.31. National Toxicology Program, 2006: Alveolar Metaplasia

E.2.31.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
gamma	4	0.010	320.093	9.886E-01	8.393E-01	power bound hit (power = 1)
logistic	4	<0.001	343.283	2.389E+00	2.052E+00	negative intercept (intercept = -1.059)
log-logistic [a]	**3**	**0.723**	**312.558**	**6.497E-01**	**3.751E-01**	
log-probit	4	0.024	318.680	1.566E+00	1.318E+00	slope bound hit (slope = 1)
multistage, 5-degree	4	0.010	320.093	9.886E-01	8.393E-01	final ß = 0
probit	4	<0.001	347.071	2.542E+00	2.219E+00	negative intercept (intercept = -0.599)
Weibull	4	0.010	320.093	9.886E-01	8.393E-01	power bound hit (power = 1)
gamma, unrestricted	3	0.426	314.011	1.642E-01	1.874E-02	unrestricted (power = 0.503)
log-probit, unrestricted	3	0.696	312.677	6.818E-01	2.740E-01	unrestricted (slope = 0.677)
Weibull, unrestricted	3	0.522	313.492	2.644E-01	6.947E-02	unrestricted (power = 0.661)

[a] Best-fitting model, BMDS output presented in this appendix

E.2.31.2. *Output for Selected Model: Log-Logistic*

National Toxicology Program, 2006: Alveolar Metaplasia

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\1\Blood\40_NTP_2006_AlvMeta_LogLogistic_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\40_NTP_2006_AlvMeta_LogLogistic_1.plt
                                              Mon Feb 08 10:58:58 2010
 ================================================================

 0
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   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
```

Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial Parameter Values
background = 0.0377358
intercept = -1.69494
slope = 1.12282

Asymptotic Correlation Matrix of Parameter Estimates

	background	intercept	slope
background	1	-0.21	0.1
intercept	-0.21	1	-0.93
slope	0.1	-0.93	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0373462	*	*	*
intercept	-1.70923	*	*	*
slope	1.13164	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-152.615	6			
Fitted model	-153.279	3	1.32728	3	0.7227
Reduced model	-216.802	1	128.374	5	<.0001

AIC: 312.558

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0373	1.979	2.000	53	0.015
2.5565	0.3682	19.881	19.000	54	-0.249
5.6937	0.5807	30.776	33.000	53	0.619
9.7882	0.7162	37.243	35.000	52	-0.690
16.5688	0.8197	43.446	45.000	53	0.555
29.6953	0.8976	46.674	46.000	52	-0.308

Chi^2 = 1.33 d.f. = 3 P-value = 0.7232

Benchmark Dose Computation

Specified effect = 0.1

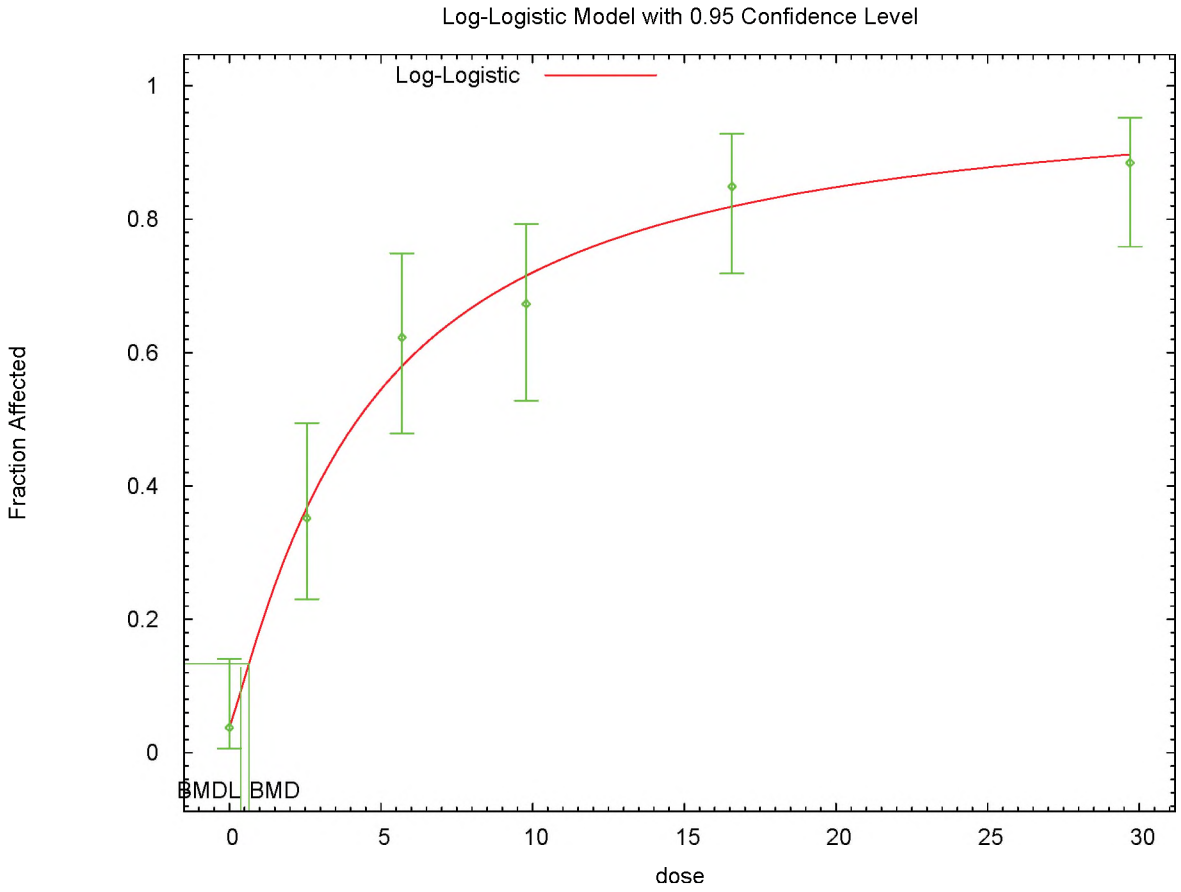
Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.64971

BMDL = 0.375051

E.2.31.3. *Figure for Selected Model: Log-Logistic*



10:58 02/08 2010

E.2.32. National Toxicology Program, 2006: Eosinophilic Focus, Liver

E.2.32.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
gamma	3	0.293	331.902	3.573E+00	2.225E+00	
logistic	4	0.405	330.400	5.949E+00	5.137E+00	negative intercept (intercept = -2.043)
log-logistic	3	0.152	333.515	4.139E+00	2.077E+00	
log-probit	4	0.192	332.312	4.889E+00	3.980E+00	slope bound hit (slope = 1)
multistage, 5-degree	3	0.752	329.328	3.393E+00	2.466E+00	
probit [a]	**4**	**0.459**	**329.945**	**5.583E+00**	**4.864E+00**	**negative intercept (intercept = -1.235)**
Weibull	3	0.324	331.628	3.770E+00	2.249E+00	
log-probit, unrestricted	3	0.116	334.150	4.146E+00	2.152E+00	unrestricted (slope = 0.895)

[a] Best-fitting model, BMDS output presented in this appendix

E.2.32.2. *Output for Selected Model: Probit*

National Toxicology Program, 2006: Eosinophilic Focus, Liver

```
 ================================================================
         Probit Model. (Version: 3.1;  Date: 05/16/2008)
         Input Data File: C:\1\Blood\45_NTP_2006_LivEosFoc_Probit_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\45_NTP_2006_LivEosFoc_Probit_1.plt
                                                Mon Feb 08 11:00:54 2010
 ================================================================

 0
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   The form of the probability function is:

   P[response] = CumNorm(Intercept+Slope*Dose),

   where CumNorm(.) is the cumulative normal distribution function


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial (and Specified) Parameter Values

background =	0	Specified
intercept =	-1.28017	
slope =	0.0712441	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -background
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	intercept	slope
intercept	1	-0.77
slope	-0.77	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
intercept	-1.23453	0.125132	-1.47979	-0.989279
slope	0.0688678	0.00823346	0.0527305	0.085005

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-161.07	6			
Fitted model	-162.972	2	3.80461	4	0.4331
Reduced model	-202.816	1	83.4925	5	<.0001

AIC: 329.945

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1085	5.751	3.000	53	-1.215
2.5565	0.1449	7.826	8.000	54	0.067
5.6937	0.1998	10.588	14.000	53	1.172
9.7882	0.2876	15.242	17.000	53	0.533
16.5688	0.4628	24.526	22.000	53	-0.696
29.6953	0.7912	41.932	42.000	53	0.023

Chi^2 = 3.62 d.f. = 4 P-value = 0.4593

Benchmark Dose Computation

Specified effect = 0.1

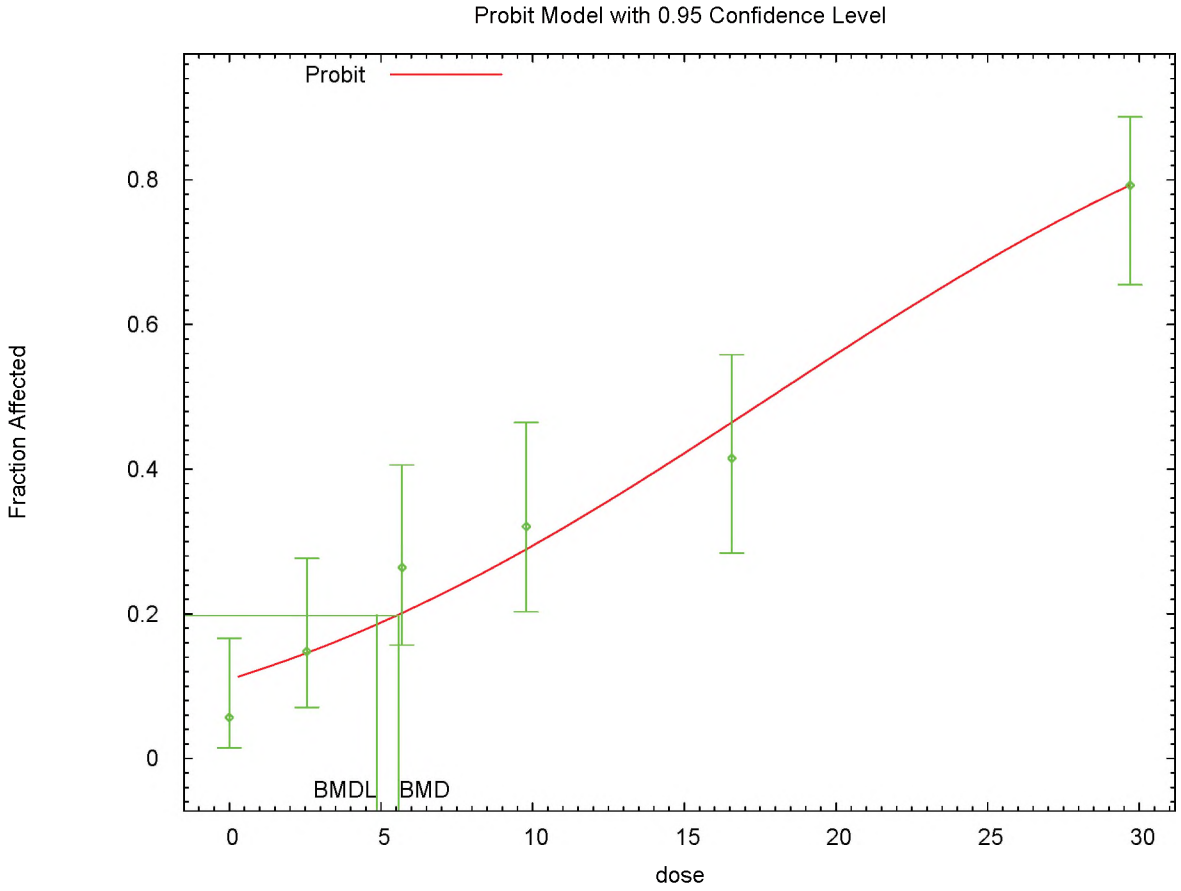
Risk Type = Extra risk

Confidence level = 0.95

BMD = 5.58309

BMDL = 4.86394

E.2.32.3. *Figure for Selected Model: Probit*



E.2.33. National Toxicology Program, 2006: Fatty Change Diffuse, Liver

E.2.33.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
gamma	4	0.659	252.348	4.028E+00	2.923E+00	
logistic	4	0.056	262.132	5.890E+00	5.042E+00	negative intercept (intercept = -2.825)
log-logistic	4	0.359	254.413	4.254E+00	3.228E+00	
log-probit	4	0.367	254.428	4.204E+00	3.277E+00	
multistage, 5-degree	3	0.581	254.045	3.524E+00	2.234E+00	
probit	4	0.075	260.915	5.567E+00	4.784E+00	negative intercept (intercept = -1.665)
Weibull [a]	**4**	**0.724**	**251.989**	**3.917E+00**	**2.856E+00**	

[a] Best-fitting model, BMDS output presented in this appendix

E.2.33.2. *Output for Selected Model: Weibull*

National Toxicology Program, 2006: Fatty Change Diffuse, Liver

```
 ================================================================
         Weibull Model using Weibull Model (Version: 2.12;  Date: 05/16/2008)
         Input Data File: C:\1\Blood\47_NTP_2006_LivFatDiff_Weibull_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\47_NTP_2006_LivFatDiff_Weibull_1.plt
                                          Mon Feb 08 11:01:56 2010
 ================================================================

 NTP_liver_fatty_change_diffuse
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]


   Dependent variable = DichEff
   Independent variable = Dose
   Power parameter is restricted as power >=1

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


                 Default Initial (and Specified) Parameter Values
                    Background =   0.00925926
                         Slope =   0.00721355
```

Power = 1.69678

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Slope	Power
Slope	1	-0.98
Power	-0.98	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	NA		
Slope	0.0135075	0.00640459	0.00095478	0.0260603
Power	1.50444	0.168981	1.17324	1.83564

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-122.992	6			
Fitted model	-123.995	2	2.00444	4	0.7349
Reduced model	-204.846	1	163.708	5	<.0001

AIC: 251.989

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	53	0.000
2.5565	0.0539	2.912	2.000	54	-0.550
5.6937	0.1688	8.949	12.000	53	1.119
9.7882	0.3415	18.102	17.000	53	-0.319
16.5688	0.6024	31.929	30.000	53	-0.542
29.6953	0.8913	47.238	48.000	53	0.336

Chi^2 = 2.06 d.f. = 4 P-value = 0.7243

Benchmark Dose Computation

Specified effect = 0.1

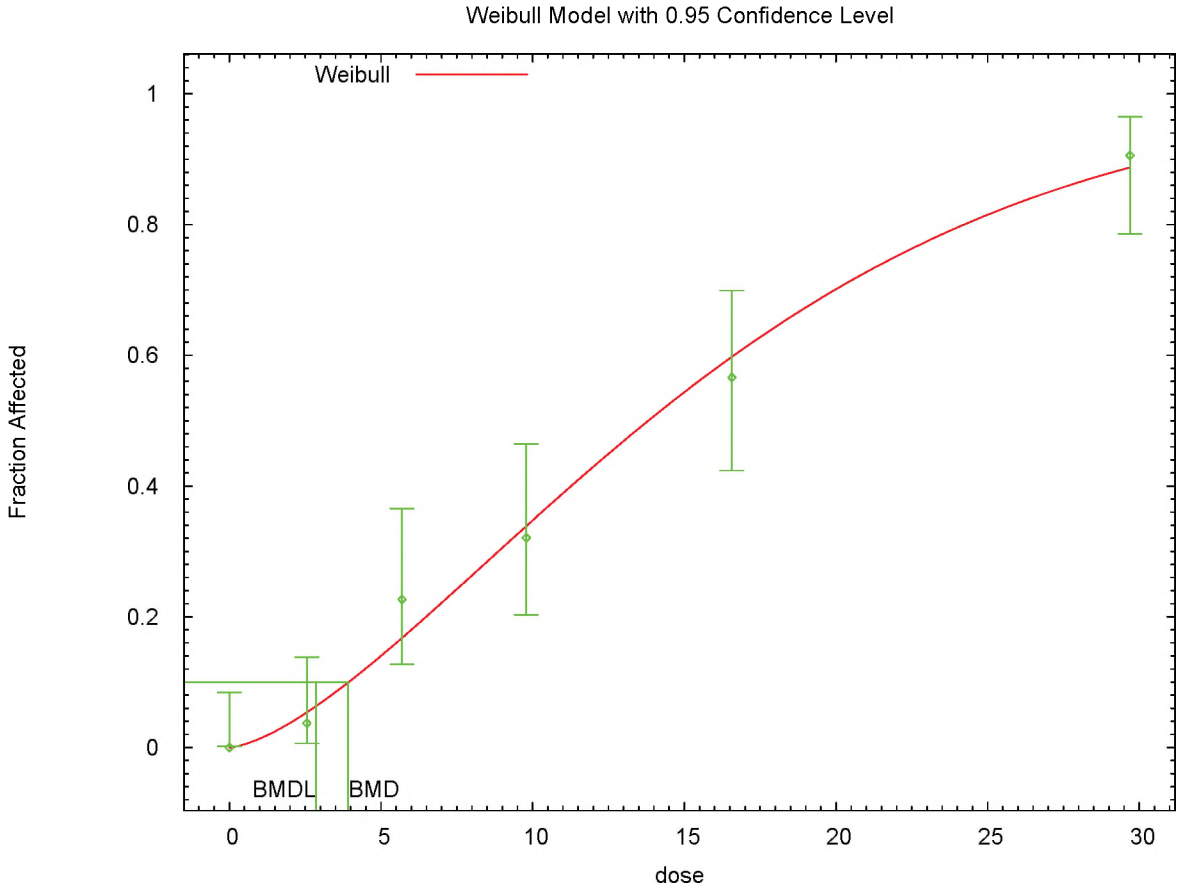
Risk Type = Extra risk

Confidence level = 0.95

BMD = 3.91723

BMDL = 2.85566

E.2.33.3. *Figure for Selected Model: Weibull*



E.2.34. National Toxicology Program, 2006: Gingival Hyperplasia, Squamous, 2 Years

E.2.34.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
gamma	4	0.036	314.985	7.743E+00	5.166E+00	power bound hit (power = 1)
logistic	4	0.016	318.602	1.392E+01	1.056E+01	negative intercept (intercept = -1.859)
log-logistic [a]	**4**	**0.055**	**313.351**	**5.850E+00**	**3.730E+00**	**slope bound hit (slope = 1)**
log-probit	4	0.005	321.426	1.535E+01	1.038E+01	slope bound hit (slope = 1)
multistage, 5-degree	4	0.036	314.985	7.743E+00	5.166E+00	final ß = 0
probit	4	0.018	318.240	1.318E+01	9.924E+00	negative intercept (intercept = -1.123)
Weibull	4	0.036	314.985	7.743E+00	5.166E+00	power bound hit (power = 1)
gamma, unrestricted	3	0.633	307.618	5.309E-01	9.859E-07	unrestricted (power = 0.282)
log-logistic, unrestricted [b]	3	0.655	307.507	7.049E-01	1.260E-05	unrestricted (slope = 0.374)
log-probit, unrestricted	3	0.668	307.444	8.357E-01	4.796E-05	unrestricted (slope = 0.22)
Weibull, unrestricted	3	0.644	307.562	6.143E-01	3.872E-06	unrestricted (power = 0.325)

[a] Best-fitting model, BMDS output presented in this appendix

[b] Alternate model, BMDS output also presented in this appendix

E.2.34.2. *Output for Selected Model: Log-Logistic*

National Toxicology Program, 2006: Gingival Hyperplasia, Squamous, 2 Years

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\1\Blood\42_NTP_2006_GingHypSq_LogLogistic_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\42_NTP_2006_GingHypSq_LogLogistic_1.plt
                                              Mon Feb 08 10:59:57 2010
 ================================================================

 [insert study notes]
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   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
```

```
   Slope parameter is restricted as slope >= 1

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =    0.0188679
                     intercept =     -3.75308
                         slope =            1


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -slope
                have been estimated at a boundary point, or have been specified by the user,
                and do not appear in the correlation matrix )

            background    intercept

background            1        -0.79

 intercept        -0.79            1



                                Parameter Estimates

                                                      95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background        0.0671812               *                   *                   *
      intercept         -3.96371               *                   *                   *
          slope                1               *                   *                   *

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -149.95         6
   Fitted model        -154.675         2       9.45085      4         0.05077
  Reduced model        -162.631         1       25.3627      5       0.0001186

           AIC:         313.351


                                 Goodness  of  Fit
                                                                    Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.0672         3.561     1.000          53       -1.405
     2.5565     0.1104         5.960     7.000          54        0.452
     5.6937     0.1582         8.385    14.000          53        2.113
     9.7882     0.2134        11.311    13.000          53        0.566
    16.5688     0.2905        15.394    15.000          53       -0.119
    29.6953     0.4036        21.389    16.000          53       -1.509

 Chi^2 = 9.26      d.f. = 4        P-value = 0.0550


   Benchmark Dose Computation
```

```
Specified effect =          0.1

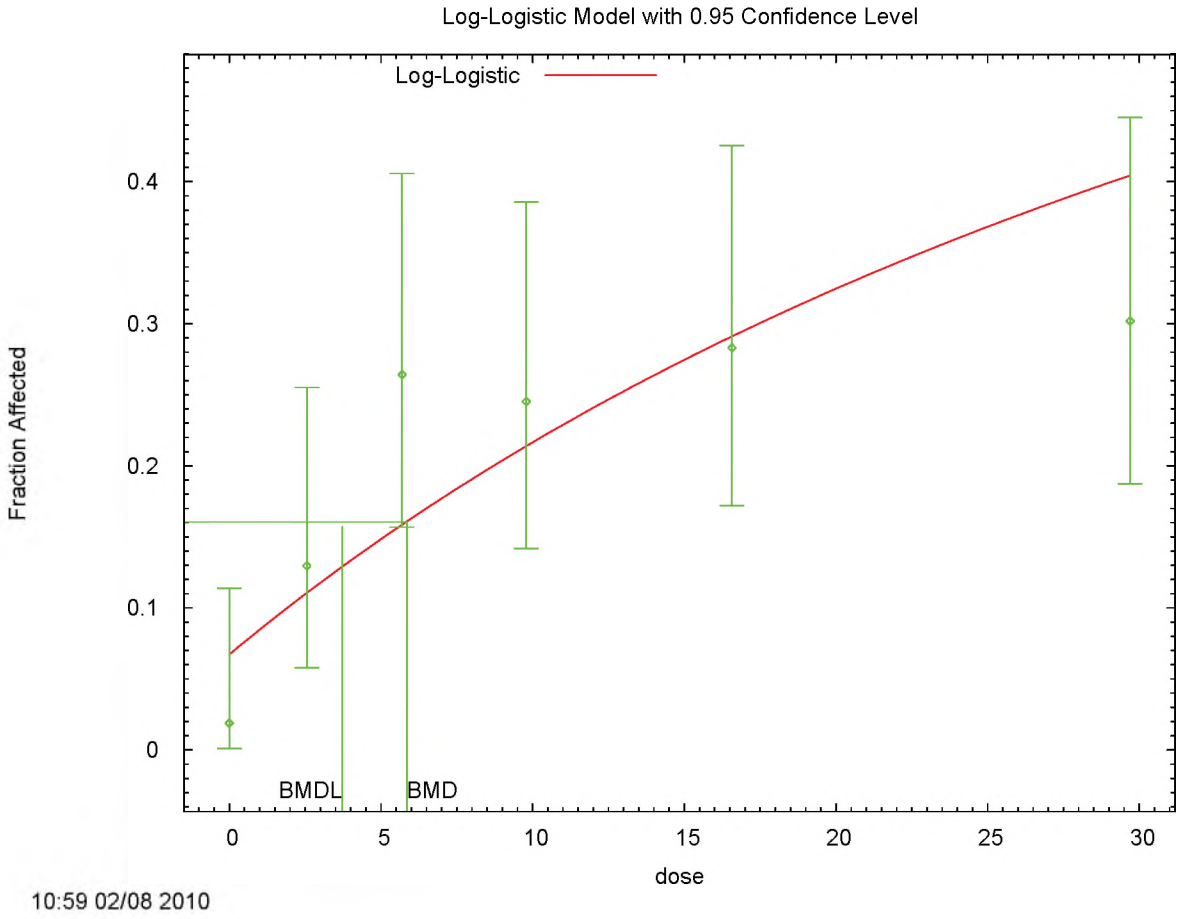
Risk Type        =      Extra risk

Confidence level =         0.95

             BMD =      5.85026

            BMDL =       3.7296
```

E.2.34.3. *Figure for Selected Model: Log-Logistic*



E.2.34.4. *Output for Additional Model Presented: Log-Logistic, Unrestricted*

National Toxicology Program, 2006: Gingival Hyperplasia, Squamous, 2 Years

```
================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\Blood\42_NTP_2006_GingHypSq_LogLogistic_U_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\42_NTP_2006_GingHypSq_LogLogistic_U_1.plt
                                          Mon Feb 08 10:59:57 2010
================================================================

[insert study notes]
```

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   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =    0.0188679
                     intercept =         -2.2
                         slope =     0.424326


           Asymptotic Correlation Matrix of Parameter Estimates

             background    intercept        slope

background            1        -0.27         0.11

 intercept        -0.27            1        -0.93

     slope         0.11        -0.93            1


                                Parameter Estimates

                                                      95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background        0.0185138            *               *                   *
      intercept         -2.06653            *               *                   *
          slope         0.373721            *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -149.95         6
   Fitted model        -150.753         3       1.60697      3          0.6578
  Reduced model        -162.631         1       25.3627      5       0.0001186

           AIC:         307.507


                                Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------
    0.0000     0.0185         0.981     1.000          53        0.019
    2.5565     0.1681         9.078     7.000          54       -0.756
    5.6937     0.2101        11.136    14.000          53        0.966
    9.7882     0.2433        12.893    13.000          53        0.034
```

```
    16.5688      0.2792         14.795     15.000           53         0.063
    29.6953      0.3230         17.117     16.000           53        -0.328

 Chi^2 = 1.62       d.f. = 3         P-value = 0.6554


   Benchmark Dose Computation

Specified effect =            0.1

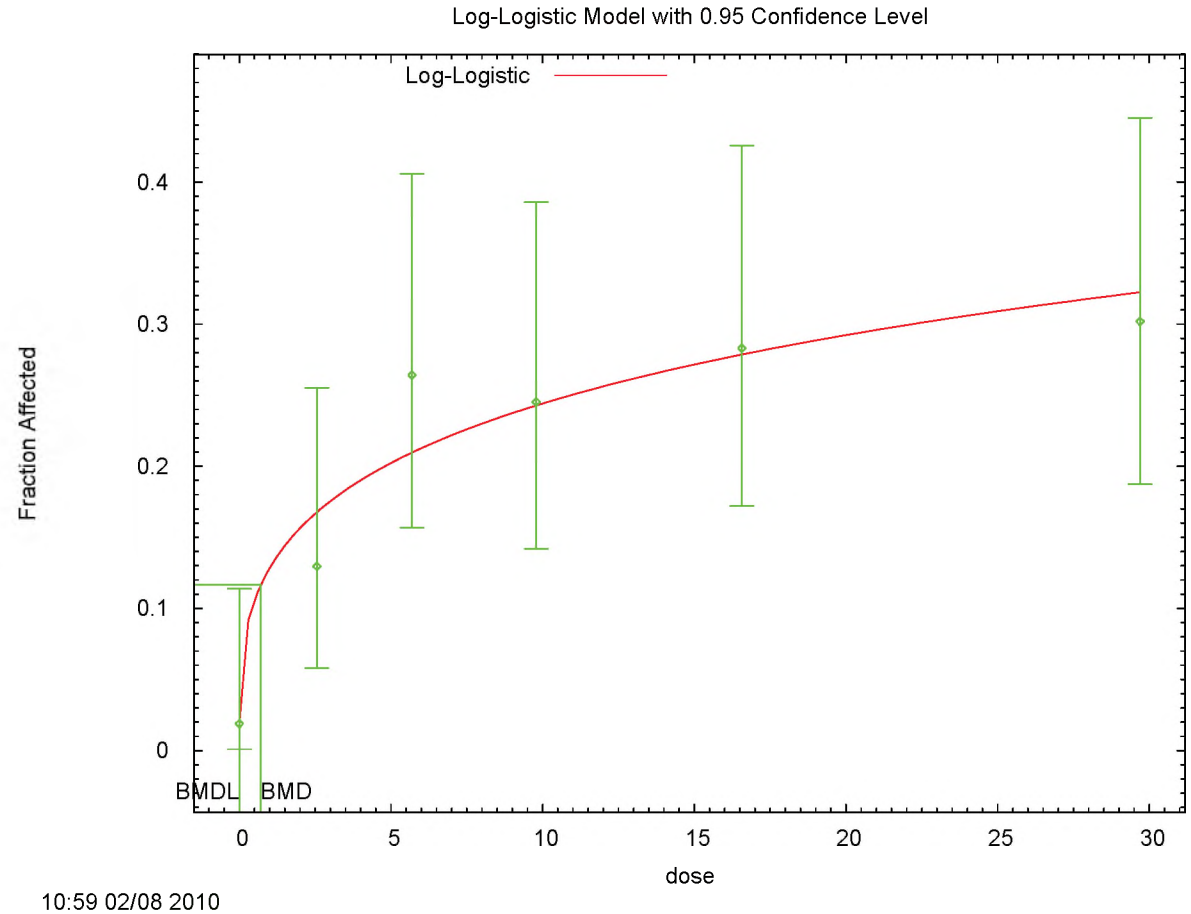
Risk Type        =       Extra risk

Confidence level =           0.95

             BMD =       0.704898

            BMDL =   1.26034e-005
```

E.2.34.5. *Figure for Additional Model Presented: Log-Logistic, Unrestricted*



E.2.35. National Toxicology Program, 2006: Hepatocyte Hypertrophy, 2 Years

E.2.35.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
gamma	5	0.034	273.875	9.091E-01	7.868E-01	power bound hit (power = 1)
logistic	4	<0.001	297.895	2.475E+00	2.122E+00	negative intercept (intercept = -1.685)
log-logistic	4	0.006	279.210	1.137E+00	6.491E-01	
log-probit	5	0.006	277.800	1.530E+00	1.321E+00	
multistage, 5-degree [a]	**4**	**0.018**	**275.693**	**9.272E-01**	**7.906E-01**	
probit	4	<0.001	299.731	2.453E+00	2.137E+00	negative intercept (intercept = -0.985)
Weibull	5	0.034	273.875	9.091E-01	7.868E-01	power bound hit (power = 1)
gamma, unrestricted	4	0.027	275.270	error	error	unrestricted (power = 0.844)
log-probit, unrestricted	4	0.008	278.360	1.191E+00	7.038E-01	unrestricted (slope = 0.864)
Weibull, unrestricted	4	0.024	275.439	7.345E-01	3.588E-01	unrestricted (power = 0.92)

[a] Best-fitting model, BMDS output presented in this appendix

E.2.35.2. *Output for Selected Model: Multistage, 5-Degree*

National Toxicology Program, 2006: Hepatocyte Hypertrophy, 2 Years

```
 ========================================================================
         Multistage Model. (Version: 3.0;  Date: 05/16/2008)
         Input Data File: C:\1\Blood\43_NTP_2006_HepHyper_Multi5_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\43_NTP_2006_HepHyper_Multi5_1.plt
                                                Mon Feb 08 11:00:25 2010
 ========================================================================

 [insert study notes]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4-beta5*dose^5)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 6
```

Total number of records with missing values = 0
Total number of parameters in model = 6
Total number of specified parameters = 0
Degree of polynomial = 5

Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values
Background = 0.112745
Beta(1) = 0.0950808
Beta(2) = 0
Beta(3) = 0
Beta(4) = 0
Beta(5) = 4.39515e-008

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background -Beta(2) -Beta(3) -Beta(4)
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Beta(1)	Beta(5)
Beta(1)	1	-0.5
Beta(5)	-0.5	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0.113632	*	*	*
Beta(2)	0	*	*	*
Beta(3)	0	*	*	*
Beta(4)	0	*	*	*
Beta(5)	1.71322e-008	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-129.986	6			
Fitted model	-135.847	2	11.7216	4	0.01955
Reduced model	-219.97	1	179.968	5	<.0001

AIC: 275.693

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	53	0.000
2.5565	0.2521	13.614	19.000	54	1.688
5.6937	0.4764	25.251	19.000	53	-1.719
9.7882	0.6717	35.599	42.000	53	1.872
16.5688	0.8510	45.106	41.000	53	-1.584
29.6953	0.9769	51.778	52.000	53	0.203

```
 Chi^2 = 11.86      d.f. = 4        P-value = 0.0184


   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

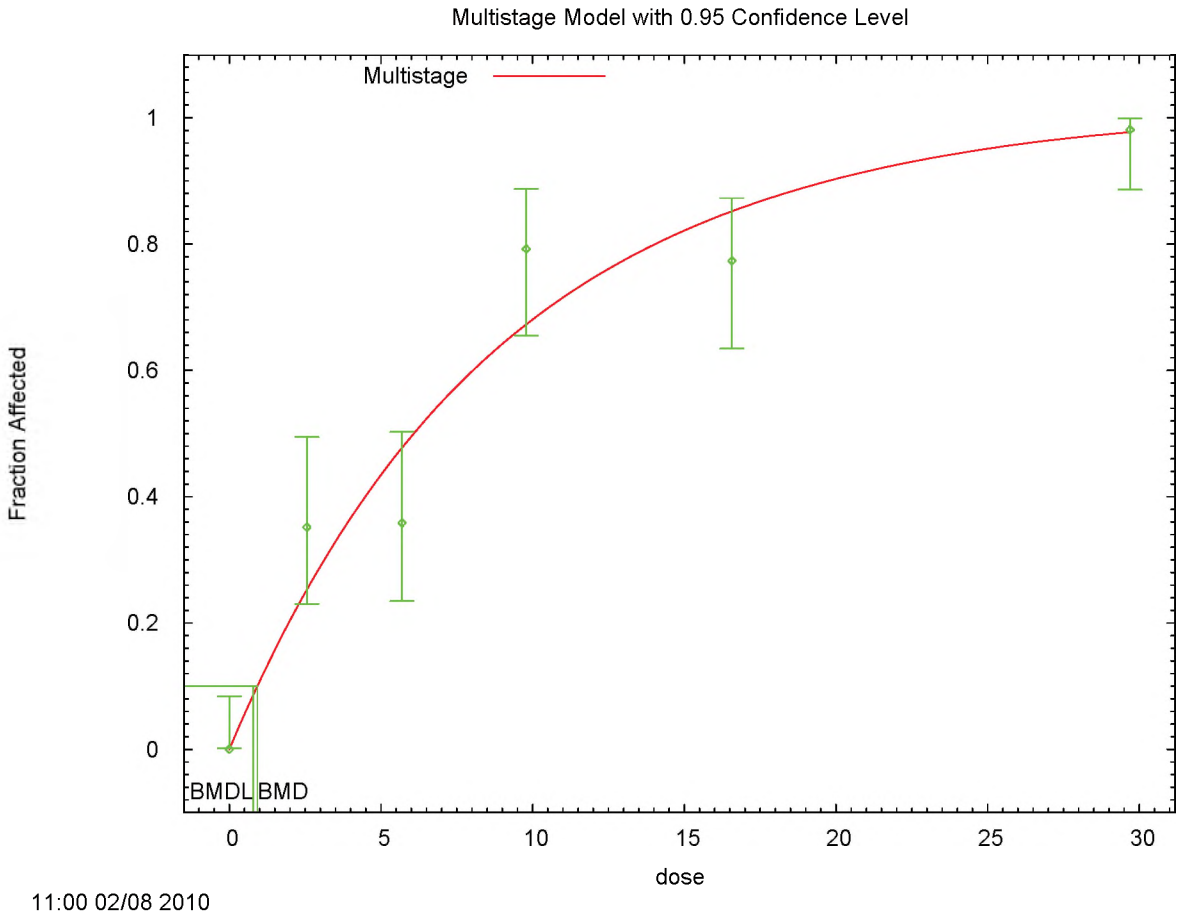
             BMD =       0.92721

            BMDL =      0.790637

            BMDU =       1.14523

Taken together, (0.790637, 1.14523) is a 90      % two-sided confidence
interval for the BMD
```

E.2.35.3. *Figure for Selected Model: Multistage, 5-Degree*



E.2.36. National Toxicology Program, 2006: Necrosis, Liver

E.2.36.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
gamma	4	0.939	234.400	8.655E+00	6.340E+00	power bound hit (power = 1)
logistic	4	0.601	236.742	1.484E+01	1.240E+01	negative intercept (intercept = -2.818)
log-logistic	4	0.943	234.382	7.928E+00	5.605E+00	slope bound hit (slope = 1)
log-probit	4	0.572	236.863	1.333E+01	1.024E+01	slope bound hit (slope = 1)
multistage, 5-degree	4	0.939	234.400	8.655E+00	6.340E+00	final ß = 0
probit	4	0.666	236.293	1.393E+01	1.154E+01	negative intercept (intercept = -1.626)
Weibull	4	0.939	234.400	8.655E+00	6.340E+00	power bound hit (power = 1)
gamma, unrestricted	3	0.883	236.290	7.726E+00	3.453E+00	unrestricted (power = 0.87)
log-logistic, unrestricted	3	0.860	236.377	7.733E+00	3.536E+00	unrestricted (slope = 0.974)
log-probit, unrestricted [a]	**3**	**0.805**	**236.598**	**7.501E+00**	**3.504E+00**	**unrestricted (slope = 0.517)**
Weibull, unrestricted	3	0.879	236.302	7.763E+00	3.508E+00	unrestricted (power = 0.895)

[a] Best-fitting model, BMDS output presented in this appendix

E.2.36.2. *Output for Selected Model: Log-Probit, Unrestricted*

National Toxicology Program, 2006: Necrosis, Liver

```
 ================================================================
         Probit Model. (Version: 3.1;  Date: 05/16/2008)
         Input Data File: C:\1\Blood\50_NTP_2006_LivNec_LogProbit_U_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\50_NTP_2006_LivNec_LogProbit_U_1.plt
                                              Mon Feb 08 11:29:30 2010
 ================================================================

 NTP_liver_necrosis
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = Background
               + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),

   where CumNorm(.) is the cumulative normal distribution function


   Dependent variable = DichEff
```

```
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                 Default Initial (and Specified) Parameter Values
                    background =    0.0188679
                     intercept =     -2.16223
                         slope =     0.457376


           Asymptotic Correlation Matrix of Parameter Estimates

             background    intercept        slope

background            1        -0.65         0.55

 intercept        -0.65            1        -0.97

     slope         0.55        -0.97            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background        0.0221151        0.0221351         -0.0212689            0.065499
      intercept         -2.32352         0.556343           -3.41393           -1.23311
          slope         0.517104         0.185064           0.154385           0.879823


                         Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -114.813         6
   Fitted model         -115.299         3      0.972184      3           0.808
  Reduced model          -127.98         1       26.3331      5         <.0001

           AIC:         236.598


                                Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size        Residual
   ----------------------------------------------------------------------
    0.0000     0.0221         1.172     1.000          53        -0.161
    2.5565     0.0544         2.938     4.000          54         0.637
    5.6937     0.0976         5.174     4.000          53        -0.543
    9.7882     0.1457         7.720     8.000          53         0.109
   16.5688     0.2096        11.106    10.000          53        -0.373
   29.6953     0.3002        15.908    17.000          53         0.327

 Chi^2 = 0.99      d.f. = 3        P-value = 0.8048


   Benchmark Dose Computation

Specified effect =            0.1
```

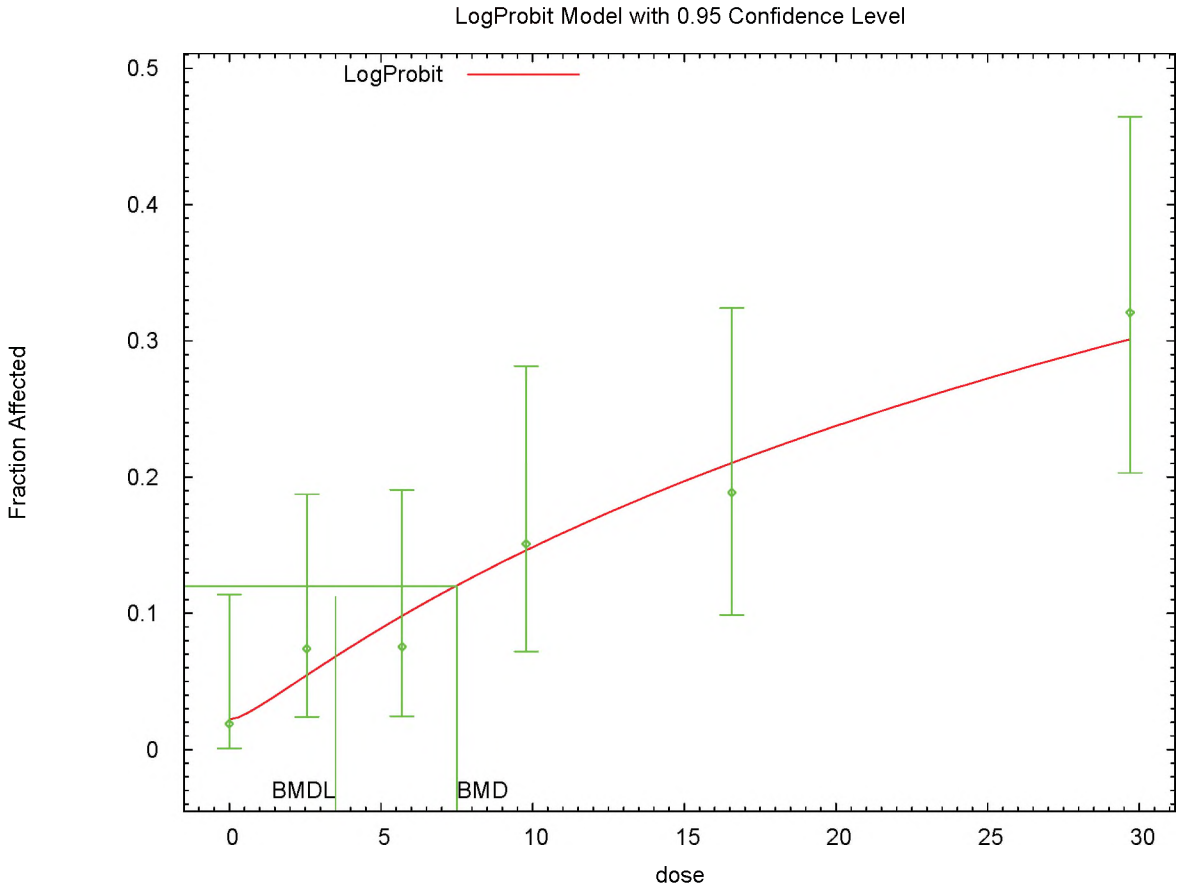
```
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        7.50077

            BMDL =         3.5039
```

E.2.36.3. *Figure for Selected Model: Log-Probit, Unrestricted*



E.2.37. National Toxicology Program, 2006: Oval Cell Hyperplasia

E.2.37.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
gamma	3	0.074	199.468	6.739E+00	5.074E+00	
logistic	4	0.171	196.803	6.064E+00	5.145E+00	negative intercept (intercept = -3.834)
log-logistic	3	0.042	201.659	6.936E+00	5.604E+00	
log-probit	3	0.072	200.121	7.090E+00	5.931E+00	
multistage, 5-degree	3	0.207	195.962	4.785E+00	3.105E+00	
probit [a]	**4**	**0.227**	**195.448**	**5.673E+00**	**4.793E+00**	**negative intercept (intercept = -2.19)**
Weibull [b]	3	0.077	198.375	5.718E+00	4.088E+00	

[a] Best-fitting model, BMDS output presented in this appendix

[b] Alternate model, BMDS output also presented in this appendix

E.2.37.2. *Output for Selected Model: Probit*

National Toxicology Program, 2006: Oval Cell Hyperplasia

```
 ================================================================
         Probit Model. (Version: 3.1;  Date: 05/16/2008)
         Input Data File: C:\1\Blood\53_NTP_2006_OvalHyper_Probit_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\53_NTP_2006_OvalHyper_Probit_1.plt
                                              Mon Feb 08 13:25:23 2010
 ================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = CumNorm(Intercept+Slope*Dose),

   where CumNorm(.) is the cumulative normal distribution function


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial (and Specified) Parameter Values
background = 0 Specified
intercept = -2.29925
slope = 0.169545

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -background
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	intercept	slope
intercept	1	-0.87
slope	-0.87	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
intercept	-2.18988	0.208021	-2.5976	-1.78217
slope	0.172453	0.0182446	0.136694	0.208211

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-92.4898	6			
Fitted model	-95.7242	2	6.46873	4	0.1668
Reduced model	-210.191	1	235.402	5	<.0001

AIC: 195.448

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0143	0.756	0.000	53	-0.876
2.5565	0.0401	2.168	4.000	54	1.270
5.6937	0.1135	6.017	3.000	53	-1.306
9.7882	0.3079	16.317	20.000	53	1.096
16.5688	0.7478	39.631	38.000	53	-0.516
29.6953	0.9983	52.911	53.000	53	0.299

Chi^2 = 5.64 d.f. = 4 P-value = 0.2274

Benchmark Dose Computation

Specified effect = 0.1

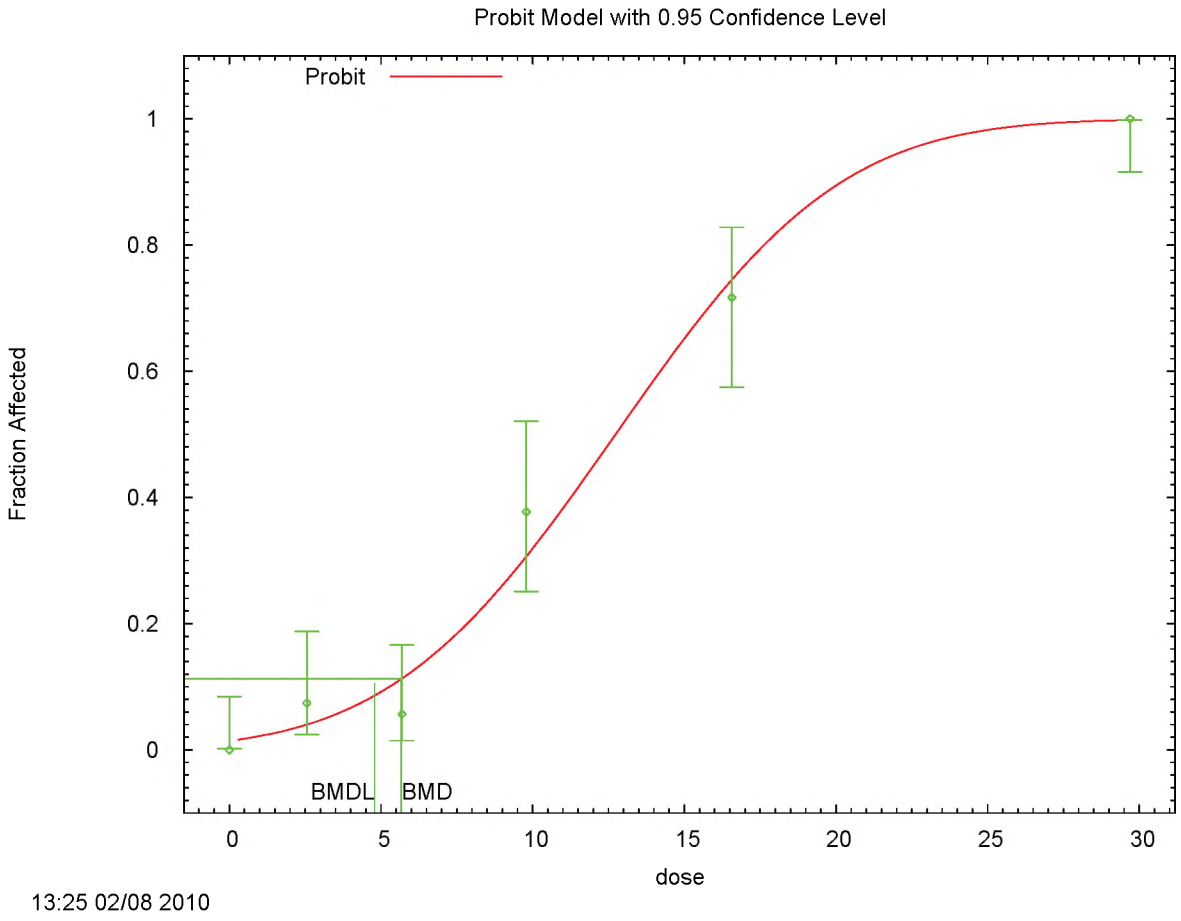
Risk Type = Extra risk

Confidence level = 0.95

BMD = 5.67298

BMDL = 4.79341

E.2.37.3. *Figure for Selected Model: Probit*



E.2.37.4. *Output for Additional Model Presented: Weibull*

National Toxicology Program, 2006: Oval Cell Hyperplasia

```
 ================================================================
         Weibull Model using Weibull Model (Version: 2.12;  Date: 05/16/2008)
         Input Data File: C:\1\Blood\53_NTP_2006_OvalHyper_Weibull_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\53_NTP_2006_OvalHyper_Weibull_1.plt
                                              Mon Feb 08 13:25:23 2010
 ================================================================

 0
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]


   Dependent variable = DichEff
   Independent variable = Dose
   Power parameter is restricted as power >=1

   Total number of observations = 6
```

Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial (and Specified) Parameter Values
Background = 0.00925926
Slope = 0.00296825
Power = 2.17092

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Slope	Power
Background	1	-0.72	0.7
Slope	-0.72	1	-0.99
Power	0.7	-0.99	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0164137	0.0221488	-0.0269971	0.0598245
Slope	0.00162074	0.00202897	-0.00235596	0.00559745
Power	2.39427	0.455116	1.50226	3.28628

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-92.4898	6			
Fitted model	-96.1875	3	7.3953	3	0.06031
Reduced model	-210.191	1	235.402	5	<.0001

AIC: 198.375

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0164	0.870	0.000	53	-0.940
2.5565	0.0314	1.695	4.000	54	1.799
5.6937	0.1138	6.034	3.000	53	-1.312
9.7882	0.3285	17.411	20.000	53	0.757
16.5688	0.7440	39.431	38.000	53	-0.450
29.6953	0.9957	52.774	53.000	53	0.476

Chi^2 = 6.85 d.f. = 3 P-value = 0.0770

Benchmark Dose Computation

Specified effect = 0.1

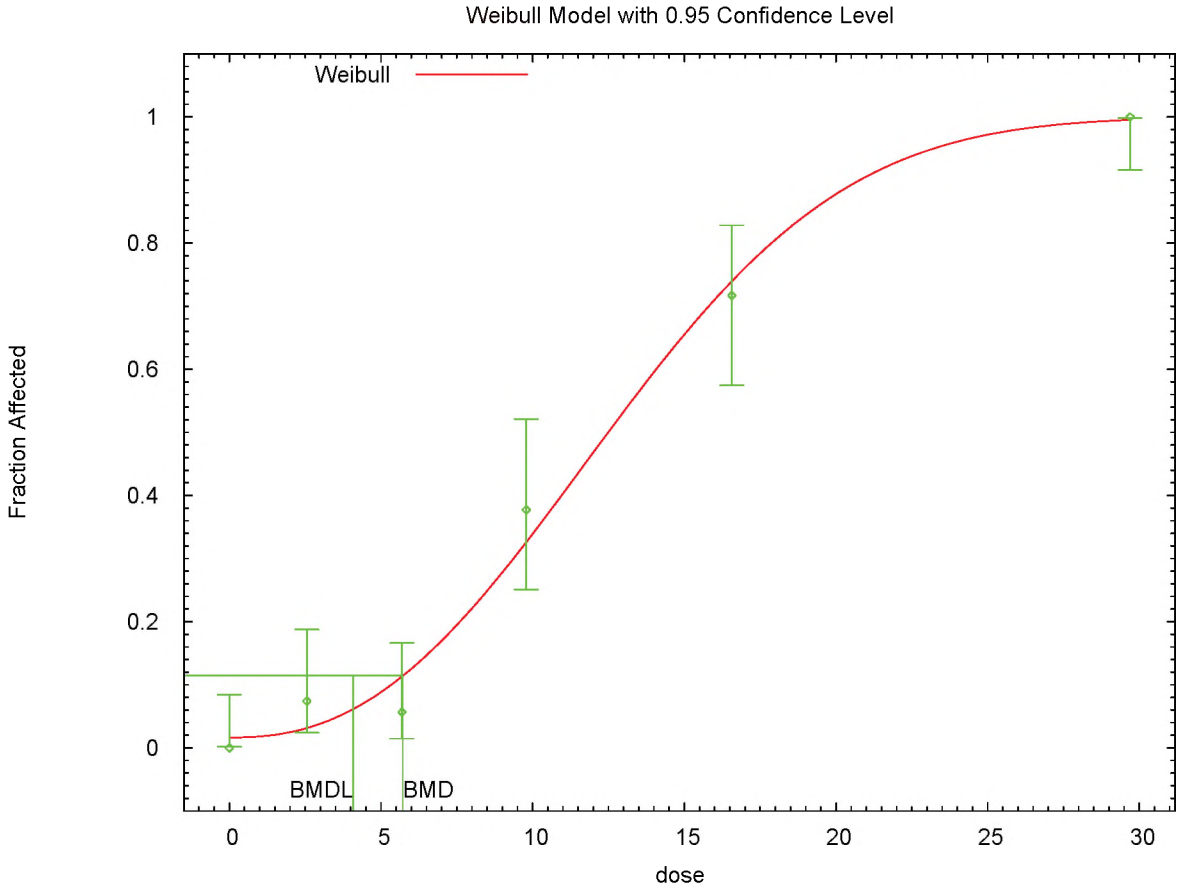
Risk Type = Extra risk

Confidence level = 0.95

BMD = 5.71754

BMDL = 4.08823

E.2.37.5. *Figure for Additional Model Presented: Weibull*



E.2.38. National Toxicology Program, 2006: Pigmentation, Liver

E.2.38.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
gamma	3	0.552	196.971	2.172E+00	1.493E+00	
logistic	4	0.247	197.066	1.853E+00	1.521E+00	negative intercept (intercept = -2.51)
log-logistic	3	0.984	195.530	2.566E+00	1.937E+00	
log-probit [a]	**3**	**0.962**	**195.526**	**2.463E+00**	**1.890E+00**	
multistage, 5-degree	3	0.058	199.955	1.822E+00	9.916E-01	final ß = 0
probit	4	0.004	200.504	1.710E+00	1.430E+00	negative intercept (intercept = -1.392)
Weibull	3	0.219	199.007	1.756E+00	1.190E+00	

[a] Best-fitting model, BMDS output presented in this appendix

E.2.38.2. *Output for Selected Model: Log-Probit*

National Toxicology Program, 2006: Pigmentation, Liver

```
 ================================================================
         Probit Model. (Version: 3.1;  Date: 05/16/2008)
         Input Data File: C:\1\Blood\54_NTP_2006_Pigment_LogProbit_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\54_NTP_2006_Pigment_LogProbit_1.plt
                                          Mon Feb 08 13:25:55 2010
 ================================================================

 0
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   The form of the probability function is:

   P[response] = Background
               + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),

   where CumNorm(.) is the cumulative normal distribution function


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
background = 0.0754717
intercept = -2.48683
slope = 1.53221

Asymptotic Correlation Matrix of Parameter Estimates

	background	intercept	slope
background	1	-0.42	0.33
intercept	-0.42	1	-0.96
slope	0.33	-0.96	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0725473	0.0338856	0.00613263	0.138962
intercept	-2.93268	0.487158	-3.8875	-1.97787
slope	1.83184	0.246868	1.34798	2.31569

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-94.6177	6			
Fitted model	-94.7632	3	0.291072	3	0.9617
Reduced model	-210.717	1	232.198	5	<.0001

AIC: 195.526

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0725	3.845	4.000	53	0.082
2.5565	0.1769	9.553	9.000	54	-0.197
5.6937	0.6291	33.342	34.000	53	0.187
9.7882	0.9013	47.771	48.000	53	0.105
16.5688	0.9874	52.334	52.000	53	-0.412
29.6953	0.9995	52.974	53.000	53	0.160

Chi^2 = 0.29 d.f. = 3 P-value = 0.9624

Benchmark Dose Computation

Specified effect = 0.1

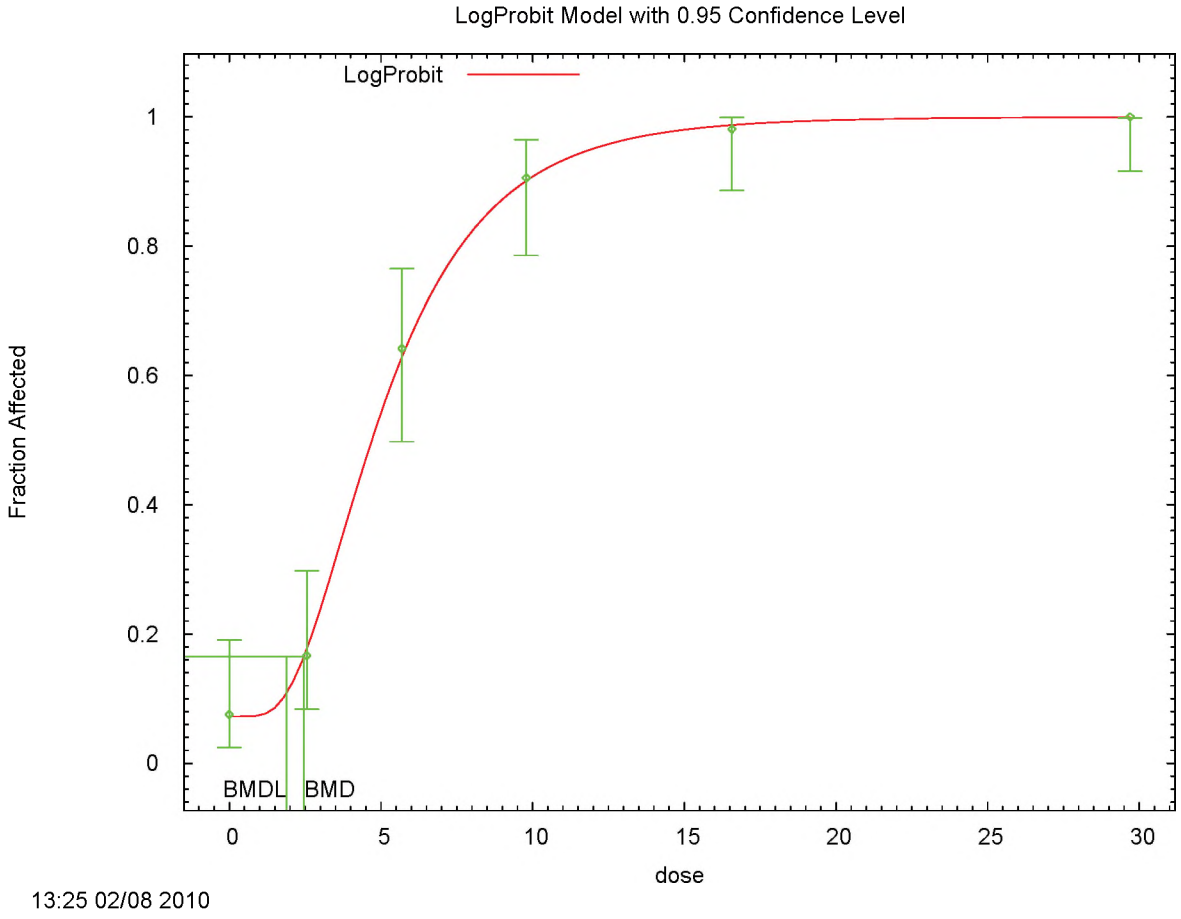
Risk Type = Extra risk

Confidence level = 0.95

BMD = 2.46293

BMDL = 1.88981

E.2.38.3. *Figure for Selected Model: Log-Probit*



E.2.39. National Toxicology Program, 2006: Toxic Hepatopathy

E.2.39.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
gamma	4	0.754	185.763	4.302E+00	3.463E+00	
logistic	4	0.159	191.136	4.833E+00	4.068E+00	negative intercept (intercept = -3.756)
log-logistic	3	0.391	189.577	4.697E+00	3.818E+00	
log-probit	3	0.394	189.580	4.972E+00	3.780E+00	
multistage, 5-degree [a]	**4**	**0.693**	**185.924**	**3.980E+00**	**3.059E+00**	**final ß = 0**
probit	4	0.231	189.820	4.621E+00	3.860E+00	negative intercept (intercept = -2.172)
Weibull	4	0.716	185.785	4.089E+00	3.215E+00	

[a] Best-fitting model, BMDS output presented in this appendix

E.2.39.2. *Output for Selected Model: Multistage, 5-Degree*

National Toxicology Program, 2006: Toxic Hepatopathy

```
 ======================================================================
          Multistage Model. (Version: 3.0;  Date: 05/16/2008)
          Input Data File: C:\1\Blood\55_NTP_2006_ToxHepa_Multi5_1.(d)
          Gnuplot Plotting File:  C:\1\Blood\55_NTP_2006_ToxHepa_Multi5_1.plt
                                                Mon Feb 08 13:26:28 2010
 ======================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4-beta5*dose^5)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 6
 Total number of specified parameters = 0
 Degree of polynomial = 5


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
```

Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

Background =	0
Beta(1) =	0
Beta(2) =	0
Beta(3) =	0
Beta(4) =	0
Beta(5) =	4.36963e+012

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background -Beta(1) -Beta(4) -Beta(5)
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Beta(2)	Beta(3)
Beta(2)	1	-0.95
Beta(3)	-0.95	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0.00639021	*	*	*
Beta(3)	6.5404e-005	*	*	*
Beta(4)	0	*	*	*
Beta(5)	0	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-89.8076	6			
Fitted model	-90.9619	2	2.30853	4	0.6792
Reduced model	-218.207	1	256.799	5	<.0001

AIC: 185.924

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	53	0.000
2.5565	0.0420	2.265	2.000	54	-0.180
5.6937	0.1969	10.434	8.000	53	-0.841
9.7882	0.4901	25.976	30.000	53	1.106
16.5688	0.8715	46.189	45.000	53	-0.488
29.6953	0.9994	52.966	53.000	53	0.185

Chi^2 = 2.23 d.f. = 4 P-value = 0.6928

Benchmark Dose Computation

Specified effect = 0.1

```
Risk Type        =      Extra risk

Confidence level =           0.95

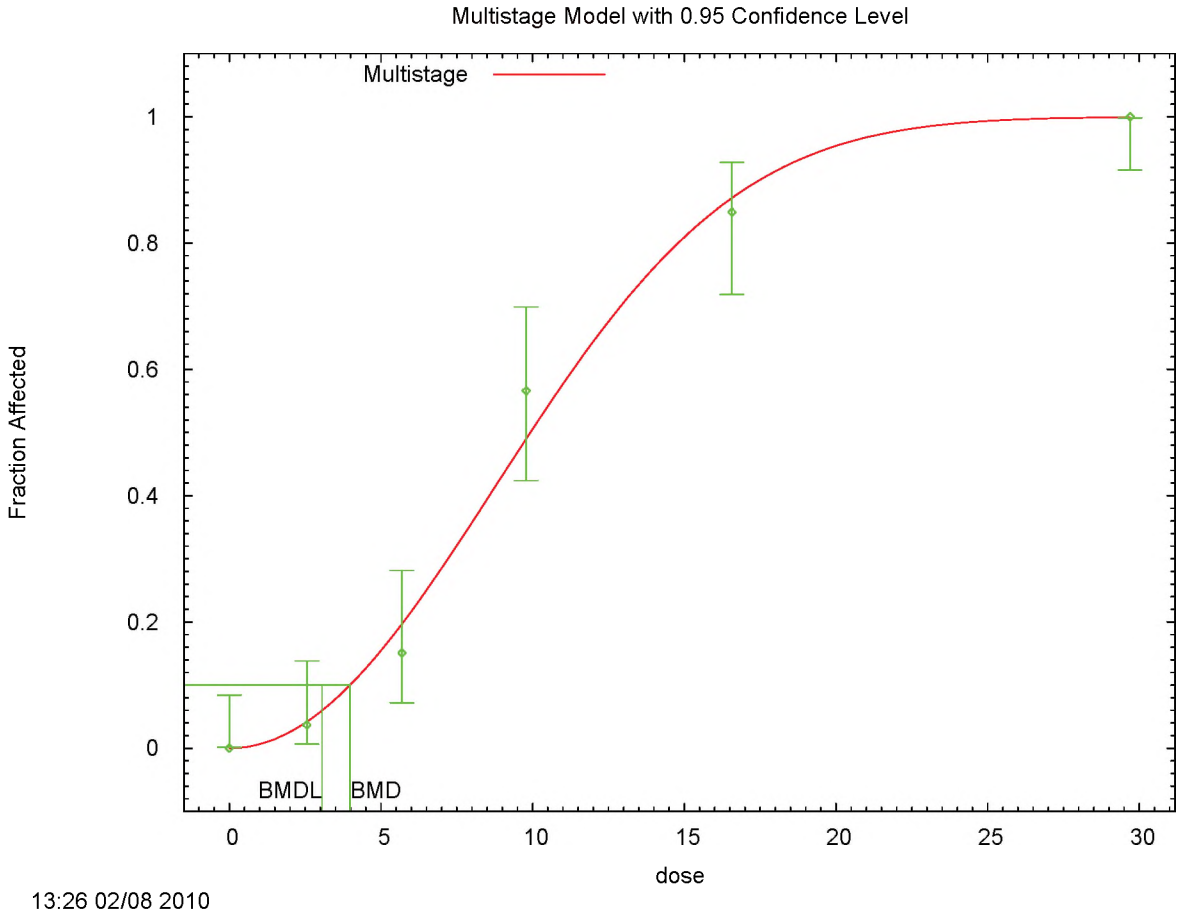
             BMD =        3.98025

            BMDL =        3.05855

            BMDU =        4.89735

Taken together, (3.05855, 4.89735) is a 90      % two-sided confidence
interval for the BMD
```

E.2.39.3. *Figure for Selected Model: Multistage, 5-Degree*



E.2.40. Ohsako et al., 2001: Ano-Genital Length, PND 120

E.2.40.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	3	0.027	171.073	2.592E+01	1.750E+01	
exponential (M3)	3	0.027	171.073	2.592E+01	1.750E+01	power hit bound (d = 1)
exponential (M4)	2	0.106	168.392	2.248E+00	8.445E-01	
exponential (M5)	1	0.049	169.789	2.193E+00	9.382E-01	
Hill [b]	**2**	**0.154**	**167.647**	**2.879E+00**	**8.028E-01**	**n lower bound hit (n = 1)**
linear	3	0.025	171.258	2.700E+01	1.881E+01	
polynomial, 4-degree	3	0.025	171.258	2.700E+01	1.881E+01	
power	3	0.025	171.258	2.700E+01	1.881E+01	power bound hit (power = 1)
Hill, unrestricted [c]	1	0.056	169.555	3.494E+00	3.046E-01	unrestricted (n = 0.591)
power, unrestricted	2	0.153	167.654	4.151E+00	2.395E-01	unrestricted (power = 0.291)

[a] Constant variance model selected ($p = 0.165$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.2.40.2. *Output for Selected Model: Hill*

Ohsako et al., 2001: Ano-Genital Length, PND 120

```
 ======================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\1\Blood\56_Ohsako_2001_Anogen_HillCV_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\56_Ohsako_2001_Anogen_HillCV_1.plt
                                                Mon Feb 08 13:27:02 2010
 ======================================================================

 Figure 7
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
```

```
   Power parameter restricted to be greater than 1
   A constant variance model is fit

   Total number of dose groups = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                        alpha =      7.27386
                          rho =            0   Specified
                    intercept =       28.905
                            v =      -5.1065
                            n =      1.57046
                            k =       2.4317


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho    -n
                have been estimated at a boundary point, or have been specified by the user,
                and do not appear in the correlation matrix )

                  alpha    intercept            v            k

      alpha           1     4.4e-008    -9.8e-008     7.2e-008

  intercept     4.4e-008            1        -0.57        -0.52

          v    -9.8e-008        -0.57            1        -0.23

          k     7.2e-008        -0.52        -0.23            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
           alpha          7.07394          1.36138            4.40568              9.7422
       intercept          28.9732          0.74996            27.5034             30.4431
               v         -5.02686          1.05086           -7.08651             -2.9672
               n                1               NA
               k          2.56203          2.11462           -1.58255             6.70661

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.



     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0    12       28.9           29         3.13         2.66        -0.0889
 1.04    10       27.9         27.5          2.5         2.66          0.495
3.471    10       25.2         26.1         3.21         2.66          -1.09
11.36    10         26         24.9         2.85         2.66           1.35
38.42    12       23.8         24.3         1.56         2.66         -0.602


 Model Descriptions for likelihoods calculated
```

```
Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
              A1          -77.952340           6     167.904680
              A2          -74.703868          10     169.407736
              A3          -77.952340           6     167.904680
          fitted          -79.823277           4     167.646555
               R          -89.824703           2     183.649405


                    Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value

  Test 1              30.2417          8       0.0001916
  Test 2              6.49694          4           0.165
  Test 3              6.49694          4           0.165
  Test 4              3.74187          2           0.154

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =             1

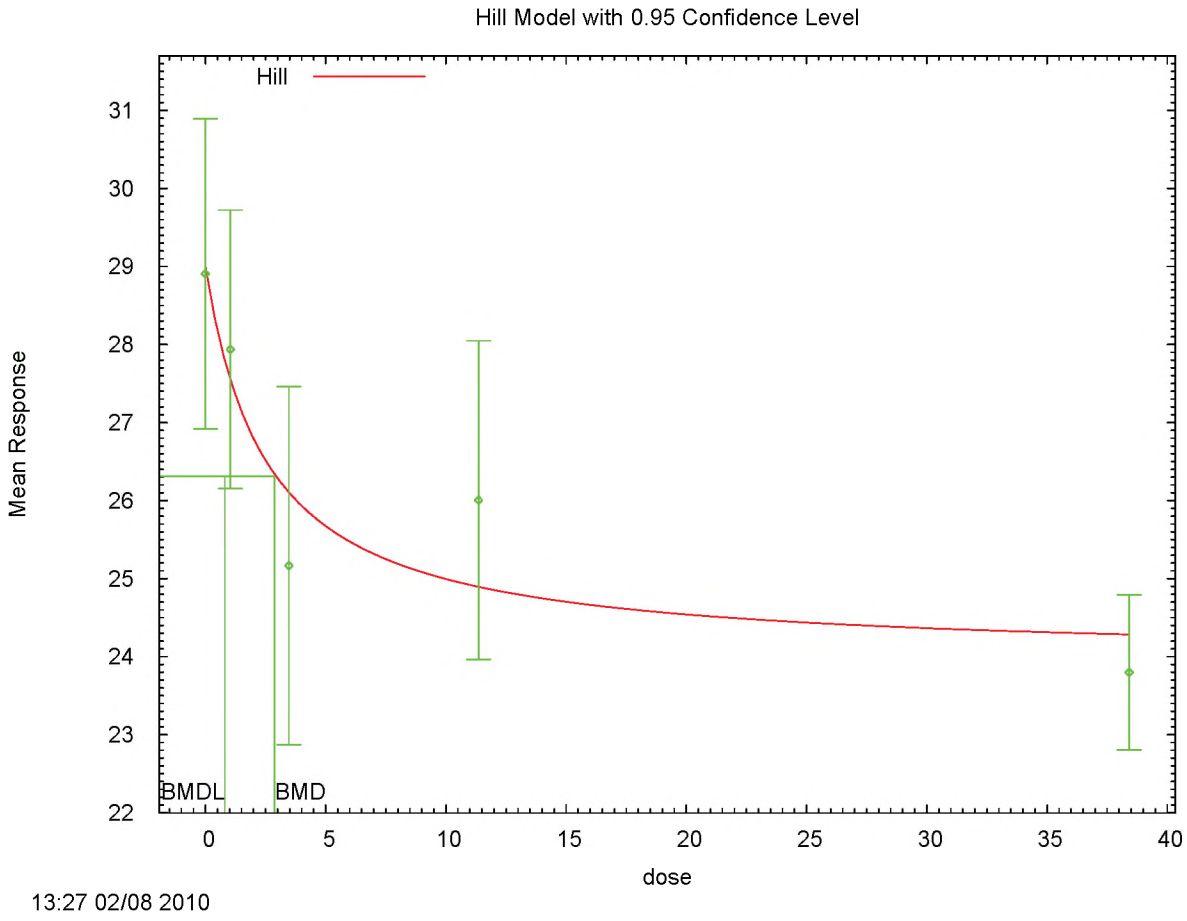
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =        2.87863

            BMDL =      0.802782
```

E.2.40.3. *Figure for Selected Model: Hill*



E.2.40.4. *Output for Additional Model Presented: Hill, Unrestricted*

Ohsako et al., 2001: Ano-Genital Length, PND 120

```
 ================================================================================
          Hill Model. (Version: 2.14;  Date: 06/26/2008)
          Input Data File: C:\1\Blood\56_Ohsako_2001_Anogen_HillCV_U_1.(d)
          Gnuplot Plotting File:  C:\1\Blood\56_Ohsako_2001_Anogen_HillCV_U_1.plt
                                                 Mon Feb 08 13:27:04 2010
 ================================================================================

 Figure 7
 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter is not restricted
   A constant variance model is fit
```

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

alpha =	7.27386	
rho =	0	Specified
intercept =	28.905	
v =	-5.1065	
n =	1.57046	
k =	2.4317	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	intercept	v	n	k
alpha	1	-3.1e-008	7.5e-009	1.7e-008	-8.8e-009
intercept	-3.1e-008	1	0.001	0.0016	-0.13
v	7.5e-009	0.001	1	0.98	-0.99
n	1.7e-008	0.0016	0.98	1	-0.97
k	-8.8e-009	-0.13	-0.99	-0.97	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	7.06192	1.35907	4.3982	9.72564
intercept	28.9618	0.754441	27.4831	30.4404
v	-6.82284	11.1104	-28.5989	14.9532
n	0.591421	1.04	-1.44695	2.62979
k	7.47064	48.002	-86.6115	101.553

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	12	28.9	29	3.13	2.66	-0.074
1.04	10	27.9	27.3	2.5	2.66	0.71
3.471	10	25.2	26.3	3.21	2.66	-1.36
11.36	10	26	25.1	2.85	2.66	1.04
38.42	12	23.8	24	1.56	2.66	-0.284

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)

```
           Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
      Model A3 uses any fixed variance parameters that
      were specified by the user

 Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1          -77.952340           6     167.904680
             A2          -74.703868          10     169.407736
             A3          -77.952340           6     167.904680
          fitted         -79.777354           5     169.554709
              R          -89.824703           2     183.649405


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              30.2417          8       0.0001916
   Test 2              6.49694          4           0.165
   Test 3              6.49694          4           0.165
   Test 4              3.65003          1         0.05607

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1.  You may want to try a different
model


        Benchmark Dose Computation

Specified effect =            1

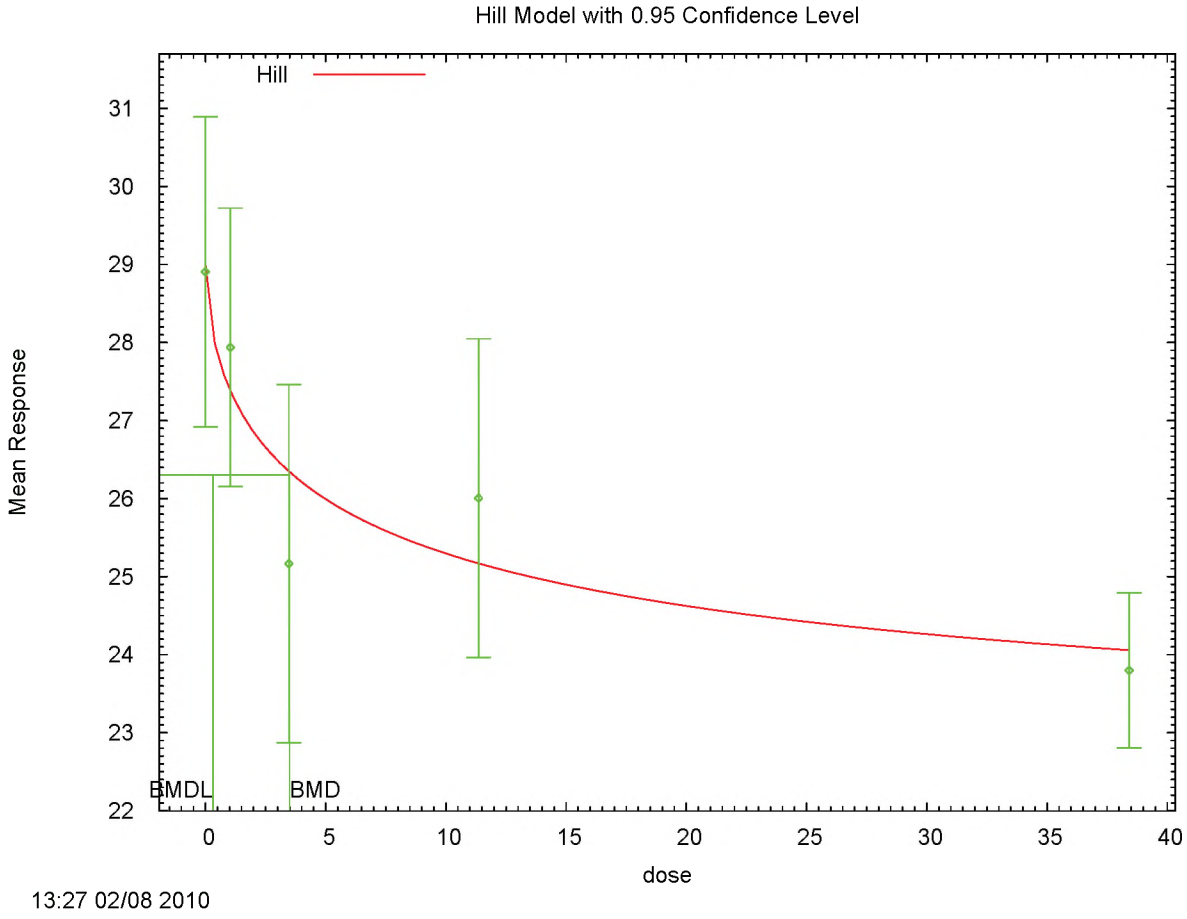
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =       3.49389

            BMDL =      0.304602
```

E.2.40.5. *Figure for Additional Model Presented: Hill, Unrestricted*



E.2.41. Sewall et al., 1995: T4 In Serum

E.2.41.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	3	0.722	204.495	1.869E+01	1.243E+01	
exponential (M3)	3	0.722	204.495	1.869E+01	1.243E+01	power hit bound (d = 1)
exponential (M4)	2	0.854	205.483	1.106E+01	4.650E+00	
exponential (M5)	2	0.854	205.483	1.106E+01	4.650E+00	power hit bound (d = 1)
Hill [b]	**2**	**0.898**	**205.382**	**1.031E+01**	**3.603E+00**	**n lower bound hit (n = 1)**
linear	3	0.576	205.150	2.238E+01	1.619E+01	
polynomial, 4-degree	3	0.576	205.150	2.238E+01	1.619E+01	
power	3	0.576	205.150	2.238E+01	1.619E+01	power bound hit (power = 1)
Hill, unrestricted [c]	1	0.864	207.196	9.706E+00	1.973E+00	unrestricted (n = 0.569)
power, unrestricted	2	0.985	205.197	9.726E+00	1.914E+00	unrestricted (power = 0.538)

[a] Constant variance model selected ($p = 0.4078$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.2.41.2. *Output for Selected Model: Hill*

Sewall et al., 1995: T4 In Serum

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\1\Blood\58_Sewall_1995_T4_HillCV_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\58_Sewall_1995_T4_HillCV_1.plt
                                          Mon Feb 08 13:28:15 2010
 ================================================================

 Figure 1, Saline noninitiated
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter restricted to be greater than 1
```

```
A constant variance model is fit

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                 Default Initial Parameter Values
                        alpha =      33.0913
                          rho =            0   Specified
                    intercept =      30.6979
                            v =     -12.2937
                            n =     0.950815
                            k =      12.5808


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho    -n
                have been estimated at a boundary point, or have been specified by the user,
                and do not appear in the correlation matrix )

                   alpha    intercept            v            k

      alpha            1    -1.2e-009    -1.8e-008     1.5e-008

  intercept    -1.2e-009            1          0.3        -0.65

          v    -1.8e-008          0.3            1        -0.89

          k     1.5e-008        -0.65        -0.89            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
           alpha          29.5556          6.23087             17.3433             41.7679
       intercept          30.3957          1.68747             27.0883             33.7031
               v         -18.2488          7.72836            -33.3961            -3.10154
               n                1               NA
               k          24.2883           26.743             -28.127             76.7035

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0       9       30.7         30.4         4.66         5.44          0.167
3.291       9       27.9         28.2         7.17         5.44         -0.188
7.107       9       25.9         26.3         6.81         5.44         -0.204
16.63       9       23.6           23         5.38         5.44          0.319
44.66       9       18.4         18.6         4.12         5.44        -0.0942


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
```

```
            Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = Sigma^2
        Model A3 uses any fixed variance parameters that
        were specified by the user

 Model  R:         Yi = Mu + e(i)
             Var{e(i)} = Sigma^2


                       Likelihoods of Interest

             Model      Log(likelihood)   # Param's      AIC
              A1          -98.583448           6     209.166896
              A2          -96.590204          10     213.180407
              A3          -98.583448           6     209.166896
           fitted         -98.691143           4     205.382286
               R         -109.013252           2     222.026503


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              24.8461          8        0.001651
   Test 2              3.98649          4          0.4078
   Test 3              3.98649          4          0.4078
   Test 4              0.21539          2          0.8979

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =             1

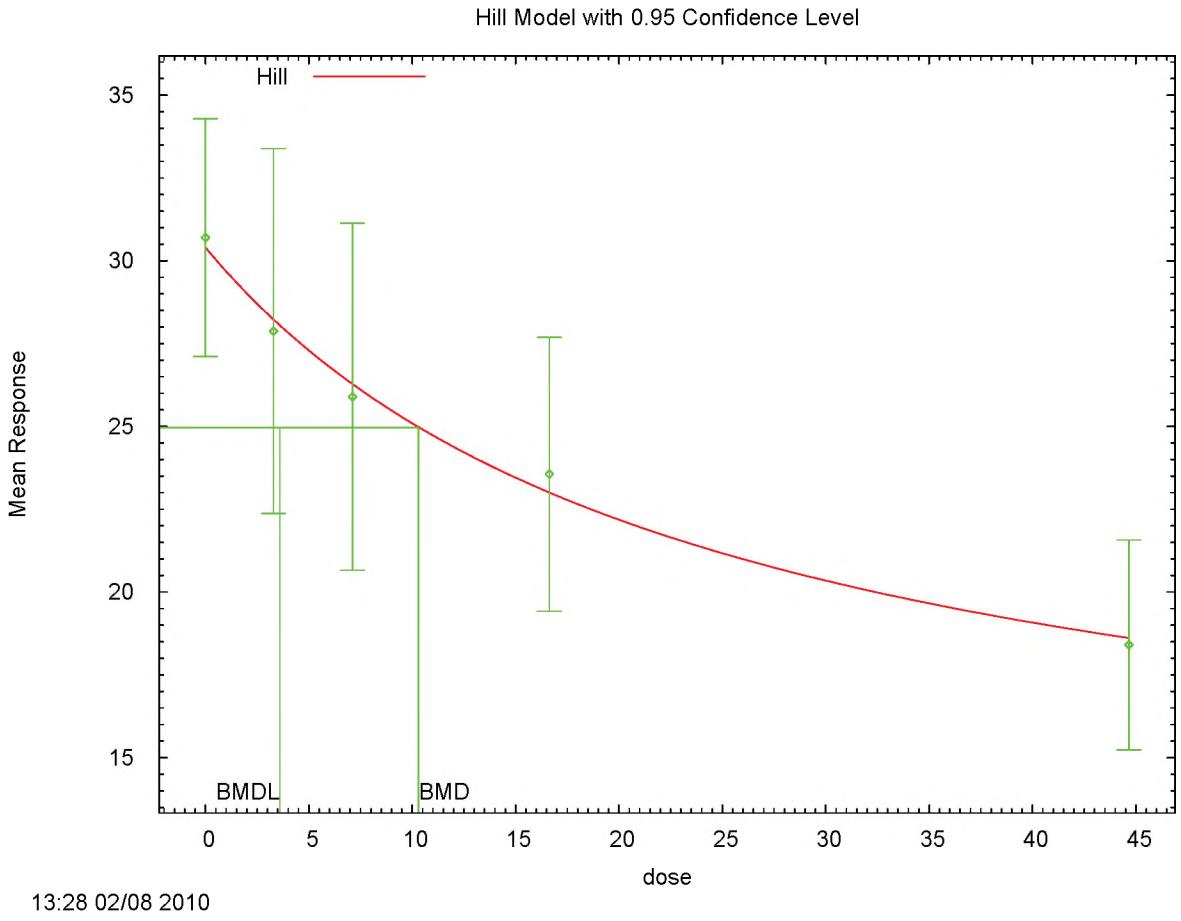
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =         10.306

            BMDL =       3.60269
```

E.2.41.3. *Figure for Selected Model: Hill*



E.2.41.4. *Output for Additional Model Presented: Hill, Unrestricted*

Sewall et al., 1995: T4 In Serum

```
 ================================================================================
          Hill Model. (Version: 2.14;  Date: 06/26/2008)
          Input Data File: C:\1\Blood\58_Sewall_1995_T4_HillCV_U_1.(d)
          Gnuplot Plotting File:  C:\1\Blood\58_Sewall_1995_T4_HillCV_U_1.plt
                                                 Mon Feb 08 13:28:15 2010
 ================================================================================

 Figure 1, Saline noninitiated
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter is not restricted
   A constant variance model is fit
```

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

alpha =	33.0913	
rho =	0	Specified
intercept =	30.6979	
v =	-12.2937	
n =	0.950815	
k =	12.5808	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	intercept	v	n	k
alpha	1	-3.9e-005	0.00022	0.00021	-0.00022
intercept	-3.9e-005	1	-0.17	-0.31	0.18
v	0.00022	-0.17	1	0.97	-1
n	0.00021	-0.31	0.97	1	-0.98
k	-0.00022	0.18	-1	-0.98	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	29.4337	6.20518	17.2718	41.5957
intercept	30.7096	1.79801	27.1855	34.2336
v	-143.244	3972.28	-7928.78	7642.29
n	0.569063	0.947248	-1.28751	2.42564
k	2856.29	171186	-332662	338374

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	9	30.7	30.7	4.66	5.43	-0.00646
3.291	9	27.9	27.7	7.17	5.43	0.0842
7.107	9	25.9	26.1	6.81	5.43	-0.134
16.63	9	23.6	23.4	5.38	5.43	0.0657
44.66	9	18.4	18.4	4.12	5.43	-0.00948

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)

```
            Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = Sigma^2
      Model A3 uses any fixed variance parameters that
      were specified by the user

 Model  R:         Yi = Mu + e(i)
             Var{e(i)} = Sigma^2


                        Likelihoods of Interest

             Model      Log(likelihood)   # Param's      AIC
               A1          -98.583448           6     209.166896
               A2          -96.590204          10     213.180407
               A3          -98.583448           6     209.166896
           fitted          -98.598183           5     207.196367
                R         -109.013252           2     222.026503


                     Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                       Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              24.8461          8        0.001651
   Test 2              3.98649          4          0.4078
   Test 3              3.98649          4          0.4078
   Test 4            0.0294713          1          0.8637

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =            1

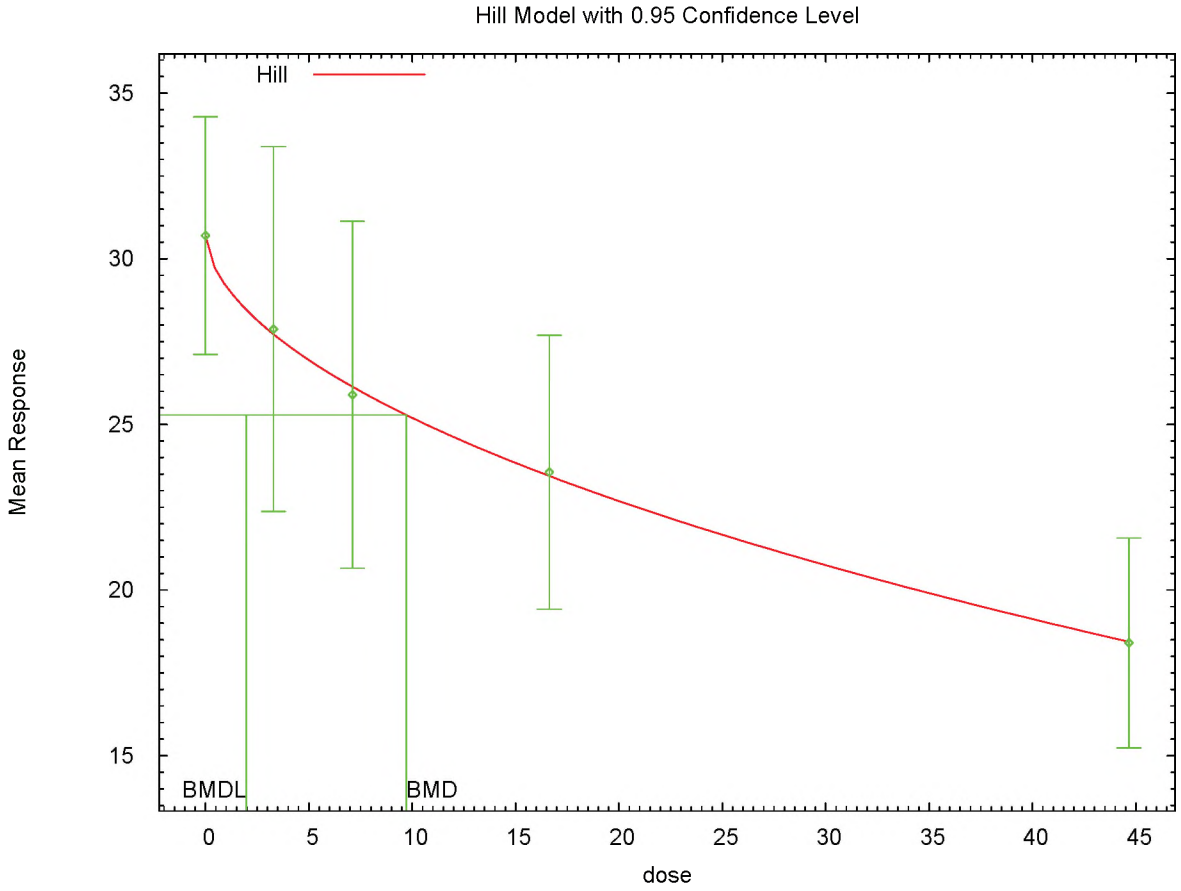
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =       9.70574

            BMDL =       1.97319
```

E.2.41.5. *Figure for Additional Model Presented: Hill, Unrestricted*



E.2.42. Shi et al., 2007: Estradiol 17B, PE9

E.2.42.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	3	0.010	391.638	6.976E+00	3.761E+00	
exponential (M3)	3	0.010	391.638	6.976E+00	3.761E+00	power hit bound (d = 1)
exponential (M4) [b]	**2**	**0.690**	**382.969**	**8.068E-01**	**3.544E-01**	
exponential (M5)	2	0.690	382.969	8.068E-01	3.544E-01	power hit bound (d = 1)
Hill	2	0.975	382.278	7.239E-01	error	n lower bound hit (n = 1)
linear	3	0.003	394.308	9.841E+00	6.687E+00	
polynomial, 4-degree	3	0.003	394.308	9.841E+00	6.687E+00	
power	3	0.003	394.308	9.841E+00	6.687E+00	power bound hit (power = 1)
Hill, unrestricted	1	0.897	384.243	7.086E-01	error	unrestricted (n = 0.875)
power, unrestricted	2	0.506	383.590	6.280E-01	3.304E-02	unrestricted (power = 0.222)

[a] Non-constant variance model selected ($p = 0.0521$)

[b] Best-fitting model, BMDS output presented in this appendix

E.2.42.2. *Output for Selected Model: Exponential (M4)*

Shi et al., 2007: Estradiol 17B, PE9

```
=============================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\Blood\59_Shi_2007_Estradiol_Exp_1.(d)
        Gnuplot Plotting File:
                                                  Mon Feb 08 13:28:52 2010
=============================================================================

 Figure 4 PE9 only
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.
```

```
   Model 2 is nested within Models 3 and 4.
   Model 3 is nested within Model 5.
   Model 4 is nested within Model 5.


Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


                Initial Parameter Values

                Variable          Model 4
                --------          --------
                  lnalpha            2.65881
                      rho            0.913414
                        a                 108
                        b            0.277637
                        c            0.340136
                        d                   1



                  Parameter Estimates

                 Variable          Model 4
                 --------          -------
                  lnalpha            1.66773
                      rho            1.15314
                        a            103.146
                        b            1.00685
                        c           0.418742
                        d                  1


         Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0     10        102.9        41.41
 0.3418      10        86.19        19.58
 1.075     10        63.33        29.36
  5.23     10         48.1        18.82
 13.91     10        38.57        22.59


              Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
      0         103.1        33.35         -0.02738
 0.3418         85.69        29.96          0.05296
  1.075         63.51        25.21         -0.02238
   5.23          43.5        20.27           0.7167
  13.91         43.19        20.19          -0.7237


Other models for which likelihoods are calculated:
```

```
  Model A1:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
              Var{e(ij)} = Sigma^2


                              Likelihoods of Interest

                    Model      Log(likelihood)      DF         AIC
                    -------    -----------------    ----   ------------
                       A1       -188.3615           6      388.7231
                       A2        -183.667          10      387.3339
                       A3       -186.1132           7      386.2263
                        R       -203.3606           2      410.7211
                        4       -186.4844           5      382.9687


Additive constant for all log-likelihoods =     -45.95.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.


                               Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)


                           Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                         39.39           8            < 0.0001
  Test 2                         9.389           4             0.05208
  Test 3                         4.892           3              0.1798
 Test 6a                        0.7424           2              0.6899


  The p-value for Test 1 is less than .05.  There appears to be a
  difference between response and/or variances among the dose
  levels, it seems appropriate to model the data.

  The p-value for Test 2 is less than .1.  A non-homogeneous
  variance model appears to be appropriate.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 6a is greater than .1.  Model 4 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 1.000000

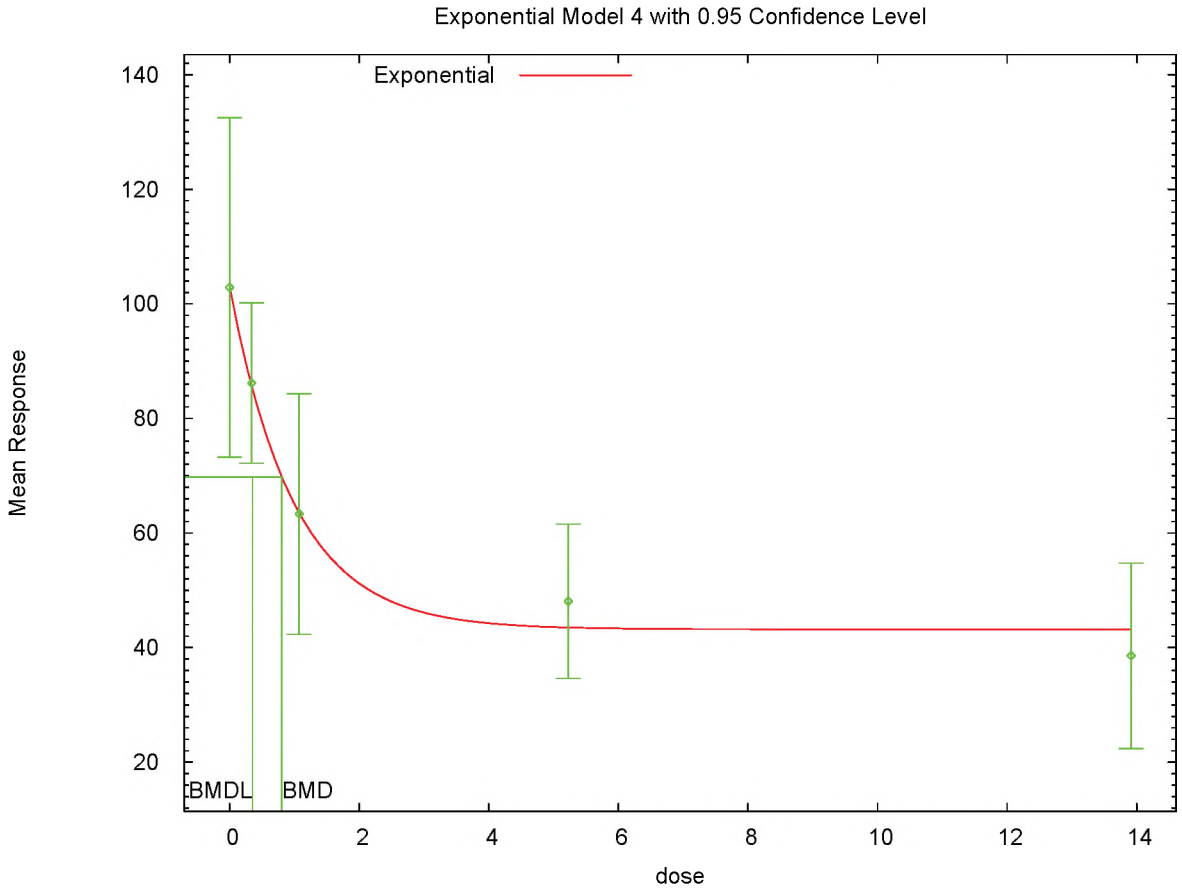
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000
```

BMD = 0.806817

BMDL = 0.354366

E.2.42.3. *Figure for Selected Model: Exponential (M4)*



13:28 02/08 2010

E.2.43. Smialowicz et al., 2008: PFC per 10^6 Cells

E.2.43.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	3	0.101	901.897	8.343E+00	5.064E+00	
exponential (M3)	3	0.101	901.897	8.343E+00	5.064E+00	power hit bound (d = 1)
exponential (M4)	2	0.044	903.897	8.325E+00	1.465E+00	
exponential (M5)	2	0.044	903.897	8.325E+00	1.465E+00	power hit bound (d = 1)
Hill	2	0.063	903.192	3.669E+00	6.970E-01	n lower bound hit (n = 1)
linear	3	0.048	903.585	1.373E+01	1.053E+01	
polynomial, 4-degree	3	0.048	903.585	1.374E+01	1.053E+01	
power	3	0.048	903.585	1.373E+01	1.053E+01	power bound hit (power = 1)
Hill, unrestricted	1	0.213	901.219	1.928E+00	2.208E-01	unrestricted (n = 0.35)
power, unrestricted [b]	**2**	**0.481**	**899.130**	**1.902E+00**	**2.158E-01**	**unrestricted (power = 0.333)**

[a] Constant variance model selected (p = <0.0001)

[b] Best-fitting model, BMDS output presented in this appendix

E.2.43.2. *Output for Selected Model: Power, Unrestricted*

Smialowicz et al., 2008: PFC per 10^6 Cells

```
 ================================================================
          Power Model. (Version: 2.15;  Date: 04/07/2008)
          Input Data File: C:\1\Blood\60_Smial_2008_PFCcells_PwrCV_U_1.(d)
          Gnuplot Plotting File:  C:\1\Blood\60_Smial_2008_PFCcells_PwrCV_U_1.plt
                                          Mon Feb 08 13:29:38 2010
 ================================================================

 Anti Response to SRBCs, PFC per 10to6 cells, Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   The power is not restricted
   A constant variance model is fit
```

```
Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                         alpha =       232385
                           rho =            0   Specified
                       control =         1491
                         slope =     -491.716
                         power =     0.288021


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been specified by the user,
                and do not appear in the correlation matrix )

                  alpha      control        slope        power

    alpha             1    -3.4e-009     1.8e-009    -1.2e-010

  control    -3.4e-009            1        -0.82        -0.65

    slope     1.8e-009        -0.82            1         0.94

    power    -1.2e-010        -0.65         0.94            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         alpha           219793          37974.5             145365              294222
       control          1470.48           123.73            1227.98             1712.99
         slope         -378.406          157.002           -686.125            -70.6872
         power         0.333124         0.113501           0.110666            0.555581


      Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0    15  1.49e+003    1.47e+003          716          469          0.169
0.438    14  1.13e+003    1.18e+003          171          469         -0.431
2.464    15        945          959          516          469          -0.12
 13.4    15        677          572          465          469          0.867
31.65     8        161          274          117          469         -0.684


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
```

```
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1         -444.832859           6     901.665718
             A2         -425.402825          10     870.805651
             A3         -444.832859           6     901.665718
          fitted        -445.564823           4     899.129647
              R         -463.753685           2     931.507371


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              76.7017          8          <.0001
   Test 2              38.8601          4          <.0001
   Test 3              38.8601          4          <.0001
   Test 4              1.46393          2           0.481

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  Consider running a
non-homogeneous variance model

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


               Benchmark Dose Computation

Specified effect =             1

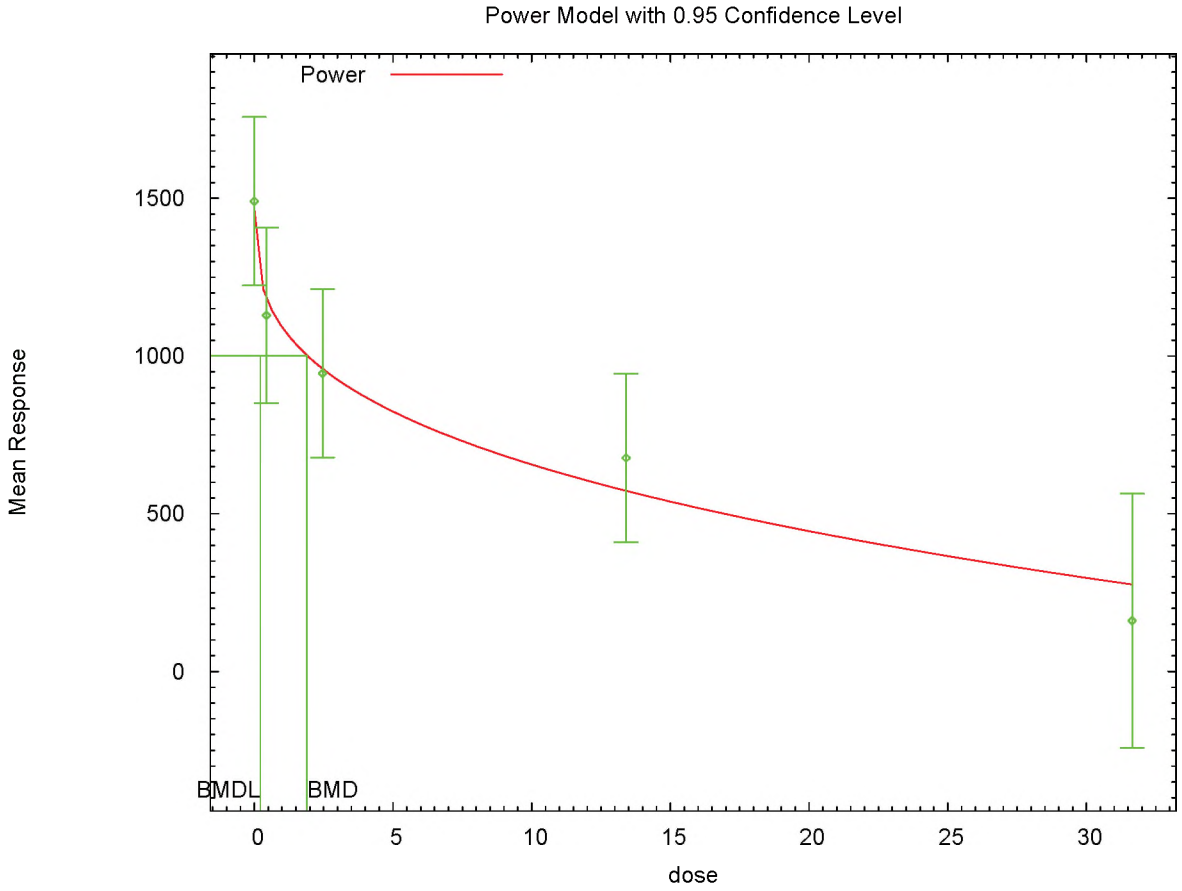
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 1.90249


            BMDL = 0.215843
```

E.2.43.3. *Figure for Selected Model: Power, Unrestricted*



E.2.44. Smialowicz et al., 2008: PFC per Spleen

E.2.44.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	3	0.124	377.565	1.334E+01	8.593E+00	
exponential (M3)	2	0.069	379.138	1.536E+01	8.895E+00	
exponential (M4)	3	0.124	377.565	1.334E+01	8.593E+00	
exponential (M5)	1	0.021	381.138	1.536E+01	8.895E+00	
Hill	2	0.116	378.108	1.568E+01	error	n lower bound hit (n = 1)
linear	3	0.126	377.522	2.055E+01	1.624E+01	
polynomial, 4-degree	3	0.126	377.522	2.055E+01	1.624E+01	
power	3	0.126	377.522	2.055E+01	1.624E+01	power bound hit (power = 1)
Hill, unrestricted	1	0.103	378.463	1.202E+01	error	unrestricted (n = 0.544)
power, unrestricted [b]	**2**	**0.270**	**376.420**	**1.187E+01**	**3.762E+00**	**unrestricted (power = 0.531)**

[a] Non-constant variance model selected ($p = 0.0011$)

[b] Best-fitting model, BMDS output presented in this appendix

E.2.44.2. *Output for Selected Model: Power, Unrestricted*

Smialowicz et al., 2008: PFC per Spleen

```
 ======================================================================
          Power Model. (Version: 2.15;  Date: 04/07/2008)
          Input Data File: C:\1\Blood\61_Smial_2008_PFCspleen_Pwr_U_1.(d)
          Gnuplot Plotting File:  C:\1\Blood\61_Smial_2008_PFCspleen_Pwr_U_1.plt
                                                Mon Feb 08 13:30:16 2010
 ======================================================================

 Anti Response to SRBCs - PFC x 10 to the 4 per spleen, Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   The power is not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)
```

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	4.76607
rho =	0
control =	27.8
slope =	-9.21898
power =	0.286443

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	control	slope	power
lalpha	1	-0.98	0.25	-0.28	-0.22
rho	-0.98	1	-0.3	0.28	0.22
control	0.25	-0.3	1	-0.83	-0.74
slope	-0.28	0.28	-0.83	1	0.99
power	-0.22	0.22	-0.74	0.99	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	0.746922	1.02058	-1.25337	2.74721
rho	1.36826	0.355827	0.67085	2.06567
control	25.3816	2.96691	19.5666	31.1967
slope	-3.5662	2.52558	-8.51626	1.38385
power	0.531216	0.175728	0.186796	0.875637

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	15	27.8	25.4	13.4	13.3	0.706
0.438	14	21	23.1	13.6	12.4	-0.626
2.464	15	17.6	19.6	9.4	11.1	-0.704
13.4	15	12.6	11.2	8.7	7.6	0.702
31.65	8	3	3.03	3.1	3.1	-0.0313

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that
were specified by the user

```
Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                       Likelihoods of Interest

           Model      Log(likelihood)   # Param's      AIC
            A1         -190.565019           6     393.130038
            A2         -181.476284          10     382.952569
            A3         -181.900030           7     377.800059
         fitted        -183.210137           5     376.420274
             R         -204.636496           2     413.272993


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              46.3204          8          <.0001
   Test 2              18.1775          4        0.001139
   Test 3              0.84749          3          0.8381
   Test 4              2.62021          2          0.2698

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


               Benchmark Dose Computation

Specified effect =            1

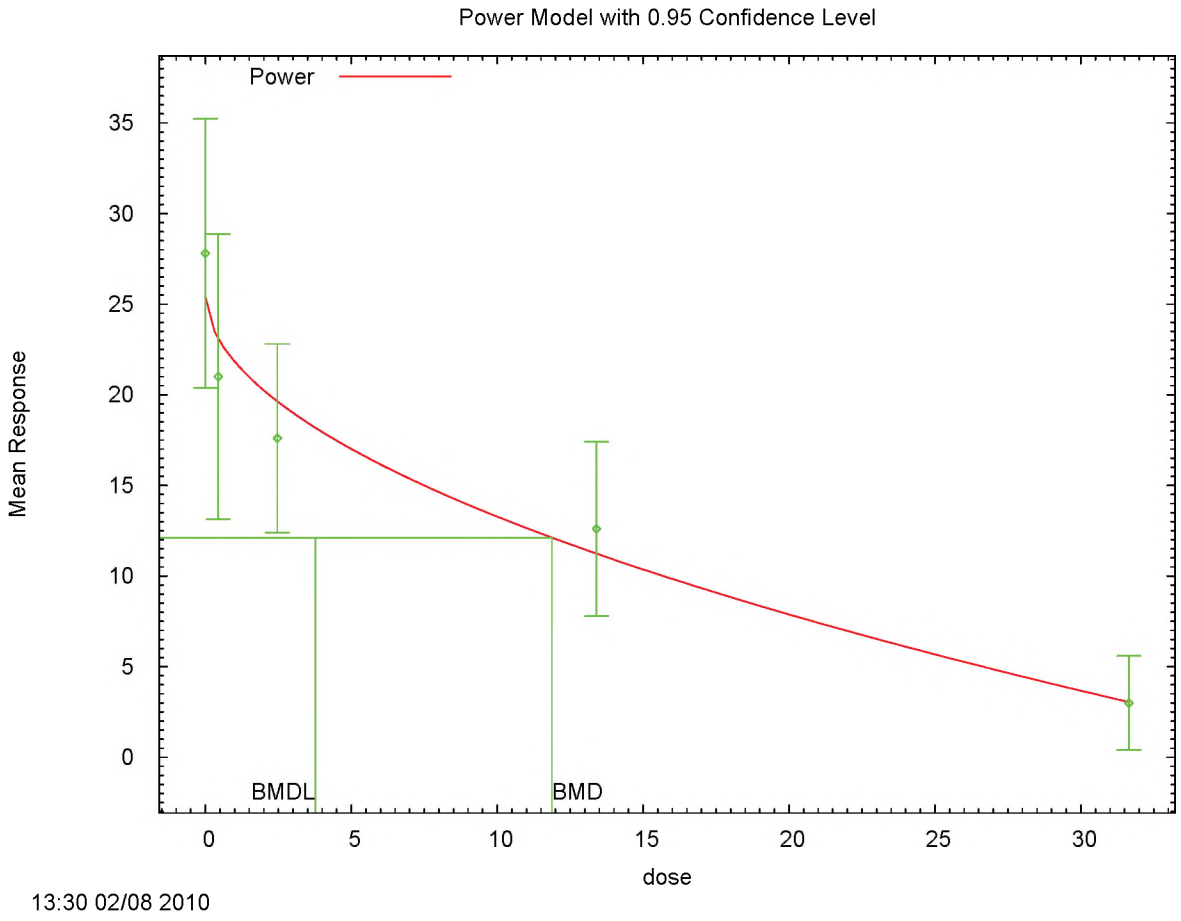
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 11.8748


            BMDL = 3.76161
```

E.2.44.3. *Figure for Selected Model: Power, Unrestricted*



E.2.45. Toth et al., 1979: Amyloidosis

E.2.45.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
gamma	2	0.040	149.120	1.965E+01	1.283E+01	power bound hit (power = 1)
logistic	2	0.019	151.340	3.701E+01	2.858E+01	negative intercept (intercept = -2.16)
log-logistic [a]	**2**	**0.053**	**148.269**	**1.503E+01**	**8.747E+00**	**slope bound hit (slope = 1)**
log-probit	2	0.009	152.855	3.782E+01	2.502E+01	slope bound hit (slope = 1)
multistage, 3-degree	2	0.040	149.120	1.965E+01	1.283E+01	final ß = 0
probit	2	0.021	151.115	3.467E+01	2.657E+01	negative intercept (intercept = -1.276)
Weibull	2	0.040	149.120	1.965E+01	1.283E+01	power bound hit (power = 1)
gamma, unrestricted	2	0.959	140.119	4.349E-01	2.891E-03	unrestricted (power = 0.254)
log-logistic, unrestricted [b]	2	0.903	140.240	4.843E-01	5.312E-03	unrestricted (slope = 0.326)
log-probit, unrestricted	2	0.870	140.315	4.960E-01	7.292E-03	unrestricted (slope = 0.186)
Weibull, unrestricted	2	0.933	140.174	4.641E-01	4.069E-03	unrestricted (power = 0.289)

[a] Best-fitting model, BMDS output presented in this appendix

[b] Alternate model, BMDS output also presented in this appendix

E.2.45.2. *Output for Selected Model: Log-Logistic*

Toth et al., 1979: Amyloidosis

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\1\Blood\62_Toth_1979_Amylyr_LogLogistic_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\62_Toth_1979_Amylyr_LogLogistic_1.plt
                                                Mon Feb 08 13:30:54 2010
 ================================================================

 Table 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
```

```
    Slope parameter is restricted as slope >= 1

    Total number of observations = 4
    Total number of records with missing values = 0
    Maximum number of iterations = 250
    Relative Function Convergence has been set to: 1e-008
    Parameter Convergence has been set to: 1e-008



    User has chosen the log transformed model


                  Default Initial Parameter Values
                     background =            0
                      intercept =     -4.54593
                          slope =            1


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -slope
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

             background    intercept

background            1        -0.49

 intercept        -0.49            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background        0.0699918            *               *                   *
      intercept         -4.90704            *               *                   *
          slope                1            *               *                   *

* - Indicates that this value is not calculated.



                         Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -68.017         4
   Fitted model        -72.1346         2       8.23525      2         0.01628
  Reduced model        -82.0119         1         27.99      3         <.0001

           AIC:         148.269


                                 Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------
    0.0000     0.0700         2.660     0.000          38       -1.691
    0.5732     0.0739         3.252     5.000          44        1.007
   14.2123     0.1584         6.971    10.000          44        1.251
   91.2070     0.4446        19.117    17.000          43       -0.650

 Chi^2 = 5.86      d.f. = 2        P-value = 0.0534


   Benchmark Dose Computation

Specified effect =           0.1
```

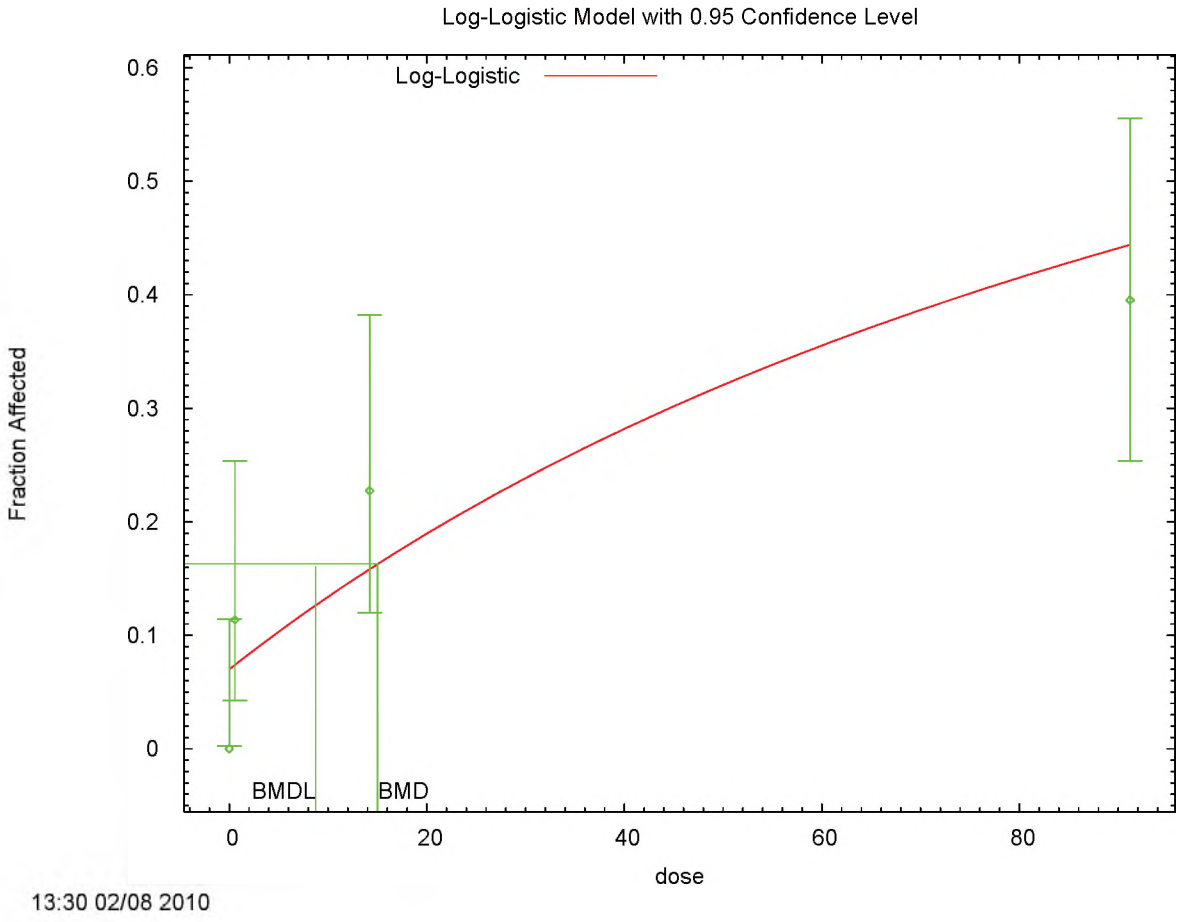
```
Risk Type          =      Extra risk

Confidence level =           0.95

              BMD =        15.0264

             BMDL =        8.74665
```

E.2.45.3. *Figure for Selected Model: Log-Logistic*



E.2.45.4. *Output for Additional Model Presented: Log-Logistic, Unrestricted*

Toth et al., 1979: Amyloidosis

```
 ========================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\1\Blood\62_Toth_1979_Amy1yr_LogLogistic_U_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\62_Toth_1979_Amy1yr_LogLogistic_U_1.plt
                                                Mon Feb 08 13:30:54 2010
 ========================================================================

 Table 2
 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
```

```
The form of the probability function is:

P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


Dependent variable = DichEff
Independent variable = Dose
Slope parameter is not restricted

Total number of observations = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



User has chosen the log transformed model


                Default Initial Parameter Values
                   background =            0
                    intercept =     -1.92722
                        slope =     0.314472


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -background
                have been estimated at a boundary point, or have been specified by the user,
                and do not appear in the correlation matrix )

             intercept        slope

 intercept            1        -0.84

     slope        -0.84            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background                0            *               *                   *
      intercept         -1.96073            *               *                   *
          slope         0.326156            *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -68.017         4
   Fitted model        -68.1201         2      0.206341      2           0.902
  Reduced model        -82.0119         1         27.99      3         <.0001

          AIC:          140.24


                                Goodness  of  Fit
                                                                    Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
 ----------------------------------------------------------------------
   0.0000     0.0000         0.000     0.000          38        0.000
   0.5732     0.1051         4.623     5.000          44        0.186
  14.2123     0.2507        11.029    10.000          44       -0.358
  91.2070     0.3802        16.348    17.000          43        0.205
```

```
 Chi^2 = 0.20      d.f. = 2        P-value = 0.9028


   Benchmark Dose Computation

Specified effect =            0.1

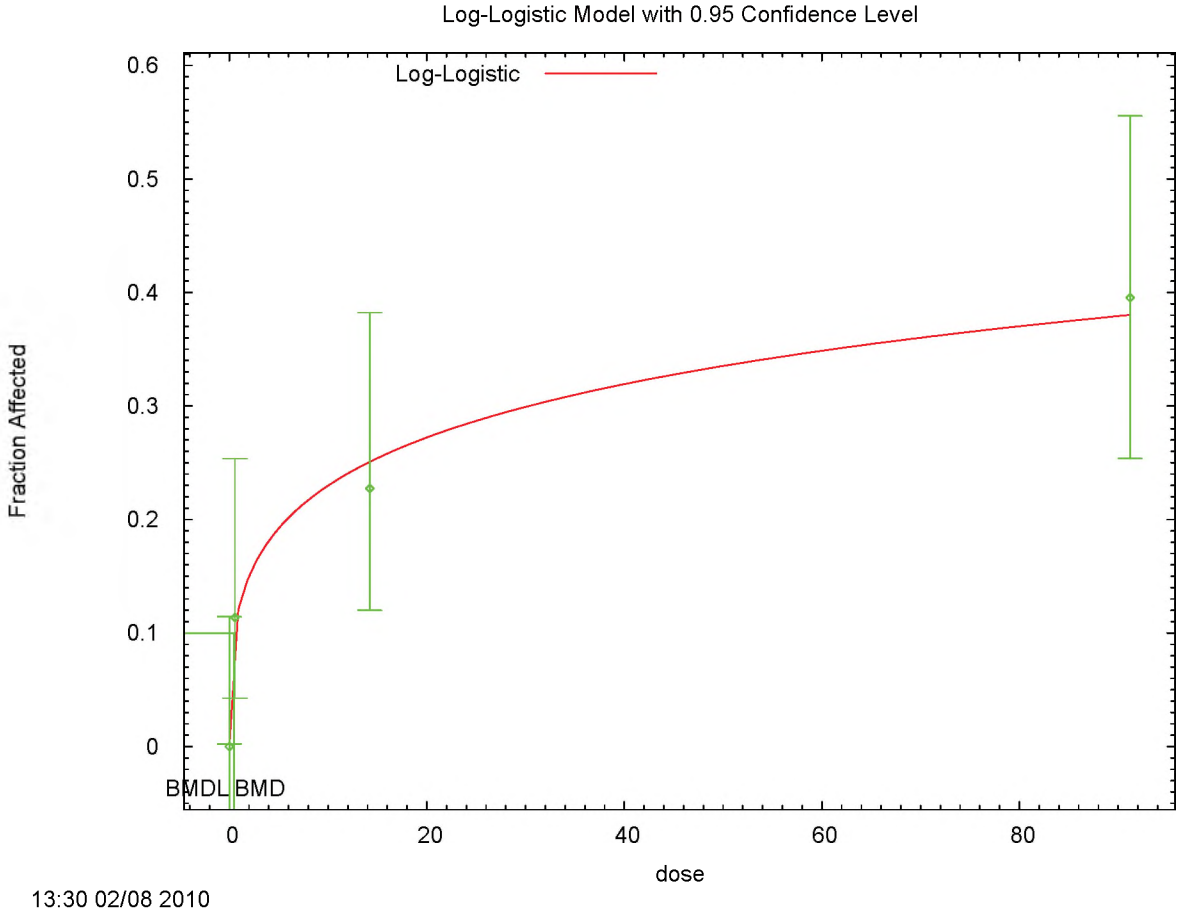
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.484272

            BMDL =     0.00531211
```

E.2.45.5. *Figure for Additional Model Presented: Log-Logistic, Unrestricted*



E.2.46. Toth et al., 1979: Skin Lesions

E.2.46.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
gamma	2	0.032	156.346	1.037E+01	7.470E+00	power bound hit (power = 1)
logistic	2	0.005	161.421	2.487E+01	1.982E+01	negative intercept (intercept = -1.999)
log-logistic [a]	**2**	**0.078**	**153.963**	**6.413E+00**	**4.025E+00**	**slope bound hit (slope = 1)**
log-probit	2	0.003	161.788	1.887E+01	1.280E+01	slope bound hit (slope = 1)
multistage, 3-degree	2	0.032	156.346	1.037E+01	7.470E+00	final ß = 0
probit	2	0.006	160.991	2.309E+01	1.858E+01	negative intercept (intercept = -1.198)
Weibull	2	0.032	156.346	1.037E+01	7.470E+00	power bound hit (power = 1)
gamma, unrestricted	2	0.945	147.148	error	error	unrestricted (power = 0.341)
log-logistic, unrestricted [b]	2	0.744	147.631	5.969E-01	6.773E-02	unrestricted (slope = 0.48)
log-probit, unrestricted	2	0.670	147.844	5.939E-01	8.147E-02	unrestricted (slope = 0.279)
Weibull, unrestricted	2	0.866	147.324	5.539E-01	5.181E-02	unrestricted (power = 0.405)

[a] Best-fitting model, BMDS output presented in this appendix

[b] Alternate model, BMDS output also presented in this appendix

E.2.46.2. *Output for Selected Model: Log-Logistic*

Toth et al., 1979: Skin Lesions

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\1\Blood\63_Toth_1979_SkinLes_LogLogistic_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\63_Toth_1979_SkinLes_LogLogistic_1.plt
                                              Wed Feb 10 14:47:53 2010
 ================================================================

 Table 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
```

```
   Slope parameter is restricted as slope >= 1

   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =            0
                     intercept =     -3.94312
                         slope =            1


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -slope
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

             background    intercept

background            1        -0.43

 intercept        -0.43            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background        0.0564562            *               *                   *
      intercept         -4.05558            *               *                   *
          slope                1            *               *                   *

* - Indicates that this value is not calculated.



                         Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -71.5177         4
   Fitted model         -74.9813         2       6.92722      2         0.03132
  Reduced model         -95.8498         1       48.6642      3         <.0001

           AIC:          153.963


                                  Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size        Residual
   ---------------------------------------------------------------------
    0.0000     0.0565         2.145     0.000          38        -1.508
    0.5732     0.0657         2.892     5.000          44         1.282
   14.2123     0.2429        10.687    13.000          44         0.813
   91.2070     0.6343        27.275    25.000          43        -0.720

 Chi^2 = 5.10      d.f. = 2        P-value = 0.0782


   Benchmark Dose Computation

Specified effect =           0.1
```

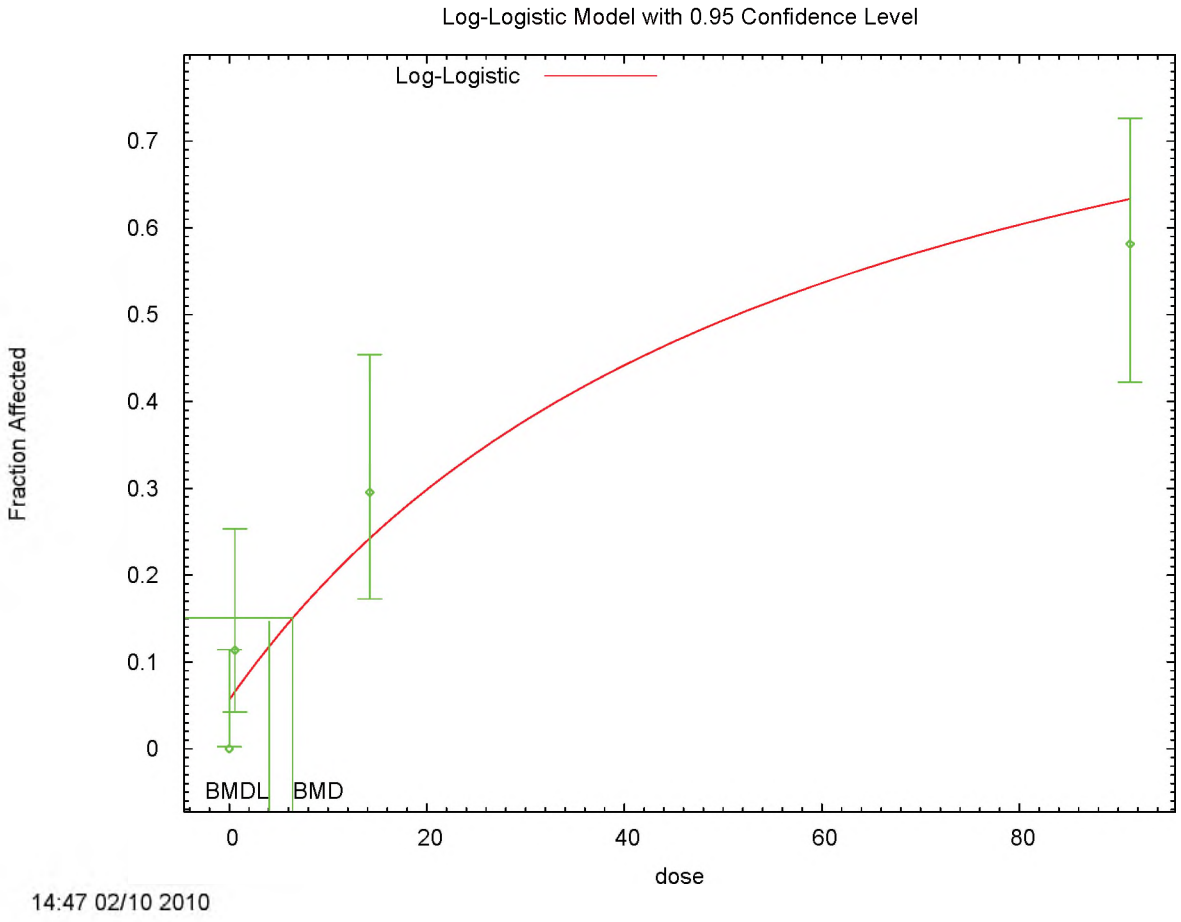
```
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =         6.4132

            BMDL =         4.0249
```

E.2.46.3. *Figure for Selected Model: Log-Logistic*



E.2.46.4. *Output for Additional Model Presented: Log-Logistic, Unrestricted*

Toth et al., 1979: Skin Lesions

```
================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\Blood\63_Toth_1979_SkinLes_LogLogistic_U_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\63_Toth_1979_SkinLes_LogLogistic_U_1.plt
                                          Wed Feb 10 14:47:54 2010
================================================================

Table 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
```

The form of the probability function is:

P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]

Dependent variable = DichEff
Independent variable = Dose
Slope parameter is not restricted

Total number of observations = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial Parameter Values
background = 0
intercept = -1.87608
slope = 0.458888

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -background
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	intercept	slope
intercept	1	-0.86
slope	-0.86	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0	*	*	*
intercept	-1.94946	*	*	*
slope	0.4802	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-71.5177	4			
Fitted model	-71.8153	2	0.59526	2	0.7426
Reduced model	-95.8498	1	48.6642	3	<.0001

AIC: 147.631

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	38	0.000
0.5732	0.0983	4.323	5.000	44	0.343
14.2123	0.3374	14.845	13.000	44	-0.588
91.2070	0.5542	23.832	25.000	43	0.358

```
 Chi^2 = 0.59      d.f. = 2        P-value = 0.7438


   Benchmark Dose Computation

Specified effect =           0.1

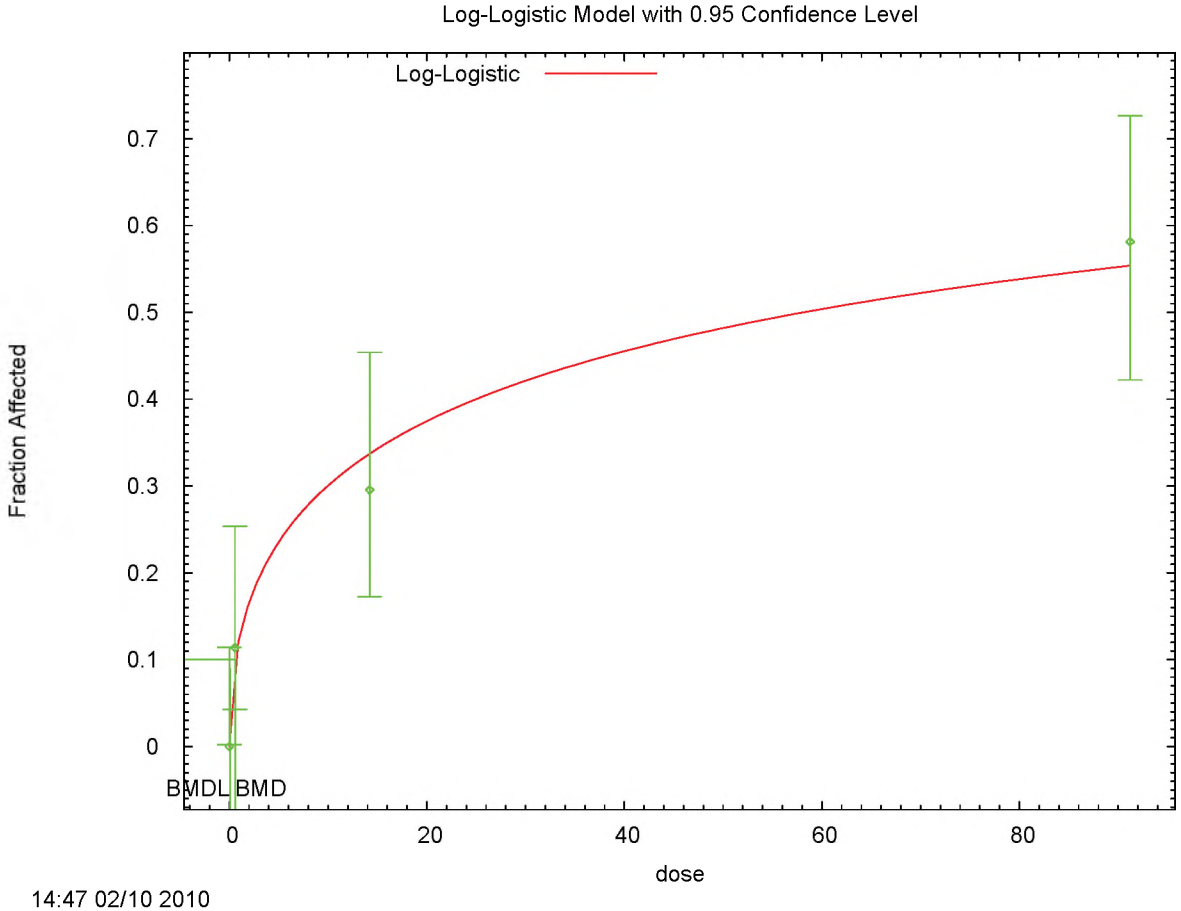
Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =      0.596932

            BMDL =       0.06773
```

E.2.46.5. *Figure for Additional Model Presented: Log-Logistic, Unrestricted*



E.2.47. Van Birgelen et al., 1995a: Hepatic Retinol

E.2.47.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	4	<0.0001	159.735	7.790E+00	4.150E+00	
exponential (M3)	4	<0.0001	3222.700	5.542E+01	error	power hit bound (d = 1)
exponential (M4) [b]	**3**	**<0.001**	**141.454**	**2.488E+01**	**3.363E+00**	
exponential (M5)	3	<0.001	141.454	2.488E+01	3.363E+00	power hit bound (d = 1)
Hill	3	0.239	124.865	5.316E+00	error	n lower bound hit (n = 1)
linear	4	<0.0001	176.828	1.877E+02	1.437E+02	
polynomial, 5-degree	4	<0.0001	176.828	1.877E+02	1.437E+02	
power	4	<0.0001	176.828	1.877E+02	1.437E+02	power bound hit (power = 1)
Hill, unrestricted	2	0.241	125.495	3.595E+00	error	unrestricted (n = 0.763)
power, unrestricted [c]	3	0.011	131.771	3.802E-01	1.393E-02	unrestricted (power = 0.14)

[a] Non-constant variance model selected (p = <0.0001)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.2.47.2. *Output for Selected Model: Exponential (M4)*

Van Birgelen et al., 1995a: Hepatic Retinol

```
 ================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\1\Blood\65_VanB_1995a_HepRet_Exp_1.(d)
         Gnuplot Plotting File:
                                                Mon Feb 08 13:32:00 2010
 ================================================================

 Tbl3, hepatic retinol
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
```

```
      sign = -1 for decreasing trend.

   Model 2 is nested within Models 3 and 4.
   Model 3 is nested within Model 5.
   Model 4 is nested within Model 5.


Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


              Initial Parameter Values

              Variable          Model 4
              --------          --------
                lnalpha            -1.16065
                    rho             1.53688
                      a              15.645
                      b           0.0254351
                      c           0.0365247
                      d                   1



                Parameter Estimates

               Variable          Model 4
               --------          -------
                lnalpha           -0.92683
                    rho            1.77262
                      a            11.5049
                      b          0.0286598
                      c          0.0653043
                      d                  1


        Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0      8         14.9        8.768
  7.204      8          8.4        3.394
  11.76      8          8.2        2.263
  18.09      8          5.1       0.8485
  86.41      8          2.2       0.8485
  250.2      8          0.6       0.5657


              Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
      0          11.5        5.483            1.751
  7.204         9.499        4.627          -0.6719
  11.76         8.428        4.161          -0.1552
  18.09         7.154        3.599           -1.615
  86.41         1.655       0.9832            1.568
  250.2        0.7596       0.4931          -0.9155
```

Other models for which likelihoods are calculated:

```
  Model A1:        Yij = Mu(i) + e(ij)
                Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
                Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
                Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
                Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-87.1567	7	188.3134
A2	-47.28742	12	118.5748
A3	-55.32422	8	126.6484
R	-109.967	2	223.934
4	-65.72714	5	141.4543

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	125.4	10	< 0.0001
Test 2	79.74	5	< 0.0001
Test 3	16.07	4	0.002922
Test 6a	20.81	3	0.0001155

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

The p-value for Test 3 is less than .1. You may want to consider a different variance model.

The p-value for Test 6a is less than .1. Model 4 may not adequately describe the data; you may want to consider another model.

Benchmark Dose Computations:

Specified Effect = 1.000000

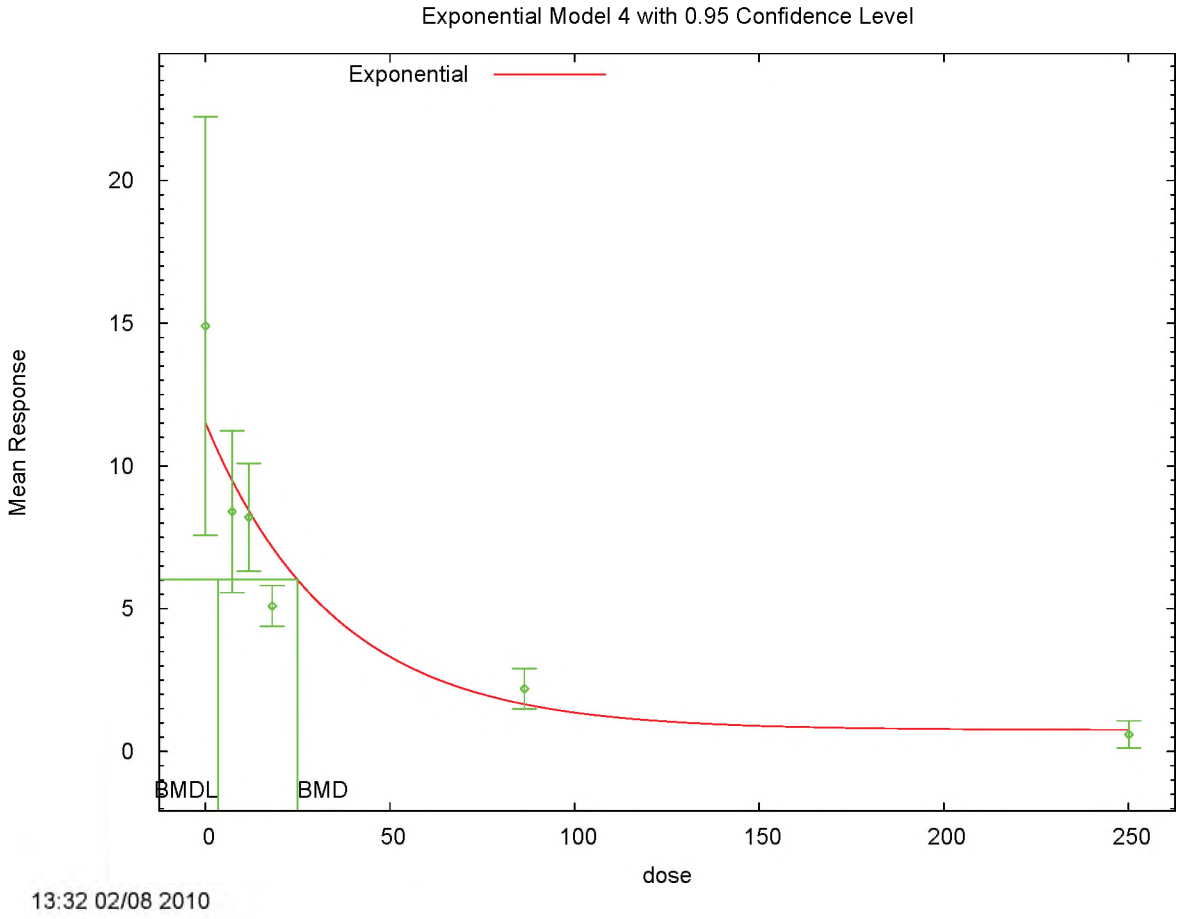
```
            Risk Type = Estimated standard deviations from control

      Confidence Level = 0.950000

                   BMD =      24.8811

                  BMDL =      3.36281
```

E.2.47.3. *Figure for Selected Model: Exponential (M4)*



E.2.47.4. *Output for Additional Model Presented: Power, Unrestricted*

Van Birgelen et al., 1995a: Hepatic Retinol

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\1\Blood\65_VanB_1995a_HepRet_Pwr_U_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\65_VanB_1995a_HepRet_Pwr_U_1.plt
                                              Mon Feb 08 13:32:03 2010
 ================================================================

 Tbl3, hepatic retinol
 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
```

The form of the response function is:

Y[dose] = control + slope * dose^power

Dependent variable = Mean
Independent variable = Dose
The power is not restricted
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	2.76506
rho =	0
control =	14.9
slope =	-3.98831
power =	0.231232

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	control	slope	power
lalpha	1	-0.8	-0.042	0.038	0.063
rho	-0.8	1	-0.089	0.0044	-0.1
control	-0.042	-0.089	1	-0.95	-0.81
slope	0.038	0.0044	-0.95	1	0.95
power	0.063	-0.1	-0.81	0.95	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-0.986251	0.394722	-1.75989	-0.212609
rho	1.67858	0.202896	1.28091	2.07625
control	16.9266	2.23237	12.5513	21.302
slope	-7.51118	2.04379	-11.5169	-3.50543
power	0.139871	0.0269576	0.0870351	0.192707

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	14.9	16.9	8.77	6.56	-0.874
7.204	8	8.4	7.03	3.39	3.14	1.24
11.76	8	8.2	6.32	2.26	2.87	1.85
18.09	8	5.1	5.67	0.849	2.62	-0.611
86.41	8	2.2	2.91	0.849	1.5	-1.34
250.2	8	0.6	0.666	0.566	0.434	-0.427

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
              A1          -87.156698           7     188.313395
              A2          -47.287416          12     118.574833
              A3          -55.324218           8     126.648436
          fitted          -60.885746           5     131.771493
               R         -109.967018           2     223.934036


                   Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value

  Test 1              125.359         10          <.0001
  Test 2              79.7386          5          <.0001
  Test 3              16.0736          4        0.002922
  Test 4              11.1231          3         0.01108

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

The p-value for Test 4 is less than .1.  You may want to try a different
model


               Benchmark Dose Computation

Specified effect =             1

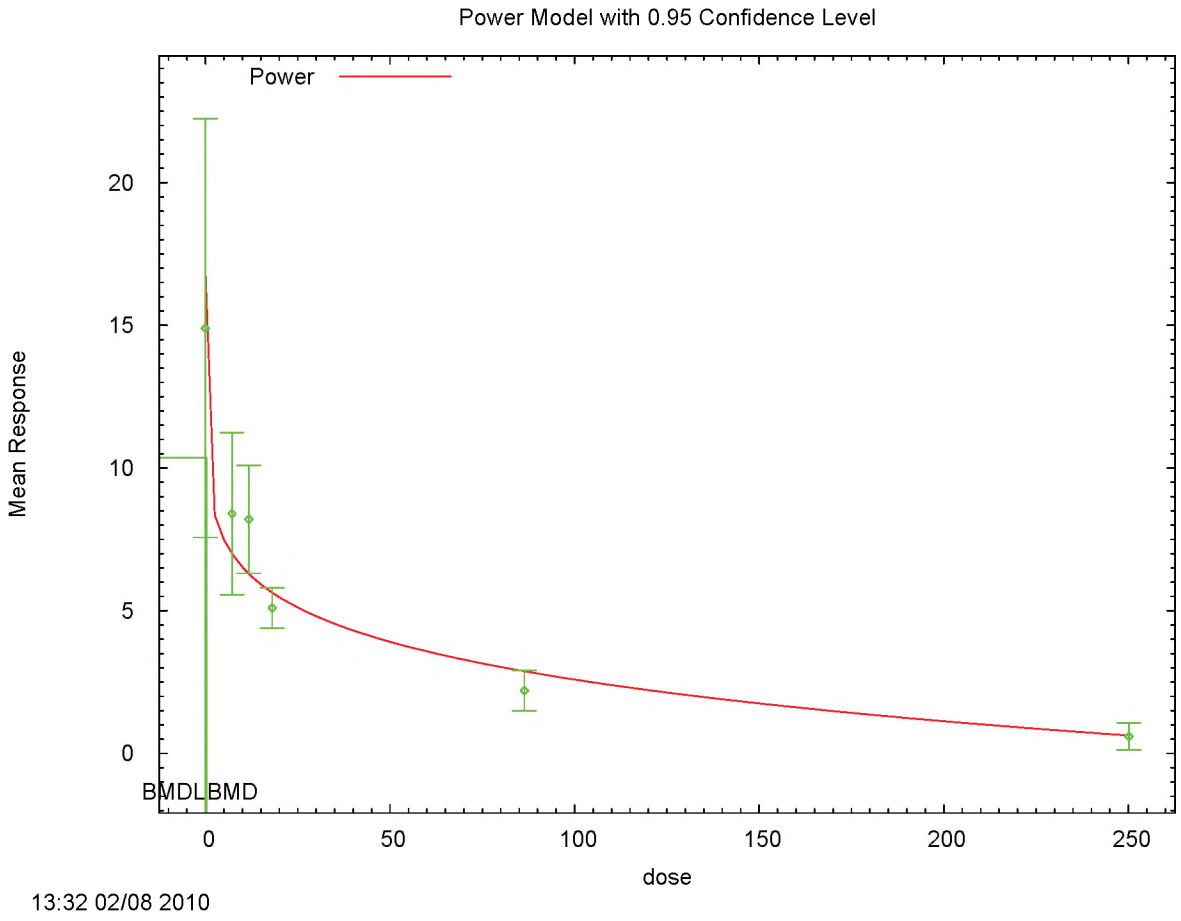
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 0.380208


             BMDL = 0.013927
```

E.2.47.5. *Figure for Additional Model Presented: Power, Unrestricted*



E.2.48. Van Birgelen et al., 1995a: Hepatic Retinol Palmitate

E.2.48.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	4	<0.0001	460.282	error	error	
exponential (M3)	4	<0.0001	460.282	error	error	power hit bound (d = 1)
exponential (M4) [b]	**3**	**<0.0001**	**446.995**	**1.415E+02**	**3.647E+01**	
exponential (M5)	3	<0.0001	446.995	1.415E+02	3.647E+01	power hit bound (d = 1)
Hill	3	0.009	416.233	3.657E+00	error	n lower bound hit (n = 1)
linear	4	<0.0001	486.375	3.487E+02	2.412E+02	
polynomial, 5-degree	0	N/A	584.170	error	5.617E+02	
power	4	<0.0001	486.375	3.487E+02	2.412E+02	power bound hit (power = 1)
Hill, unrestricted	3	<0.0001	527.310	6.875E-14	6.875E-14	unrestricted (n = 0.613)
power, unrestricted [c]	3	0.239	408.982	5.262E-02	5.889E-05	unrestricted (power = 0.064)

[a] Non-constant variance model selected (*p* = <0.0001)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.2.48.2. *Output for Selected Model: Exponential (M4)*

Van Birgelen et al., 1995a: Hepatic Retinol Palmitate

```
 ================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\1\Blood\66_VanB_1995a_HepRetPalm_Exp_1.(d)
         Gnuplot Plotting File:
                                                 Mon Feb 08 13:32:41 2010
 ================================================================

 Tbl3, hepatic retinol palmitate
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
```

```
      sign = -1 for decreasing trend.

   Model 2 is nested within Models 3 and 4.
   Model 3 is nested within Model 5.
   Model 4 is nested within Model 5.


Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


              Initial Parameter Values

              Variable          Model 4
              --------          --------
                lnalpha          0.284674
                    rho           1.77158
                      a             495.6
                      b         0.0337826
                      c        0.00576502
                      d                 1


                Parameter Estimates

               Variable          Model 4
               --------          -------
                lnalpha         -0.241601
                    rho           2.03456
                      a           223.848
                      b         0.0300737
                      c         0.0129253
                      d                 1

  NC = No Convergence


        Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0      8           472        271.5
  7.204      8            94        67.88
  11.76      8           107        76.37
  18.09      8            74         39.6
  86.41      8            22        22.63
  250.2      8             3        2.828


              Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
  ------    ----------    ---------    ----------------
      0         223.8        217.8            3.222
  7.204         180.8        175.3           -1.401
  11.76           158        152.9          -0.9443
  18.09         131.1        126.4           -1.278
  86.41         19.33        18.03           0.4197
```

```
  250.2         3.013        2.721         -0.01317


Other models for which likelihoods are calculated:

  Model A1:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
              Var{e(ij)} = Sigma^2


                            Likelihoods of Interest

                  Model      Log(likelihood)      DF         AIC
                 -------    -----------------    ----   ------------
                     A1       -250.5548           7      515.1096
                     A2       -196.7557          12      417.5115
                     A3       -197.3832           8      410.7663
                      R       -276.7896           2      557.5793
                      4       -218.4977           5      446.9954


Additive constant for all log-likelihoods =     -44.11.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.


                              Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)


                          Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                      160.1            10           < 0.0001
  Test 2                      107.6             5           < 0.0001
  Test 3                      1.255             4              0.869
 Test 6a                      42.23             3           < 0.0001


  The p-value for Test 1 is less than .05.  There appears to be a
  difference between response and/or variances among the dose
  levels, it seems appropriate to model the data.

  The p-value for Test 2 is less than .1.  A non-homogeneous
  variance model appears to be appropriate.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 6a is less than .1.  Model 4 may not adequately
  describe the data; you may want to consider another model.


Benchmark Dose Computations:
```

```
Specified Effect = 1.000000

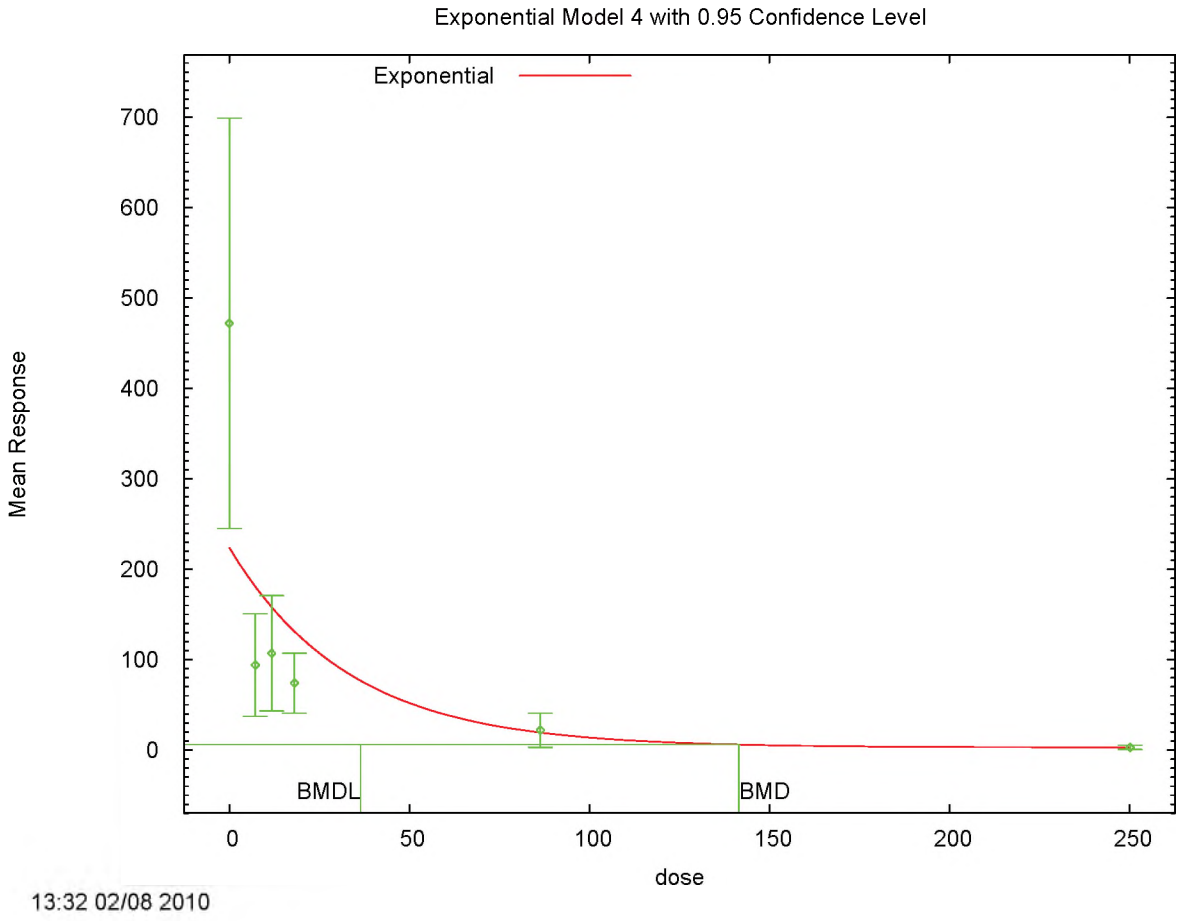
        Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

             BMD =      141.528

            BMDL =      36.4721
```

E.2.48.3. *Figure for Selected Model: Exponential (M4)*



E.2.48.4. *Output for Additional Model Presented: Power, Unrestricted*

Van Birgelen et al., 1995a: Hepatic Retinol Palmitate

```
================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\Blood\66_VanB_1995a_HepRetPalm_Pwr_U_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\66_VanB_1995a_HepRetPalm_Pwr_U_1.plt
                                          Mon Feb 08 13:32:47 2010
================================================================

Tbl3, hepatic retinol palmitate
```

~~~~~~

The form of the response function is:

Y[dose] = control + slope * dose^power

Dependent variable = Mean
Independent variable = Dose
The power is not restricted
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	9.57332
rho =	0
control =	472
slope =	-320.514
power =	0.0711173

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	control	slope	power
lalpha	1	-0.95	0.3	-0.31	-0.3
rho	-0.95	1	-0.41	0.39	0.29
control	0.3	-0.41	1	-0.98	-0.82
slope	-0.31	0.39	-0.98	1	0.9
power	-0.3	0.29	-0.82	0.9	1

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
lalpha	0.0640168	0.859472	-1.62052	1.74855
rho	1.81132	0.197468	1.42429	2.19835
control	464.29	87.5705	292.655	635.925
slope	-324.216	83.3327	-487.545	-160.887
power	0.0639088	0.0139778	0.0365129	0.0913048

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	472	464	272	269	0.0812
7.204	8	94	96.5	67.9	64.7	-0.108
11.76	8	107	84.8	76.4	57.6	1.09
18.09	8	74	74.2	39.6	51	-0.00941
86.41	8	22	33.2	22.6	24.6	-1.28
250.2	8	3	2.86	2.83	2.68	0.145
~~~~~~

```
Model Descriptions for likelihoods calculated


Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
              A1         -250.554817           7     515.109634
              A2         -196.755746          12     417.511491
              A3         -197.383174           8     410.766347
          fitted         -199.490808           5     408.981615
               R         -276.789644           2     557.579287


                   Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              160.068         10          <.0001
   Test 2              107.598          5          <.0001
   Test 3              1.25486          4           0.869
   Test 4              4.21527          3          0.2391

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


               Benchmark Dose Computation

Specified effect =             1

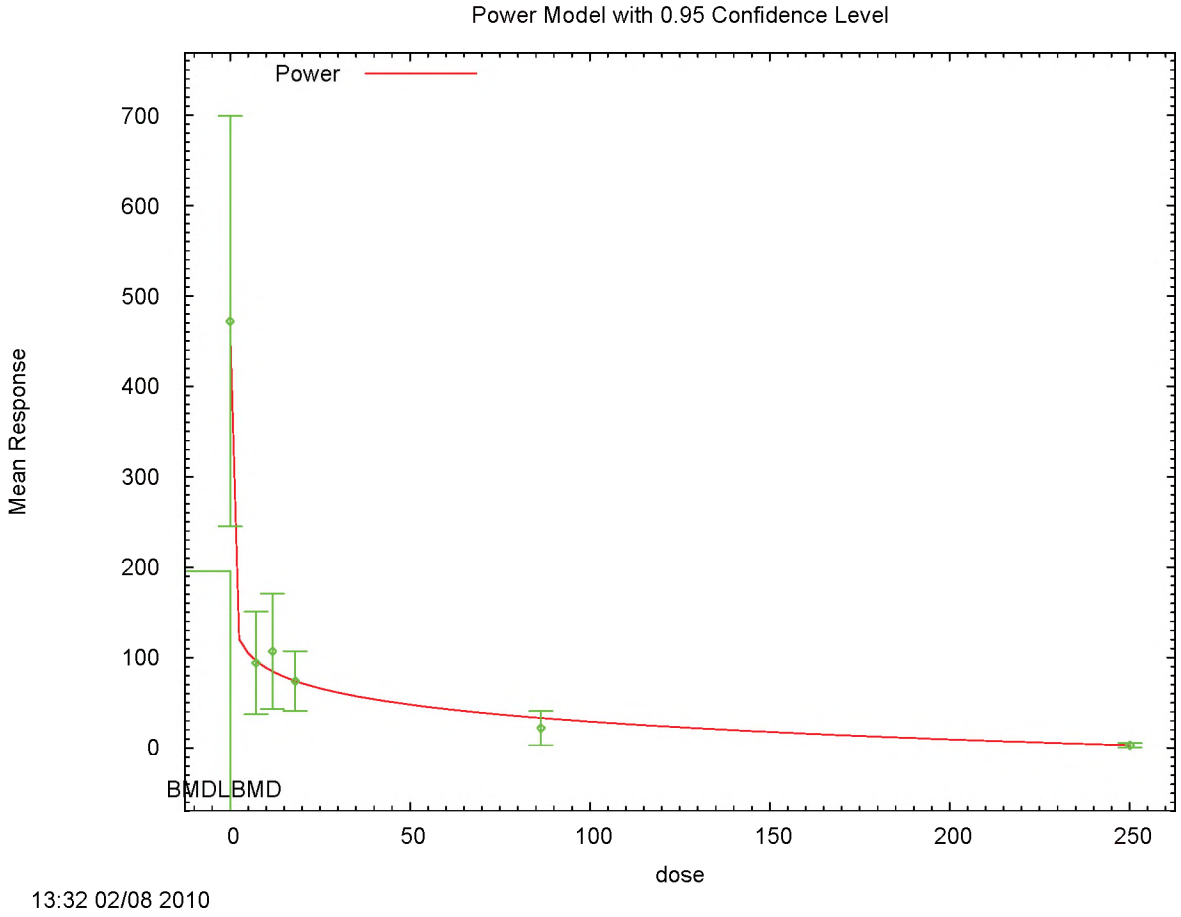
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 0.0526247
```

BMDL = 5.88883e-005

E.2.48.5. *Figure for Additional Model Presented: Power, Unrestricted*



E.2.49. White et al., 1986: CH50

E.2.49.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	5	0.002	389.664	1.957E+01	1.261E+01	
exponential (M3)	5	0.002	389.664	1.957E+01	1.261E+01	power hit bound (d = 1)
exponential (M4)	4	0.001	390.632	1.411E+01	5.177E+00	
exponential (M5)	4	0.001	390.632	1.411E+01	5.177E+00	power hit bound (d = 1)
Hill [b]	**4**	**0.002**	**389.601**	**8.632E+00**	**1.498E+00**	**n lower bound hit (n = 1)**
linear	5	<0.001	394.446	3.497E+01	2.568E+01	
polynomial, 6-degree	5	<0.001	394.446	3.497E+01	2.568E+01	
power	5	<0.001	394.446	3.497E+01	2.568E+01	power bound hit (power = 1)
Hill, unrestricted [c]	3	0.071	381.520	1.481E-01	4.351E-03	unrestricted (n = 0.246)
power, unrestricted	4	0.148	379.265	1.211E-01	1.225E-03	unrestricted (power = 0.227)

[a] Non-constant variance model selected ($p = 0.0871$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.2.49.2. *Output for Selected Model: Hill*

White et al., 1986: CH50

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\1\Blood\71_White_1986_CH50_Hill_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\71_White_1986_CH50_Hill_1.plt
                                                Mon Feb 08 13:35:56 2010
 ================================================================

 [insert study notes]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   Power parameter restricted to be greater than 1
```

```
The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

Total number of dose groups = 7
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                       lalpha =      5.60999
                          rho =            0
                    intercept =           91
                            v =          -74
                            n =     0.118036
                            k =        1.094


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -n
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

                 lalpha          rho    intercept            v            k

    lalpha            1        -0.99         0.27         0.23        -0.32

       rho        -0.99            1        -0.28        -0.24         0.33

 intercept         0.27        -0.28            1         0.39        -0.78

         v         0.23        -0.24         0.39            1        -0.85

         k        -0.32         0.33        -0.78        -0.85            1


                                 Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha            4.581          1.66273            1.32211             7.83989
            rho          0.31293         0.431616          -0.533022             1.15888
      intercept          74.6365          6.33673            62.2167             87.0562
              v         -66.2096          14.7876           -95.1928            -37.2264
              n                1               NA
              k          20.8286          21.3237             -20.965             62.6223

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     8         91         74.6         14.1         19.4           2.39
1.094     8         54         71.3         8.49         19.3          -2.54
4.085     8         63         63.8         11.3         18.9         -0.117
 7.14     8         56         57.7         25.5         18.6         -0.263
26.81     8         41         37.4           17         17.4          0.589
48.72     8         32         28.3           17         16.7          0.636
90.56     8         17         20.8           17         15.9         -0.678
```

```
Model Descriptions for likelihoods calculated


Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
              A1         -181.340979           8     378.681959
              A2         -175.820265          14     379.640529
              A3         -181.238690           9     380.477380
          fitted         -189.800288           5     389.600575
               R         -212.367055           2     428.734109


                    Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              73.0936         12          <.0001
   Test 2              11.0414          6          0.0871
   Test 3              10.8369          5         0.05471
   Test 4              17.1232          4        0.001829

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

The p-value for Test 4 is less than .1.  You may want to try a different
model


        Benchmark Dose Computation

Specified effect =             1

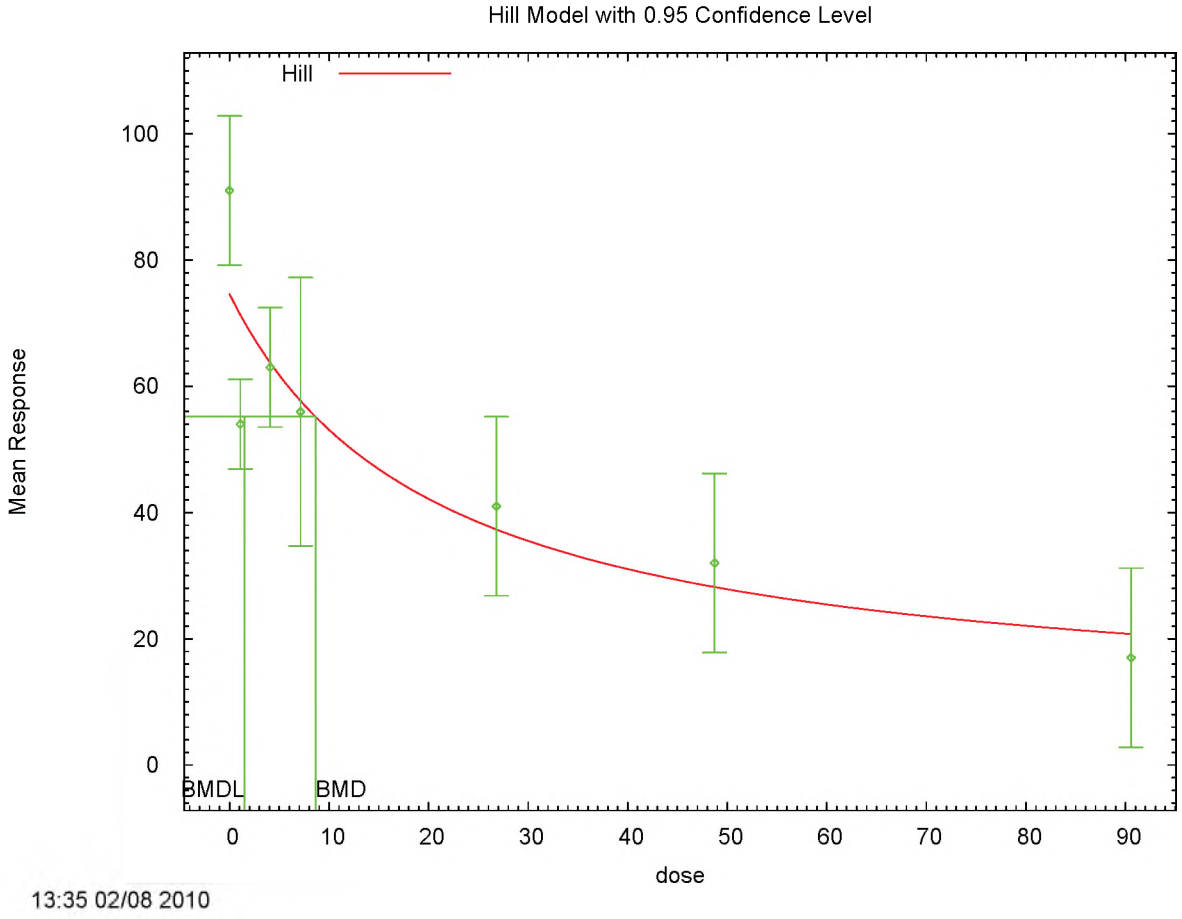
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =       8.63239
```

```
BMDL =        1.49823
```

E.2.49.3. *Figure for Selected Model: Hill*



E.2.49.4. *Output for Additional Model Presented: Hill, Unrestricted*

White et al., 1986: CH50

```
=============================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\Blood\71_White_1986_CH50_Hill_U_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\71_White_1986_CH50_Hill_U_1.plt
                                                Mon Feb 08 13:35:57 2010
=============================================================================

[insert study notes]

  The form of the response function is:

  Y[dose] = intercept + v*dose^n/(k^n + dose^n)


  Dependent variable = Mean
```

Independent variable = Dose
Power parameter is not restricted
The variance is to be modeled as Var(i) = exp(lalpha + rho * ln(mean(i)))

Total number of dose groups = 7
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	5.60999
rho =	0
intercept =	91
v =	-74
n =	0.118036
k =	1.094

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	intercept	v	n	k
lalpha	1	-1	0.16	0.19	-0.4	-0.014
rho	-1	1	-0.16	-0.19	0.4	0.011
intercept	0.16	-0.16	1	0.15	-0.58	0.015
v	0.19	-0.19	0.15	1	-0.02	-0.93
n	-0.4	0.4	-0.58	-0.02	1	-0.35
k	-0.014	0.011	0.015	-0.93	-0.35	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	6.54093	2.08879	2.44698	10.6349
rho	-0.245847	0.541645	-1.30745	0.815757
intercept	89.6302	5.59428	78.6656	100.595
v	-628.486	727.973	-2055.29	798.315
n	0.246409	0.058636	0.131484	0.361333
k	493877	2.74838e+006	-4.89284e+006	5.88059e+006

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	91	89.6	14.1	15.1	0.256
1.094	8	54	65.2	8.49	15.8	-2.01
4.085	8	63	56.3	11.3	16	1.17
7.14	8	56	51.7	25.5	16.2	0.746
26.81	8	41	38.3	17	16.8	0.453
48.72	8	32	30.9	17	17.3	0.175
90.56	8	17	22.3	17	18	-0.831

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
              A1         -181.340979           8     378.681959
              A2         -175.820265          14     379.640529
              A3         -181.238690           9     380.477380
          fitted         -184.759769           6     381.519538
               R         -212.367055           2     428.734109


                    Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value

  Test 1              73.0936         12          <.0001
  Test 2              11.0414          6          0.0871
  Test 3              10.8369          5         0.05471
  Test 4              7.04216          3         0.07057

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

The p-value for Test 4 is less than .1.  You may want to try a different
model


        Benchmark Dose Computation

Specified effect =             1

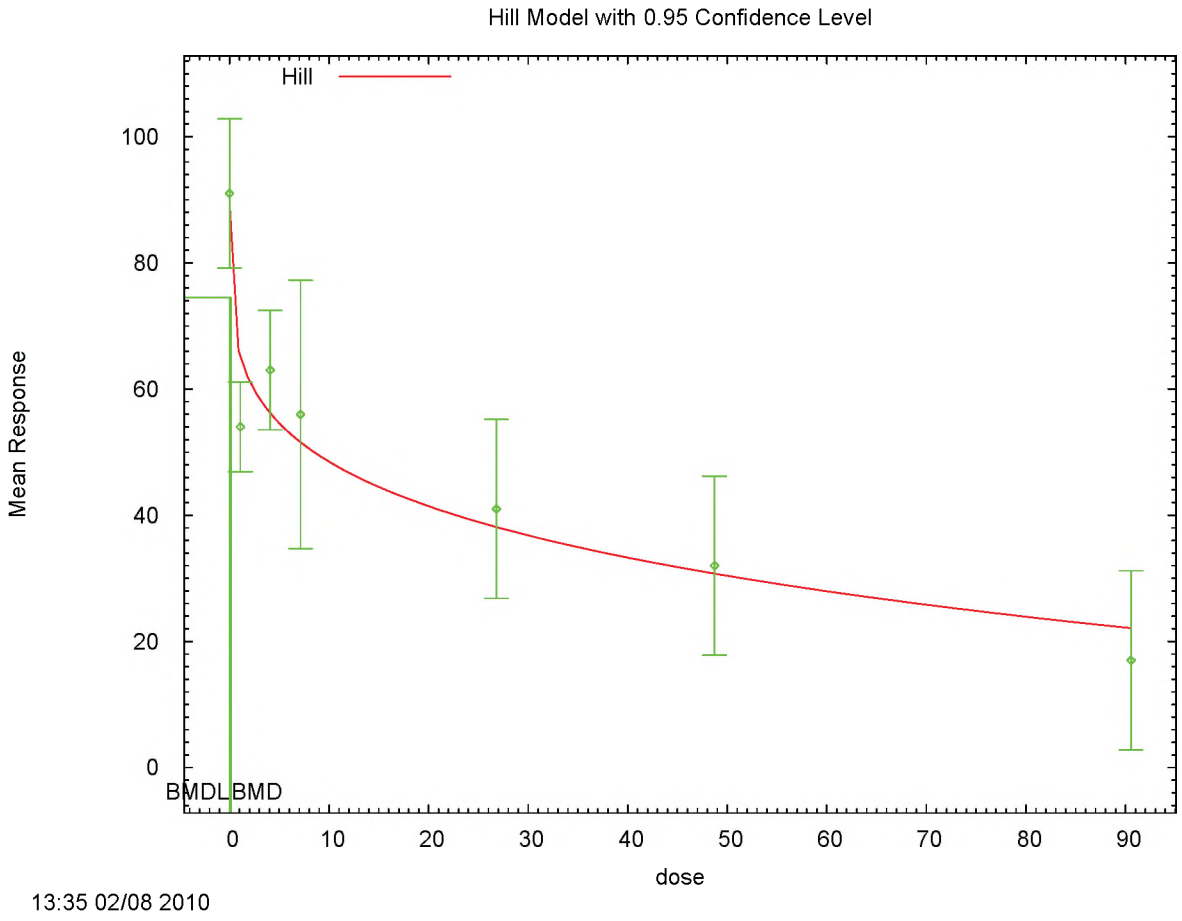
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =       0.148074

            BMDL =    0.00435112
```

E.2.49.5. *Figure for Additional Model Presented: Hill, Unrestricted*



E.3. ADMINISTERED DOSE BMDS RESULTS

E.3.1. Amin et al., 2000: 0.25% Saccharin Consumed, Female

E.3.1.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
linear [b]	**1**	**0.358**	**179.702**	**8.816E+01**	**5.890E+01**	
polynomial, 2-degree	1	0.358	179.702	8.816E+01	5.890E+01	
power	1	0.358	179.702	8.816E+01	5.890E+01	power bound hit (power = 1)
power, unrestricted [c]	0	N/A	180.858	7.530E+01	2.537E+01	unrestricted (power = 0.605)

[a] Non-constant variance model selected ($p = 0.0005$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.3.1.2. *Output for Selected Model: Linear*

Amin et al., 2000: 0.25% Saccharin Consumed, Female

```
 ================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\1\1_Amin_2000_25_SC_Linear_1.(d)
         Gnuplot Plotting File:  C:\1\1_Amin_2000_25_SC_Linear_1.plt
                                                Tue Feb 16 17:22:16 2010
 ================================================================

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   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   Signs of the polynomial coefficients are not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


                 Default Initial Parameter Values
                        lalpha =      5.29482
                           rho =            0
                        beta_0 =      30.8266
                        beta_1 =    -0.204134
```

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	beta_0	beta_1
lalpha	1	-0.99	-0.016	0.03
rho	-0.99	1	0.013	-0.026
beta_0	-0.016	0.013	1	-0.94
beta_1	0.03	-0.026	-0.94	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-2.55843	1.66185	-5.8156	0.698746
rho	2.42056	0.545617	1.35117	3.48995
beta_0	30.3968	4.03582	22.4868	38.3069
beta_1	-0.196699	0.0443352	-0.283594	-0.109803

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	31.7	30.4	20.6	17.3	0.233
25	10	24.6	25.5	12	14	-0.2
100	10	10.7	10.7	5.33	4.92	-0.0204

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-92.841935	4	193.683870
A2	-85.255316	6	182.510632
A3	-85.429148	5	180.858295
fitted	-85.851107	4	179.702213
R	-98.136607	2	200.273213

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)

```
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              25.7626          4          <.0001
   Test 2              15.1732          2       0.0005072
   Test 3             0.347663          1          0.5554
   Test 4             0.843918          1          0.3583

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


              Benchmark Dose Computation

Specified effect =             1

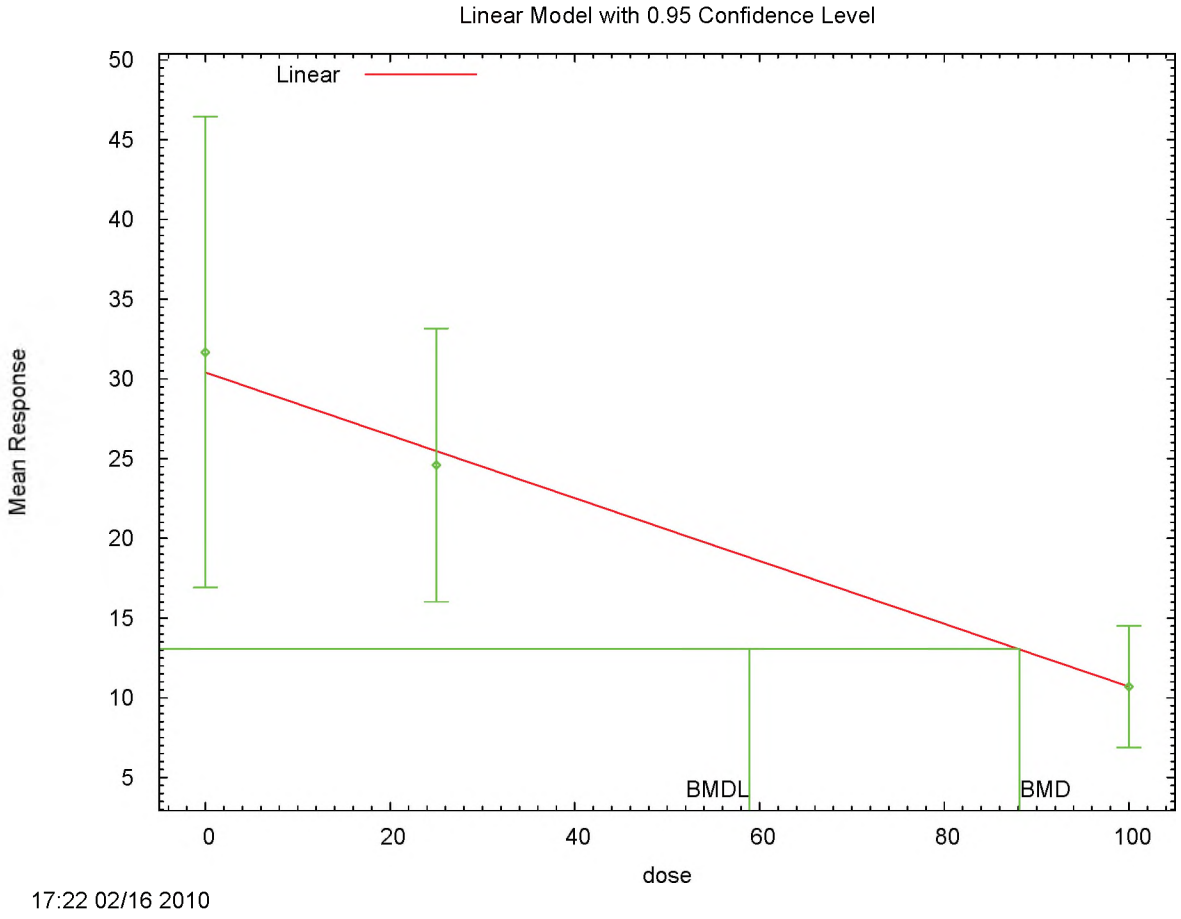
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

              BMD =        88.1623


             BMDL =        58.9029
```

E.3.1.3. *Figure for Selected Model: Linear*



E.3.1.4. *Output for Additional Model Presented: Power, Unrestricted*

Amin et al., 2000: 0.25% Saccharin Consumed, Female

```
================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\1_Amin_2000_25_SC_Pwr_U_1.(d)
        Gnuplot Plotting File:  C:\1\1_Amin_2000_25_SC_Pwr_U_1.plt
                                          Tue Feb 16 17:22:17 2010
================================================================

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  The form of the response function is:

  Y[dose] = control + slope * dose^power


  Dependent variable = Mean
  Independent variable = Dose
  The power is not restricted
  The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)
```

Total number of dose groups = 3
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	5.29482
rho =	0
control =	31.6727
slope =	-0.567889
power =	0.783745

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	control	slope	power
lalpha	1	-0.99	0.34	-0.14	-0.061
rho	-0.99	1	-0.42	0.15	0.068
control	0.34	-0.42	1	-0.67	-0.56
slope	-0.14	0.15	-0.67	1	0.99
power	-0.061	0.068	-0.56	0.99	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-2.48291	2.08669	-6.57274	1.60693
rho	2.38455	0.692047	1.02817	3.74094
control	32.99	5.40754	22.3914	43.5886
slope	-1.36469	2.01258	-5.30927	2.5799
power	0.605364	0.288476	0.0399625	1.17077

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	31.7	33	20.6	18.7	-0.223
25	10	24.6	23.4	12	12.4	0.302
100	10	10.7	10.8	5.33	4.94	-0.08

Warning: Likelihood for fitted model larger than the Likelihood for model A3.

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that

```
     were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                       Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1          -92.841935            4     193.683870
             A2          -85.255316            6     182.510632
             A3          -85.429148            5     180.858295
          fitted         -85.429148            5     180.858295
              R          -98.136607            2     200.273213


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              25.7626          4          <.0001
   Test 2              15.1732          2       0.0005072
   Test 3             0.347663          1          0.5554
   Test 4         -8.2423e-013          0             NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-Square
     test for fit is not valid


               Benchmark Dose Computation

Specified effect =            1

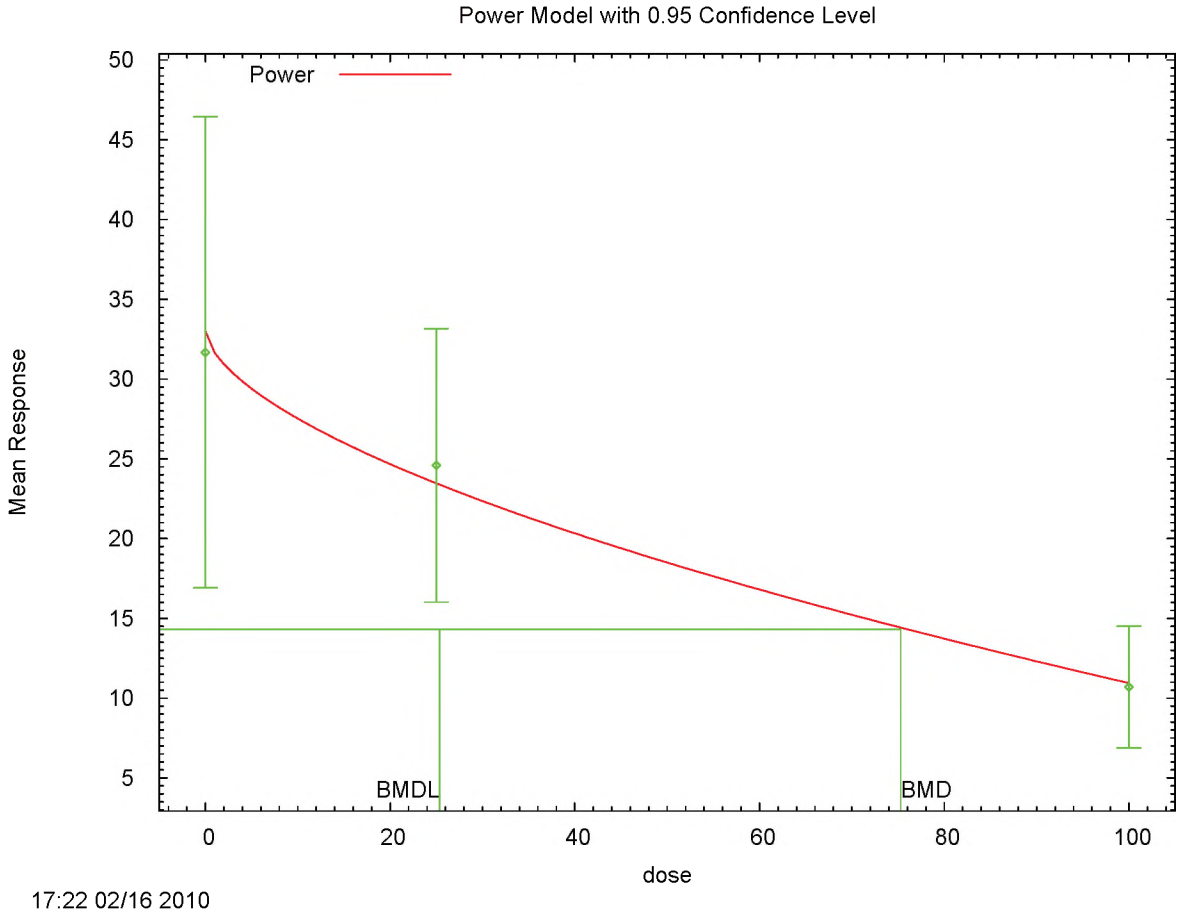
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 75.2994


            BMDL = 25.3717
```

E.3.1.5. *Figure for Additional Model Presented: Power, Unrestricted*



E.3.2. Amin et al., 2000: 0.25% Saccharin Preference Ratio, Female

E.3.2.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
linear [b]	**1**	**0.002**	**228.094**	**1.264E+02**	**6.128E+01**	
polynomial, 2-degree	1	0.002	228.094	1.264E+02	6.128E+01	
power	1	0.002	228.094	1.264E+02	6.128E+01	power bound hit (power = 1)

[a] Non-constant variance model selected ($p = 0.0135$)

[b] Best-fitting model, BMDS output presented in this appendix

E.3.2.2. *Output for Selected Model: Linear*

Amin et al., 2000: 0.25% Saccharin Preference Ratio, Female

```
 ================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\1\2_Amin_2000_25_SP_Linear_1.(d)
         Gnuplot Plotting File:  C:\1\2_Amin_2000_25_SP_Linear_1.plt
                                                 Tue Feb 16 17:22:44 2010
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   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   Signs of the polynomial coefficients are not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                        lalpha =      6.34368
                           rho =            0
                        beta_0 =      74.2008
                        beta_1 =    -0.219781


          Asymptotic Correlation Matrix of Parameter Estimates

                   lalpha          rho       beta_0       beta_1

    lalpha            1           -1          0.2        -0.28
```

rho	-1	1	-0.19	0.28
beta_0	0.2	-0.19	1	-0.76
beta_1	-0.28	0.28	-0.76	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	0.338774	9.23768	-17.7667	18.4443
rho	1.43998	2.21674	-2.90476	5.78472
beta_0	73.6633	6.6623	60.6054	86.7211
beta_1	-0.207175	0.101074	-0.405276	-0.00907442

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	82.1	73.7	13.3	26.2	1.02
25	10	58.1	68.5	33.9	24.8	-1.32
100	10	54.9	52.9	19.5	20.6	0.295

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-108.574798	4	225.149597
A2	-104.269377	6	220.538754
A3	-105.147952	5	220.295903
fitted	-110.046917	4	228.093834
R	-112.382522	2	228.765045

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

```
   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              16.2263          4         0.00273
   Test 2              8.61084          2          0.0135
   Test 3              1.75715          1           0.185
   Test 4              9.79793          1        0.001747

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1.  You may want to try a different
model


             Benchmark Dose Computation

Specified effect =             1

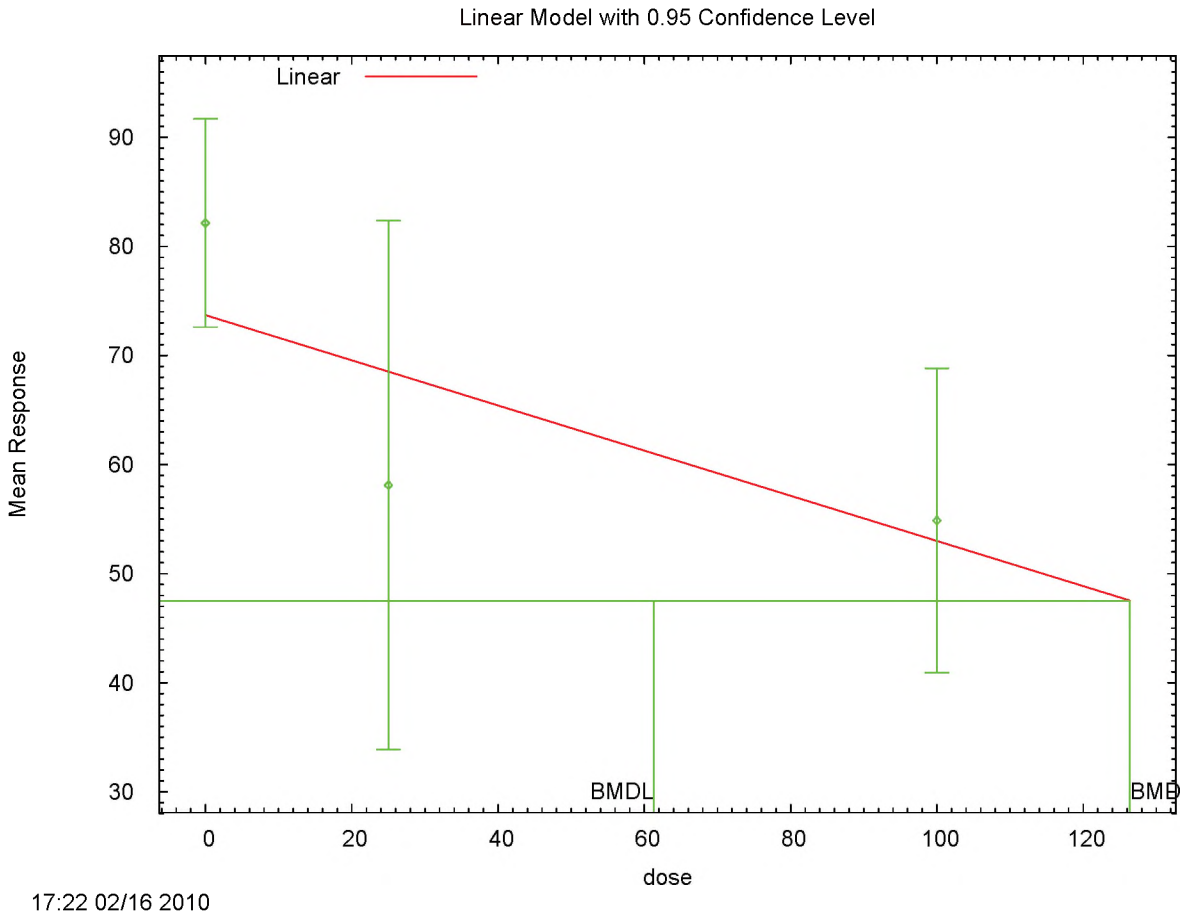
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =        126.365


            BMDL =        61.2812
```

E.3.2.3. *Figure for Selected Model: Linear*



E.3.3. Amin et al., 2000: 0.50% Saccharin Consumed, Female

E.3.3.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
linear [b]	**1**	**0.031**	**159.737**	**9.874E+01**	**6.417E+01**	
polynomial, 2-degree	1	0.031	159.737	9.874E+01	6.417E+01	
power	1	0.031	159.737	9.874E+01	6.417E+01	power bound hit (power = 1)
power, unrestricted [c]	0	N/A	157.060	5.610E+01	6.781E+00	unrestricted (power = 0.325)

[a] Non-constant variance model selected (p = <0.0001)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.3.3.2. *Output for Selected Model: Linear*

Amin et al., 2000: 0.50% Saccharin Consumed, Female

```
 ================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\1\3_Amin_2000_50_SC_Linear_1.(d)
         Gnuplot Plotting File:  C:\1\3_Amin_2000_50_SC_Linear_1.plt
                                                Tue Feb 16 17:23:14 2010
 ================================================================

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   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   Signs of the polynomial coefficients are not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                        lalpha =      4.68512
                           rho =            0
                        beta_0 =      19.3484
                        beta_1 =    -0.158141


           Asymptotic Correlation Matrix of Parameter Estimates
```

	lalpha	rho	beta_0	beta_1
lalpha	1	-0.97	0.018	-0.0021
rho	-0.97	1	-0.027	0.014
beta_0	0.018	-0.027	1	-0.95
beta_1	-0.0021	0.014	-0.95	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-0.997428	0.992786	-2.94325	0.948397
rho	2.13634	0.404989	1.34257	2.9301
beta_0	18.1144	3.10302	12.0326	24.1962
beta_1	-0.135736	0.0331501	-0.200709	-0.0707631

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	22.4	18.1	16	13.4	1
25	10	11.4	14.7	7.66	10.7	-0.983
100	10	4.54	4.54	3.33	3.06	-0.00393

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-83.696404	4	175.392808
A2	-73.511830	6	159.023660
A3	-73.530233	5	157.060467
fitted	-75.868688	4	159.737377
R	-90.294746	2	184.589492

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)

(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	33.5658	4	<.0001
Test 2	20.3691	2	<.0001
Test 3	0.0368066	1	0.8479
Test 4	4.67691	1	0.03057

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

Specified effect = 1

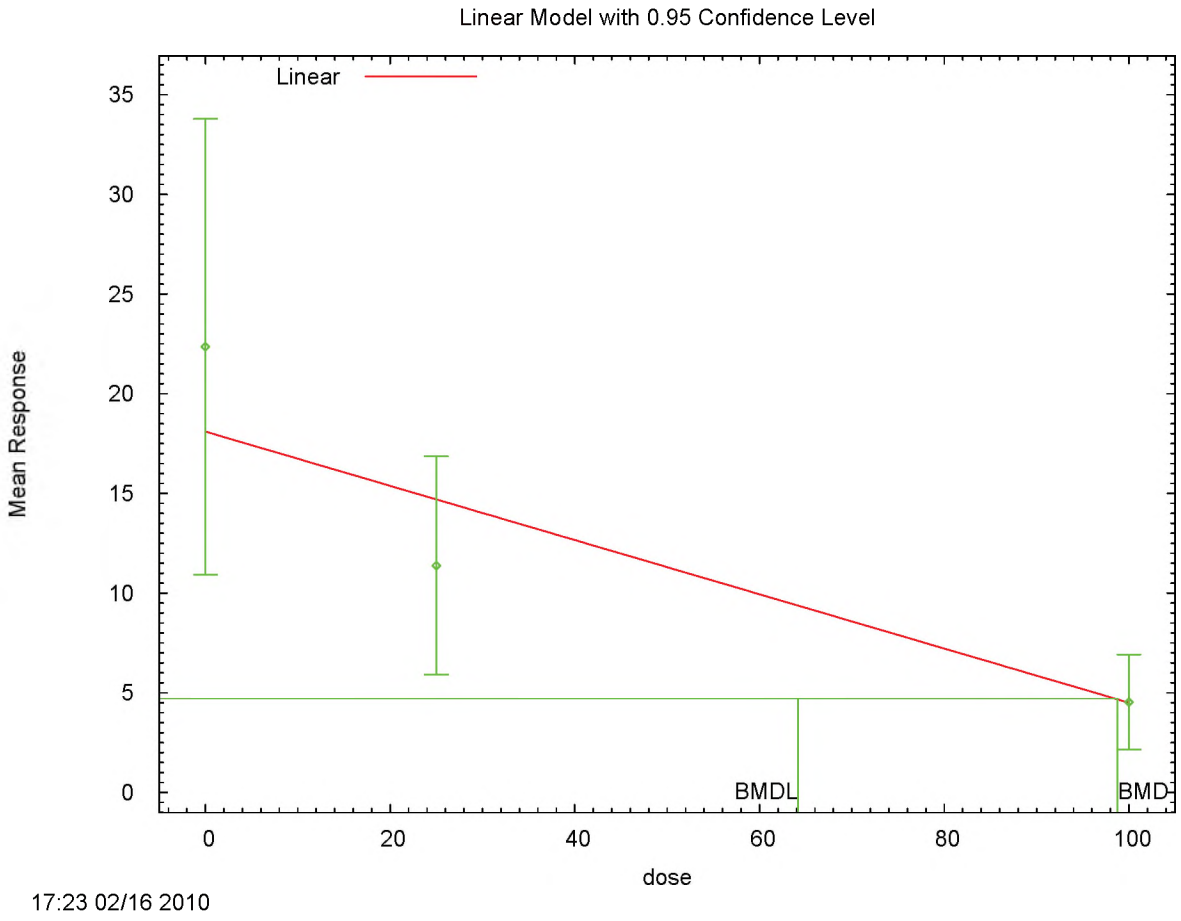
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 98.7409

BMDL = 64.169

E.3.3.3. *Figure for Selected Model: Linear*



E.3.3.4. *Output for Additional Model Presented: Power, Unrestricted*

Amin et al., 2000: 0.50% Saccharin Consumed, Female

```
================================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\3_Amin_2000_50_SC_Pwr_U_1.(d)
        Gnuplot Plotting File:  C:\1\3_Amin_2000_50_SC_Pwr_U_1.plt
                                          Tue Feb 16 17:23:15 2010
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  The form of the response function is:

  Y[dose] = control + slope * dose^power


  Dependent variable = Mean
  Independent variable = Dose
  The power is not restricted
  The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)
```

```
Total number of dose groups = 3
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                         lalpha =      4.68512
                            rho =            0
                        control =      22.3564
                          slope =     -3.55874
                          power =     0.349799


           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho      control        slope        power

  lalpha              1        -0.96         0.34        -0.26        -0.15

     rho          -0.96            1        -0.47          0.3         0.15

 control           0.34        -0.47            1        -0.73        -0.52

   slope          -0.26          0.3        -0.73            1         0.96

   power          -0.15         0.15        -0.52         0.96            1


                                Parameter Estimates

                                                      95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
        lalpha        -0.708629            1.298          -3.25267             1.83541
           rho          1.96142         0.529653           0.923323             2.99953
       control          22.6293          4.48416            13.8405             31.4181
         slope         -4.03215          3.21302           -10.3296             2.26526
         power         0.325414         0.138761           0.053447            0.597381


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

   0    10       22.4         22.6           16           15        -0.0577
  25    10       11.4         11.1         7.66         7.46          0.105
 100    10       4.54         4.58         3.33         3.12        -0.0475

Warning: Likelihood for fitted model larger than the Likelihood for model A3.


Model Descriptions for likelihoods calculated


Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user
```

```
Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                       Likelihoods of Interest

           Model      Log(likelihood)   # Param's      AIC
            A1          -83.696404           4     175.392808
            A2          -73.511830           6     159.023660
            A3          -73.530233           5     157.060467
         fitted         -73.530233           5     157.060467
             R          -90.294746           2     184.589492


                  Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              33.5658          4          <.0001
   Test 2              20.3691          2          <.0001
   Test 3            0.0368066          1          0.8479
   Test 4        -2.84217e-014          0              NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-Square
     test for fit is not valid


               Benchmark Dose Computation

Specified effect =            1

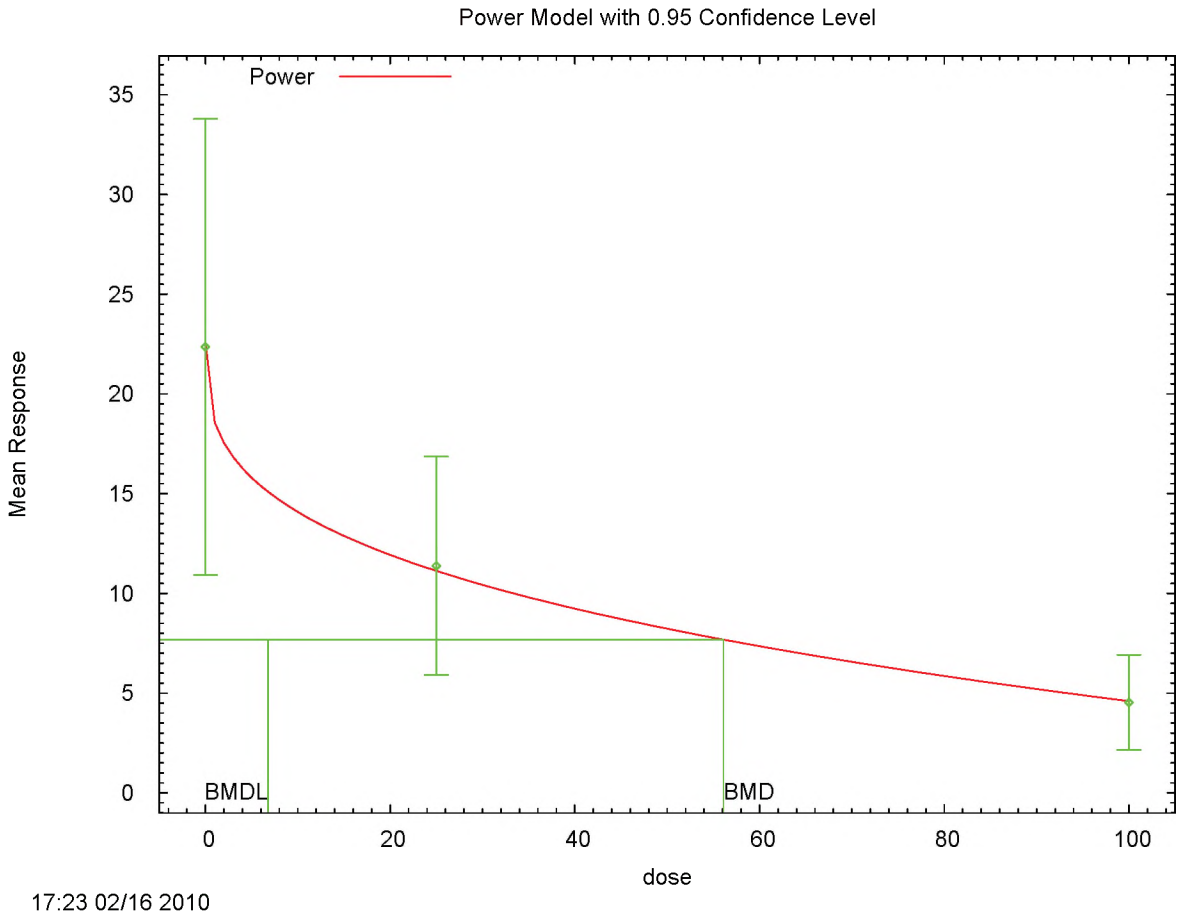
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 56.0967


            BMDL = 6.78112
```

E.3.3.5. *Figure for Additional Model Presented: Power, Unrestricted*



E.3.4. Amin et al., 2000: 0.50% Saccharin Preference Ratio, Female

E.3.4.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
linear [b]	**1**	**0.088**	**234.936**	**8.278E+01**	**5.100E+01**	
polynomial, 2-degree	1	0.088	234.936	8.278E+01	5.100E+01	
power	1	0.088	234.936	8.278E+01	5.100E+01	power bound hit (power = 1)
power, unrestricted [c]	0	N/A	234.020	1.817E+01	1.000E-13	unrestricted (power = 0.232)

[a] Constant variance model selected ($p = 0.5593$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.3.4.2. *Output for Selected Model: Linear*

Amin et al., 2000: 0.50% Saccharin Preference Ratio, Female

```
 ================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\1\4_Amin_2000_50_SP_LinearCV_1.(d)
         Gnuplot Plotting File:  C:\1\4_Amin_2000_50_SP_LinearCV_1.plt
                                                Tue Feb 16 17:23:43 2010
 ================================================================

 -
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


                 Default Initial Parameter Values
                         alpha =      764.602
                           rho =            0   Specified
                        beta_0 =      64.1858
                        beta_1 =    -0.332668
```

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	beta_0	beta_1
alpha	1	2e-008	1.4e-009
beta_0	2e-008	1	-0.7
beta_1	1.4e-009	-0.7	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	758.396	195.817	374.602	1142.19
beta_0	64.1858	7.04184	50.3841	77.9876
beta_1	-0.332668	0.118327	-0.564584	-0.100752

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	72.7	64.2	24.6	27.5	0.981
25	10	44.5	55.9	32.9	27.5	-1.31
100	10	33.8	30.9	24.6	27.5	0.327

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that
were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.009921	4	234.019841
A2	-112.428886	6	236.857773
A3	-113.009921	4	234.019841
fitted	-114.468091	3	234.936183
R	-117.976057	2	239.952114

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)

```
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              11.0943          4         0.02552
   Test 2              1.16207          2          0.5593
   Test 3              1.16207          2          0.5593
   Test 4              2.91634          1         0.08769

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1.  You may want to try a different
model


             Benchmark Dose Computation

Specified effect =             1

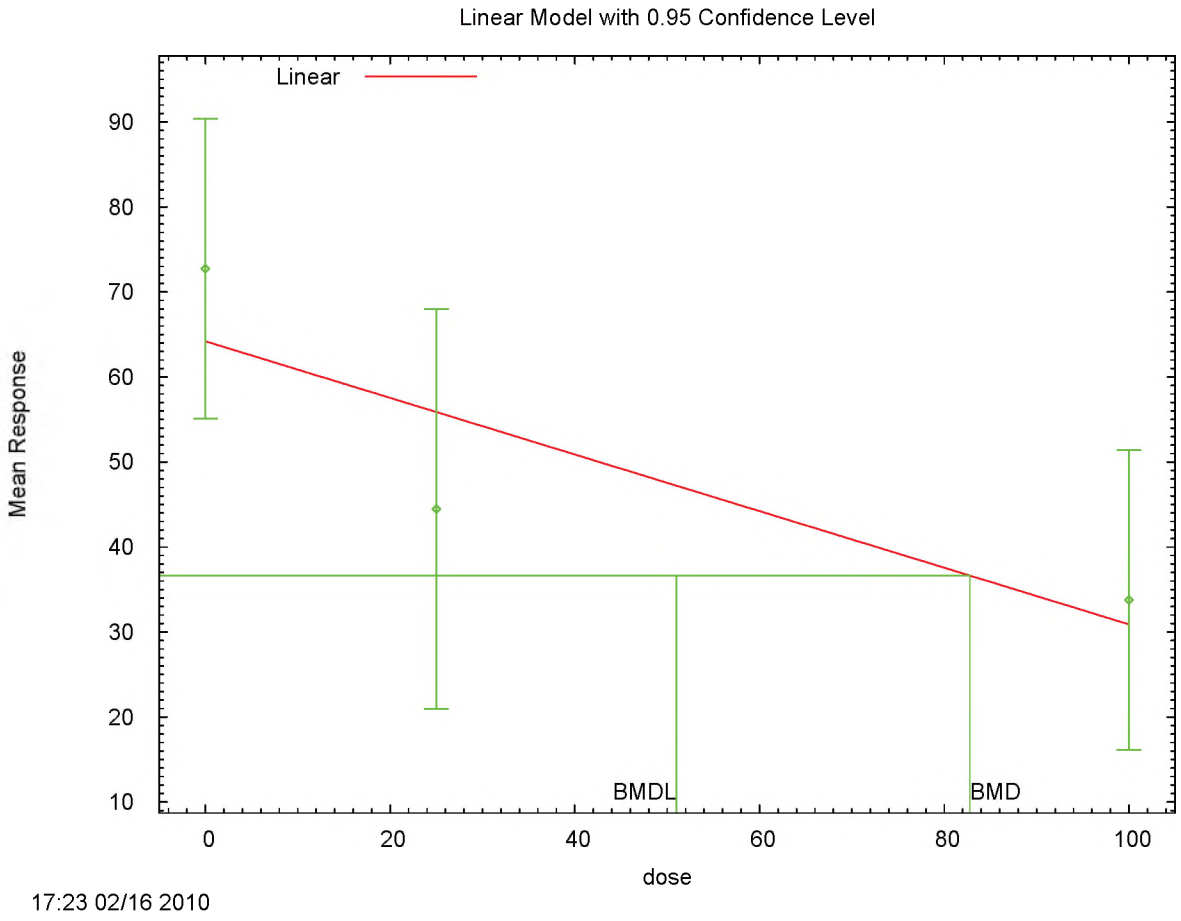
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

              BMD =        82.7823


             BMDL =        50.9971
```

E.3.4.3. *Figure for Selected Model: Linear*



E.3.4.4. *Output for Additional Model Presented: Power, Unrestricted*

Amin et al., 2000: 0.50% Saccharin Preference Ratio, Female

```
================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\4_Amin_2000_50_SP_PwrCV_U_1.(d)
        Gnuplot Plotting File:  C:\1\4_Amin_2000_50_SP_PwrCV_U_1.plt
                                        Tue Feb 16 17:23:44 2010
================================================================

-
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the response function is:

  Y[dose] = control + slope * dose^power


  Dependent variable = Mean
  Independent variable = Dose
  rho is set to 0
  The power is not restricted
  A constant variance model is fit
```

```
   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                         alpha =      764.602
                           rho =            0   Specified
                       control =      72.7273
                         slope =      -13.387
                         power =     0.231973


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been specified by the user,
                and do not appear in the correlation matrix )

                  alpha      control        slope        power

     alpha            1    -1.3e-008     5.9e-009     2.5e-009

   control    -1.3e-008            1         -0.4        -0.22

     slope     5.9e-009         -0.4            1         0.97

     power     2.5e-009        -0.22         0.97            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
          alpha          688.142          177.677             339.9             1036.38
        control          72.7273          8.29543           56.4686              88.986
          slope          -13.387          15.9957           -44.738             17.9639
          power         0.231973         0.268067         -0.293429            0.757376


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0    10       72.7         72.7         24.6         26.2      5.16e-008
   25    10       44.5         44.5         32.9         26.2     -1.27e-008
  100    10       33.8         33.8         24.6         26.2        -2e-008

Degrees of freedom for Test A3 vs fitted <= 0


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
```

```
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                       Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
              A1         -113.009921            4     234.019841
              A2         -112.428886            6     236.857773
              A3         -113.009921            4     234.019841
          fitted         -113.009921            4     234.019841
               R         -117.976057            2     239.952114


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              11.0943          4         0.02552
   Test 2              1.16207          2          0.5593
   Test 3              1.16207          2          0.5593
   Test 4                    0          0             NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-Square
     test for fit is not valid


               Benchmark Dose Computation

Specified effect =             1

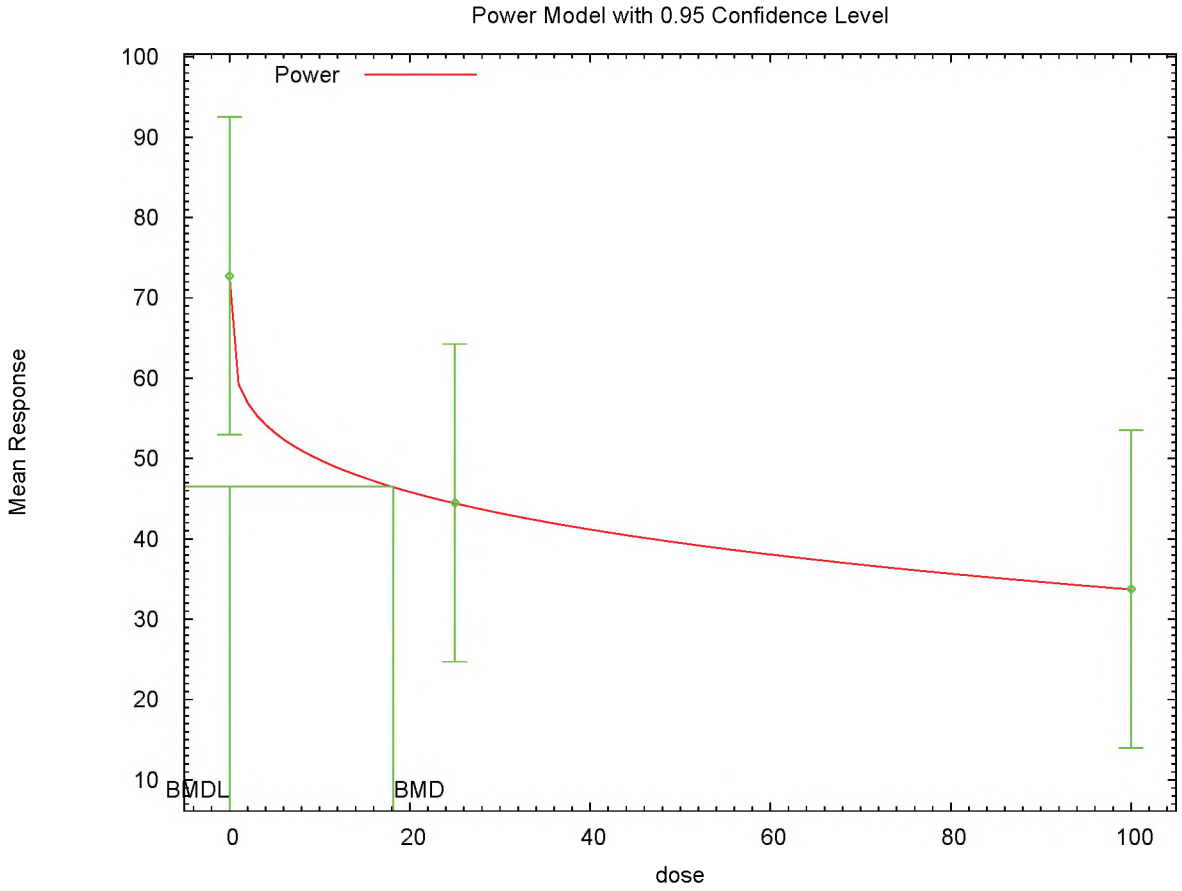
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 18.1732


            BMDL = 1e-013
```

E.3.4.5. *Figure for Additional Model Presented: Power, Unrestricted*



E.3.5. Bell et al., 2007a: Balano-Preputial Separation, Postnatal Day 49

E.3.5.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
gamma	2	0.369	113.514	7.332E+00	4.687E+00	power bound hit (power = 1)
logistic	2	0.237	114.853	1.501E+01	1.137E+01	negative intercept (intercept = -2.07)
log-logistic [a]	**2**	**0.456**	**112.952**	**5.209E+00**	**2.870E+00**	**slope bound hit (slope = 1)**
log-probit	2	0.178	115.488	1.428E+01	9.138E+00	slope bound hit (slope = 1)
multistage, 3-degree	2	0.369	113.514	7.332E+00	4.687E+00	final ß = 0
probit	2	0.248	114.723	1.399E+01	1.061E+01	negative intercept (intercept = -1.23)
Weibull	2	0.369	113.514	7.332E+00	4.687E+00	power bound hit (power = 1)
gamma, unrestricted	1	0.566	113.746	1.894E+00	7.609E-02	unrestricted (power = 0.506)
log-logistic, unrestricted [b]	1	0.484	113.908	2.127E+00	1.363E-01	unrestricted (slope = 0.67)
log-probit, unrestricted	1	0.439	114.021	2.179E+00	1.671E-01	unrestricted (slope = 0.389)
Weibull, unrestricted	1	0.534	113.802	2.007E+00	1.075E-01	unrestricted (power = 0.574)

[a] Best-fitting model, BMDS output presented in this appendix

[b] Alternate model, BMDS output also presented in this appendix

E.3.5.2.

E.3.5.3. *Output for Selected Model: Log-Logistic*

Bell et al., 2007a: Balano-Preputial Separation, Postnatal Day 49

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\1\5_Bell_2007_BPS_LogLogistic_1.(d)
         Gnuplot Plotting File:  C:\1\5_Bell_2007_BPS_LogLogistic_1.plt
                                              Tue Feb 16 17:24:10 2010
 ================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1
```

```
   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                  Default Initial Parameter Values
                     background =    0.0333333
                      intercept =     -3.75371
                          slope =            1


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -slope
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

             background    intercept

background            1        -0.58

 intercept        -0.58            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background        0.0635251            *               *                   *
      intercept         -3.84765            *               *                   *
          slope                1            *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -53.7077         4
   Fitted model          -54.476         2       1.53661      2          0.4638
  Reduced model         -63.9797         1        20.544      3       0.0001309

           AIC:          112.952


                                  Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------
    0.0000     0.0635         1.906     1.000          30       -0.678
    2.4000     0.1091         3.274     5.000          30        1.011
    8.0000     0.2000         6.001     6.000          30       -0.000
   46.0000     0.5273        15.819    15.000          30       -0.300

 Chi^2 = 1.57      d.f. = 2        P-value = 0.4559


   Benchmark Dose Computation

Specified effect =            0.1
```

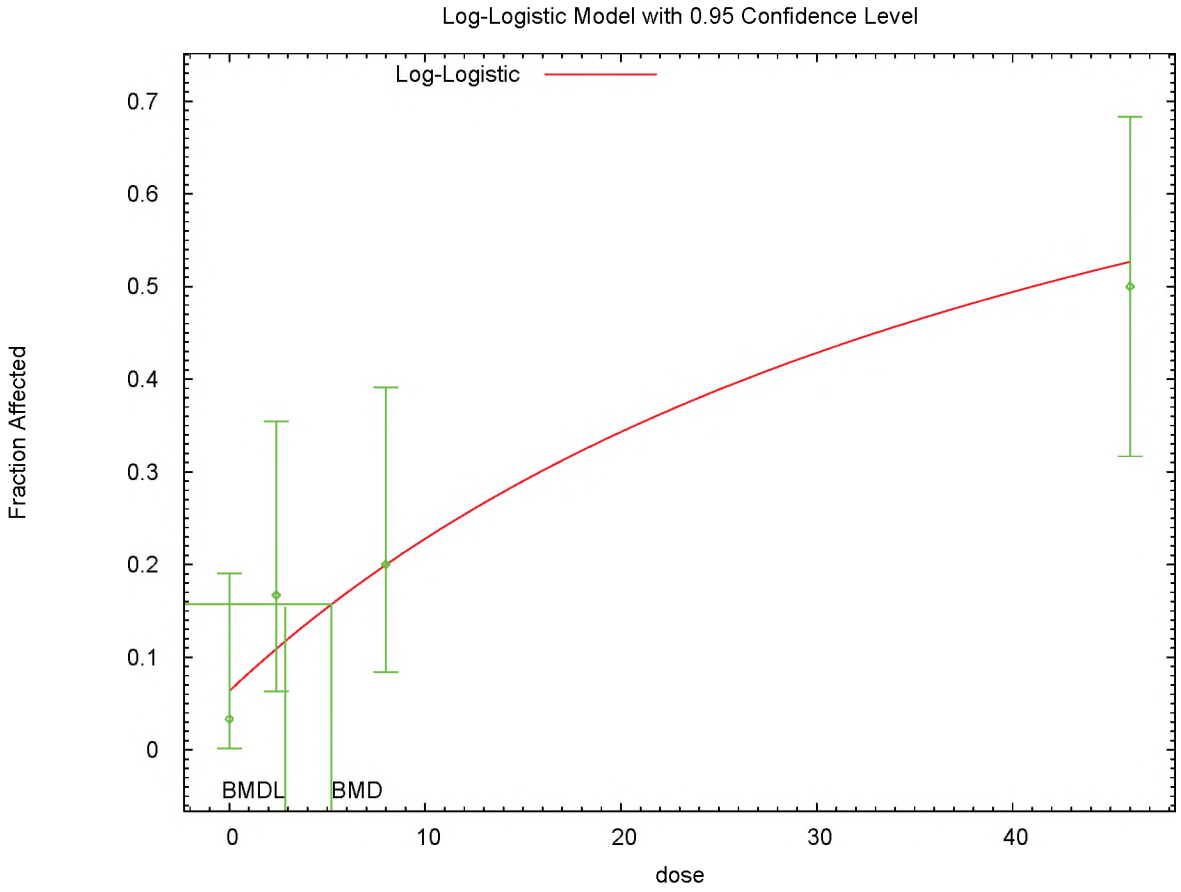
```
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        5.20918

            BMDL =        2.86991
```

E.3.5.4. *Figure for Selected Model: Log-Logistic*



E.3.5.5. *Output for Additional Model Presented: Log-Logistic, Unrestricted*

Bell et al., 2007a: Balano-Preputial Separation, Postnatal Day 49

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\1\5_Bell_2007_BPS_LogLogistic_U_1.(d)
         Gnuplot Plotting File:  C:\1\5_Bell_2007_BPS_LogLogistic_U_1.plt
                                              Tue Feb 16 17:24:10 2010
 ================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =    0.0333333
                     intercept =     -2.54947
                         slope =     0.615936


           Asymptotic Correlation Matrix of Parameter Estimates

             background    intercept        slope

background            1        -0.49         0.35

 intercept        -0.49            1        -0.93

     slope         0.35        -0.93            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background        0.0354714            *                *                   *
      intercept         -2.70296            *                *                   *
          slope         0.670238            *                *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
      Full model        -53.7077         4
```

Fitted model	-53.9541	3	0.492844	1	0.4827
Reduced model	-63.9797	1	20.544	3	0.0001309

AIC: 113.908

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0355	1.064	1.000	30	-0.063
2.4000	0.1392	4.176	5.000	30	0.435
8.0000	0.2405	7.216	6.000	30	-0.520
46.0000	0.4848	14.544	15.000	30	0.167

Chi^2 = 0.49 d.f. = 1 P-value = 0.4836

Benchmark Dose Computation

Specified effect = 0.1

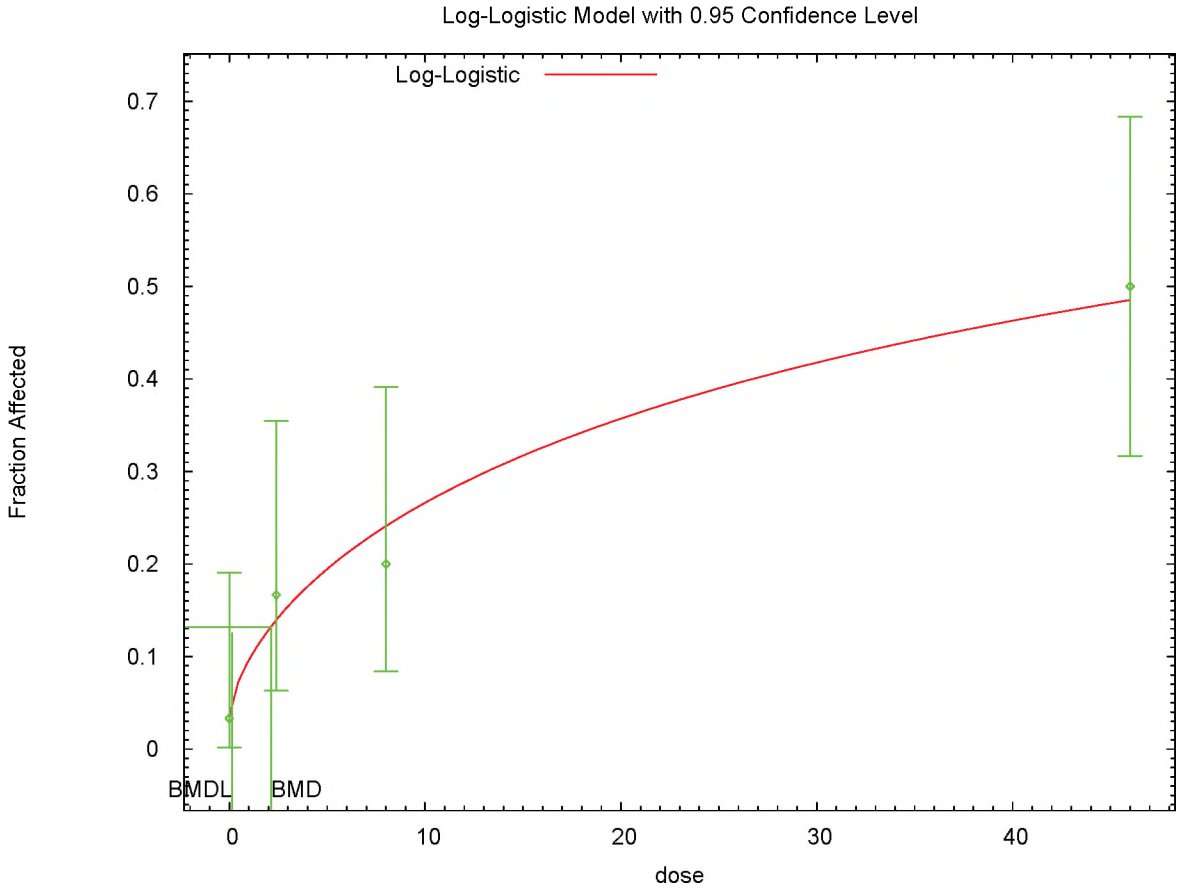
Risk Type = Extra risk

Confidence level = 0.95

BMD = 2.12667

BMDL = 0.13633

E.3.5.6. *Figure for Additional Model Presented: Log-Logistic, Unrestricted*



E.3.6. Cantoni et al., 1981: Urinary Coproporhyrins, 3 Months

E.3.6.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2)	2	0.002	33.792	1.101E+02	5.318E+01	
exponential (M3)	2	0.002	33.792	1.101E+02	5.318E+01	power hit bound (d = 1)
exponential (M4) [b]	**1**	**0.341**	**23.881**	**3.741E-01**	**1.253E-01**	
exponential (M5)	1	0.341	23.881	3.741E-01	1.253E-01	power hit bound (d = 1)
Hill	1	0.535	23.359	3.273E-01	error	n lower bound hit (n = 1)
linear	2	0.002	33.301	7.734E+01	1.975E+01	
polynomial, 3-degree	2	0.002	33.301	7.734E+01	1.975E+01	
power	2	0.002	33.301	7.734E+01	1.975E+01	power bound hit (power = 1)
power, unrestricted [c]	1	0.665	23.162	4.637E-03	8.796E-08	unrestricted (power = 0.22)
Hill, unrestricted	0	N/A	24.974	7.264E-02	1.656E-04	unrestricted (n = 0.48)

[a] Non-constant variance model selected ($p = 0.0039$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.3.6.2. *Output for Selected Model: Exponential (M4)*

Cantoni et al., 1981: Urinary Coproporhyrins, 3 Months

```
 ================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\1\6_Cantoni_1981_UriCopro_Exp_1.(d)
         Gnuplot Plotting File:
                                                Tue Feb 16 17:24:39 2010
 ================================================================

 Figure1-UrinaryCoproporphyrin_3months
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
```

```
      sign = -1 for decreasing trend.

   Model 2 is nested within Models 3 and 4.
   Model 3 is nested within Model 5.
   Model 4 is nested within Model 5.


Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


              Initial Parameter Values

              Variable          Model 4
              --------          --------
                lnalpha             -1.50063
                    rho              2.60979
                      a             0.704303
                      b            0.0205927
                      c              4.47268
                      d                    1



                Parameter Estimates

               Variable          Model 4
               --------          -------
                lnalpha            -1.74154
                    rho             2.66803
                      a            0.755982
                      b              0.3715
                      c             3.93845
                      d                   1


        Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
     0      4        0.7414       0.3475
  1.43      4         1.807       0.8341
  14.3      4         2.734        1.506
   143      4             3          2.6


              Estimated Values of Interest

  Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
     0         0.756       0.2882          -0.1014
  1.43         1.671       0.8307           0.3265
  14.3         2.966        1.786          -0.2607
   143         2.977        1.794          0.02532


Other models for which likelihoods are calculated:
```

```
  Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
           Var{e(ij)} = Sigma^2


                            Likelihoods of Interest

                 Model      Log(likelihood)      DF         AIC
                -------    -----------------    ----   ------------
                    A1       -12.90166           5      35.80333
                    A2       -6.203643           8      28.40729
                    A3       -6.487204           6      24.97441
                     R       -15.73713           2      35.47427
                     4       -6.940389           5      23.88078


Additive constant for all log-likelihoods =      -14.7.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.


                             Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)


                          Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                        19.07           6            0.004052
  Test 2                         13.4           3            0.003854
  Test 3                       0.5671           2              0.7531
 Test 6a                       0.9064           1              0.3411


  The p-value for Test 1 is less than .05.  There appears to be a
  difference between response and/or variances among the dose
  levels, it seems appropriate to model the data.

  The p-value for Test 2 is less than .1.  A non-homogeneous
  variance model appears to be appropriate.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 6a is greater than .1.  Model 4 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 1.000000

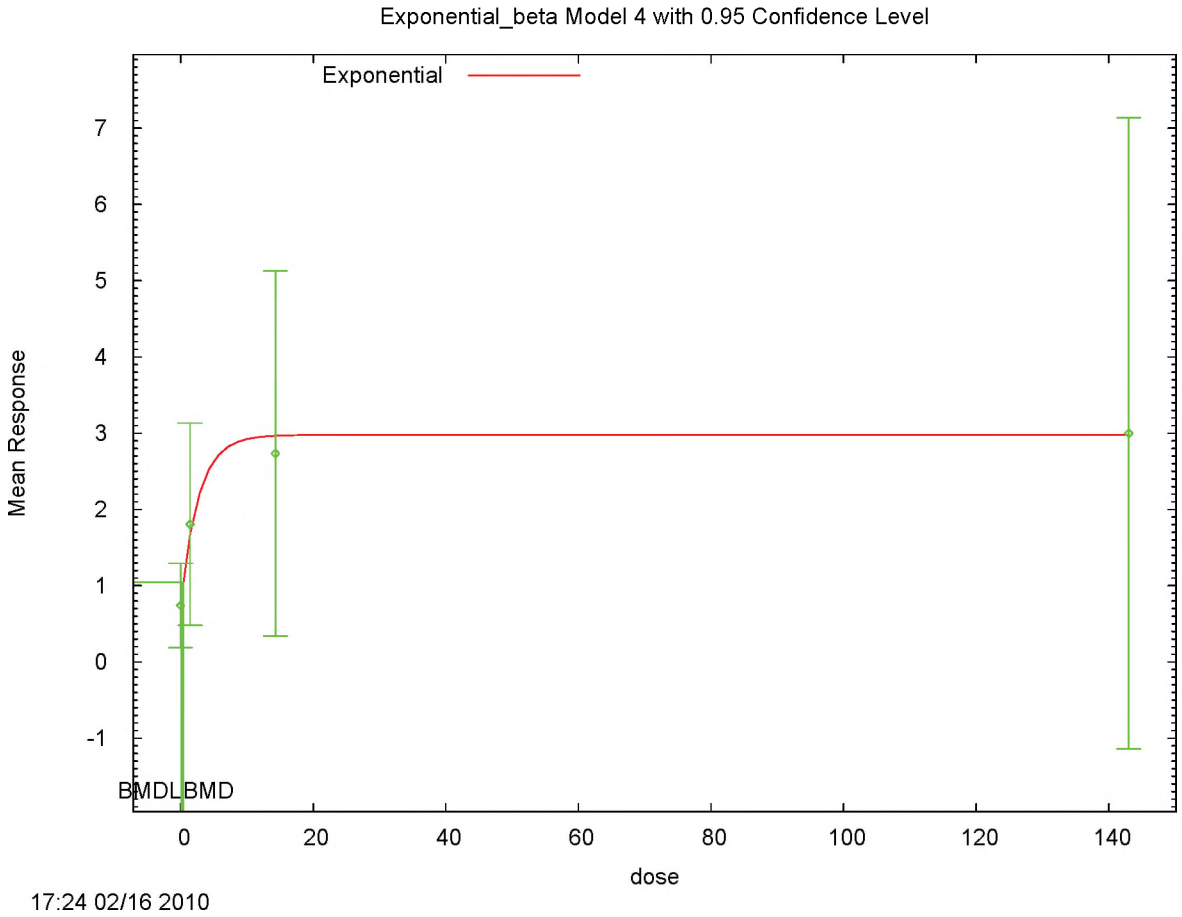
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000
```

```
BMD =      0.374114

BMDL =     0.125287
```

E.3.6.3. *Figure for Selected Model: Exponential (M4)*



E.3.6.4. *Output for Additional Model Presented: Power, Unrestricted*

Cantoni et al., 1981: Urinary Coproporhyrins, 3 Months

```
================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\6_Cantoni_1981_UriCopro_Pwr_U_1.(d)
        Gnuplot Plotting File:  C:\1\6_Cantoni_1981_UriCopro_Pwr_U_1.plt
                                          Tue Feb 16 17:24:41 2010
================================================================

Figure1-UrinaryCoproporphyrin_3months
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the response function is:

  Y[dose] = control + slope * dose^power
```

Dependent variable = Mean
Independent variable = Dose
The power is not restricted
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	0.90039
rho =	0
control =	0.741372
slope =	1.00533
power =	0.163111

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	control	slope	power
lalpha	1	-0.62	-0.53	-0.038	0.027
rho	-0.62	1	0.43	-0.24	-0.16
control	-0.53	0.43	1	-0.3	0.09
slope	-0.038	-0.24	-0.3	1	-0.72
power	0.027	-0.16	0.09	-0.72	1

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
lalpha	-1.78404	0.61698	-2.9933	-0.57478
rho	2.6428	0.74449	1.18363	4.10197
control	0.757242	0.139966	0.482915	1.03157
slope	0.927009	0.325923	0.288212	1.56581
power	0.220276	0.0964599	0.031218	0.409334

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	4	0.741	0.757	0.348	0.284	-0.112
1.43	4	1.81	1.76	0.834	0.865	0.108
14.3	4	2.73	2.42	1.51	1.32	0.471
143	4	3	3.52	2.6	2.16	-0.483

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

```
Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                        Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1          -12.901663            5      35.803325
             A2           -6.203643            8      28.407287
             A3           -6.487204            6      24.974409
         fitted           -6.580755            5      23.161510
              R          -15.737135            2      35.474269


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1               19.067          6        0.004052
   Test 2               13.396          3        0.003854
   Test 3             0.567122          2          0.7531
   Test 4             0.187101          1          0.6653

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


               Benchmark Dose Computation

Specified effect =             1

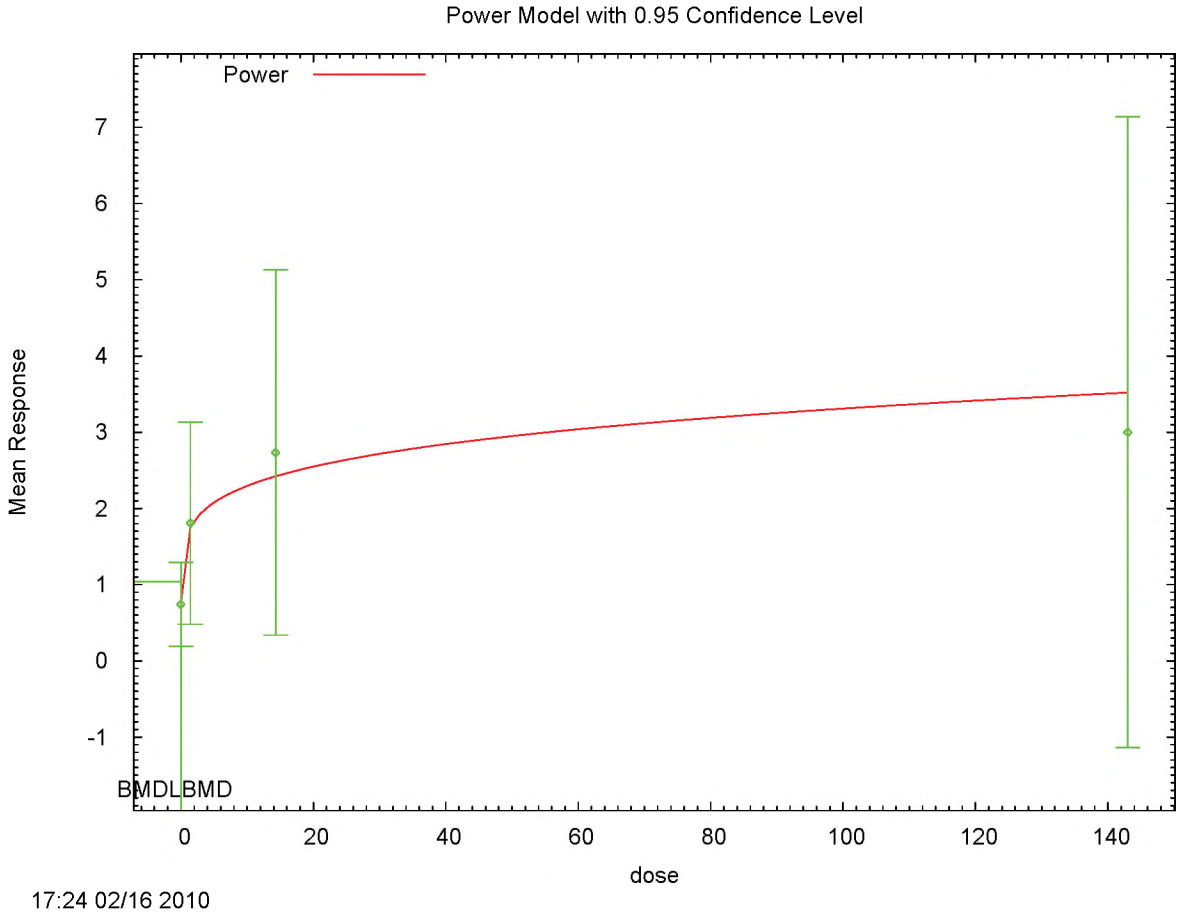
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 0.00463746


            BMDL = 8.79634e-008
```

E.3.6.5. *Figure for Additional Model Presented: Power, Unrestricted*



E.3.7. Cantoni et al., 1981: Urinary Porphyrins

E.3.7.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2) [b]	**2**	**<0.0001**	**58.753**	**1.223E+01**	**9.037E+00**	
exponential (M3)	2	<0.0001	58.753	1.223E+01	9.037E+00	power hit bound (d = 1)
exponential (M4)	1	<0.0001	63.138	2.227E-01	1.137E-01	
exponential (M5)	1	<0.0001	63.138	2.227E-01	1.137E-01	power hit bound (d = 1)
Hill	0	N/A	62.356	9.363E+00	4.664E+00	
linear	2	<0.0001	62.487	7.732E-01	2.816E-01	
polynomial, 3-degree	1	<0.0001	10.000	error	error	
power	2	<0.0001	62.487	7.732E-01	2.816E-01	power bound hit (power = 1)
power, unrestricted	1	<0.0001	59.914	1.025E-01	2.389E-02	unrestricted (power = 0.746)

[a] Non-constant variance model selected (p = <0.0001)

[b] Best-fitting model, BMDS output presented in this appendix

E.3.7.2. *Output for Selected Model: Exponential (M2)*

Cantoni et al., 1981: Urinary Porphyrins

```
 ================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\1\7_Cantoni_1981_UriPor_Exp_1.(d)
         Gnuplot Plotting File:
                                                 Tue Feb 16 17:25:14 2010
 ================================================================

 Table 1, dose converted to ng per kg per day
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.
```

Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 2
lnalpha	-3.57509
rho	2.23456
a	3.83141
b	0.0277822
c	0
d	1

Parameter Estimates

Variable	Model 2
lnalpha	-1.55886
rho	1.77962
a	4.17268
b	0.0270415
c	0
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	4	2.27	0.49
1.43	4	5.55	0.85
14.3	3	7.62	1.79
143	3	196.9	63.14

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	4.173	1.635	-2.327
1.43	4.337	1.692	1.433
14.3	6.143	2.307	1.109
143	199.4	51.04	-0.08645

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

```
  Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
           Var{e(ij)} = Sigma^2


                              Likelihoods of Interest

                   Model      Log(likelihood)      DF         AIC
                  -------    -----------------    ----   ------------
                      A1       -51.42175            5      112.8435
                      A2       -15.31211            8      46.62422
                      A3       -15.66963            6      43.33925
                       R       -68.75058            2      141.5012
                       2       -25.37651            4      58.75302


Additive constant for all log-likelihoods =     -12.87.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.


                                Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does Model 2 fit the data? (A3 vs. 2)


                           Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                      106.9             6           < 0.0001
  Test 2                      72.22             3           < 0.0001
  Test 3                      0.715             2             0.6994
  Test 4                      19.41             2           < 0.0001


  The p-value for Test 1 is less than .05.  There appears to be a
  difference between response and/or variances among the dose
  levels, it seems appropriate to model the data.

  The p-value for Test 2 is less than .1.  A non-homogeneous
  variance model appears to be appropriate.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 4 is less than .1.  Model 2 may not adequately
  describe the data; you may want to consider another model.


Benchmark Dose Computations:

  Specified Effect = 1.000000

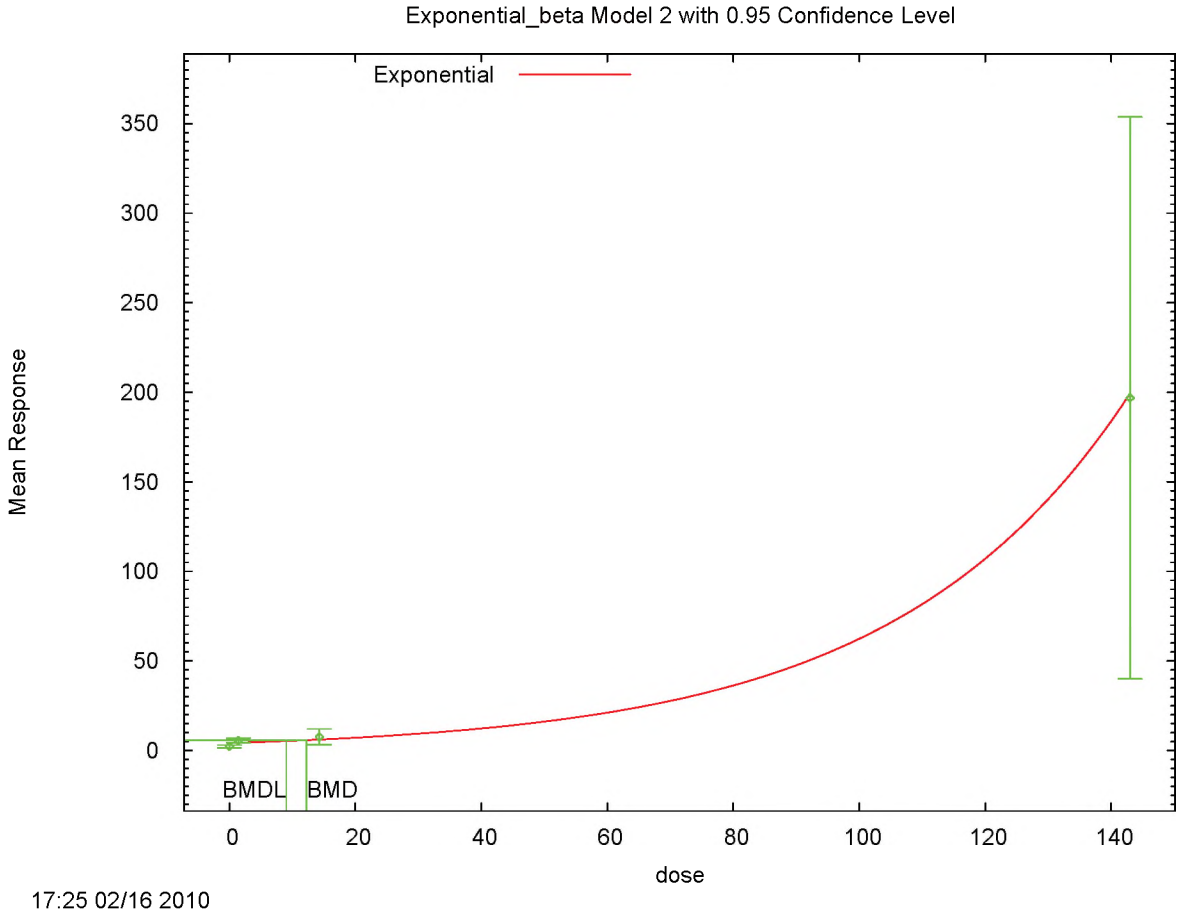
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD =      12.2272

              BMDL =      9.03732
```

E.3.7.3. *Figure for Selected Model: Exponential (M2)*



E.3.8. Crofton et al., 2005: Serum, T4

E.3.8.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2)	8	<0.0001	518.241	2.136E+03	1.157E+03	
exponential (M3)	8	<0.0001	518.241	2.136E+03	1.157E+03	power hit bound (d = 1)
exponential (M4) [b]	7	**0.957**	**476.204**	**5.633E+01**	**3.006E+01**	
exponential (M5)	7	0.957	476.204	5.633E+01	3.006E+01	power hit bound (d = 1)
Hill	6	0.973	477.434	5.564E+01	2.590E+01	
linear	8	<0.0001	523.518	4.246E+03	3.086E+03	
polynomial, 8-degree	8	<0.0001	523.518	4.246E+03	3.086E+03	
power	8	<0.0001	523.518	4.246E+03	3.086E+03	power bound hit (power = 1)
power, unrestricted	7	0.030	489.670	2.179E+01	2.271E+00	unrestricted (power = 0.217)

[a] Constant variance model selected ($p = 0.7647$)

[b] Best-fitting model, BMDS output presented in this appendix

E.3.8.2. *Output for Selected Model: Exponential (M4)*

Crofton et al., 2005: Serum, T4

```
 ================================================================================
          Exponential Model. (Version: 1.61;  Date: 7/24/2009)
          Input Data File: C:\1\8_Crofton_2005_T4_ExpCV_1.(d)
          Gnuplot Plotting File:
                                                    Tue Feb 16 17:26:01 2010
 ================================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

    The form of the response function by Model:
       Model 2:     Y[dose] = a * exp{sign * b * dose}
       Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
       Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
       Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

      Note: Y[dose] is the median response for exposure = dose;
            sign = +1 for increasing trend in data;
            sign = -1 for decreasing trend.

       Model 2 is nested within Models 3 and 4.
       Model 3 is nested within Model 5.
       Model 4 is nested within Model 5.
```

Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 10
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	5.47437
rho(S)	0
a	104.999
b	0.000371694
c	0.445764
d	1

(S) = Specified

Parameter Estimates

Variable	Model 4
lnalpha	5.50283
rho	0
a	99.776
b	0.00728387
c	0.533516
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	14	100	15.44
0.1	6	96.27	14.98
3	12	98.57	18.11
10	6	99.76	19.04
30	6	93.32	12.11
100	6	70.94	12.74
300	6	62.52	14.75
1000	6	52.68	22.73
3000	6	54.66	19.71
1e+004	4	49.15	11.15

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	99.78	15.66	0.05325
0.1	99.74	15.66	-0.5434
3	98.77	15.66	-0.04357
10	96.51	15.66	0.5085
30	90.64	15.66	0.4195

100	75.7	15.66	-0.744
300	58.47	15.66	0.6334
1000	53.26	15.66	-0.09133
3000	53.23	15.66	0.2237
1e+004	53.23	15.66	-0.5218

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

Model R: Yij = Mu + e(i)
Var{e(ij)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-233.0774	11	488.1549
A2	-230.2028	20	500.4056
A3	-233.0774	11	488.1549
R	-268.4038	2	540.8076
4	-234.1019	4	476.2038

Additive constant for all log-likelihoods = -66.16. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	76.4	18	< 0.0001
Test 2	5.749	9	0.7647
Test 3	5.749	9	0.7647
Test 6a	2.049	7	0.9571

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data.

```
Benchmark Dose Computations:

  Specified Effect = 1.000000

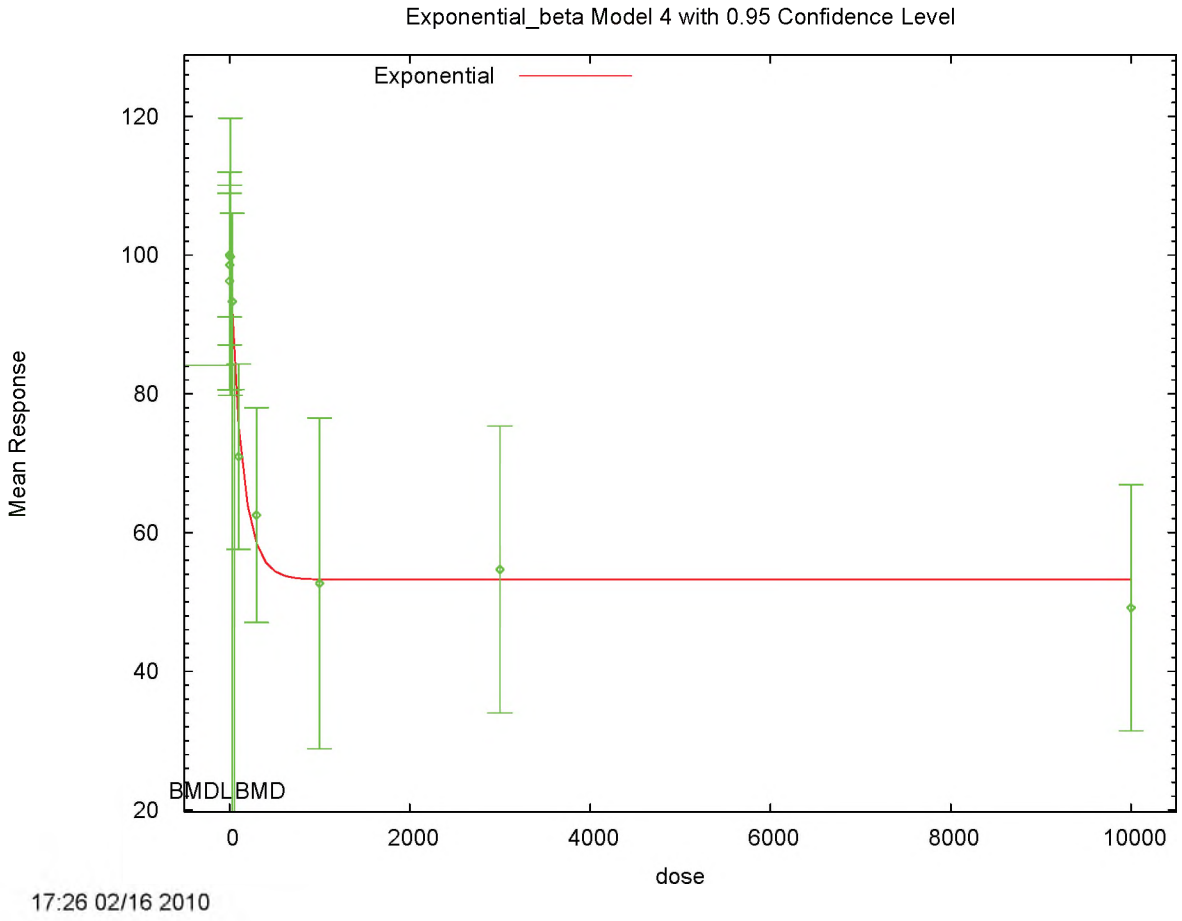
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD =      56.3321

              BMDL =      30.0635
```

E.3.8.3. *Figure for Selected Model: Exponential (M4)*



E.3.9. Franc et al., 2001: S-D Rats, Relative Liver Weight

E.3.9.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Hill	1	0.797	236.371	1.826E+01	5.463E+00	n lower bound hit (n = 1)
exponential (M2)	2	0.935	234.440	2.262E+01	1.757E+01	
exponential (M3)	2	0.935	234.440	2.262E+01	1.757E+01	power hit bound (d = 1)
exponential (M4)	1	0.797	236.371	1.827E+01	6.112E+00	
exponential (M5)	1	0.797	236.371	1.827E+01	6.112E+00	power hit bound (d = 1)
linear	2	0.967	234.372	1.861E+01	1.339E+01	
polynomial, 3-degree	2	0.967	234.372	1.861E+01	1.339E+01	
power [b]	2	0.967	234.372	1.861E+01	1.339E+01	power bound hit (power = 1)
Hill, unrestricted	0	N/A	238.366	1.726E+01	2.022E+00	unrestricted (n = 0.965)
power, unrestricted [c]	1	0.805	236.365	1.725E+01	2.003E+00	unrestricted (power = 0.962)

[a] Constant variance model selected ($p = 0.107$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.3.9.2. *Output for Selected Model: Power*

Franc et al., 2001: S-D Rats, Relative Liver Weight

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\1\88_Franc_2001_SD_RelLivWt_PowerCV_1.(d)
         Gnuplot Plotting File:  C:\1\88_Franc_2001_SD_RelLivWt_PowerCV_1.plt
                                              Fri Apr 16 16:28:45 2010
 ================================================================

 Figure 5, SD rats, relative liver weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
```

```
   The power is restricted to be greater than or equal to 1
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


                 Default Initial Parameter Values
                        alpha =      527.447
                          rho =            0   Specified
                      control =          100
                        slope =      1.15946
                        power =     0.839423


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho    -power
                have been estimated at a boundary point, or have been specified by the user,
                and do not appear in the correlation matrix )

                  alpha      control        slope

     alpha            1     1.3e-012    -6.2e-013

   control     1.3e-012            1        -0.67

     slope    -6.2e-013        -0.67            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
          alpha          462.485          115.621             235.872             689.099
        control          101.047          5.10511             91.0415             111.053
          slope         0.542984        0.0973507            0.352181            0.733788
          power                1               NA

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     8        100          101           14         21.5         -0.138
   10     8        108          106         16.9         21.5          0.208
   30     8        117          117         25.9         21.5        -0.0702
  100     8        155          155         30.9         21.5       0.000298


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2
```

```
Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                        Likelihoods of Interest

             Model      Log(likelihood)   # Param's      AIC
              A1         -114.152281            5     238.304562
              A2         -111.103649            8     238.207299
              A3         -114.152281            5     238.304562
          fitted         -114.185827            3     234.371654
               R         -125.052064            2     254.104127


                    Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value

  Test 1              27.8968          6          <.0001
  Test 2              6.09726          3           0.107
  Test 3              6.09726          3           0.107
  Test 4            0.0670927          2           0.967

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


               Benchmark Dose Computation

Specified effect =           0.1

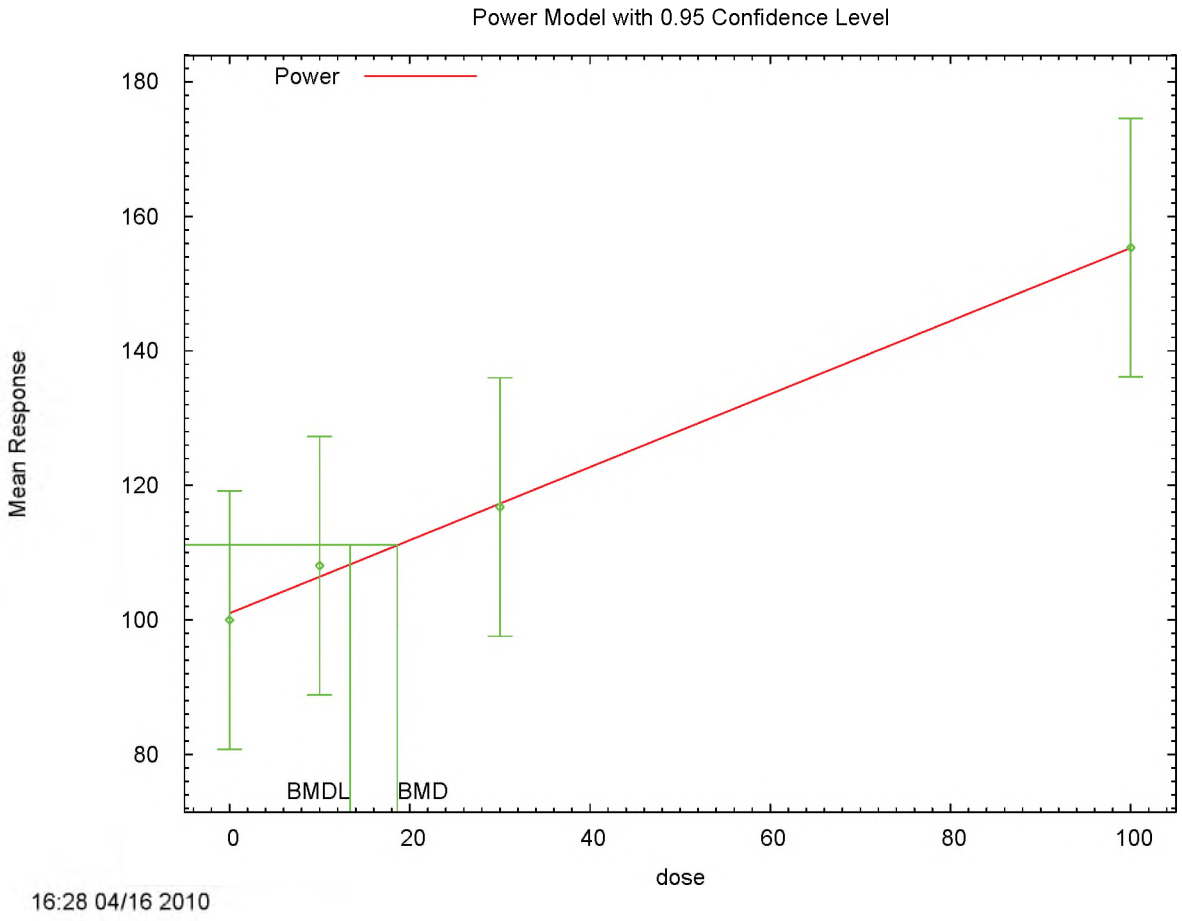
Risk Type        =     Relative risk

Confidence level =          0.95

             BMD = 18.6096


            BMDL = 13.3879
```

E.3.9.3. *Figure for Selected Model: Power*



E.3.9.4. *Output for Additional Model Presented: Power, Unrestricted*

Franc et al., 2001: S-D Rats, Relative Liver Weight

```
  ================================================================
          Power Model. (Version: 2.15;  Date: 04/07/2008)
          Input Data File: C:\1\88_Franc_2001_SD_RelLivWt_PowerCV_U_1.(d)
          Gnuplot Plotting File:  C:\1\88_Franc_2001_SD_RelLivWt_PowerCV_U_1.plt
                                                Fri Apr 16 16:28:46 2010
  ================================================================

 Figure 5, SD rats, relative liver weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

    The form of the response function is:

    Y[dose] = control + slope * dose^power


    Dependent variable = Mean
    Independent variable = Dose
    rho is set to 0
    The power is not restricted
    A constant variance model is fit
```

```
   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                          alpha =      527.447
                            rho =            0   Specified
                        control =          100
                          slope =      1.15946
                          power =     0.839423


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been specified by the user,
                and do not appear in the correlation matrix )

                    alpha      control        slope        power

      alpha             1       1e-009    -6.2e-010     4.7e-010

    control       1e-009            1        -0.74         0.71

      slope    -6.2e-010        -0.74            1           -1

      power     4.7e-010         0.71           -1            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
          alpha          462.394          115.598           235.825             688.963
        control          100.636          7.29156           86.3448             114.927
          slope         0.650456          1.43713          -2.16627             3.46718
          power         0.961853         0.465182         0.0501134             1.87359


      Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     8        100          101           14         21.5        -0.0836
   10     8        108          107         16.9         21.5          0.192
   30     8        117          118         25.9         21.5         -0.128
  100     8        155          155         30.9         21.5         0.0192


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
      Model A3 uses any fixed variance parameters that
      were specified by the user
```

```
Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                       Likelihoods of Interest

           Model      Log(likelihood)   # Param's      AIC
            A1         -114.152281            5     238.304562
            A2         -111.103649            8     238.207299
            A3         -114.152281            5     238.304562
         fitted        -114.182670            4     236.365340
             R         -125.052064            2     254.104127


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              27.8968          6          <.0001
   Test 2              6.09726          3           0.107
   Test 3              6.09726          3           0.107
   Test 4            0.0607785          1          0.8053

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


               Benchmark Dose Computation

Specified effect =           0.1

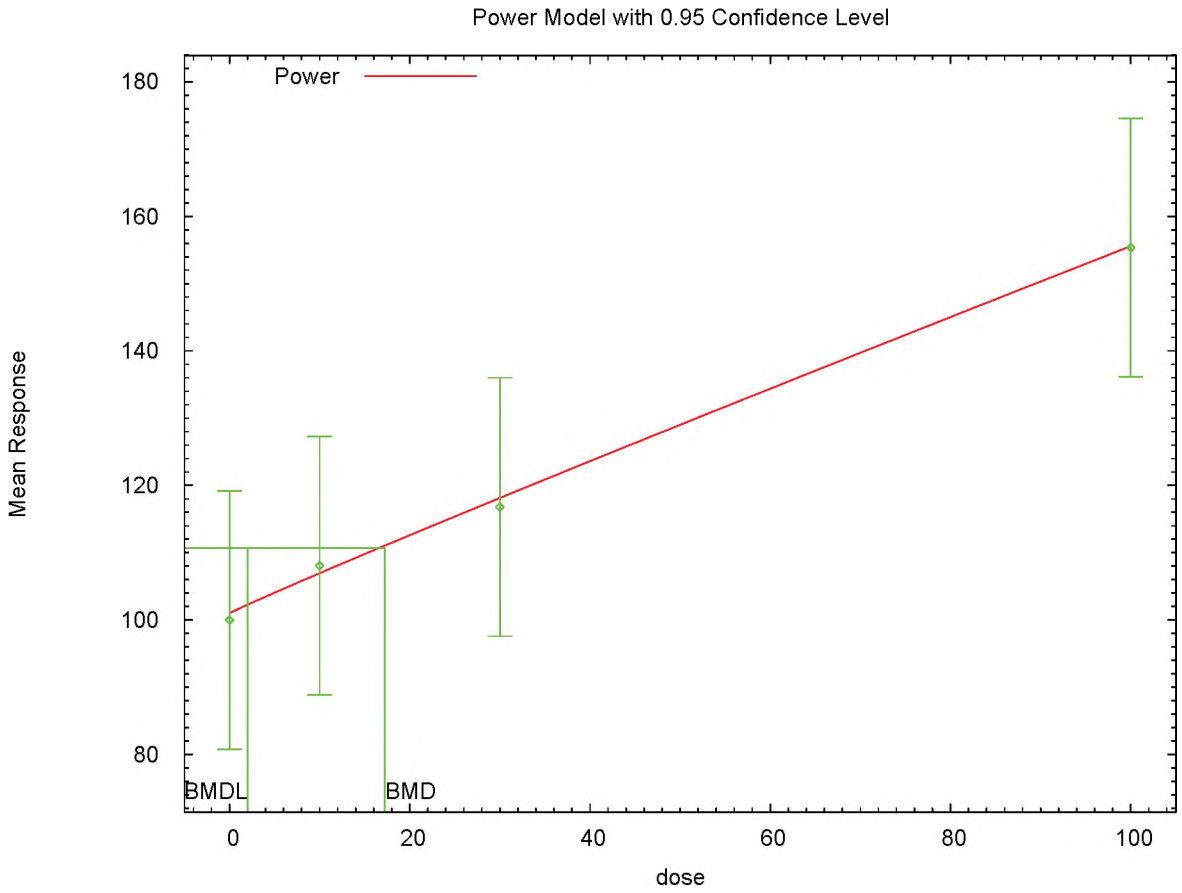
Risk Type        =     Relative risk

Confidence level =          0.95

             BMD = 17.2469


            BMDL = 2.00336
```

E.3.9.5. *Figure for Additional Model Presented: Power, Unrestricted*



E.3.10. Franc et al., 2001: L-E Rats, Relative Liver Weight

E.3.10.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2)	2	0.245	210.148	5.143E+01	3.188E+01	
exponential (M3)	2	0.245	210.148	5.143E+01	3.188E+01	power hit bound (d = 1)
exponential (M4)	1	0.607	209.599	1.476E+01	3.702E+00	
exponential (M5)	1	0.607	209.599	1.476E+01	3.702E+00	power hit bound (d = 1)
Hill [b]	1	0.703	209.480	1.321E+01	1.591E+00	n lower bound hit (n = 1)
linear	2	0.273	209.933	4.753E+01	2.788E+01	
polynomial, 3-degree	1	<0.0001	10.000	1.505E+01	error	
power	2	0.273	209.933	4.753E+01	2.788E+01	power bound hit (power = 1)
Hill, unrestricted [c]	0	N/A	211.341	1.163E+01	9.756E-01	unrestricted (n = 0.418)
power, unrestricted	1	0.940	209.340	1.155E+01	1.513E-02	unrestricted (power = 0.394)

[a] Non-constant variance model selected ($p = 0.0632$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.3.10.2. *Output for Selected Model: Hill*

Franc et al., 2001: L-E Rats, Relative Liver Weight

```
 ======================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\1\89_Franc_2001_LE_RelLivWt_Hill_1.(d)
         Gnuplot Plotting File:  C:\1\89_Franc_2001_LE_RelLivWt_Hill_1.plt
                                              Fri Apr 16 16:29:20 2010
 ======================================================================

 Figure 5, L-E rats, relative liver weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   Power parameter restricted to be greater than 1
```

The variance is to be modeled as Var(i) = exp(lalpha + rho * ln(mean(i)))

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	5.41581
rho =	0
intercept =	100
v =	22.225
n =	0.329526
k =	40.8403

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -n
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	lalpha	rho	intercept	v	k
lalpha	1	-1	-0.18	0.38	0.2
rho	-1	1	0.17	-0.38	-0.2
intercept	-0.18	0.17	1	-0.13	0.39
v	0.38	-0.38	-0.13	1	0.77
k	0.2	-0.2	0.39	0.77	1

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
lalpha	-15.3958	17.0376	-48.7889	17.9973
rho	4.38043	3.61867	-2.71204	11.4729
intercept	99.5667	3.7178	92.28	106.853
v	28.8965	12.6477	4.10739	53.6856
n	1	NA		
k	25.1273	30.138	-33.9421	84.1966

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	100	99.6	10	10.8	0.114
10	8	106	108	17.9	12.8	-0.329
30	8	117	115	8.97	14.9	0.288
100	8	122	123	19.9	17	-0.0723

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                      Likelihoods of Interest

           Model      Log(likelihood)   # Param's      AIC
            A1         -100.516456            5     211.032912
            A2          -96.870820            8     209.741641
            A3          -99.666984            6     211.333969
        fitted          -99.739888            5     209.479776
             R         -105.717087            2     215.434174


                  Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value

  Test 1              17.6925          6        0.007048
  Test 2              7.29127          3         0.06317
  Test 3              5.59233          2         0.06104
  Test 4             0.145807          1          0.7026

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =           0.1

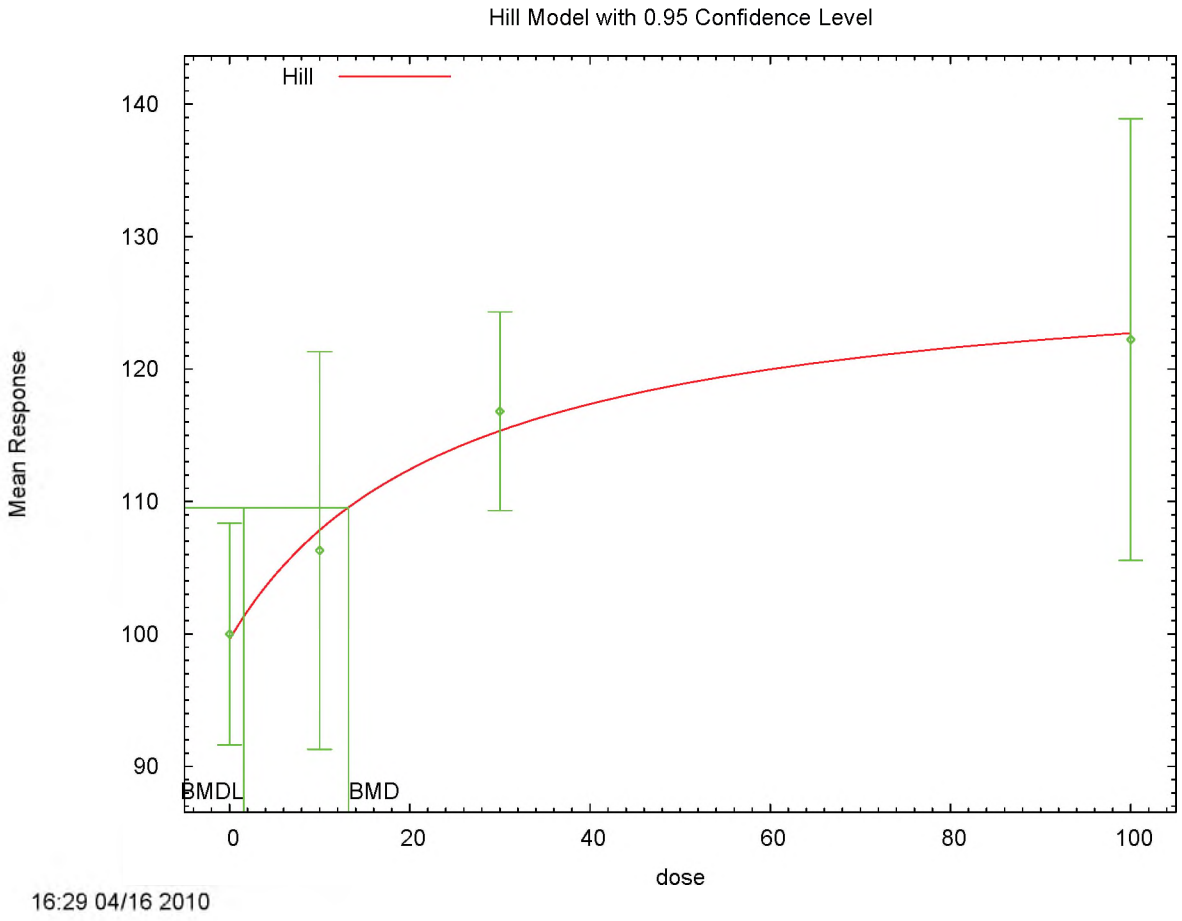
Risk Type        =     Relative risk

Confidence level =           0.95

             BMD =        13.2094

            BMDL =       1.59127
```

E.3.10.3. *Figure for Selected Model: Hill*



E.3.10.4. *Output for Additional Model Presented: Hill, Unrestricted*

Franc et al., 2001: L-E Rats, Relative Liver Weight

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\1\89_Franc_2001_LE_RelLivWt_Hill_U_1.(d)
         Gnuplot Plotting File:  C:\1\89_Franc_2001_LE_RelLivWt_Hill_U_1.plt
                                          Fri Apr 16 16:29:27 2010
 ================================================================

 Figure 5, L-E rats, relative liver weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   Power parameter is not restricted
   The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

   Total number of dose groups = 4
```

```
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                         lalpha =      5.41581
                            rho =            0
                      intercept =          100
                              v =       22.225
                              n =     0.329526
                              k =      40.8403


           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho    intercept            v            n            k

    lalpha            1           -1        -0.21       -0.099         0.23        -0.13

       rho           -1            1         0.21        0.099        -0.23         0.13

 intercept        -0.21         0.21            1        0.023         0.14        0.011

         v       -0.099        0.099        0.023            1        -0.84            1

         n         0.23        -0.23         0.14        -0.84            1        -0.88

         k        -0.13         0.13        0.011            1        -0.88            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha         -18.8355         18.0637           -54.2397             16.5688
            rho           5.1098         3.83743           -2.41144              12.631
      intercept            99.526         3.53402            92.5994             106.453
              v          286.422          4487.2           -8508.33             9081.17
              n         0.418159         0.457476          -0.478477             1.31479
              k          32981.9     1.52481e+006       -2.95559e+006        3.02155e+006


      Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     8        100          99.5           10         10.3           0.13
   10     8        106           109         17.9           13         -0.563
   30     8        117           114         8.97         14.6          0.529
  100     8        122           123         19.9         17.7        -0.0942

Degrees of freedom for Test A3 vs fitted <= 0


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2
```

```
Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1         -100.516456            5     211.032912
             A2          -96.870820            8     209.741641
             A3          -99.666984            6     211.333969
          fitted         -99.670736            6     211.341472
              R         -105.717087            2     215.434174


                   Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value

  Test 1              17.6925          6        0.007048
  Test 2              7.29127          3         0.06317
  Test 3              5.59233          2         0.06104
  Test 4           0.00750301          0              NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-Square
     test for fit is not valid


        Benchmark Dose Computation

Specified effect =           0.1

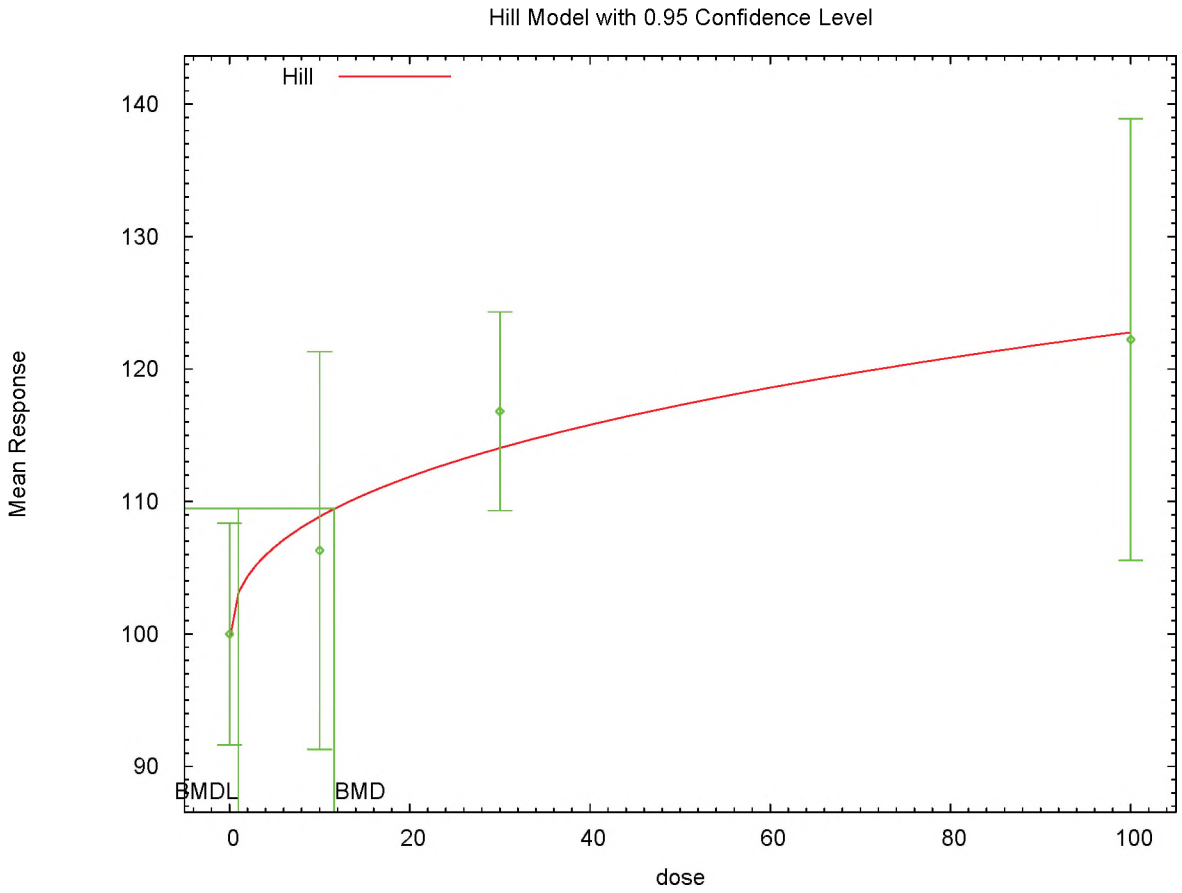
Risk Type        =     Relative risk

Confidence level =           0.95

             BMD =        11.6342

            BMDL =      0.975601
```

E.3.10.5. *Figure for Additional Model Presented: Hill, Unrestricted*



E.3.11. Franc et al., 2001: S-D Rats, Relative Thymus Weight

E.3.11.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2)	2	0.551	285.890	6.730E+00	3.627E+00	
exponential (M3)	1	<0.0001	303.995	3.858E+02	6.615E-01	
exponential (M4) [b]	1	0.972	286.698	3.559E+00	1.714E+00	
exponential (M5)	0	N/A	288.696	3.796E+00	1.714E+00	
Hill	0	N/A	288.696	4.299E+00	9.311E-01	
linear	2	0.252	287.456	1.330E+01	1.062E+01	
polynomial, 3-degree [c]	2	0.252	287.456	1.330E+01	1.062E+01	
power	2	0.252	287.456	1.330E+01	1.062E+01	power bound hit (power = 1)
power, unrestricted	1	0.510	287.131	5.049E-01	4.411E-04	unrestricted (power = 0.388)

[a] Non-constant variance model selected ($p = 0.0320$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.3.11.2. *Output for Selected Model: Exponential (M4)*

Franc et al., 2001: S-D Rats, Relative Thymus Weight

```
 ================================================================
          Exponential Model. (Version: 1.61;  Date: 7/24/2009)
          Input Data File: C:\1\91_Franc_2001_SD_RelThyWt_Exp_1.(d)
          Gnuplot Plotting File:
                                                 Fri Apr 16 16:30:07 2010
 ================================================================

 Figure 5, SD rats, relative thymus weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
```

```
   Model 3 is nested within Model 5.
   Model 4 is nested within Model 5.


Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


                Initial Parameter Values

                Variable          Model 4
                --------          --------
                  lnalpha             3.35464
                      rho             1.08199
                        a                 105
                        b           0.0424361
                        c            0.206726
                        d                   1



                  Parameter Estimates

                 Variable          Model 4
                 --------          -------
                  lnalpha            2.54324
                      rho            1.25901
                        a            108.904
                        b          0.0379343
                        c           0.208146
                        d                  1


         Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
     0      8          100          83.2
    10      8        91.17        47.97
    30      8        51.41        43.48
   100      8        22.79        29.98


                Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
     0         108.9        68.33          -0.3686
    10         81.68        57.01           0.4706
    30          50.3        42.02           0.0748
   100         24.61        26.79           -0.192


Other models for which likelihoods are calculated:

  Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

```

```
  Model A2:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
              Var{e(ij)} = Sigma^2


                            Likelihoods of Interest

                  Model      Log(likelihood)      DF         AIC
                 -------    ------------------    ----   ------------
                     A1       -141.9834            5      293.9669
                     A2       -137.5818            8      291.1637
                     A3       -138.3482            6      288.6964
                      R       -146.9973            2      297.9946
                      4       -138.3488            5      286.6976


Additive constant for all log-likelihoods =     -29.41.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.


                             Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)


                         Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                      18.83             6           0.004459
  Test 2                      8.803             3            0.03203
  Test 3                      1.533             2             0.4647
 Test 6a                   0.001216             1             0.9722


  The p-value for Test 1 is less than .05.  There appears to be a
  difference between response and/or variances among the dose
  levels, it seems appropriate to model the data.

  The p-value for Test 2 is less than .1.  A non-homogeneous
  variance model appears to be appropriate.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 6a is greater than .1.  Model 4 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 0.100000

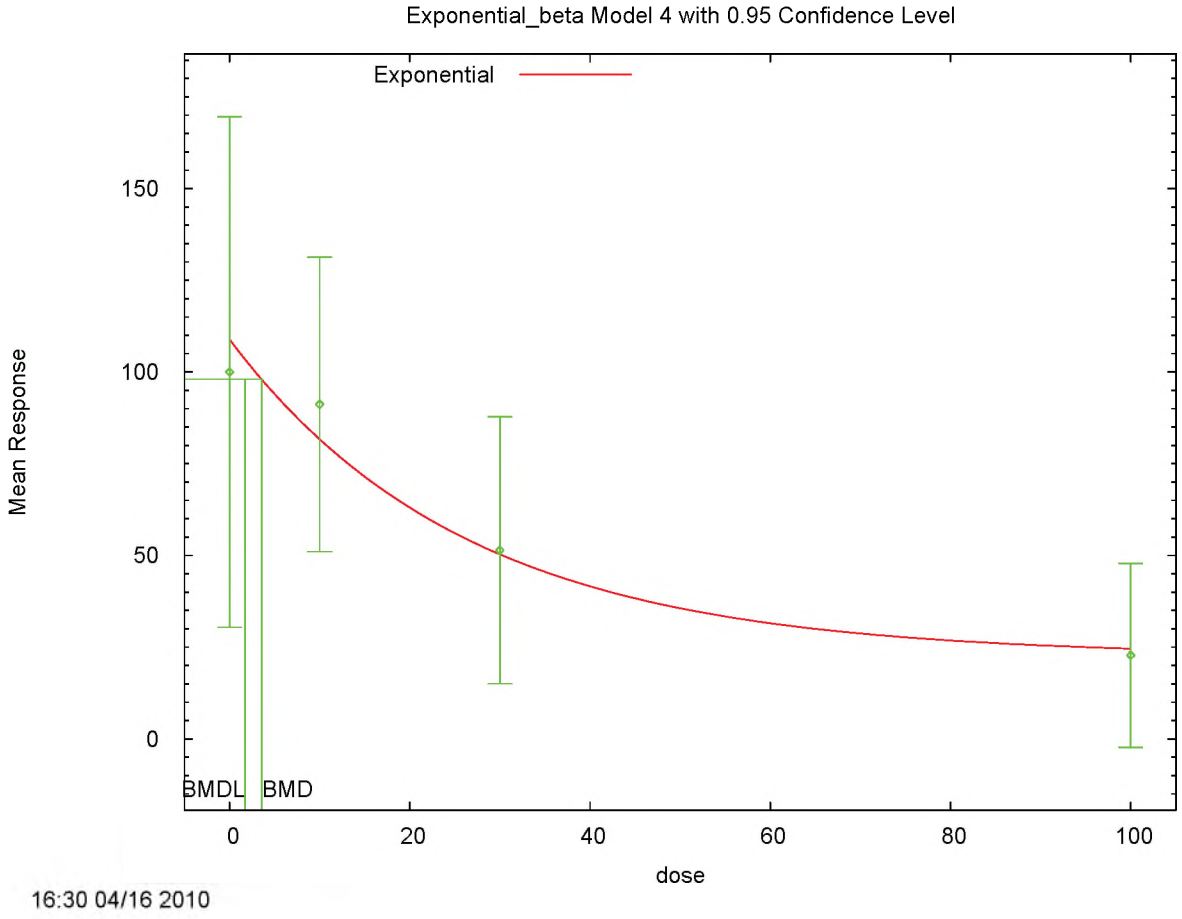
         Risk Type = Relative deviation

  Confidence Level = 0.950000

               BMD =      3.55883

              BMDL =      1.71399
```

E.3.11.3. *Figure for Selected Model: Exponential (M4)*



E.3.11.4. *Output for Additional Model Presented: Polynomial, 3-Degree*

Franc et al., 2001: S-D Rats, Relative Thymus Weight

```
 ================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\1\91_Franc_2001_SD_RelThyWt_Poly_1.(d)
         Gnuplot Plotting File:  C:\1\91_Franc_2001_SD_RelThyWt_Poly_1.plt
                                              Fri Apr 16 16:30:11 2010
 ================================================================

 Figure 5, SD rats, relative thymus weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   The polynomial coefficients are restricted to be negative
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 4
```

```
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                         lalpha =       8.0075
                            rho =            0
                         beta_0 =          100
                         beta_1 =    -0.352259
                         beta_2 =   -0.0585481
                         beta_3 =            0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -beta_2    -beta_3
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

                 lalpha          rho       beta_0       beta_1

    lalpha            1        -0.99        0.031       -0.016

       rho        -0.99            1       -0.034        0.022

    beta_0        0.031       -0.034            1        -0.84

    beta_1       -0.016        0.022        -0.84            1


                                 Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha          2.92328           1.7394          -0.485884             6.33243
            rho          1.18295         0.423359           0.353177             2.01271
         beta_0           89.841          13.7418            62.9076             116.774
         beta_1        -0.675682         0.175538           -1.01973           -0.331634
         beta_2                0               NA
         beta_3                0               NA

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0       8        100         89.8         83.2         61.7          0.466
   10       8       91.2         83.1           48         58.9          0.388
   30       8       51.4         69.6         43.5           53         -0.968
  100       8       22.8         22.3           30           27         0.0543


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
```

```
            Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
      Model A3 uses any fixed variance parameters that
      were specified by the user

 Model  R:         Yi = Mu + e(i)
             Var{e(i)} = Sigma^2


                        Likelihoods of Interest

             Model      Log(likelihood)   # Param's      AIC
              A1         -141.983433            5     293.966865
              A2         -137.581833            8     291.163667
              A3         -138.348184            6     288.696368
           fitted        -139.728204            4     287.456407
               R         -146.997301            2     297.994602


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                      Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              18.8309          6        0.004459
   Test 2               8.8032          3         0.03203
   Test 3               1.5327          2          0.4647
   Test 4              2.76004          2          0.2516

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


             Benchmark Dose Computation

Specified effect =           0.1

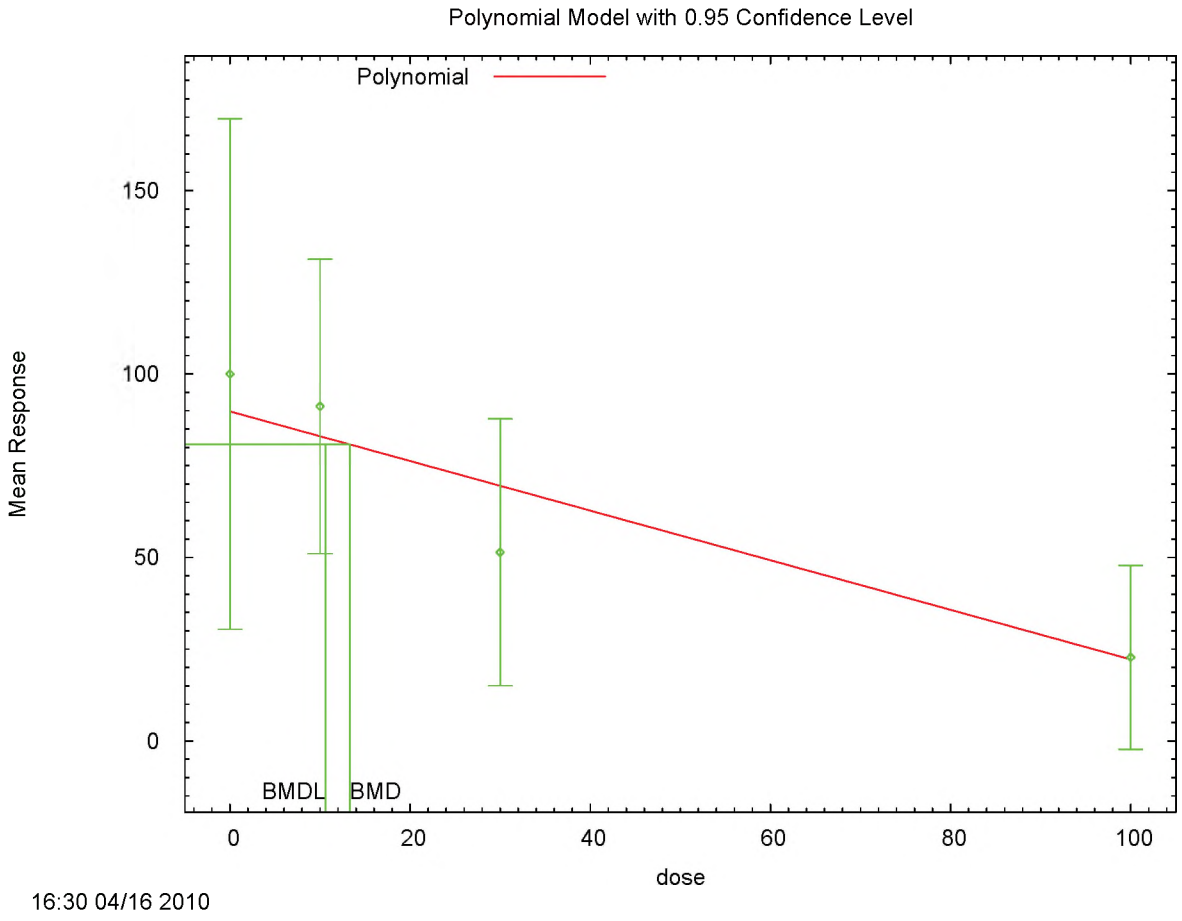
Risk Type        =     Relative risk

Confidence level =          0.95

             BMD =        13.2963


             BMDL =        10.6163
```

E.3.11.5. *Figure for Additional Model Presented: Polynomial, 3-Degree*



E.3.12. Franc et al., 2001: L-E Rats, Relative Thymus Weight

E.3.12.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2)	2	0.394	301.666	6.406E+00	2.122E+00	
exponential (M3)	2	0.394	301.666	6.406E+00	2.122E+00	power hit bound (d = 1)
exponential (M4) [b]	1	0.317	302.808	3.520E+00	1.067E+00	
exponential (M5)	0	N/A	303.805	1.280E+01	1.450E+00	
Hill	0	N/A	303.805	1.195E+01	9.965E-01	
linear	2	0.236	302.690	1.429E+01	9.087E+00	
polynomial, 3-degree	2	0.236	302.690	1.429E+01	9.087E+00	
power	2	0.236	302.690	1.429E+01	9.087E+00	power bound hit (power = 1)
power, unrestricted	1	0.175	303.643	1.297E+00	2.703E-08	unrestricted (power = 0.454)

[a] Constant variance model selected ($p = 0.5063$)

[b] Best-fitting model, BMDS output presented in this appendix

E.3.12.2. *Output for Selected Model: Exponential (M4)*

Franc et al., 2001: L-E Rats, Relative Thymus Weight

```
 ========================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\1\92_Franc_2001_LE_RelThyWt_ExpCV_1.(d)
         Gnuplot Plotting File:
                                                  Fri Apr 16 16:30:58 2010
 ========================================================================

 Figure 5, L-E rats, relative thymus weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.
```

Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	8.1814
rho(S)	0
a	105
b	0.0413945
c	0.3173
d	1

(S) = Specified

Parameter Estimates

Variable	Model 4
lnalpha	8.21275
rho	0
a	106.57
b	0.0425967
c	0.28189
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	8	100	54.72
10	8	95.41	70.46
30	8	38.69	47.97
100	8	34.98	77.96

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	106.6	60.73	-0.306
10	80.03	60.73	0.7164
30	51.36	60.73	-0.5902
100	31.12	60.73	0.1798

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

```
  Model A2:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
              Var{e(ij)} = Sigma^2


                            Likelihoods of Interest

                  Model      Log(likelihood)      DF         AIC
                 -------    -----------------    ----   ------------
                     A1       -146.9024            5      303.8049
                     A2       -145.7361            8      307.4723
                     A3       -146.9024            5      303.8049
                      R       -150.6049            2      305.2098
                      4        -147.404            4      302.8079


Additive constant for all log-likelihoods =     -29.41.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.


                             Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)


                         Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                      9.738             6             0.1362
  Test 2                      2.333             3             0.5063
  Test 3                      2.333             3             0.5063
 Test 6a                      1.003             1             0.3166


  The p-value for Test 1 is greater than .05.  There may not be a
  diffence between responses and/or variances among the dose levels
  Modelling the data with a dose/response curve may not be appropriate.

  The p-value for Test 2 is greater than .1.  A homogeneous
  variance model appears to be appropriate here.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 6a is greater than .1.  Model 4 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 0.100000

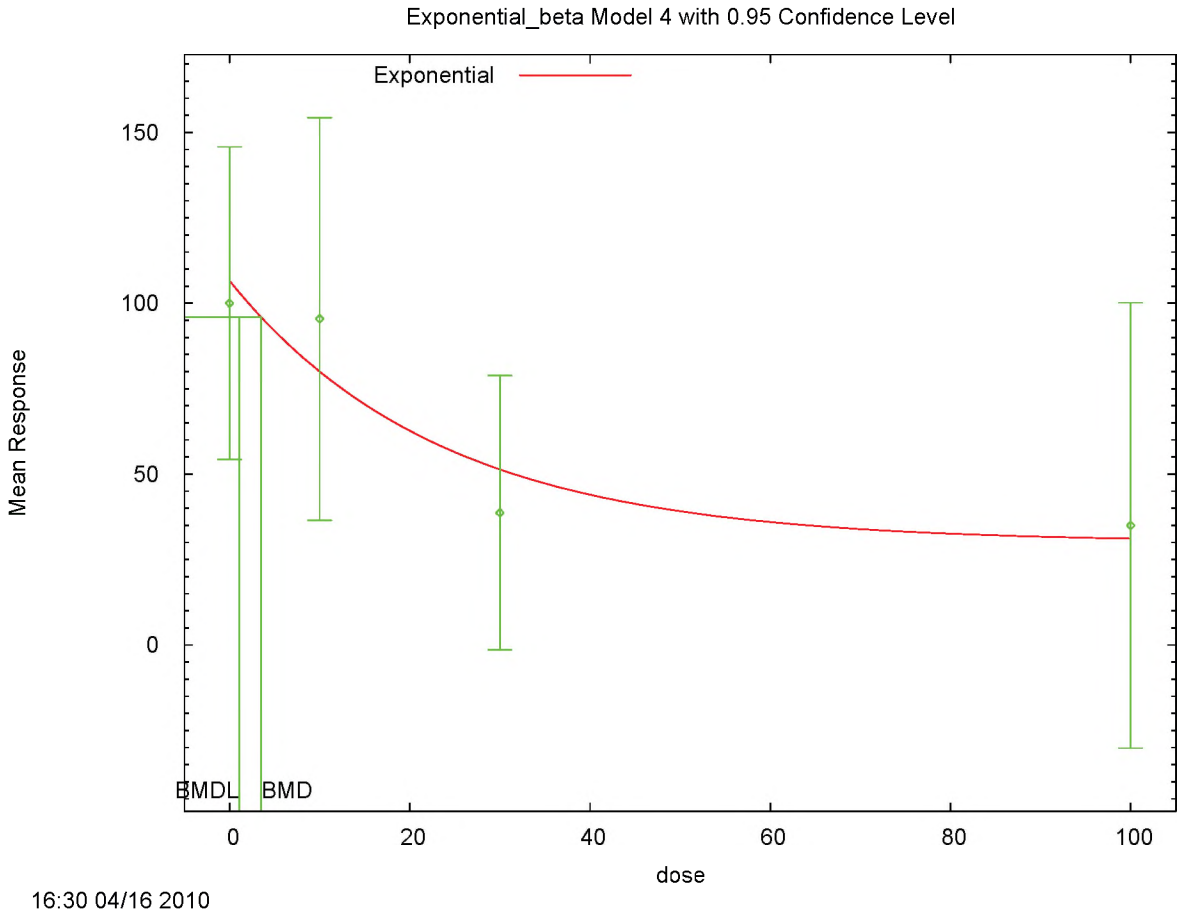
         Risk Type = Relative deviation

  Confidence Level = 0.950000

               BMD =      3.52038
```

BMDL = 1.06729

E.3.12.3. *Figure for Selected Model: Exponential (M4)*



16:30 04/16 2010

E.3.13. Franc et al., 2001: H/W Rats, Relative Thymus Weight

E.3.13.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2) [c]	2	0.682	261.694	1.366E+01	8.014E+00	
exponential (M3)	2	0.682	261.694	1.366E+01	8.014E+00	power hit bound (d = 1)
exponential (M4) [b]	1	0.512	263.358	8.820E+00	3.219E+00	
exponential (M5)	0	N/A	264.927	1.776E+01	3.500E+00	
Hill	0	N/A	264.927	1.701E+01	2.729E+00	
linear	2	0.543	262.148	1.919E+01	1.373E+01	
polynomial, 3-degree	2	0.543	262.148	1.919E+01	1.373E+01	
power	2	0.543	262.148	1.919E+01	1.373E+01	power bound hit (power = 1)
power, unrestricted	1	0.381	263.694	8.127E+00	1.406E-01	unrestricted (power = 0.665)

[a] Constant variance model selected ($p = 0.4331$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.3.13.2. *Output for Selected Model: Exponential (M2)*

Franc et al., 2001: H/W Rats, Relative Thymus Weight

```
 ================================================================
          Exponential Model. (Version: 1.61;  Date: 7/24/2009)
          Input Data File: C:\1\93_Franc_2001_HW_RelThyWt_ExpCV_1.(d)
          Gnuplot Plotting File:
                                                 Fri Apr 16 16:31:40 2010
 ================================================================

 Figure 5, H/W rats, relative thymus weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
```

```
   Model 3 is nested within Model 5.
   Model 4 is nested within Model 5.


Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


               Initial Parameter Values

               Variable          Model 2
               --------          --------
                 lnalpha             6.96647
                     rho(S)                0
                       a              59.5084
                       b            0.00715458
                       c                     0
                       d                     1

  (S) = Specified


                  Parameter Estimates

                Variable          Model 2
                --------          -------
                 lnalpha           6.99043
                     rho                 0
                       a           99.7761
                       b        0.00771341
                       c                 0
                       d                 1


         Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
     0      8          100         35.98
    10      8         97.53        32.98
    30      8         71.02        23.99
   100      8         49.29        43.48


               Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
      0         99.78        32.96          0.01921
     10         92.37        32.96           0.4426
     30         79.16        32.96          -0.6986
    100         46.14        32.96            0.271


Other models for which likelihoods are calculated:
```

```
  Model A1:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
              Var{e(ij)} = Sigma^2


                              Likelihoods of Interest

                    Model      Log(likelihood)      DF         AIC
                    -------    -----------------    ----   ------------
                       A1       -127.4636           5      264.9271
                       A2       -126.0925           8       268.185
                       A3       -127.4636           5      264.9271
                        R        -132.935           2        269.87
                        2        -127.8469          3      261.6939


Additive constant for all log-likelihoods =     -29.41.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.


                               Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does Model 2 fit the data? (A3 vs. 2)


                           Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                        13.69           6             0.03336
  Test 2                        2.742           3              0.4331
  Test 3                        2.742           3              0.4331
  Test 4                       0.7668           2              0.6815


  The p-value for Test 1 is less than .05.  There appears to be a
  difference between response and/or variances among the dose
  levels, it seems appropriate to model the data.

  The p-value for Test 2 is greater than .1.  A homogeneous
  variance model appears to be appropriate here.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 4 is greater than .1.  Model 2 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 0.100000

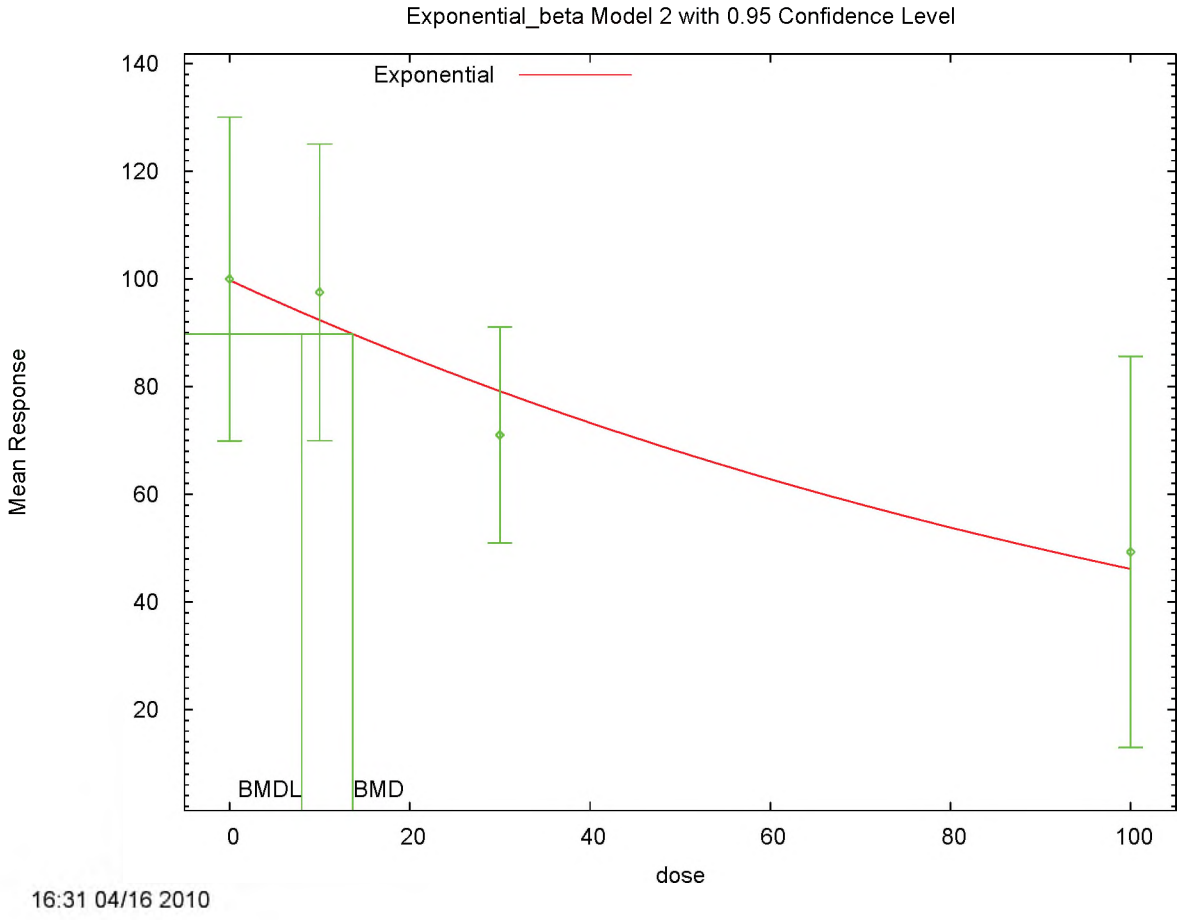
         Risk Type = Relative deviation

  Confidence Level = 0.950000

              BMD =      13.6594
```

```
BMDL =      8.01373
```

E.3.13.3. *Figure for Selected Model: Exponential (M2)*



E.3.13.4. *Output for Additional Model Presented: Exponential (M4)*

Franc et al., 2001: H/W Rats, Relative Thymus Weight

```
==============================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\93_Franc_2001_HW_RelThyWt_ExpCV_1.(d)
        Gnuplot Plotting File:
                                                  Fri Apr 16 16:31:40 2010
==============================================================================

 Figure 5, H/W rats, relative thymus weight
------------------------------------------------------------------------------

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.
```

```
   Model 2 is nested within Models 3 and 4.
   Model 3 is nested within Model 5.
   Model 4 is nested within Model 5.


Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


              Initial Parameter Values

              Variable          Model 4
              --------          --------
                lnalpha             6.96647
                    rho(S)                0
                      a                 105
                      b             0.03169
                      c            0.447105
                      d                   1

  (S) = Specified


                Parameter Estimates

               Variable          Model 4
               --------          -------
                lnalpha            6.97993
                    rho                  0
                      a            103.091
                      b            0.02048
                      c           0.394904
                      d                  1


        Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
     0      8          100        35.98
    10      8         97.53       32.98
    30      8         71.02       23.99
   100      8         49.29       43.48


              Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
     0         103.1        32.78          -0.2667
    10         91.54        32.78           0.5166
    30         74.46        32.78          -0.2961
   100         48.76        32.78          0.04621
```

Other models for which likelihoods are calculated:

```
  Model A1:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
              Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-127.4636	5	264.9271
A2	-126.0925	8	268.185
A3	-127.4636	5	264.9271
R	-132.935	2	269.87
4	-127.6789	4	263.3577

Additive constant for all log-likelihoods = -29.41. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	13.69	6	0.03336
Test 2	2.742	3	0.4331
Test 3	2.742	3	0.4331
Test 6a	0.4306	1	0.5117

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data.

Benchmark Dose Computations:

Specified Effect = 0.100000

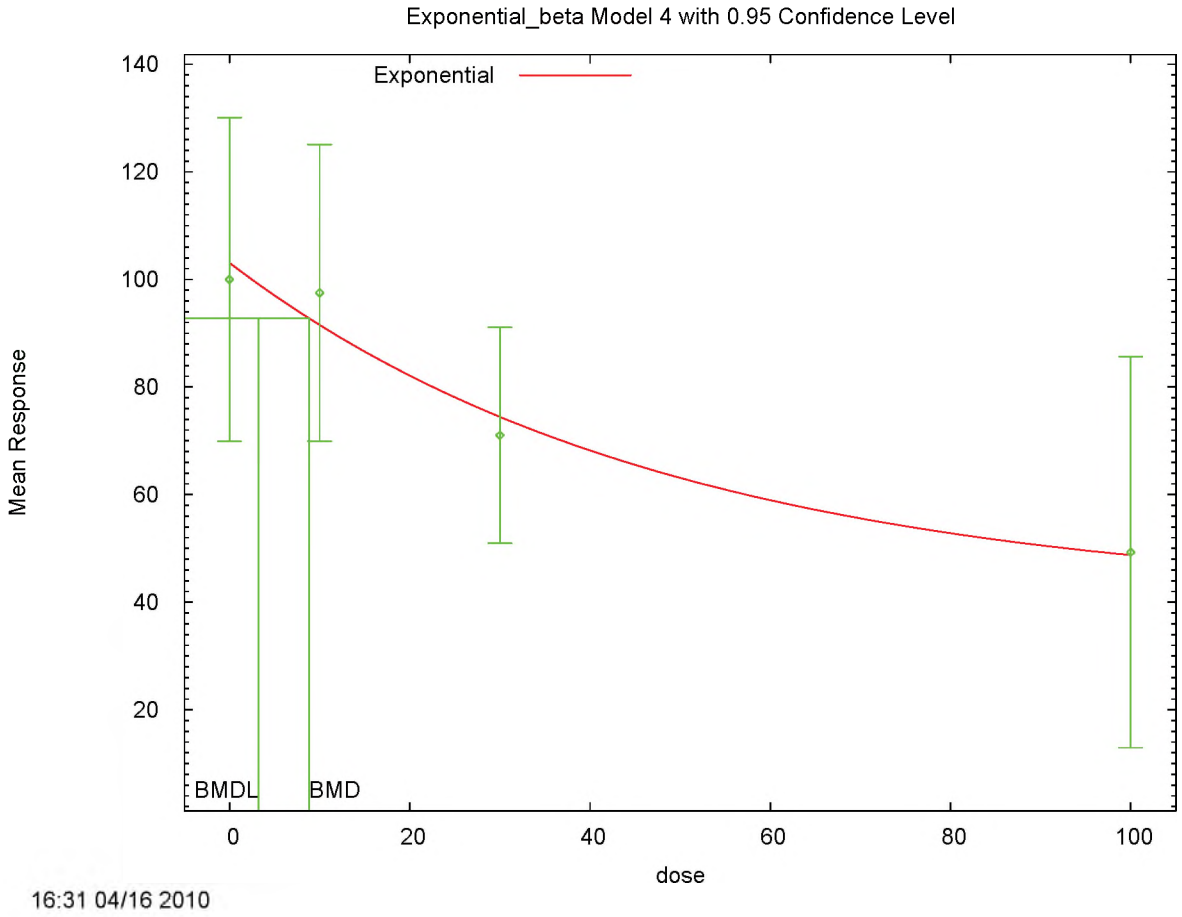
Risk Type = Relative deviation

```
Confidence Level = 0.950000

BMD =      8.82023

BMDL =      3.21928
```

E.3.13.5. *Figure for Additional Model Presented: Exponential (M4)*



E.3.14. Hojo et al., 2002: DRL Reinforce Per Minute

E.3.14.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Hill	0	N/A	6.465	2.060E+01	1.713E-05	
linear [b]	**2**	**0.008**	**9.552**	**2.677E+02**	**1.100E+02**	
polynomial, 3-degree	2	0.008	9.552	2.677E+02	1.100E+02	
power	2	0.008	9.552	2.677E+02	1.100E+02	power bound hit (power = 1)
power, unrestricted	1	0.025	6.780	2.187E+00	4.612E-08	unrestricted (power = 0.089)
exponential (M2)	2	0.006	9.894	3.043E+02	1.505E+02	
exponential (M3)	2	0.006	9.894	3.043E+02	1.505E+02	power hit bound (d = 1)
exponential (M4) [c]	1	0.062	5.241	1.734E+01	3.827E-02	
exponential (M5)	0	N/A	6.465	2.140E+01	1.240E-05	

[a] Constant variance model selected ($p = 0.4321$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.3.14.2. *Output for Selected Model: Linear*

Hojo et al., 2002: DRL Reinforce Per Minute

```
 ================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\1\20_Hojo_2002_DRLrein_LinearCV_1.(d)
         Gnuplot Plotting File:  C:\1\20_Hojo_2002_DRLrein_LinearCV_1.plt
                                              Tue Feb 16 17:29:42 2010
 ================================================================

 Table 5
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   Total number of dose groups = 4
```

```
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                          alpha =     0.337763
                            rho =            0   Specified
                         beta_0 =       -0.404
                         beta_1 =   0.00249615


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -rho
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

                    alpha       beta_0       beta_1

      alpha             1    -1.4e-008     2.2e-008

     beta_0    -1.4e-008            1        -0.69

     beta_1     2.2e-008        -0.69            1


                                Parameter Estimates

                                                                95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
           alpha         0.435671         0.134451           0.172152             0.69919
          beta_0        -0.372098         0.198702          -0.761547            0.017352
          beta_1       0.00246548       0.00211361         -0.00167711          0.00660807


       Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

   0        5     -0.814       -0.372        0.448         0.66           -1.5
  20        5     -0.364       -0.323        0.821         0.66          -0.14
  60        6      0.374       -0.224         0.54         0.66           2.22
 180        5     -0.163       0.0717        0.443         0.66         -0.795


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	3.115550	5	3.768900
A2	4.489557	8	7.020886
A3	3.115550	5	3.768900
fitted	-1.775882	3	9.551763
R	-2.435087	2	8.870174

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	13.8493	6	0.03137
Test 2	2.74801	3	0.4321
Test 3	2.74801	3	0.4321
Test 4	9.78286	2	0.007511

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance
model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears
to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different
model

Benchmark Dose Computation

Specified effect = 1

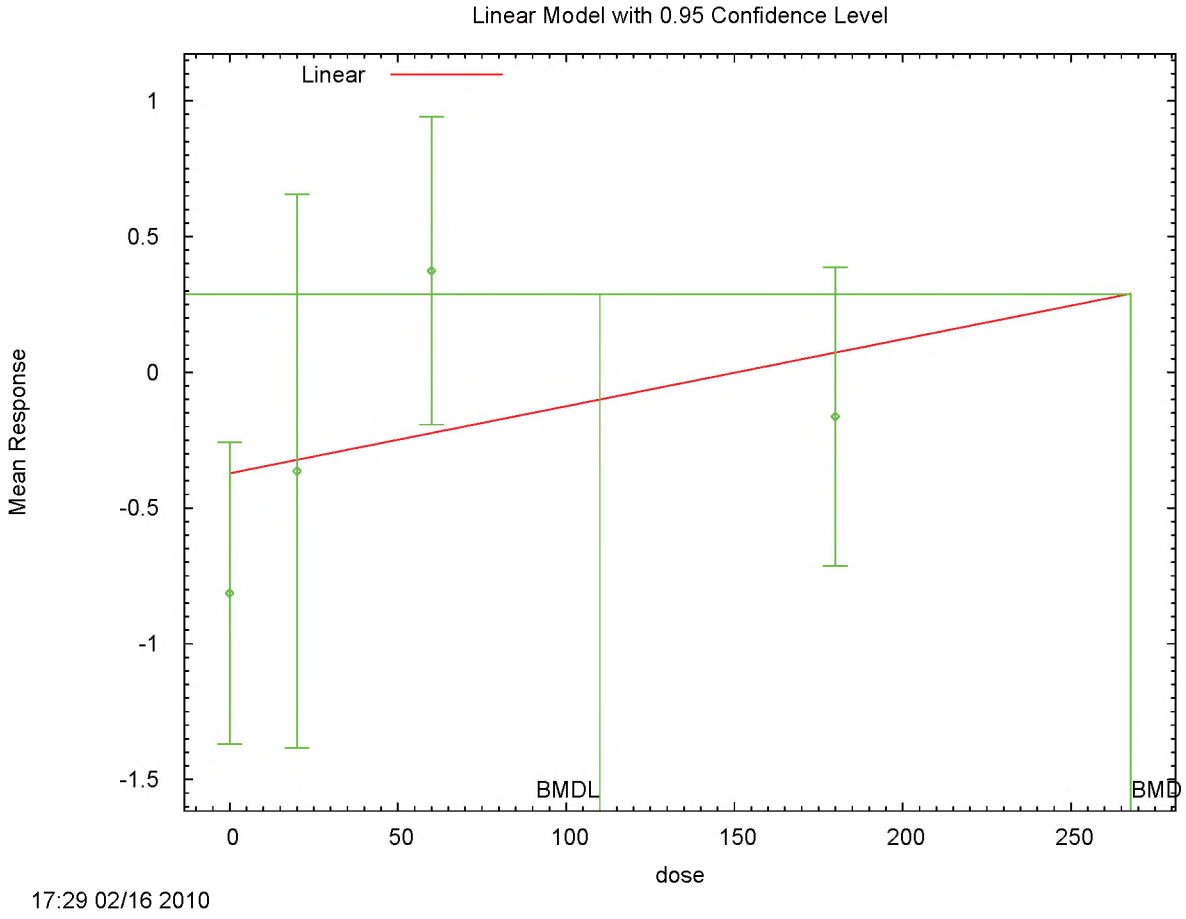
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 267.718

BMDL = 110.032

E.3.14.3. *Figure for Selected Model: Linear*



E.3.14.4. *Output for Additional Model Presented: Exponential (M4)*

Hojo et al., 2002: DRL Reinforce Per Minute

```
 ======================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\1\21_Hojo_2002_DRLrein_ExpCV_1.(d)
         Gnuplot Plotting File:
                                                Tue Feb 16 17:30:21 2010
 ======================================================================

 Table 5, values adjusted by a constant to allow exponential model
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.
```

```
   Model 2 is nested within Models 3 and 4.
   Model 3 is nested within Model 5.
   Model 4 is nested within Model 5.


Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


                Initial Parameter Values

                Variable          Model 4
                --------          --------
                  lnalpha             -1.29672
                      rho(S)                 0
                        a                0.0817
                        b             0.00880867
                        c                16.3733
                        d                      1

  (S) = Specified


                   Parameter Estimates

                  Variable          Model 4
                  --------          -------
                   lnalpha            -1.13136
                       rho                   0
                         a           0.0542868
                         b           0.0525016
                         c             18.5072
                         d                   1


          Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
     0       5        0.086        0.448
    20       5        0.536        0.821
    60       6        1.274         0.54
   180       5        0.737        0.443


                Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
      0       0.05429        0.568           0.1249
     20        0.6721        0.568          -0.5359
     60         0.964        0.568            1.337
    180         1.005        0.568           -1.054


Other models for which likelihoods are calculated:
```

```
  Model A1:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
              Var{e(ij)} = Sigma^2


                           Likelihoods of Interest

                 Model      Log(likelihood)      DF         AIC
                -------    -----------------    ----   ------------
                    A1         3.11555            5        3.7689
                    A2        4.489557            8       7.020886
                    A3         3.11555            5        3.7689
                     R        -2.435087           2       8.870174
                     4         1.379312           4       5.241376


Additive constant for all log-likelihoods =      -19.3.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.


                             Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)


                         Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                      13.85             6             0.03137
  Test 2                      2.748             3              0.4321
  Test 3                      2.748             3              0.4321
 Test 6a                      3.472             1              0.0624


  The p-value for Test 1 is less than .05.  There appears to be a
  difference between response and/or variances among the dose
  levels, it seems appropriate to model the data.

  The p-value for Test 2 is greater than .1.  A homogeneous
  variance model appears to be appropriate here.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 6a is less than .1.  Model 4 may not adequately
  describe the data; you may want to consider another model.


Benchmark Dose Computations:

  Specified Effect = 1.000000

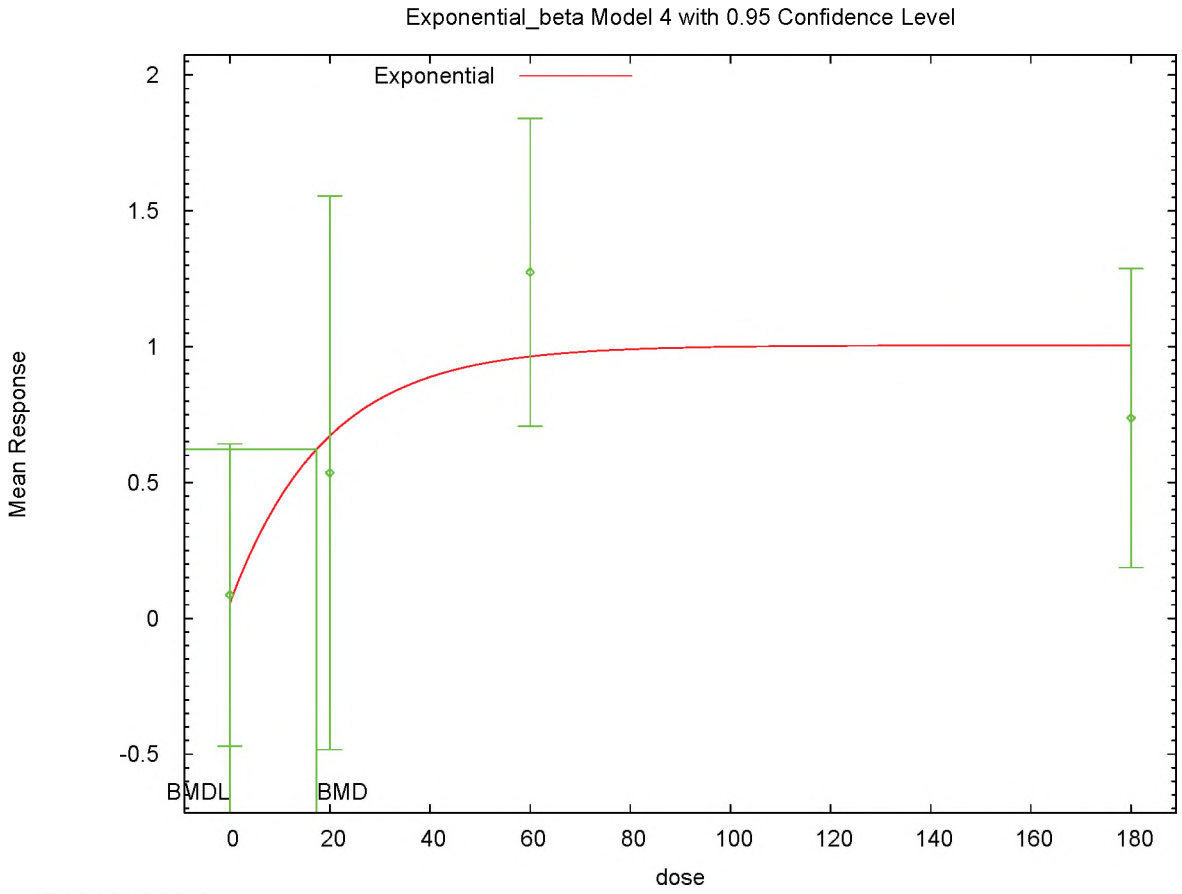
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000
```

```
BMD =      17.3391

BMDL =     0.0382689
```

E.3.14.5. *Figure for Additional Model Presented: Exponential (M4)*



E.3.15. Hojo et al., 2002: DRL Response Per Minute

E.3.15.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Hill	0	N/A	126.353	1.646E+01	1.800E-13	
linear	2	0.004	132.825	2.067E+02	9.757E+01	
polynomial, 3-degree	2	0.004	132.825	2.067E+02	9.757E+01	
power	2	0.004	132.825	2.067E+02	9.757E+01	power bound hit (power = 1)
power, unrestricted	2	0.741	122.455	1.800E+04	error	unrestricted (power = 0)
exponential (M2)	2	0.568	122.985	6.184E+00	error	
exponential (M3)	2	0.568	122.985	6.184E+00	error	power hit bound (d = 1)
exponential (M4) [b]	**1**	**0.479**	**124.356**	**4.775E+00**	**2.704E-01**	
exponential (M5)	0	N/A	126.353	1.118E+01	2.127E-01	

[a] Constant variance model selected ($p = 0.3004$)

[b] Best-fitting model, BMDS output presented in this appendix

E.3.15.2. *Output for Selected Model: Exponential (M4)*

Hojo et al., 2002: DRL Response Per Minute

```
 ================================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\1\23_Hojo_2002_DRLresp_ExpCV_1.(d)
         Gnuplot Plotting File:
                                                  Tue Feb 16 17:31:24 2010
 ================================================================================

 Table 5, values adjusted by a constant to allow exponential model
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.
```

Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	4.51689
rho(S)	0
a	24.6362
b	0.0212679
c	0.0184785
d	1

(S) = Specified

Parameter Estimates

Variable	Model 4
lnalpha	4.54075
rho	0
a	23.465
b	0.12859
c	0.100615
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	5	23.46	7.986
20	5	4.013	10.96
60	6	0.478	7.194
180	5	4.594	15.23

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	23.47	9.683	-0.0004677
20	3.973	9.683	0.009182
60	2.37	9.683	-0.4787
180	2.361	9.683	0.5157

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

```
  Model A2:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
              Var{e(ij)} = Sigma^2


                            Likelihoods of Interest

                 Model      Log(likelihood)      DF         AIC
                -------    -----------------    ----   ------------
                    A1       -57.92733           5      125.8547
                    A2       -56.09669           8      128.1934
                    A3       -57.92733           5      125.8547
                     R       -64.49611           2      132.9922
                     4       -58.17787           4      124.3557


Additive constant for all log-likelihoods =      -19.3.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.


                             Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)


                         Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                      16.8              6             0.01005
  Test 2                     3.661              3              0.3004
  Test 3                     3.661              3              0.3004
 Test 6a                    0.5011              1               0.479


  The p-value for Test 1 is less than .05.  There appears to be a
  difference between response and/or variances among the dose
  levels, it seems appropriate to model the data.

  The p-value for Test 2 is greater than .1.  A homogeneous
  variance model appears to be appropriate here.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 6a is greater than .1.  Model 4 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 1.000000

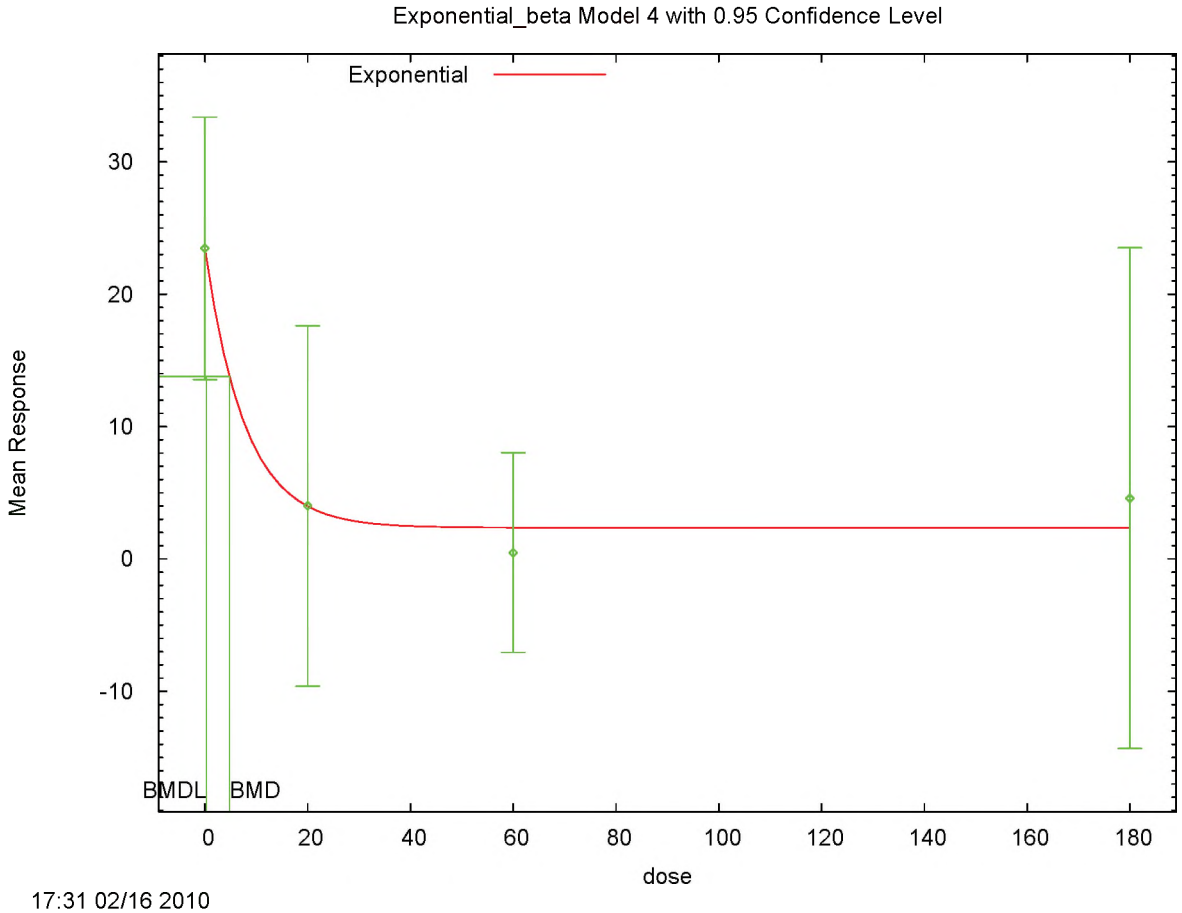
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD =      4.77493
```

BMDL = 0.270447

E.3.15.3. *Figure for Selected Model: Exponential (M4)*



E.3.16. Kattainen et al., 2001: 3rd Molar Eruption, Female

E.3.16.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
logistic	3	0.292	89.060	1.941E+02	1.390E+02	negative intercept (intercept = -1.508)
log-logistic [a]	**3**	**0.923**	**85.535**	**4.763E+01**	**2.481E+01**	**slope bound hit (slope = 1)**
log-probit	3	0.390	88.231	1.574E+02	9.512E+01	slope bound hit (slope = 1)
probit	3	0.306	88.919	1.858E+02	1.370E+02	negative intercept (intercept = -0.927)
multistage, 4-degree	3	0.641	86.798	8.677E+01	5.520E+01	final ß = 0
log-logistic, unrestricted [b]	2	0.952	87.157	2.599E+01	1.730E+00	unrestricted (slope = 0.794)
log-probit, unrestricted	2	0.941	87.179	2.813E+01	2.334E+00	unrestricted (slope = 0.478)

[a] Best-fitting model, BMDS output presented in this appendix

[b] Alternate model, BMDS output also presented in this appendix

E.3.16.2. *Output for Selected Model: Log-Logistic*

Kattainen et al., 2001: 3rd Molar Eruption, Female

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\1\24_Katt_2001_Erup_LogLogistic_BMR1.(d)
         Gnuplot Plotting File:  C:\1\24_Katt_2001_Erup_LogLogistic_BMR1.plt
                                              Tue Feb 16 17:31:52 2010
 ================================================================

 Figure 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model
```

```
                    Default Initial Parameter Values
                       background =       0.0625
                        intercept =       -6.063
                            slope =            1


             Asymptotic Correlation Matrix of Parameter Estimates

             ( *** The model parameter(s)  -slope
                   have been estimated at a boundary point, or have been specified by the user,
                   and do not appear in the correlation matrix )

               background    intercept

background            1        -0.56

 intercept        -0.56            1


                                  Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background        0.0846785            *               *                   *
      intercept         -6.06063            *               *                   *
          slope                1            *               *                   *

* - Indicates that this value is not calculated.


                         Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -40.5286         5
    Fitted model       -40.7674         2      0.477533      3          0.9238
   Reduced model       -50.7341         1        20.411      4        0.0004142

            AIC:         85.5347


                                  Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size        Residual
   ---------------------------------------------------------------------
     0.0000     0.0847         1.355     1.000          16       -0.319
    30.0000     0.1445         2.457     3.000          17        0.374
   100.0000     0.2578         3.867     4.000          15        0.078
   300.0000     0.4615         5.538     6.000          12        0.267
  1000.0000     0.7254        13.782    13.000          19       -0.402

 Chi^2 = 0.48      d.f. = 3        P-value = 0.9231


    Benchmark Dose Computation

Specified effect =           0.1

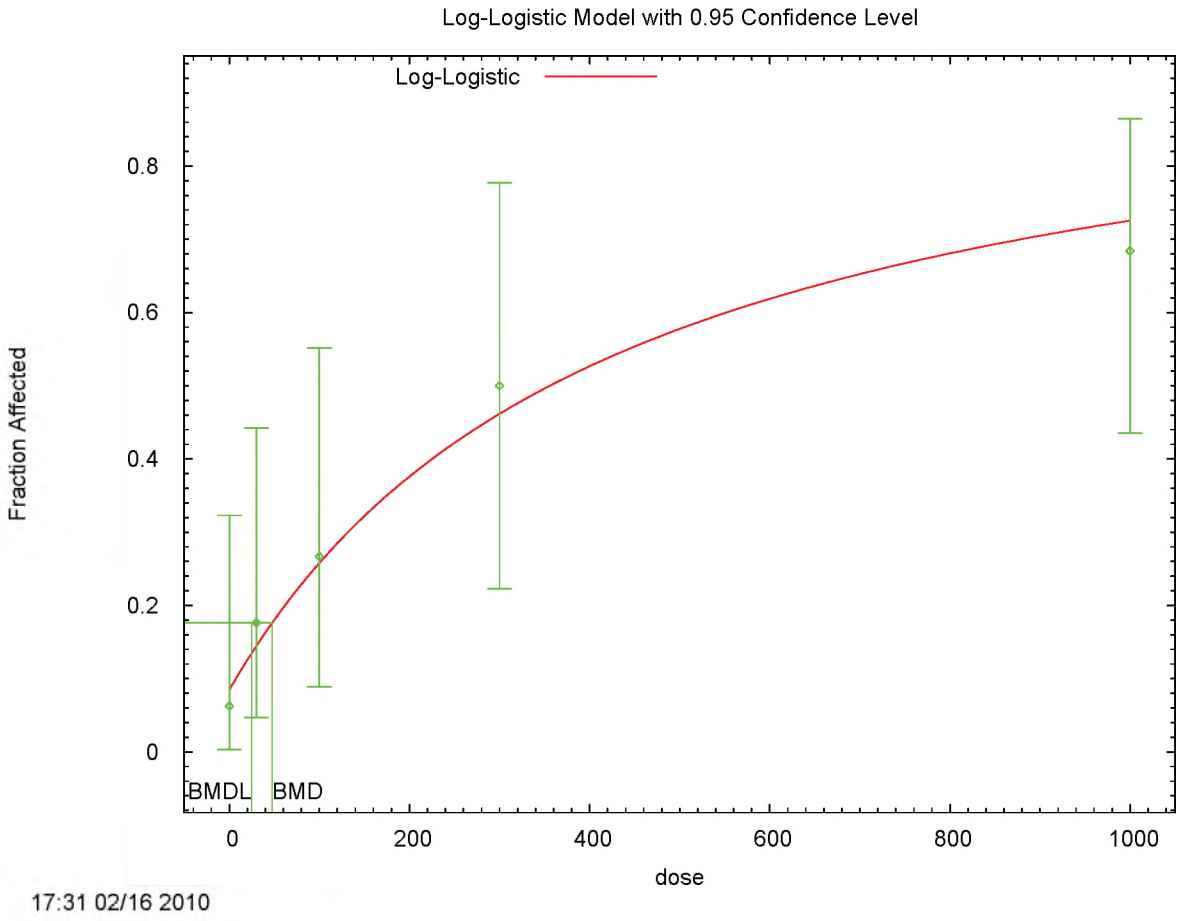
Risk Type        =      Extra risk

Confidence level =          0.95

              BMD =        47.6274

             BMDL =        24.8121
```

E.3.16.3. *Figure for Selected Model: Log-Logistic*



E.3.16.4. *Output for Additional Model Presented: Log-Logistic, Unrestricted*

Kattainen et al., 2001: 3rd Molar Eruption, Female

```
================================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\24_Katt_2001_Erup_LogLogistic_U_BMR1.(d)
        Gnuplot Plotting File:  C:\1\24_Katt_2001_Erup_LogLogistic_U_BMR1.plt
                                                Tue Feb 16 17:31:53 2010
================================================================================

Figure 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the probability function is:

  P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


  Dependent variable = DichEff
  Independent variable = Dose
  Slope parameter is not restricted
```

```
   Total number of observations = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model

                 Default Initial Parameter Values
                    background =       0.0625
                     intercept =     -4.71231
                         slope =     0.782659


           Asymptotic Correlation Matrix of Parameter Estimates

             background    intercept        slope

background            1        -0.48         0.39

 intercept        -0.48            1        -0.98

     slope         0.39        -0.98            1


                               Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background        0.0633217            *               *                   *
      intercept         -4.78282            *               *                   *
          slope         0.793723            *               *                   *

* - Indicates that this value is not calculated.


                         Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -40.5286         5
   Fitted model        -40.5783         3     0.0994416      2          0.9515
  Reduced model        -50.7341         1        20.411      4       0.0004142

           AIC:         87.1566


                                 Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size        Residual
   ---------------------------------------------------------------------
     0.0000     0.0633         1.013     1.000          16       -0.013
    30.0000     0.1670         2.840     3.000          17        0.104
   100.0000     0.2924         4.387     4.000          15       -0.219
   300.0000     0.4721         5.666     6.000          12        0.193
  1000.0000     0.6892        13.095    13.000          19       -0.047

 Chi^2 = 0.10      d.f. = 2        P-value = 0.9518


   Benchmark Dose Computation

Specified effect =            0.1

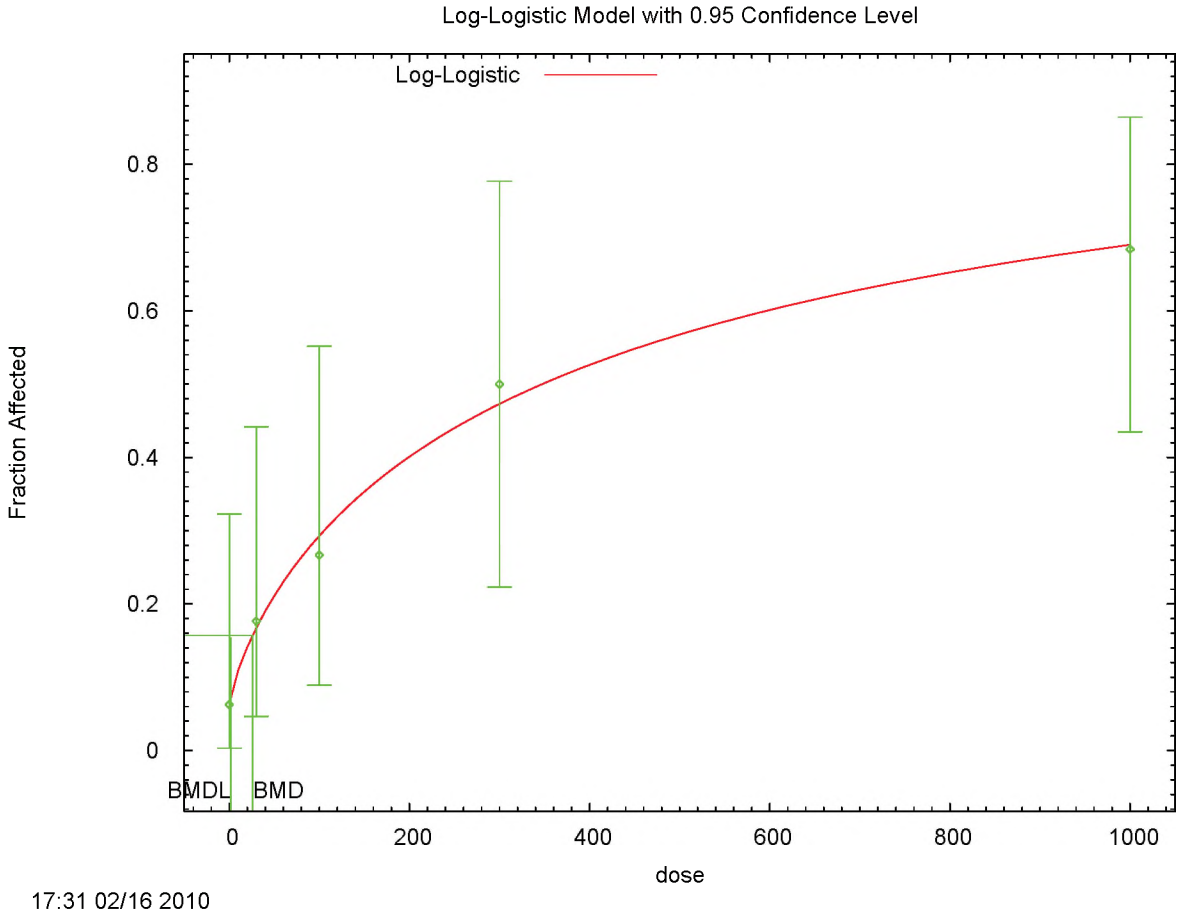
Risk Type        =      Extra risk
```

```
Confidence level =          0.95

             BMD =        25.986

            BMDL =       1.73001
```

E.3.16.5. *Figure for Additional Model Presented: Log-Logistic, Unrestricted*



E.3.17. Kattainen et al., 2001: 3rd Molar Length, Female

E.3.17.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2)	3	<0.0001	-122.954	4.027E+02	2.366E+02	
exponential (M3)	3	<0.0001	-122.954	4.027E+02	2.366E+02	power hit bound (d = 1)
exponential (M4)	2	<0.0001	-80.747	error	error	
exponential (M5)	1	<0.0001	-78.747	error	error	
Hill [b]	**2**	**0.013**	**-151.152**	**4.052E+00**	**2.144E+00**	**n lower bound hit (n = 1)**
linear	3	<0.0001	-122.325	4.659E+02	2.963E+02	
polynomial, 4-degree	3	<0.0001	-122.325	4.659E+02	2.963E+02	
power	3	<0.0001	-122.325	4.659E+02	2.963E+02	power bound hit (power = 1)
Hill, unrestricted [c]	1	0.087	-154.939	1.913E-02	1.928E-04	unrestricted (n = 0.197)
power, unrestricted	2	0.250	-157.093	9.098E-03	9.097E-03	unrestricted (power = 0.169)

[a] Non-constant variance model selected (p = <0.0001)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.3.17.2. *Output for Selected Model: Hill*

Kattainen et al., 2001: 3rd Molar Length, Female

```
 ======================================================================
          Hill Model. (Version: 2.14;  Date: 06/26/2008)
          Input Data File: C:\1\25_Katt_2001_Length_Hill_1.(d)
          Gnuplot Plotting File:  C:\1\25_Katt_2001_Length_Hill_1.plt
                                                Tue Feb 16 17:32:21 2010
 ======================================================================

 Figure 3 female only
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   Power parameter restricted to be greater than 1
   The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))
```

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	-2.37155
rho =	0
intercept =	1.85591
v =	-0.507874
n =	0.826204
k =	27.3305

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -n
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	lalpha	rho	intercept	v	k
lalpha	1	-0.98	-0.16	0.84	-0.37
rho	-0.98	1	0.2	-0.79	0.39
intercept	-0.16	0.2	1	-0.31	-0.11
v	0.84	-0.79	-0.31	1	-0.48
k	-0.37	0.39	-0.11	-0.48	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	3.34561	1.40443	0.592981	6.09824
rho	-14.3325	2.62129	-19.4701	-9.19484
intercept	1.8548	0.0159017	1.82364	1.88597
v	-0.441166	0.058852	-0.556513	-0.325818
n	1	NA		
k	24.0343	7.84495	8.65852	39.4101

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	16	1.86	1.85	0.0661	0.0637	0.0692
30	17	1.58	1.61	0.185	0.176	-0.768
100	15	1.6	1.5	0.265	0.293	1.28
300	12	1.5	1.45	0.221	0.378	0.527
1000	19	1.35	1.42	0.515	0.423	-0.783

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
              A1           56.758717            6    -101.517434
              A2           85.856450           10    -151.712901
              A3           84.934314            7    -155.868628
          fitted           80.575940            5    -151.151880
               R           45.373551            2     -86.747101


                   Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value

  Test 1              80.9658          8          <.0001
  Test 2              58.1955          4          <.0001
  Test 3              1.84427          3          0.6053
  Test 4              8.71675          2          0.0128

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1.  You may want to try a different
model


        Benchmark Dose Computation

Specified effect =             1

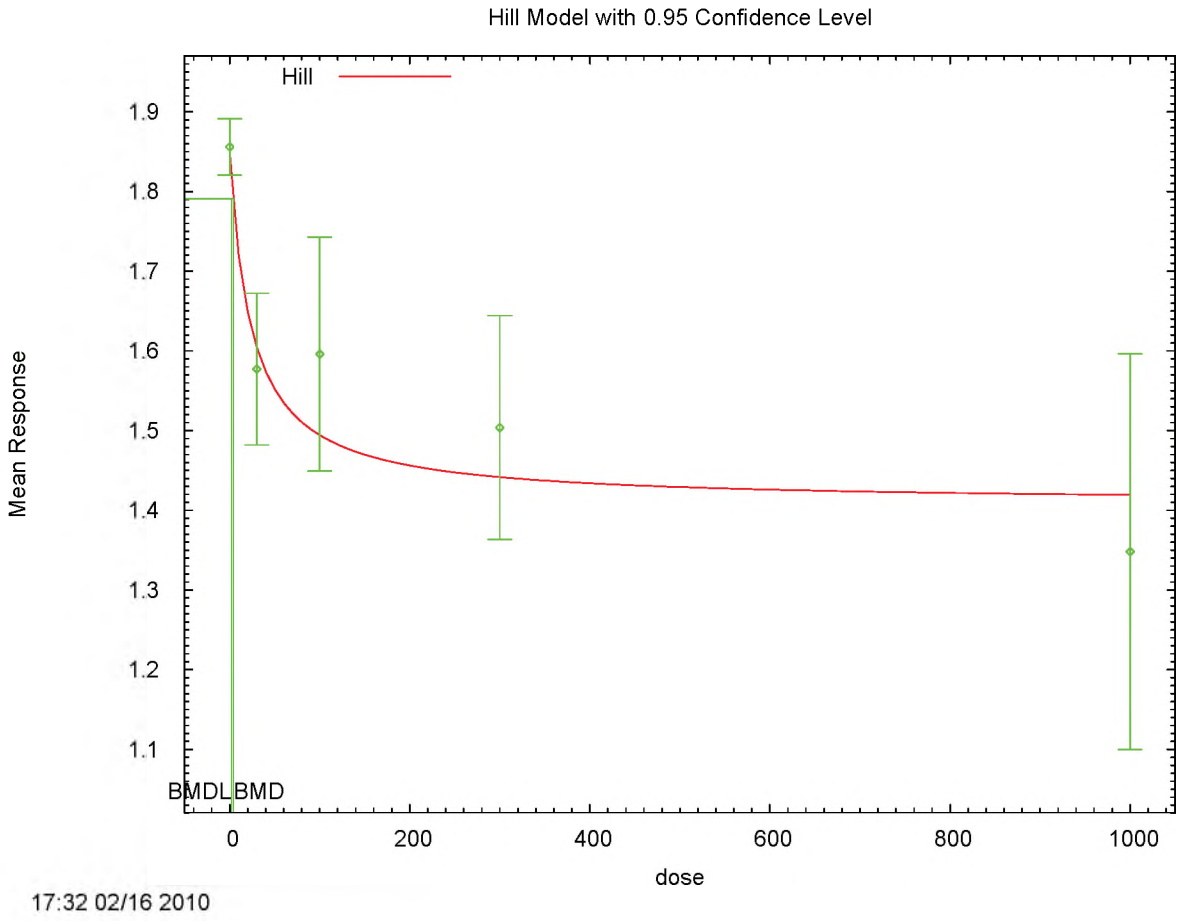
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =        4.05231

            BMDL =       2.14357
```

E.3.17.3. *Figure for Selected Model: Hill*



E.3.17.4. *Output for Additional Model Presented: Hill, Unrestricted*

Kattainen et al., 2001: 3rd Molar Length, Female

```
 ================================================================================
          Hill Model. (Version: 2.14;  Date: 06/26/2008)
          Input Data File: C:\1\25_Katt_2001_Length_Hill_U_1.(d)
          Gnuplot Plotting File:  C:\1\25_Katt_2001_Length_Hill_U_1.plt
                                                 Tue Feb 16 17:32:21 2010
 ================================================================================

 Figure 3 female only
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   Power parameter is not restricted
   The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))
```

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	-2.37155
rho =	0
intercept =	1.85591
v =	-0.507874
n =	0.826204
k =	27.3305

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	intercept	v	n	k
lalpha	1	-0.98	-0.18	0.18	-0.28	-0.011
rho	-0.98	1	0.22	-0.18	0.29	0.011
intercept	-0.18	0.22	1	-0.025	-0.059	0.0019
v	0.18	-0.18	-0.025	1	0.51	-0.96
n	-0.28	0.29	-0.059	0.51	1	-0.71
k	-0.011	0.011	0.0019	-0.96	-0.71	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	3.21882	1.4221	0.431563	6.00607
rho	-14.0862	2.68292	-19.3446	-8.82777
intercept	1.85564	0.0160224	1.82424	1.88704
v	-2.48572	2.89658	-8.16291	3.19148
n	0.196925	0.0499318	0.0990606	0.29479
k	1.92967e+006	1.60869e+007	-2.96e+007	3.34593e+007

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	16	1.86	1.86	0.0661	0.0643	0.0164
30	17	1.58	1.6	0.185	0.18	-0.598
100	15	1.6	1.54	0.265	0.234	0.857
300	12	1.5	1.48	0.221	0.316	0.259
1000	19	1.35	1.4	0.515	0.471	-0.466

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

```
Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
              A1           56.758717            6    -101.517434
              A2           85.856450           10    -151.712901
              A3           84.934314            7    -155.868628
          fitted           83.469680            6    -154.939361
               R           45.373551            2     -86.747101


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

    Test 1              80.9658          8          <.0001
    Test 2              58.1955          4          <.0001
    Test 3              1.84427          3          0.6053
    Test 4              2.92927          1         0.08699

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1.  You may want to try a different
model


        Benchmark Dose Computation

Specified effect =             1

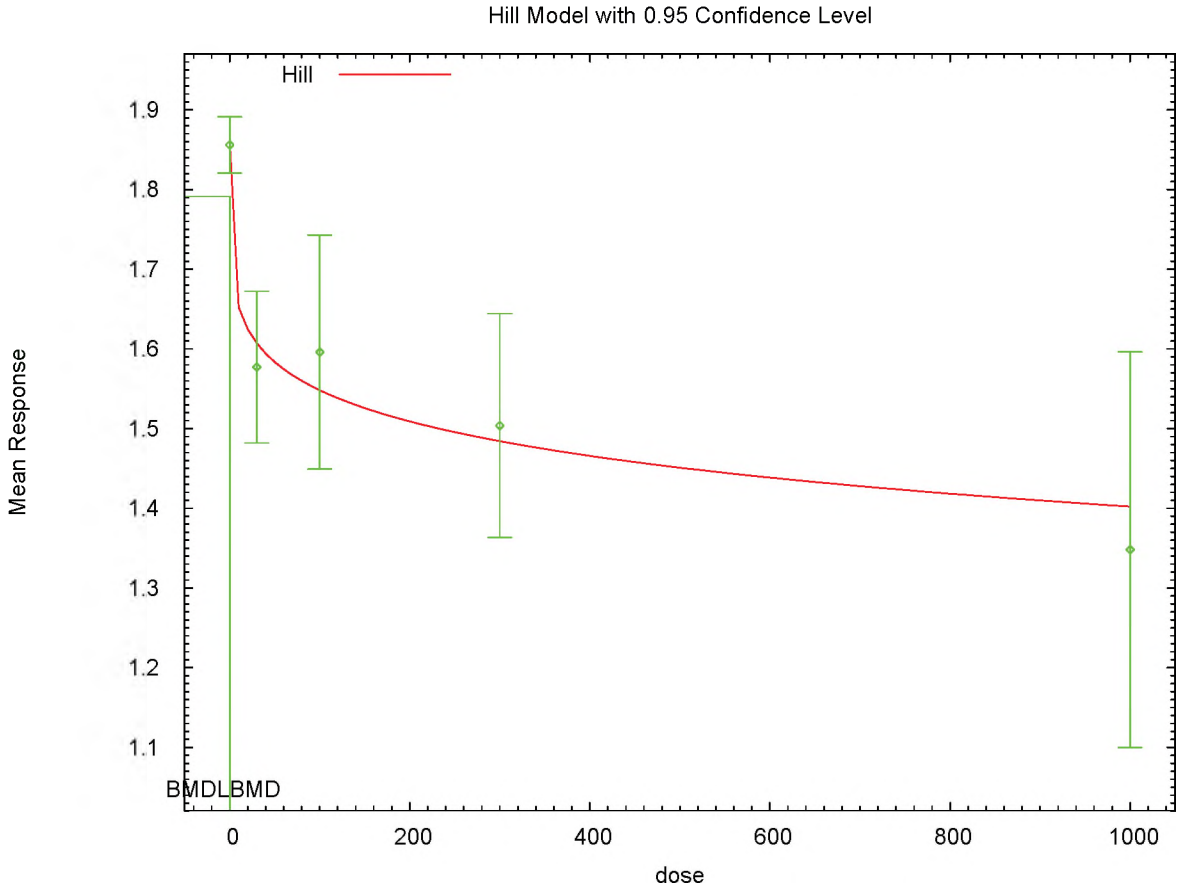
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =      0.0191282

            BMDL =     0.0001928
```

E.3.17.5. *Figure for Additional Model Presented: Hill, Unrestricted*



E.3.18. Keller et al., 2007: Missing Mandibular Molars, CBA J

E.3.18.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
gamma	1	0.105	52.490	7.293E+01	2.027E+01	
logistic	2	0.320	50.095	7.168E+01	5.142E+01	negative intercept (intercept = -3.372)
log-logistic	1	0.105	52.524	9.278E+01	5.273E+01	
log-probit	1	0.105	52.524	8.849E+01	5.297E+01	
multistage, 1-degree [a]	**3**	**0.276**	**49.409**	**2.778E+01**	**1.884E+01**	
multistage, 2-degree	1	0.126	51.515	4.619E+01	2.214E+01	
multistage, 3-degree	1	0.141	51.222	4.253E+01	2.212E+01	
probit	2	0.325	50.032	6.848E+01	4.775E+01	negative intercept (intercept = -1.851)
Weibull	1	0.108	52.216	6.079E+01	2.078E+01	

[a] Best-fitting model, BMDS output presented in this appendix

E.3.18.2. *Output for Selected Model: Multistage, 1-Degree*

Keller et al., 2007: Missing Mandibular Molars, CBA J

```
 ======================================================================
         Multistage Model. (Version: 3.0;  Date: 05/16/2008)
         Input Data File: C:\1\26_Keller_2007_Molars_Multi1_1.(d)
         Gnuplot Plotting File:  C:\1\26_Keller_2007_Molars_Multi1_1.plt
                                                Tue Feb 16 17:32:56 2010
 ======================================================================

 Table 1 using mandibular molars only
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
```

```
Degree of polynomial = 1


Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                    Background =           0
                       Beta(1) = 1.02909e+017


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)

  Beta(1)           1



                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background                0            *               *                   *
        Beta(1)       0.00379264            *               *                   *

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -21.5798         4
    Fitted model        -23.7044         1       4.24924      3          0.2358
  Reduced model          -71.326         1       99.4926      3         <.0001

           AIC:          49.4088


                                 Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          29        0.000
    10.0000     0.0372         0.856     2.000          23        1.260
   100.0000     0.3156         9.153     6.000          29       -1.260
  1000.0000     0.9775        29.324    30.000          30        0.832

 Chi^2 = 3.87      d.f. = 3        P-value = 0.2762


   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

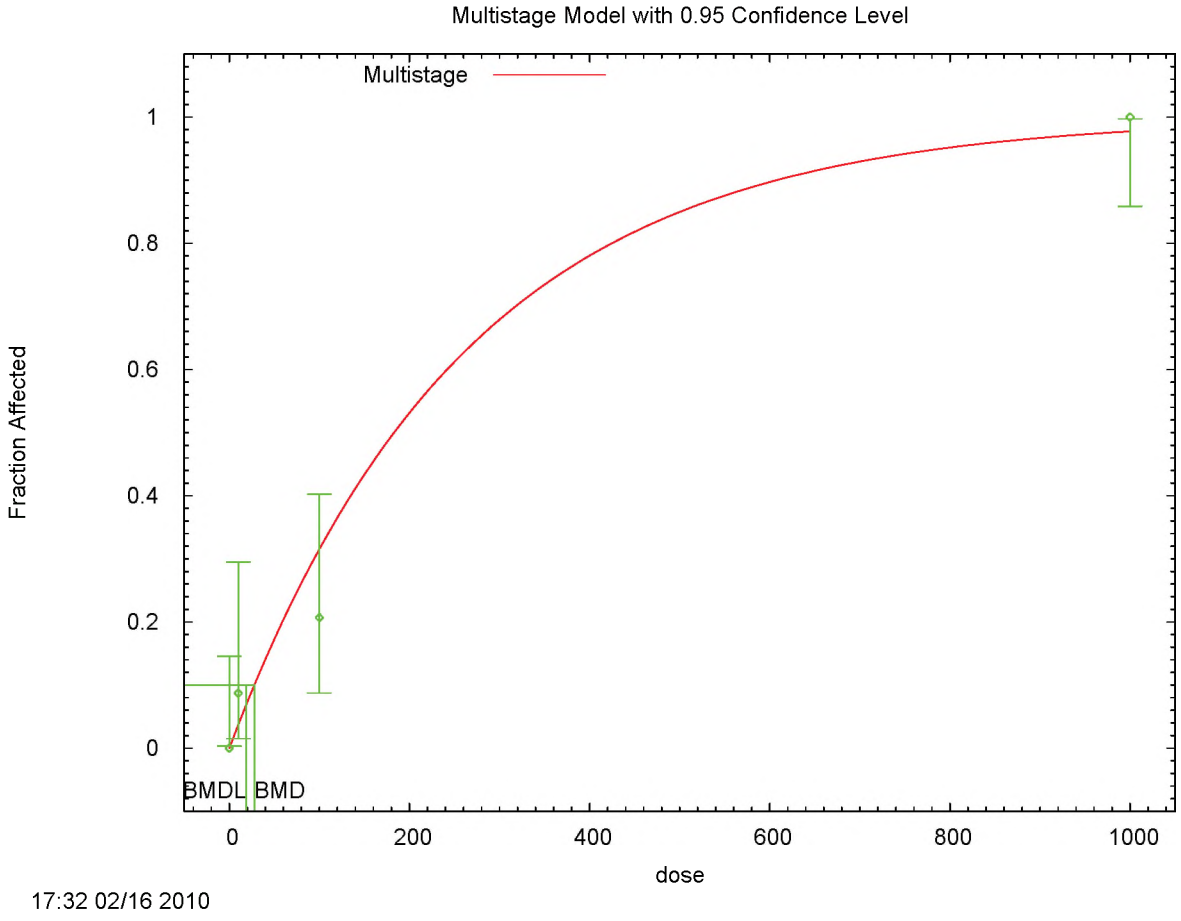
             BMD =        27.7803

            BMDL =        18.8447
```

```
            BMDU =        41.7256

Taken together, (18.8447, 41.7256) is a 90      % two-sided confidence
interval for the BMD
```

E.3.18.3. *Figure for Selected Model: Multistage, 1-Degree*



E.3.19. Kociba et al., 1978: Urinary Coproporphyrin, Females

E.3.19.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2)	2	<0.0001	84.006	7.054E+01	4.341E+01	
exponential (M3)	2	<0.0001	84.006	7.054E+01	4.341E+01	power hit bound (d = 1)
exponential (M4) [b]	**1**	**0.040**	**70.556**	**1.625E+00**	**7.300E-01**	
exponential (M5)	0	N/A	69.092	3.128E+00	1.024E+00	
Hill	0	N/A	69.047	6.677E+00	error	
linear	2	<0.0001	83.713	6.195E+01	3.112E+01	
polynomial, 3-degree	2	<0.0001	83.713	6.195E+01	3.112E+01	
power	2	<0.0001	83.713	6.195E+01	3.112E+01	power bound hit (power = 1)
power, unrestricted	1	0.001	78.260	7.808E-01	1.693E-08	unrestricted (power = 0.306)

[a] Non-constant variance model selected ($p = 0.0298$)

[b] Best-fitting model, BMDS output presented in this appendix

E.3.19.2. *Output for Selected Model: Exponential (M4)*

Kociba et al., 1978: Urinary Coproporphyrin, Females

```
 ======================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\1\29_Kociba_1978_Copro_Exp_1.(d)
         Gnuplot Plotting File:
                                                Tue Feb 16 17:34:45 2010
 ======================================================================

 Table2-UrinaryCoproporphyrin
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.
```

Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	-5.58269
rho	2.98472
a	8.17
b	0.0259469
c	2.23623
d	1

Parameter Estimates

Variable	Model 4
lnalpha	-4.94473
rho	2.76088
a	8.93039
b	0.136554
c	1.9753
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	5	9.8	1.3
1	5	8.6	2
10	5	16.4	4.7
100	5	17.4	4

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	8.93	1.733	1.122
1	10.04	2.038	-1.582
10	15.42	3.683	0.5967
100	17.64	4.436	-0.1211

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

```
  Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
           Var{e(ij)} = Sigma^2


                            Likelihoods of Interest

                 Model      Log(likelihood)      DF         AIC
                -------    -----------------    ----   ------------
                    A1       -31.69739            5      73.39478
                    A2       -27.21541            8      70.43081
                    A3       -28.16434            6      68.32868
                     R       -41.73188            2      87.46376
                     4       -30.27804            5      70.55608


Additive constant for all log-likelihoods =     -18.38.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.


                              Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)


                         Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                      29.03             6           < 0.0001
  Test 2                      8.964             3            0.02977
  Test 3                      1.898             2             0.3872
 Test 6a                      4.227             1            0.03978


  The p-value for Test 1 is less than .05.  There appears to be a
  difference between response and/or variances among the dose
  levels, it seems appropriate to model the data.

  The p-value for Test 2 is less than .1.  A non-homogeneous
  variance model appears to be appropriate.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 6a is less than .1.  Model 4 may not adequately
  describe the data; you may want to consider another model.


Benchmark Dose Computations:

  Specified Effect = 1.000000

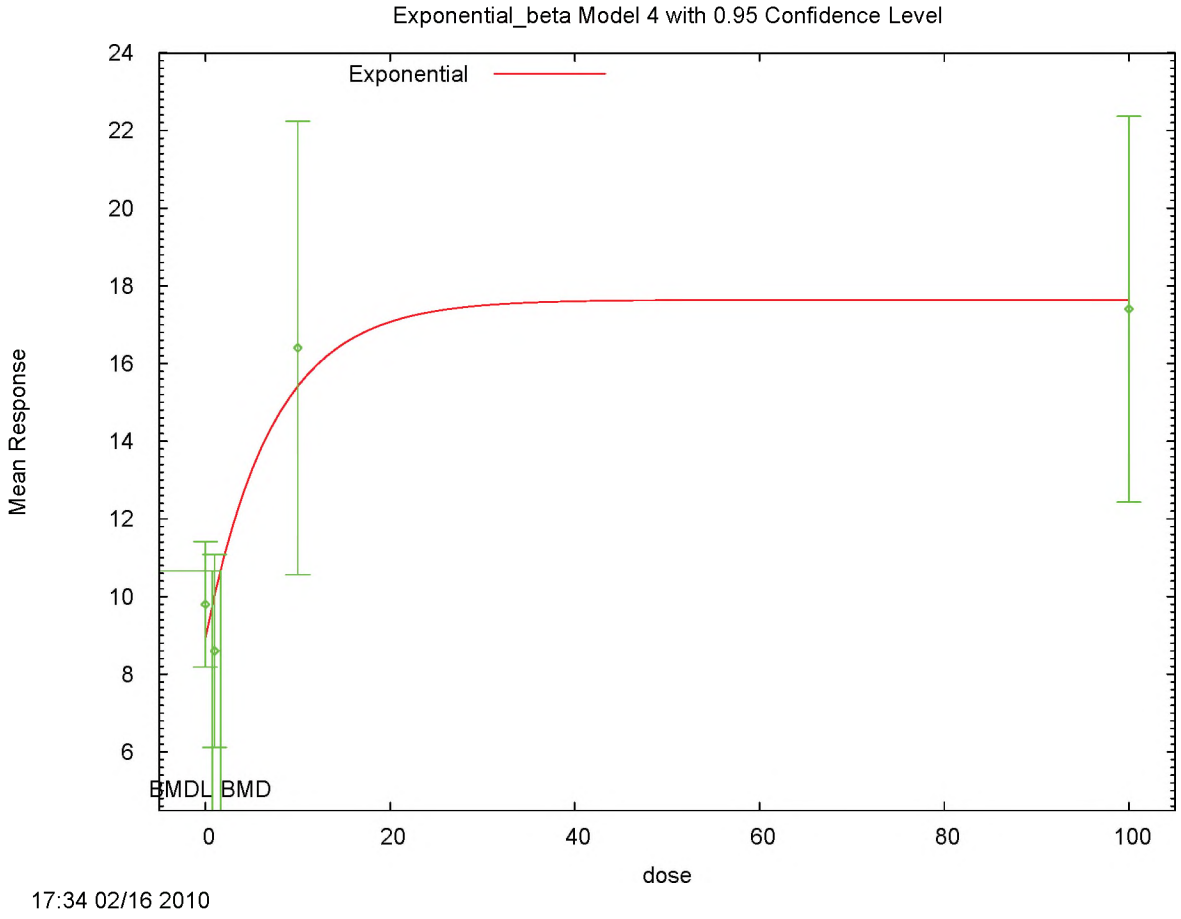
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD =      1.62505

              BMDL =     0.729987
```

E.3.19.3. *Figure for Selected Model: Exponential (M4)*



E.3.20. Kociba et al., 1978: Uroporphyrin per Creatinine, Female

E.3.20.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2)	2	0.661	-93.561	4.357E+01	3.328E+01	
exponential (M3)	2	0.661	-93.561	4.357E+01	3.328E+01	power hit bound (d = 1)
exponential (M4)	1	0.576	-92.078	1.719E+01	5.516E+00	
exponential (M5)	0	N/A	-90.190	1.080E+01	5.613E+00	
Hill	0	N/A	-90.190	1.099E+01	5.088E+00	
linear [b]	**2**	**0.720**	**-93.735**	**3.522E+01**	**2.500E+01**	
polynomial, 3-degree	2	0.720	-93.735	3.522E+01	2.500E+01	
power	2	0.720	-93.735	3.522E+01	2.500E+01	power bound hit (power = 1)
power, unrestricted	1	0.515	-91.967	2.274E+01	3.334E+00	unrestricted (power = 0.731)

[a] Constant variance model selected ($p = 0.4919$)

[b] Best-fitting model, BMDS output presented in this appendix

E.3.20.2. *Output for Selected Model: Linear*

Kociba et al., 1978: Uroporphyrin per Creatinine, Female

```
 ================================================================
          Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
          Input Data File: C:\1\28_Kociba_1978_Uropor_LinearCV_1.(d)
          Gnuplot Plotting File:  C:\1\28_Kociba_1978_Uropor_LinearCV_1.plt
                                                Tue Feb 16 17:34:12 2010
 ================================================================

 Table 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
```

```
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                          alpha =    0.0030385
                            rho =            0   Specified
                         beta_0 =     0.154759
                         beta_1 =    0.0014231

          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been specified by the user,
                and do not appear in the correlation matrix )

                  alpha       beta_0       beta_1

     alpha            1    -2.2e-009     3.5e-009

    beta_0    -2.2e-009            1        -0.55

    beta_1     3.5e-009        -0.55            1


                               Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
          alpha       0.00251184      0.000794315         0.000955015          0.00406867
         beta_0         0.154759        0.0134422            0.128413            0.181105
         beta_1        0.0014231      0.000267497         0.000898818          0.00194739


      Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   -----------

    0     5      0.157        0.155         0.05       0.0501            0.1
    1     5      0.143        0.156        0.037       0.0501         -0.588
   10     5      0.181        0.169        0.053       0.0501          0.536
  100     5      0.296        0.297        0.074       0.0501        -0.0477


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
      Model A3 uses any fixed variance parameters that
      were specified by the user

 Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                       Likelihoods of Interest
```

Model	Log(likelihood)	# Param's	AIC
A1	50.195349	5	-90.390697
A2	51.400051	8	-86.800103
A3	50.195349	5	-90.390697
fitted	49.867385	3	-93.734769
R	41.049755	2	-78.099510

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	20.7006	6	0.002076
Test 2	2.40941	3	0.4919
Test 3	2.40941	3	0.4919
Test 4	0.655928	2	0.7204

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

Benchmark Dose Computation

Specified effect = 1

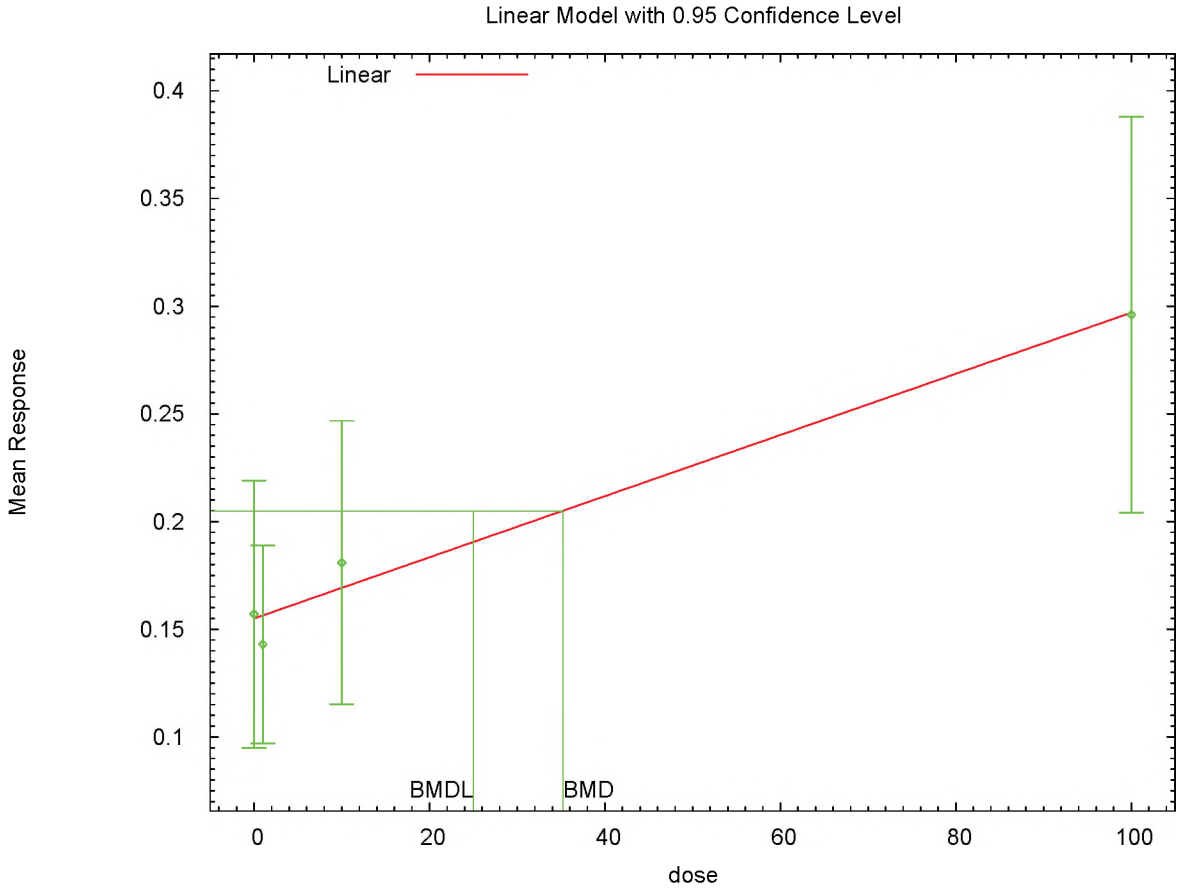
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 35.2176

BMDL = 25.0024

E.3.20.3. *Figure for Selected Model: Linear*



E.3.21. Latchoumycandane and Mathur, 2002: Sperm Production

E.3.21.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2)	2	<0.0001	95.106	7.640E+01	3.992E+01	
exponential (M3)	2	<0.0001	95.106	7.640E+01	3.992E+01	power hit bound (d = 1)
exponential (M4)	1	0.699	75.263	2.435E-01	1.016E-01	
exponential (M5)	0	N/A	77.263	3.697E-01	1.016E-01	
Hill [b]	1	0.859	75.144	1.450E-01	1.559E-02	n lower bound hit (n = 1)
linear	2	<0.0001	95.308	8.275E+01	4.852E+01	
polynomial, 3-degree	2	<0.0001	95.308	8.275E+01	4.852E+01	
power	2	<0.0001	95.308	8.275E+01	4.852E+01	power bound hit (power = 1)
Hill, unrestricted [c]	0	N/A	77.113	6.943E-02	2.060E-06	unrestricted (n = 0.709)
power, unrestricted	1	0.499	75.570	2.706E-07	2.706E-07	unrestricted (power = 0.067)

[a] Constant variance model selected ($p = 0.8506$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.3.21.2. *Output for Selected Model: Hill*

Latchoumycandane and Mathur, 2002: Sperm Production

```
 ======================================================================
          Hill Model. (Version: 2.14;  Date: 06/26/2008)
          Input Data File: C:\1\30_Latch_2002_Sperm_HillCV_1.(d)
          Gnuplot Plotting File:  C:\1\30_Latch_2002_Sperm_HillCV_1.plt
                                                Tue Feb 16 18:13:20 2010
 ======================================================================

 (x10^6) Table 1 without Vitamin E
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter restricted to be greater than 1
```

```
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                          alpha =      7.23328
                            rho =            0   Specified
                      intercept =        22.19
                              v =        -9.09
                              n =      1.80484
                              k =     0.697086


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -rho    -n
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

                    alpha    intercept            v            k

       alpha            1     6.3e-010       3e-008     8.3e-009

   intercept     6.3e-010            1        -0.78        -0.23

           v       3e-008        -0.78            1        -0.17

           k     8.3e-009        -0.23        -0.17            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
         Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
            alpha          6.03567          1.74235             2.62073             9.45061
        intercept          22.1885          1.00316             20.2223             24.1547
                v         -9.00869          1.26801            -11.4939            -6.52343
                n                1               NA
                k         0.386669         0.265663           -0.134021            0.907359

  NA - Indicates that this parameter has hit a bound
       implied by some inequality constraint and thus
       has no standard error.


       Table of Data and Estimated Values of Interest

   Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
  ------     ---   --------     --------   -----------  -----------   ----------

      0       6       22.2         22.2         2.67         2.46        0.00151
      1       6       15.7         15.7         2.65         2.46        -0.0218
     10       6       13.7         13.5         2.19         2.46          0.134
    100       6       13.1         13.2         3.16         2.46         -0.114


   Model Descriptions for likelihoods calculated


   Model A1:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma^2
```

```
Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                        Likelihoods of Interest

             Model      Log(likelihood)   # Param's      AIC
              A1          -33.556444            5      77.112888
              A2          -33.158811            8      82.317623
              A3          -33.556444            5      77.112888
           fitted         -33.572245            4      75.144490
               R          -47.392394            2      98.784788


                    Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                      Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value

  Test 1              28.4672          6          <.0001
  Test 2             0.795266          3          0.8506
  Test 3             0.795266          3          0.8506
  Test 4             0.031602          1          0.8589

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =             1

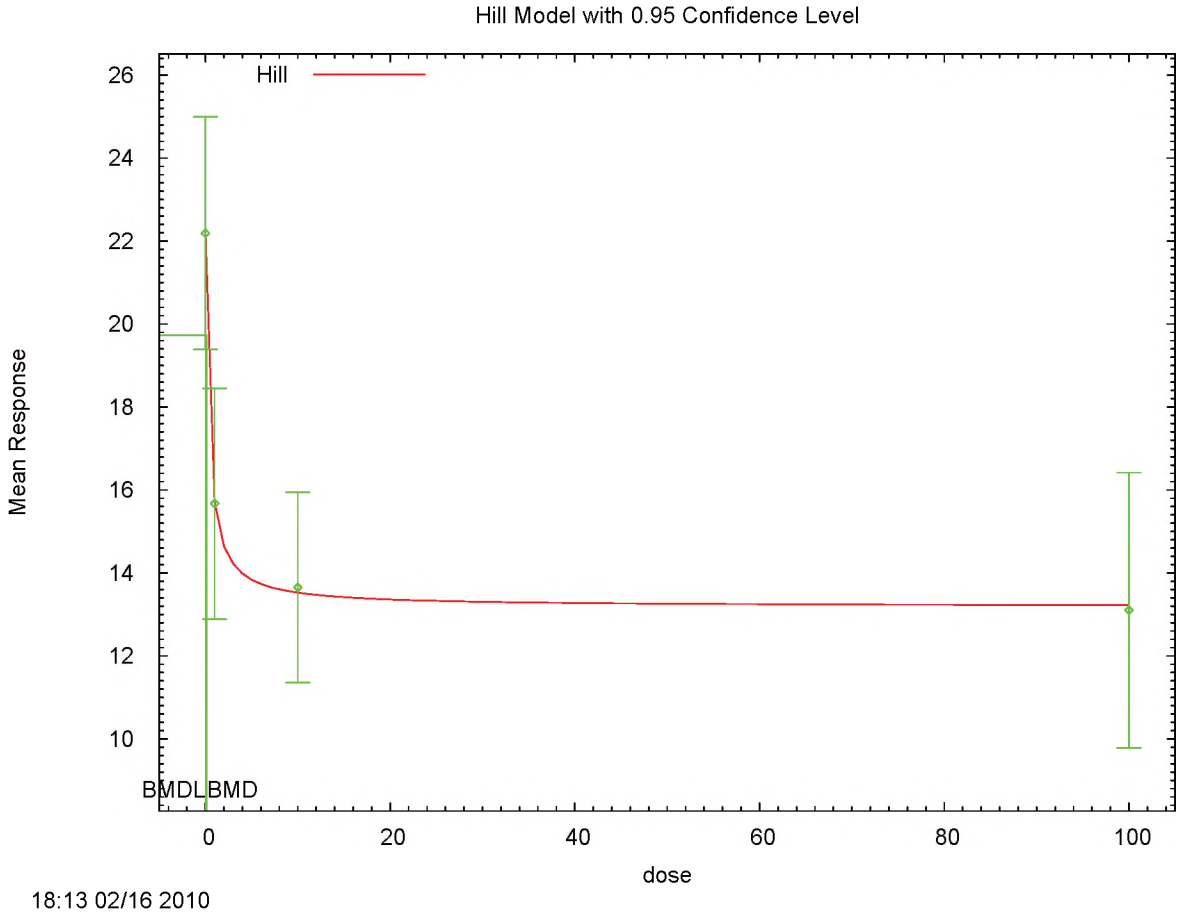
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =       0.144988

            BMDL =     0.0155926
```

E.3.21.3. *Figure for Selected Model: Hill*



E.3.21.4. *Output for Additional Model Presented: Hill, Unrestricted*

Latchoumycandane and Mathur, 2002: Sperm Production

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\1\30_Latch_2002_Sperm_HillCV_U_1.(d)
         Gnuplot Plotting File:  C:\1\30_Latch_2002_Sperm_HillCV_U_1.plt
                                          Tue Feb 16 18:13:21 2010
 ================================================================

 (x10^6) Table 1 without Vitamin E
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter is not restricted
   A constant variance model is fit
```

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

alpha =	7.23328	
rho =	0	Specified
intercept =	22.19	
v =	-9.09	
n =	1.80484	
k =	0.697086	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	intercept	v	n	k
alpha	1	-7.6e-009	8e-008	5e-008	1.9e-008
intercept	-7.6e-009	1	-0.5	-0.015	-0.13
v	8e-008	-0.5	1	0.75	0.55
n	5e-008	-0.015	0.75	1	0.86
k	1.9e-008	-0.13	0.55	0.86	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	6.02773	1.74006	2.61728	9.43818
intercept	22.19	1.00231	20.2255	24.1545
v	-9.23433	2.02073	-13.1949	-5.27378
n	0.709305	1.28329	-1.8059	3.22451
k	0.290697	0.548737	-0.784807	1.3662

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	6	22.2	22.2	2.67	2.46	2.62e-008
1	6	15.7	15.7	2.65	2.46	-1.5e-008
10	6	13.7	13.7	2.19	2.46	-4.56e-008
100	6	13.1	13.1	3.16	2.46	-3.52e-007

Degrees of freedom for Test A3 vs fitted <= 0

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

```
Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                       Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1          -33.556444            5      77.112888
             A2          -33.158811            8      82.317623
             A3          -33.556444            5      77.112888
          fitted         -33.556444            5      77.112888
              R          -47.392394            2      98.784788


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              28.4672          6          <.0001
   Test 2             0.795266          3          0.8506
   Test 3             0.795266          3          0.8506
   Test 4          2.84217e-014         0              NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-Square
     test for fit is not valid


        Benchmark Dose Computation

Specified effect =             1

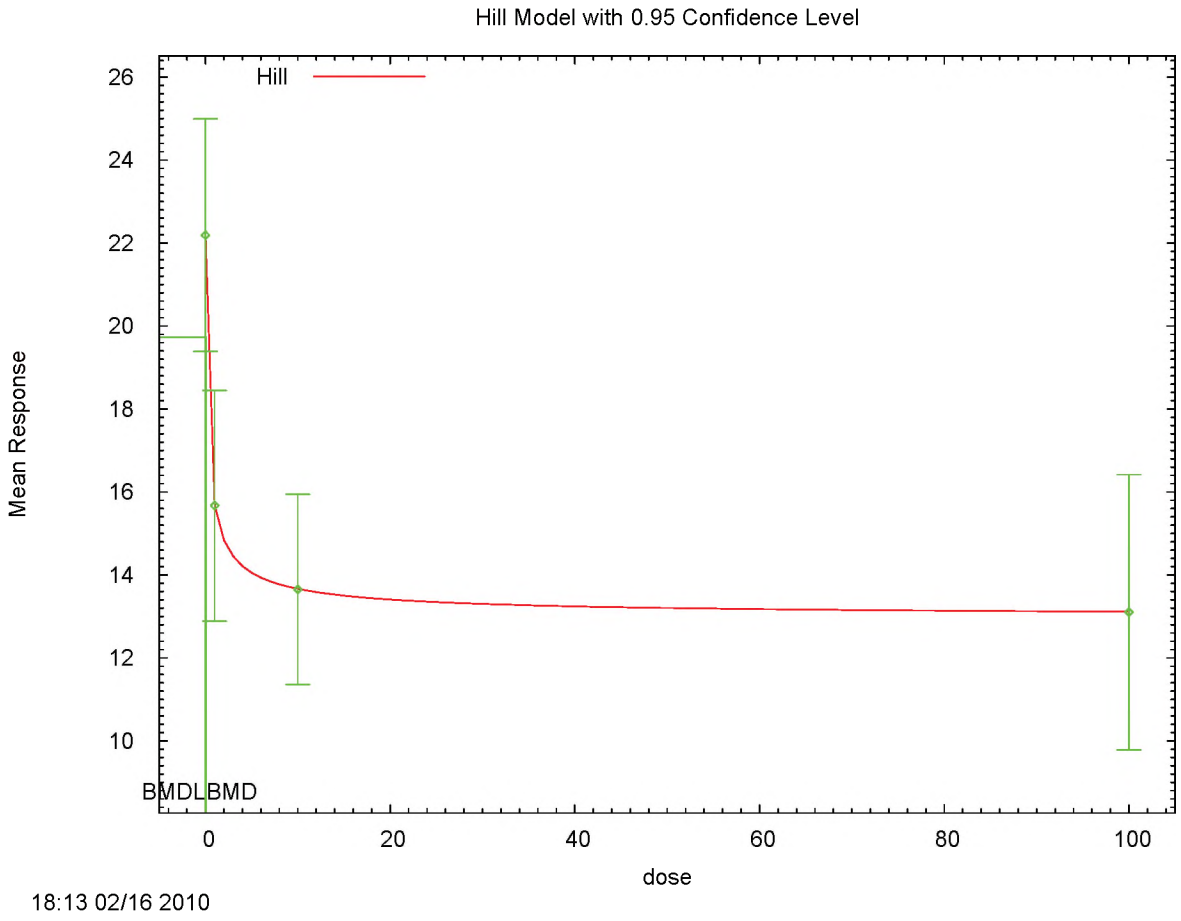
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =      0.0694325

            BMDL =  2.06007e-006
```

E.3.21.5. *Figure for Additional Model Presented: Hill, Unrestricted*



E.3.22. Li et al., 1997: FSH

E.3.22.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2)	8	<0.0001	1095.240	1.340E+04	1.060E+04	
exponential (M3)	8	<0.0001	1095.240	1.340E+04	1.060E+04	power hit bound (d = 1)
exponential (M4)	7	<0.0001	1061.243	1.031E+03	4.015E+02	
exponential (M5)	7	<0.0001	1061.243	1.031E+03	4.015E+02	power hit bound (d = 1)
Hill	7	<0.0001	1059.547	6.645E+02	error	n lower bound hit (n = 1)
linear	8	<0.0001	1078.221	5.287E+03	3.602E+03	
polynomial, 8-degree	9	<0.0001	1155.670	error	error	
power [b]	**8**	**<0.0001**	**1078.221**	**5.287E+03**	**3.602E+03**	**power bound hit (power = 1)**
Hill, unrestricted	6	0.001	1039.902	2.809E+00	6.602E-01	unrestricted (n = 0.291)
power, unrestricted [c]	7	0.002	1037.821	2.508E+00	2.525E-01	unrestricted (power = 0.279)

[a] Non-constant variance model selected (p = <0.0001)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.3.22.2. *Output for Selected Model: Power*

Li et al., 1997: FSH

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\1\72_Li_1997_FSH_Pwr_1.(d)
         Gnuplot Plotting File:  C:\1\72_Li_1997_FSH_Pwr_1.plt
                                              Tue Feb 16 20:07:31 2010
 ================================================================

 Figure 3: FSH in female S-D rats 24hr after dosing, 22 day old rats
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   The power is restricted to be greater than or equal to 1
```

The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 10
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	9.8191
rho =	0
control =	22.1591
slope =	26.1213
power =	0.264963

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -power
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	lalpha	rho	control	slope
lalpha	1	-0.99	-0.29	-0.023
rho	-0.99	1	0.2	0.023
control	-0.29	0.2	1	-0.35
slope	-0.023	0.023	-0.35	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	3.5473	1.23656	1.12369	5.9709
rho	1.26137	0.244246	0.782659	1.74009
control	88.9479	12.9114	63.6419	114.254
slope	0.0188972	0.00351723	0.0120035	0.0257908
power	1	NA		

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	23.9	88.9	29.6	99.9	-2.06
3	10	22.2	89	48.5	99.9	-2.12
10	10	85.2	89.1	94.3	100	-0.124
30	10	73.3	89.5	48.5	100	-0.511
100	10	126	90.8	159	101	1.1
300	10	132	94.6	116	104	1.14
1000	10	117	108	51.2	113	0.25
3000	10	304	146	154	136	3.68
1e+004	10	347	278	151	205	1.06
3e+004	10	455	656	286	352	-1.8

```
Model Descriptions for likelihoods calculated


Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
              A1         -535.687163          11    1093.374327
              A2         -496.367061          20    1032.734122
              A3         -502.709623          12    1029.419246
          fitted         -535.110448           4    1078.220896
               R         -574.835246           2    1153.670492


                   Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value

  Test 1              156.936         18          <.0001
  Test 2              78.6402          9          <.0001
  Test 3              12.6851          8          0.1232
  Test 4              64.8016          8          <.0001

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1.  You may want to try a different
model


               Benchmark Dose Computation

Specified effect =             1

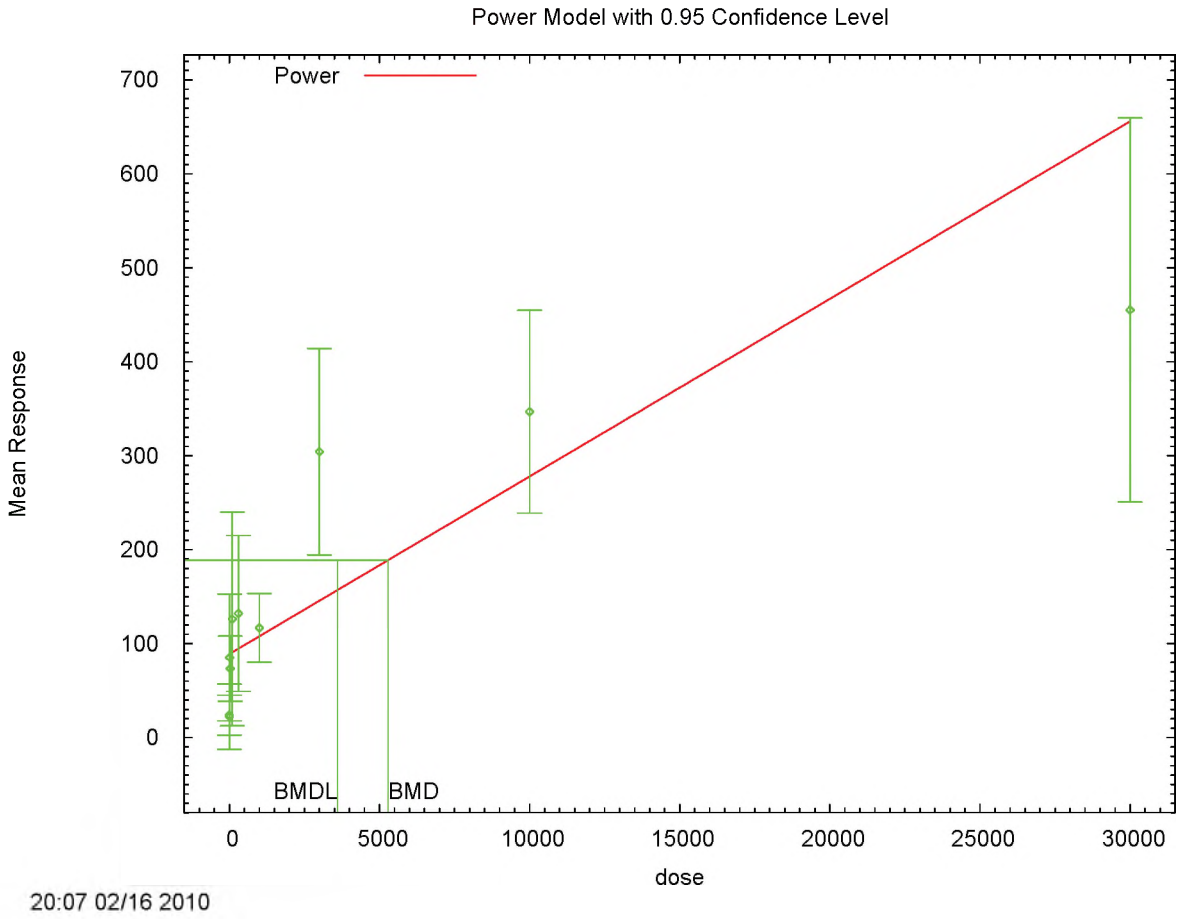
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 5286.67
```

```
BMDL = 3601.91
```

E.3.22.3. *Figure for Selected Model: Power*



E.3.22.4. *Output for Additional Model Presented: Power, Unrestricted*

Li et al., 1997: FSH

```
================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\72_Li_1997_FSH_Pwr_U_1.(d)
        Gnuplot Plotting File:  C:\1\72_Li_1997_FSH_Pwr_U_1.plt
                                          Tue Feb 16 20:07:33 2010
================================================================

Figure 3: FSH in female S-D rats 24hr after dosing, 22 day old rats

  The form of the response function is:

  Y[dose] = control + slope * dose^power


  Dependent variable = Mean
```

Independent variable = Dose
The power is not restricted
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 10
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	9.8191
rho =	0
control =	22.1591
slope =	26.1213
power =	0.264963

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	control	slope	power
lalpha	1	-0.99	-0.69	-0.15	0.28
rho	-0.99	1	0.65	0.11	-0.26
control	-0.69	0.65	1	-0.17	0.024
slope	-0.15	0.11	-0.17	1	-0.93
power	0.28	-0.26	0.024	-0.93	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	3.72156	1.13117	1.5045	5.93861
rho	1.17032	0.223249	0.732758	1.60788
control	15.7412	6.97367	2.07307	29.4094
slope	24.963	6.42976	12.3609	37.5651
power	0.278637	0.0312355	0.217417	0.339857

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	23.9	15.7	29.6	32.3	0.796
3	10	22.2	49.6	48.5	63.2	-1.38
10	10	85.2	63.2	94.3	72.7	0.96
30	10	73.3	80.1	48.5	83.6	-0.259
100	10	126	106	159	98.4	0.654
300	10	132	138	116	115	-0.164
1000	10	117	187	51.2	137	-1.62
3000	10	304	248	154	162	1.1
1e+004	10	347	341	151	195	0.0999
3e+004	10	455	457	286	232	-0.0271

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)

```
            Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
        Model A3 uses any fixed variance parameters that
        were specified by the user

 Model  R:         Yi = Mu + e(i)
             Var{e(i)} = Sigma^2


                       Likelihoods of Interest

             Model      Log(likelihood)   # Param's      AIC
              A1         -535.687163          11    1093.374327
              A2         -496.367061          20    1032.734122
              A3         -502.709623          12    1029.419246
           fitted        -513.910636           5    1037.821272
               R         -574.835246           2    1153.670492


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              156.936         18          <.0001
   Test 2              78.6402          9          <.0001
   Test 3              12.6851          8          0.1232
   Test 4               22.402          7        0.002165

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1.  You may want to try a different
model


               Benchmark Dose Computation

Specified effect =             1

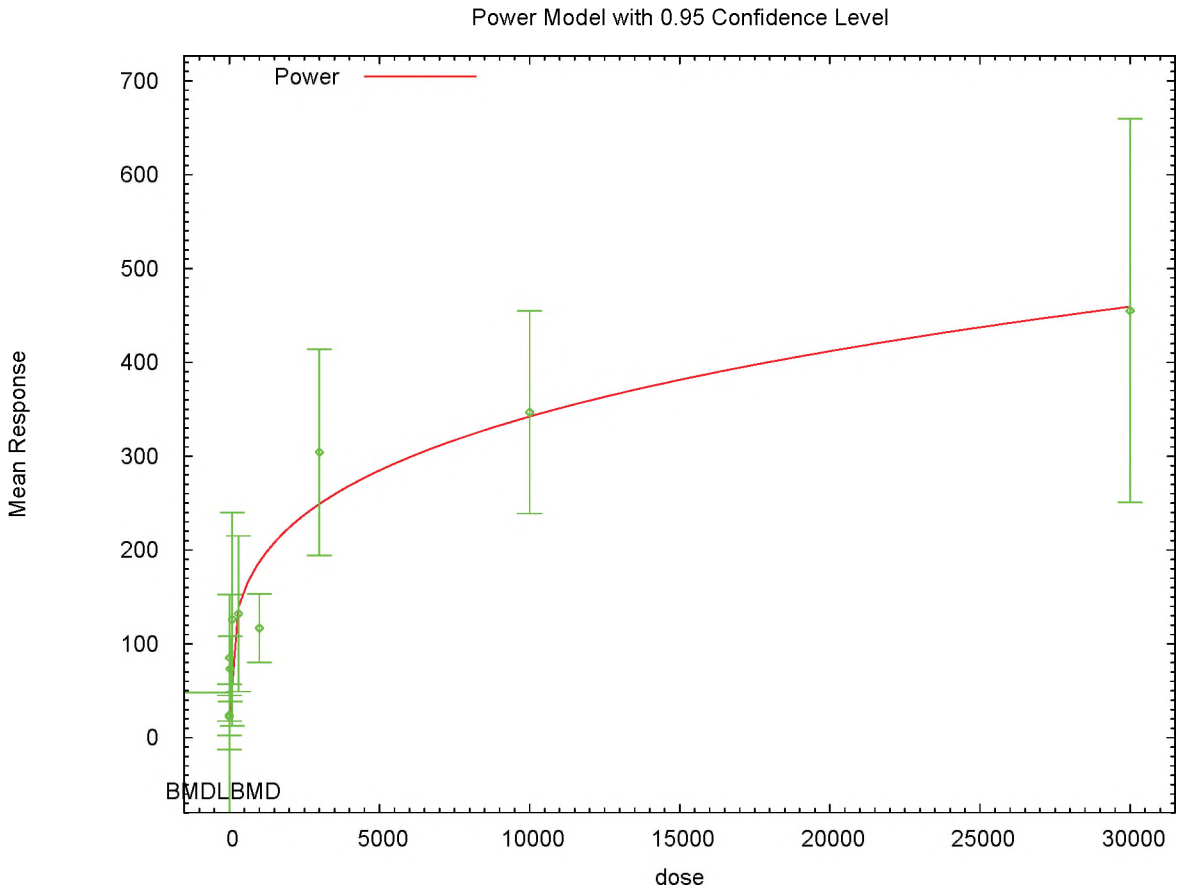
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 2.50839


            BMDL = 0.252541
```

E.3.22.5. *Figure for Additional Model Presented: Power, Unrestricted*



E.3.23. Li et al., 2006: Estradiol, 3-Day

E.3.23.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2)	2	0.147	269.146	3.044E+02	1.108E+02	
exponential (M3)	2	0.147	269.146	3.044E+02	1.108E+02	power hit bound (d = 1)
exponential (M4)	1	0.341	268.212	error	error	
exponential (M5)	0	N/A	270.212	error	error	
Hill	0	N/A	270.212	error	error	
linear [b]	**2**	**0.151**	**269.084**	**3.471E+02**	**1.082E+02**	
polynomial, 3-degree	2	0.151	269.084	3.471E+02	1.082E+02	
power	2	0.151	269.084	3.471E+02	1.082E+02	power bound hit (power = 1)
Hill, unrestricted	0	N/A	270.266	1.059E+17	1.059E+17	unrestricted (n = 0.025)
power, unrestricted	1	0.327	268.266	3.727E+14	error	unrestricted (power = 0.012)

[a] Constant variance model selected ($p = 0.4372$)

[b] Best-fitting model, BMDS output presented in this appendix

E.3.23.2. *Output for Selected Model: Linear*

Li et al., 2006: Estradiol, 3-Day

```
 ================================================================
          Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
          Input Data File: C:\1\31_Li_2006_Estra_LinearCV_1.(d)
          Gnuplot Plotting File:  C:\1\31_Li_2006_Estra_LinearCV_1.plt
                                        Tue Feb 16 18:13:56 2010
 ================================================================

 Figure 3, 3-day estradiol
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit
```

```
Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                         alpha =      267.211
                           rho =            0   Specified
                        beta_0 =      16.4428
                        beta_1 =    0.0468351


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been specified by the user,
                and do not appear in the correlation matrix )

                  alpha       beta_0       beta_1

      alpha             1    -2.6e-013    -4.5e-015

     beta_0    -2.6e-013            1        -0.68

     beta_1    -4.5e-015        -0.68            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
           alpha          264.303             59.1             148.469             380.137
         beta_0          16.4428          3.50431             9.57445             23.3111
         beta_1        0.0468351         0.062677          -0.0760095             0.16968


      Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0    10       10.2         16.4         12.2         16.3          -1.22
    2    10       19.9         16.5           20         16.3         0.656
   50    10       24.7         18.8         14.6         16.3          1.16
  100    10       18.1         21.1         17.6         16.3        -0.591


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
      Model A3 uses any fixed variance parameters that
      were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-129.653527	5	269.307054
A2	-128.294657	8	272.589314
A3	-129.653527	5	269.307054
fitted	-131.541911	3	269.083823
R	-131.819169	2	267.638338

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	7.04902	6	0.3163
Test 2	2.71774	3	0.4372
Test 3	2.71774	3	0.4372
Test 4	3.77677	2	0.1513

The p-value for Test 1 is greater than .05. There may not be a
diffence between responses and/or variances among the dose levels
Modelling the data with a dose/response curve may not be appropriate

The p-value for Test 2 is greater than .1. A homogeneous variance
model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears
to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems
to adequately describe the data

Benchmark Dose Computation

Specified effect = 1

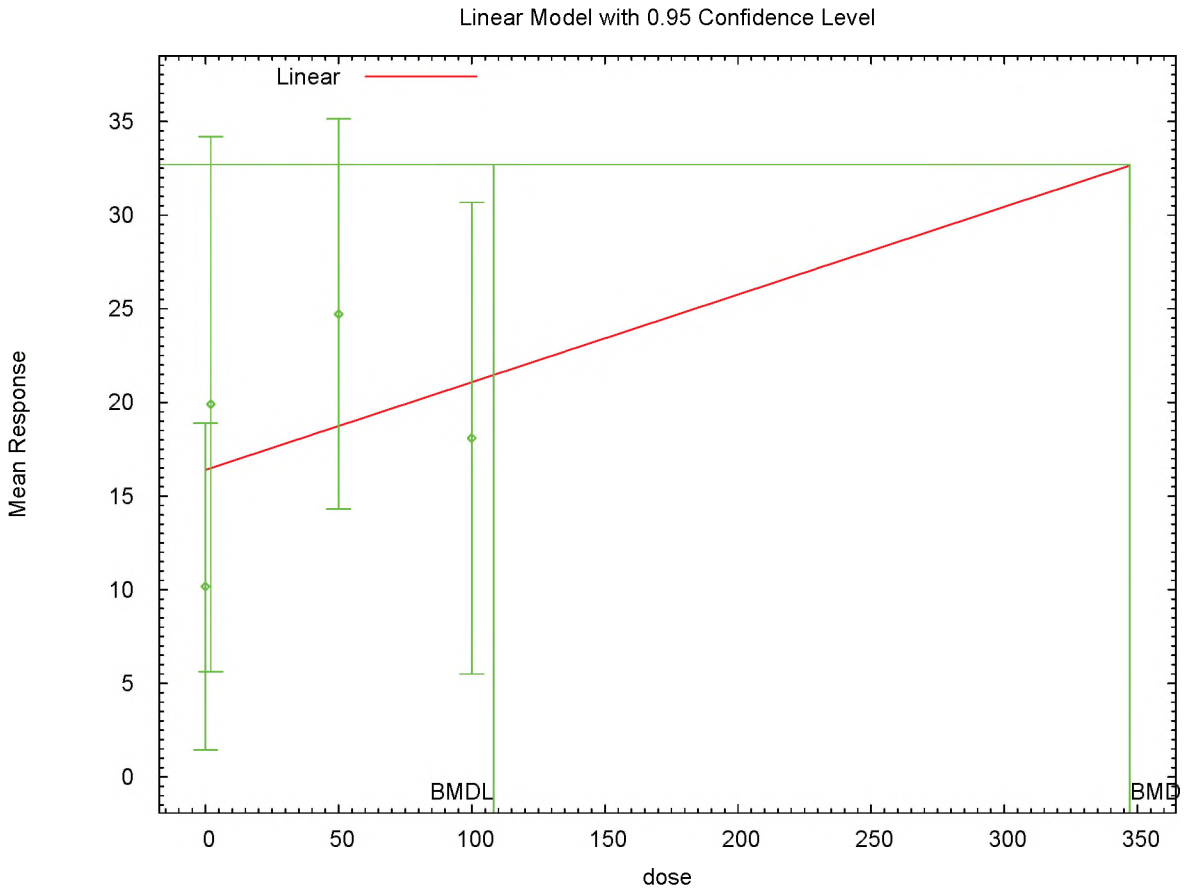
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 347.12

BMDL = 108.173

E.3.23.3. *Figure for Selected Model: Linear*



E.3.24. Li et al., 2006: Progesterone, 3-Day

E.3.24.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2)	2	<0.001	330.234	5.252E+01	error	
exponential (M3)	2	<0.001	330.234	5.252E+01	error	power hit bound (d = 1)
exponential (M4) [b]	**1**	**0.384**	**315.734**	**1.353E-01**	**8.351E-02**	
exponential (M5)	0	N/A	317.734	5.225E-01	7.503E-02	
Hill	1	0.386	315.729	1.135E-02	1.161E-05	n lower bound hit (n = 1)
linear	2	<0.001	331.121	7.765E+01	5.264E+01	
polynomial, 3-degree	2	<0.001	331.121	7.765E+01	5.264E+01	
power	2	<0.001	331.121	7.765E+01	5.264E+01	power bound hit (power = 1)
power, unrestricted	1	0.405	315.670	1.066E-63	1.066E-63	unrestricted (power = 0.009)

[a] Non-constant variance model selected ($p = 0.0013$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.3.24.2. *Output for Selected Model: Exponential (M4)*

Li et al., 2006: Progesterone, 3-Day

```
 ======================================================================
          Exponential Model. (Version: 1.61;  Date: 7/24/2009)
          Input Data File: C:\1\32_Li_2006_Progest_Exp_1.(d)
          Gnuplot Plotting File:
                                                 Tue Feb 16 18:14:31 2010
 ======================================================================

 Figure 4, 3-day progesterone
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
```

```
   Model 3 is nested within Model 5.
   Model 4 is nested within Model 5.


Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


                Initial Parameter Values

                Variable          Model 4
                --------          --------
                  lnalpha             11.3313
                      rho            -1.44835
                        a             64.8274
                        b           0.0456906
                        c            0.166844
                        d                   1



                  Parameter Estimates

                 Variable          Model 4
                 --------          -------
                  lnalpha             14.074
                      rho            -2.27065
                        a             61.7474
                        b             2.13327
                        c            0.318566
                        d                   1


         Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
     0     10         61.74         11.1
     2     10         30.56        40.48
    50     10         16.93         33.3
   100     10         11.36        43.75


                Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
     0         61.75        10.55        -0.002085
     2         20.26        37.38           0.8713
    50         19.67        38.66           -0.224
   100         19.67        38.66          -0.6801


Other models for which likelihoods are calculated:

  Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
```

```
  Model A2:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
              Var{e(ij)} = Sigma^2


                              Likelihoods of Interest

                    Model      Log(likelihood)      DF         AIC
                    -------    -----------------    ----   ------------
                       A1       -159.6327            5      329.2653
                       A2       -151.8128            8      319.6255
                       A3       -152.4882            6      316.9763
                        R       -165.6989            2      335.3978
                        4       -152.8668            5      315.7335


Additive constant for all log-likelihoods =     -36.76.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.


                               Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)


                           Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                       27.77            6          0.0001037
  Test 2                       15.64            3           0.001344
  Test 3                       1.351            2             0.5089
 Test 6a                      0.7572            1             0.3842


  The p-value for Test 1 is less than .05.  There appears to be a
  difference between response and/or variances among the dose
  levels, it seems appropriate to model the data.

  The p-value for Test 2 is less than .1.  A non-homogeneous
  variance model appears to be appropriate.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 6a is greater than .1.  Model 4 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 1.000000

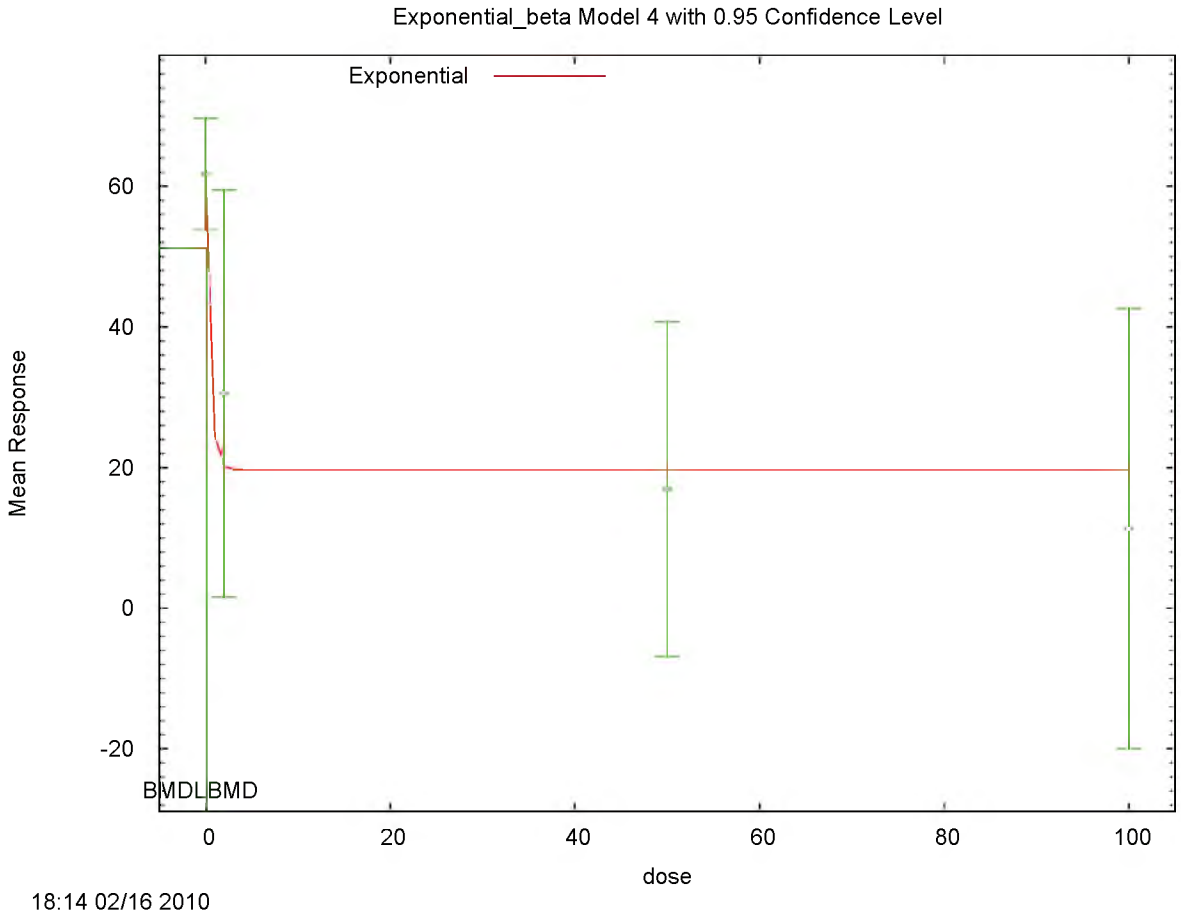
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

              BMD =     0.135296

             BMDL =    0.0835054
```

E.3.24.3. *Figure for Selected Model: Exponential (M4)*



E.3.24.4. *Output for Additional Model Presented: Hill, Unrestricted*

Li et al., 2006: Progesterone, 3-Day

```
 ======================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\1\32_Li_2006_Progest_Hill_U_1.(d)
         Gnuplot Plotting File:  C:\1\32_Li_2006_Progest_Hill_U_1.plt
                                                Tue Feb 16 18:14:41 2010
 ======================================================================

 Figure 4, 3-day progesterone
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   Power parameter is not restricted
   The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))
```

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	7.08699
rho =	0
intercept =	61.7404
v =	-50.3835
n =	1.43997
k =	1.6159

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -k
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	lalpha	rho	intercept	v	n
lalpha	1	-0.99	-0.097	0.84	NA
rho	-0.99	1	0.13	-0.81	NA
intercept	-0.097	0.13	1	-0.43	NA
v	0.84	-0.81	-0.43	1	NA
n	NA	NA	NA	NA	NA

NA - This parameter's variance has been estimated as zero or less.
THE MODEL HAS PROBABLY NOT CONVERGED!!!

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	13.9863	NA	NA	NA
rho	-2.25026	NA	NA	NA
intercept	61.7404	NA	NA	NA
v	-42.1239	NA	NA	NA
n	2.02774	NA	NA	NA
k	1e-013	NA		

At least some variance estimates are negative.
THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!
Try again from another starting point.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	61.7	61.7	11.1	10.5	9.74e-008
2	10	30.6	19.6	40.5	38.3	0.905
50	10	16.9	19.6	33.3	38.3	-0.222
100	10	11.4	19.6	43.7	38.3	-0.683

```
Model Descriptions for likelihoods calculated


Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
              A1         -159.632675           5     329.265349
              A2         -151.812765           8     319.625529
              A3         -152.488175           6     316.976349
          fitted         -152.873643           5     315.747285
               R         -165.698875           2     335.397750


                   Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value

  Test 1              27.7722          6       0.0001037
  Test 2              15.6398          3        0.001344
  Test 3              1.35082          2          0.5089
  Test 4             0.770936          1          0.3799

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =            1

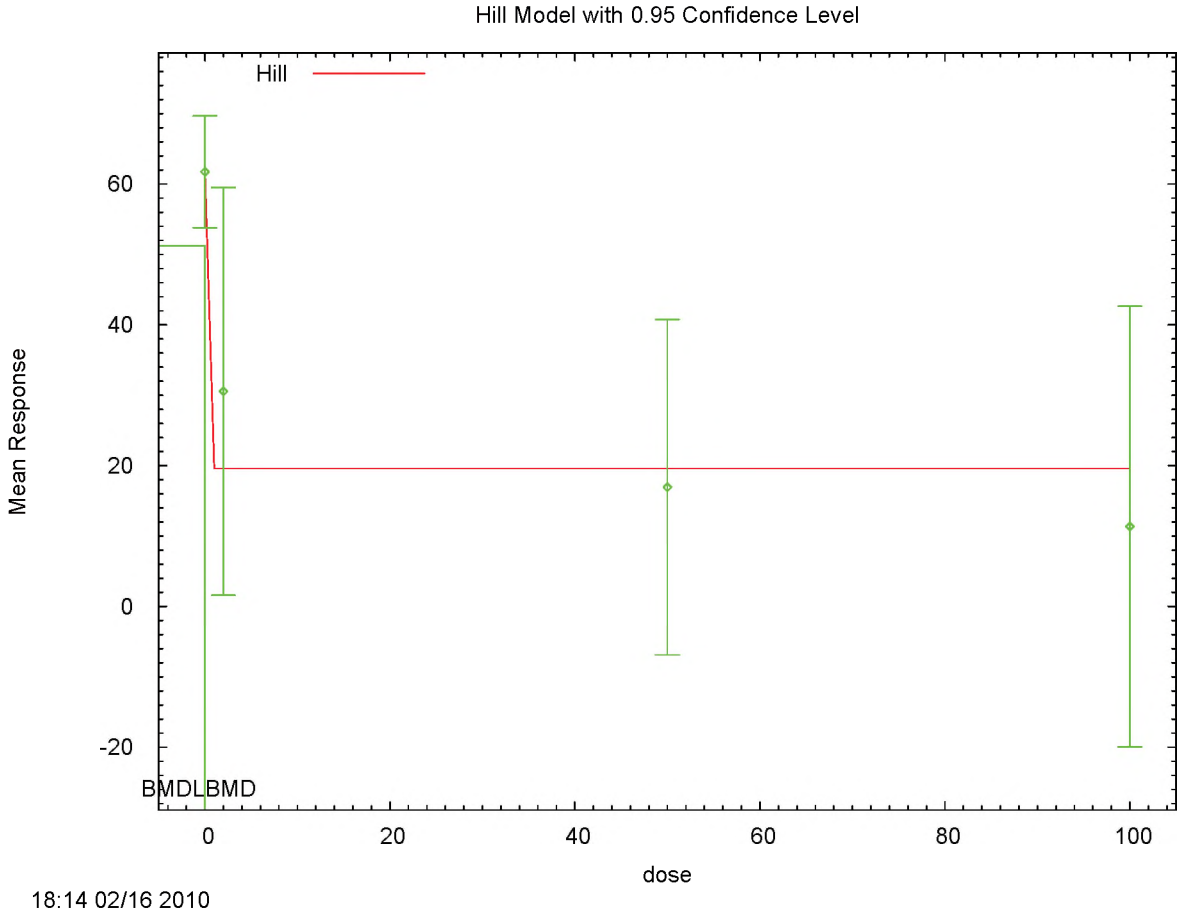
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =   5.81703e-014
```

```
BMDL =  5.81703e-014
```

E.3.24.5. *Figure for Additional Model Presented: Hill, Unrestricted*



E.3.25. Markowski et al., 2001: FR10 Run Opportunities

E.3.25.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2) [b]	**2**	**0.248**	**117.557**	**1.653E+02**	**5.025E+01**	
exponential (M3)	2	0.248	117.557	1.653E+02	5.025E+01	power hit bound (d = 1)
exponential (M4)	1	0.412	117.445	4.742E+01	1.729E-01	
exponential (M5)	0	N/A	118.918	3.178E+01	3.967E-05	
Hill	0	N/A	118.918	2.348E+01	6.728E-06	
linear	2	0.190	118.089	2.081E+02	1.051E+02	
polynomial, 3-degree	2	0.190	118.089	2.081E+02	1.051E+02	
power	2	0.190	118.089	2.081E+02	1.051E+02	power bound hit (power = 1)
power, unrestricted	1	0.238	118.164	9.153E+01	5.911E-07	unrestricted (power = 0.237)

[a] Constant variance model selected ($p = 0.1719$)

[b] Best-fitting model, BMDS output presented in this appendix

E.3.25.2. *Output for Selected Model: Exponential (M2)*

Markowski et al., 2001: FR10 Run Opportunities

```
 ======================================================================
          Exponential Model. (Version: 1.61;  Date: 7/24/2009)
          Input Data File: C:\1\33_Mark_2001_FR10opp_ExpCV_1.(d)
          Gnuplot Plotting File:
                                                  Tue Feb 16 18:15:26 2010
 ======================================================================

 Table 3
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

    The form of the response function by Model:
       Model 2:     Y[dose] = a * exp{sign * b * dose}
       Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
       Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
       Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

      Note: Y[dose] is the median response for exposure = dose;
            sign = +1 for increasing trend in data;
            sign = -1 for decreasing trend.

       Model 2 is nested within Models 3 and 4.
       Model 3 is nested within Model 5.
       Model 4 is nested within Model 5.
```

Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 2
lnalpha	3.5321
rho(S)	0
a	6.98169
b	0.00309891
c	0
d	1

(S) = Specified

Parameter Estimates

Variable	Model 2
lnalpha	3.64823
rho	0
a	11.9443
b	0.0044262
c	0
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	7	13.29	8.65
20	4	11.25	5.56
60	6	5.75	3.53
180	7	7	6.01

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	11.94	6.197	0.5745
20	10.93	6.197	0.1025
60	9.158	6.197	-1.347
180	5.385	6.197	0.6897

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

```
  Model A2:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
              Var{e(ij)} = Sigma^2


                            Likelihoods of Interest

                  Model      Log(likelihood)      DF         AIC
                 -------    -----------------    ----   ------------
                     A1       -54.38526           5      118.7705
                     A2       -51.88568           8      119.7714
                     A3       -54.38526           5      118.7705
                      R       -57.45429           2      118.9086
                      2       -55.77871           3      117.5574


Additive constant for all log-likelihoods =     -22.05.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.


                             Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does Model 2 fit the data? (A3 vs. 2)


                         Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                       11.14             6            0.08423
  Test 2                       4.999             3             0.1719
  Test 3                       4.999             3             0.1719
  Test 4                       2.787             2             0.2482


  The p-value for Test 1 is greater than .05.  There may not be a
  diffence between responses and/or variances among the dose levels
  Modelling the data with a dose/response curve may not be appropriate.

  The p-value for Test 2 is greater than .1.  A homogeneous
  variance model appears to be appropriate here.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 4 is greater than .1.  Model 2 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 1.000000

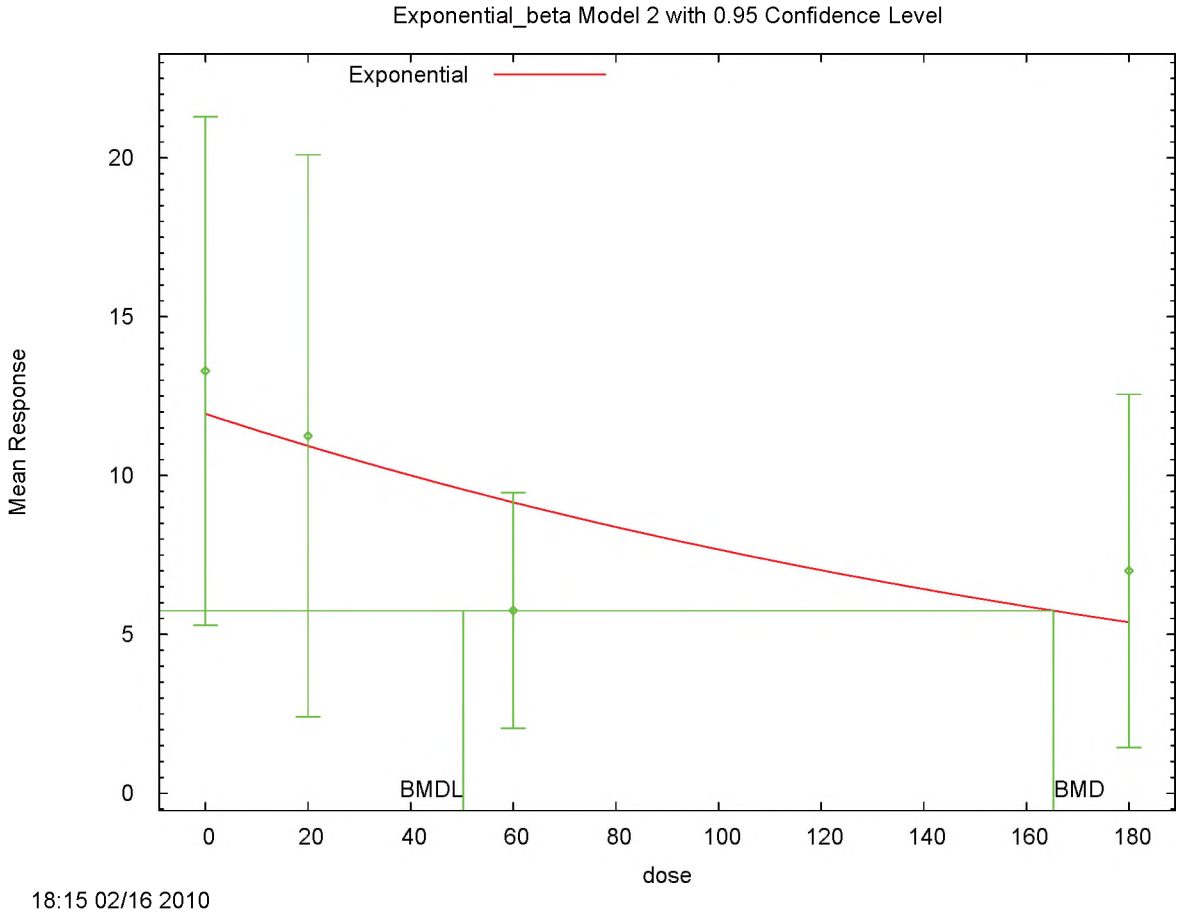
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD =      165.284

              BMDL =      50.2488
```

E.3.25.3. *Figure for Selected Model: Exponential (M2)*



E.3.26. Markowski et al., 2001: FR2 Revolutions

E.3.26.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2)	2	0.192	217.636	1.627E+02	5.807E+01	
exponential (M3)	2	0.192	217.636	1.627E+02	5.807E+01	power hit bound (d = 1)
exponential (M4)	1	0.298	217.415	4.668E+01	1.965E-01	
exponential (M5)	0	N/A	218.532	3.308E+01	1.193E+01	
Hill [b]	**0**	**N/A**	**218.532**	**2.364E+01**	**7.336E+00**	**n upper bound hit (n = 18)**
linear	2	0.150	218.129	1.989E+02	1.025E+02	
polynomial, 3-degree	2	0.150	218.129	1.989E+02	1.025E+02	
power	2	0.150	218.129	1.989E+02	1.025E+02	power bound hit (power = 1)
power, unrestricted [c]	1	0.160	218.302	9.101E+01	1.800E-13	unrestricted (power = 0.272)

[a] Constant variance model selected ($p = 0.1092$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.3.26.2. *Output for Selected Model: Hill*

Markowski et al., 2001: FR2 Revolutions

```
 ================================================================
          Hill Model. (Version: 2.14;  Date: 06/26/2008)
          Input Data File: C:\1\34_Mark_2001_FR2rev_HillCV_1.(d)
          Gnuplot Plotting File:  C:\1\34_Mark_2001_FR2rev_HillCV_1.plt
                                                Tue Feb 16 18:16:03 2010
 ================================================================

 Table 3
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter restricted to be greater than 1
   A constant variance model is fit
```

```
   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                          alpha =      2598.74
                            rho =            0   Specified
                      intercept =       119.29
                              v =       -62.79
                              n =      1.80602
                              k =        35.85


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -rho
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

                    alpha    intercept            v            n            k

      alpha             1    -8.1e-009     4.5e-008      -3e-005       3e-005

  intercept    -8.1e-009            1        -0.81     -0.00013      -0.0022

          v     4.5e-008        -0.81            1       0.0002       0.0014

          n      -3e-005     -0.00013       0.0002            1           -1

          k       3e-005      -0.0022       0.0014           -1            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
           alpha          2183.85          630.425             948.245             3419.46
       intercept           119.29          17.6629             84.6713             153.909
               v         -56.5223          21.9082            -99.4615            -13.5831
               n               18          8854.08            -17335.7             17371.7
               k          21.6708          855.263            -1654.61             1697.95


      Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     7        119          119         69.9         46.7      2.74e-008
   20     4        109          108           61         46.7      8.42e-010
   60     6       56.5         62.8         31.2         46.7         -0.329
  180     7       68.1         62.8         33.2         46.7          0.304

Degrees of freedom for Test A3 vs fitted <= 0


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
```

```
            Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = Sigma^2
        Model A3 uses any fixed variance parameters that
        were specified by the user

 Model  R:         Yi = Mu + e(i)
             Var{e(i)} = Sigma^2


                        Likelihoods of Interest

              Model      Log(likelihood)   # Param's      AIC
                A1         -104.165520            5     218.331040
                A2         -101.140174            8     218.280349
                A3         -104.165520            5     218.331040
            fitted         -104.266162            5     218.532324
                 R         -107.599268            2     219.198536


                     Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                       Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              12.9182          6         0.04435
   Test 2              6.05069          3          0.1092
   Test 3              6.05069          3          0.1092
   Test 4             0.201283          0              NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-Square
     test for fit is not valid


        Benchmark Dose Computation

Specified effect =            1

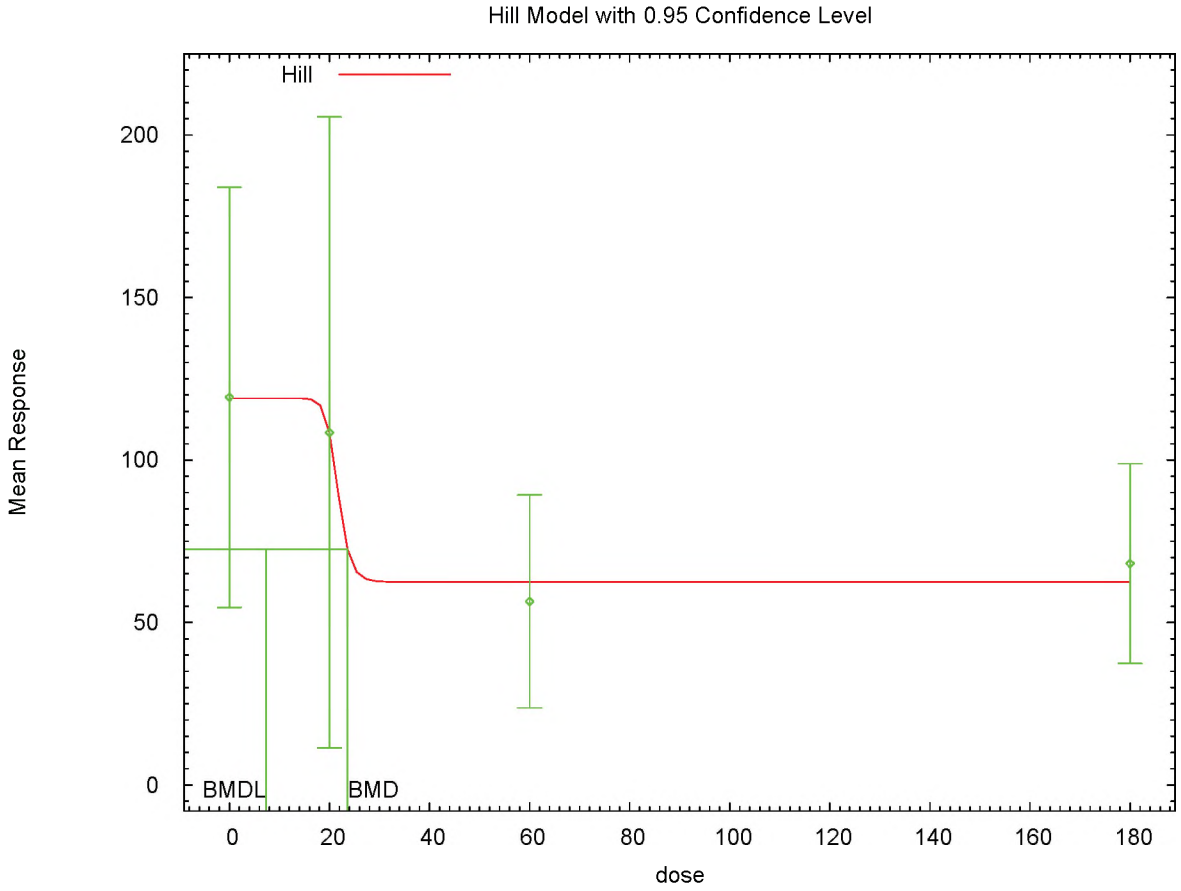
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =        23.6366

            BMDL =       7.33648
```

E.3.26.3. *Figure for Selected Model: Hill*



E.3.26.4. *Output for Additional Model Presented: Power, Unrestricted*

Markowski et al., 2001: FR2 Revolutions

```
 ================================================================
          Power Model. (Version: 2.15;  Date: 04/07/2008)
          Input Data File: C:\1\34_Mark_2001_FR2rev_PowerCV_U_1.(d)
          Gnuplot Plotting File:  C:\1\34_Mark_2001_FR2rev_PowerCV_U_1.plt
                                                Tue Feb 16 18:16:04 2010
 ================================================================

 Table 3
 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

    The form of the response function is:

    Y[dose] = control + slope * dose^power


    Dependent variable = Mean
    Independent variable = Dose
    rho is set to 0
    The power is not restricted
    A constant variance model is fit
```

```
Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                         alpha =      2598.74
                           rho =            0   Specified
                       control =       119.29
                         slope =     -1.79436
                         power =     0.708231


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been specified by the user,
                and do not appear in the correlation matrix )

                  alpha      control        slope        power

    alpha             1     9.7e-009    -1.9e-008    -1.6e-008

  control     9.7e-009            1        -0.49        -0.28

    slope    -1.9e-008        -0.49            1         0.96

    power    -1.6e-008        -0.28         0.96            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         alpha             2351          678.674            1020.82             3681.17
       control          120.074          18.0837            84.6305             155.517
         slope         -14.1965          22.2073            -57.722              29.329
         power          0.27229         0.301344          -0.318334            0.862913


      Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

   0        7        119          120         69.9         48.5        -0.0428
  20        4        109           88           61         48.5          0.846
  60        6       56.5         76.8         31.2         48.5          -1.02
 180        7       68.1         61.7         33.2         48.5          0.352


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
      Model A3 uses any fixed variance parameters that
```

were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-104.165520	5	218.331040
A2	-101.140174	8	218.280349
A3	-104.165520	5	218.331040
fitted	-105.151136	4	218.302271
R	-107.599268	2	219.198536

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	12.9182	6	0.04435
Test 2	6.05069	3	0.1092
Test 3	6.05069	3	0.1092
Test 4	1.97123	1	0.1603

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance
model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears
to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems
to adequately describe the data

Benchmark Dose Computation

Specified effect = 1

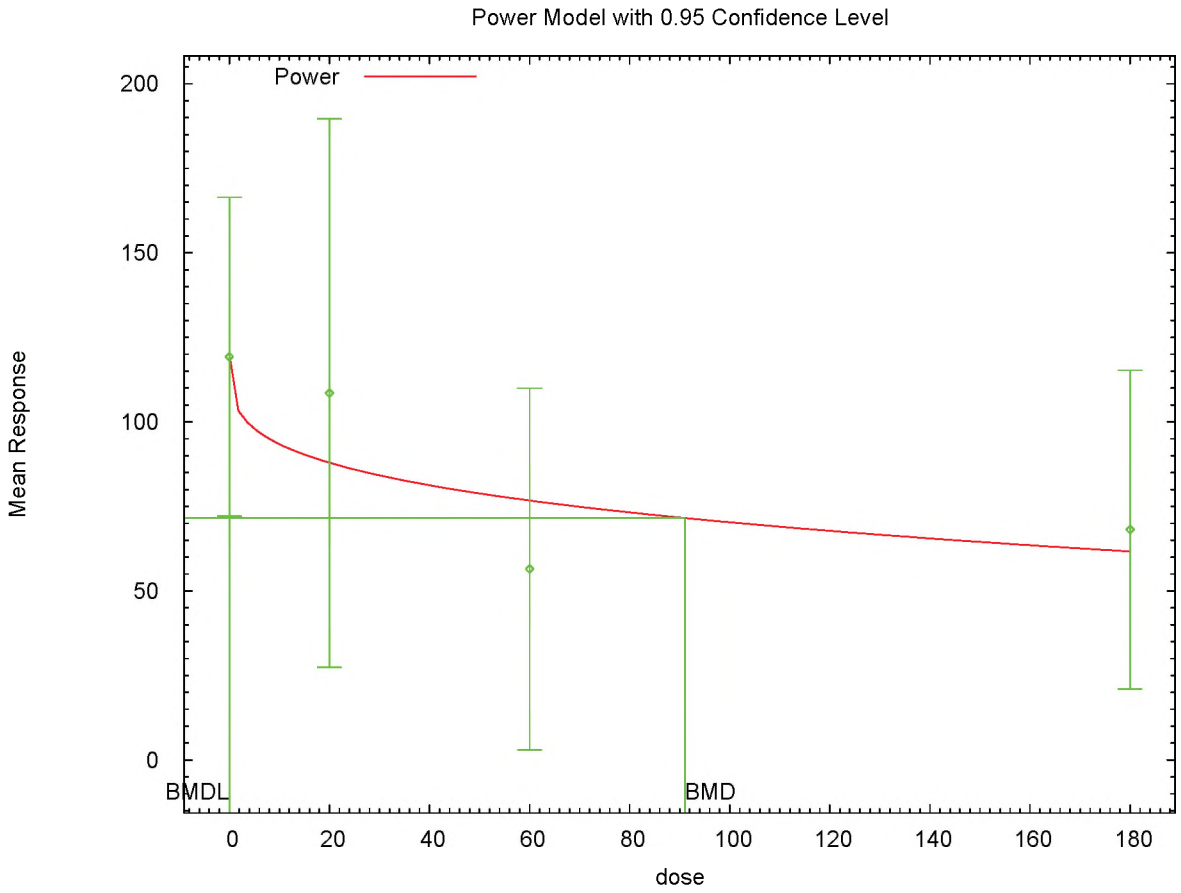
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 91.0145

BMDL = 1.8e-013

E.3.26.5. *Figure for Additional Model Presented: Power, Unrestricted*



E.3.27. Markowski et al., 2001: FR5 Run Opportunities

E.3.27.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2)	2	0.149	133.830	9.491E+01	4.324E+01	
exponential (M3)	2	0.149	133.830	9.491E+01	4.324E+01	power hit bound (d = 1)
exponential (M4)	1	0.303	133.087	2.961E+01	9.356E+00	
exponential (M5)	0	N/A	134.032	2.871E+01	1.226E+01	
Hill [b]	**1**	**0.939**	**132.032**	**2.214E+01**	**1.117E+01**	**n upper bound hit (n = 18)**
linear	2	0.091	134.825	1.349E+02	8.118E+01	
polynomial, 3-degree	2	0.091	134.825	1.349E+02	8.118E+01	
power	2	0.091	134.825	1.349E+02	8.118E+01	power bound hit (power = 1)
power, unrestricted [c]	1	0.133	134.281	3.721E+01	1.439E-07	unrestricted (power = 0.336)

[a] Constant variance model selected ($p = 0.2262$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.3.27.2. *Output for Selected Model: Hill*

Markowski et al., 2001: FR5 Run Opportunities

```
 ================================================================
          Hill Model. (Version: 2.14;  Date: 06/26/2008)
          Input Data File: C:\1\35_Mark_2001_FR5opp_HillCV_1.(d)
          Gnuplot Plotting File:  C:\1\35_Mark_2001_FR5opp_HillCV_1.plt
                                                Tue Feb 16 18:16:39 2010
 ================================================================

 Table 3
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter restricted to be greater than 1
   A constant variance model is fit
```

```
   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                          alpha =      77.4849
                            rho =            0   Specified
                      intercept =        26.14
                              v =       -13.34
                              n =      2.36002
                              k =      35.0654


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -rho    -n
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

                    alpha    intercept            v            k

      alpha             1    -3.6e-009     9.8e-009     3.6e-008

  intercept    -3.6e-009            1        -0.81        -0.51

          v     9.8e-009        -0.81            1         0.36

          k     3.6e-008        -0.51         0.36            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
           alpha          64.5863          18.6445             28.0438             101.129
       intercept            26.14          3.03753             20.1865             32.0935
               v         -13.1569           3.7676            -20.5413            -5.77257
               n               18               NA
               k          21.5963          2.68136             16.3409             26.8517

 NA - Indicates that this parameter has hit a bound
      implied by some inequality constraint and thus
      has no standard error.


      Table of Data and Estimated Values of Interest

  Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------      ---   --------     --------   -----------  -----------   ----------

     0      7       26.1         26.1         12.3         8.04      1.02e-008
    20      4       23.5         23.5         7.04         8.04     -1.39e-007
    60      6       12.8           13         6.17         8.04        -0.0558
   180      7       13.1           13         7.14         8.04         0.0517


  Model Descriptions for likelihoods calculated


  Model A1:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
```

```
           Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
      Model A3 uses any fixed variance parameters that
      were specified by the user

 Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                      Likelihoods of Interest

             Model      Log(likelihood)   # Param's      AIC
              A1          -62.013133            5     134.026266
              A2          -59.839035            8     135.678070
              A3          -62.013133            5     134.026266
           fitted         -62.016024            4     132.032049
               R          -67.530040            2     139.060081


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1               15.382          6         0.01748
   Test 2               4.3482          3          0.2262
   Test 3               4.3482          3          0.2262
   Test 4            0.0057833          1          0.9394

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =            1

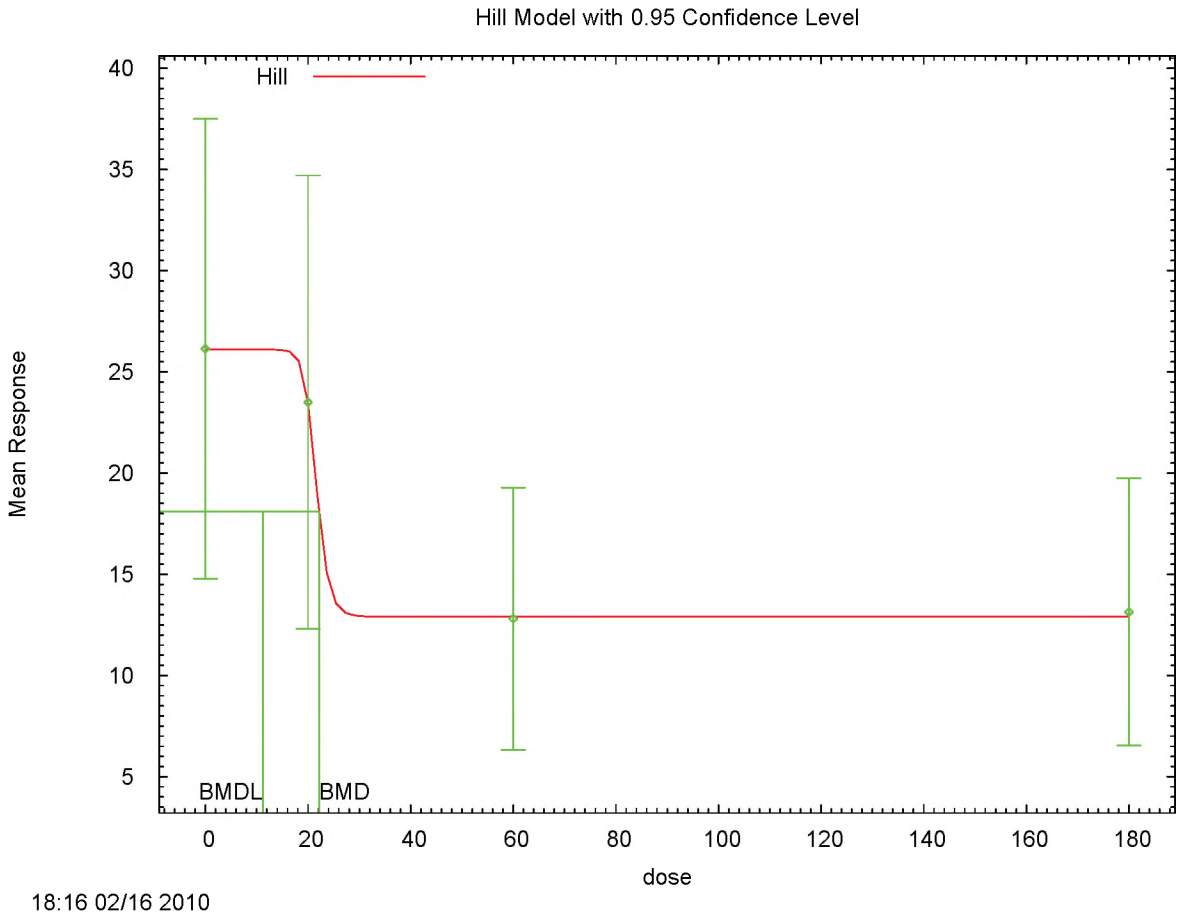
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =        22.144

            BMDL =       11.165
```

E.3.27.3. *Figure for Selected Model: Hill*



E.3.27.4. *Output for Additional Model Presented: Power, Unrestricted*

Markowski et al., 2001: FR5 Run Opportunities

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\1\35_Mark_2001_FR5opp_PwrCV_U_1.(d)
         Gnuplot Plotting File:  C:\1\35_Mark_2001_FR5opp_PwrCV_U_1.plt
                                                Tue Feb 16 18:16:40 2010
 ================================================================

 Table 3
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   The power is not restricted
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


                Default Initial Parameter Values
                        alpha =      77.4849
                          rho =            0   Specified
                      control =        26.14
                        slope =     -0.39517
                        power =     0.725538


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been specified by the user,
                and do not appear in the correlation matrix )

                 alpha      control        slope        power

    alpha            1     7.4e-009     4.3e-008     4.8e-008

  control     7.4e-009            1        -0.51        -0.34

    slope     4.3e-008        -0.51            1         0.97

    power     4.8e-008        -0.34         0.97            1


                                Parameter Estimates

                                                    95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         alpha          70.9323          20.4764             30.7993             111.065
       control          26.3567          3.13032             20.2213              32.492
         slope         -2.49841          3.16984            -8.71118             3.71437
         power         0.336003         0.242031           -0.138368            0.810375
```

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	7	26.1	26.4	12.3	8.42	-0.0681
20	4	23.5	19.5	7.04	8.42	0.945
60	6	12.8	16.5	6.17	8.42	-1.07
180	7	13.1	12.1	7.14	8.42	0.341

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that
were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-62.013133	5	134.026266
A2	-59.839035	8	135.678070
A3	-62.013133	5	134.026266
fitted	-63.140714	4	134.281428
R	-67.530040	2	139.060081

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	15.382	6	0.01748
Test 2	4.3482	3	0.2262
Test 3	4.3482	3	0.2262
Test 4	2.25516	1	0.1332

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance
model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears
to be appropriate here

```
The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


                Benchmark Dose Computation

Specified effect =             1

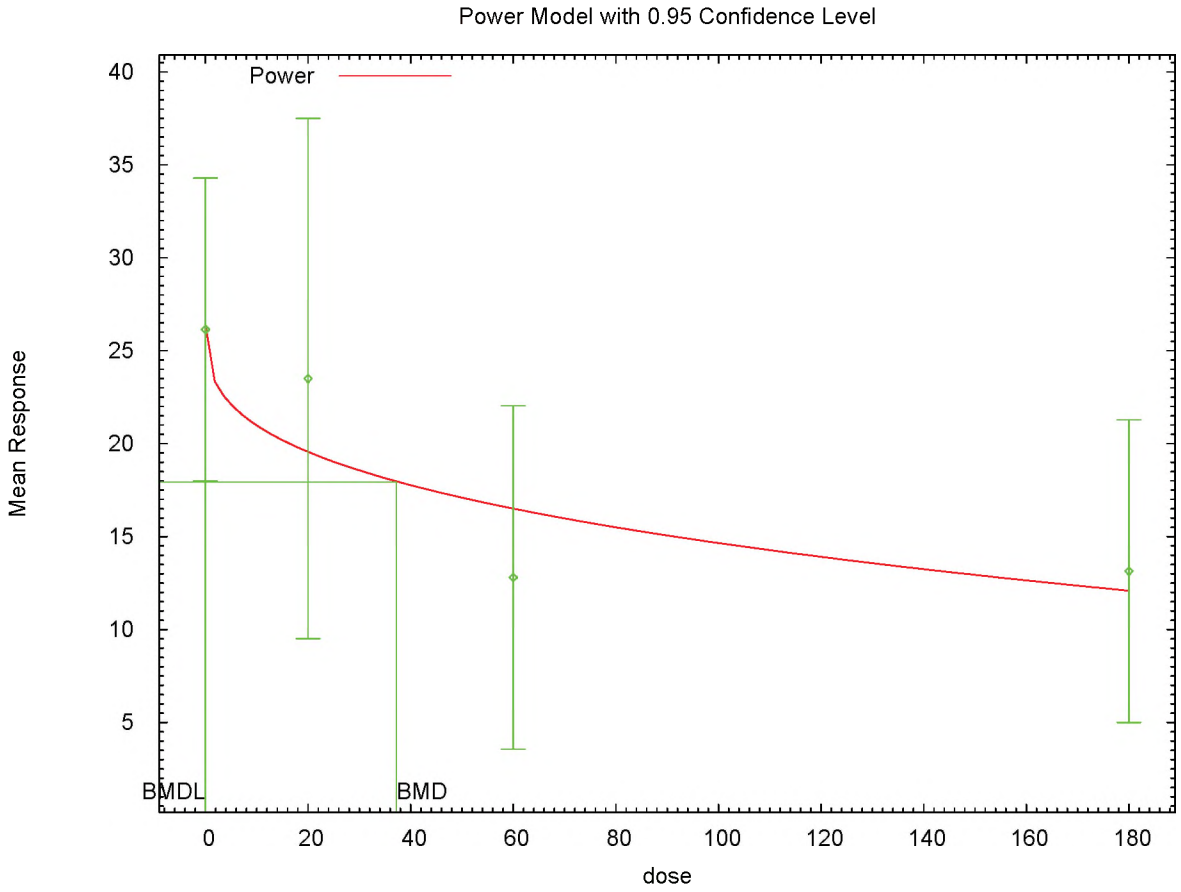
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

              BMD = 37.2131


             BMDL = 1.43926e-007
```

E.3.27.5. *Figure for Additional Model Presented: Power, Unrestricted*



18:16 02/16 2010

E.3.28. Miettinen et al., 2006: Cariogenic Lesions, Pups

E.3.28.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
gamma	3	0.345	162.699	7.505E+01	4.086E+01	power bound hit (power = 1)
logistic	3	0.315	162.909	8.991E+01	5.250E+01	
log-logistic [a]	**3**	**0.506**	**161.767**	**3.130E+01**	**1.054E+01**	**slope bound hit (slope = 1)**
log-probit	3	0.257	163.393	1.390E+02	6.729E+01	slope bound hit (slope = 1)
multistage, 4-degree	3	0.345	162.699	7.505E+01	4.086E+01	final ß = 0
probit	3	0.299	163.031	9.941E+01	6.208E+01	
Weibull	3	0.345	162.699	7.505E+01	4.086E+01	power bound hit (power = 1)
gamma, unrestricted	2	0.797	161.805	1.591E-02	1.335E-240	unrestricted (power = 0.184)
log-logistic, unrestricted [b]	2	0.723	161.998	3.713E-01	error	unrestricted (slope = 0.403)
log-probit, unrestricted	2	0.726	161.987	5.098E-01	error	unrestricted (slope = 0.25)
Weibull, unrestricted	2	0.761	161.897	1.174E-01	error	unrestricted (power = 0.281)

[a] Best-fitting model, BMDS output presented in this appendix

[b] Alternate model, BMDS output also presented in this appendix

E.3.28.2. *Output for Selected Model: Log-Logistic*

Miettinen et al., 2006: Cariogenic Lesions, Pups

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\1\36_Miet_2006_Cariogenic_LogLogistic_1.(d)
         Gnuplot Plotting File:  C:\1\36_Miet_2006_Cariogenic_LogLogistic_1.plt
                                          Tue Feb 16 18:17:16 2010
 ================================================================

 Table 2 converting the percentage into the number of animals, and control is Control II from the
study. Dose is in ng per kg and is from Table 1
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = DichEff
```

```
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                  Default Initial Parameter Values
                     background =     0.595238
                      intercept =     -5.52519
                          slope =            1


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -slope
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

             background    intercept

background            1        -0.64

 intercept        -0.64            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background         0.658158            *               *                   *
      intercept         -5.64068            *               *                   *
          slope                1            *               *                   *

* - Indicates that this value is not calculated.



                         Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -77.6769         5
   Fitted model         -78.8837         2       2.41374      3          0.4911
  Reduced model         -83.2067         1       11.0597      4          0.0259

           AIC:          161.767


                                Goodness  of  Fit
                                                                    Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
    0.0000     0.6582        27.643    25.000          42       -0.860
   30.0000     0.6911        20.041    23.000          29        1.189
  100.0000     0.7477        18.693    19.000          25        0.141
  300.0000     0.8345        20.027    20.000          24       -0.015
 1000.0000     0.9249        29.596    29.000          32       -0.400

 Chi^2 = 2.33      d.f. = 3        P-value = 0.5062


   Benchmark Dose Computation
```

```
Specified effect =           0.1

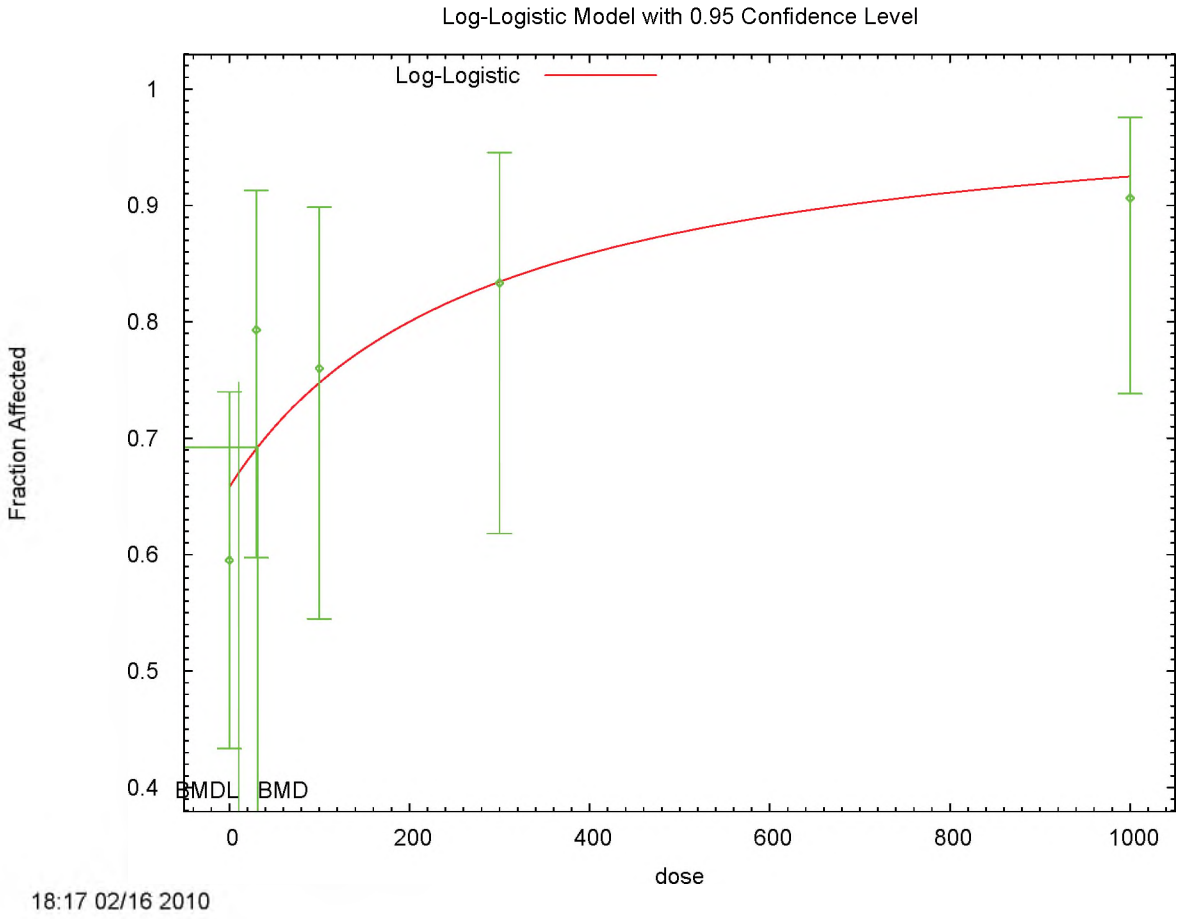
Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =       31.2951

            BMDL =       10.5354
```

E.3.28.3. *Figure for Selected Model: Log-Logistic*



E.3.28.4. *Output for Additional Model Presented: Log-Logistic, Unrestricted*

Miettinen et al., 2006: Cariogenic Lesions, Pups

```
================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\36_Miet_2006_Cariogenic_LogLogistic_U_1.(d)
        Gnuplot Plotting File:  C:\1\36_Miet_2006_Cariogenic_LogLogistic_U_1.plt
                                          Tue Feb 16 18:17:18 2010
================================================================
```

```
 Table 2 converting the percentage into the number of animals, and control is Control II from the
study. Dose is in ng per kg and is from Table 1
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =     0.595238
                     intercept =     -1.68849
                         slope =     0.382632


           Asymptotic Correlation Matrix of Parameter Estimates

             background    intercept        slope

background            1        -0.41         0.24

 intercept        -0.41            1        -0.96

     slope         0.24        -0.96            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background         0.597778            *               *                   *
      intercept         -1.79836            *               *                   *
          slope         0.402606            *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -77.6769         5
   Fitted model         -77.9988         3      0.643944      2          0.7247
  Reduced model         -83.2067         1       11.0597      4          0.0259

           AIC:         161.998


                                Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size        Residual
   ----------------------------------------------------------------------
    0.0000     0.5978        25.107    25.000          42        -0.034
   30.0000     0.7564        21.936    23.000          29         0.460
```

```
  100.0000     0.8045        20.112    19.000          25       -0.561
  300.0000     0.8480        20.351    20.000          24       -0.200
 1000.0000     0.8905        28.495    29.000          32        0.286

 Chi^2 = 0.65      d.f. = 2        P-value = 0.7227


   Benchmark Dose Computation

Specified effect =            0.1

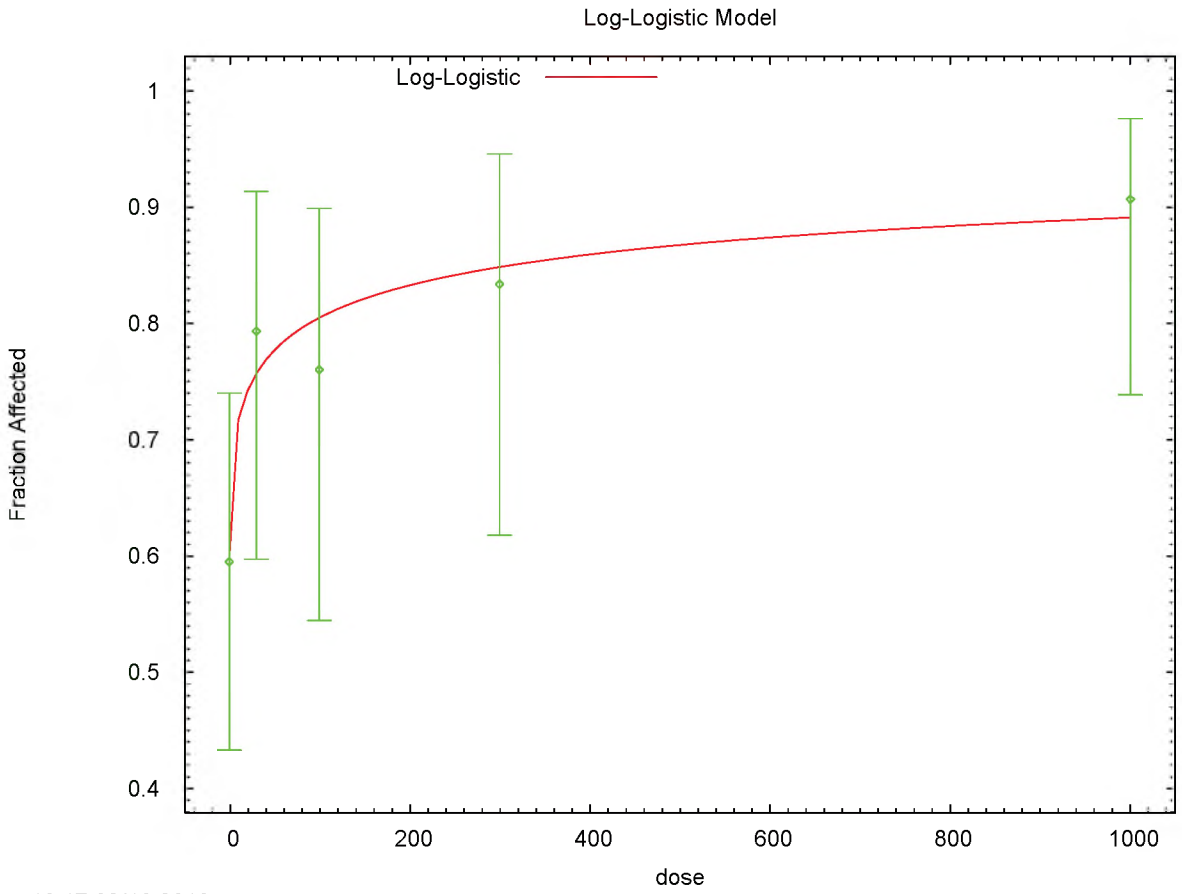
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.371315

           Benchmark dose computation failed.  Lower limit includes zero.
```

E.3.28.5. *Figure for Additional Model Presented: Log-Logistic, Unrestricted*



E.3.29. Murray et al., 1979: Fertility in F2 Generation

E.3.29.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
gamma	0	N/A	61.729	7.016E+00	1.698E+00	
logistic	1	0.072	60.497	4.007E+00	2.836E+00	negative intercept (intercept = -2.53)
log-logistic	0	N/A	61.729	7.902E+00	1.584E+00	
multistage, 1-degree	1	0.053	61.644	2.380E+00	1.320E+00	
multistage, 2-degree [a]	**1**	**0.094**	**59.935**	**4.548E+00**	**1.635E+00**	
probit	1	0.070	60.613	3.707E+00	2.615E+00	negative intercept (intercept = -1.446)
Weibull	0	N/A	61.729	8.115E+00	1.698E+00	
log-probit, unrestricted	0	N/A	61.729	6.373E+00	1.503E+00	unrestricted (slope = 2.306)

[a] Best-fitting model, BMDS output presented in this appendix

E.3.29.2. *Output for Selected Model: Multistage, 2-Degree*

Murray et al., 1979: Fertility in F2 Generation

```
 ================================================================
         Multistage Model. (Version: 3.0;  Date: 05/16/2008)
         Input Data File: C:\1\Murray_1979_fert_index_f2_Multi2_1.(d)
         Gnuplot Plotting File:  C:\1\Murray_1979_fert_index_f2_Multi2_1.plt
                                                Tue Feb 16 20:08:06 2010
 ================================================================

 Table 1 but expressed as number of dams who do not produce offspring
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2
```

```
 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                     Background =    0.0624181
                        Beta(1) =            0
                        Beta(2) =   0.00532688


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Beta(1)
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

             Background      Beta(2)

Background            1        -0.44

   Beta(2)        -0.44            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background        0.0772201            *               *                   *
        Beta(1)                0            *               *                   *
        Beta(2)       0.00509404            *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
      Full model        -25.8194         3
    Fitted model        -27.9673         2       4.29584      1         0.03821
   Reduced model        -34.0009         1        16.363      2       0.0002798

           AIC:         59.9347


                                Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size        Residual
   ---------------------------------------------------------------------
    0.0000     0.0772         2.471     4.000          32         1.013
    1.0000     0.0819         1.638     0.000          20        -1.336
   10.0000     0.4455         8.911     9.000          20         0.040

 Chi^2 = 2.81      d.f. = 1        P-value = 0.0936


   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

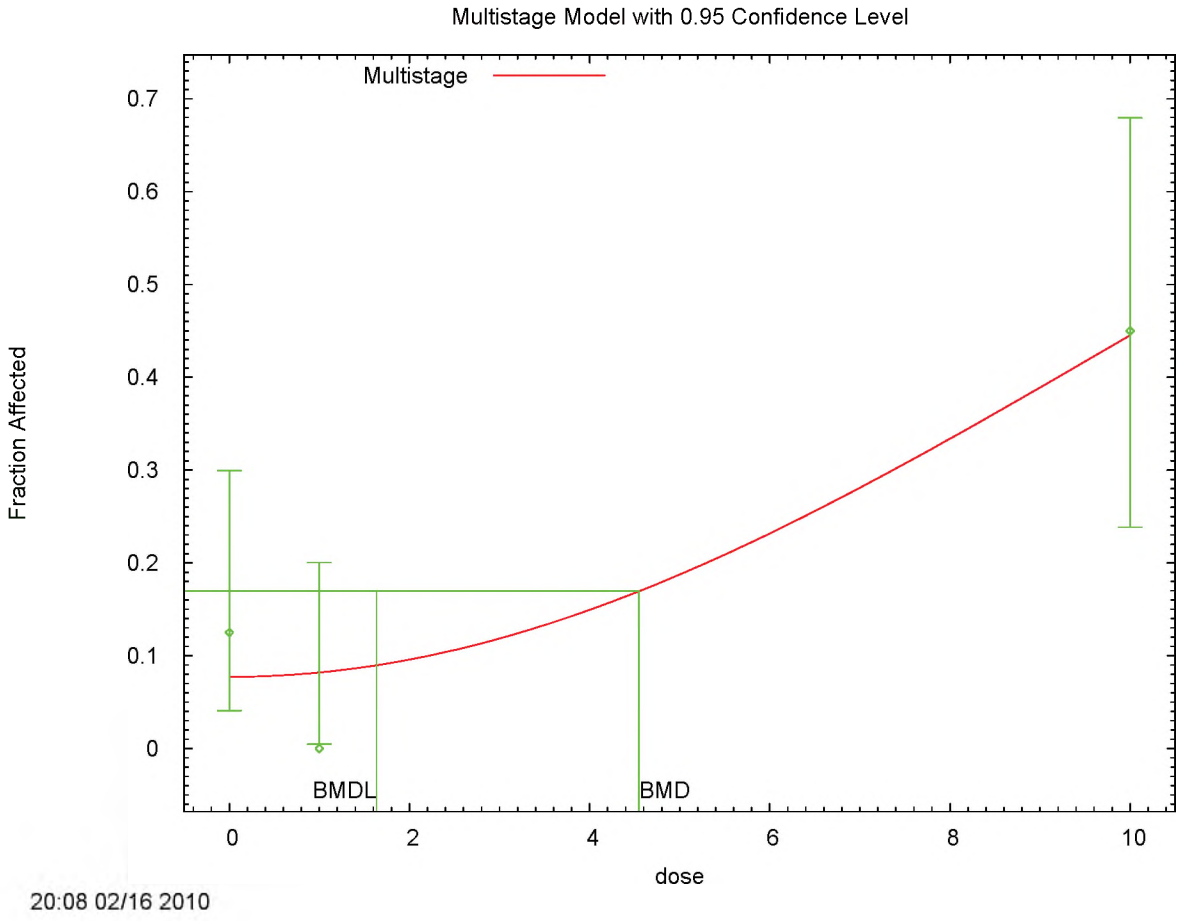
             BMD =        4.54787
```

```
                BMDL =        1.63487

                BMDU =        6.79105

Taken together, (1.63487, 6.79105) is a 90      % two-sided confidence
interval for the BMD
```

E.3.29.3. *Figure for Selected Model: Multistage, 2-Degree*



E.3.30. National Toxicology Program, 1982: Toxic Hepatitis, Male Mice

E.3.30.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
gamma	1	0.026	113.097	1.552E+01	5.155E+00	
logistic	2	0.093	110.712	1.769E+01	1.383E+01	negative intercept (intercept = -3.087)
log-logistic	1	0.027	113.093	1.499E+01	6.628E+00	
log-probit	1	0.027	113.111	1.360E+01	7.237E+00	
multistage, 3-degree [a]	**1**	**0.028**	**112.555**	**1.488E+01**	**4.676E+00**	
probit	2	0.088	110.696	1.564E+01	1.261E+01	negative intercept (intercept = -1.731)
Weibull	1	0.026	113.056	1.619E+01	4.903E+00	

[a] Best-fitting model, BMDS output presented in this appendix

E.3.30.2. *Output for Selected Model: Multistage, 3-Degree*

National Toxicology Program, 1982: Toxic Hepatitis, Male Mice

```
 ================================================================
         Multistage Model. (Version: 3.0;  Date: 05/16/2008)
         Input Data File: C:\1\37_NTP_1982_ToxHep_Multi3_1.(d)
         Gnuplot Plotting File:  C:\1\37_NTP_1982_ToxHep_Multi3_1.plt
                                          Tue Feb 16 18:17:51 2010
 ================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 4
 Total number of specified parameters = 0
 Degree of polynomial = 3


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
```

Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values
Background = 0.0525767
Beta(1) = 0.00243254
Beta(2) = 0
Beta(3) = 5.29052e-006

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Beta(2)
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Background	Beta(1)	Beta(3)
Background	1	-0.69	0.66
Beta(1)	-0.69	1	-0.98
Beta(3)	0.66	-0.98	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0383474	*	*	*
Beta(1)	0.00605732	*	*	*
Beta(2)	0	*	*	*
Beta(3)	4.60855e-006	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-51.0633	4			
Fitted model	-53.2776	3	4.42854	1	0.03534
Reduced model	-121.743	1	141.358	3	<.0001

AIC: 112.555

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0383	2.799	1.000	73	-1.097
1.4000	0.0465	2.278	5.000	49	1.847
7.1000	0.0803	3.937	3.000	49	-0.492
71.0000	0.8798	43.990	44.000	50	0.004

Chi^2 = 4.86 d.f. = 1 P-value = 0.0275

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

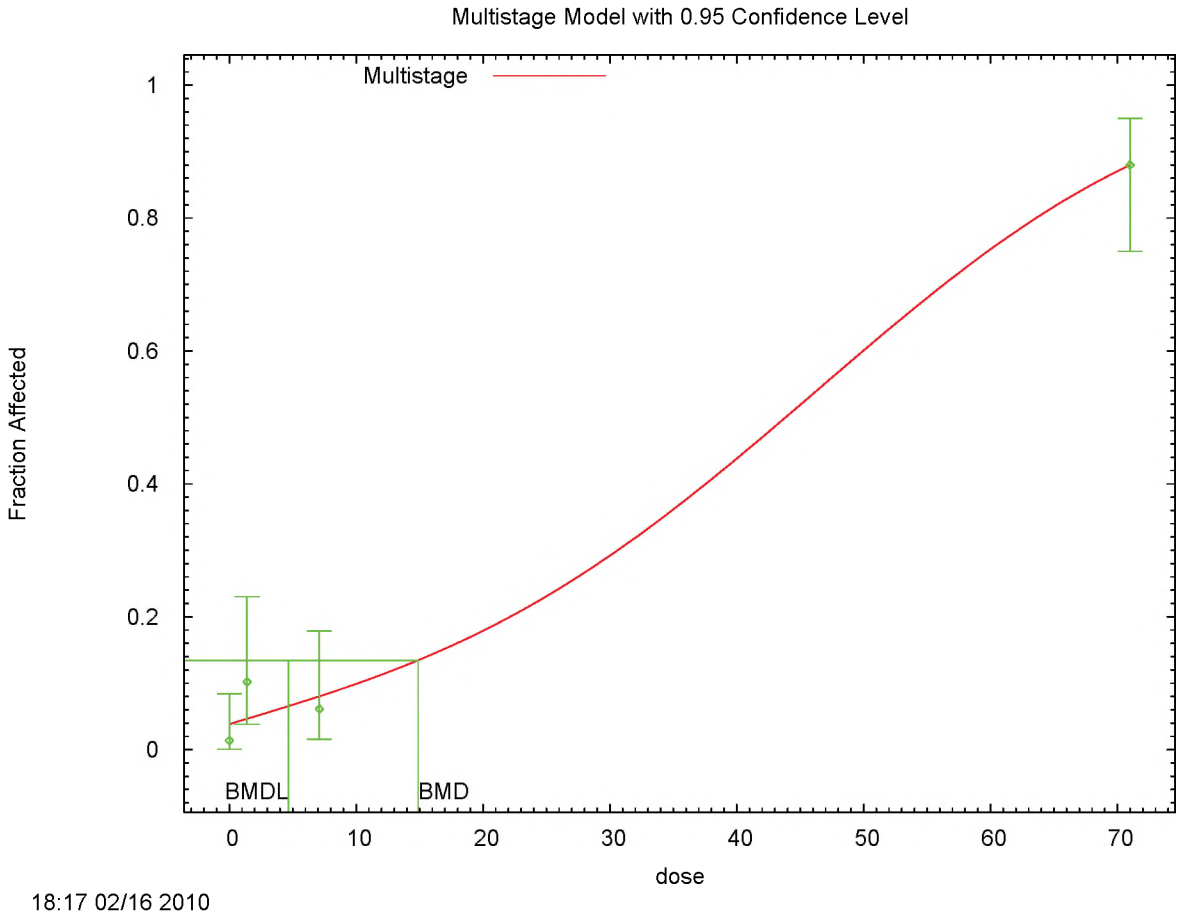
```
                BMD =        14.8848

               BMDL =        4.67636

               BMDU =        28.8293

Taken together, (4.67636, 28.8293) is a 90     % two-sided confidence
interval for the BMD
```

E.3.30.3. *Figure for Selected Model: Multistage, 3-Degree*



E.3.31. National Toxicology Program, 2006: Alveolar Metaplasia

E.3.31.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
gamma	4	<0.001	340.127	2.240E+00	1.791E+00	power bound hit (power = 1)
logistic	4	<0.001	358.346	4.997E+00	4.149E+00	negative intercept (intercept = -0.687)
log-logistic [a]	**4**	**0.409**	**312.970**	**6.644E-01**	**5.041E-01**	**slope bound hit (slope = 1)**
log-probit	4	<0.001	340.296	3.291E+00	2.517E+00	slope bound hit (slope = 1)
multistage, 5-degree	4	<0.001	340.127	2.240E+00	1.791E+00	final ß = 0
probit	4	<0.001	362.181	5.656E+00	4.810E+00	negative intercept (intercept = -0.381)
Weibull	4	<0.001	340.127	2.240E+00	1.791E+00	power bound hit (power = 1)
gamma, unrestricted	3	0.407	314.135	2.211E-02	8.081E-04	unrestricted (power = 0.297)
log-logistic, unrestricted [b]	3	0.739	312.487	3.062E-01	7.972E-02	unrestricted (slope = 0.785)
log-probit, unrestricted	3	0.727	312.543	3.316E-01	8.968E-02	unrestricted (slope = 0.471)
Weibull, unrestricted	3	0.586	313.176	9.000E-02	1.341E-02	unrestricted (power = 0.465)

[a] Best-fitting model, BMDS output presented in this appendix

[b] Alternate model, BMDS output also presented in this appendix

E.3.31.2. *Output for Selected Model: Log-Logistic*

National Toxicology Program, 2006: Alveolar Metaplasia

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\1\40_NTP_2006_AlvMeta_LogLogistic_1.(d)
         Gnuplot Plotting File:  C:\1\40_NTP_2006_AlvMeta_LogLogistic_1.plt
                                              Tue Feb 16 18:19:30 2010
 ================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
```

```
   Slope parameter is restricted as slope >= 1

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =    0.0377358
                     intercept =     -2.03745
                         slope =            1


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -slope
                have been estimated at a boundary point, or have been specified by the user,
                and do not appear in the correlation matrix )

            background    intercept

background            1         -0.4

 intercept         -0.4            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background        0.0448753            *               *                   *
      intercept         -1.78837            *               *                   *
          slope                1            *               *                   *

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -152.615         6
   Fitted model        -154.485         2        3.7393      4          0.4424
  Reduced model        -216.802         1       128.374      5         <.0001

           AIC:          312.97


                                Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size        Residual
   ---------------------------------------------------------------------
    0.0000     0.0449         2.378     2.000          53       -0.251
    2.1400     0.2966        16.017    19.000          54        0.889
    7.1400     0.5647        29.928    33.000          53        0.851
   15.7000     0.7366        38.301    35.000          52       -1.039
   32.9000     0.8531        45.214    45.000          53       -0.083
   71.4000     0.9262        48.162    46.000          52       -1.147

 Chi^2 = 3.98      d.f. = 4        P-value = 0.4088


   Benchmark Dose Computation
```

```
Specified effect =           0.1

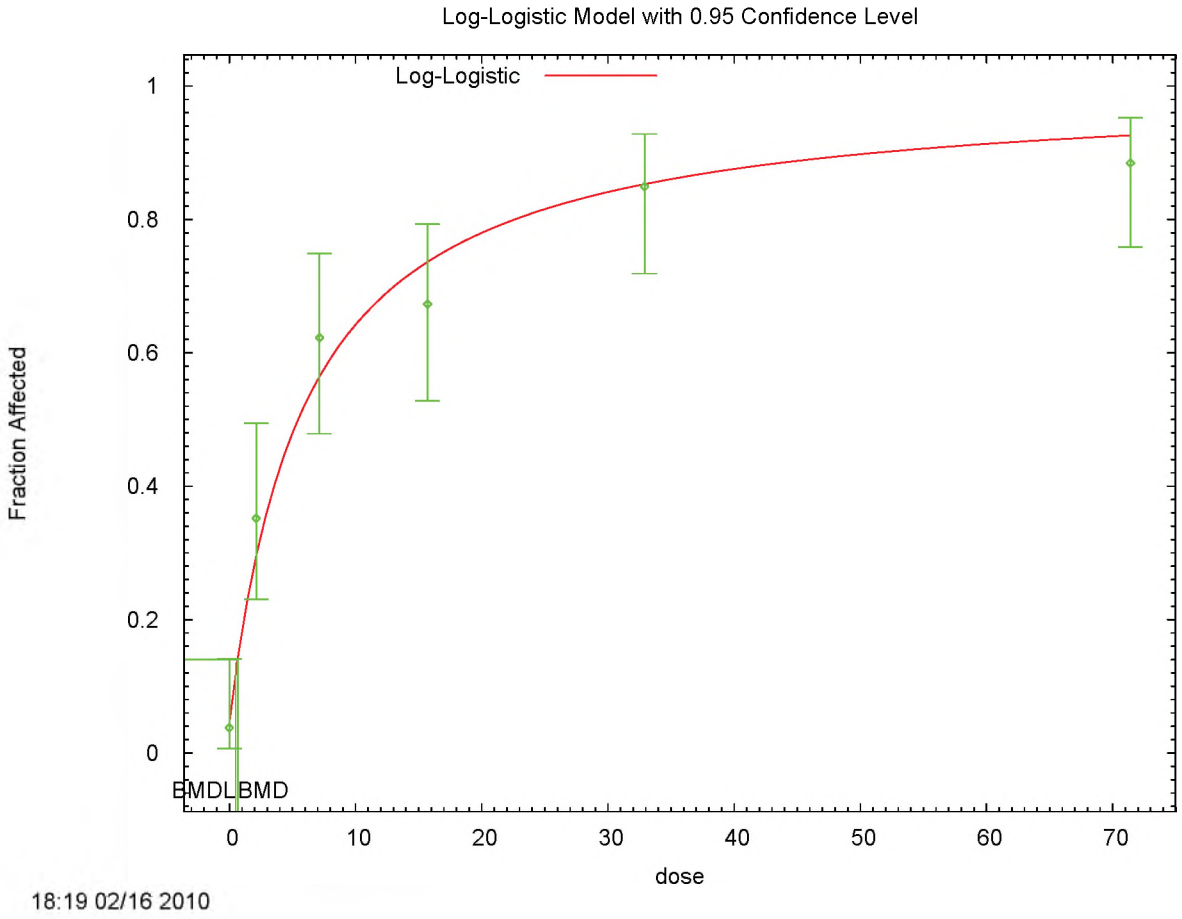
Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =      0.664411

            BMDL =      0.504109
```

E.3.31.3. *Figure for Selected Model: Log-Logistic*



E.3.31.4. *Output for Additional Model Presented: Log-Logistic, Unrestricted*

National Toxicology Program, 2006: Alveolar Metaplasia

```
================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\40_NTP_2006_AlvMeta_LogLogistic_U_1.(d)
        Gnuplot Plotting File:  C:\1\40_NTP_2006_AlvMeta_LogLogistic_U_1.plt
                                          Tue Feb 16 18:19:31 2010
================================================================

0
```

```
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =    0.0377358
                     intercept =     -1.26694
                         slope =     0.784484


           Asymptotic Correlation Matrix of Parameter Estimates

             background    intercept        slope

background            1        -0.24         0.11

 intercept        -0.24            1         -0.9

     slope         0.11         -0.9            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background        0.0375286            *               *                   *
      intercept         -1.26811            *               *                   *
          slope         0.785033            *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -152.615         6
   Fitted model        -153.244         3        1.2566      3          0.7395
  Reduced model        -216.802         1       128.374      5         <.0001

           AIC:         312.487


                                Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
    0.0000     0.0375         1.989     2.000          53        0.008
    2.1400     0.3631        19.609    19.000          54       -0.172
    7.1400     0.5845        30.980    33.000          53        0.563
   15.7000     0.7205        37.468    35.000          52       -0.763
```

```
     32.9000      0.8207         43.498     45.000          53         0.538
     71.4000      0.8934         46.455     46.000          52        -0.204

  Chi^2 = 1.26       d.f. = 3         P-value = 0.7388


    Benchmark Dose Computation

Specified effect =            0.1

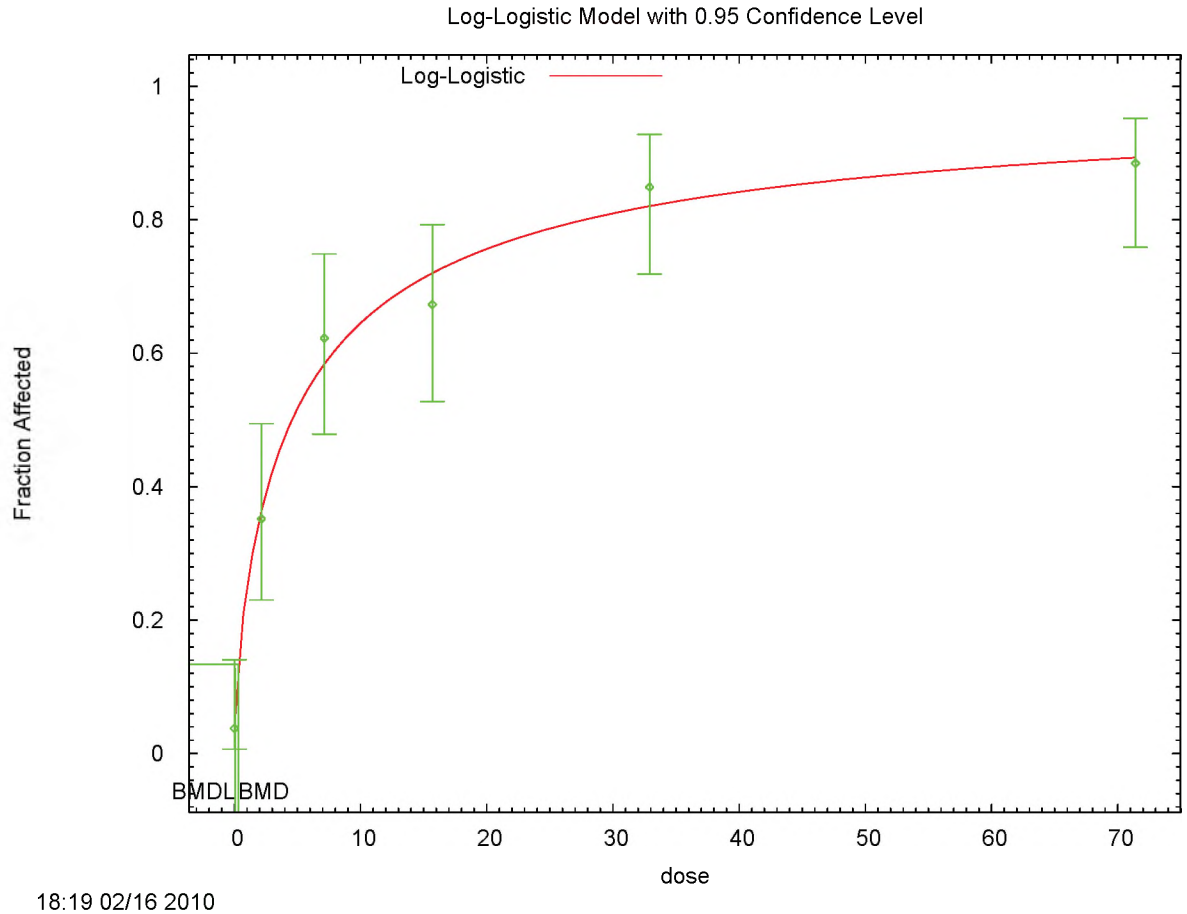
Risk Type        =       Extra risk

Confidence level =           0.95

             BMD =       0.306194

            BMDL =      0.0797223
```

E.3.31.5. *Figure for Additional Model Presented: Log-Logistic, Unrestricted*



E.3.32. National Toxicology Program, 2006: Eosinophilic Focus, Liver

E.3.32.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
gamma	4	0.367	330.457	5.676E+00	4.532E+00	power bound hit (power = 1)
logistic	4	0.167	333.343	1.258E+01	1.071E+01	negative intercept (intercept = -1.747)
log-logistic	3	0.117	334.148	4.727E+00	2.867E+00	
log-probit	4	0.084	334.683	1.078E+01	8.514E+00	
multistage, 5-degree	3	0.313	331.771	6.568E+00	4.666E+00	
probit [a]	**4**	**0.187**	**332.962**	**1.196E+01**	**1.031E+01**	**negative intercept (intercept = -1.061)**
Weibull	4	0.367	330.457	5.675E+00	4.532E+00	power bound hit (power = 1)
log-probit, unrestricted	3	0.087	334.849	4.750E+00	1.757E+00	unrestricted (slope = 0.643)

[a] Best-fitting model, BMDS output presented in this appendix

E.3.32.2. *Output for Selected Model: Probit*

National Toxicology Program, 2006: Eosinophilic Focus, Liver

```
 ================================================================
         Probit Model. (Version: 3.1;  Date: 05/16/2008)
         Input Data File: C:\1\45_NTP_2006_LivEosFoc_Probit_1.(d)
         Gnuplot Plotting File:  C:\1\45_NTP_2006_LivEosFoc_Probit_1.plt
                                              Tue Feb 16 18:25:56 2010
 ================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = CumNorm(Intercept+Slope*Dose),

   where CumNorm(.) is the cumulative normal distribution function


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial (and Specified) Parameter Values
background = 0 Specified
intercept = -1.11935
slope = 0.0279665

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -background
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	intercept	slope
intercept	1	-0.69
slope	-0.69	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
intercept	-1.06148	0.109177	-1.27546	-0.847497
slope	0.0269279	0.00327788	0.0205034	0.0333525

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-161.07	6			
Fitted model	-164.481	2	6.8221	4	0.1456
Reduced model	-202.816	1	83.4925	5	<.0001

AIC: 332.962

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1442	7.645	3.000	53	-1.816
2.1400	0.1577	8.517	8.000	54	-0.193
7.1400	0.1924	10.195	14.000	53	1.326
15.7000	0.2615	13.860	17.000	53	0.982
32.9000	0.4303	22.807	22.000	53	-0.224
71.4000	0.8054	42.688	42.000	53	-0.239

Chi^2 = 6.16 d.f. = 4 P-value = 0.1873

Benchmark Dose Computation

Specified effect = 0.1

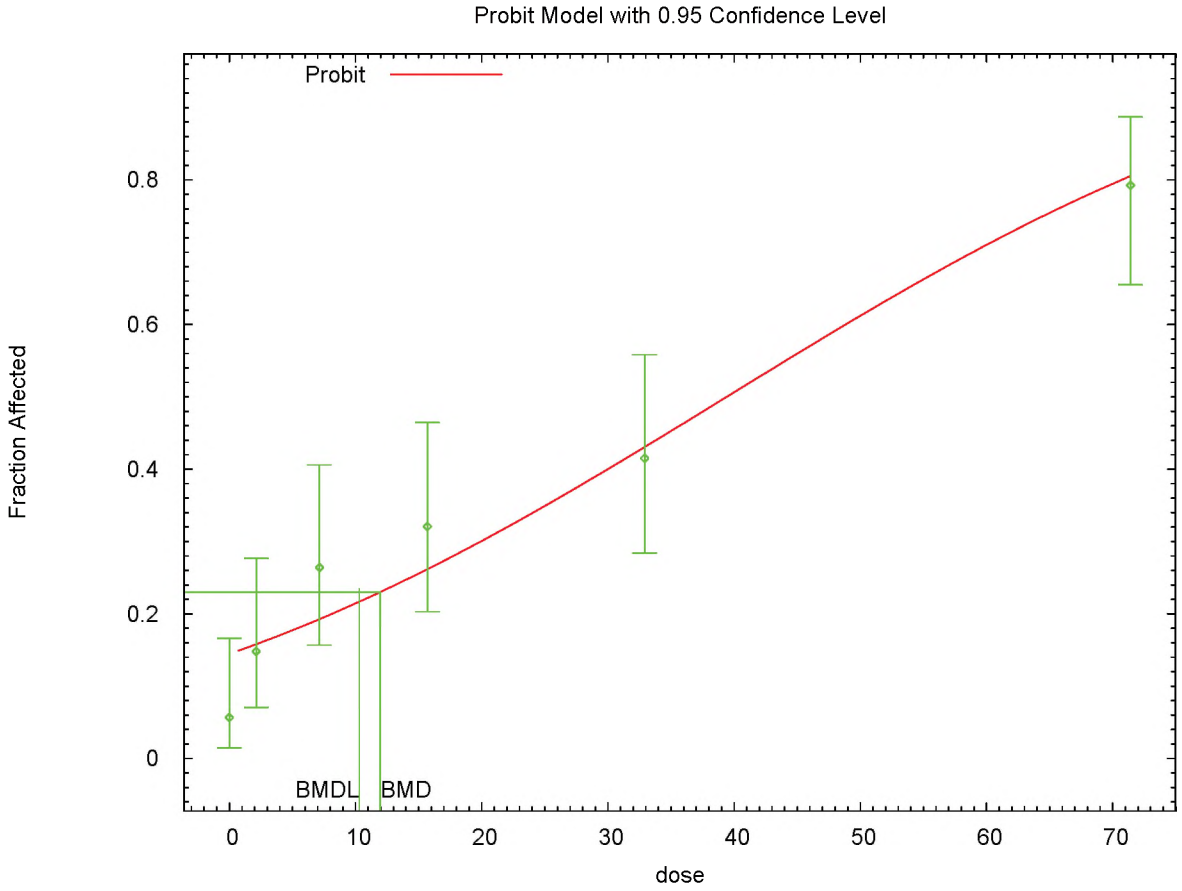
Risk Type = Extra risk

Confidence level = 0.95

BMD = 11.9584

BMDL = 10.3075

E.3.32.3. *Figure for Selected Model: Probit*



E.3.33. National Toxicology Program, 2006: Fatty Change Diffuse, Liver

E.3.33.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
gamma	4	0.668	252.294	4.224E+00	3.166E+00	
logistic	4	0.005	269.825	1.092E+01	9.292E+00	negative intercept (intercept = -2.298)
log-logistic	4	0.292	255.082	4.697E+00	3.153E+00	
log-probit	4	0.118	257.548	6.236E+00	5.204E+00	slope bound hit (slope = 1)
multistage, 5-degree	4	0.808	251.545	4.021E+00	3.250E+00	
probit	4	0.005	269.430	1.052E+01	9.068E+00	negative intercept (intercept = -1.36)
Weibull [a]	**4**	**0.679**	**252.218**	**4.252E+00**	**3.174E+00**	
log-probit, unrestricted	4	0.282	255.258	4.581E+00	3.193E+00	unrestricted (slope = 0.824)

[a] Best-fitting model, BMDS output presented in this appendix

E.3.33.2. *Output for Selected Model: Weibull*

National Toxicology Program, 2006: Fatty Change Diffuse, Liver

```
 ======================================================================
         Weibull Model using Weibull Model (Version: 2.12;  Date: 05/16/2008)
         Input Data File: C:\1\47_NTP_2006_LivFatDiff_Weibull_1.(d)
         Gnuplot Plotting File:  C:\1\47_NTP_2006_LivFatDiff_Weibull_1.plt
                                                Tue Feb 16 18:26:57 2010
 ======================================================================

 NTP_liver_fatty_change_diffuse
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]


   Dependent variable = DichEff
   Independent variable = Dose
   Power parameter is restricted as power >=1

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial (and Specified) Parameter Values
Background = 0.00925926
Slope = 0.00962604
Power = 1.28042

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Slope	Power
Slope	1	-0.97
Power	-0.97	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	NA		
Slope	0.0223474	0.00951041	0.0037073	0.0409874
Power	1.07133	0.122134	0.831952	1.31071

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-122.992	6			
Fitted model	-124.109	2	2.23388	4	0.6928
Reduced model	-204.846	1	163.708	5	<.0001

AIC: 252.218

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	53	0.000
2.1400	0.0492	2.659	2.000	54	-0.414
7.1400	0.1677	8.889	12.000	53	1.144
15.7000	0.3475	18.420	17.000	53	-0.409
32.9000	0.6107	32.365	30.000	53	-0.666
71.4000	0.8851	46.909	48.000	53	0.470

Chi^2 = 2.31 d.f. = 4 P-value = 0.6785

Benchmark Dose Computation

Specified effect = 0.1

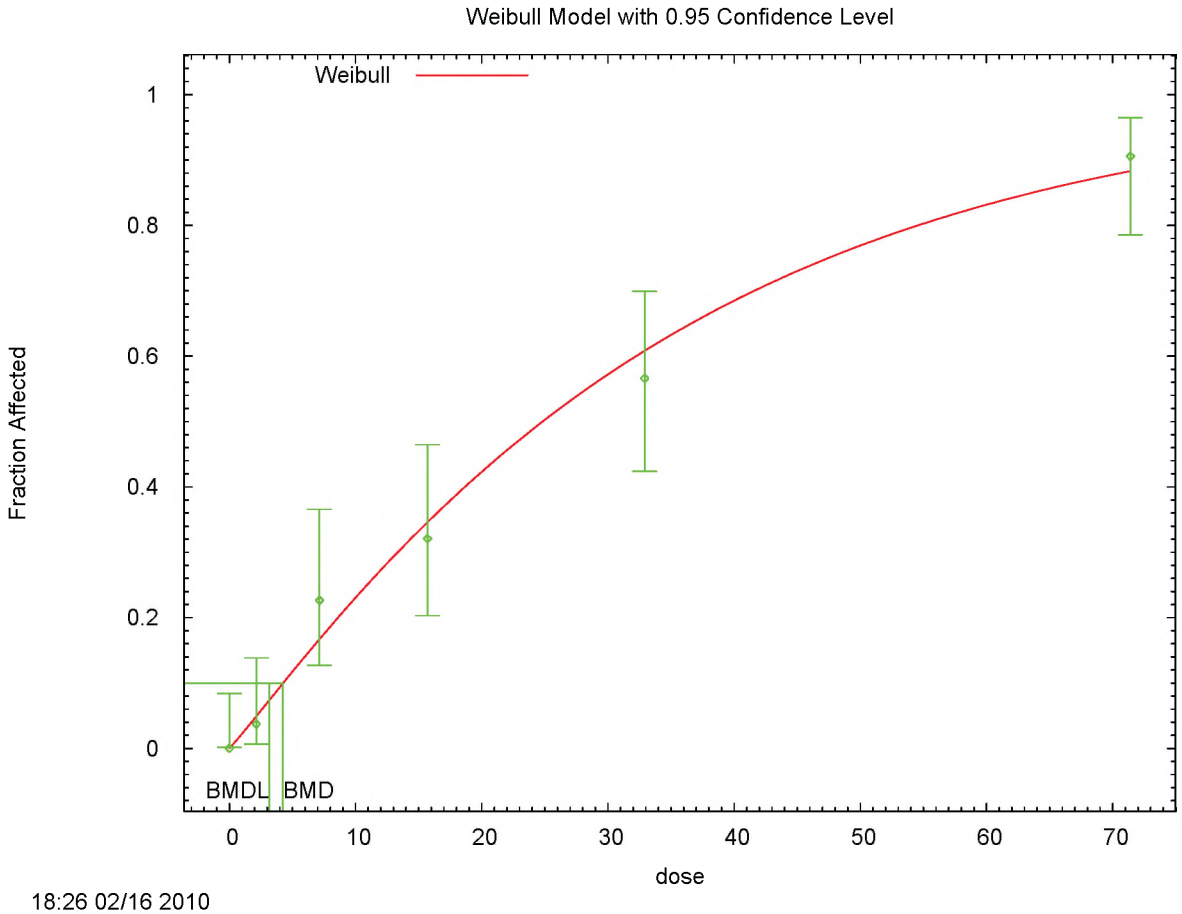
Risk Type = Extra risk

Confidence level = 0.95

BMD = 4.25219

BMDL = 3.17375

E.3.33.3. *Figure for Selected Model: Weibull*



18:26 02/16 2010

E.3.34. National Toxicology Program, 2006: Gingival Hyperplasia, Squamous, 2 Years

E.3.34.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
gamma	4	0.012	318.867	2.295E+01	1.417E+01	power bound hit (power = 1)
logistic	4	0.008	320.908	3.594E+01	2.564E+01	negative intercept (intercept = -1.711)
log-logistic [a]	**4**	**0.015**	**317.969**	**1.838E+01**	**1.044E+01**	**slope bound hit (slope = 1)**
log-probit	4	0.003	323.633	4.313E+01	2.794E+01	slope bound hit (slope = 1)
multistage, 5-degree	4	0.012	318.867	2.295E+01	1.417E+01	final ß = 0
probit	4	0.008	320.687	3.436E+01	2.425E+01	negative intercept (intercept = -1.034)
Weibull	4	0.012	318.867	2.295E+01	1.417E+01	power bound hit (power = 1)
gamma, unrestricted	3	0.651	307.529	2.480E-01	5.096E-09	unrestricted (power = 0.199)
log-logistic, unrestricted [b]	3	0.675	307.416	3.710E-01	1.505E-07	unrestricted (slope = 0.265)
log-probit, unrestricted	3	0.688	307.354	4.688E-01	8.851E-07	unrestricted (slope = 0.156)
Weibull, unrestricted	3	0.663	307.471	3.076E-01	3.210E-08	unrestricted (power = 0.23)

[a] Best-fitting model, BMDS output presented in this appendix

[b] Alternate model, BMDS output also presented in this appendix

E.3.34.2. *Output for Selected Model: Log-Logistic*

National Toxicology Program, 2006: Gingival Hyperplasia, Squamous, 2 Years

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\1\42_NTP_2006_GingHypSq_LogLogistic_1.(d)
         Gnuplot Plotting File:  C:\1\42_NTP_2006_GingHypSq_LogLogistic_1.plt
                                              Tue Feb 16 18:20:29 2010
 ================================================================

 [insert study notes]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
```

```
   Slope parameter is restricted as slope >= 1

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =    0.0188679
                     intercept =      -4.5509
                         slope =            1


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -slope
                have been estimated at a boundary point, or have been specified by the user,
                and do not appear in the correlation matrix )

            background    intercept

background            1        -0.71

 intercept        -0.71            1



                                Parameter Estimates

                                                      95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background         0.117717            *               *                   *
      intercept         -5.10866            *               *                   *
          slope                1            *               *                   *

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -149.95         6
   Fitted model        -156.985         2       14.0696      4        0.007076
  Reduced model        -162.631         1       25.3627      5       0.0001186

           AIC:         317.969


                                 Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size        Residual
   ---------------------------------------------------------------------
    0.0000     0.1177         6.239     1.000          53       -2.233
    2.1400     0.1290         6.965     7.000          54        0.014
    7.1400     0.1542         8.174    14.000          53        2.216
   15.7000     0.1942        10.292    13.000          53        0.940
   32.9000     0.2641        13.995    15.000          53        0.313
   71.4000     0.3837        20.335    16.000          53       -1.225

 Chi^2 = 12.38     d.f. = 4        P-value = 0.0147


   Benchmark Dose Computation
```

```
Specified effect =          0.1

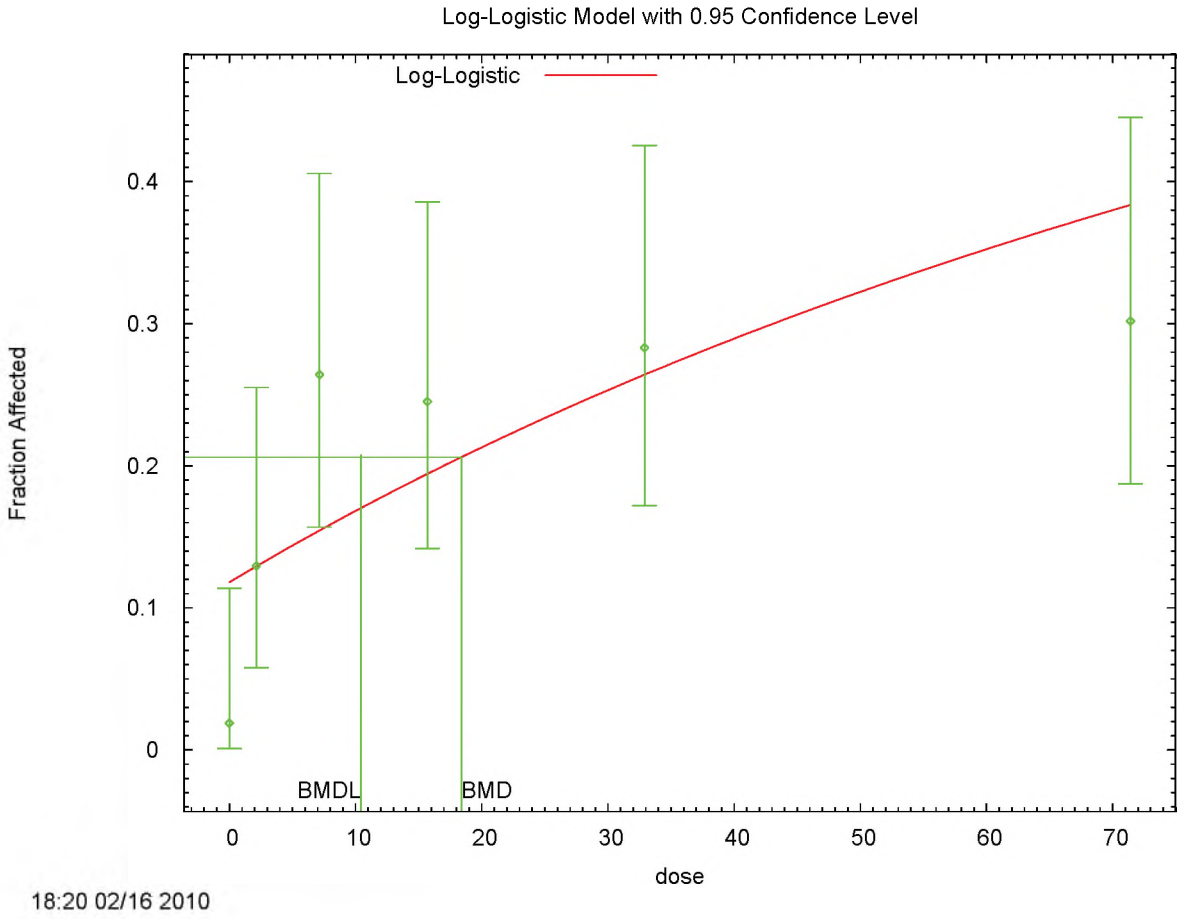
Risk Type        =     Extra risk

Confidence level =         0.95

             BMD =      18.3832

            BMDL =      10.4359
```

E.3.34.3. *Figure for Selected Model: Log-Logistic*



E.3.34.4. *Output for Additional Model Presented: Log-Logistic, Unrestricted*

National Toxicology Program, 2006: Gingival Hyperplasia, Squamous, 2 Years

```
================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\42_NTP_2006_GingHypSq_LogLogistic_U_1.(d)
        Gnuplot Plotting File:  C:\1\42_NTP_2006_GingHypSq_LogLogistic_U_1.plt
                                          Tue Feb 16 18:20:29 2010
================================================================

[insert study notes]
```

```
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =    0.0188679
                     intercept =     -2.04571
                         slope =     0.299277


           Asymptotic Correlation Matrix of Parameter Estimates

             background    intercept        slope

background            1         -0.3         0.12

 intercept         -0.3            1        -0.91

     slope         0.12        -0.91            1


                                Parameter Estimates

                                                      95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background        0.0185126            *               *                   *
      intercept         -1.93464            *               *                   *
          slope         0.264795            *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -149.95         6
   Fitted model        -150.708         3        1.5163      3          0.6785
  Reduced model        -162.631         1       25.3627      5       0.0001186

           AIC:         307.416


                                Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
    0.0000     0.0185         0.981     1.000          53         0.019
    2.1400     0.1659         8.959     7.000          54        -0.717
    7.1400     0.2105        11.155    14.000          53         0.959
   15.7000     0.2447        12.972    13.000          53         0.009
```

```
     32.9000      0.2806        14.873    15.000          53        0.039
     71.4000      0.3219        17.059    16.000          53       -0.311

  Chi^2 = 1.53      d.f. = 3        P-value = 0.6750


    Benchmark Dose Computation

Specified effect =            0.1

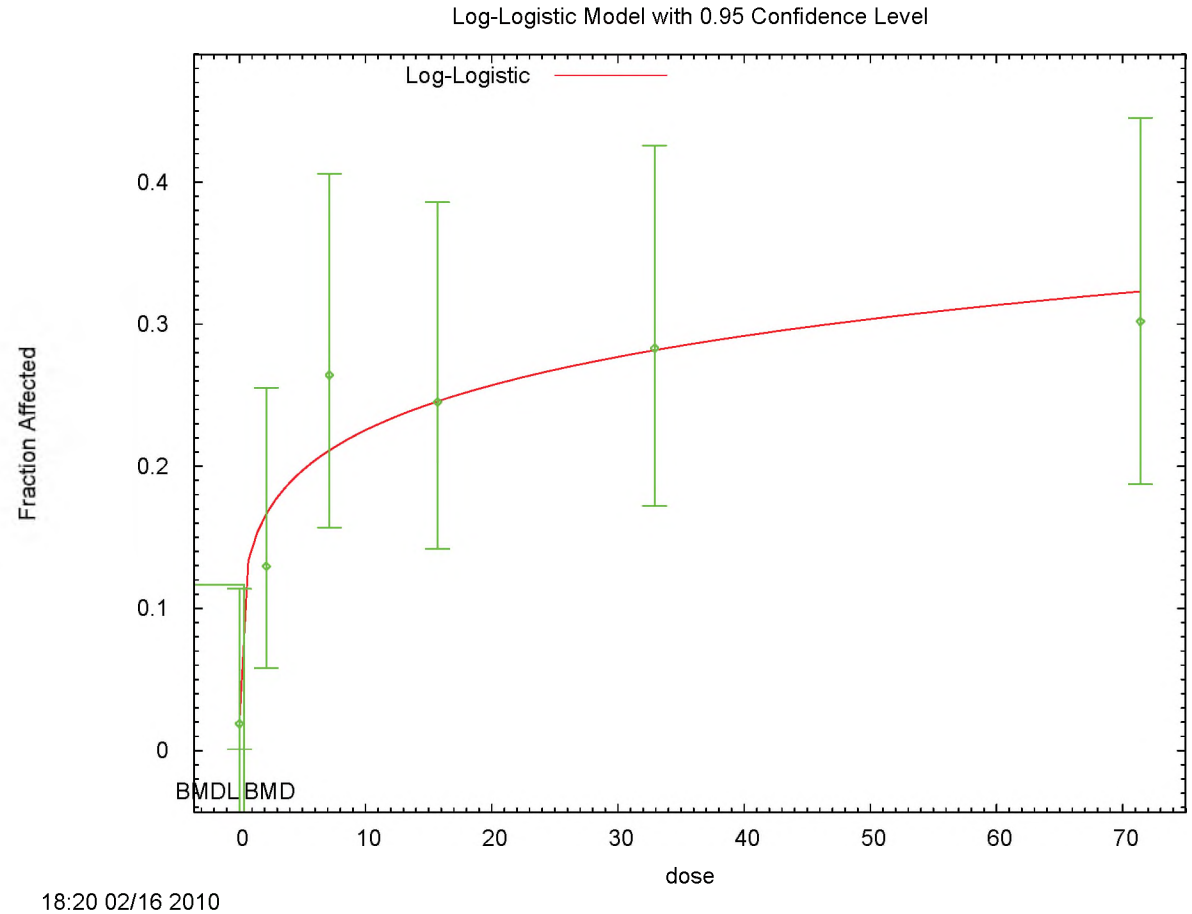
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.370958

            BMDL =   1.50494e-007
```

E.3.34.5. *Figure for Additional Model Presented: Log-Logistic, Unrestricted*



E.3.35. National Toxicology Program, 2006: Hepatocyte Hypertrophy, 2 Years

E.3.35.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
gamma	4	<0.001	290.365	1.647E+00	1.340E+00	power bound hit (power = 1)
logistic	4	<0.001	310.492	4.315E+00	3.650E+00	negative intercept (intercept = -1.237)
log-logistic	5	0.010	278.082	6.978E-01	5.454E-01	slope bound hit (slope = 1)
log-probit	4	<0.001	297.168	2.930E+00	2.267E+00	slope bound hit (slope = 1)
multistage, 5-degree [a]	**4**	**<0.001**	**290.365**	**1.647E+00**	**1.340E+00**	**final ß = 0**
probit	4	<0.001	313.841	4.564E+00	3.923E+00	negative intercept (intercept = -0.714)
Weibull	4	<0.001	290.365	1.647E+00	1.340E+00	power bound hit (power = 1)
gamma, unrestricted	4	0.029	275.042	error	error	unrestricted (power = 0.478)
log-logistic, unrestricted	4	0.005	280.068	6.672E-01	2.939E-01	unrestricted (slope = 0.984)
log-probit, unrestricted	4	0.006	279.204	7.167E-01	3.322E-01	unrestricted (slope = 0.594)
Weibull, unrestricted	4	0.019	275.967	3.709E-01	1.315E-01	unrestricted (power = 0.64)

[a] Best-fitting model, BMDS output presented in this appendix

E.3.35.2. *Output for Selected Model: Multistage, 5-Degree*

National Toxicology Program, 2006: Hepatocyte Hypertrophy, 2 Years

```
 ================================================================
         Multistage Model. (Version: 3.0;  Date: 05/16/2008)
         Input Data File: C:\1\43_NTP_2006_HepHyper_Multi5_1.(d)
         Gnuplot Plotting File:  C:\1\43_NTP_2006_HepHyper_Multi5_1.plt
                                              Tue Feb 16 18:21:00 2010
 ================================================================

 [insert study notes]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4-beta5*dose^5)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
```

```
  Independent variable = Dose

Total number of observations = 6
Total number of records with missing values = 0
Total number of parameters in model = 6
Total number of specified parameters = 0
Degree of polynomial = 5


Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =     0.232262
                        Beta(1) =     0.045074
                        Beta(2) =            0
                        Beta(3) =            0
                        Beta(4) =            0
                        Beta(5) = 2.59945e-010


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Beta(2)    -Beta(3)    -Beta(4)    -Beta(5)
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

             Background      Beta(1)

Background            1        -0.64

   Beta(1)        -0.64            1



                               Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background        0.0541647            *               *                   *
        Beta(1)        0.0639585            *               *                   *
        Beta(2)                0            *               *                   *
        Beta(3)                0            *               *                   *
        Beta(4)                0            *               *                   *
        Beta(5)                0            *               *                   *

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -129.986         6
   Fitted model        -143.183         2       26.3932      4      2.6361629e-005
  Reduced model         -219.97         1       179.968      5         <.0001

           AIC:         290.365


                                 Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size        Residual
   ----------------------------------------------------------------------
    0.0000     0.0542         2.871     0.000          53       -1.742
    2.1400     0.1752         9.458    19.000          54        3.416
    7.1400     0.4009        21.248    19.000          53       -0.630
```

```
    15.7000      0.6535        34.635     42.000          53         2.126
    32.9000      0.8847        46.887     41.000          53        -2.532
    71.4000      0.9902        52.479     52.000          53        -0.667

 Chi^2 = 26.48      d.f. = 4        P-value = 0.0000


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

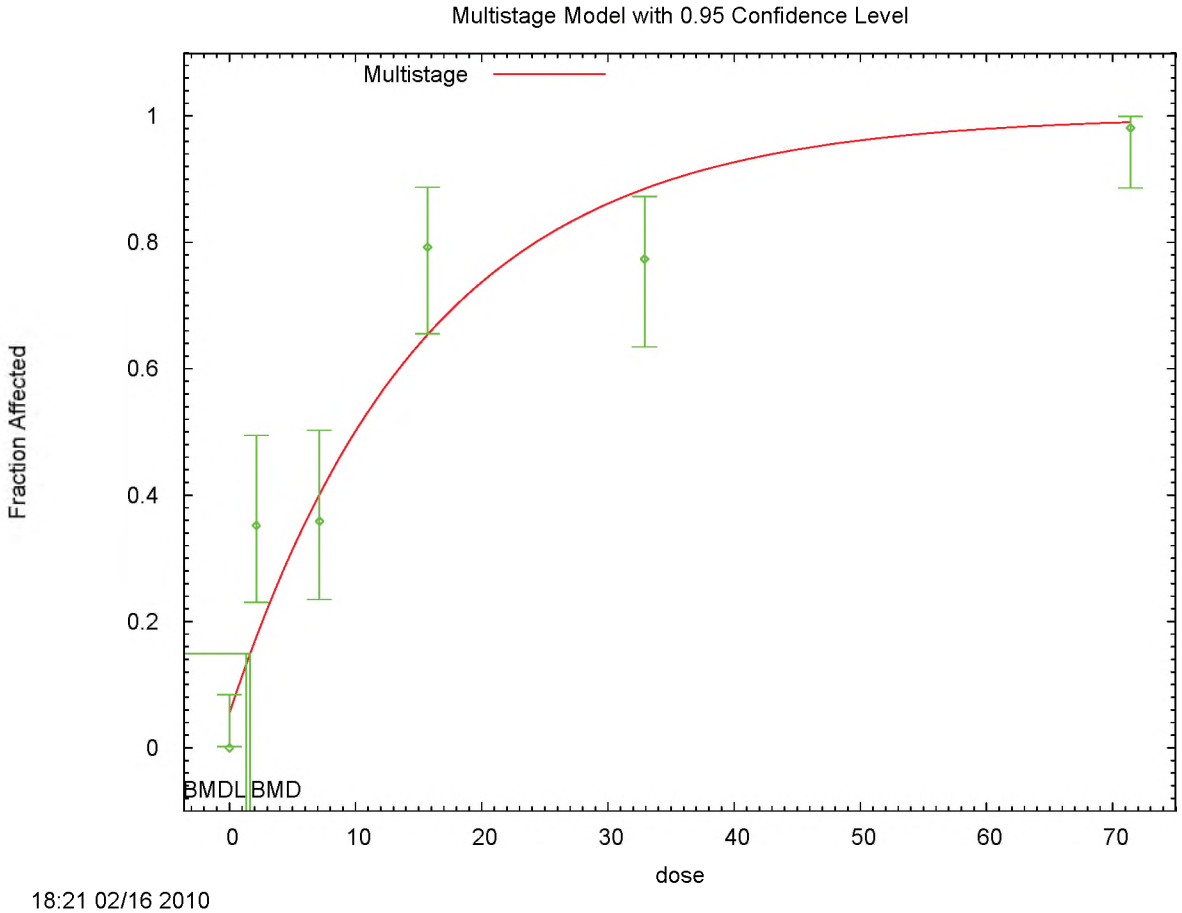
             BMD =        1.64733

            BMDL =        1.34007

            BMDU =         2.0581

Taken together, (1.34007, 2.0581 ) is a 90      % two-sided confidence
interval for the BMD
```

E.3.35.3. *Figure for Selected Model: Multistage, 5-Degree*



E.3.36. National Toxicology Program, 2006: Necrosis, Liver

E.3.36.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
logistic	4	0.397	238.314	3.484E+01	2.842E+01	negative intercept (intercept = -2.601)
log-logistic	4	0.810	235.265	1.791E+01	1.194E+01	slope bound hit (slope = 1)
log-probit	4	0.290	239.107	3.205E+01	2.382E+01	slope bound hit (slope = 1)
multistage, 5-degree	4	0.763	235.581	2.019E+01	1.419E+01	final ß = 0
probit	4	0.445	237.888	3.266E+01	2.637E+01	negative intercept (intercept = -1.508)
Weibull	4	0.763	235.581	2.019E+01	1.419E+01	power bound hit (power = 1)
gamma, unrestricted	3	0.869	236.344	1.114E+01	3.487E+00	unrestricted (power = 0.599)
log-logistic, unrestricted	3	0.833	236.483	1.112E+01	3.581E+00	unrestricted (slope = 0.695)
log-probit, unrestricted [a]	**3**	**0.768**	**236.742**	**1.061E+01**	**3.498E+00**	**unrestricted (slope = 0.367)**
Weibull, unrestricted	3	0.856	236.393	1.117E+01	3.554E+00	unrestricted (power = 0.64)

[a] Best-fitting model, BMDS output presented in this appendix

E.3.36.2. *Output for Selected Model: Log-Probit, Unrestricted*

National Toxicology Program, 2006: Necrosis, Liver

```
 ================================================================
         Probit Model. (Version: 3.1;  Date: 05/16/2008)
         Input Data File: C:\1\50_NTP_2006_LivNec_LogProbit_U_1.(d)
         Gnuplot Plotting File:  C:\1\50_NTP_2006_LivNec_LogProbit_U_1.plt
                                              Tue Feb 16 18:34:31 2010
 ================================================================

 NTP_liver_necrosis
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = Background
               + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),

   where CumNorm(.) is the cumulative normal distribution function


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is not restricted
```

```
   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model

                 Default Initial (and Specified) Parameter Values
                    background =    0.0188679
                     intercept =     -1.98094
                         slope =     0.316942


           Asymptotic Correlation Matrix of Parameter Estimates

             background    intercept        slope

background            1        -0.69         0.59

 intercept        -0.69            1        -0.97

     slope         0.59        -0.97            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background        0.0228339        0.0230818         -0.0224057           0.0680734
      intercept         -2.14844         0.527256           -3.18184            -1.11503
          slope         0.367034         0.139055          0.0944904            0.639577


                          Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
      Full model        -114.813         6
    Fitted model        -115.371         3        1.1157      3          0.7733
   Reduced model         -127.98         1       26.3331      5         <.0001

           AIC:         236.742


                                Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size        Residual
   ----------------------------------------------------------------------
    0.0000     0.0228         1.210     1.000          53        -0.193
    2.1400     0.0529         2.858     4.000          54         0.694
    7.1400     0.0979         5.187     4.000          53        -0.549
   15.7000     0.1475         7.819     8.000          53         0.070
   32.9000     0.2116        11.215    10.000          53        -0.409
   71.4000     0.2968        15.729    17.000          53         0.382

 Chi^2 = 1.14      d.f. = 3        P-value = 0.7678


   Benchmark Dose Computation

Specified effect =           0.1

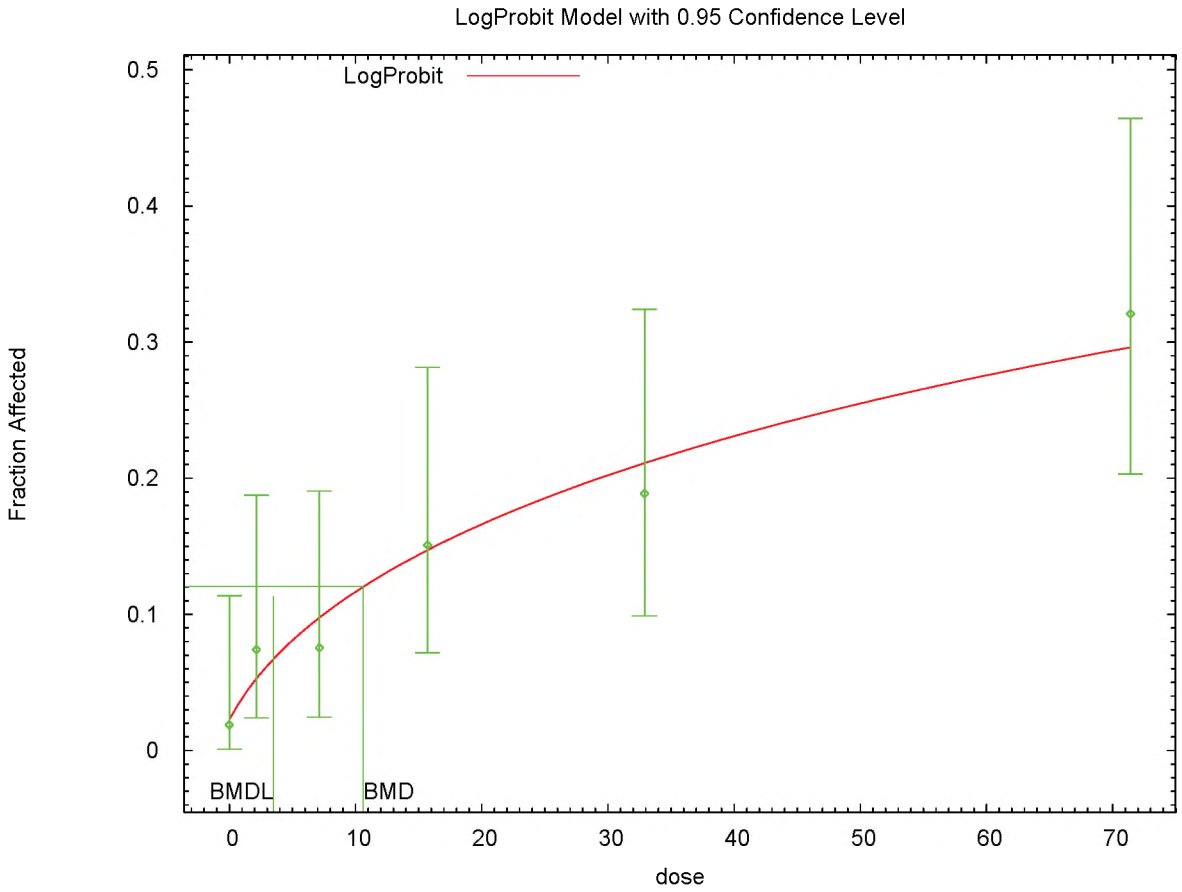
Risk Type        =      Extra risk

Confidence level =          0.95
```

```
BMD =         10.6107

BMDL =        3.49791
```

E.3.36.3. *Figure for Selected Model: Log-Probit, Unrestricted*



E.3.37. National Toxicology Program, 2006: Oval Cell Hyperplasia

E.3.37.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
gamma	3	0.072	199.446	8.970E+00	5.499E+00	
logistic	4	0.069	199.875	9.792E+00	8.245E+00	negative intercept (intercept = -3.116)
log-logistic	3	0.039	202.012	9.708E+00	7.247E+00	
log-probit	3	0.068	200.421	9.968E+00	7.758E+00	
multistage, 5-degree	2	0.066	198.641	5.424E+00	3.514E+00	
probit [a]	**4**	**0.112**	**198.166**	**9.103E+00**	**7.701E+00**	**negative intercept (intercept = -1.821)**
Weibull [b]	3	0.075	198.690	7.712E+00	4.692E+00	

[a] Best-fitting model, BMDS output presented in this appendix

[b] Alternate model, BMDS output also presented in this appendix

E.3.37.2. *Output for Selected Model: Probit*

National Toxicology Program, 2006: Oval Cell Hyperplasia

```
 ================================================================
          Probit Model. (Version: 3.1;  Date: 05/16/2008)
          Input Data File: C:\1\53_NTP_2006_OvalHyper_Probit_1.(d)
          Gnuplot Plotting File:  C:\1\53_NTP_2006_OvalHyper_Probit_1.plt
                                                Tue Feb 16 19:51:52 2010
 ================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = CumNorm(Intercept+Slope*Dose),

   where CumNorm(.) is the cumulative normal distribution function


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial (and Specified) Parameter Values
background = 0 Specified
intercept = -1.92612
slope = 0.0670004

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -background
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	intercept	slope
intercept	1	-0.8
slope	-0.8	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
intercept	-1.82129	0.16954	-2.15359	-1.489
slope	0.0767832	0.00835175	0.060414	0.0931523

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-92.4898	6			
Fitted model	-97.0832	2	9.18683	4	0.0566
Reduced model	-210.191	1	235.402	5	<.0001

AIC: 198.166

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0343	1.817	0.000	53	-1.372
2.1400	0.0488	2.633	4.000	54	0.864
7.1400	0.1015	5.379	3.000	53	-1.082
15.7000	0.2690	14.258	20.000	53	1.779
32.9000	0.7596	40.256	38.000	53	-0.725
71.4000	0.9999	52.993	53.000	53	0.082

Chi^2 = 7.50 d.f. = 4 P-value = 0.1119

Benchmark Dose Computation

Specified effect = 0.1

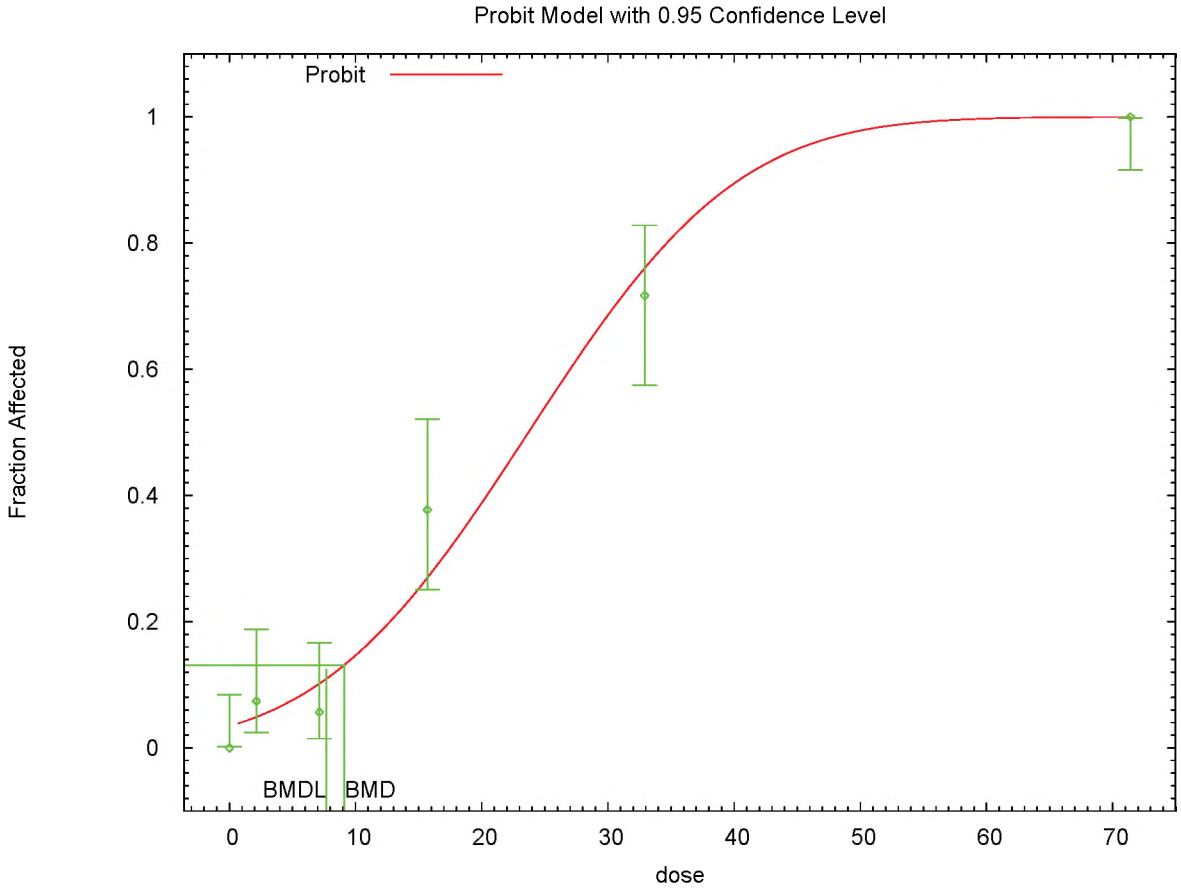
Risk Type = Extra risk

Confidence level = 0.95

BMD = 9.1026

BMDL = 7.7011

E.3.37.3. *Figure for Selected Model: Probit*



E.3.37.4. *Output for Additional Model Presented: Weibull*

National Toxicology Program, 2006: Oval Cell Hyperplasia

```
 ================================================================
         Weibull Model using Weibull Model (Version: 2.12;  Date: 05/16/2008)
         Input Data File: C:\1\53_NTP_2006_OvalHyper_Weibull_1.(d)
         Gnuplot Plotting File:  C:\1\53_NTP_2006_OvalHyper_Weibull_1.plt
                                          Tue Feb 16 19:51:53 2010
 ================================================================

 0
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]


   Dependent variable = DichEff
   Independent variable = Dose
   Power parameter is restricted as power >=1

   Total number of observations = 6
```

Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial (and Specified) Parameter Values
Background = 0.00925926
Slope = 0.0044452
Power = 1.63009

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Slope	Power
Background	1	-0.63	0.61
Slope	-0.63	1	-0.99
Power	0.61	-0.99	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.021258	0.0198428	-0.0176332	0.0601492
Slope	0.0028715	0.00303327	-0.0030736	0.0088166
Power	1.76359	0.309457	1.15706	2.37011

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-92.4898	6			
Fitted model	-96.3448	3	7.70998	3	0.0524
Reduced model	-210.191	1	235.402	5	<.0001

AIC: 198.69

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0213	1.127	0.000	53	-1.073
2.1400	0.0320	1.725	4.000	54	1.760
7.1400	0.1073	5.685	3.000	53	-1.192
15.7000	0.3234	17.138	20.000	53	0.840
32.9000	0.7490	39.698	38.000	53	-0.538
71.4000	0.9953	52.750	53.000	53	0.501

Chi^2 = 6.92 d.f. = 3 P-value = 0.0746

Benchmark Dose Computation

Specified effect = 0.1

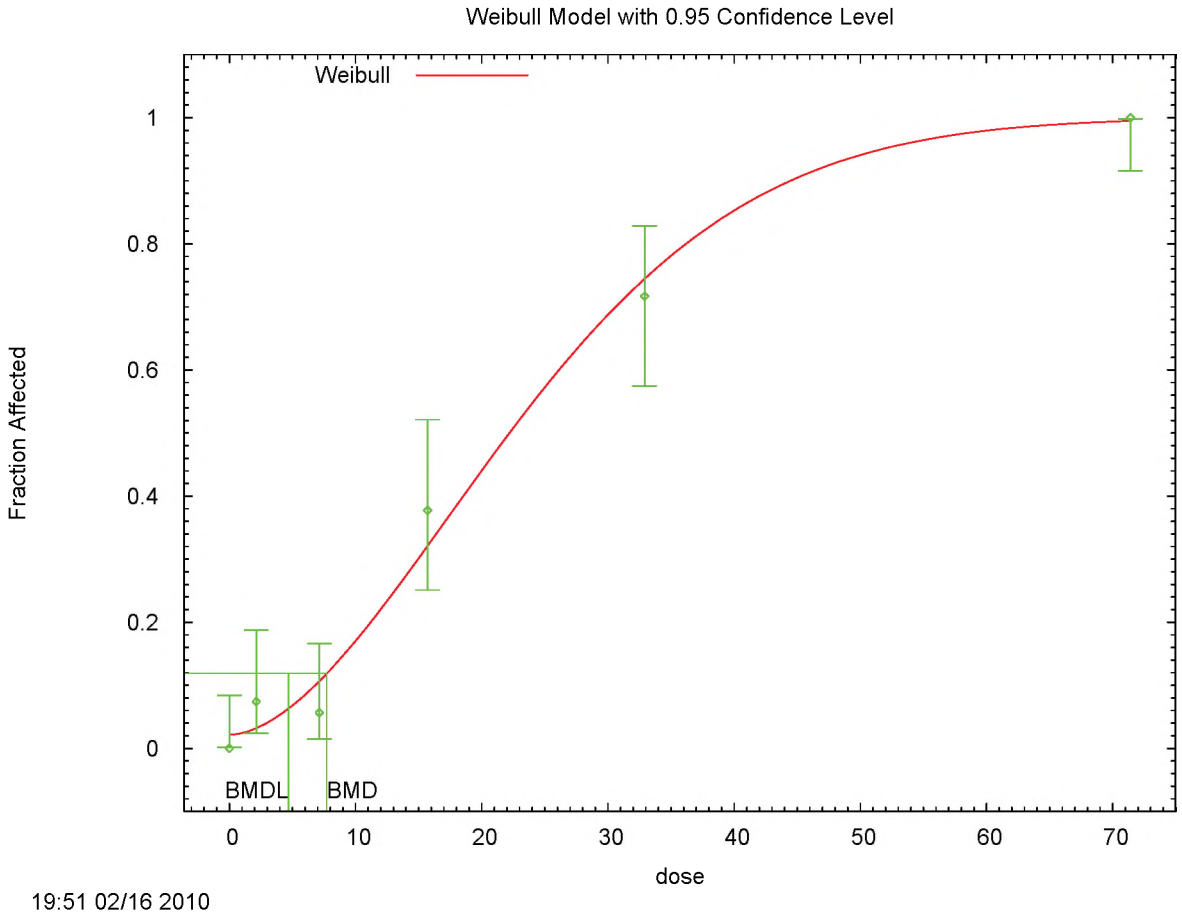
Risk Type = Extra risk

Confidence level = 0.95

BMD = 7.71171

BMDL = 4.69152

E.3.37.5. *Figure for Additional Model Presented: Weibull*



E.3.38. National Toxicology Program, 2006: Pigmentation, Liver

E.3.38.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
gamma	3	0.385	197.655	1.547E+00	8.055E-01	
logistic	4	<0.001	203.517	2.259E+00	1.872E+00	negative intercept (intercept = -1.925)
log-logistic	3	0.978	195.600	2.212E+00	1.452E+00	
log-probit [a]	**3**	**0.980**	**195.450**	**2.072E+00**	**1.399E+00**	
multistage, 5-degree	3	0.210	199.850	9.396E-01	7.079E-01	final ß = 0
probit	4	<0.001	210.309	2.259E+00	1.916E+00	negative intercept (intercept = -1.057)
Weibull	3	0.290	198.489	1.280E+00	7.518E-01	

[a] Best-fitting model, BMDS output presented in this appendix

E.3.38.2. *Output for Selected Model: Log-Probit*

National Toxicology Program, 2006: Pigmentation, Liver

```
 ================================================================
         Probit Model. (Version: 3.1;  Date: 05/16/2008)
         Input Data File: C:\1\54_NTP_2006_Pigment_LogProbit_1.(d)
         Gnuplot Plotting File:  C:\1\54_NTP_2006_Pigment_LogProbit_1.plt
                                          Tue Feb 16 19:52:19 2010
 ================================================================

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   The form of the probability function is:

   P[response] = Background
               + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),

   where CumNorm(.) is the cumulative normal distribution function


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
background = 0.0754717
intercept = -1.91144
slope = 1.07385

Asymptotic Correlation Matrix of Parameter Estimates

	background	intercept	slope
background	1	-0.45	0.35
intercept	-0.45	1	-0.94
slope	0.35	-0.94	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0735956	0.0343284	0.00631316	0.140878
intercept	-2.19294	0.400053	-2.97703	-1.40885
slope	1.25068	0.169731	0.918012	1.58335

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-94.6177	6			
Fitted model	-94.7248	3	0.214232	3	0.9753
Reduced model	-210.717	1	232.198	5	<.0001

AIC: 195.45

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0736	3.901	4.000	53	0.052
2.1400	0.1729	9.338	9.000	54	-0.122
7.1400	0.6338	33.591	34.000	53	0.117
15.7000	0.9023	47.822	48.000	53	0.082
32.9000	0.9863	52.275	52.000	53	-0.325
71.4000	0.9992	52.959	53.000	53	0.202

Chi^2 = 0.18 d.f. = 3 P-value = 0.9801

Benchmark Dose Computation

Specified effect = 0.1

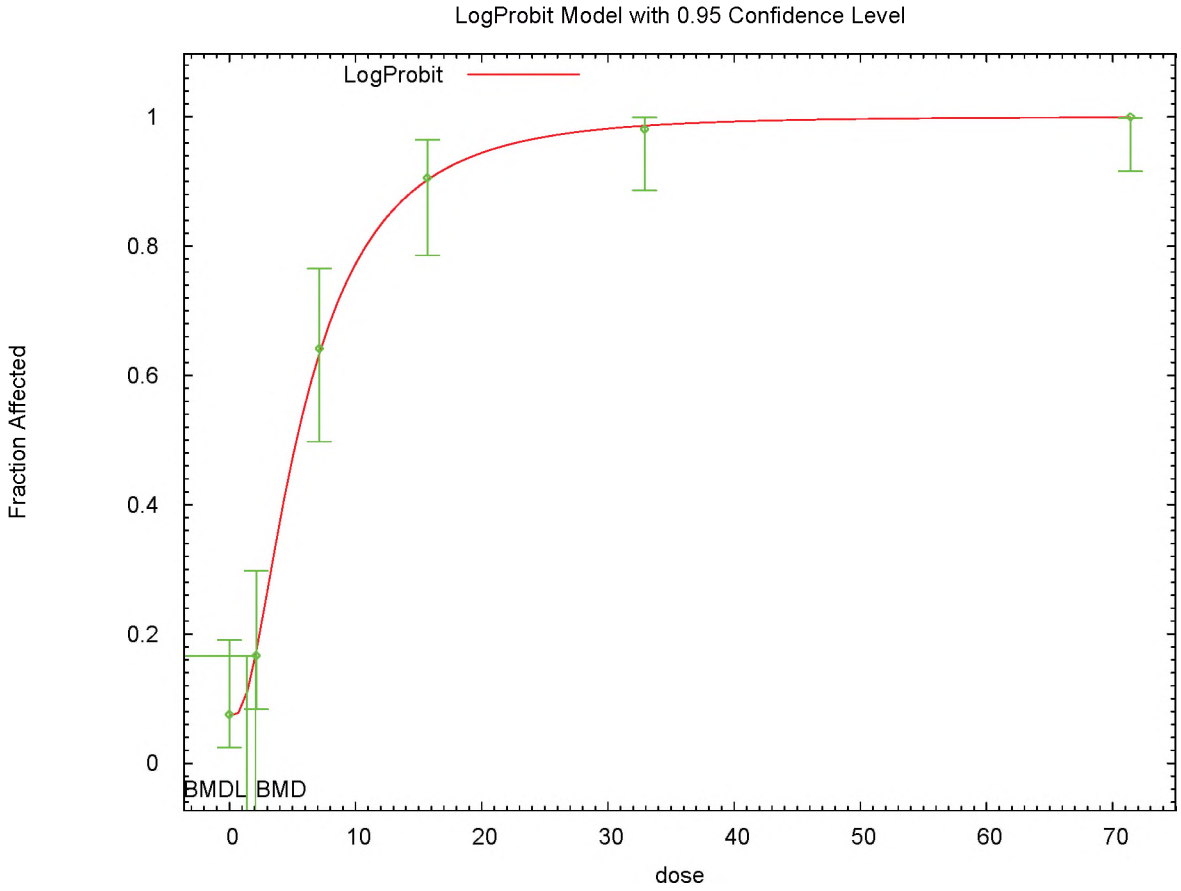
Risk Type = Extra risk

Confidence level = 0.95

BMD = 2.07241

BMDL = 1.39932

E.3.38.3. *Figure for Selected Model: Log-Probit*



E.3.39. National Toxicology Program, 2006: Toxic Hepatopathy

E.3.39.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
gamma	4	0.772	185.634	4.668E+00	3.317E+00	
logistic	4	0.012	198.445	7.070E+00	5.925E+00	negative intercept (intercept = -2.925)
log-logistic	3	0.362	190.061	5.676E+00	4.040E+00	
log-probit	3	0.378	189.858	6.061E+00	4.079E+00	
multistage, 5-degree [a]	**4**	**0.577**	**186.521**	**4.163E+00**	**2.701E+00**	**final ß = 0**
probit	4	0.019	197.159	6.784E+00	5.712E+00	negative intercept (intercept = -1.724)
Weibull	4	0.745	185.657	4.454E+00	3.159E+00	

[a] Best-fitting model, BMDS output presented in this appendix

E.3.39.2. *Output for Selected Model: Multistage, 5-Degree*

National Toxicology Program, 2006: Toxic Hepatopathy

```
 ======================================================================
          Multistage Model. (Version: 3.0;  Date: 05/16/2008)
          Input Data File: C:\1\55_NTP_2006_ToxHepa_Multi5_1.(d)
          Gnuplot Plotting File:  C:\1\55_NTP_2006_ToxHepa_Multi5_1.plt
                                              Tue Feb 16 19:52:49 2010
 ======================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4-beta5*dose^5)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 6
 Total number of specified parameters = 0
 Degree of polynomial = 5


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
```

Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

Background =	0
Beta(1) =	0
Beta(2) =	0
Beta(3) =	0
Beta(4) =	0
Beta(5) =	5.40983e+010

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background -Beta(3) -Beta(4) -Beta(5)
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Beta(1)	Beta(2)
Beta(1)	1	-0.91
Beta(2)	-0.91	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0.019656	*	*	*
Beta(2)	0.00135796	*	*	*
Beta(3)	0	*	*	*
Beta(4)	0	*	*	*
Beta(5)	0	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-89.8076	6			
Fitted model	-91.2606	2	2.90597	4	0.5737
Reduced model	-218.207	1	256.799	5	<.0001

AIC: 186.521

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	53	0.000
2.1400	0.0471	2.545	2.000	54	-0.350
7.1400	0.1891	10.021	8.000	53	-0.709
15.7000	0.4745	25.146	30.000	53	1.335
32.9000	0.8796	46.616	45.000	53	-0.682
71.4000	0.9998	52.987	53.000	53	0.113

Chi^2 = 2.89 d.f. = 4 P-value = 0.5771

Benchmark Dose Computation

Specified effect = 0.1

```
Risk Type          =      Extra risk

Confidence level =            0.95

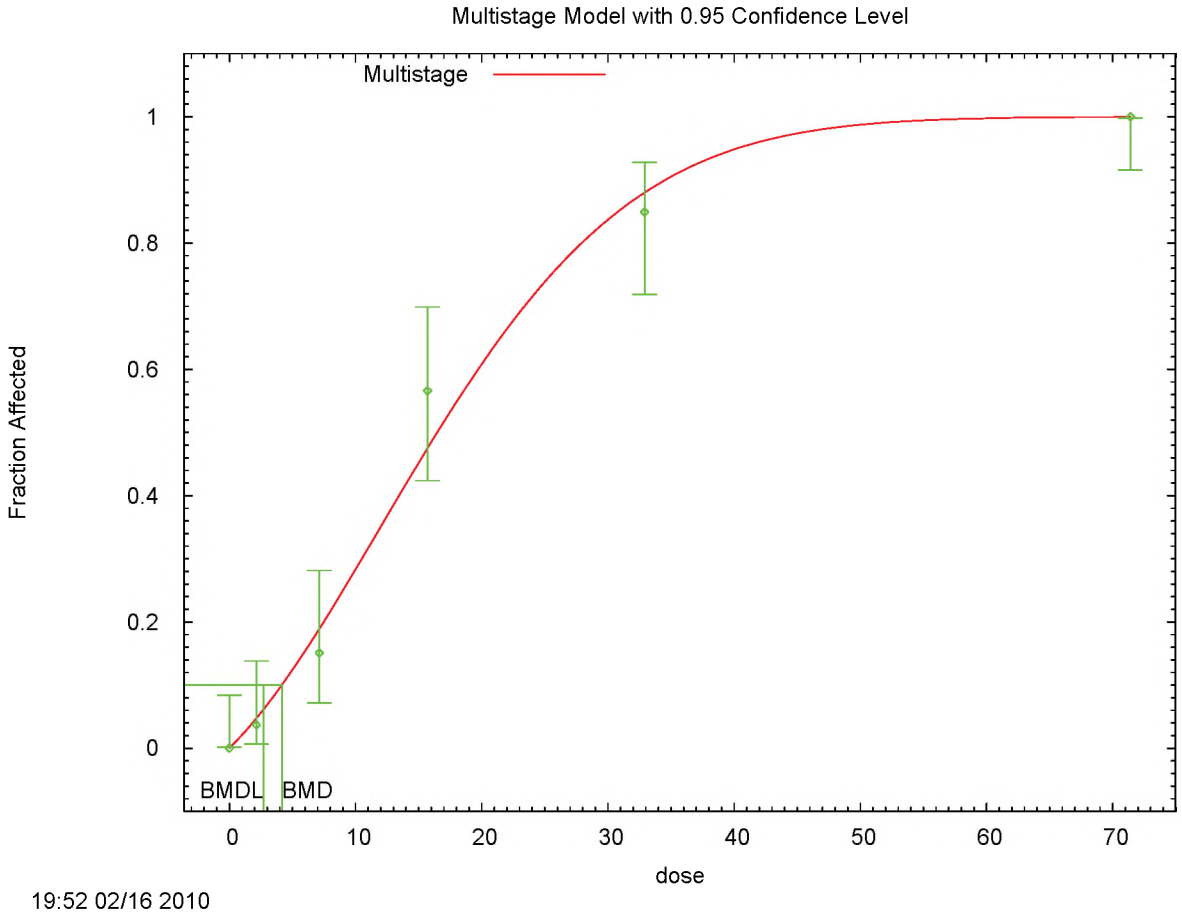
              BMD =         4.16294

             BMDL =         2.70063

             BMDU =         6.00186

Taken together, (2.70063, 6.00186) is a 90      % two-sided confidence
interval for the BMD
```

E.3.39.3. *Figure for Selected Model: Multistage, 5-Degree*



E.3.40. Ohsako et al., 2001: Ano-Genital Length, PND 120

E.3.40.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2)	3	0.019	171.804	5.650E+02	3.785E+02	
exponential (M3)	3	0.019	171.804	5.650E+02	3.785E+02	power hit bound (d = 1)
exponential (M4)	2	0.117	168.204	2.854E+01	1.054E+01	
exponential (M5)	1	0.049	169.789	2.948E+01	1.135E+01	
Hill [b]	**2**	**0.148**	**167.727**	**3.722E+01**	**9.752E+00**	**n lower bound hit (n = 1)**
linear	3	0.018	171.954	5.852E+02	4.047E+02	
polynomial, 4-degree	3	0.018	171.954	5.852E+02	4.047E+02	
power	3	0.018	171.954	5.852E+02	4.047E+02	power bound hit (power = 1)
Hill, unrestricted [c]	1	0.055	169.600	5.101E+01	3.066E+00	unrestricted (n = 0.502)
power, unrestricted	2	0.151	167.689	6.200E+01	2.291E+00	unrestricted (power = 0.252)

[a] Constant variance model selected ($p = 0.165$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.3.40.2. *Output for Selected Model: Hill*

Ohsako et al., 2001: Ano-Genital Length, PND 120

```
 ======================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\1\56_Ohsako_2001_Anogen_HillCV_1.(d)
         Gnuplot Plotting File:  C:\1\56_Ohsako_2001_Anogen_HillCV_1.plt
                                                Tue Feb 16 19:53:25 2010
 ======================================================================

 Figure 7
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
```

Power parameter restricted to be greater than 1
A constant variance model is fit

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

alpha =	7.27386	
rho =	0	Specified
intercept =	28.905	
v =	-5.1065	
n =	1.40226	
k =	33.9669	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho -n
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	intercept	v	k
alpha	1	-2.2e-009	-2.4e-008	-7.2e-009
intercept	-2.2e-009	1	-0.66	-0.5
v	-2.4e-008	-0.66	1	-0.11
k	-7.2e-009	-0.5	-0.11	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	7.08444	1.3634	4.41223	9.75666
intercept	28.9809	0.745637	27.5195	30.4423
v	-4.79692	0.983318	-6.72418	-2.86965
n	1	NA		
k	29.8628	24.4463	-18.0511	77.7767

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	12	28.9	29	3.13	2.66	-0.0988
12.5	10	27.9	27.6	2.5	2.66	0.442
50	10	25.2	26	3.21	2.66	-0.963
200	10	26	24.8	2.85	2.66	1.42
800	12	23.8	24.4	1.56	2.66	-0.726

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
              A1          -77.952340           6     167.904680
              A2          -74.703868          10     169.407736
              A3          -77.952340           6     167.904680
          fitted          -79.863340           4     167.726680
               R          -89.824703           2     183.649405


                    Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value

  Test 1              30.2417          8       0.0001916
  Test 2              6.49694          4           0.165
  Test 3              6.49694          4           0.165
  Test 4                3.822          2          0.1479

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =             1

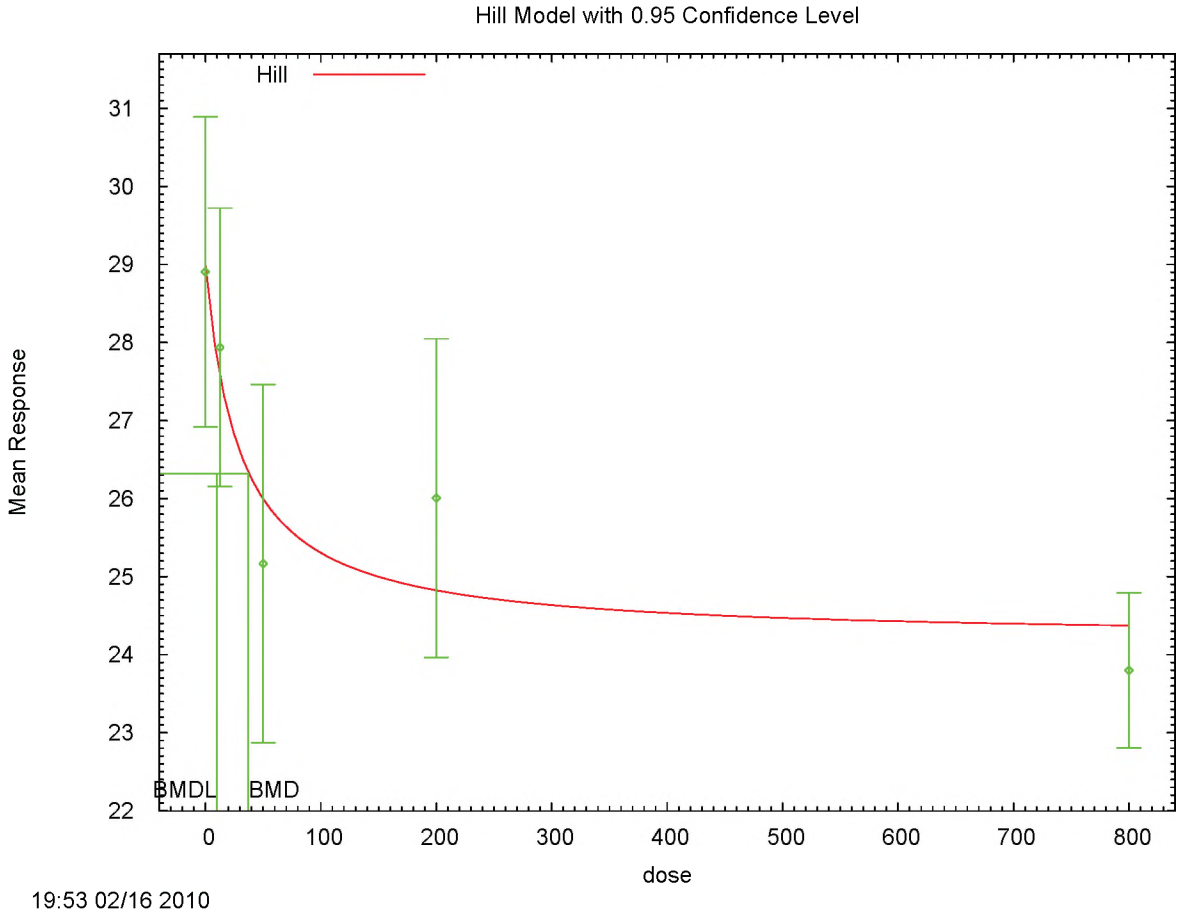
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =        37.2249

            BMDL =       9.75249
```

E.3.40.3. *Figure for Selected Model: Hill*



E.3.40.4. *Output for Additional Model Presented: Hill, Unrestricted*

Ohsako et al., 2001: Ano-Genital Length, PND 120

```
 ================================================================================
          Hill Model. (Version: 2.14;  Date: 06/26/2008)
          Input Data File: C:\1\56_Ohsako_2001_Anogen_HillCV_U_1.(d)
          Gnuplot Plotting File:  C:\1\56_Ohsako_2001_Anogen_HillCV_U_1.plt
                                                 Tue Feb 16 19:53:26 2010
 ================================================================================

 Figure 7
 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

    The form of the response function is:

    Y[dose] = intercept + v*dose^n/(k^n + dose^n)


    Dependent variable = Mean
    Independent variable = Dose
    rho is set to 0
    Power parameter is not restricted
    A constant variance model is fit
```

```
   Total number of dose groups = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                          alpha =      7.27386
                            rho =            0   Specified
                      intercept =       28.905
                              v =      -5.1065
                              n =      1.40226
                              k =      33.9669


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -rho
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

                    alpha    intercept            v            n            k

       alpha            1     2.1e-009    -1.8e-008    -1.7e-008     1.6e-008

   intercept     2.1e-009            1        0.012       0.0075        -0.13

           v    -1.8e-008        0.012            1         0.98        -0.99

           n    -1.7e-008       0.0075         0.98            1        -0.97

           k     1.6e-008        -0.13        -0.99        -0.97            1



                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
           alpha          7.06785          1.36021             4.40189             9.73381
       intercept          28.9608         0.755363             27.4803             30.4413
               v         -6.94236          12.2514            -30.9547               17.07
               n         0.501942         0.915162            -1.29174             2.29563
               k          131.957           1071.9            -1968.92             2232.84


      Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0    12       28.9           29         3.13         2.66        -0.0727
 12.5    10       27.9         27.3          2.5         2.66           0.72
   50    10       25.2         26.3         3.21         2.66          -1.37
  200    10         26         25.1         2.85         2.66           1.04
  800    12       23.8           24         1.56         2.66         -0.287


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
```

```
           Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
      Model A3 uses any fixed variance parameters that
      were specified by the user

 Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1          -77.952340           6     167.904680
             A2          -74.703868          10     169.407736
             A3          -77.952340           6     167.904680
          fitted         -79.800035           5     169.600070
              R          -89.824703           2     183.649405


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              30.2417          8       0.0001916
   Test 2              6.49694          4           0.165
   Test 3              6.49694          4           0.165
   Test 4              3.69539          1         0.05456

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1.  You may want to try a different
model


        Benchmark Dose Computation

Specified effect =            1

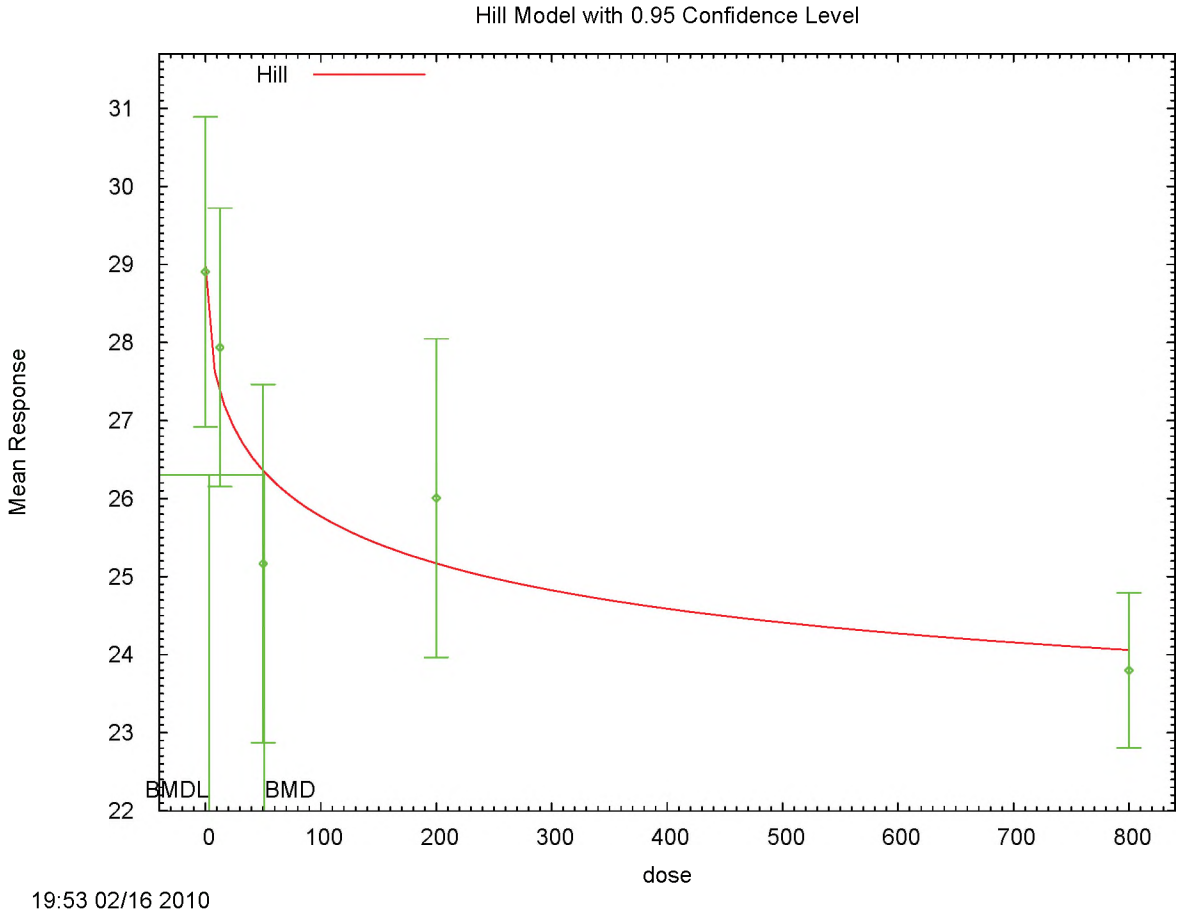
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =        51.0107

            BMDL =       3.06631
```

E.3.40.5. *Figure for Additional Model Presented: Hill, Unrestricted*



E.3.41. Sewall et al., 1995: T4 In Serum

E.3.41.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2)	3	0.424	205.966	5.762E+01	3.783E+01	
exponential (M3)	3	0.424	205.966	5.762E+01	3.783E+01	power hit bound (d = 1)
exponential (M5)	2	0.611	206.152	2.523E+01	8.442E+00	power hit bound (d = 1)
Hill [b]	**2**	**0.702**	**205.875**	**2.071E+01**	**5.164E+00**	**n lower bound hit (n = 1)**
linear	3	0.332	206.584	6.788E+01	4.858E+01	
polynomial, 4-degree	3	0.332	206.584	6.788E+01	4.858E+01	
power	3	0.332	206.584	6.788E+01	4.858E+01	power bound hit (power = 1)
Hill, unrestricted [c]	1	0.844	207.205	1.657E+01	1.903E+00	unrestricted (n = 0.427)
power, unrestricted	2	0.983	205.200	1.658E+01	1.820E+00	unrestricted (power = 0.403)

[a] Constant variance model selected ($p = 0.4078$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.3.41.2. *Output for Selected Model: Hill*

Sewall et al., 1995: T4 In Serum

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\1\58_Sewall_1995_T4_HillCV_1.(d)
         Gnuplot Plotting File:  C:\1\58_Sewall_1995_T4_HillCV_1.plt
                                                Tue Feb 16 19:54:30 2010
 ================================================================

 Figure 1, Saline noninitiated
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/{k^n + dose^n}


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter restricted to be greater than 1
   A constant variance model is fit

   Total number of dose groups = 5
   Total number of records with missing values = 0
```

```
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                          alpha =      33.0913
                            rho =            0   Specified
                      intercept =      30.6979
                              v =     -12.2937
                              n =     0.695384
                              k =      24.6674


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -rho    -n
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

                    alpha    intercept            v            k

      alpha             1     1.2e-008     4.1e-008    -2.4e-008

  intercept     1.2e-008            1         0.14        -0.66

          v     4.1e-008         0.14            1        -0.76

          k    -2.4e-008        -0.66        -0.76            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
           alpha          29.8807          6.29941            17.5341             42.2274
       intercept          29.9609          1.64749            26.7319             33.1899
               v         -14.2338          4.35645           -22.7723            -5.69537
               n                1               NA
               k          33.2198          37.0852           -39.4658             105.905

 NA - Indicates that this parameter has hit a bound
      implied by some inequality constraint and thus
      has no standard error.


      Table of Data and Estimated Values of Interest

  Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------      ---   --------     --------   -----------  -----------   ----------

     0      9       30.7           30         4.66         5.47          0.404
   3.5      9       27.9         28.6         7.17         5.47         -0.399
  10.7      9       25.9         26.5         6.81         5.47         -0.328
    35      9       23.6         22.7         5.38         5.47          0.493
   125      9       18.4         18.7         4.12         5.47         -0.171


  Model Descriptions for likelihoods calculated


  Model A1:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma(i)^2
```

```
Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                       Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
              A1          -98.583448           6     209.166896
              A2          -96.590204          10     213.180407
              A3          -98.583448           6     209.166896
          fitted          -98.937315           4     205.874631
               R         -109.013252           2     222.026503


                    Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value

  Test 1              24.8461          8        0.001651
  Test 2              3.98649          4          0.4078
  Test 3              3.98649          4          0.4078
  Test 4             0.707735          2           0.702

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =             1

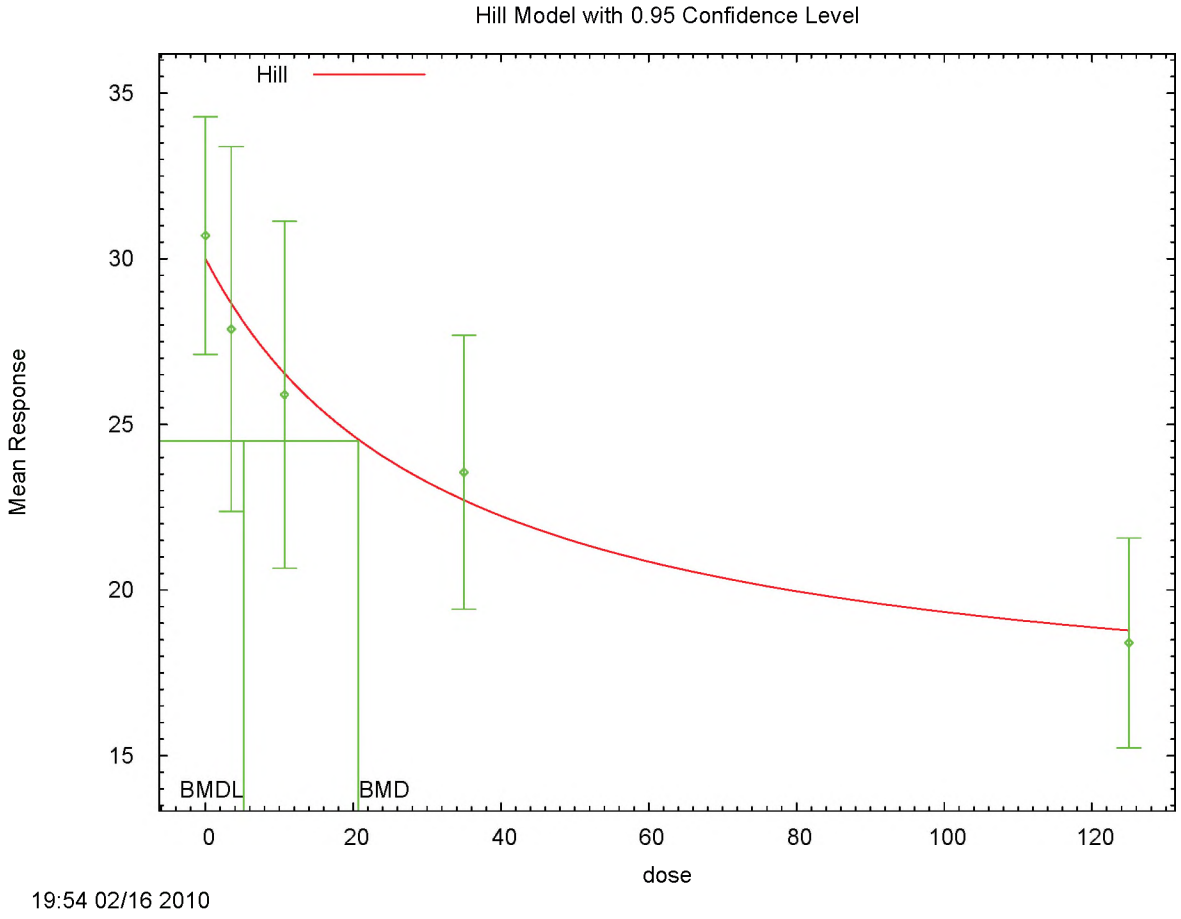
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =        20.7117

            BMDL =       5.16405
```

E.3.41.3. *Figure for Selected Model: Hill*



E.3.41.4. *Output for Additional Model Presented: Hill, Unrestricted*

Sewall et al., 1995: T4 In Serum

```
 ================================================================================
          Hill Model. (Version: 2.14;  Date: 06/26/2008)
          Input Data File: C:\1\58_Sewall_1995_T4_HillCV_U_1.(d)
          Gnuplot Plotting File:  C:\1\58_Sewall_1995_T4_HillCV_U_1.plt
                                                 Tue Feb 16 19:54:31 2010
 ================================================================================

 Figure 1, Saline noninitiated
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

    The form of the response function is:

    Y[dose] = intercept + v*dose^n/(k^n + dose^n)


    Dependent variable = Mean
    Independent variable = Dose
    rho is set to 0
    Power parameter is not restricted
    A constant variance model is fit
```

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

alpha =	33.0913	
rho =	0	Specified
intercept =	30.6979	
v =	-12.2937	
n =	0.695384	
k =	24.6674	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	intercept	v	n	k
alpha	1	-0.0004	0.0059	0.0048	-0.0059
intercept	-0.0004	1	-0.026	-0.44	0.07
v	0.0059	-0.026	1	0.77	-1
n	0.0048	-0.44	0.77	1	-0.82
k	-0.0059	0.07	-1	-0.82	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	29.4396	6.20653	17.2751	41.6042
intercept	30.6757	1.77521	27.1963	34.155
v	-141.324	1202.4	-2497.98	2215.33
n	0.426599	0.262207	-0.0873175	0.940515
k	31487	770429	-1.47853e+006	1.5415e+006

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	9	30.7	30.7	4.66	5.43	0.0123
3.5	9	27.9	27.8	7.17	5.43	0.0279
10.7	9	25.9	26.1	6.81	5.43	-0.137
35	9	23.6	23.3	5.38	5.43	0.132
125	9	18.4	18.5	4.12	5.43	-0.0354

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)

```
           Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
      Model A3 uses any fixed variance parameters that
      were specified by the user

 Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1          -98.583448           6     209.166896
             A2          -96.590204          10     213.180407
             A3          -98.583448           6     209.166896
          fitted         -98.602701           5     207.205403
              R         -109.013252           2     222.026503


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              24.8461          8        0.001651
   Test 2              3.98649          4          0.4078
   Test 3              3.98649          4          0.4078
   Test 4            0.0385071          1          0.8444

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =            1

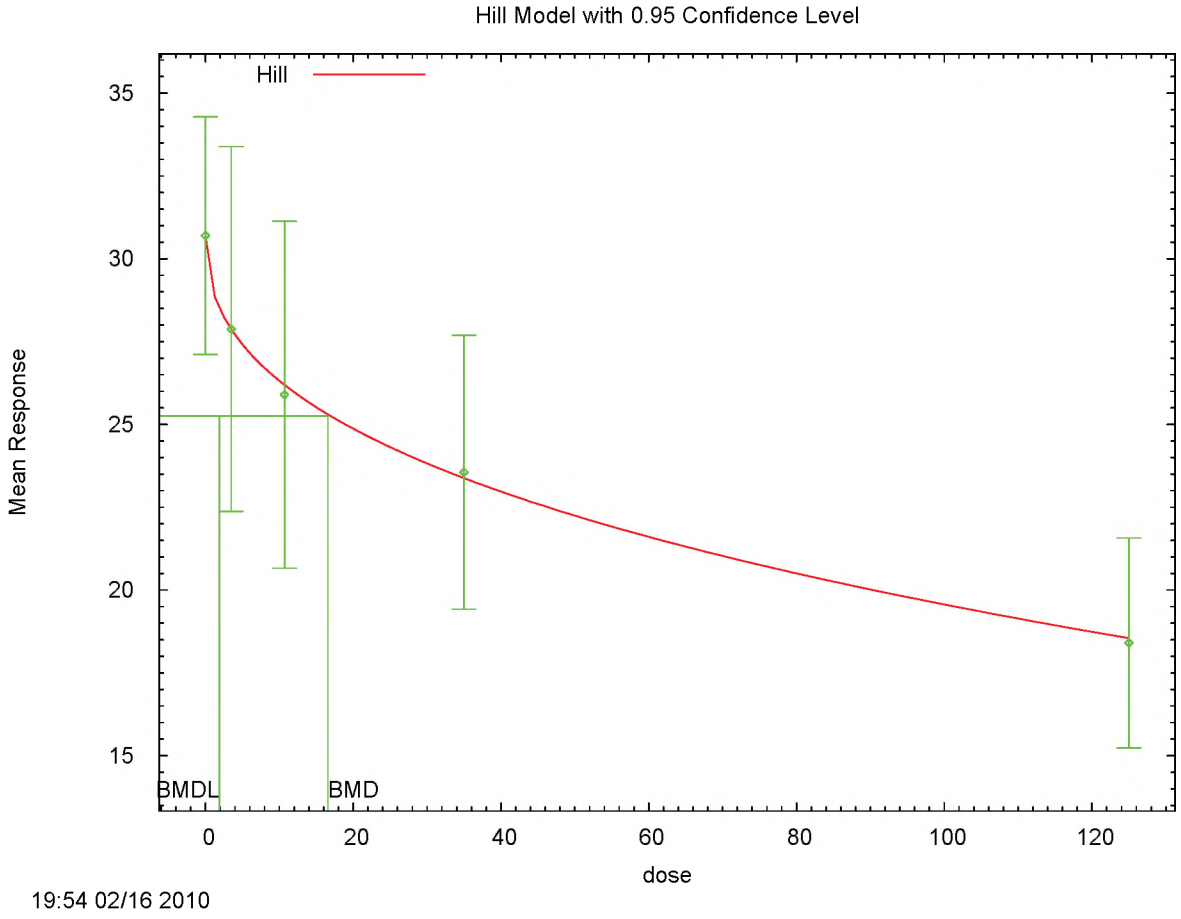
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =        16.5689

            BMDL =       1.90347
```

E.3.41.5. *Figure for Additional Model Presented: Hill, Unrestricted*



E.3.42. Shi et al., 2007: Estradiol 17B, PE9

E.3.42.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2)	3	0.001	395.701	1.729E+01	8.956E+00	
exponential (M3)	3	0.001	395.701	1.729E+01	8.956E+00	power hit bound (d = 1)
exponential (M4) [b]	**2**	**0.494**	**383.635**	**5.559E-01**	**2.236E-01**	
exponential (M5)	2	0.494	383.635	5.559E-01	2.236E-01	power hit bound (d = 1)
Hill	2	0.773	382.743	4.434E-01	error	n lower bound hit (n = 1)
linear	3	0.001	397.484	2.243E+01	1.523E+01	
polynomial, 4-degree	3	0.001	397.484	2.243E+01	1.523E+01	
power	3	0.001	397.484	2.243E+01	1.523E+01	power bound hit (power = 1)
Hill, unrestricted	1	0.874	384.251	3.998E-01	error	unrestricted (n = 0.616)
power, unrestricted	2	0.506	383.589	3.409E-01	5.002E-03	unrestricted (power = 0.155)

[a] Non-constant variance model selected ($p = 0.0521$)

[b] Best-fitting model, BMDS output presented in this appendix

E.3.42.2. *Output for Selected Model: Exponential (M4)*

Shi et al., 2007: Estradiol 17B, PE9

```
 ========================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\1\59_Shi_2007_Estradiol_Exp_1.(d)
         Gnuplot Plotting File:
                                                 Tue Feb 16 19:55:06 2010
 ========================================================================

 Figure 4 PE9 only
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
```

```
   Model 3 is nested within Model 5.
   Model 4 is nested within Model 5.


Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


                Initial Parameter Values

                Variable          Model 4
                --------          --------
                  lnalpha             2.65881
                      rho            0.913414
                        a                 108
                        b            0.136287
                        c            0.340136
                        d                   1



                  Parameter Estimates

                 Variable          Model 4
                 --------          -------
                  lnalpha            1.81331
                      rho            1.12126
                        a            100.526
                        b            1.53823
                        c           0.431796
                        d                  1


         Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0     10        102.9         41.41
  0.143     10        86.19         19.58
  0.714     10        63.33         29.36
   7.14     10         48.1         18.82
   28.6     10        38.57         22.59


              Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
      0         100.5        32.83           0.2245
  0.143         89.25        30.71          -0.3147
  0.714         62.45        25.14           0.1108
   7.14         43.41         20.5            0.723
   28.6         43.41         20.5          -0.7458


Other models for which likelihoods are calculated:

  Model A1:        Yij = Mu(i) + e(ij)
```

```
            Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
            Var{e(ij)} = Sigma^2


                              Likelihoods of Interest

                   Model      Log(likelihood)      DF         AIC
                  -------    -----------------    ----   ------------
                      A1       -188.3615           6      388.7231
                      A2        -183.667          10      387.3339
                      A3       -186.1132           7      386.2263
                       R       -203.3606           2      410.7211
                       4       -186.8176           5      383.6352


Additive constant for all log-likelihoods =     -45.95.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.


                               Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)


                           Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                        39.39           8            < 0.0001
  Test 2                        9.389           4             0.05208
  Test 3                        4.892           3              0.1798
 Test 6a                        1.409           2              0.4944


  The p-value for Test 1 is less than .05.  There appears to be a
  difference between response and/or variances among the dose
  levels, it seems appropriate to model the data.

  The p-value for Test 2 is less than .1.  A non-homogeneous
  variance model appears to be appropriate.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 6a is greater than .1.  Model 4 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 1.000000

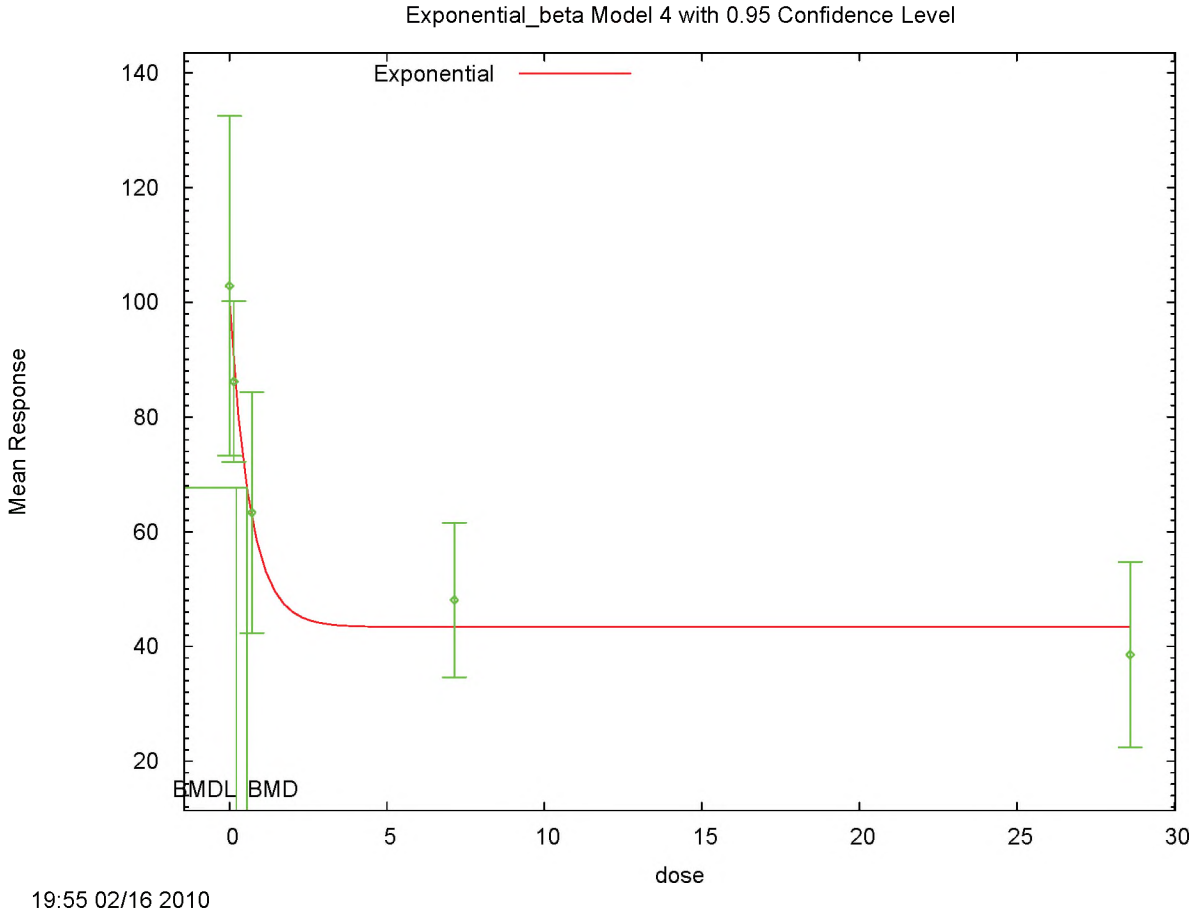
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

              BMD =     0.555948
```

BMDL = 0.223612

E.3.42.3. *Figure for Selected Model: Exponential (M4)*



E.3.43. Smialowicz et al., 2008: PFC per 10^6 Cells

E.3.43.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2)	3	0.048	903.586	8.234E+01	4.833E+01	
exponential (M3)	3	0.048	903.586	8.234E+01	4.833E+01	power hit bound (d = 1)
exponential (M4)	2	0.019	905.578	8.032E+01	6.220E+00	
exponential (M5)	2	0.019	905.578	8.032E+01	6.220E+00	power hit bound (d = 1)
Hill	2	0.026	904.975	1.617E+01	2.214E+00	n lower bound hit (n = 1)
linear	3	0.016	905.992	1.450E+02	1.102E+02	
polynomial, 4-degree	2	<0.0001	1198.471	1.375E+03	3.331E+01	
power [c]	3	0.016	905.992	1.450E+02	1.102E+02	power bound hit (power = 1)
Hill, unrestricted	1	0.183	901.442	8.297E+00	4.172E-01	unrestricted (n = 0.266)
power, unrestricted [b]	**2**	**0.446**	**899.282**	**7.676E+00**	**4.087E-01**	**unrestricted (power = 0.249)**

[a] Constant variance model selected (*p* = <0.0001)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.3.43.2. *Output for Selected Model: Power, Unrestricted*

Smialowicz et al., 2008: PFC per 10^6 Cells

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\1\60_Smial_2008_PFCcells_PwrCV_U_1.(d)
         Gnuplot Plotting File:  C:\1\60_Smial_2008_PFCcells_PwrCV_U_1.plt
                                              Tue Feb 16 19:55:53 2010
 ================================================================

 Anti Response to SRBCs, PFC per 10to6 cells, Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
```

```
   The power is not restricted
   A constant variance model is fit

   Total number of dose groups = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                          alpha =       232385
                            rho =            0   Specified
                        control =         1491
                          slope =     -384.362
                          power =     0.215085


            Asymptotic Correlation Matrix of Parameter Estimates

            ( *** The model parameter(s)  -rho
                  have been estimated at a boundary point, or have been specified by the user,
                  and do not appear in the correlation matrix )

                   alpha      control        slope        power

      alpha            1    -1.5e-009    -8.2e-009    -1.1e-008

    control    -1.5e-009            1        -0.79        -0.65

      slope    -8.2e-009        -0.79            1         0.96

      power    -1.1e-008        -0.65         0.96            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
           alpha           220294          38061.1             145696              294893
         control          1470.38           124.07            1227.21             1713.55
           slope         -282.777          145.113           -567.193             1.64025
           power         0.248621        0.0856348          0.0807799            0.416462


      Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0    15  1.49e+003    1.47e+003          716          469           0.17
 1.07    14  1.13e+003    1.18e+003          171          469         -0.429
 10.7    15        945          961          516          469         -0.129
  107    15        677          567          465          469           0.91
  321     8        161          283          117          469         -0.735


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2
```

```
Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                       Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1         -444.832859            6     901.665718
             A2         -425.402825           10     870.805651
             A3         -444.832859            6     901.665718
         fitted         -445.641102            4     899.282205
              R         -463.753685            2     931.507371


                   Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value

  Test 1              76.7017          8          <.0001
  Test 2              38.8601          4          <.0001
  Test 3              38.8601          4          <.0001
  Test 4              1.61649          2          0.4456

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  Consider running a
non-homogeneous variance model

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


               Benchmark Dose Computation

Specified effect =             1

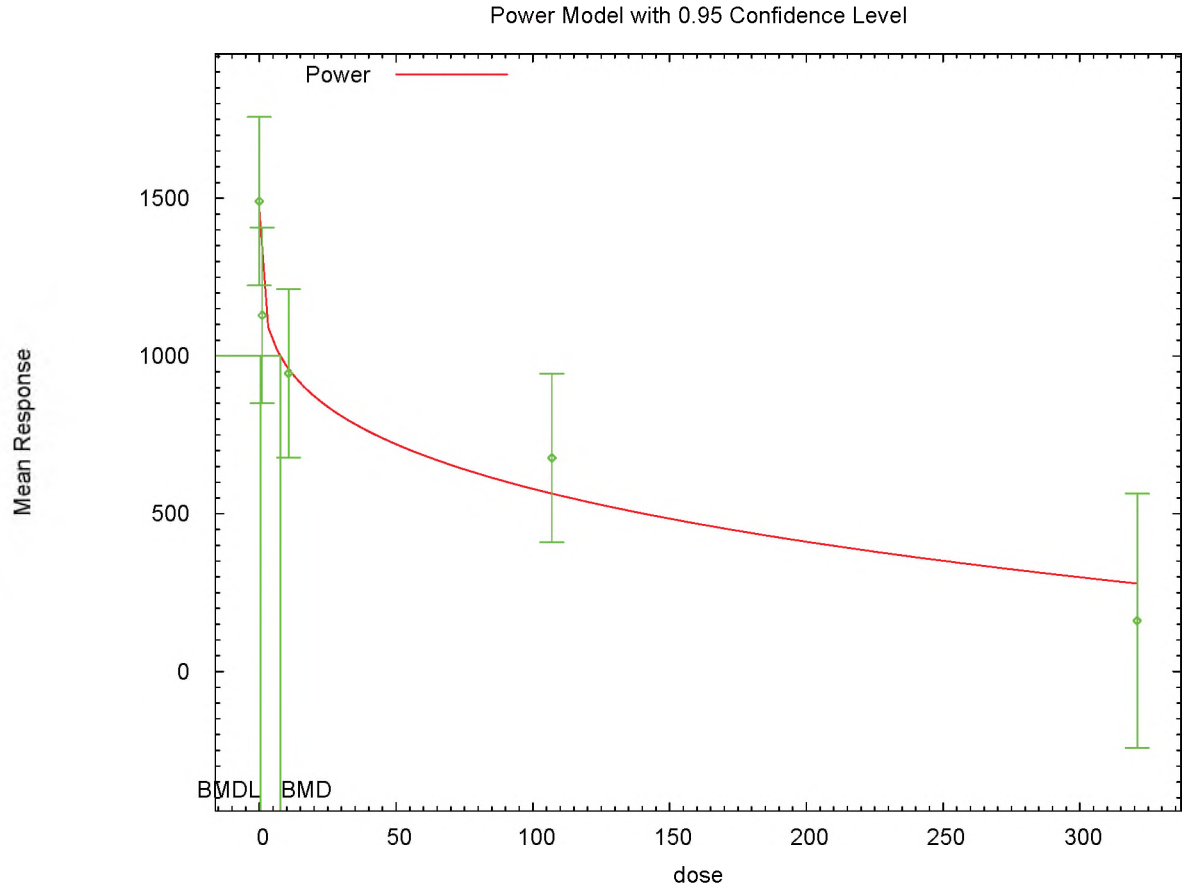
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 7.67564


             BMDL = 0.408661
```

E.3.43.3. *Figure for Selected Model: Power, Unrestricted*



E.3.43.4. *Output for Additional Model Presented: Power*

Smialowicz et al., 2008: PFC per 10^6 Cells

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\1\60_Smial_2008_PFCcells_PwrCV_1.(d)
         Gnuplot Plotting File:  C:\1\60_Smial_2008_PFCcells_PwrCV_1.plt
                                          Tue Feb 16 19:55:53 2010
 ================================================================

 Anti Response to SRBCs, PFC per 10to6 cells, Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   The power is restricted to be greater than or equal to 1
   A constant variance model is fit
```

```
   Total number of dose groups = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                          alpha =       232385
                            rho =            0   Specified
                        control =         1491
                          slope =     -2925.99
                          power =    -0.136613


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -rho    -power
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

                    alpha      control        slope

     alpha              1     3.6e-009    -1.2e-008

   control     3.6e-009            1        -0.53

     slope    -1.2e-008        -0.53            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
          alpha           250878          43345.1             165923              335833
        control          1176.24          72.2586            1034.61             1317.86
          slope         -3.45384         0.592114           -4.61436            -2.29332
          power                1               NA

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0    15  1.49e+003    1.18e+003          716          501           2.43
 1.07    14  1.13e+003    1.17e+003          171          501         -0.325
 10.7    15        945    1.14e+003          516          501           -1.5
  107    15        677          807          465          501             -1
  321     8        161         67.6          117          501          0.528


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2
```

```
Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                       Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
              A1         -444.832859            6     901.665718
              A2         -425.402825           10     870.805651
              A3         -444.832859            6     901.665718
          fitted         -449.996183            3     905.992366
               R         -463.753685            2     931.507371


                   Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value

  Test 1              76.7017          8          <.0001
  Test 2              38.8601          4          <.0001
  Test 3              38.8601          4          <.0001
  Test 4              10.3266          3         0.01598

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  Consider running a
non-homogeneous variance model

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

The p-value for Test 4 is less than .1.  You may want to try a different
model


               Benchmark Dose Computation

Specified effect =             1

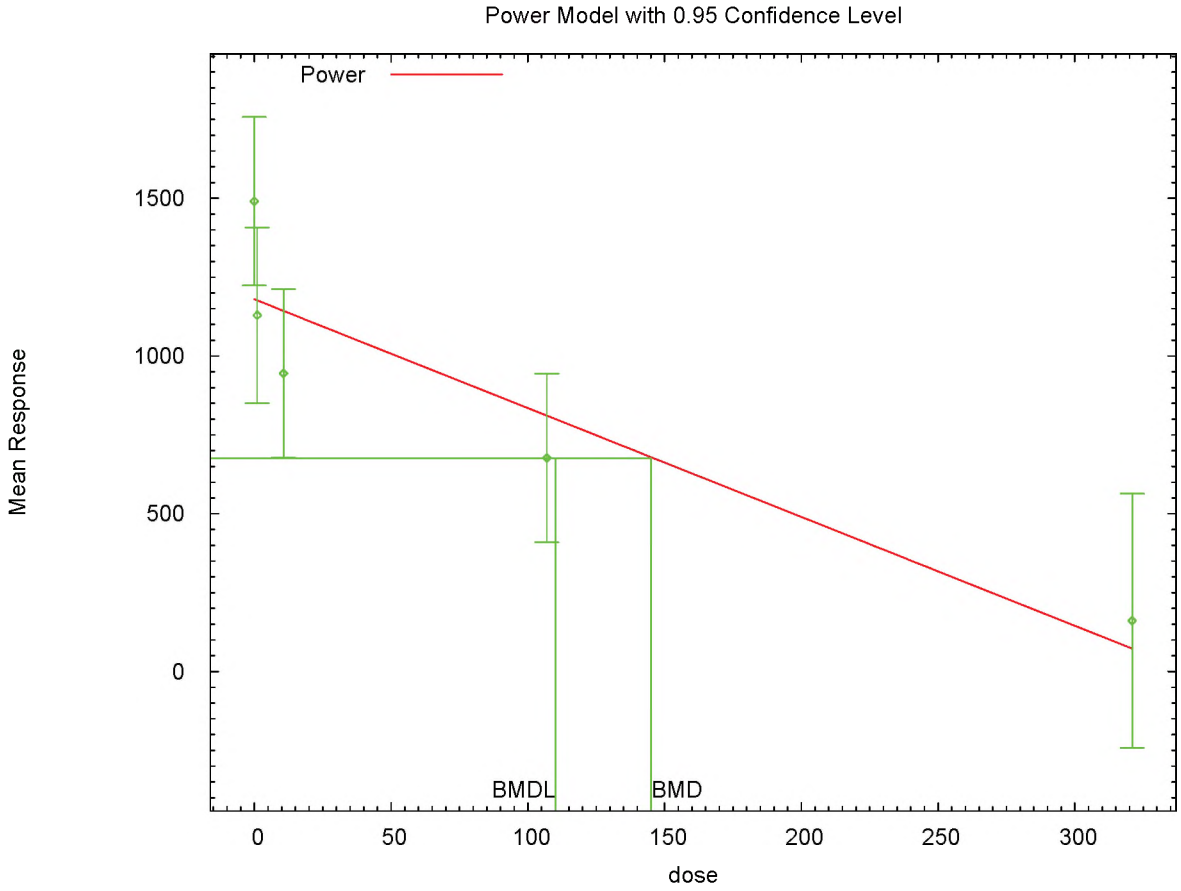
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 145.02


            BMDL = 110.161
```

E.3.43.5. *Figure for Additional Model Presented: Power*



E.3.44. Smialowicz et al., 2008: PFC per Spleen

E.3.44.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2)	3	0.133	377.395	1.320E+02	8.431E+01	
exponential (M3)	3	0.133	377.395	1.320E+02	8.431E+01	power hit bound (d = 1)
exponential (M4)	3	0.133	377.395	1.320E+02	8.184E+01	
exponential (M5)	2	0.061	379.395	1.320E+02	8.184E+01	power hit bound (d = 1)
Hill	2	0.069	379.150	1.401E+02	error	n lower bound hit (n = 1)
linear	3	0.044	379.895	2.151E+02	1.704E+02	
polynomial, 4-degree	3	0.044	379.895	2.151E+02	1.704E+02	
power[c]	3	0.044	379.895	2.151E+02	1.704E+02	power bound hit (power = 1)
Hill, unrestricted	2	<0.0001	441.885	7.545E-23	error	unrestricted (n = 0.038)
power, unrestricted[b]	**2**	**0.230**	**376.738**	**9.374E+01**	**2.088E+01**	**unrestricted (power = 0.418)**

[a] Non-constant variance model selected ($p = 0.0011$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.3.44.2. *Output for Selected Model: Power, Unrestricted*

Smialowicz et al., 2008: PFC per Spleen

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\1\61_Smial_2008_PFCspleen_Pwr_U_1.(d)
         Gnuplot Plotting File:  C:\1\61_Smial_2008_PFCspleen_Pwr_U_1.plt
                                              Tue Feb 16 19:56:26 2010
 ================================================================

 Anti Response to SRBCs - PFC x 10 to the 4 per spleen, Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   The power is not restricted
```

The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	4.76607
rho =	0
control =	27.8
slope =	-7.21601
power =	0.213905

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	control	slope	power
lalpha	1	-0.98	0.25	-0.27	-0.23
rho	-0.98	1	-0.31	0.28	0.23
control	0.25	-0.31	1	-0.81	-0.74
slope	-0.27	0.28	-0.81	1	0.99
power	-0.23	0.23	-0.74	0.99	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	0.747155	1.0244	-1.26063	2.75494
rho	1.36972	0.357098	0.66982	2.06962
control	25.1733	2.93169	19.4273	30.9193
slope	-1.98465	1.82113	-5.554	1.5847
power	0.417867	0.141932	0.139686	0.696048

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	15	27.8	25.2	13.4	13.2	0.769
1.07	14	21	23.1	13.6	12.5	-0.639
10.7	15	17.6	19.8	9.4	11.2	-0.768
107	15	12.6	11.2	8.7	7.59	0.721
321	8	3	3.04	3.1	3.11	-0.0353

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))

```
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1         -190.565019           6     393.130038
             A2         -181.476284          10     382.952569
             A3         -181.900030           7     377.800059
          fitted        -183.369059           5     376.738118
              R         -204.636496           2     413.272993


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              46.3204          8          <.0001
   Test 2              18.1775          4        0.001139
   Test 3              0.84749          3          0.8381
   Test 4              2.93806          2          0.2301

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


               Benchmark Dose Computation

Specified effect =             1

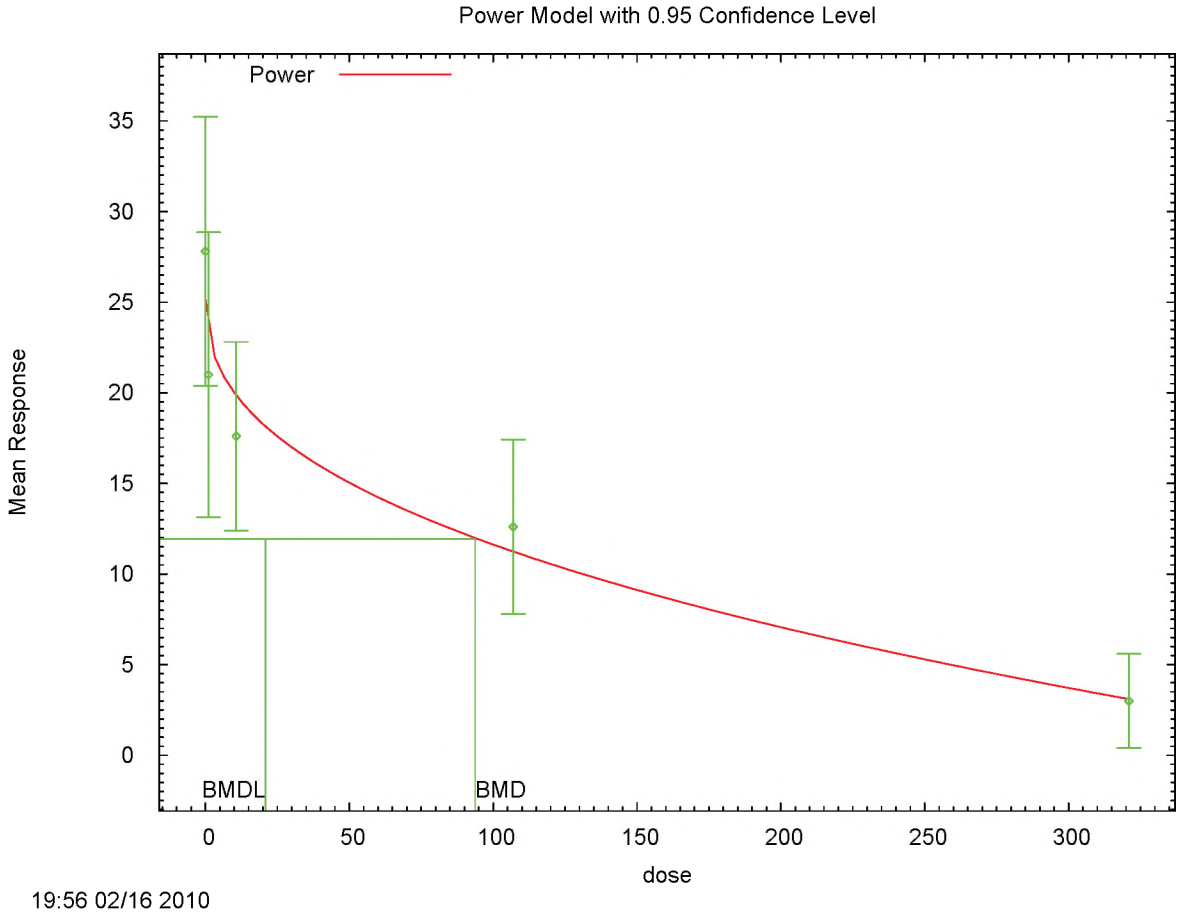
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 93.7416


            BMDL = 20.8758
```

E.3.44.3. *Figure for Selected Model: Power, Unrestricted*



E.3.44.4. *Output for Additional Model Presented: Power*

Smialowicz et al., 2008: PFC per Spleen

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\1\61_Smial_2008_PFCspleen_Pwr_1.(d)
         Gnuplot Plotting File:  C:\1\61_Smial_2008_PFCspleen_Pwr_1.plt
                                          Tue Feb 16 19:56:25 2010
 ================================================================

 Anti Response to SRBCs - PFC x 10 to the 4 per spleen, Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   The power is restricted to be greater than or equal to 1
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)
```

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	4.76607
rho =	0
control =	27.8
slope =	-54.5244
power =	-0.136501

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -power
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	lalpha	rho	control	slope
lalpha	1	-0.98	0.16	-0.48
rho	-0.98	1	-0.25	0.54
control	0.16	-0.25	1	-0.88
slope	-0.48	0.54	-0.88	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	0.474614	1.09569	-1.6729	2.62213
rho	1.48709	0.385029	0.732449	2.24173
control	21.3571	1.69233	18.0402	24.674
slope	-0.0574184	0.00632057	-0.0698064	-0.0450303
power	1	NA		

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	15	27.8	21.4	13.4	12.3	2.02
1.07	14	21	21.3	13.6	12.3	-0.0898
10.7	15	17.6	20.7	9.4	12.1	-1.01
107	15	12.6	15.2	8.7	9.6	-1.05
321	8	3	2.93	3.1	2.82	0.0745

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)

```
           Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1         -190.565019           6     393.130038
             A2         -181.476284          10     382.952569
             A3         -181.900030           7     377.800059
          fitted        -185.947278           4     379.894555
              R         -204.636496           2     413.272993


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              46.3204          8          <.0001
   Test 2              18.1775          4        0.001139
   Test 3              0.84749          3          0.8381
   Test 4               8.0945          3          0.0441

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1.  You may want to try a different
model


               Benchmark Dose Computation

Specified effect =            1

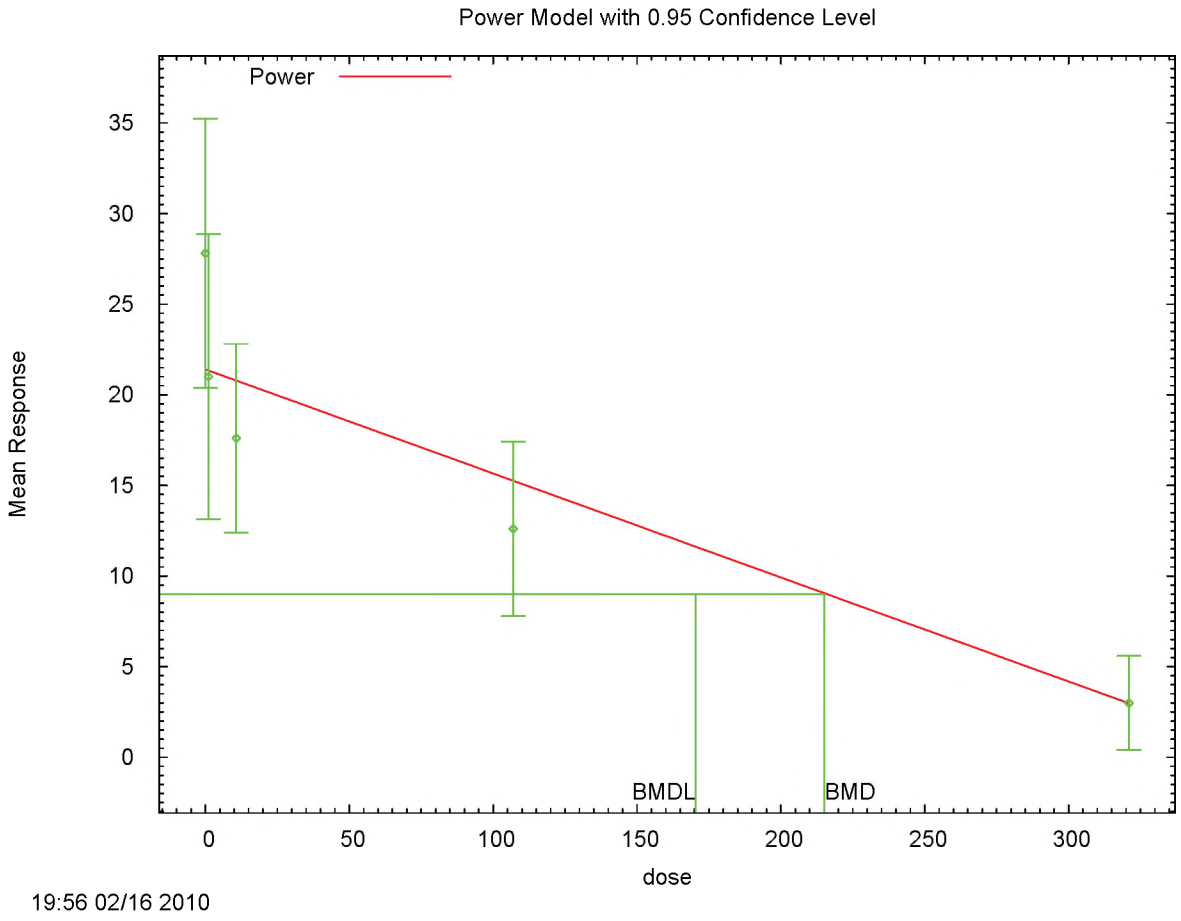
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 215.073


            BMDL = 170.412
```

E.3.44.5. *Figure for Additional Model Presented: Power*



E.3.45. Toth et al., 1979: Amyloidosis

E.3.45.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
gamma	2	0.022	150.666	2.296E+02	1.460E+02	power bound hit (power = 1)
logistic	2	0.013	152.187	4.088E+02	3.125E+02	negative intercept (intercept = -2.098)
log-logistic [a]	**2**	**0.028**	**149.984**	**1.759E+02**	**9.729E+01**	**slope bound hit (slope = 1)**
log-probit	2	0.007	153.479	4.402E+02	2.965E+02	slope bound hit (slope = 1)
multistage, 3-degree	2	0.022	150.666	2.296E+02	1.460E+02	final ß = 0
probit	2	0.014	152.040	3.846E+02	2.911E+02	negative intercept (intercept = -1.238)
Weibull	2	0.022	150.666	2.296E+02	1.460E+02	power bound hit (power = 1)
gamma, unrestricted	2	0.917	140.208	7.687E-01	7.637E-04	unrestricted (power = 0.187)
log-logistic, unrestricted [b]	2	0.847	140.370	8.465E-01	1.565E-03	unrestricted (slope = 0.238)
log-probit, unrestricted	2	0.811	140.458	8.545E-01	2.334E-03	unrestricted (slope = 0.135)
Weibull, unrestricted	2	0.882	140.287	8.179E-01	1.140E-03	unrestricted (power = 0.212)

[a] Best-fitting model, BMDS output presented in this appendix

[b] Alternate model, BMDS output also presented in this appendix

E.3.45.2. *Output for Selected Model: Log-Logistic*

Toth et al., 1979: Amyloidosis

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\1\62_Toth_1979_Amy1yr_LogLogistic_1.(d)
         Gnuplot Plotting File:  C:\1\62_Toth_1979_Amy1yr_LogLogistic_1.plt
                                              Tue Feb 16 19:56:59 2010
 ================================================================

 Table 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
```

```
   Slope parameter is restricted as slope >= 1

   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =            0
                     intercept =     -6.90711
                         slope =            1


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -slope
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

             background    intercept

background            1        -0.47

 intercept        -0.47            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background        0.0848984            *               *                   *
      intercept         -7.36716            *               *                   *
          slope                1            *               *                   *

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -68.017         4
   Fitted model        -72.9918         2        9.9496      2         0.00691
  Reduced model        -82.0119         1         27.99      3         <.0001

           AIC:         149.984


                                 Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
    0.0000     0.0849         3.226     0.000          38       -1.878
    1.0000     0.0855         3.761     5.000          44        0.668
  100.0000     0.1393         6.128    10.000          44        1.686
 1000.0000     0.4392        18.884    17.000          43       -0.579

 Chi^2 = 7.15      d.f. = 2        P-value = 0.0280


   Benchmark Dose Computation

Specified effect =           0.1
```

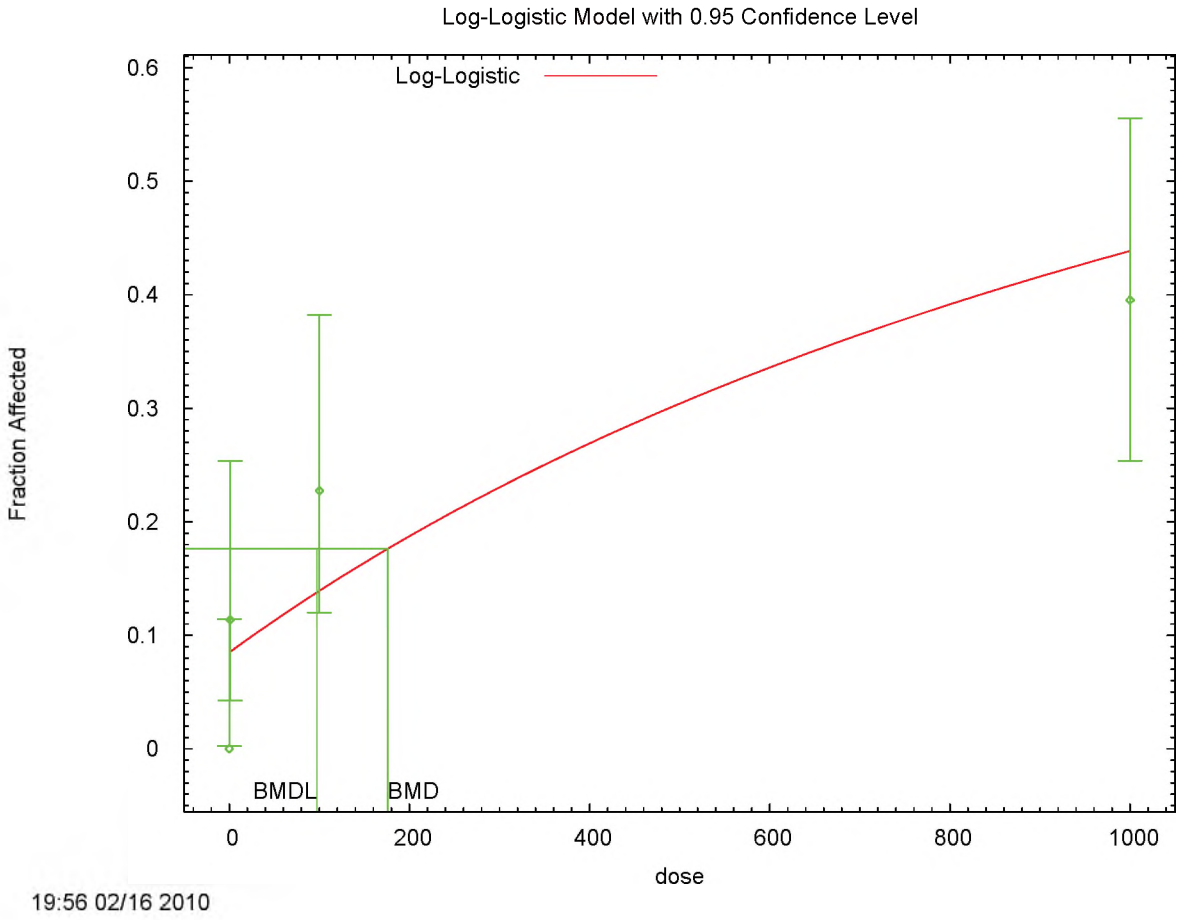
```
Risk Type          =      Extra risk

Confidence level   =           0.95

              BMD  =        175.903

             BMDL  =        97.2899
```

E.3.45.3. *Figure for Selected Model: Log-Logistic*



E.3.45.4. *Output for Additional Model Presented: Log-Logistic, Unrestricted*

Toth et al., 1979: Amyloidosis

```
 ========================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\1\62_Toth_1979_Amylyr_LogLogistic_U_1.(d)
         Gnuplot Plotting File:  C:\1\62_Toth_1979_Amylyr_LogLogistic_U_1.plt
                                                 Tue Feb 16 19:57:00 2010
 ========================================================================

 Table 2
 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
```

```
The form of the probability function is:

P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


Dependent variable = DichEff
Independent variable = Dose
Slope parameter is not restricted

Total number of observations = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



User has chosen the log transformed model


                Default Initial Parameter Values
                   background =            0
                    intercept =     -2.10894
                        slope =     0.227921


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -background
                have been estimated at a boundary point, or have been specified by the user,
                and do not appear in the correlation matrix )

             intercept        slope

 intercept            1        -0.89

     slope        -0.89            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background                0            *               *                   *
      intercept         -2.15753            *               *                   *
          slope         0.238304            *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -68.017         4
   Fitted model        -68.1848         2       0.33571      2          0.8455
  Reduced model        -82.0119         1         27.99      3         <.0001

           AIC:          140.37


                                Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          38        0.000
     1.0000     0.1036         4.560     5.000          44        0.218
   100.0000     0.2573        11.321    10.000          44       -0.456
  1000.0000     0.3749        16.119    17.000          43        0.277
```

```
 Chi^2 = 0.33      d.f. = 2        P-value = 0.8471


   Benchmark Dose Computation

Specified effect =            0.1

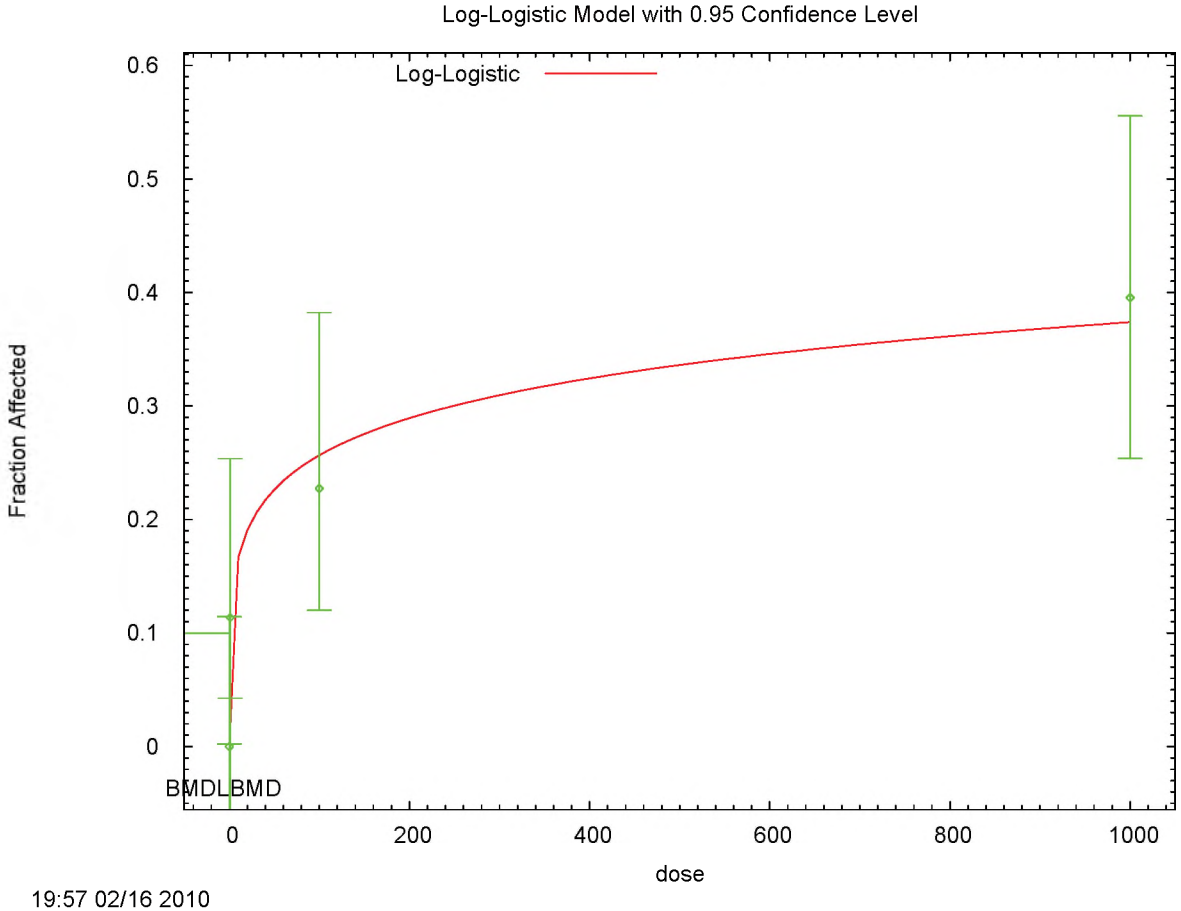
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.846547

            BMDL =     0.00156534
```

E.3.45.5. *Figure for Additional Model Presented: Log-Logistic, Unrestricted*



E.3.46. Toth et al., 1979: Skin Lesions

E.3.46.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
gamma	2	0.009	159.223	1.181E+02	8.308E+01	power bound hit (power = 1)
logistic [a]	**2**	**0.002**	**162.974**	**2.709E+02**	**2.147E+02**	**negative intercept (intercept = -2.098)**
log-logistic	2	0.029	156.567	6.750E+01	4.057E+01	slope bound hit (slope = 1)
log-probit	2	0.001	164.598	2.446E+02	1.626E+02	slope bound hit (slope = 1)
multistage, 3-degree	2	0.009	159.223	1.181E+02	8.308E+01	final ß = 0
probit	2	0.003	162.684	2.522E+02	2.015E+02	negative intercept (intercept = -1.238)
Weibull	2	0.009	159.223	1.181E+02	8.308E+01	power bound hit (power = 1)
gamma, unrestricted	2	0.882	147.287	error	error	unrestricted (power = 0.251)
log-logistic, unrestricted [b]	2	0.630	147.969	1.137E+00	5.477E-02	unrestricted (slope = 0.351)
log-probit, unrestricted	2	0.558	148.218	1.096E+00	6.847E-02	unrestricted (slope = 0.202)
Weibull, unrestricted	2	0.762	147.581	1.077E+00	4.080E-02	unrestricted (power = 0.3)

[a] Best-fitting model, BMDS output presented in this appendix

[b] Alternate model, BMDS output also presented in this appendix

E.3.46.2. *Output for Selected Model: Logistic*

Toth et al., 1979: Skin Lesions

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\1\63_Toth_1979_SkinLes_Logistic_1.(d)
         Gnuplot Plotting File:  C:\1\63_Toth_1979_SkinLes_Logistic_1.plt
                                              Tue Feb 16 19:57:29 2010
 ================================================================

 Table 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = 1/[1+EXP(-intercept-slope*dose)]


   Dependent variable = DichEff
   Independent variable = Dose
```

```
   Slope parameter is not restricted

   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                    background =            0   Specified
                     intercept =     -2.53484
                         slope =   0.00299511


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -background
                have been estimated at a boundary point, or have been specified by the user,
                and do not appear in the correlation matrix )

             intercept        slope

intercept            1        -0.67

    slope        -0.67            1



                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     intercept         -1.91768          0.26892            -2.44475            -1.39061
         slope       0.00230499      0.000419329          0.00148312          0.00312686



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
    Full model         -71.5177         4
  Fitted model          -79.487         2       15.9387      2       0.0003459
 Reduced model         -95.8498         1       48.6642      3         <.0001

          AIC:         162.974


                                 Goodness  of  Fit
                                                                    Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.1281         4.869     0.000          38       -2.363
     1.0000     0.1284         5.649     5.000          44       -0.292
   100.0000     0.1561         6.870    13.000          44        2.546
  1000.0000     0.5956        25.612    25.000          43       -0.190

 Chi^2 = 12.19     d.f. = 2        P-value = 0.0023


   Benchmark Dose Computation

Specified effect =           0.1

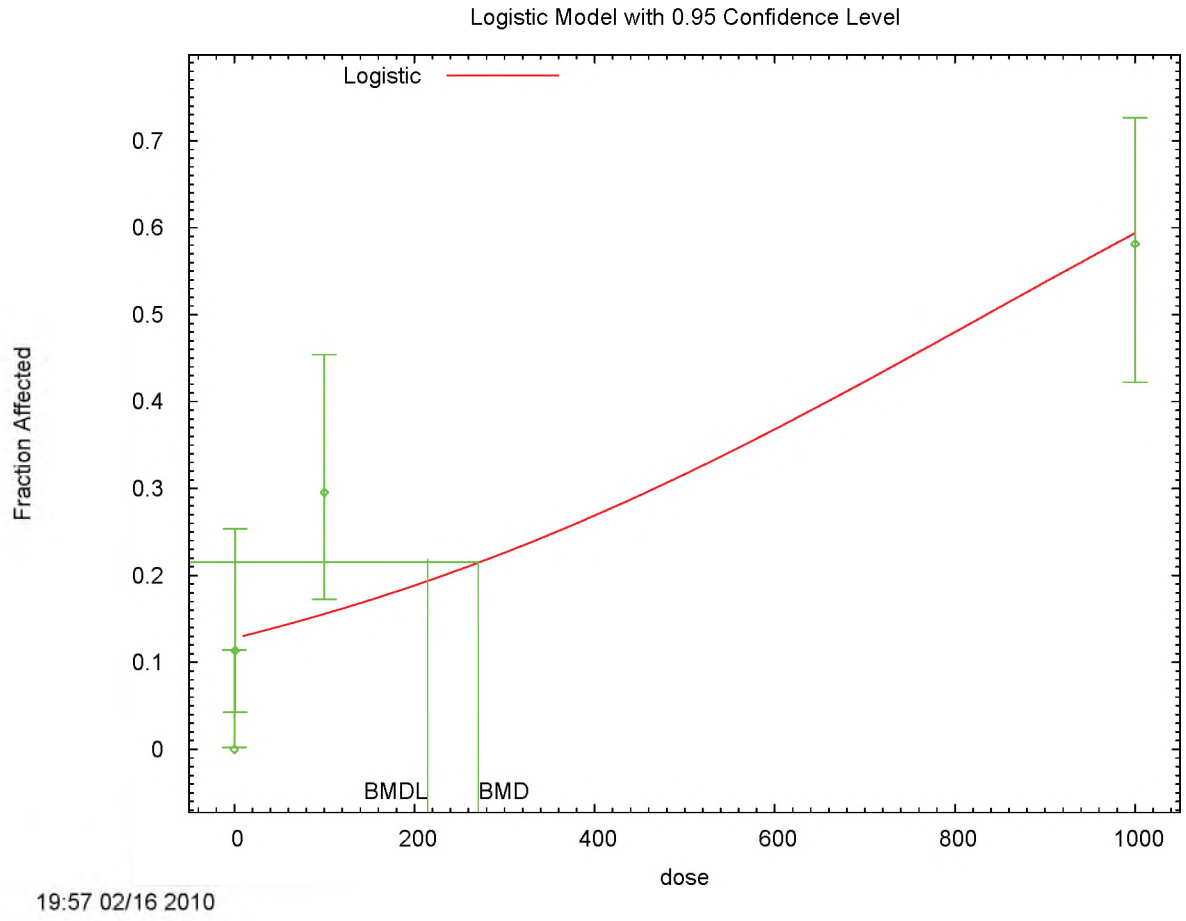
Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =        270.917
```

```
BMDL =          214.66
```

E.3.46.3. *Figure for Selected Model: Logistic*



E.3.46.4. *Output for Additional Model Presented: Log-Logistic, Unrestricted*

Toth et al., 1979: Skin Lesions

```
========================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\63_Toth_1979_SkinLes_LogLogistic_U_1.(d)
        Gnuplot Plotting File:  C:\1\63_Toth_1979_SkinLes_LogLogistic_U_1.plt
                                          Tue Feb 16 20:01:56 2010
========================================================================

Table 2
------------------------------------------------------------------------

  The form of the probability function is:

  P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


  Dependent variable = DichEff
```

```
  Independent variable = Dose
  Slope parameter is not restricted

  Total number of observations = 4
  Total number of records with missing values = 0
  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008



  User has chosen the log transformed model


                Default Initial Parameter Values
                   background =            0
                    intercept =     -2.14055
                        slope =     0.332409


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -background
                have been estimated at a boundary point, or have been specified by the user,
                and do not appear in the correlation matrix )

             intercept        slope

 intercept            1         -0.9

     slope         -0.9            1



                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background                0               *                 *                   *
      intercept         -2.24241               *                 *                   *
          slope         0.350932               *                 *                   *

* - Indicates that this value is not calculated.


                         Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -71.5177         4
   Fitted model         -71.9844         2       0.93345      2          0.6271
  Reduced model         -95.8498         1       48.6642      3         <.0001

           AIC:          147.969


                                Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
    0.0000     0.0000          0.000     0.000          38         0.000
    1.0000     0.0960          4.224     5.000          44         0.397
  100.0000     0.3483         15.327    13.000          44        -0.736
 1000.0000     0.5453         23.448    25.000          43         0.475

 Chi^2 = 0.93      d.f. = 2        P-value = 0.6295


   Benchmark Dose Computation
```

```
Specified effect =          0.1

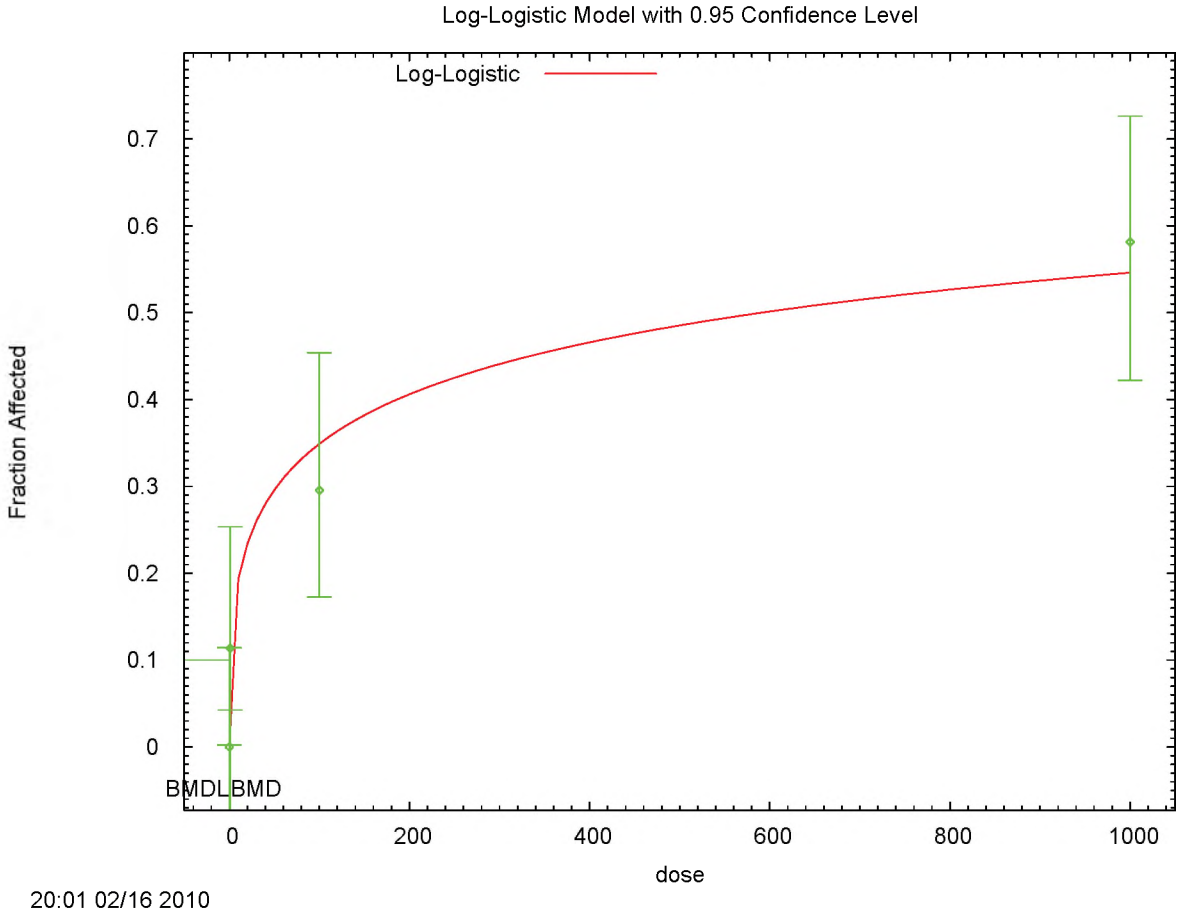
Risk Type        =      Extra risk

Confidence level =         0.95

             BMD =       1.1374

            BMDL =    0.0547689
```

E.3.46.5. *Figure for Additional Model Presented: Log-Logistic, Unrestricted*



E.3.47. Van Birgelen et al., 1995a: Hepatic Retinol

E.3.47.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2)	4	<0.0001	164.340	2.912E+02	error	
exponential (M3)	4	<0.0001	164.340	2.912E+02	error	power hit bound (d = 1)
exponential (M4) [b]	**3**	**<0.0001**	**148.052**	**1.151E+02**	**7.098E+01**	
exponential (M5)	3	<0.0001	148.052	1.151E+02	7.098E+01	power hit bound (d = 1)
Hill	3	0.044	128.757	1.314E+01	error	n lower bound hit (n = 1)
linear	4	<0.0001	178.734	7.815E+02	5.997E+02	
polynomial, 5-degree	0	N/A	283.606	2.481E+03	error	
power	4	<0.0001	178.734	7.815E+02	5.997E+02	power bound hit (power = 1)
Hill, unrestricted	2	0.269	125.273	5.561E+00	error	unrestricted (n = 0.571)
power, unrestricted [c]	3	0.025	129.990	4.205E-01	8.504E-03	unrestricted (power = 0.118)

[a] Non-constant variance model selected (p = <0.0001)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.3.47.2. *Output for Selected Model: Exponential (M4)*

Van Birgelen et al., 1995a: Hepatic Retinol

```
 ================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\1\65_VanB_1995a_HepRet_Exp_1.(d)
         Gnuplot Plotting File:
                                                Tue Feb 16 20:03:05 2010
 ================================================================

 Tbl3, hepatic retinol
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
```

```
      sign = -1 for decreasing trend.

   Model 2 is nested within Models 3 and 4.
   Model 3 is nested within Model 5.
   Model 4 is nested within Model 5.


Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


              Initial Parameter Values

              Variable          Model 4
              --------          --------
                lnalpha            -1.16065
                    rho             1.53688
                      a              15.645
                      b           0.00625117
                      c            0.0365247
                      d                    1



                Parameter Estimates

               Variable          Model 4
               --------          -------
                lnalpha           -0.882225
                    rho             1.82707
                      a             10.5294
                      b           0.00720346
                      c            0.0688661
                      d                    1


        Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
     0      8         14.9         8.768
    14      8          8.4         3.394
    26      8          8.2         2.263
    47      8          5.1        0.8485
   320      8          2.2        0.8485
  1024      8          0.6        0.5657


              Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
  ------    ----------    ---------    ----------------
      0         10.53        5.526            2.237
     14         9.589        5.073          -0.6628
     26         8.855        4.717          -0.3926
     47         7.714        4.159           -1.778
    320         1.703        1.046            1.343
   1024        0.7313       0.4833          -0.7681
```

Other models for which likelihoods are calculated:

```
  Model A1:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
              Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-87.1567	7	188.3134
A2	-47.28742	12	118.5748
A3	-55.32422	8	126.6484
R	-109.967	2	223.934
4	-69.02619	5	148.0524

Additive constant for all log-likelihoods = -44.11. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	125.4	10	< 0.0001
Test 2	79.74	5	< 0.0001
Test 3	16.07	4	0.002922
Test 6a	27.4	3	< 0.0001

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

The p-value for Test 3 is less than .1. You may want to consider a different variance model.

The p-value for Test 6a is less than .1. Model 4 may not adequately describe the data; you may want to consider another model.

Benchmark Dose Computations:

Specified Effect = 1.000000

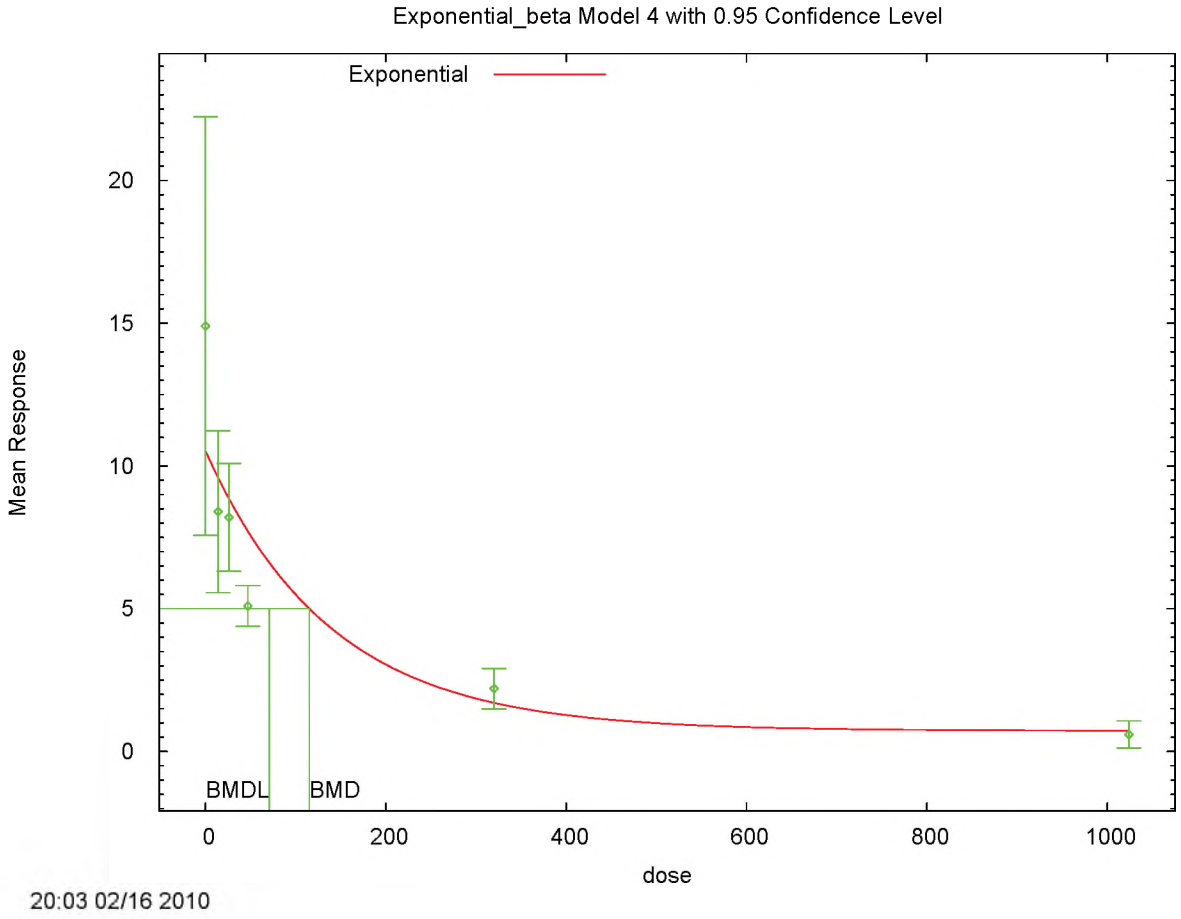
```
            Risk Type = Estimated standard deviations from control

      Confidence Level = 0.950000

                   BMD =      115.128

                  BMDL =       70.981
```

E.3.47.3. *Figure for Selected Model: Exponential (M4)*



E.3.47.4. *Output for Additional Model Presented: Power, Unrestricted*

Van Birgelen et al., 1995a: Hepatic Retinol

```
  ================================================================
          Power Model. (Version: 2.15;  Date: 04/07/2008)
          Input Data File: C:\1\65_VanB_1995a_HepRet_Pwr_U_1.(d)
          Gnuplot Plotting File:  C:\1\65_VanB_1995a_HepRet_Pwr_U_1.plt
                                                Tue Feb 16 20:03:11 2010
  ================================================================

  Tbl3, hepatic retinol
 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

    The form of the response function is:
```

```
Y[dose] = control + slope * dose^power


Dependent variable = Mean
Independent variable = Dose
The power is not restricted
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                Default Initial Parameter Values
                       lalpha =      2.76506
                          rho =            0
                      control =         14.9
                        slope =     -3.78637
                        power =     0.191713


          Asymptotic Correlation Matrix of Parameter Estimates

                lalpha          rho      control        slope        power

    lalpha           1         -0.8       -0.047        0.042        0.065

       rho        -0.8            1       -0.085      -0.0029        -0.11

   control      -0.047       -0.085            1        -0.95        -0.81

     slope       0.042      -0.0029        -0.95            1         0.96

     power       0.065        -0.11        -0.81         0.96            1


                                Parameter Estimates

                                                    95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha         -1.02622         0.389164            -1.78897           -0.263475
            rho          1.68421         0.199212             1.29376             2.07466
        control          16.9577          2.21133             12.6235             21.2918
          slope         -7.19097          1.99708            -11.1052            -3.27676
          power         0.117935        0.0225396           0.0737578            0.162111


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0       8       14.9           17         8.77         6.49         -0.896
   14       8        8.4         7.14         3.39         3.13           1.14
   26       8        8.2          6.4         2.26         2.86           1.78
   47       8        5.1         5.63        0.849         2.57         -0.588
  320       8        2.2         2.76        0.849         1.41          -1.12
 1024       8        0.6        0.672        0.566        0.428         -0.475


 Model Descriptions for likelihoods calculated
```

```
Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
              A1          -87.156698           7     188.313395
              A2          -47.287416          12     118.574833
              A3          -55.324218           8     126.648436
          fitted          -59.994980           5     129.989960
               R         -109.967018           2     223.934036


                    Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value

  Test 1              125.359         10          <.0001
  Test 2              79.7386          5          <.0001
  Test 3              16.0736          4        0.002922
  Test 4              9.34152          3         0.02508

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

The p-value for Test 4 is less than .1.  You may want to try a different
model


               Benchmark Dose Computation

Specified effect =             1

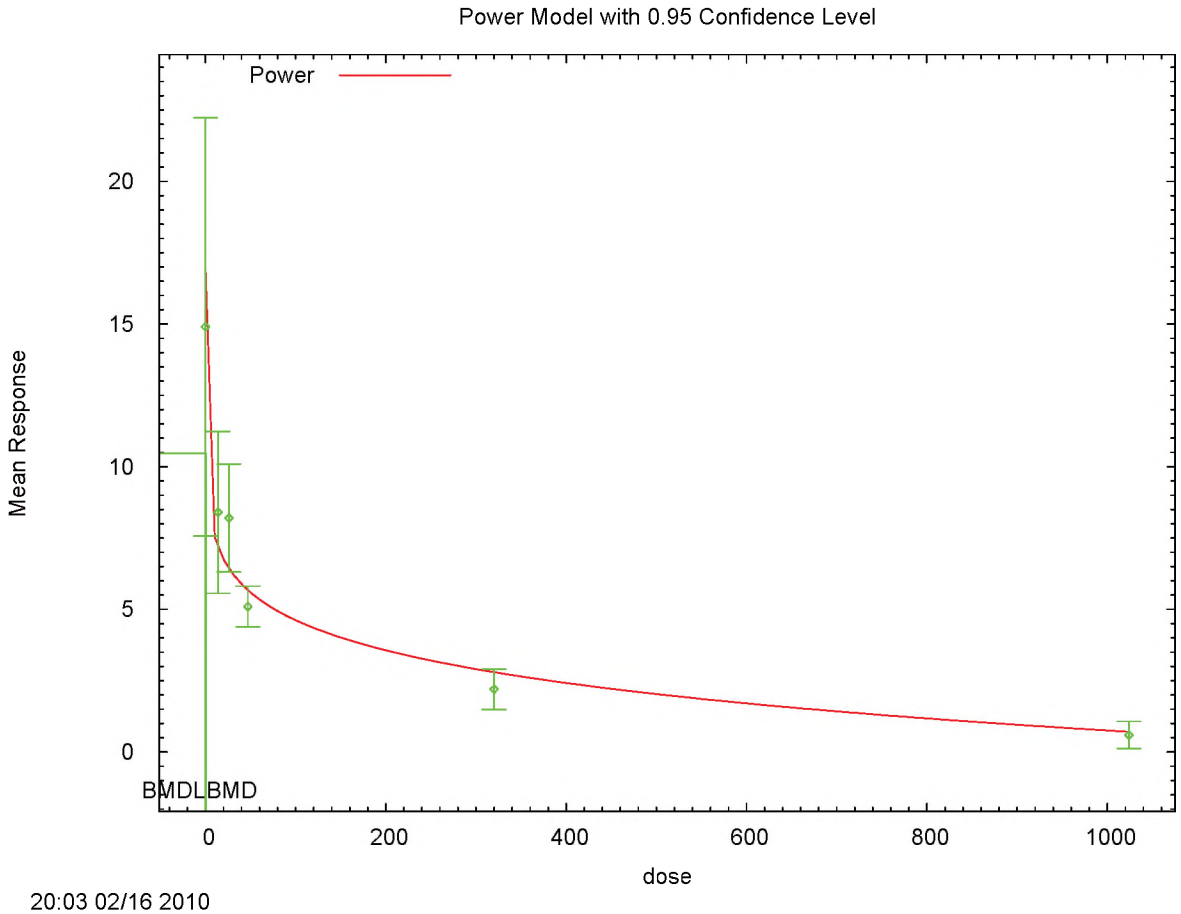
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 0.420475


            BMDL = 0.00850422
```

E.3.47.5. *Figure for Additional Model Presented: Power, Unrestricted*



E.3.48. Van Birgelen et al., 1995a: Hepatic Retinol Palmitate

E.3.48.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2)	4	<0.0001	467.446	error	error	
exponential (M3)	4	<0.0001	467.446	error	error	power hit bound (d = 1)
exponential (M4)	3	<0.0001	454.087	error	error	
exponential (M5)	3	<0.0001	454.087	error	error	power hit bound (d = 1)
Hill	3	<0.0001	563.579	error	error	
linear [b]	**4**	**<0.0001**	**488.446**	**1.420E+03**	**9.889E+02**	
polynomial, 5-degree	0	N/A	573.977	error	error	
power	4	<0.0001	488.446	1.420E+03	9.889E+02	power bound hit (power = 1)
Hill, unrestricted	3	<0.0001	522.322	2.418E-12	2.418E-12	unrestricted (n = 0.452)
power, unrestricted [c]	3	0.348	408.062	3.765E-02	1.208E-05	unrestricted (power = 0.054)

[a] Non-constant variance model selected (p = <0.0001)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.3.48.2. *Output for Selected Model: Linear*

Van Birgelen et al., 1995a: Hepatic Retinol Palmitate

```
 ================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\1\66_VanB_1995a_HepRetPalm_Linear_1.(d)
         Gnuplot Plotting File:  C:\1\66_VanB_1995a_HepRetPalm_Linear_1.plt
                                              Tue Feb 16 20:03:46 2010
 ================================================================

 Tbl3, hepatic retinol palmitate
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   Signs of the polynomial coefficients are not restricted
```

The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	9.57332
rho =	0
beta_0 =	177.506
beta_1 =	-0.204775

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	beta_0	beta_1
lalpha	1	-0.95	-0.017	0.022
rho	-0.95	1	0.00019	-0.0048
beta_0	-0.017	0.00019	1	-1
beta_1	0.022	-0.0048	-1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-0.723216	0.638291	-1.97424	0.527811
rho	2.26615	0.140196	1.99137	2.54093
beta_0	150.535	31.5457	88.7064	212.363
beta_1	-0.143931	0.0308317	-0.20436	-0.0835018

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	472	151	272	204	4.45
14	8	94	149	67.9	201	-0.766
26	8	107	147	76.4	199	-0.567
47	8	74	144	39.6	194	-1.02
320	8	22	104	22.6	135	-1.73
1024	8	3	3.15	2.83	2.56	-0.166

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that
were specified by the user

```
Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1         -250.554817           7     515.109634
             A2         -196.755746          12     417.511491
             A3         -197.383174           8     410.766347
          fitted        -240.223107           4     488.446215
              R         -276.789644           2     557.579287


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              160.068         10          <.0001
   Test 2              107.598          5          <.0001
   Test 3              1.25486          4           0.869
   Test 4              85.6799          4          <.0001

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1.  You may want to try a different
model


              Benchmark Dose Computation

Specified effect =             1

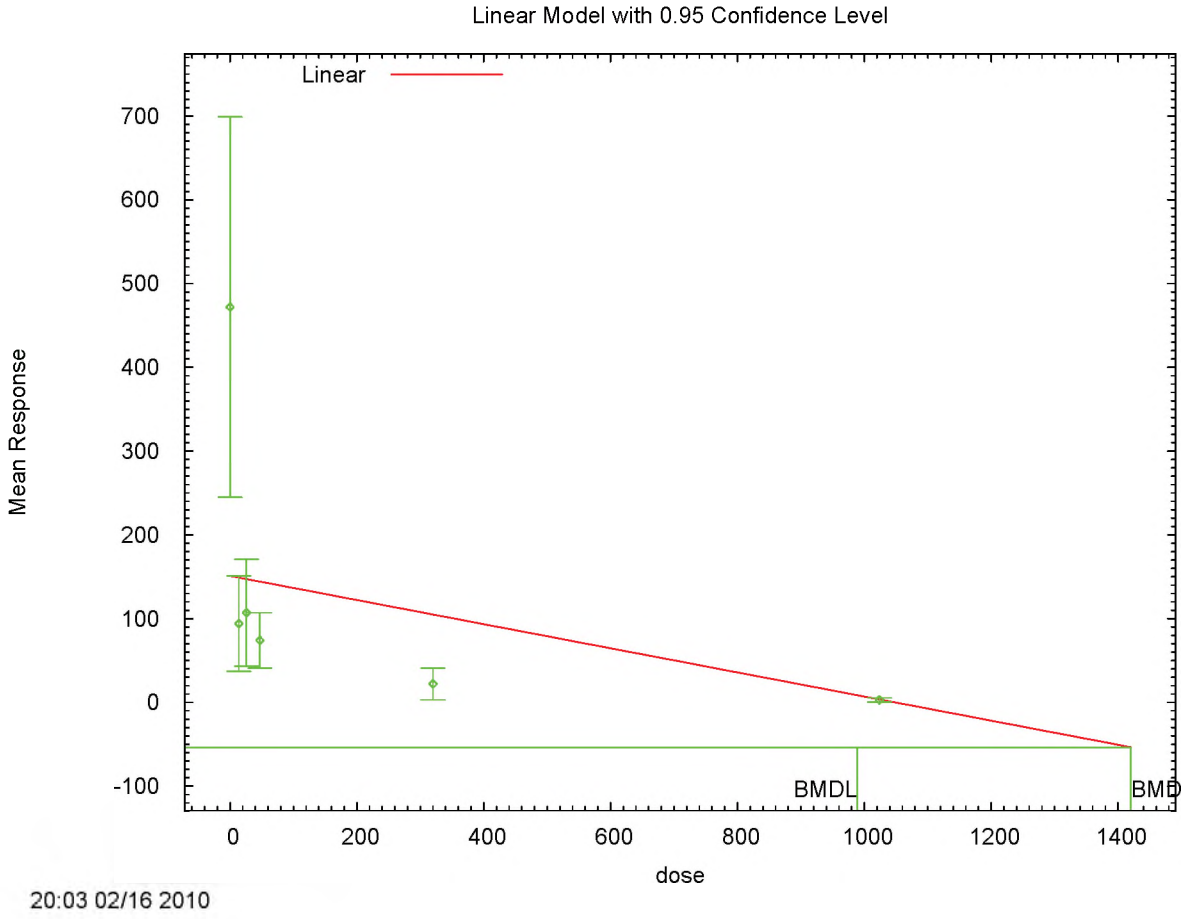
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

              BMD =        1419.81


             BMDL =        988.945
```

E.3.48.3. *Figure for Selected Model: Linear*



E.3.48.4. *Output for Additional Model Presented: Power, Unrestricted*

Van Birgelen et al., 1995a: Hepatic Retinol Palmitate

```
 ======================================================================
          Power Model. (Version: 2.15;  Date: 04/07/2008)
          Input Data File: C:\1\66_VanB_1995a_HepRetPalm_Pwr_U_1.(d)
          Gnuplot Plotting File:  C:\1\66_VanB_1995a_HepRetPalm_Pwr_U_1.plt
                                                Tue Feb 16 20:03:50 2010
 ======================================================================

 Tbl3, hepatic retinol palmitate
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

    The form of the response function is:

    Y[dose] = control + slope * dose^power


    Dependent variable = Mean
    Independent variable = Dose
    The power is not restricted
    The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)
```

```
Total number of dose groups = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                         lalpha =      9.57332
                            rho =            0
                        control =          472
                          slope =     -315.054
                          power =    0.0586881


           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho      control        slope        power

  lalpha              1        -0.95         0.29        -0.31         -0.3

     rho          -0.95            1        -0.4         0.39         0.29

 control           0.29        -0.4            1        -0.98        -0.82

   slope          -0.31         0.39        -0.98            1         0.91

   power           -0.3         0.29        -0.82         0.91            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
        lalpha        0.0734958         0.849559           -1.59161              1.7386
           rho          1.80632         0.194602            1.42491             2.18774
       control          465.497           86.914            295.149             635.845
         slope          -318.06          82.4127           -479.586            -156.534
         power        0.0540573        0.0117709          0.0309869           0.0771278


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0       8        472          465          272          266          0.069
   14       8         94         98.7         67.9         65.6         -0.201
   26       8        107         86.2         76.4         58.1           1.01
   47       8         74         73.8         39.6         50.5         0.0086
  320       8         22         31.1         22.6         23.1          -1.11
 1024       8          3         2.86         2.83         2.68          0.145


Model Descriptions for likelihoods calculated


Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
```

were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-250.554817	7	515.109634
A2	-196.755746	12	417.511491
A3	-197.383174	8	410.766347
fitted	-199.031154	5	408.062307
R	-276.789644	2	557.579287

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	160.068	10	<.0001
Test 2	107.598	5	<.0001
Test 3	1.25486	4	0.869
Test 4	3.29596	3	0.3482

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears
to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems
to adequately describe the data

Benchmark Dose Computation

Specified effect = 1

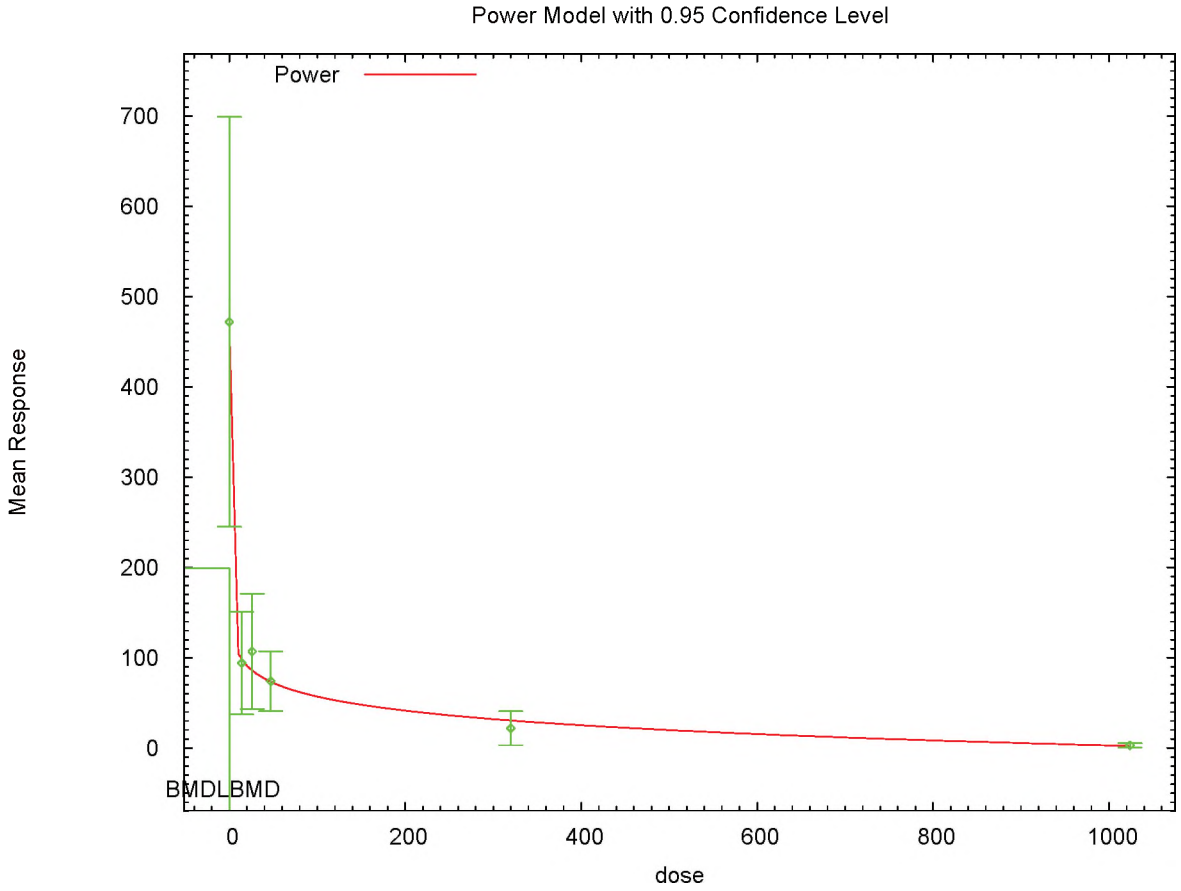
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 0.0376489

BMDL = 1.20769e-005

E.3.48.5. *Figure for Additional Model Presented: Power, Unrestricted*



E.3.49. White et al., 1986: CH50

E.3.49.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2)	5	0.001	391.472	4.480E+02	2.844E+02	
exponential (M3)	5	0.001	391.472	4.480E+02	2.844E+02	power hit bound (d = 1)
exponential (M4)	4	0.001	392.128	3.126E+02	1.140E+02	
exponential (M5)	4	0.001	392.128	3.126E+02	1.140E+02	power hit bound (d = 1)
Hill [b]	**4**	**0.001**	**391.223**	**2.042E+02**	**3.585E+01**	**n lower bound hit (n = 1)**
linear	5	<0.0001	396.430	8.065E+02	5.899E+02	
polynomial, 6-degree	3	<0.0001	643.059	9.600E+02	error	
power	5	<0.0001	396.430	8.065E+02	5.899E+02	power bound hit (power = 1)
Hill, unrestricted [c]	3	0.058	381.943	9.677E-01	1.900E-01	unrestricted (n = 0.211)
power, unrestricted	4	0.131	379.574	7.186E-01	1.157E-02	unrestricted (power = 0.188)

[a] Non-constant variance model selected ($p = 0.0871$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.3.49.2. *Output for Selected Model: Hill*

White et al., 1986: CH50

```
 ================================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\1\71_White_1986_CH50_Hill_1.(d)
         Gnuplot Plotting File:  C:\1\71_White_1986_CH50_Hill_1.plt
                                                 Tue Feb 16 20:06:45 2010
 ================================================================================

 [insert study notes]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   Power parameter restricted to be greater than 1
```

The variance is to be modeled as Var(i) = exp(lalpha + rho * ln(mean(i)))

Total number of dose groups = 7
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	5.60999
rho =	0
intercept =	91
v =	-74
n =	0.0969998
k =	10

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -n
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	lalpha	rho	intercept	v	k
lalpha	1	-0.99	0.19	0.13	-0.22
rho	-0.99	1	-0.2	-0.14	0.23
intercept	0.19	-0.2	1	0.33	-0.7
v	0.13	-0.14	0.33	1	-0.86
k	-0.22	0.23	-0.7	-0.86	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	4.34761	1.59601	1.21948	7.47574
rho	0.381496	0.413764	-0.429467	1.19246
intercept	71.6585	5.38454	61.105	82.212
v	-62.7464	14.9646	-92.0765	-33.4163
n	1	NA		
k	441.016	460.151	-460.864	1342.9

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	91	71.7	14.1	19.9	2.75
10	8	54	70.3	8.49	19.8	-2.33
50	8	63	65.3	11.3	19.5	-0.329
100	8	56	60.1	25.5	19.2	-0.598
500	8	41	38.3	17	17.6	0.43
1000	8	32	28.1	17	16.6	0.661
2000	8	17	20.2	17	15.6	-0.589

```
Model Descriptions for likelihoods calculated


Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
              A1         -181.340979           8     378.681959
              A2         -175.820265          14     379.640529
              A3         -181.238690           9     380.477380
          fitted         -190.611743           5     391.223485
               R         -212.367055           2     428.734109


                    Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value

  Test 1              73.0936         12          <.0001
  Test 2              11.0414          6          0.0871
  Test 3              10.8369          5         0.05471
  Test 4              18.7461          4       0.0008815

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

The p-value for Test 4 is less than .1.  You may want to try a different
model


        Benchmark Dose Computation

Specified effect =             1

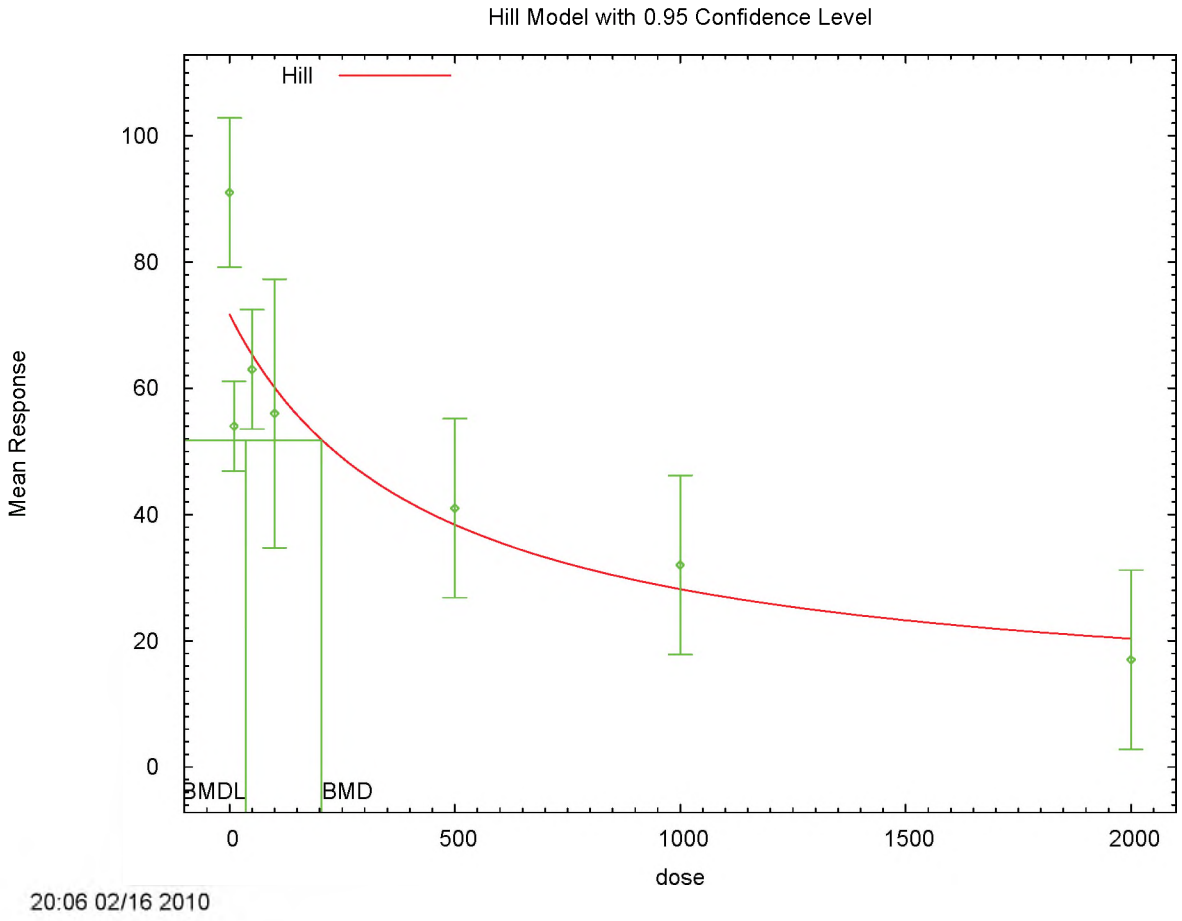
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =       204.214
```

```
BMDL =        35.8504
```

E.3.49.3. *Figure for Selected Model: Hill*



E.3.49.4. *Output for Additional Model Presented: Hill, Unrestricted*

White et al., 1986: CH50

```
=============================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\71_White_1986_CH50_Hill_U_1.(d)
        Gnuplot Plotting File:  C:\1\71_White_1986_CH50_Hill_U_1.plt
                                                Tue Feb 16 20:06:46 2010
=============================================================================

[insert study notes]

  The form of the response function is:

  Y[dose] = intercept + v*dose^n/(k^n + dose^n)


  Dependent variable = Mean
```

```
Independent variable = Dose
Power parameter is not restricted
The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

Total number of dose groups = 7
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                       lalpha =      5.60999
                          rho =            0
                    intercept =           91
                            v =          -74
                            n =    0.0969998
                            k =           10


           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho    intercept            v            n            k

    lalpha            1           -1         0.17         0.22        -0.42       -0.022

       rho           -1            1        -0.17        -0.22         0.42        0.019

 intercept         0.17        -0.17            1         0.16        -0.58       0.0069

         v         0.22        -0.22         0.16            1       -0.048        -0.91

         n        -0.42         0.42        -0.58       -0.048            1        -0.35

         k       -0.022        0.019       0.0069        -0.91        -0.35            1


                                 Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha          6.62767          2.14235           2.42875             10.8266
            rho        -0.266376         0.555274          -1.35469            0.821941
      intercept           89.579          5.61106           78.5815             100.576
              v         -458.615          402.837          -1248.16              330.93
              n         0.210614        0.0503369          0.111956            0.309273
              k     9.00638e+006     4.61231e+007      -8.13933e+007       9.94061e+007


    Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0      8         91         89.6         14.1         15.1          0.266
   10      8         54         65.4         8.49         15.8          -2.04
   50      8         63         56.3         11.3         16.1           1.18
  100      8         56         51.5         25.5         16.3          0.777
  500      8         41         37.9           17         16.9          0.516
 1000      8         32         30.8           17         17.4          0.191
 2000      8         17         22.9           17         18.1         -0.927


Model Descriptions for likelihoods calculated
```

```
Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
              A1         -181.340979           8     378.681959
              A2         -175.820265          14     379.640529
              A3         -181.238690           9     380.477380
          fitted         -184.971691           6     381.943382
               R         -212.367055           2     428.734109


                    Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value

  Test 1              73.0936         12          <.0001
  Test 2              11.0414          6          0.0871
  Test 3              10.8369          5         0.05471
  Test 4                7.466          3         0.05844

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

The p-value for Test 4 is less than .1.  You may want to try a different
model


        Benchmark Dose Computation

Specified effect =             1

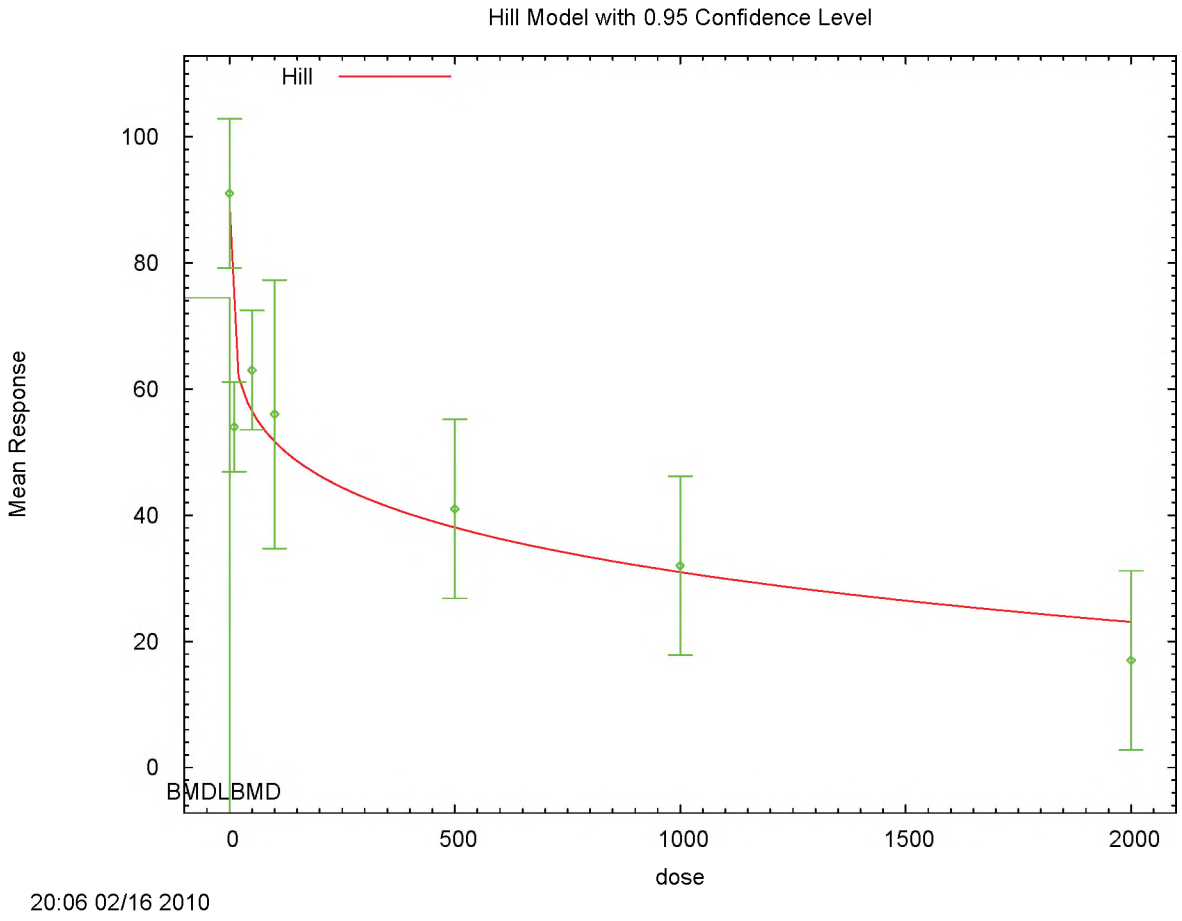
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =       0.967689

            BMDL =      0.189992
```

E.3.49.5. *Figure for Additional Model Presented: Hill, Unrestricted*



E.4. REFERENCES

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APPENDIX F

Cancer Benchmark Dose Modeling

NOTICE

THIS DOCUMENT IS AN EXTERNAL REVIEW DRAFT. It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH

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APPENDIX F. CANCER BENCHMARK DOSE MODELING

F.1. BLOOD BMDS RESULTS

F.1.1. Kociba et al., 1978: Stratified squamous cell carcinoma of hard palate or nasal turbinates

F.1.1.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**3**	**0.815**	**31.564**	**5.763E+00**	**2.795E+00**	
Multistage Cancer, 2-Degree	3	0.985	30.170	1.369E+01	3.416E+00	
Multistage Cancer, 3-Degree	3	0.999	29.930	1.917E+01	3.578E+00	

[a] Best-fitting model, BMDS output presented in this appendix

F.1.1.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

Kociba et al., 1978: Stratified squamous cell carcinoma of hard palate or nasal turbinates

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\4\Blood\1_msc1_1Perc_palate_nasal.(d)
         Gnuplot Plotting File:  C:\4\Blood\1_msc1_1Perc_palate_nasal.plt
                                              Thu Apr 01 15:56:03 2010
 ======================================================================

 Source - Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008
```

```
                  Default Initial Parameter Values
                     Background =           0
                        Beta(1) =   0.00226154


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)

   Beta(1)            1



                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background                0            *               *                   *
        Beta(1)        0.0017438            *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -13.9385         4
   Fitted model        -14.7819         1       1.68696      3          0.6398
  Reduced model        -20.2589         1       12.6409      3        0.005481

           AIC:         31.5639


                                Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000          85        0.000
    1.5617     0.0027         0.136     0.000          50       -0.369
    7.1600     0.0124         0.620     0.000          50       -0.793
   38.7212     0.0653         3.265     4.000          50        0.421

 Chi^2 = 0.94      d.f. = 3        P-value = 0.8153


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        5.76347

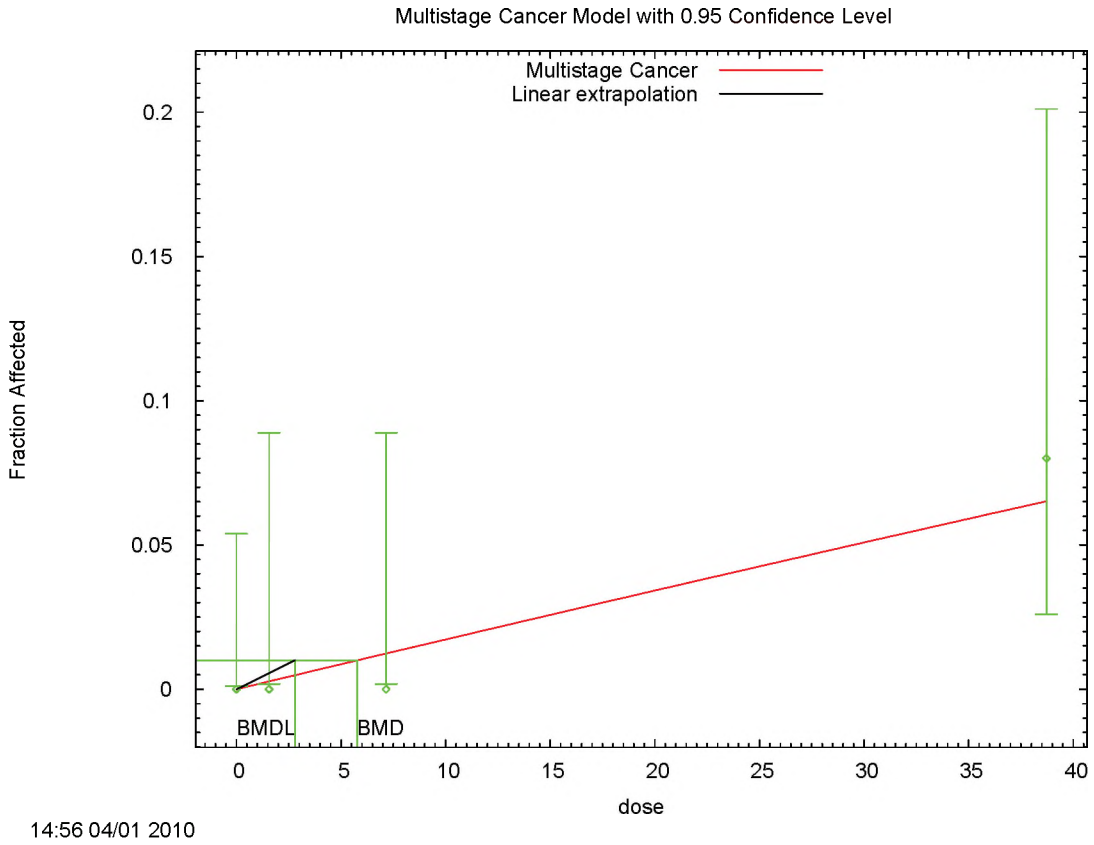
            BMDL =        2.79485

            BMDU =        14.9396

Taken together, (2.79485, 14.9396) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =      0.003578
```

F.1.1.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



Kociba et al., 1978: Stratified squamous cell carcinoma of hard palate or nasal turbinates

F.1.2. Kociba et al., 1978: Stratified squamous cell carcinoma of tongue

F.1.2.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**2**	**0.472**	**47.933**	**6.091E+00**	**2.600E+00**	
Multistage Cancer, 2-Degree	2	0.472	47.933	6.091E+00	2.600E+00	final ß=0
Multistage Cancer, 3-Degree	2	0.472	47.933	6.091E+00	2.600E+00	final ß=0

[a] Best-fitting model, BMDS output presented in this appendix

F.1.2.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

Kociba et al., 1978: Stratified squamous cell carcinoma of tongue

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\4\Blood\2_msc1_1Perc_tongue.(d)
         Gnuplot Plotting File:  C:\4\Blood\2_msc1_1Perc_tongue.plt
                                                Thu Apr 01 15:56:35 2010
 ======================================================================

 Source - Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =    0.0092514
                        Beta(1) =   0.00137224
```

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.58
Beta(1)	-0.58	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.00510501	*	*	*
Beta(1)	0.00165011	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-21.1523	4			
Fitted model	-21.9667	2	1.62881	2	0.4429
Reduced model	-24.1972	1	6.08976	3	0.1073

AIC: 47.9334

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0051	0.434	0.000	85	-0.660
1.5617	0.0077	0.383	1.000	50	1.000
7.1600	0.0168	0.840	1.000	50	0.177
38.7212	0.0667	3.334	3.000	50	-0.189

Chi^2 = 1.50 d.f. = 2 P-value = 0.4716

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 6.0907

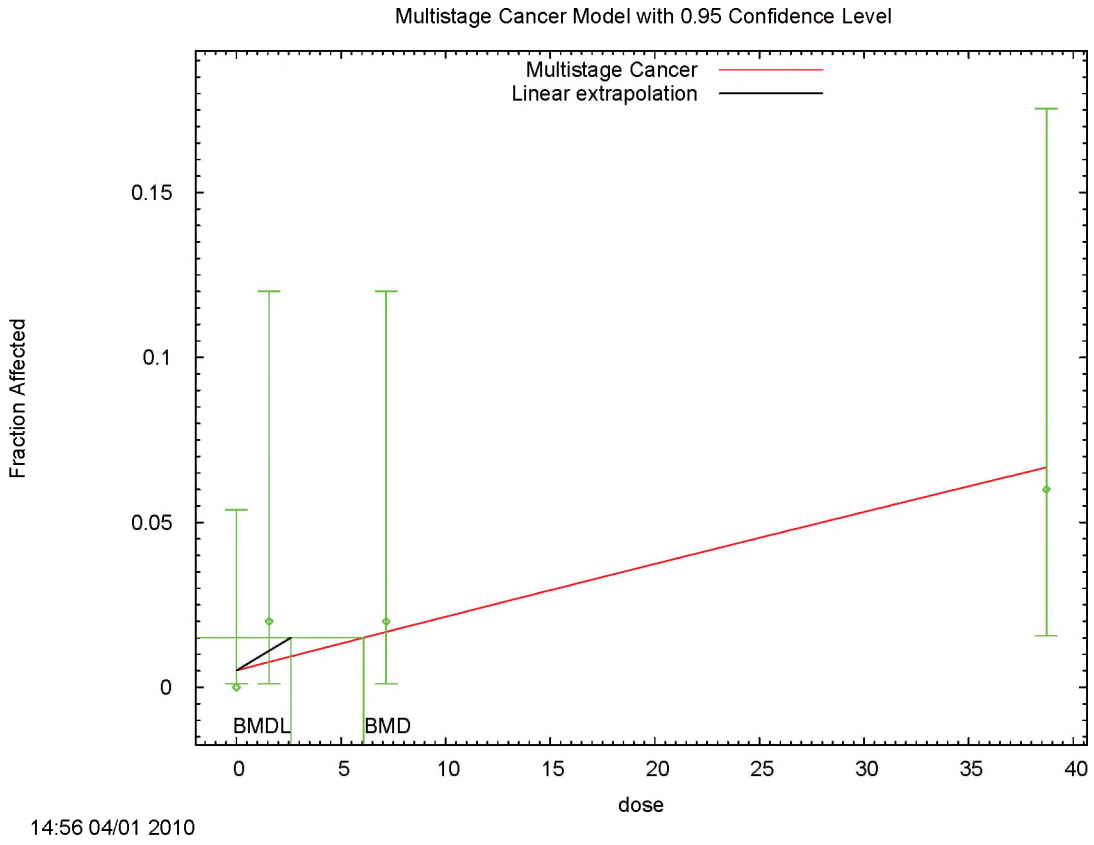
BMDL = 2.60049

BMDU = 519124

Taken together, (2.60049, 519124) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00384542

F.1.2.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



Kociba et al., 1978: Stratified squamous cell carcinoma of tongue

F.1.3. Kociba et al., 1978: Adenoma of adrenal cortex

F.1.3.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**3**	**0.779**	**52.488**	**3.254E+00**	**1.852E+00**	
Multistage Cancer, 2-Degree	3	0.779	52.488	3.254E+00	1.852E+00	final ß=0
Multistage Cancer, 3-Degree	3	0.779	52.488	3.254E+00	1.852E+00	final ß=0

[a] Best-fitting model, BMDS output presented in this appendix

F.1.3.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

Kociba et al., 1978: Adenoma of adrenal cortex

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\4\Blood\3_msc1_1Perc_adre_adenoma.(d)
         Gnuplot Plotting File:  C:\4\Blood\3_msc1_1Perc_adre_adenoma.plt
                                                Thu Apr 01 15:57:07 2010
 ================================================================

 Source - Table 5
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =   0.00493756
                        Beta(1) =    0.0026639
```

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Beta(1)
Beta(1)	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0.00308883	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-24.6514	4			
Fitted model	-25.2438	1	1.18487	3	0.7566
Reduced model	-31.4904	1	13.6781	3	0.003378

AIC: 52.4876

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	85	0.000
1.5617	0.0048	0.241	0.000	50	-0.492
7.1600	0.0219	1.094	2.000	50	0.876
38.7212	0.1127	5.636	5.000	50	-0.285

Chi^2 = 1.09 d.f. = 3 P-value = 0.7793

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 3.25376

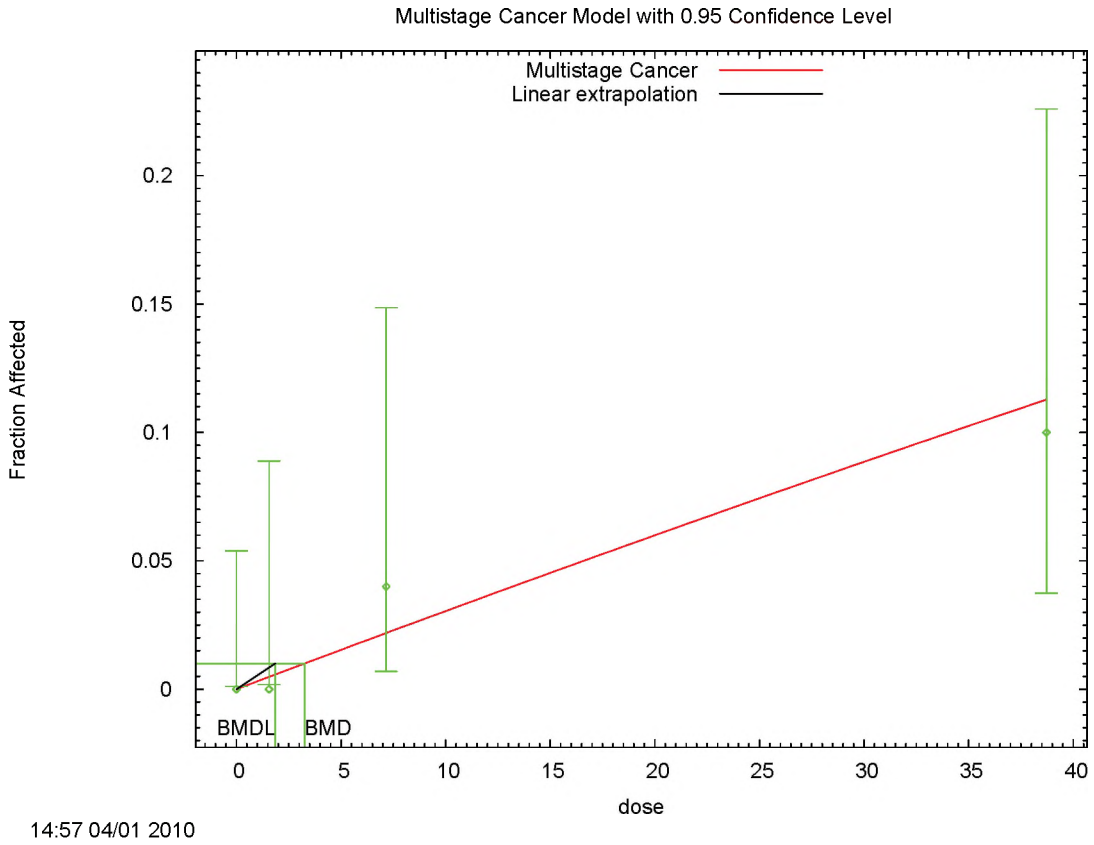
BMDL = 1.85162

BMDU = 6.58595

Taken together, (1.85162, 6.58595) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00540067

F.1.3.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



Kociba et al., 1978: Adenoma of adrenal cortex

F.1.4. Kociba et al., 1978: Hepatocellular adenoma(s) or carcinoma(s)

F.1.4.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**2**	**0.245**	**143.261**	**7.010E-01**	**5.013E-01**	
Multistage Cancer, 2-Degree	2	0.245	143.261	7.010E-01	5.013E-01	final ß=0
Multistage Cancer, 3-Degree	2	0.245	143.261	7.010E-01	5.013E-01	final ß=0

[a] Best-fitting model, BMDS output presented in this appendix

F.1.4.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

Kociba et al., 1978: Hepatocellular adenoma(s) or carcinoma(s)

```
=================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File: C:\4\Blood\4_msc1_1Perc_liver_ad_carc.(d)
        Gnuplot Plotting File:  C:\4\Blood\4_msc1_1Perc_liver_ad_carc.plt
                                          Thu Apr 01 15:57:41 2010
=================================================================

Source - Table 1 in Goodman and Sauer 1992
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the probability function is:

  P[response] = background + (1-background)*[1-EXP(
               -beta1*dose^1)]

  The parameter betas are restricted to be positive


  Dependent variable = Mean
  Independent variable = Dose

Total number of observations = 4
Total number of records with missing values = 0
Total number of parameters in model = 2
Total number of specified parameters = 0
Degree of polynomial = 1


Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                 Default Initial Parameter Values
                    Background =    0.0400263
                       Beta(1) =    0.0124752
```

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.51
Beta(1)	-0.51	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0221468	*	*	*
Beta(1)	0.0143372	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-68.2561	4			
Fitted model	-69.6304	2	2.74857	2	0.253
Reduced model	-89.1983	1	41.8843	3	<.0001

AIC: 143.261

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0221	1.905	2.000	86	0.070
1.5473	0.0436	2.180	1.000	50	-0.817
7.1546	0.1175	5.874	9.000	50	1.373
38.5608	0.4374	19.685	18.000	45	-0.506

Chi^2 = 2.81 d.f. = 2 P-value = 0.2449

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.700996

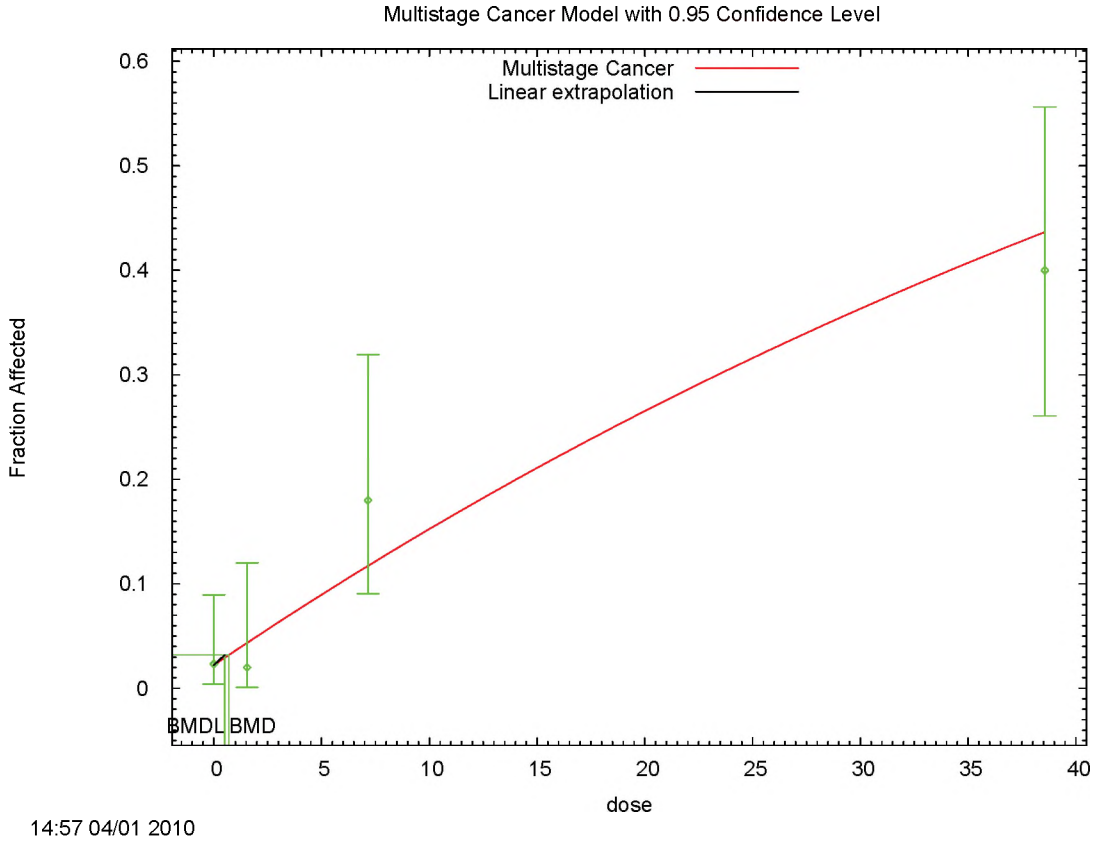
BMDL = 0.501345

BMDU = 1.04839

Taken together, (0.501345, 1.04839) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0199463

F.1.4.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



Kociba et al., 1978: Hepatocellular adenoma(s) or carcinoma(s)

F.1.5. Kociba et al., 1978: Stratified squamous cell carcinoma of hard palate or nasal turbinates

F.1.5.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**3**	**0.815**	**31.564**	**5.763E+00**	**2.795E+00**	
Multistage Cancer, 2-Degree	3	0.985	30.170	1.369E+01	3.416E+00	
Multistage Cancer, 3-Degree	3	0.999	29.930	1.917E+01	3.578E+00	

[a] Best-fitting model, BMDS output presented in this appendix

F.1.5.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

Kociba et al., 1978: Stratified squamous cell carcinoma of hard palate or nasal turbinates

```
=================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File: C:\4\Blood\5_msc1_1Perc_nasal.(d)
        Gnuplot Plotting File:  C:\4\Blood\5_msc1_1Perc_nasal.plt
                                          Thu Apr 01 15:58:14 2010
=================================================================

Source - Table 5
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  The form of the probability function is:

  P[response] = background + (1-background)*[1-EXP(
               -beta1*dose^1)]

  The parameter betas are restricted to be positive


  Dependent variable = Mean
  Independent variable = Dose

Total number of observations = 4
Total number of records with missing values = 0
Total number of parameters in model = 2
Total number of specified parameters = 0
Degree of polynomial = 1


Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                Default Initial Parameter Values
                   Background = 7.10818e-005
                      Beta(1) =   0.00222324
```

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Beta(1)
Beta(1)	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0.0022294	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-18.7562	4			
Fitted model	-18.9547	1	0.397012	3	0.9409
Reduced model	-24.1972	1	10.882	3	0.01238

AIC: 39.9093

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	86	0.000
1.5473	0.0034	0.172	0.000	50	-0.416
7.1546	0.0158	0.791	1.000	50	0.237
38.5608	0.0824	4.036	4.000	49	-0.019

Chi^2 = 0.23 d.f. = 3 P-value = 0.9728

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 4.50809

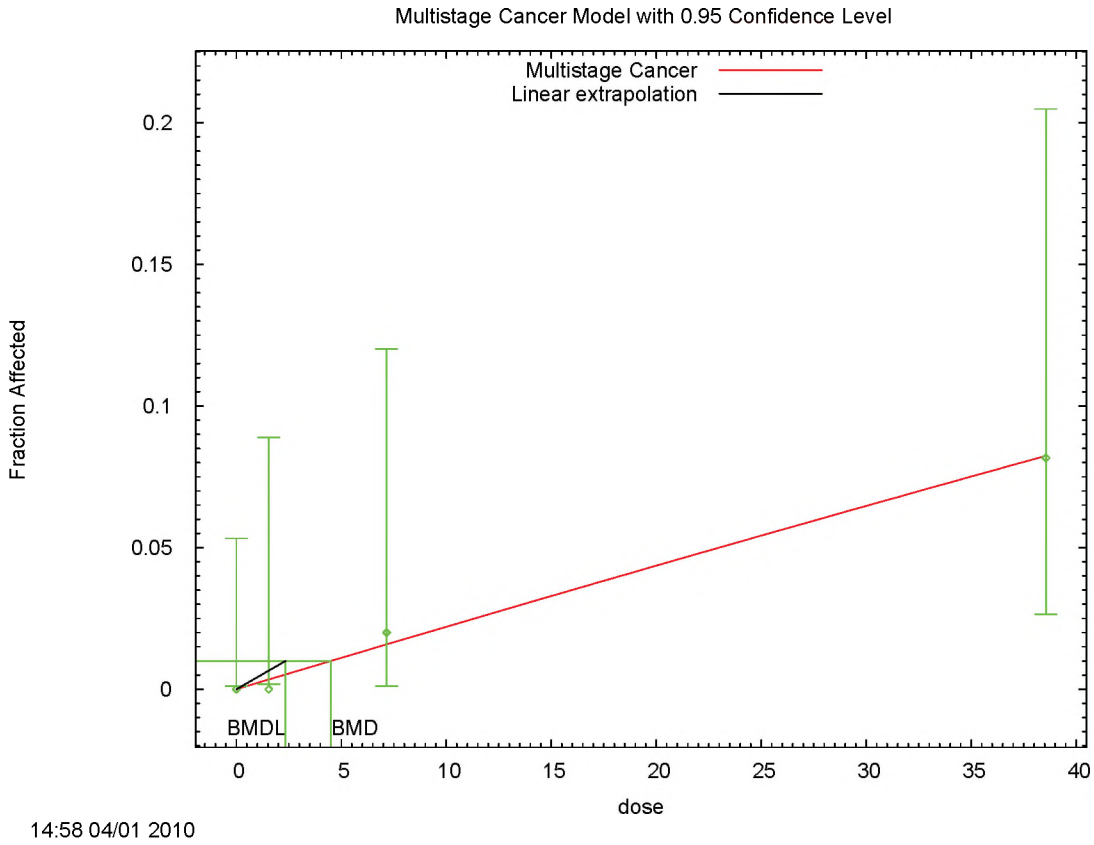
BMDL = 2.34012

BMDU = 10.4588

Taken together, (2.34012, 10.4588) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00427329

F.1.5.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



Kociba et al., 1978: Stratified squamous cell carcinoma of hard palate or nasal turbinates

F.1.6. Kociba et al., 1978: Keratinizing squamous cell carcinoma of lung

F.1.6.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**3**	**0.626**	**45.298**	**3.140E+00**	**1.786E+00**	
Multistage Cancer, 2-Degree	3	0.964	42.736	1.004E+01	2.707E+00	
Multistage Cancer, 3-Degree	3	0.997	42.291	1.556E+01	3.135E+00	

[a] Best-fitting model, BMDS output presented in this appendix

F.1.6.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

Kociba et al., 1978: Keratinizing squamous cell carcinoma of lung

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\4\Blood\6_msc1_1Perc_kera_carc.(d)
         Gnuplot Plotting File:  C:\4\Blood\6_msc1_1Perc_kera_carc.plt
                                                Thu Apr 01 15:58:49 2010
 ================================================================

 Source - Table 5
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =   0.00419802
```

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Beta(1)
Beta(1)	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0.00320098	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-20.0957	4			
Fitted model	-21.6489	1	3.10639	3	0.3755
Reduced model	-31.4904	1	22.7894	3	<.0001

AIC: 45.2978

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	86	0.000
1.5473	0.0049	0.247	0.000	50	-0.498
7.1546	0.0226	1.132	0.000	50	-1.076
38.5608	0.1161	5.690	7.000	49	0.584

Chi^2 = 1.75 d.f. = 3 P-value = 0.6263

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 3.13977

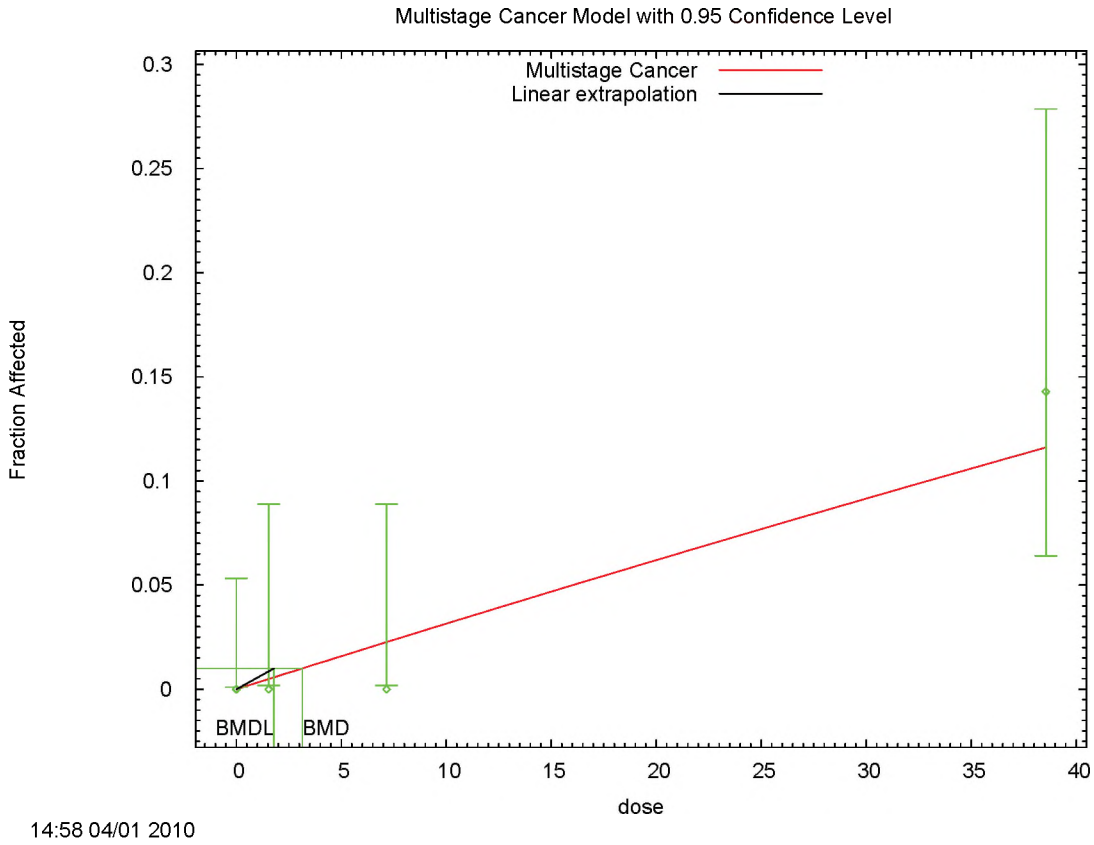
BMDL = 1.78648

BMDU = 6.28288

Taken together, (1.78648, 6.28288) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0055976

F.1.6.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



Kociba et al., 1978: Keratinizing squamous cell carcinoma of lung

F.1.7. National Toxicology Program, 1982: Subcutaneous Tissue: Fibrosarcoma

F.1.7.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree[a]	**2**	**0.179**	**75.385**	**3.127E+00**	**1.380E+00**	
Multistage Cancer, 2-Degree	2	0.179	75.385	3.127E+00	1.380E+00	final ß=0
Multistage Cancer, 3-Degree	2	0.179	75.385	3.127E+00	1.380E+00	final ß=0

[a] Best-fitting model, BMDS output presented in this appendix

F.1.7.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

National Toxicology Program, 1982: Subcutaneous Tissue: Fibrosarcoma

```
=================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File: C:\4\Blood\7_msc1_1Perc_sub_fibro.(d)
        Gnuplot Plotting File:  C:\4\Blood\7_msc1_1Perc_sub_fibro.plt
                                          Thu Apr 01 15:59:25 2010
=================================================================

Source - Table 10
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  The form of the probability function is:

  P[response] = background + (1-background)*[1-EXP(
               -beta1*dose^1)]

  The parameter betas are restricted to be positive


  Dependent variable = Mean
  Independent variable = Dose

Total number of observations = 4
Total number of records with missing values = 0
Total number of parameters in model = 2
Total number of specified parameters = 0
Degree of polynomial = 1


Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                 Default Initial Parameter Values
                    Background =    0.0268183
                       Beta(1) =   0.00211524
```

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.63
Beta(1)	-0.63	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0149841	*	*	*
Beta(1)	0.00321423	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-33.5998	4			
Fitted model	-35.6923	2	4.18508	2	0.1234
Reduced model	-37.7465	1	8.29346	3	0.04032

AIC: 75.3847

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0150	1.124	0.000	75	-1.068
1.9574	0.0212	1.058	2.000	50	0.926
5.6942	0.0328	1.642	3.000	50	1.077
29.7519	0.1048	5.136	4.000	49	-0.530

Chi^2 = 3.44 d.f. = 2 P-value = 0.1792

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 3.12683

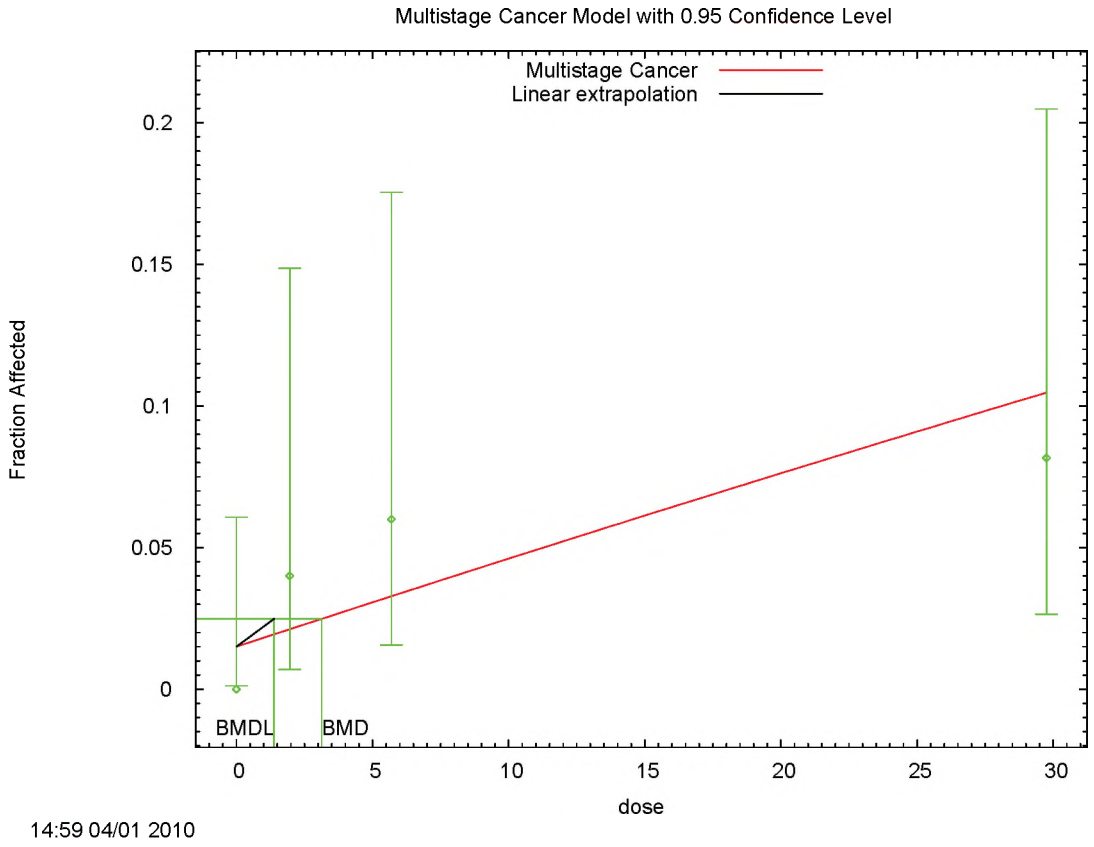
BMDL = 1.38047

BMDU = 2.18232e+006

Taken together, (1.38047, 2.18232e+006) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00724391

F.1.7.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



National Toxicology Program, 1982: Subcutaneous Tissue: Fibrosarcoma

F.1.8. National Toxicology Program, 1982: Liver: Neoplastic Nodule or Hepatocellular Carcinoma

F.1.8.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**2**	**0.218**	**135.190**	**1.169E+00**	**7.375E-01**	
Multistage Cancer, 2-Degree	2	0.491	133.447	5.578E+00	8.771E-01	
Multistage Cancer, 3-Degree	1	0.239	135.435	7.204E+00	8.786E-01	

[a] Best-fitting model, BMDS output presented in this appendix

F.1.8.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

National Toxicology Program, 1982: Liver: Neoplastic Nodule or Hepatocellular Carcinoma

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\4\Blood\8_msc1_1Perc_liver_nod.(d)
         Gnuplot Plotting File:  C:\4\Blood\8_msc1_1Perc_liver_nod.plt
                                                 Thu Apr 01 16:00:00 2010
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 Source - Table 10
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                    Background =    0.0261097
                       Beta(1) =    0.0102165
```

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.52
Beta(1)	-0.52	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0424738	*	*	*
Beta(1)	0.00859382	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-63.9149	4			
Fitted model	-65.5949	2	3.36005	2	0.1864
Reduced model	-74.0195	1	20.2092	3	0.0001536

AIC: 135.19

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0425	3.186	5.000	75	1.039
1.9574	0.0584	2.864	1.000	49	-1.135
5.6942	0.0882	4.410	3.000	50	-0.703
29.7519	0.2585	12.667	14.000	49	0.435

Chi^2 = 3.05 d.f. = 2 P-value = 0.2175

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 1.16948

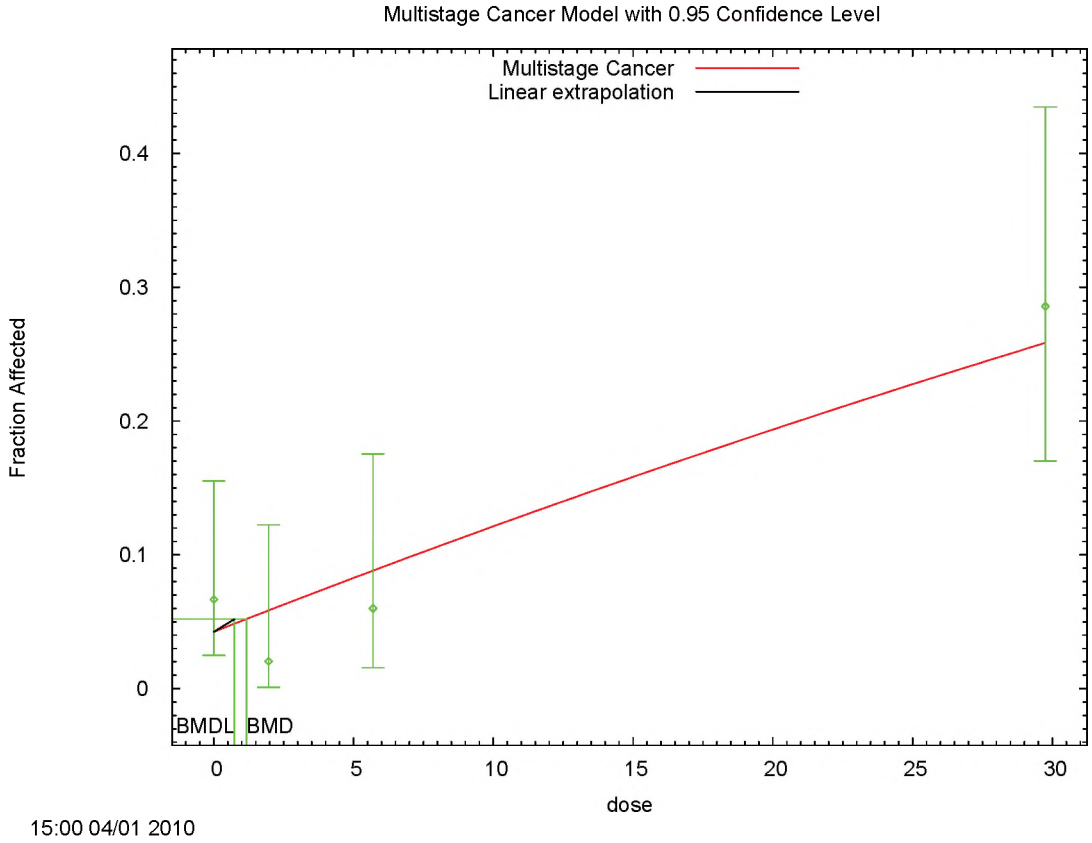
BMDL = 0.737535

BMDU = 2.17906

Taken together, (0.737535, 2.17906) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0135587

F.1.8.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



National Toxicology Program, 1982: Liver: Neoplastic Nodule or Hepatocellular Carcinoma

F.1.9. National Toxicology Program, 1982: Adrenal: Cortical Adenoma, or Carcinoma or Adenoma, NOS

F.1.9.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**2**	**0.337**	**203.824**	**1.611E+00**	**8.140E-01**	
Multistage Cancer, 2-Degree	2	0.470	203.033	6.652E+00	8.904E-01	
Multistage Cancer, 3-Degree	2	0.505	202.868	1.091E+01	9.100E-01	

[a] Best-fitting model, BMDS output presented in this appendix

F.1.9.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

National Toxicology Program, 1982: Adrenal: Cortical Adenoma, or Carcinoma or Adenoma, NOS

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\4\Blood\9_msc1_1Perc_adre_cort_ad_carc.(d)
         Gnuplot Plotting File:  C:\4\Blood\9_msc1_1Perc_adre_cort_ad_carc.plt
                                                Thu Apr 01 16:06:15 2010
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 Source - Table 10
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
```

```
                      Background =     0.134165
                         Beta(1) =    0.0069662


            Asymptotic Correlation Matrix of Parameter Estimates

              Background      Beta(1)

Background            1        -0.54

   Beta(1)        -0.54            1


                                 Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background         0.139854            *               *                   *
        Beta(1)       0.00623778           *               *                   *

* - Indicates that this value is not calculated.


                         Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -98.7282         4
   Fitted model         -99.912         2       2.36764      2          0.3061
  Reduced model        -102.201         1       6.94636      3         0.07363

           AIC:         203.824


                                 Goodness  of  Fit
                                                                      Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------------
    0.0000     0.1399        10.209    11.000          73        0.267
    1.9574     0.1503         7.364     9.000          49        0.654
    5.6942     0.1699         8.324     5.000          49       -1.264
   29.7519     0.2855        13.135    14.000          46        0.282

 Chi^2 = 2.18      d.f. = 2        P-value = 0.3367


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =         1.6112

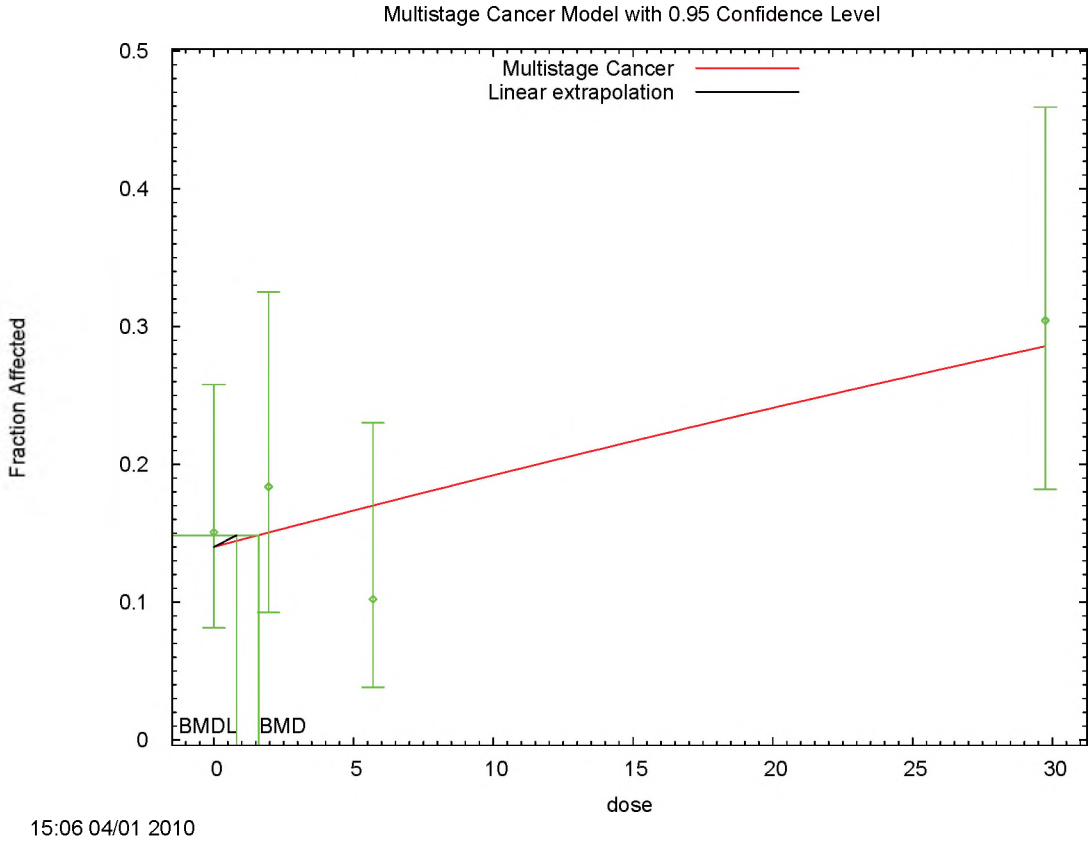
            BMDL =        0.81404

            BMDU =         370555

Taken together, (0.81404, 370555 ) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =     0.0122844
```

F.1.9.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



National Toxicology Program, 1982: Adrenal: Cortical Adenoma, or Carcinoma or Adenoma, NOS

F.1.10. National Toxicology Program, 1982: Thyroid: Follicular-Cell Adenoma

F.1.10.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree[a]	**2**	**0.568**	**92.411**	**3.376E+00**	**1.553E+00**	
Multistage Cancer, 2-Degree	2	0.735	91.749	9.526E+00	1.690E+00	
Multistage Cancer, 3-Degree	2	0.773	91.626	1.385E+01	1.720E+00	

[a] Best-fitting model, BMDS output presented in this appendix

F.1.10.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

National Toxicology Program, 1982: Thyroid: Follicular-Cell Adenoma

```
=================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File: C:\4\Blood\10_msc1_1Perc_thy_ad.(d)
        Gnuplot Plotting File:  C:\4\Blood\10_msc1_1Perc_thy_ad.plt
                                          Thu Apr 01 16:06:53 2010
=================================================================

Source - Table 10
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  The form of the probability function is:

  P[response] = background + (1-background)*[1-EXP(
               -beta1*dose^1)]

  The parameter betas are restricted to be positive


  Dependent variable = Mean
  Independent variable = Dose

Total number of observations = 4
Total number of records with missing values = 0
Total number of parameters in model = 2
Total number of specified parameters = 0
Degree of polynomial = 1


Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                    Background =    0.0283212
                       Beta(1) =   0.00346762
```

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.54
Beta(1)	-0.54	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0332432	*	*	*
Beta(1)	0.00297726	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-43.5264	4			
Fitted model	-44.2053	2	1.35778	2	0.5072
Reduced model	-46.2299	1	5.40699	3	0.1443

AIC: 92.4106

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0332	2.427	3.000	73	0.374
1.9574	0.0389	1.749	2.000	45	0.194
5.6942	0.0495	2.425	1.000	49	-0.939
29.7519	0.1152	5.414	6.000	47	0.268

Chi^2 = 1.13 d.f. = 2 P-value = 0.5682

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 3.3757

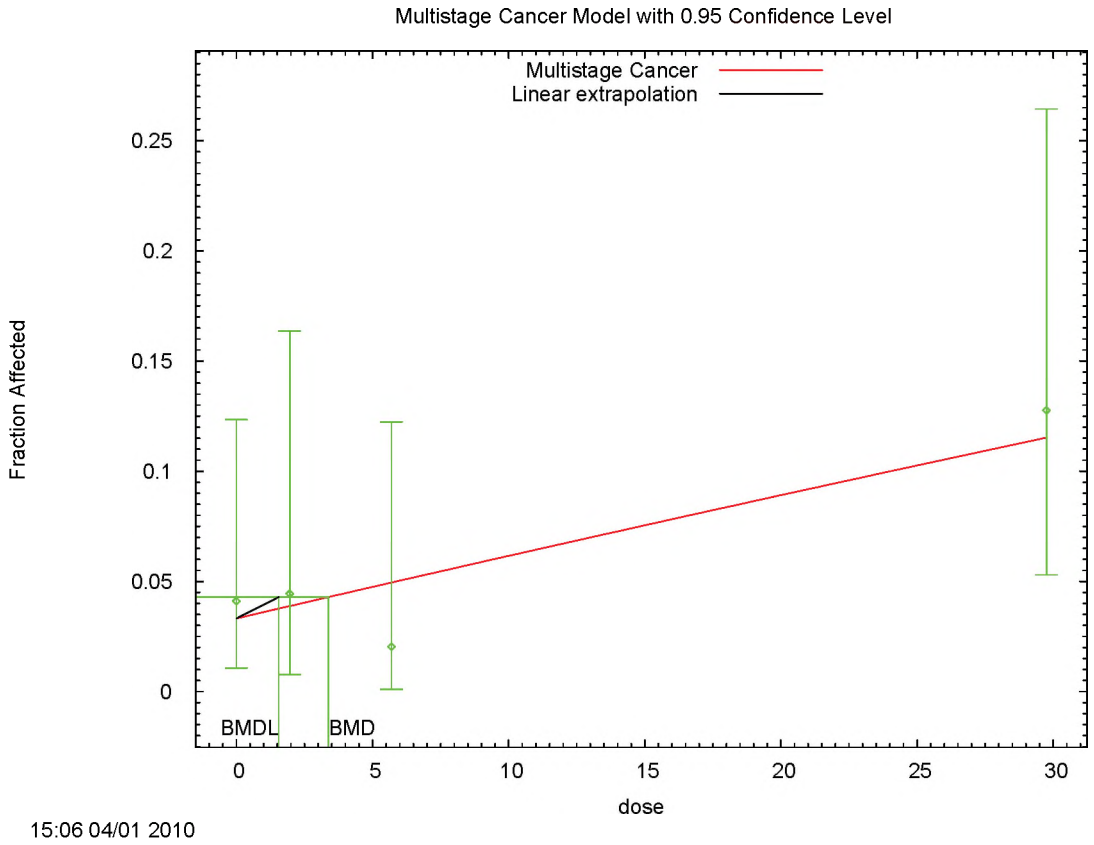
BMDL = 1.55287

BMDU = 306341

Taken together, (1.55287, 306341) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00643967

F.1.10.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



National Toxicology Program, 1982: Thyroid: Follicular-Cell Adenoma

F.1.11. National Toxicology Program, 1982: Liver: Neoplastic Nodule or Hepatocellular Carcinoma

F.1.11.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**2**	**0.218**	**135.190**	**1.169E+00**	**7.375E-01**	
Multistage Cancer, 2-Degree	2	0.491	133.447	5.578E+00	8.771E-01	
Multistage Cancer, 3-Degree	1	0.239	135.435	7.204E+00	8.786E-01	

[a] Best-fitting model, BMDS output presented in this appendix

F.1.11.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

National Toxicology Program, 1982: Liver: Neoplastic Nodule or Hepatocellular Carcinoma

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\4\Blood\11_msc1_1Perc_liver_nod.(d)
         Gnuplot Plotting File:  C:\4\Blood\11_msc1_1Perc_liver_nod.plt
                                                 Thu Apr 01 16:07:28 2010
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 Source - Table 9
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                    Background =            0
                       Beta(1) =   0.00219894
```

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Beta(1)
Beta(1)	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0.00163808	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-11.3484	4			
Fitted model	-12.0522	1	1.40767	3	0.7037
Reduced model	-15.9189	1	9.14109	3	0.02747

AIC: 26.1044

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	74	0.000
1.9569	0.0032	0.160	0.000	50	-0.401
5.7027	0.0093	0.465	0.000	50	-0.685
29.8723	0.0478	2.388	3.000	50	0.406

Chi^2 = 0.79 d.f. = 3 P-value = 0.8507

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 6.13543

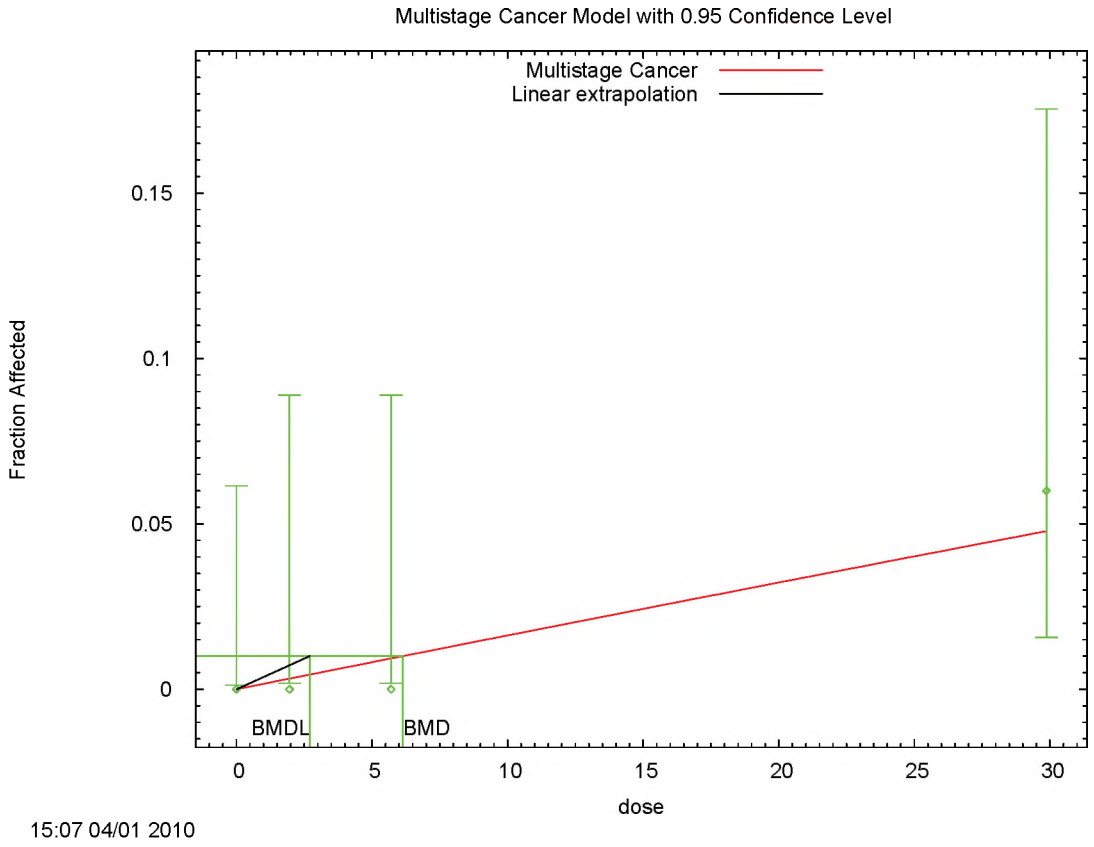
BMDL = 2.70101

BMDU = 18.9354

Taken together, (2.70101, 18.9354) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00370232

F.1.11.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



National Toxicology Program, 1982: Liver: Neoplastic Nodule or Hepatocellular Carcinoma

F.1.12. National Toxicology Program, 1982: Thyroid: Follicular-Cell Adenoma or Carcinoma

F.1.12.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**2**	**0.057**	**149.263**	**1.208E+00**	**6.984E-01**	
Multistage Cancer, 2-Degree	2	0.057	149.263	1.208E+00	6.984E-01	final ß=0
Multistage Cancer, 3-Degree	2	0.057	149.263	1.208E+00	6.984E-01	final ß=0

[a] Best-fitting model, BMDS output presented in this appendix

F.1.12.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

National Toxicology Program, 1982: Thyroid: Follicular-Cell Adenoma or Carcinoma

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\4\Blood\12_msc1_1Perc_thyroid.(d)
         Gnuplot Plotting File:  C:\4\Blood\12_msc1_1Perc_thyroid.plt
                                                 Thu Apr 01 16:08:03 2010
 ======================================================================

 Source - Table 9
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                    Background =    0.0768555
                       Beta(1) =   0.00606248
```

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.62
Beta(1)	-0.62	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0529006	*	*	*
Beta(1)	0.00831706	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-69.5946	4			
Fitted model	-72.6315	2	6.07383	2	0.04798
Reduced model	-77.5267	1	15.8643	3	0.001209

AIC: 149.263

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0529	3.650	1.000	69	-1.425
1.9569	0.0682	3.273	5.000	48	0.989
5.7027	0.0968	4.839	8.000	50	1.512
29.8723	0.2613	13.063	11.000	50	-0.664

Chi^2 = 5.74 d.f. = 2 P-value = 0.0568

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 1.2084

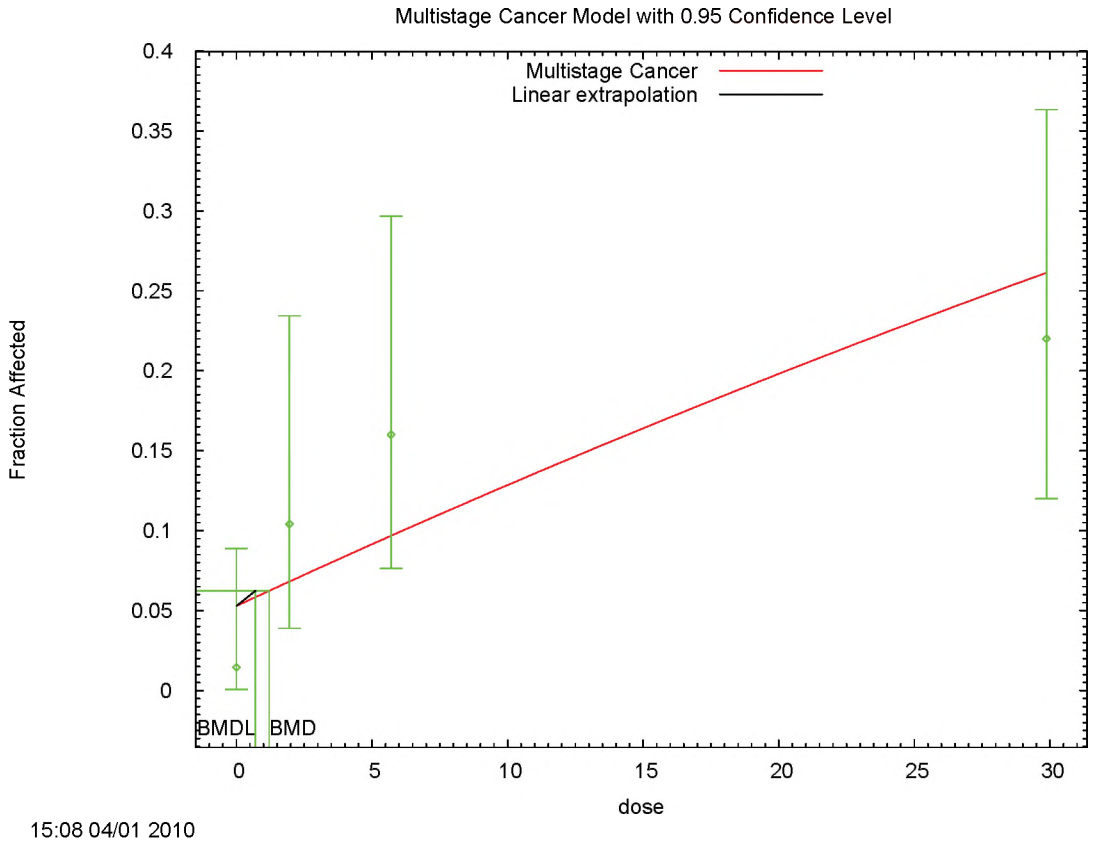
BMDL = 0.698436

BMDU = 2.89109

Taken together, (0.698436, 2.89109) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0143177

F.1.12.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



National Toxicology Program, 1982: Thyroid: Follicular-Cell Adenoma or Carcinoma

F.1.13. National Toxicology Program, 1982: Adrenal cortex: Adenoma

F.1.13.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**2**	**0.062**	**199.309**	**3.977E+00**	**1.223E+00**	
Multistage Cancer, 2-Degree	2	0.062	199.309	3.977E+00	1.223E+00	final ß=0
Multistage Cancer, 3-Degree	2	0.062	199.309	3.977E+00	1.223E+00	final ß=0

[a] Best-fitting model, BMDS output presented in this appendix

F.1.13.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

National Toxicology Program, 1982: Adrenal cortex: Adenoma

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\1\Blood\13_msc1_1Perc_adre_cort.(d)
         Gnuplot Plotting File:  C:\1\Blood\13_msc1_1Perc_adre_cort.plt
                                           Fri Apr 02 10:53:16 2010
 ======================================================================

 Source - Table 9
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =     0.163685
                        Beta(1) =   0.00144687
```

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.6
Beta(1)	-0.6	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.146079	*	*	*
Beta(1)	0.00252696	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-94.8672	4			
Fitted model	-97.6546	2	5.57468	2	0.06158
Reduced model	-98.0432	1	6.35197	3	0.09569

AIC: 199.309

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1461	10.518	6.000	72	-1.507
1.9569	0.1503	7.515	9.000	50	0.588
5.7027	0.1583	7.756	12.000	49	1.661
29.8723	0.2082	10.200	9.000	49	-0.422

Chi^2 = 5.55 d.f. = 2 P-value = 0.0622

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

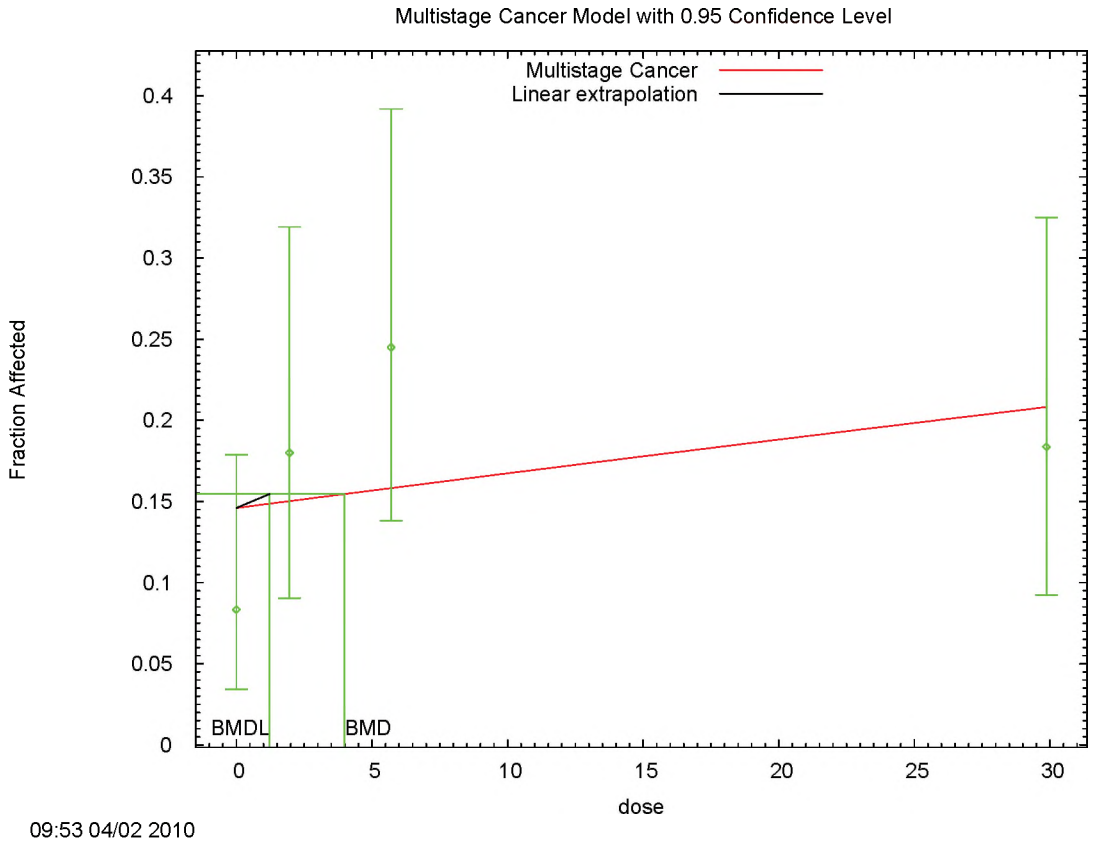
Confidence level = 0.95

BMD = 3.97724

BMDL = 1.22286

BMDU did not converge for BMR = 0.010000
BMDU calculation failed
BMDU = Inf

F.1.13.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



National Toxicology Program, 1982: Adrenal cortex: Adenoma

F.1.14. National Toxicology Program, 1982: Subcutaneous Tissue: Fibrosarcoma

F.1.14.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree[a]	**2**	**0.179**	**75.385**	**3.127E+00**	**1.380E+00**	
Multistage Cancer, 2-Degree	2	0.179	75.385	3.127E+00	1.380E+00	final ß=0
Multistage Cancer, 3-Degree	2	0.179	75.385	3.127E+00	1.380E+00	final ß=0

[a] Best-fitting model, BMDS output presented in this appendix

F.1.14.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

National Toxicology Program, 1982: Subcutaneous Tissue: Fibrosarcoma

```
=================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File: C:\1\Blood\14_msc1_1Perc_subcu_fibro.(d)
        Gnuplot Plotting File:  C:\1\Blood\14_msc1_1Perc_subcu_fibro.plt
                                          Fri Apr 02 10:59:38 2010
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  The form of the probability function is:

  P[response] = background + (1-background)*[1-EXP(
               -beta1*dose^1)]

  The parameter betas are restricted to be positive


  Dependent variable = Mean
  Independent variable = Dose

Total number of observations = 4
Total number of records with missing values = 0
Total number of parameters in model = 2
Total number of specified parameters = 0
Degree of polynomial = 1


Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                 Default Initial Parameter Values
                    Background =     0.010477
                       Beta(1) =   0.00314237
```

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.55
Beta(1)	-0.55	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0124357	*	*	*
Beta(1)	0.0029518	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-30.9876	4			
Fitted model	-31.0692	2	0.163345	2	0.9216
Reduced model	-34.3291	1	6.68308	3	0.08272

AIC: 66.1385

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0124	0.920	1.000	74	0.084
1.9460	0.0181	0.905	1.000	50	0.101
5.8440	0.0293	1.408	1.000	48	-0.349
32.0560	0.1016	4.775	5.000	47	0.109

Chi^2 = 0.15 d.f. = 2 P-value = 0.9274

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 3.40481

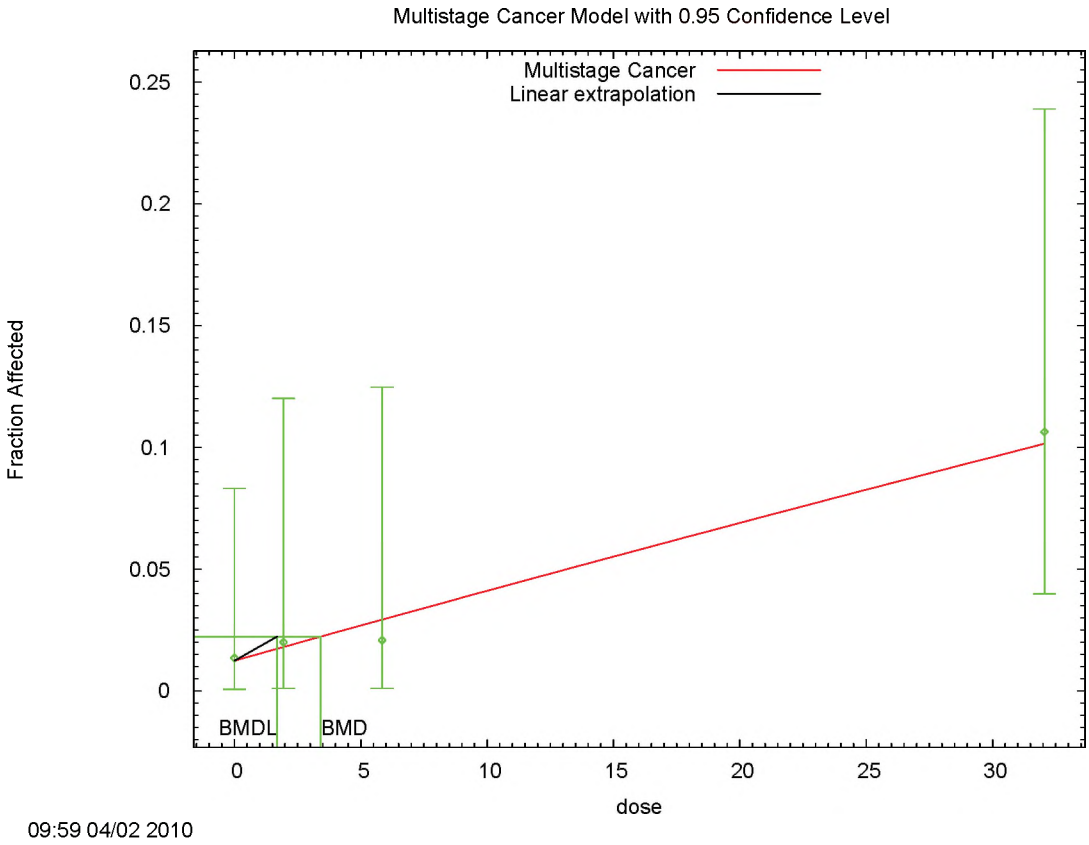
BMDL = 1.68615

BMDU = 11.3501

Taken together, (1.68615, 11.3501) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00593067

F.1.14.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



National Toxicology Program, 1982: Subcutaneous Tissue: Fibrosarcoma

F.1.15. National Toxicology Program, 1982: Hematopoietio System: Lymphoma or Leukemia

F.1.15.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**2**	**0.977**	**261.445**	**1.145E+00**	**6.091E-01**	
Multistage Cancer, 2-Degree	1	0.869	263.426	1.704E+00	6.102E-01	
Multistage Cancer, 3-Degree	1	0.869	263.426	1.704E+00	6.102E-01	final ß=0

[a] Best-fitting model, BMDS output presented in this appendix

F.1.15.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

National Toxicology Program, 1982: Hematopoietio System: Lymphoma or Leukemia

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\1\Blood\15_msc1_1Perc_mice_f_lymphoma.(d)
         Gnuplot Plotting File:  C:\1\Blood\15_msc1_1Perc_mice_f_lymphoma.plt
                                                 Fri Apr 02 11:00:07 2010
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 Table 15 page 64 Hematopoietic System Lymphoma or Leukemia
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                    Background =      0.23423
                       Beta(1) =   0.00892991
```

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.54
Beta(1)	-0.54	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.236159	*	*	*
Beta(1)	0.00877894	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-128.699	4			
Fitted model	-128.723	2	0.0465401	2	0.977
Reduced model	-131.412	1	5.42487	3	0.1432

AIC: 261.445

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.2362	17.476	18.000	74	0.143
1.9460	0.2491	12.455	12.000	50	-0.149
5.8440	0.2744	13.169	13.000	48	-0.055
32.0560	0.4235	19.905	20.000	47	0.028

Chi^2 = 0.05 d.f. = 2 P-value = 0.9770

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 1.14482

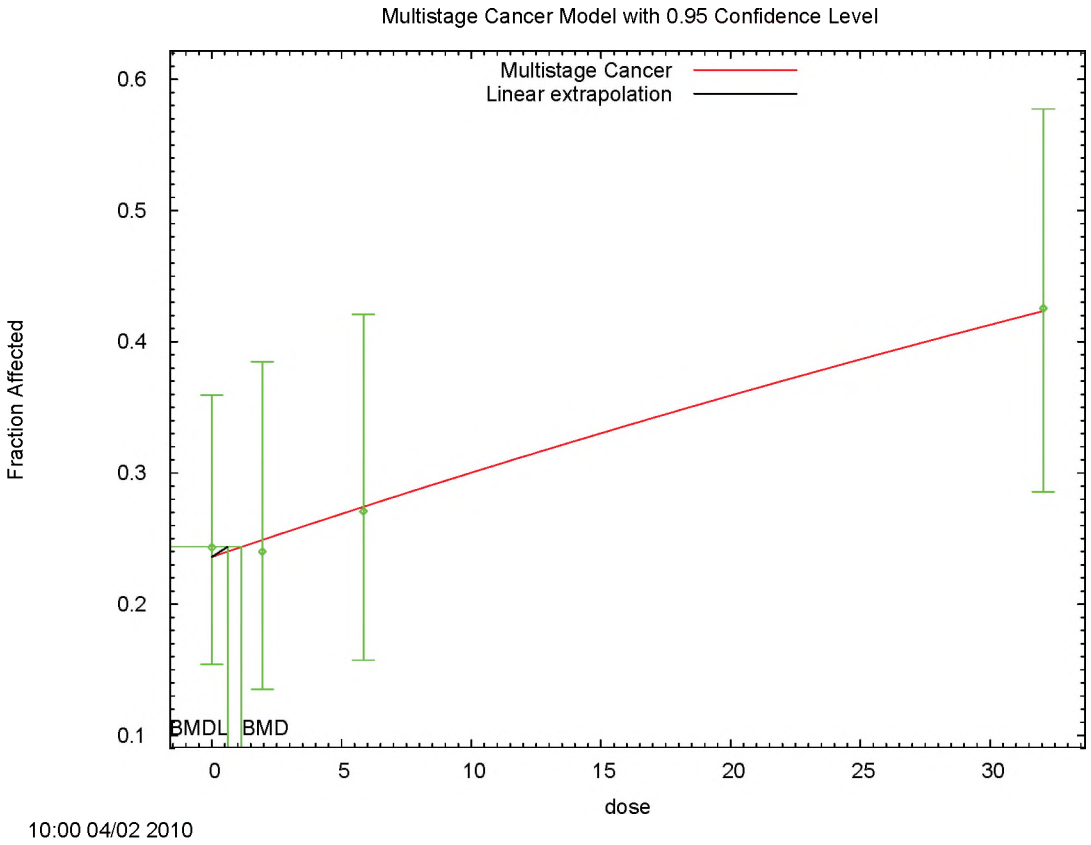
BMDL = 0.609084

BMDU = 4.29581

Taken together, (0.609084, 4.29581) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0164181

F.1.15.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



National Toxicology Program, 1982: Hematopoietio System: Lymphoma or Leukemia

F.1.16. National Toxicology Program, 1982: Liver: Hepatooellular Adenoma or Carcinoma

F.1.16.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**2**	**0.340**	**155.213**	**1.488E+00**	**8.265E-01**	
Multistage Cancer, 2-Degree	2	0.340	155.213	1.488E+00	8.265E-01	final ß=0
Multistage Cancer, 3-Degree	2	0.340	155.213	1.488E+00	8.265E-01	final ß=0

[a] Best-fitting model, BMDS output presented in this appendix

F.1.16.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

National Toxicology Program, 1982: Liver: Hepatooellular Adenoma or Carcinoma

```
=================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File: C:\1\Blood\16_msc1_1Perc_mf_LivAdenCarc.(d)
        Gnuplot Plotting File:  C:\1\Blood\16_msc1_1Perc_mf_LivAdenCarc.plt
                                          Fri Apr 02 11:04:11 2010
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  The form of the probability function is:

  P[response] = background + (1-background)*[1-EXP(
               -beta1*dose^1)]

  The parameter betas are restricted to be positive


  Dependent variable = Mean
  Independent variable = Dose

Total number of observations = 4
Total number of records with missing values = 0
Total number of parameters in model = 2
Total number of specified parameters = 0
Degree of polynomial = 1


Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                Default Initial Parameter Values
                   Background =     0.080941
                      Beta(1) =   0.00583089
```

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.57
Beta(1)	-0.57	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0692161	*	*	*
Beta(1)	0.00675636	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-74.5177	4			
Fitted model	-75.6063	2	2.17736	2	0.3367
Reduced model	-79.6703	1	10.3053	3	0.01614

AIC: 155.213

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0692	5.053	3.000	73	-0.947
1.9460	0.0814	4.069	6.000	50	0.999
5.8440	0.1053	5.052	6.000	48	0.446
32.0560	0.2505	11.772	11.000	47	-0.260

Chi^2 = 2.16 d.f. = 2 P-value = 0.3395

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 1.48754

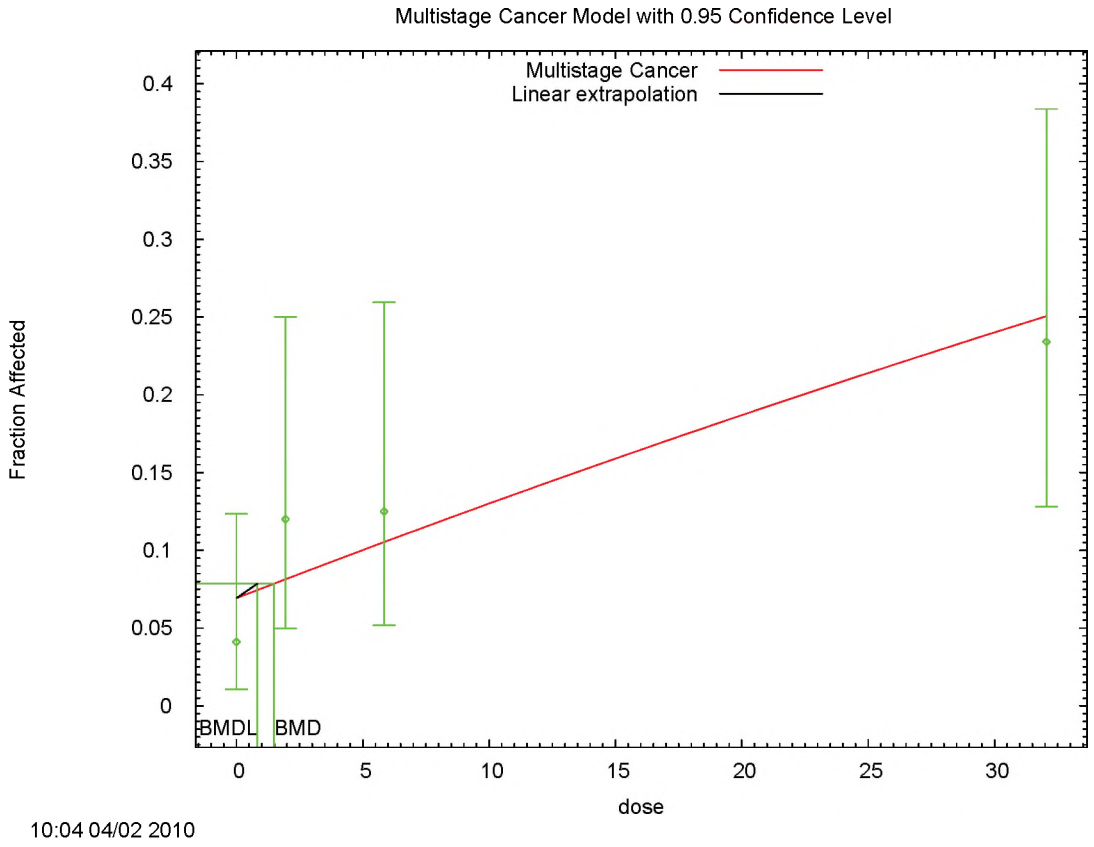
BMDL = 0.826482

BMDU = 3.9863

Taken together, (0.826482, 3.9863) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0120995

F.1.16.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



National Toxicology Program, 1982: Liver: Hepatooellular Adenoma or Carcinoma

F.1.17. National Toxicology Program, 1982: Subcutaneous Tissue: Fibrosarcoma

F.1.17.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree[a]	**2**	**0.179**	**75.385**	**3.127E+00**	**1.380E+00**	
Multistage Cancer, 2-Degree	2	0.179	75.385	3.127E+00	1.380E+00	final ß=0
Multistage Cancer, 3-Degree	2	0.179	75.385	3.127E+00	1.380E+00	final ß=0

[a] Best-fitting model, BMDS output presented in this appendix

F.1.17.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

National Toxicology Program, 1982: Subcutaneous Tissue: Fibrosarcoma

```
=================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File: C:\1\Blood\17_msc1_1Perc_mice_f_thyroid_aden.(d)
        Gnuplot Plotting File:  C:\1\Blood\17_msc1_1Perc_mice_f_thyroid_aden.plt
                                          Fri Apr 02 11:04:39 2010
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  The form of the probability function is:

  P[response] = background + (1-background)*[1-EXP(
               -beta1*dose^1)]

  The parameter betas are restricted to be positive


  Dependent variable = Mean
  Independent variable = Dose

Total number of observations = 4
Total number of records with missing values = 0
Total number of parameters in model = 2
Total number of specified parameters = 0
Degree of polynomial = 1


Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                Default Initial Parameter Values
                   Background =    0.0202346
                      Beta(1) =   0.00292833
```

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.58
Beta(1)	-0.58	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0153082	*	*	*
Beta(1)	0.00329742	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-32.0017	4			
Fitted model	-34.3904	2	4.77738	2	0.09175
Reduced model	-37.2405	1	10.4776	3	0.01491

AIC: 72.7807

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0153	1.056	0.000	69	-1.036
1.9460	0.0216	1.080	3.000	50	1.867
5.8440	0.0341	1.603	1.000	47	-0.484
32.0560	0.1141	5.248	5.000	46	-0.115

Chi^2 = 4.81 d.f. = 2 P-value = 0.0904

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 3.04794

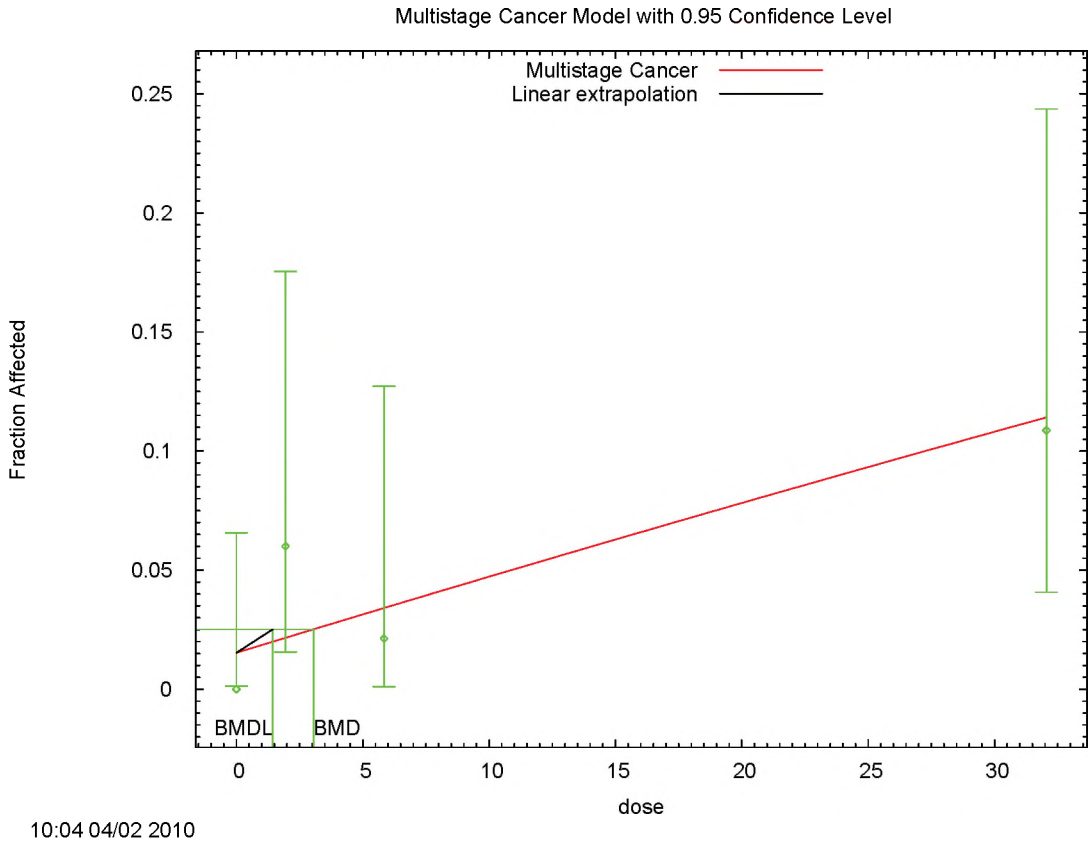
BMDL = 1.43569

BMDU = 138876

Taken together, (1.43569, 138876) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00696528

F.1.17.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



National Toxicology Program, 1982: Subcutaneous Tissue: Fibrosarcoma

F.1.18. National Toxicology Program, 1982: Lung: Alveolar/Bronchiolar Adenoma or Carcinoma

F.1.18.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree	2	0.088	168.342	6.499E-01	3.512E-01	
Multistage Cancer, 2-Degree [a]	**2**	**0.167**	**166.946**	**2.528E+00**	**4.135E-01**	
Multistage Cancer, 3-Degree	2	0.182	166.799	4.147E+00	4.230E-01	

[a] Best-fitting model, BMDS output presented in this appendix

F.1.18.2. *Output for Selected Model: Multistage Cancer, 2-Degree*

National Toxicology Program, 1982: Lung: Alveolar/Bronchiolar Adenoma or Carcinoma

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\1\Blood\18_msc2_1Perc_lung_aden_carc.(d)
         Gnuplot Plotting File:  C:\1\Blood\18_msc2_1Perc_lung_aden_carc.plt
                                                 Fri Apr 02 11:05:09 2010
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                    Background =    0.0868577
                       Beta(1) =            0
```

```
                        Beta(2) =   0.00165722


            Asymptotic Correlation Matrix of Parameter Estimates

            ( *** The model parameter(s)  -Beta(1)
                  have been estimated at a boundary point, or have been specified by the user,
                  and do not appear in the correlation matrix )

              Background      Beta(2)

Background            1        -0.46

   Beta(2)        -0.46            1


                                  Parameter Estimates

                                                                  95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background        0.0942466            *               *                   *
        Beta(1)                0            *               *                   *
        Beta(2)       0.00157255            *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

      Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -79.5959         4
   Fitted model        -81.4729         2         3.754      2           0.153
  Reduced model        -85.3351         1       11.4782      3        0.009402

           AIC:         166.946


                                  Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size        Residual
  ---------------------------------------------------------------------------
    0.0000     0.0942         6.692    10.000          71         1.344
    0.7665     0.0951         4.564     2.000          48        -1.262
    2.2711     0.1016         4.875     4.000          48        -0.418
   11.2437     0.2575        12.877    13.000          50         0.040

 Chi^2 = 3.57      d.f. = 2        P-value = 0.1674


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        2.52806

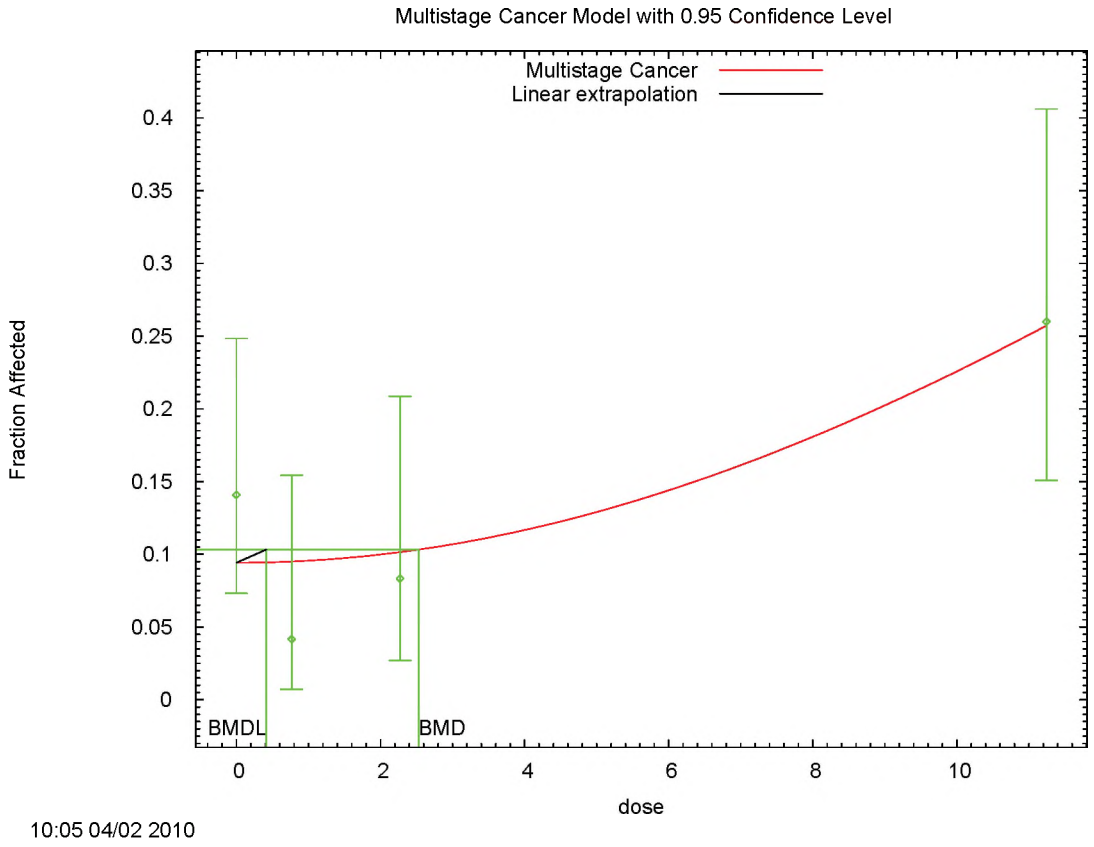
            BMDL =       0.413504

            BMDU =        4.19905

Taken together, (0.413504, 4.19905) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =     0.0241835
```

F.1.18.3. *Figure for Selected Model: Multistage Cancer, 2-Degree*



National Toxicology Program, 1982: Lung: Alveolar/Bronchiolar Adenoma or Carcinoma

F.1.19. National Toxicology Program, 1982: Liver: Hepatocellular Adenoma or Carcinoma

F.1.19.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**2**	**0.928**	**258.548**	**2.110E-01**	**1.378E-01**	
Multistage Cancer, 2-Degree	1	0.779	260.475	3.072E-01	1.385E-01	
Multistage Cancer, 3-Degree	1	0.790	260.468	2.934E-01	1.385E-01	

[a] Best-fitting model, BMDS output presented in this appendix

F.1.19.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

National Toxicology Program, 1982: Liver: Hepatocellular Adenoma or Carcinoma

```
 ========================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\1\Blood\19_msc1_1Perc_mice_m_liver_aden_carc.(d)
         Gnuplot Plotting File:  C:\1\Blood\19_msc1_1Perc_mice_m_liver_aden_carc.plt
                                                 Fri Apr 02 11:05:36 2010
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =     0.201679
                        Beta(1) =    0.0486492


           Asymptotic Correlation Matrix of Parameter Estimates
```

	Background	Beta(1)
Background	1	-0.53
Beta(1)	-0.53	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.204258	*	*	*
Beta(1)	0.0476385	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-127.199	4			
Fitted model	-127.274	2	0.149955	2	0.9278
Reduced model	-135.589	1	16.7801	3	0.0007843

AIC: 258.548

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.2043	14.911	15.000	73	0.026
0.7665	0.2328	11.407	12.000	49	0.201
2.2711	0.2859	14.007	13.000	49	-0.318
11.2437	0.5343	26.713	27.000	50	0.081

Chi^2 = 0.15 d.f. = 2 P-value = 0.9283

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.210971

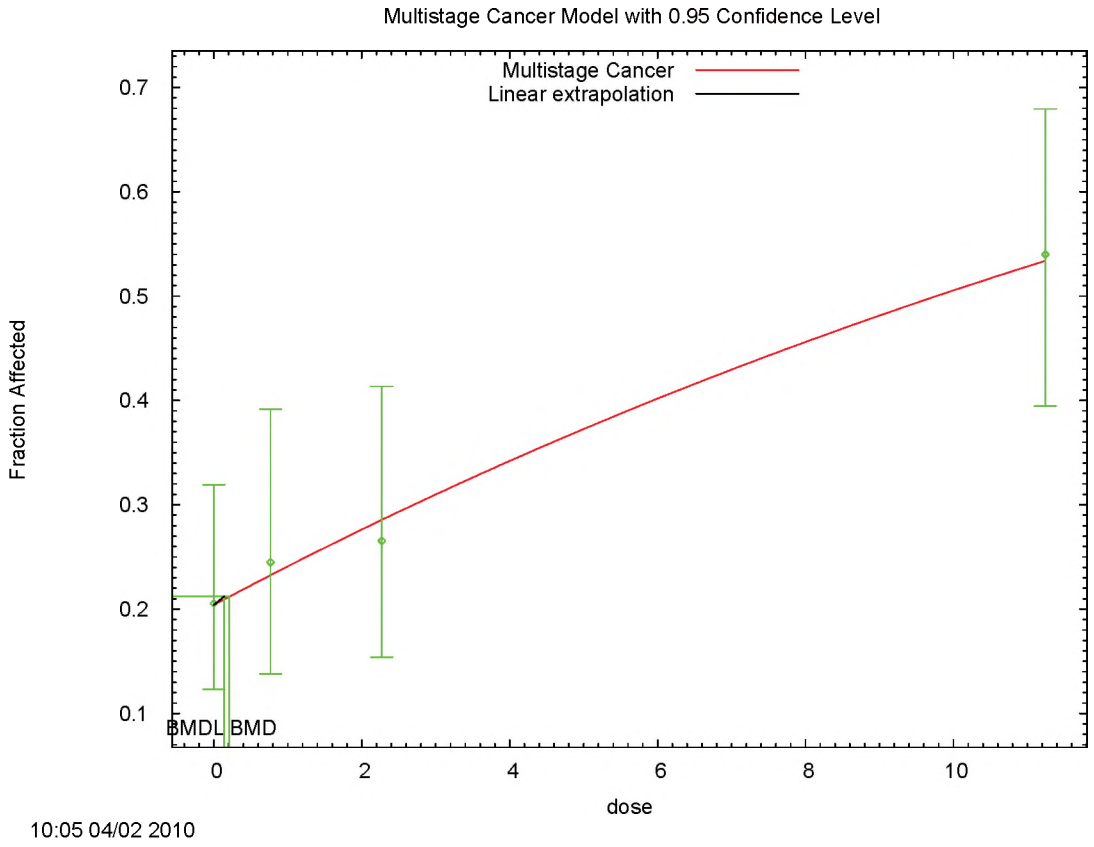
BMDL = 0.137771

BMDU = 0.383981

Taken together, (0.137771, 0.383981) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0725843

F.1.19.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



National Toxicology Program, 1982: Liver: Hepatocellular Adenoma or Carcinoma

F.1.20. National Toxicology Program, 2006: Liver: Cholangiocarcinoma

F.1.20.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree	5	0.001	138.456	9.481E-01	7.114E-01	
Multistage Cancer, 2-Degree	5	0.405	119.374	4.263E+00	2.959E+00	
Multistage Cancer, 3-Degree [a]	**5**	**0.993**	**113.508**	**7.574E+00**	**4.133E+00**	

[a] Best-fitting model, BMDS output presented in this appendix

F.1.20.2. *Output for Selected Model: Multistage Cancer, 3-Degree*

National Toxicology Program, 2006: Liver: Cholangiocarcinoma

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\1\Blood\20_msc3_1Perc_liv_cho-carc.(d)
         Gnuplot Plotting File:  C:\1\Blood\20_msc3_1Perc_liv_cho-carc.plt
                                                Fri Apr 02 11:06:03 2010
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 4
 Total number of specified parameters = 0
 Degree of polynomial = 3


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =            0
                        Beta(2) =            0
                        Beta(3) = 2.44727e-005
```

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background -Beta(1) -Beta(2)
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Beta(3)
Beta(3)	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0	*	*	*
Beta(3)	2.31301e-005	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-55.408	6			
Fitted model	-55.7538	1	0.691671	5	0.9834
Reduced model	-96.9934	1	83.1708	5	<.0001

AIC: 113.508

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	49	0.000
2.5565	0.0004	0.019	0.000	48	-0.136
5.6937	0.0043	0.196	0.000	46	-0.444
9.7882	0.0215	1.073	1.000	50	-0.071
16.5688	0.0999	4.893	4.000	49	-0.426
29.6953	0.4543	24.078	25.000	53	0.254

Chi^2 = 0.47 d.f. = 5 P-value = 0.9933

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 7.57416

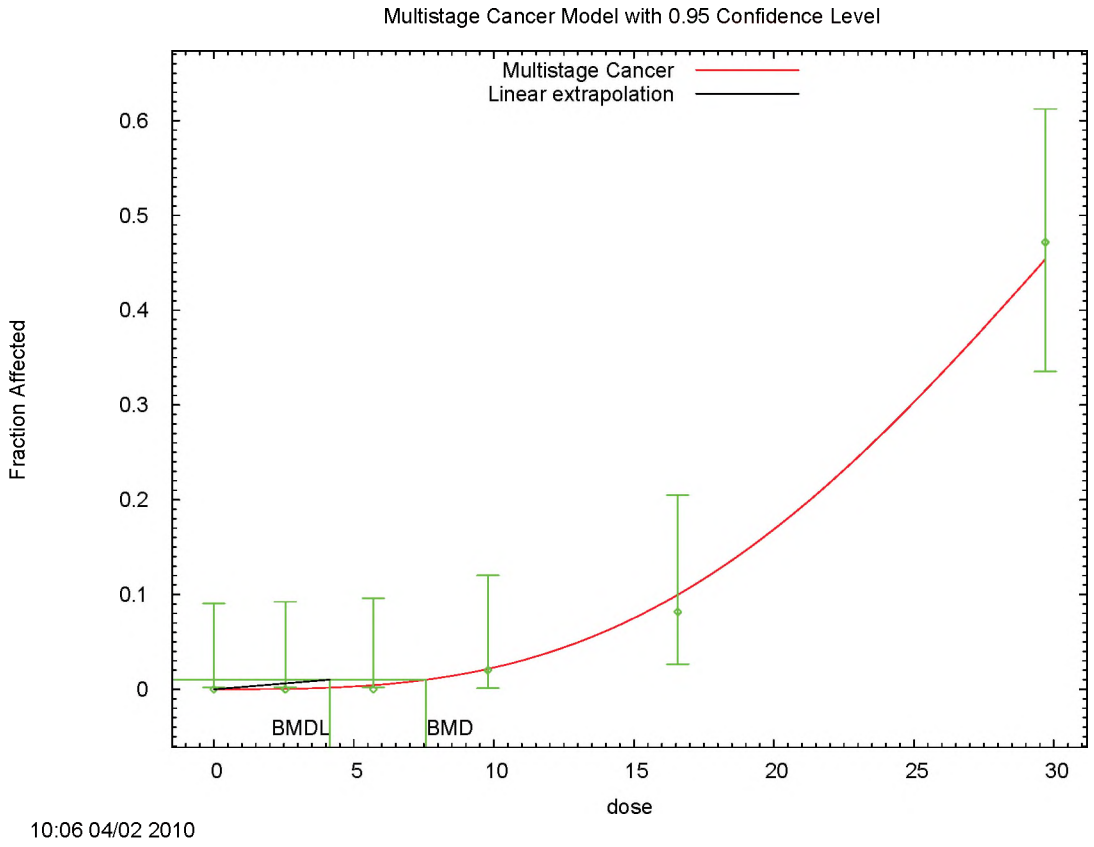
BMDL = 4.13304

BMDU = 8.42557

Taken together, (4.13304, 8.42557) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00241953

F.1.20.3. *Figure for Selected Model: Multistage Cancer, 3-Degree*



National Toxicology Program, 2006: Liver: Cholangiocarcinoma

F.1.21. National Toxicology Program, 2006: Liver: Hepatocellular adenoma

F.1.21.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree	5	0.026	87.024	2.192E+00	1.455E+00	
Multistage Cancer, 2-Degree	5	0.509	76.982	6.602E+00	4.342E+00	
Multistage Cancer, 3-Degree [a]	**5**	**0.933**	**72.782**	**1.022E+01**	**6.527E+00**	

[a] Best-fitting model, BMDS output presented in this appendix

F.1.21.2. *Output For Selected Model: Multistage Cancer, 3-Degree*

National Toxicology Program, 2006: Liver: Hepatocellular adenoma

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\1\Blood\21_msc3_1Perc_liv_hepat_ad.(d)
         Gnuplot Plotting File:  C:\1\Blood\21_msc3_1Perc_liv_hepat_ad.plt
                                                Fri Apr 02 11:06:32 2010
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 4
 Total number of specified parameters = 0
 Degree of polynomial = 3


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =            0
                        Beta(2) =            0
                        Beta(3) = 1.08896e-005

            Asymptotic Correlation Matrix of Parameter Estimates

            ( *** The model parameter(s)  -Background    -Beta(1)    -Beta(2)
```

have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Beta(3)
Beta(3)	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0	*	*	*
Beta(3)	9.41228e-006	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-34.4075	6			
Fitted model	-35.3907	1	1.96648	5	0.8538
Reduced model	-56.3333	1	43.8515	5	<.0001

AIC: 72.7815

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	49	0.000
2.5565	0.0002	0.008	0.000	48	-0.087
5.6937	0.0017	0.080	0.000	46	-0.283
9.7882	0.0088	0.439	0.000	50	-0.666
16.5688	0.0419	2.054	1.000	49	-0.751
29.6953	0.2184	11.577	13.000	53	0.473

Chi^2 = 1.32 d.f. = 5 P-value = 0.9330

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 10.221

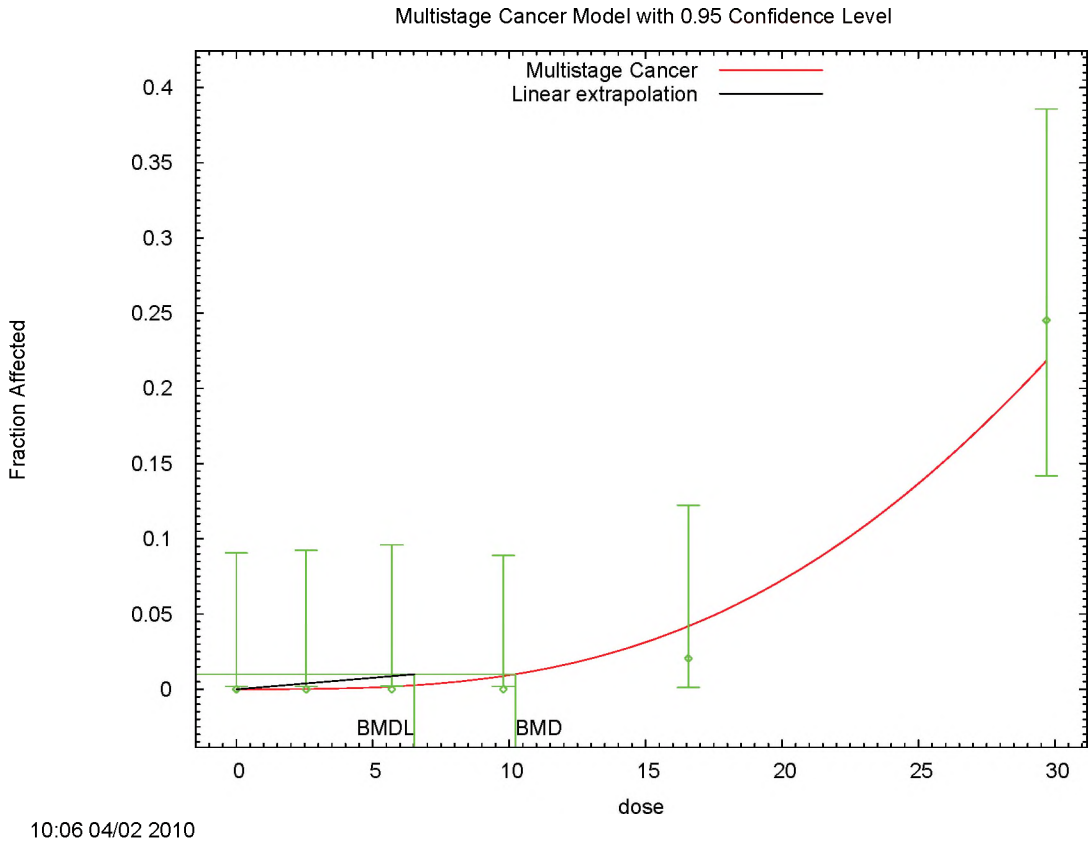
BMDL = 6.52683

BMDU = 11.9754

Taken together, (6.52683, 11.9754) is a 90 % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor = 0.00153214

F.1.21.3. *Figure For Selected Model: Multistage Cancer, 3-Degree*



National Toxicology Program, 2006: Liver: Hepatocellular adenoma

F.1.22. National Toxicology Program, 2006: Oral mucosa: squamous cell carcinoma

F.1.22.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**4**	**0.270**	**126.963**	**2.204E+00**	**1.389E+00**	
Multistage Cancer, 2-Degree	4	0.538	123.896	7.108E+00	2.158E+00	
Multistage Cancer, 3-Degree	4	0.565	123.295	1.103E+01	2.298E+00	

[a] Best-fitting model, BMDS output presented in this appendix

F.1.22.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

National Toxicology Program, 2006: Oral mucosa: squamous cell carcinoma

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\1\Blood\22_msc1_1Perc_oral_carc.(d)
         Gnuplot Plotting File:  C:\1\Blood\22_msc1_1Perc_oral_carc.plt
                                              Fri Apr 02 11:07:00 2010
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =   0.00629243


           Asymptotic Correlation Matrix of Parameter Estimates
```

	Background	Beta(1)
Background	1	-0.67
Beta(1)	-0.67	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0139169	*	*	*
Beta(1)	0.00456055	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-57.5353	6			
Fitted model	-61.4815	2	7.89233	4	0.0956
Reduced model	-67.7782	1	20.4858	5	0.001013

AIC: 126.963

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0139	0.682	1.000	49	0.388
2.5565	0.0253	1.217	2.000	48	0.719
5.6937	0.0392	1.803	1.000	46	-0.610
9.7882	0.0570	2.848	0.000	50	-1.738
16.5688	0.0857	4.198	4.000	49	-0.101
29.6953	0.1388	7.357	10.000	53	1.050

Chi^2 = 5.17 d.f. = 4 P-value = 0.2700

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 2.20376

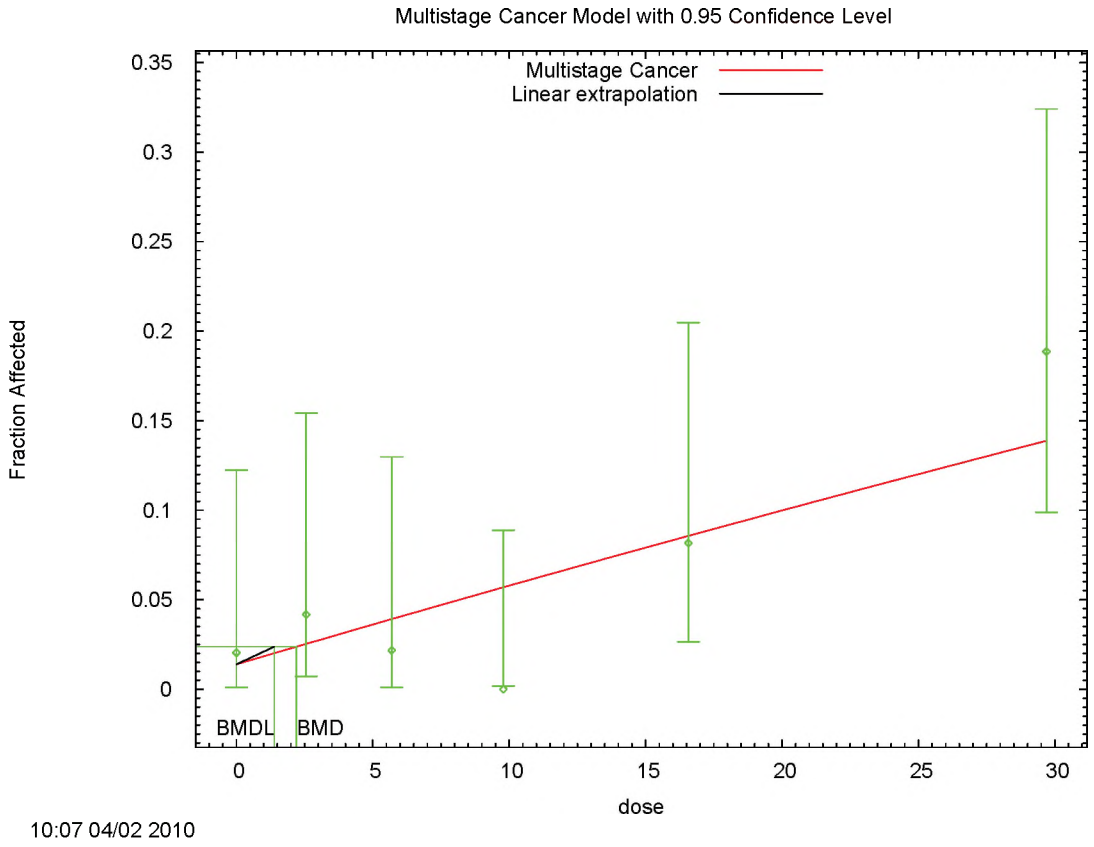
BMDL = 1.38901

BMDU = 4.3103

Taken together, (1.38901, 4.3103) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00719939

F.1.22.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



National Toxicology Program, 2006: Oral mucosa: squamous cell carcinoma

F.1.23. National Toxicology Program, 2006: Pancreas: adenoma or carcinoma

F.1.23.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**5**	**0.640**	**29.373**	**1.052E+01**	**4.630E+00**	
Multistage Cancer, 2-Degree	5	0.929	27.061	1.458E+01	7.227E+00	
Multistage Cancer, 3-Degree	5	0.986	25.972	1.739E+01	9.373E+00	

[a] Best-fitting model, BMDS output presented in this appendix

F.1.23.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

National Toxicology Program, 2006: Pancreas: adenoma or carcinoma

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\1\Blood\23_msc1_1Perc_panc_ad_carc.(d)
         Gnuplot Plotting File:  C:\1\Blood\23_msc1_1Perc_panc_ad_carc.plt
                                                Fri Apr 02 11:07:29 2010
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =   0.00191132


           Asymptotic Correlation Matrix of Parameter Estimates
```

(*** The model parameter(s) -Background
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

Beta(1)

Beta(1) 1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0.000955662	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-11.4096	6			
Fitted model	-13.6865	1	4.55375	5	0.4727
Reduced model	-16.7086	1	10.598	5	0.05996

AIC: 29.373

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	48	-0.007
2.5565	0.0024	0.117	0.000	48	-0.343
5.6937	0.0054	0.250	0.000	46	-0.501
9.7882	0.0093	0.466	0.000	50	-0.686
16.5688	0.0157	0.754	0.000	48	-0.875
29.6953	0.0280	1.427	3.000	51	1.336

Chi^2 = 3.39 d.f. = 5 P-value = 0.6403

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 10.5166

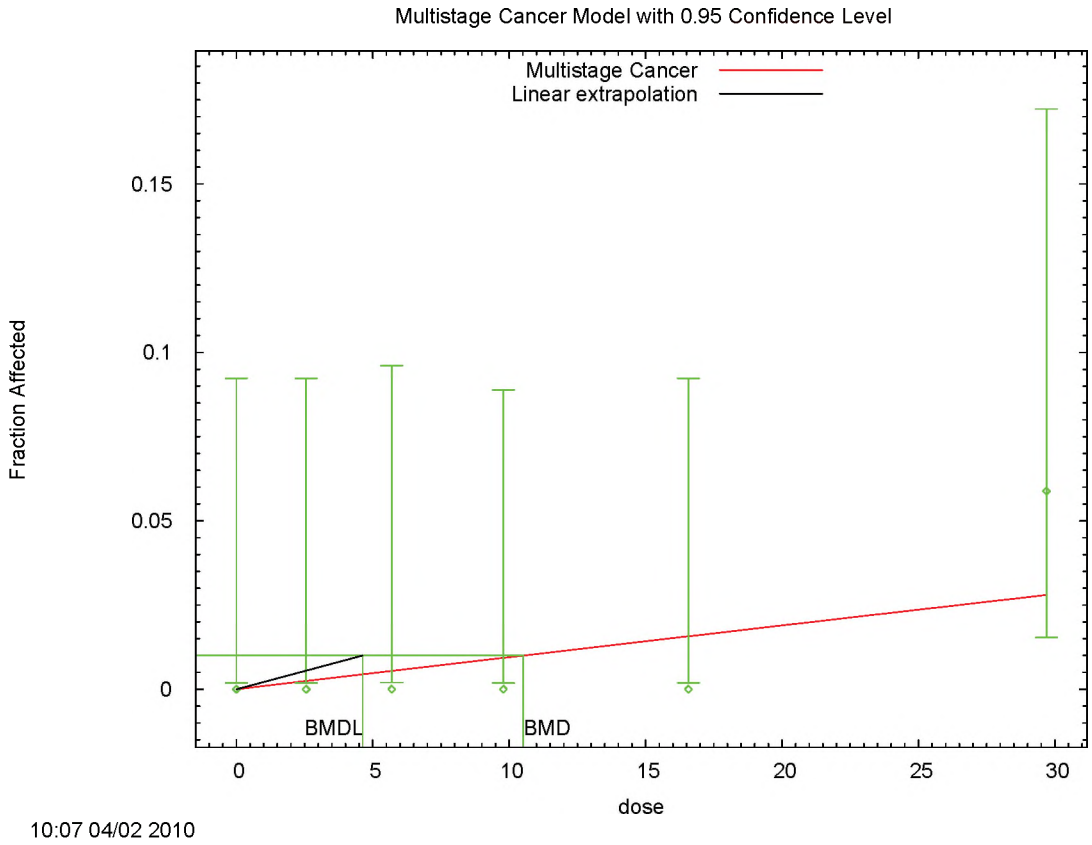
BMDL = 4.62967

BMDU = 32.8573

Taken together, (4.62967, 32.8573) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00215998

F.1.23.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



National Toxicology Program, 2006: Pancreas: adenoma or carcinoma

F.1.24. National Toxicology Program, 2006: Lung: Cystic keratinizing epithelioma

F.1.24.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree	5	0.062	64.034	3.445E+00	2.084E+00	
Multistage Cancer, 2-Degree [a]	**5**	**0.507**	**56.943**	**8.304E+00**	**5.245E+00**	
Multistage Cancer, 3-Degree	5	0.845	53.558	1.193E+01	7.765E+00	

[a] Best-fitting model, BMDS output presented in this appendix

F.1.24.2. *Output for Selected Model: Multistage Cancer, 2-Degree*

National Toxicology Program, 2006: Lung: Cystic keratinizing epithelioma

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\1\Blood\24_msc2_1Perc_lung_epith.(d)
         Gnuplot Plotting File:  C:\1\Blood\24_msc2_1Perc_lung_epith.plt
                                                 Fri Apr 02 11:07:57 2010
 ================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =           0
                        Beta(1) =           0
                        Beta(2) =  0.000216412
```

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background -Beta(1)
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Beta(2)
Beta(2)	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0.000145744	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-23.958	6			
Fitted model	-27.4714	1	7.02662	5	0.2187
Reduced model	-40.2069	1	32.4976	5	<.0001

AIC: 56.9427

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	49	0.000
2.5565	0.0010	0.046	0.000	48	-0.214
5.6937	0.0047	0.217	0.000	46	-0.467
9.7882	0.0139	0.679	0.000	49	-0.830
16.5688	0.0392	1.922	0.000	49	-1.414
29.6953	0.1206	6.271	9.000	52	1.162

Chi^2 = 4.30 d.f. = 5 P-value = 0.5067

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 8.30415

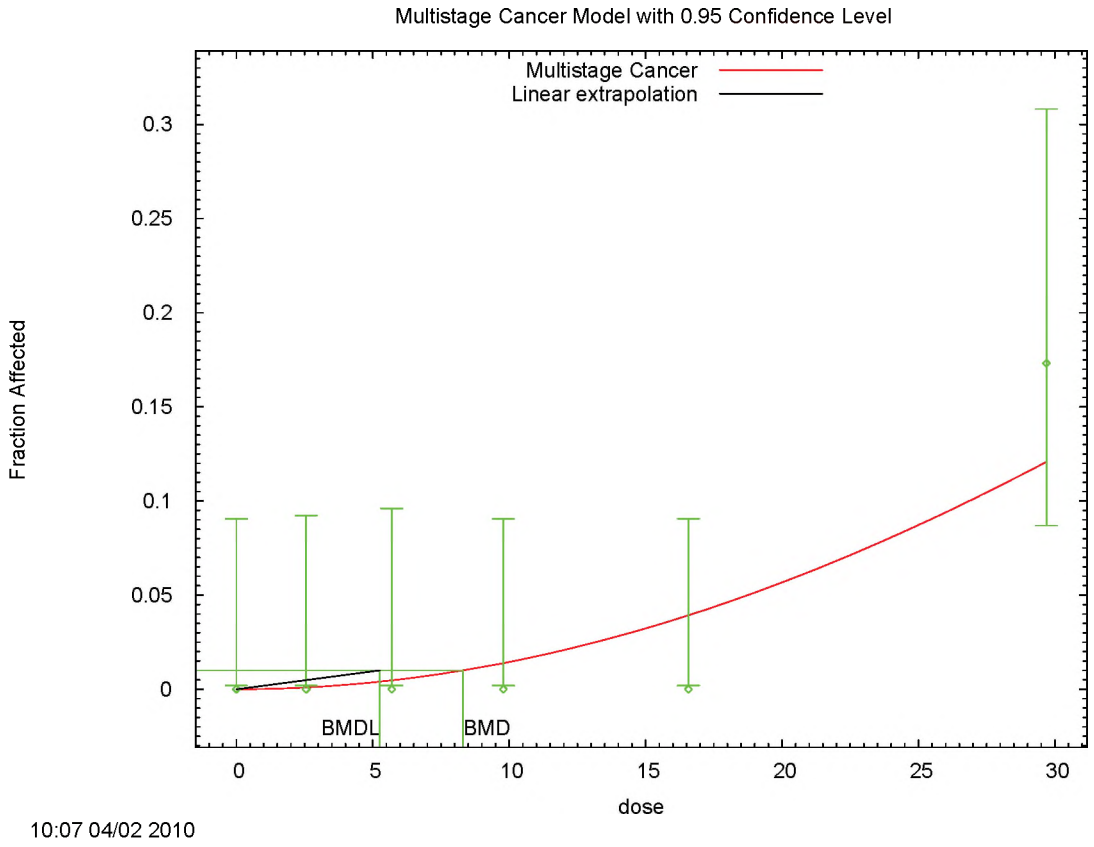
BMDL = 5.24499

BMDU = 11.2298

Taken together, (5.24499, 11.2298) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00190658

F.1.24.3. *Figure for Selected Model: Multistage Cancer, 2-Degree*



National Toxicology Program, 2006: Lung: Cystic keratinizing epithelioma

F.1.25. Toth et al., 1979: Liver: Tumors

F.1.25.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**1**	**0.293**	**155.740**	**3.684E-01**	**2.096E-01**	
Multistage Cancer, 2-Degree	1	0.293	155.740	3.684E-01	2.096E-01	final ß=0

[a] Best-fitting model, BMDS output presented in this appendix

F.1.25.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

Toth et al., 1979: Liver: Tumors

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\1\Blood\25_msc1_1Perc_adr_cor_1yr.(d)
         Gnuplot Plotting File:  C:\1\Blood\25_msc1_1Perc_adr_cor_1yr.plt
                                              Fri Apr 02 11:08:26 2010
 ================================================================

 Table 1
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 1
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =     0.234952
                        Beta(1) =    0.0269892


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)
```

Background	1	-0.55
Beta(1)	-0.55	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.235297	*	*	*
Beta(1)	0.0272796	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-75.3127	3			
Fitted model	-75.8702	2	1.11506	1	0.291
Reduced model	-79.4897	1	8.35401	2	0.01534

AIC: 155.74

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.2353	8.941	7.000	38	-0.742
0.5732	0.2472	10.875	13.000	44	0.743
14.2123	0.4811	21.167	21.000	44	-0.050

Chi^2 = 1.11 d.f. = 1 P-value = 0.2931

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.368419

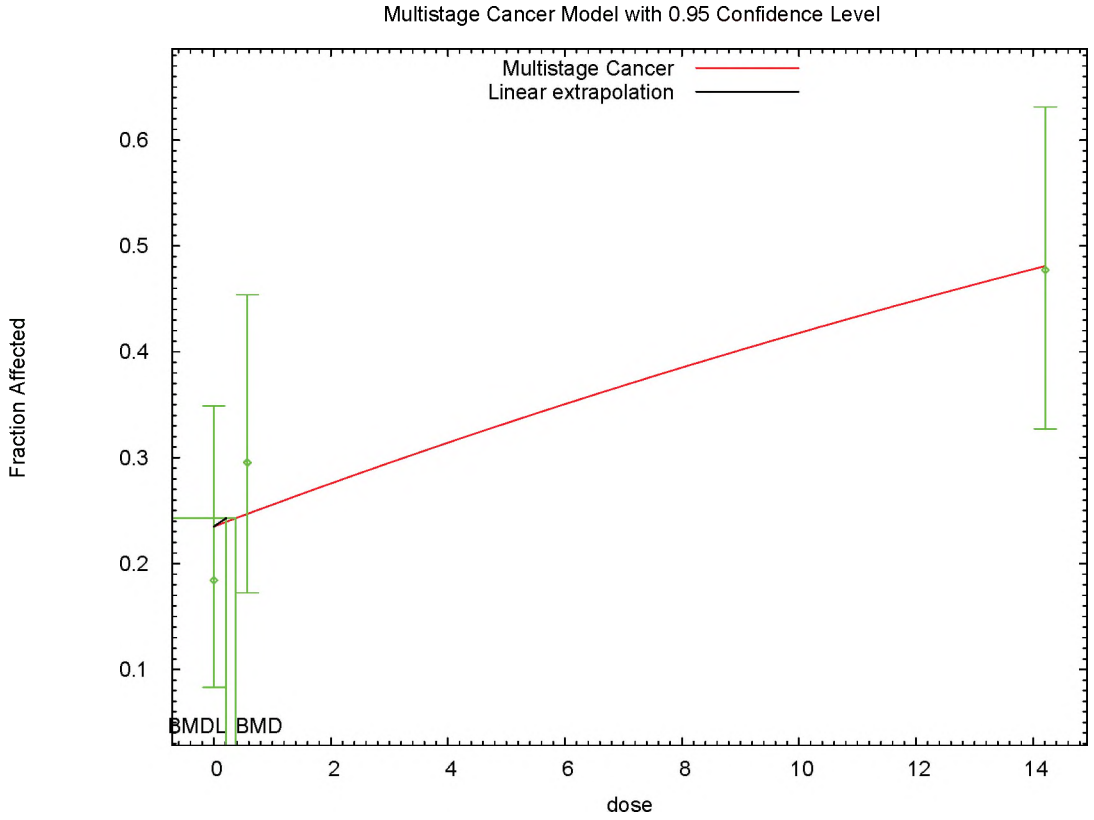
BMDL = 0.209642

BMDU = 1.01064

Taken together, (0.209642, 1.01064) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0477004

F.1.25.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



Toth et al., 1979: Liver: Tumors

F.1.26. Della Porta et al., 1987: Table 4, B6C3 mice, male, hepatocellular carcinoma

F.1.26.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree	1	0.036	165.333	9.239E-01	6.933E-01	
Multistage Cancer, 2-Degree [a]	**1**	**0.525**	**161.217**	**7.143E+00**	**1.170E+00**	

[a] Best-fitting model, BMDS output presented in this appendix

F.1.26.2. *Output for Selected Model: Multistage Cancer, 2-Degree*

Della Porta et al., 1987: Table 4, B6C3 mice, male, hepatocellular carcinoma

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\1\Blood\94_DPorta_1987_Male_Hep_Carc_MultiCanc2_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\94_DPorta_1987_Male_Hep_Carc_MultiCanc2_1.plt
                                                Fri Apr 02 13:52:21 2010
 ======================================================================

 Table 4, B6C3 mice, Male, Hepatocellular carcinoma
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =    0.0865895
                        Beta(1) =            0
                        Beta(2) =  0.000211877


            Asymptotic Correlation Matrix of Parameter Estimates
```

(*** The model parameter(s) -Beta(1)
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Background	Beta(2)
Background	1	-0.64
Beta(2)	-0.64	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.107218	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0.00019698	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-78.4036	3			
Fitted model	-78.6083	2	0.409345	1	0.5223
Reduced model	-94.7394	1	32.6717	2	<.0001

AIC: 161.217

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1072	4.610	5.000	43	0.192
37.9990	0.3282	16.740	15.000	51	-0.519
67.7695	0.6387	31.936	33.000	50	0.313

Chi^2 = 0.40 d.f. = 1 P-value = 0.5249

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 7.14298

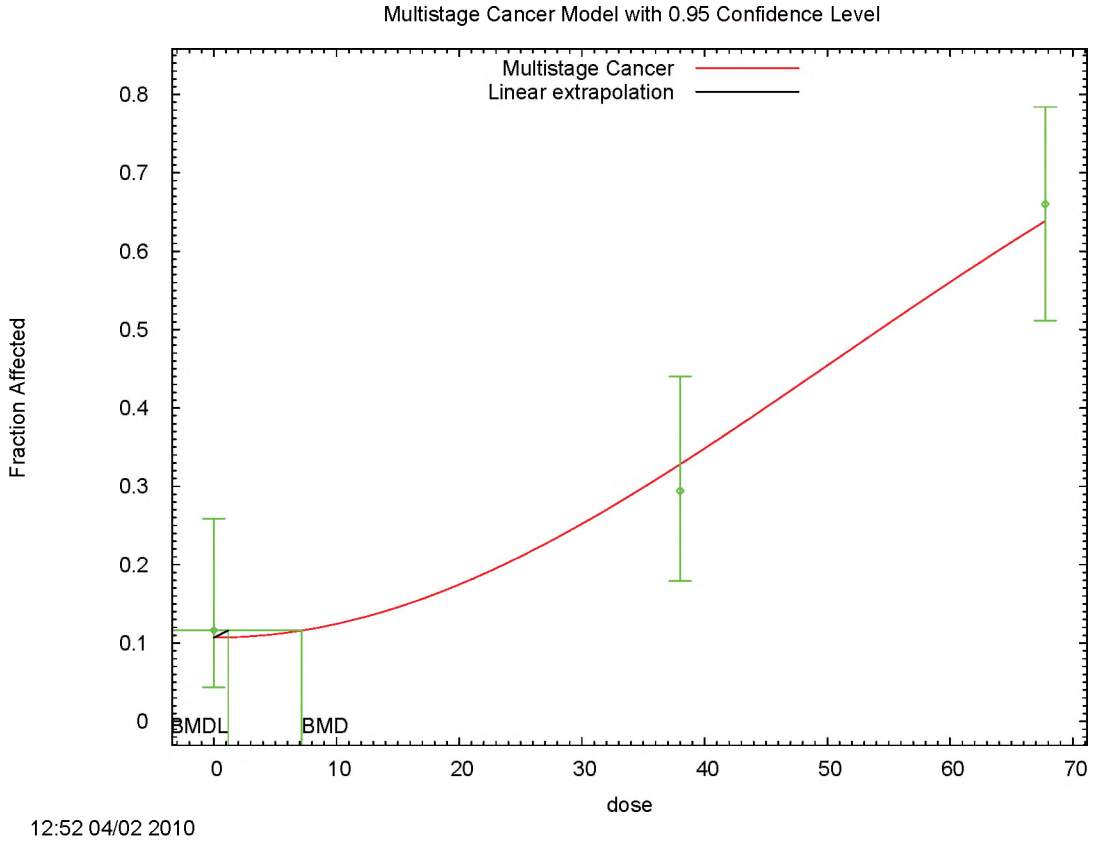
BMDL = 1.16991

BMDU = 8.58118

Taken together, (1.16991, 8.58118) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0085477

F.1.26.3. *Figure for Selected Model: Multistage Cancer, 2-Degree*



Della Porta et al., 1987: Table 4, B6C3 mice, male, hepatocellular carcinoma

F.1.27. Della Porta et al., 1987: Table 4, B6C3 mice, female, hepatocellular adenoma

F.1.27.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree	1	0.380	99.614	3.599E+00	2.186E+00	
Multistage Cancer, 2-Degree [a]	**1**	**0.863**	**98.833**	**1.449E+01**	**2.342E+00**	

[a] Best-fitting model, BMDS output presented in this appendix

F.1.27.2. *Output for Selected Model: Multistage Cancer, 2-Degree*

Della Porta et al., 1987: Table 4, B6C3 mice, female, hepatocellular adenoma

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\1\Blood\95_DPorta_1987_Female_Hep_Aden_MultiCanc2_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\95_DPorta_1987_Female_Hep_Aden_MultiCanc2_1.plt
                                                 Fri Apr 02 13:52:51 2010
 ======================================================================

 Table 4, B6C3 mice, Female, Hepatocellular adenoma
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =    0.0364319
                        Beta(1) =            0
                        Beta(2) = 4.92861e-005


            Asymptotic Correlation Matrix of Parameter Estimates
```

(*** The model parameter(s) -Beta(1)
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Background	Beta(2)
Background	1	-0.69
Beta(2)	-0.69	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0392633	*	*	*
Beta(1)	0	*	*	*
Beta(2)	4.78928e-005	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-47.4015	3			
Fitted model	-47.4165	2	0.0299957	1	0.8625
Reduced model	-51.6367	1	8.47042	2	0.01448

AIC: 98.8329

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0393	1.924	2.000	49	0.056
37.5865	0.1021	4.289	4.000	42	-0.147
66.9741	0.2250	10.800	11.000	48	0.069

Chi^2 = 0.03 d.f. = 1 P-value = 0.8634

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 14.4862

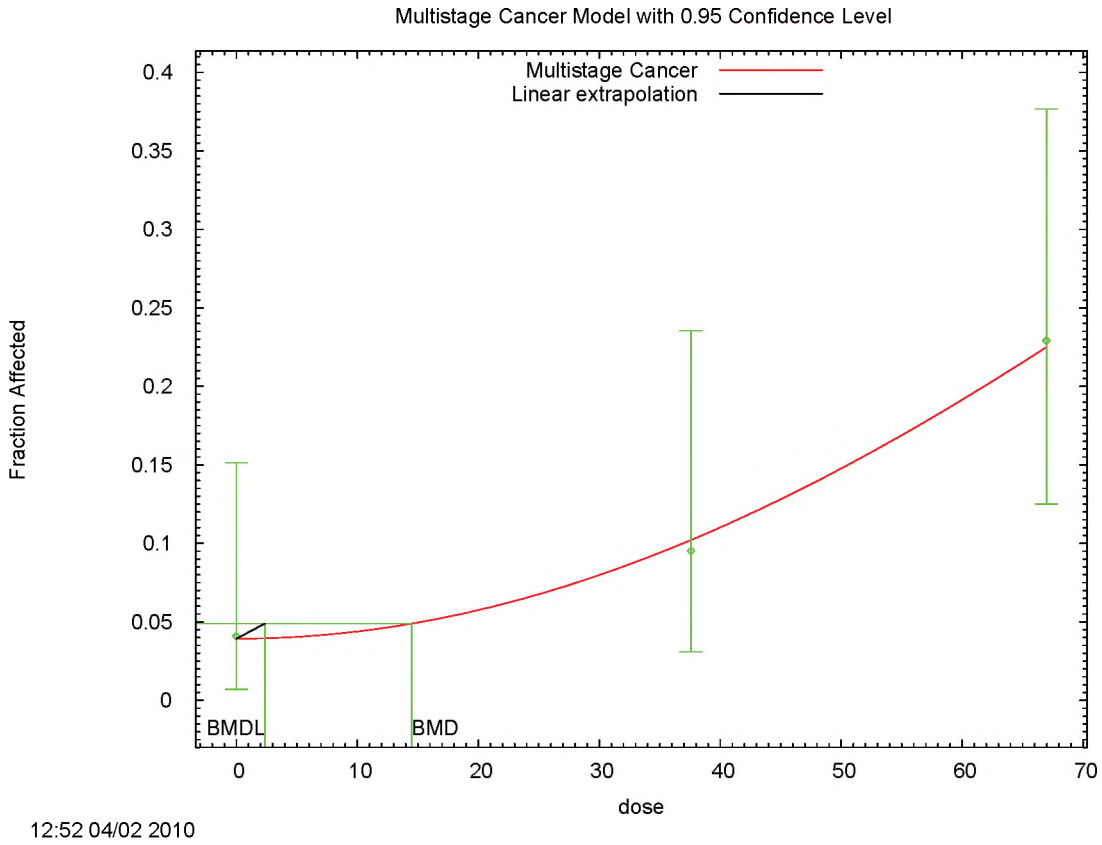
BMDL = 2.3421

BMDU = 22.1663

Taken together, (2.3421 , 22.1663) is a 90 % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor = 0.00426967

F.1.27.3. *Figure for Selected Model: Multistage Cancer, 2-Degree*



Della Porta et al., 1987: Table 4, B6C3 mice, female, hepatocellular adenoma

F.1.28. Della Porta et al., 1987: Table 4, B6C3 mice, female, hepatocellular carcinoma

F.1.28.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**1**	**0.019**	**115.539**	**2.302E+00**	**1.545E+00**	
Multistage Cancer, 2-Degree	1	0.019	115.539	2.302E+00	1.545E+00	final ß=0

[a] Best-fitting model, BMDS output presented in this appendix

F.1.28.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

Della Porta et al., 1987: Table 4, B6C3 mice, female, hepatocellular carcinoma

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\1\Blood\96_DPorta_1987_Female_Hep_Carc_MultiCanc1_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\96_DPorta_1987_Female_Hep_Carc_MultiCanc1_1.plt
                                                Fri Apr 02 13:53:20 2010
 ======================================================================

 Table 4, B6C3 mice, Female, Hepatocellular carcinoma
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =    0.0787329
                        Beta(1) =   0.00304814


            Asymptotic Correlation Matrix of Parameter Estimates

              Background      Beta(1)
```

Background	1	-0.8
Beta(1)	-0.8	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0268873	*	*	*
Beta(1)	0.00436529	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-53.1726	3			
Fitted model	-55.7697	2	5.19425	1	0.02266
Reduced model	-60.7146	1	15.084	2	0.0005303

AIC: 115.539

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0269	1.317	1.000	49	-0.280
37.5865	0.1741	7.314	12.000	42	1.907
66.9741	0.2736	13.131	9.000	48	-1.338

Chi^2 = 5.50 d.f. = 1 P-value = 0.0190

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 2.30233

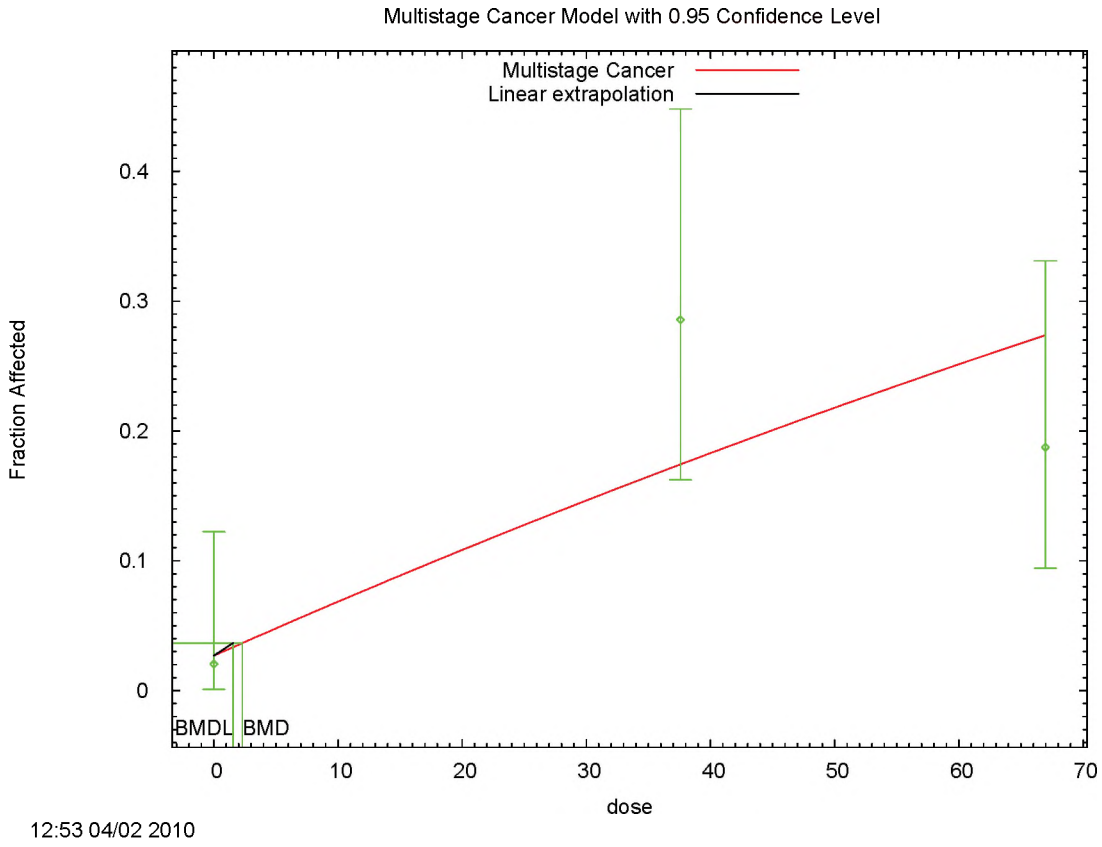
BMDL = 1.54479

BMDU = 4.37768

Taken together, (1.54479, 4.37768) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00647339

F.1.28.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



Della Porta et al., 1987: Table 4, B6C3 mice, female, hepatocellular carcinoma

F.2. ADMINISTERED DOSE BMDS RESULTS

F.2.1. Kociba et al., 1978: Stratified squamous cell carcinoma of hard palate or nasal turbinates

F.2.1.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**3**	**0.928**	**30.745**	**1.344E+01**	**6.515E+00**	
Multistage Cancer, 2-Degree	3	0.998	29.961	3.490E+01	7.216E+00	
Multistage Cancer, 3-Degree	3	1.000	29.885	4.941E+01	7.297E+00	

[a] Best-fitting model, BMDS output presented in this appendix

F.2.1.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

Kociba et al., 1978: Stratified squamous cell carcinoma of hard palate or nasal turbinates

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Canc\1_msc1_1Perc_palate_nasal.(d)
         Gnuplot Plotting File:  C:\Canc\1_msc1_1Perc_palate_nasal.plt
                                                 Thu Apr 01 12:47:40 2010
 ======================================================================

 Source - Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
```

```
                    Background =            0
                       Beta(1) =  0.000858074


            Asymptotic Correlation Matrix of Parameter Estimates

            ( *** The model parameter(s)  -Background
                  have been estimated at a boundary point, or have been specified by the user,
                  and do not appear in the correlation matrix )

                 Beta(1)

    Beta(1)            1



                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
      Background                0            *                *                   *
         Beta(1)       0.00074801            *                *                   *

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
      Full model        -13.9385         4
     Fitted model       -14.3726         1      0.868297      3          0.8331
   Reduced model        -20.2589         1       12.6409      3        0.005481

            AIC:         30.7452


                                Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          85        0.000
     1.0000     0.0007         0.037     0.000          50       -0.193
    10.0000     0.0075         0.373     0.000          50       -0.613
   100.0000     0.0721         3.604     4.000          50        0.217

 Chi^2 = 0.46      d.f. = 3        P-value = 0.9276


    Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        13.4361

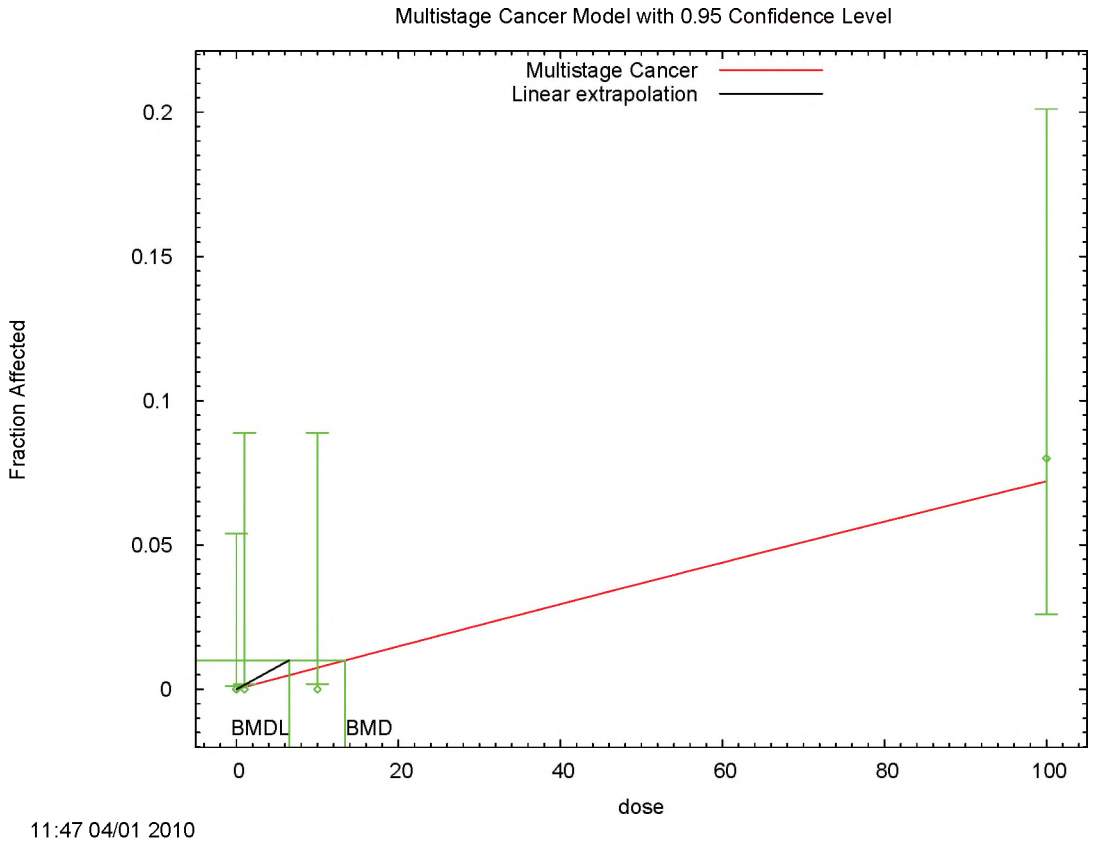
             BMDL =        6.51522

             BMDU =         34.829

Taken together, (6.51522, 34.829 ) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =    0.00153487
```

F.2.1.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



Kociba et al., 1978: Stratified squamous cell carcinoma of hard palate or nasal turbinates

F.2.2. Kociba et al., 1978: Stratified squamous cell carcinoma of tongue

F.2.2.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**2**	**0.451**	**48.368**	**1.742E+01**	**7.146E+00**	
Multistage Cancer, 2-Degree	2	0.451	48.368	1.742E+01	7.146E+00	final ß=0
Multistage Cancer, 3-Degree	2	0.451	48.368	1.742E+01	7.146E+00	final ß=0

[a] Best-fitting model, BMDS output presented in this appendix

F.2.2.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

Kociba et al., 1978: Stratified squamous cell carcinoma of tongue

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Canc\2_msc1_1Perc_tongue.(d)
         Gnuplot Plotting File:  C:\Canc\2_msc1_1Perc_tongue.plt
                                                Thu Apr 01 12:48:16 2010
 ======================================================================

 Source - Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =    0.0113883
                        Beta(1) =  0.000508703
```

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.52
Beta(1)	-0.52	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.00809154	*	*	*
Beta(1)	0.000576915	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-21.1523	4			
Fitted model	-22.1838	2	2.06309	2	0.3565
Reduced model	-24.1972	1	6.08976	3	0.1073

AIC: 48.3677

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0081	0.688	0.000	85	-0.833
1.0000	0.0087	0.433	1.000	50	0.865
10.0000	0.0138	0.690	1.000	50	0.376
100.0000	0.0637	3.185	3.000	50	-0.107

Chi^2 = 1.59 d.f. = 2 P-value = 0.4506

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 17.4208

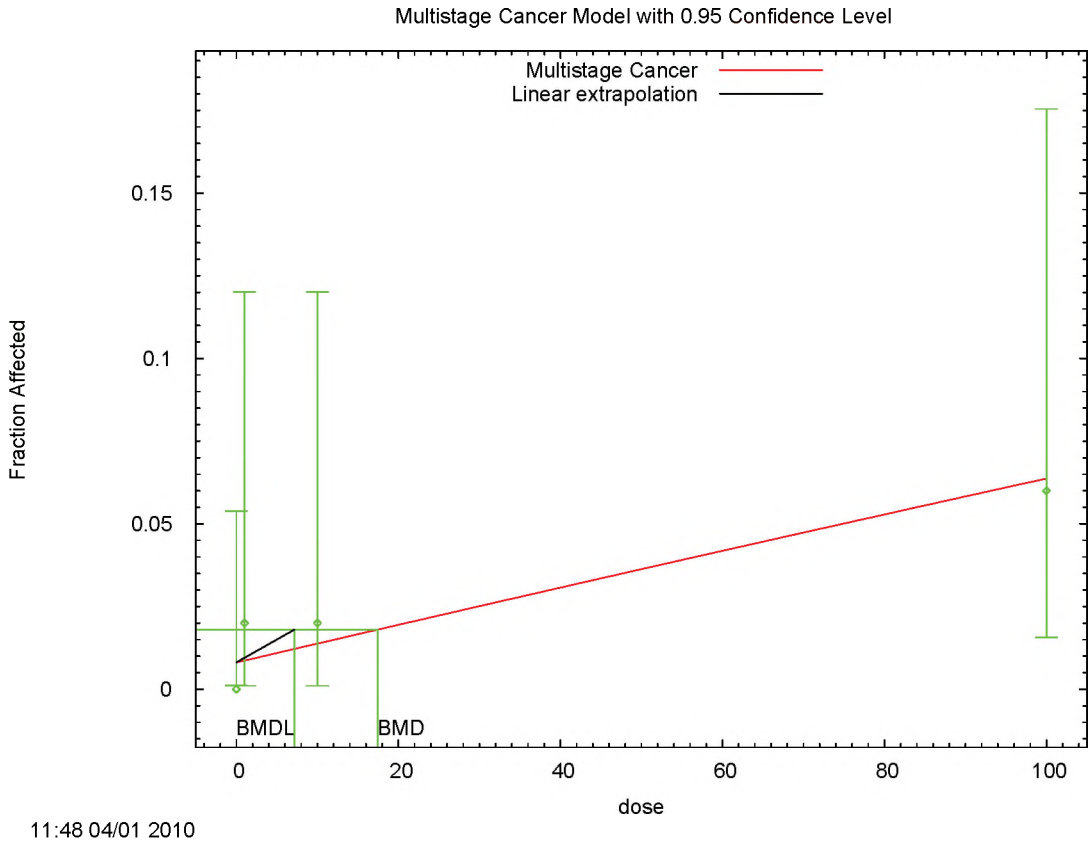
BMDL = 7.14637

BMDU = 3.20359e+006

Taken together, (7.14637, 3.20359e+006) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00139931

F.2.2.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



Kociba et al., 1978: Stratified squamous cell carcinoma of tongue

F.2.3. Kociba et al., 1978: Adenoma of adrenal cortex

F.2.3.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**3**	**0.376**	**53.518**	**7.587E+00**	**4.317E+00**	
Multistage Cancer, 2-Degree	3	0.376	53.518	7.587E+00	4.317E+00	final ß=0
Multistage Cancer, 3-Degree	3	0.376	53.518	7.587E+00	4.317E+00	final ß=0

[a] Best-fitting model, BMDS output presented in this appendix

F.2.3.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

Kociba et al., 1978: Adenoma of adrenal cortex

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Canc\3_msc1_1Perc_adre_adenoma.(d)
         Gnuplot Plotting File:  C:\Canc\3_msc1_1Perc_adre_adenoma.plt
                                                 Thu Apr 01 12:48:52 2010
 ======================================================================

 Source - Table 5
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =   0.00927818
                        Beta(1) =   0.00098105
```

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Beta(1)
Beta(1)	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0.00132464	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-24.6514	4			
Fitted model	-25.759	1	2.2152	3	0.529
Reduced model	-31.4904	1	13.6781	3	0.003378

AIC: 53.5179

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	85	0.000
1.0000	0.0013	0.066	0.000	50	-0.257
10.0000	0.0132	0.658	2.000	50	1.666
100.0000	0.1241	6.203	5.000	50	-0.516

Chi^2 = 3.11 d.f. = 3 P-value = 0.3755

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 7.58722

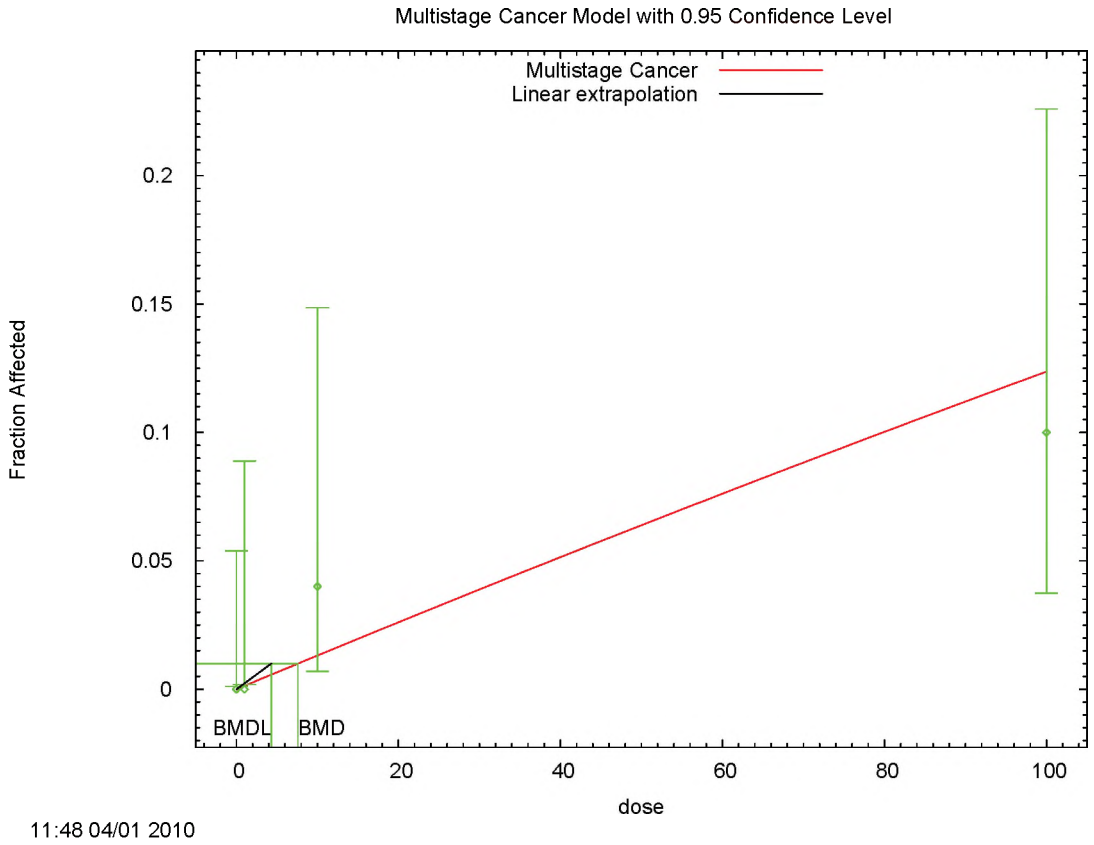
BMDL = 4.31737

BMDU = 17.638

Taken together, (4.31737, 17.638) is a 90 % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor = 0.00231623

F.2.3.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



Kociba et al., 1978: Adenoma of adrenal cortex

F.2.4. Kociba et al., 1978: Hepatocellular adenoma(s) or carcinoma(s)

F.2.4.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**2**	**0.034**	**146.199**	**1.769E+00**	**1.225E+00**	
Multistage Cancer, 2-Degree	2	0.034	146.199	1.768E+00	1.225E+00	final ß=0
Multistage Cancer, 3-Degree	2	0.034	146.199	1.768E+00	1.225E+00	final ß=0

[a] Best-fitting model, BMDS output presented in this appendix

F.2.4.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

Kociba et al., 1978: Hepatocellular adenoma(s) or carcinoma(s)

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Canc\4_msc1_1Perc_liver_ad_carc.(d)
         Gnuplot Plotting File:  C:\Canc\4_msc1_1Perc_liver_ad_carc.plt
                                                Thu Apr 01 12:49:25 2010
 ======================================================================

 Source - Table 1 in Goodman and Sauer 1992
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =    0.0591902
                        Beta(1) =   0.00458516
```

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.47
Beta(1)	-0.47	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0328755	*	*	*
Beta(1)	0.00568299	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-68.2561	4			
Fitted model	-71.0993	2	5.68634	2	0.05824
Reduced model	-89.1983	1	41.8843	3	<.0001

AIC: 146.199

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0329	2.827	2.000	86	-0.500
1.0000	0.0384	1.918	1.000	50	-0.676
10.0000	0.0863	4.315	9.000	50	2.359
100.0000	0.4521	20.346	18.000	45	-0.703

Chi^2 = 6.77 d.f. = 2 P-value = 0.0339

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 1.7685

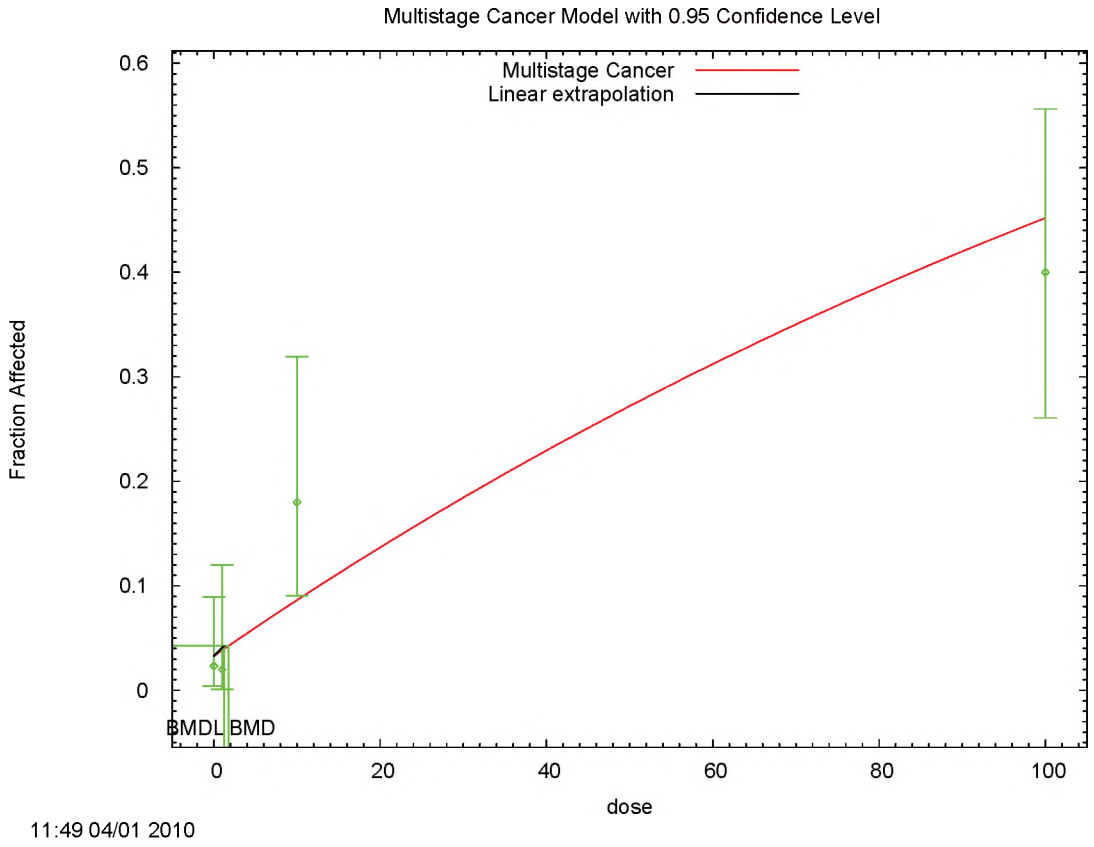
BMDL = 1.22517

BMDU = 2.77641

Taken together, (1.22517, 2.77641) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00816214

F.2.4.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



Kociba et al., 1978: Hepatocellular adenoma(s) or carcinoma(s)

F.2.5. Kociba et al., 1978: Stratified squamous cell carcinoma of hard palate or nasal turbinates

F.2.5.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**3**	**0.928**	**30.745**	**1.344E+01**	**6.515E+00**	
Multistage Cancer, 2-Degree	3	0.998	29.961	3.490E+01	7.216E+00	
Multistage Cancer, 3-Degree	3	1.000	29.885	4.941E+01	7.297E+00	

[a] Best-fitting model, BMDS output presented in this appendix

F.2.5.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

Kociba et al., 1978: Stratified squamous cell carcinoma of hard palate or nasal turbinates

```
=================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File: C:\Canc\5_msc1_1Perc_nasal.(d)
        Gnuplot Plotting File:  C:\Canc\5_msc1_1Perc_nasal.plt
                                          Thu Apr 01 12:49:59 2010
=================================================================

Source - Table 5
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the probability function is:

  P[response] = background + (1-background)*[1-EXP(
               -beta1*dose^1)]

  The parameter betas are restricted to be positive


  Dependent variable = Mean
  Independent variable = Dose

Total number of observations = 4
Total number of records with missing values = 0
Total number of parameters in model = 2
Total number of specified parameters = 0
Degree of polynomial = 1


Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                Default Initial Parameter Values
                   Background =   0.00343283
                      Beta(1) =  0.000825276
```

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Beta(1)
Beta(1)	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0.000953868	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-18.7562	4			
Fitted model	-19.0532	1	0.594034	3	0.8978
Reduced model	-24.1972	1	10.882	3	0.01238

AIC: 40.1064

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	86	0.000
1.0000	0.0010	0.048	0.000	50	-0.218
10.0000	0.0095	0.475	1.000	50	0.766
100.0000	0.0910	4.458	4.000	49	-0.227

Chi^2 = 0.69 d.f. = 3 P-value = 0.8764

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 10.5364

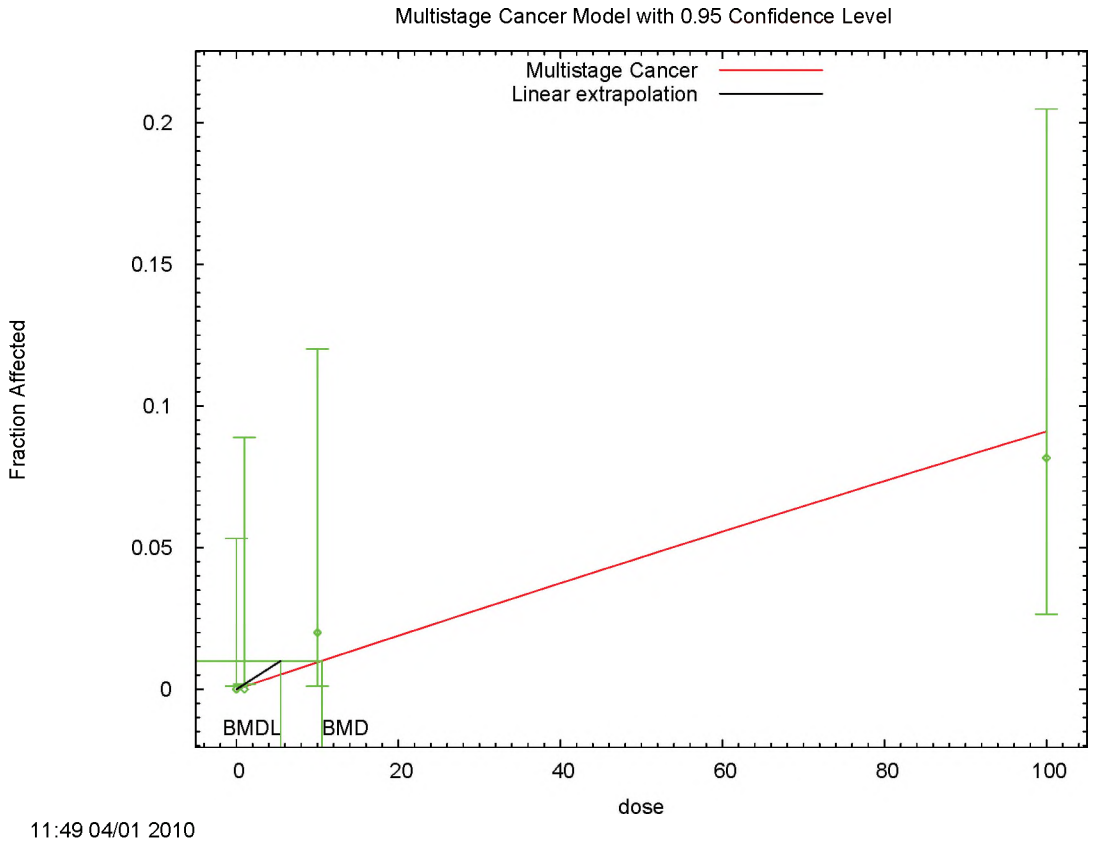
BMDL = 5.46907

BMDU = 25.864

Taken together, (5.46907, 25.864) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00182846

F.2.5.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



Kociba et al., 1978: Stratified squamous cell carcinoma of hard palate or nasal turbinates

F.2.6. Kociba et al., 1978: Keratinizing squamous cell carcinoma of lung

F.2.6.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**3**	**0.837**	**43.792**	**7.311E+00**	**4.159E+00**	
Multistage Cancer, 2-Degree	3	0.994	42.346	2.568E+01	4.917E+00	
Multistage Cancer, 3-Degree	3	1.000	42.207	4.026E+01	5.022E+00	

[a] Best-fitting model, BMDS output presented in this appendix

F.2.6.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

Kociba et al., 1978: Keratinizing squamous cell carcinoma of lung

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Canc\6_msc1_1Perc_kera_carc.(d)
         Gnuplot Plotting File:  C:\Canc\6_msc1_1Perc_kera_carc.plt
                                                Thu Apr 01 12:50:34 2010
 ================================================================

 Source - Table 5
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =   0.00158635
```

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Beta(1)
Beta(1)	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0.0013747	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-20.0957	4			
Fitted model	-20.8959	1	1.60041	3	0.6593
Reduced model	-31.4904	1	22.7894	3	<.0001

AIC: 43.7918

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	86	0.000
1.0000	0.0014	0.069	0.000	50	-0.262
10.0000	0.0137	0.683	0.000	50	-0.832
100.0000	0.1284	6.294	7.000	49	0.302

Chi^2 = 0.85 d.f. = 3 P-value = 0.8370

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 7.31091

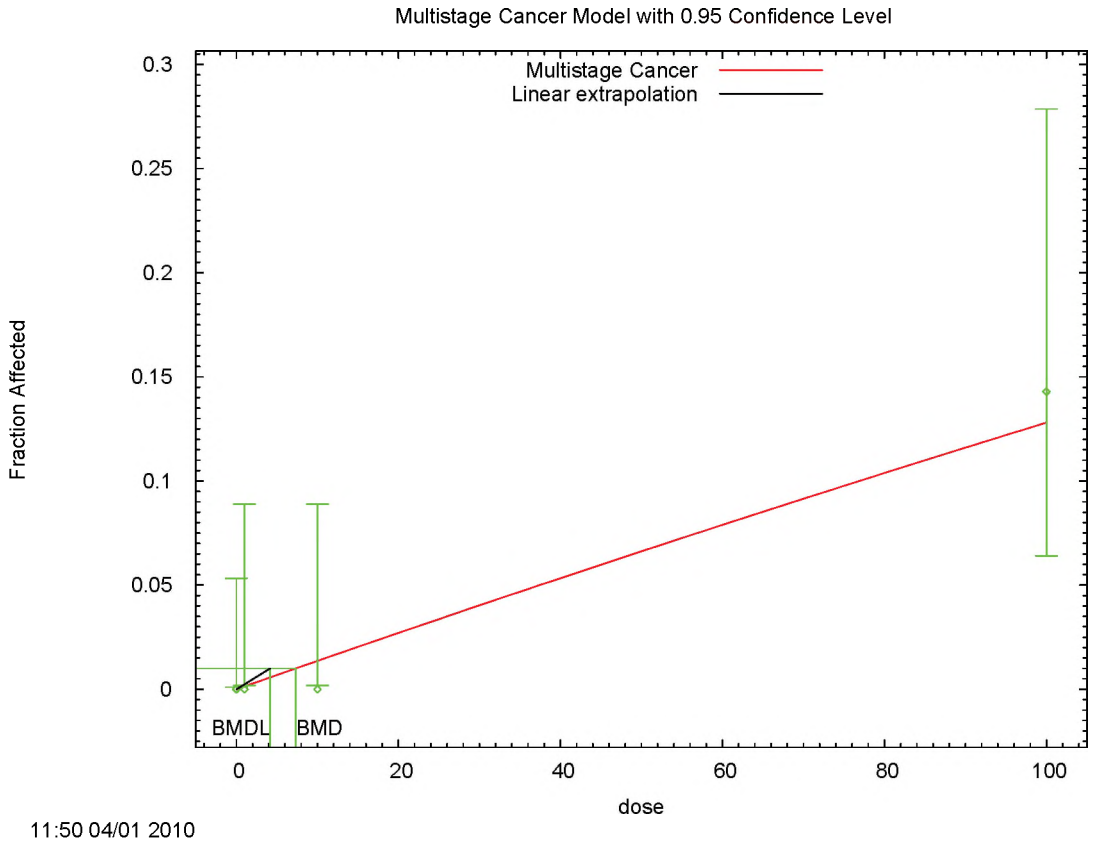
BMDL = 4.15929

BMDU = 14.6306

Taken together, (4.15929, 14.6306) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00240426

F.2.6.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



Kociba et al., 1978: Keratinizing squamous cell carcinoma of lung

F.2.7. National Toxicology Program, 1982: Subcutaneous Tissue: Fibrosarcoma

F.2.7.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**2**	**0.146**	**76.377**	**9.761E+00**	**3.964E+00**	
Multistage Cancer, 2-Degree	2	0.146	76.377	9.761E+00	3.964E+00	final ß=0
Multistage Cancer, 3-Degree	2	0.146	76.377	9.761E+00	3.964E+00	final ß=0

[a] Best-fitting model, BMDS output presented in this appendix

F.2.7.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

National Toxicology Program, 1982: Subcutaneous Tissue: Fibrosarcoma

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Canc\7_msc1_1Perc_sub_fibro.(d)
         Gnuplot Plotting File:  C:\Canc\7_msc1_1Perc_sub_fibro.plt
                                                 Thu Apr 01 12:51:07 2010
 ======================================================================

 Source - Table 10
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =     0.030595
                        Beta(1) =  0.000799545
```

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.54
Beta(1)	-0.54	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0231556	*	*	*
Beta(1)	0.00102962	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-33.5998	4			
Fitted model	-36.1883	2	5.17698	2	0.07513
Reduced model	-37.7465	1	8.29346	3	0.04032

AIC: 76.3766

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0232	1.737	0.000	75	-1.333
1.4000	0.0246	1.228	2.000	50	0.705
7.1000	0.0303	1.514	3.000	50	1.227
71.0000	0.0920	4.509	4.000	49	-0.252

Chi^2 = 3.84 d.f. = 2 P-value = 0.1463

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 9.76124

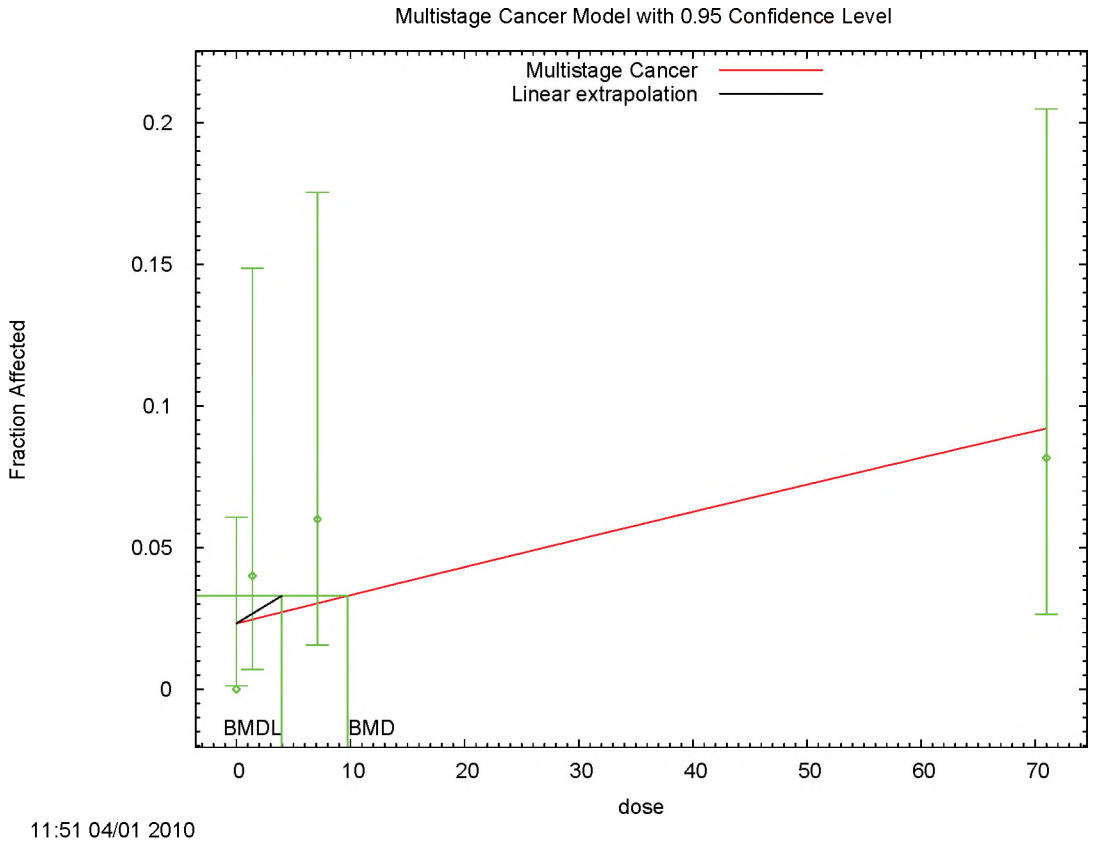
BMDL = 3.96354

BMDU = 1.03301e+006

Taken together, (3.96354, 1.03301e+006) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.002523

F.2.7.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



National Toxicology Program, 1982: Subcutaneous Tissue: Fibrosarcoma

F.2.8. National Toxicology Program, 1982: Liver: Neoplastic Nodule or Hepatocellular Carcinoma

F.2.8.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**2**	**0.398**	**133.832**	**2.554E+00**	**1.600E+00**	
Multistage Cancer, 2-Degree	2	0.503	133.436	1.334E+01	1.652E+00	
Multistage Cancer, 3-Degree	2	0.503	133.436	1.334E+01	1.652E+00	final ß=0

[a] Best-fitting model, BMDS output presented in this appendix

F.2.8.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

National Toxicology Program, 1982: Liver: Neoplastic Nodule or Hepatocellular Carcinoma

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Canc\8_msc1_1Perc_liver_nod.(d)
         Gnuplot Plotting File:  C:\Canc\8_msc1_1Perc_liver_nod.plt
                                              Thu Apr 01 12:51:41 2010
 ================================================================

 Source - Table 10
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =    0.0383072
                        Beta(1) =   0.00417257
```

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.47
Beta(1)	-0.47	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0451327	*	*	*
Beta(1)	0.00393556	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-63.9149	4			
Fitted model	-64.916	2	2.00214	2	0.3675
Reduced model	-74.0195	1	20.2092	3	0.0001536
AIC:	133.832				

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0451	3.385	5.000	75	0.898
1.4000	0.0504	2.469	1.000	49	-0.959
7.1000	0.0714	3.572	3.000	50	-0.314
71.0000	0.2779	13.618	14.000	49	0.122

Chi^2 = 1.84 d.f. = 2 P-value = 0.3984

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 2.55373

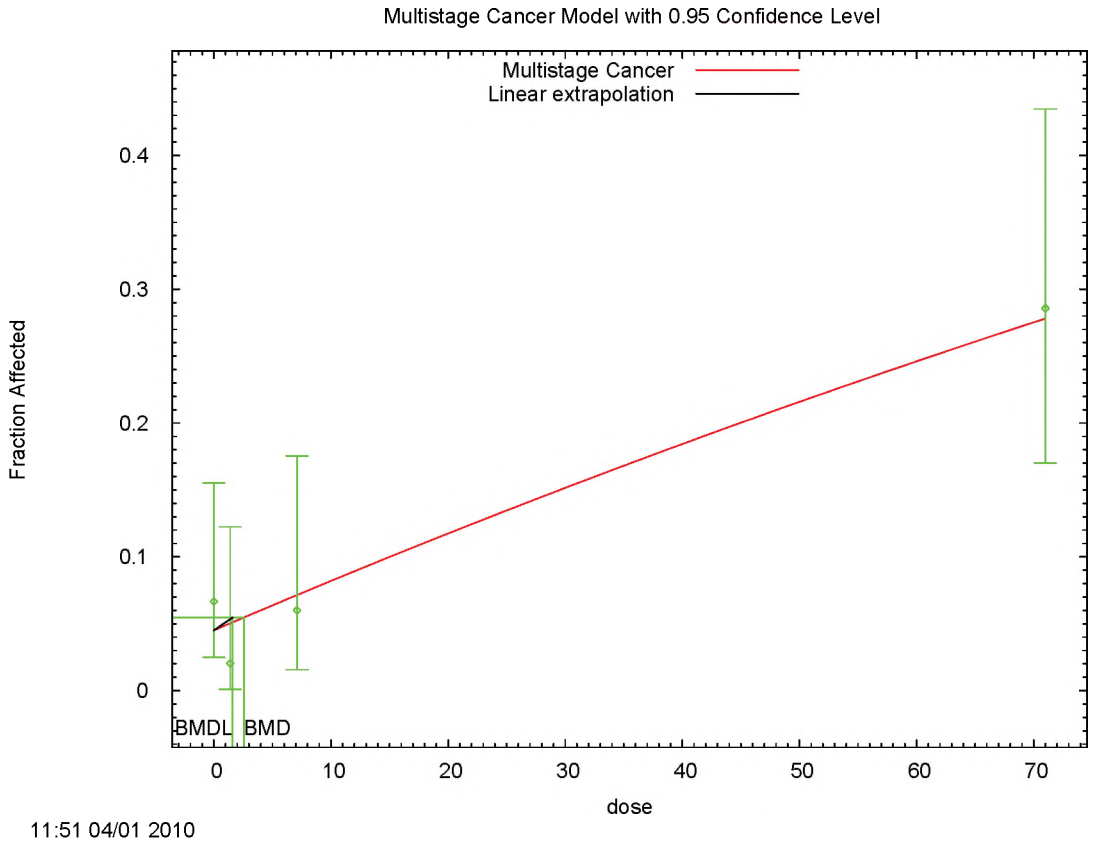
BMDL = 1.59983

BMDU = 4.74206

Taken together, (1.59983, 4.74206) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00625067

F.2.8.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



National Toxicology Program, 1982: Liver: Neoplastic Nodule or Hepatocellular Carcinoma

F.2.9. National Toxicology Program, 1982: Adrenal: Cortical Adenoma, or Carcinoma or Adenoma, NOS

F.2.9.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**2**	**0.405**	**203.380**	**3.672E+00**	**1.871E+00**	
Multistage Cancer, 2-Degree	2	0.501	202.885	1.577E+01	1.974E+00	
Multistage Cancer, 3-Degree	2	0.513	202.832	2.600E+01	1.986E+00	

[a] Best-fitting model, BMDS output presented in this appendix

F.2.9.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

National Toxicology Program, 1982: Adrenal: Cortical Adenoma, or Carcinoma or Adenoma, NOS

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Canc\9_msc1_1Perc_adre_cort_ad_carc.(d)
         Gnuplot Plotting File:  C:\Canc\9_msc1_1Perc_adre_cort_ad_carc.plt
                                                Thu Apr 01 12:53:57 2010
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 Source - Table 10
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =     0.140663
```

Beta(1) = 0.00289845

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.48
Beta(1)	-0.48	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.143284	*	*	*
Beta(1)	0.00273674	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-98.7282	4			
Fitted model	-99.6898	2	1.92318	2	0.3823
Reduced model	-102.201	1	6.94636	3	0.07363

AIC: 203.38

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1433	10.460	11.000	73	0.180
1.4000	0.1466	7.181	9.000	49	0.735
7.1000	0.1598	7.829	5.000	49	-1.103
71.0000	0.2946	13.551	14.000	46	0.145

Chi^2 = 1.81 d.f. = 2 P-value = 0.4046

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 3.67237

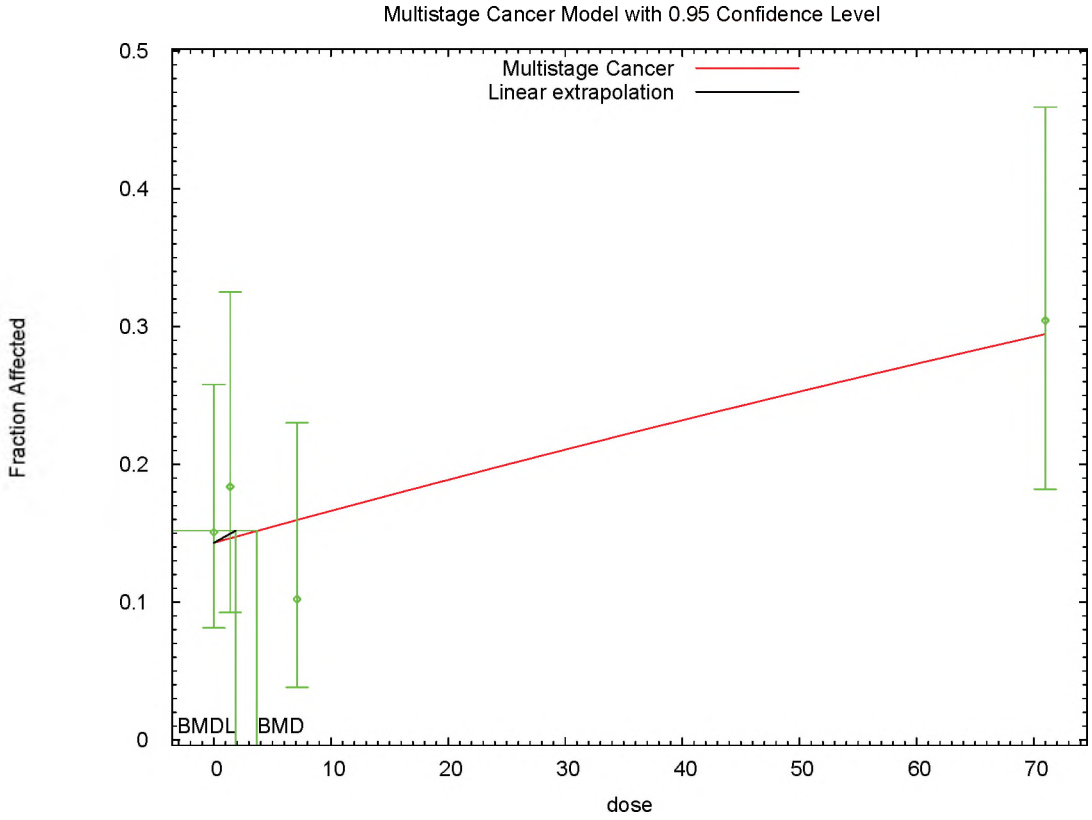
BMDL = 1.87133

BMDU = 15.4002

Taken together, (1.87133, 15.4002) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00534381

F.2.9.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



National Toxicology Program, 1982: Adrenal: Cortical Adenoma, or Carcinoma or Adenoma, NOS

F.2.10. National Toxicology Program, 1982: Thyroid: Follicular-Cell Adenoma

F.2.10.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**2**	**0.661**	**92.020**	**7.571E+00**	**3.488E+00**	
Multistage Cancer, 2-Degree	2	0.769	91.639	2.257E+01	3.656E+00	
Multistage Cancer, 3-Degree	2	0.781	91.601	3.302E+01	3.675E+00	

[a] Best-fitting model, BMDS output presented in this appendix

F.2.10.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

National Toxicology Program, 1982: Thyroid: Follicular-Cell Adenoma

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Canc\10_msc1_1Perc_thy_ad.(d)
         Gnuplot Plotting File:  C:\Canc\10_msc1_1Perc_thy_ad.plt
                                                Thu Apr 01 12:54:31 2010
 ================================================================

 Source - Table 10
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =     0.032089
                        Beta(1) =   0.00143599
```

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.5
Beta(1)	-0.5	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0345958	*	*	*
Beta(1)	0.00132742	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-43.5264	4			
Fitted model	-44.0098	2	0.966786	2	0.6167
Reduced model	-46.2299	1	5.40699	3	0.1443

AIC: 92.0196

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0346	2.525	3.000	73	0.304
1.4000	0.0364	1.637	2.000	45	0.289
7.1000	0.0437	2.139	1.000	49	-0.796
71.0000	0.1214	5.707	6.000	47	0.131

Chi^2 = 0.83 d.f. = 2 P-value = 0.6614

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 7.57131

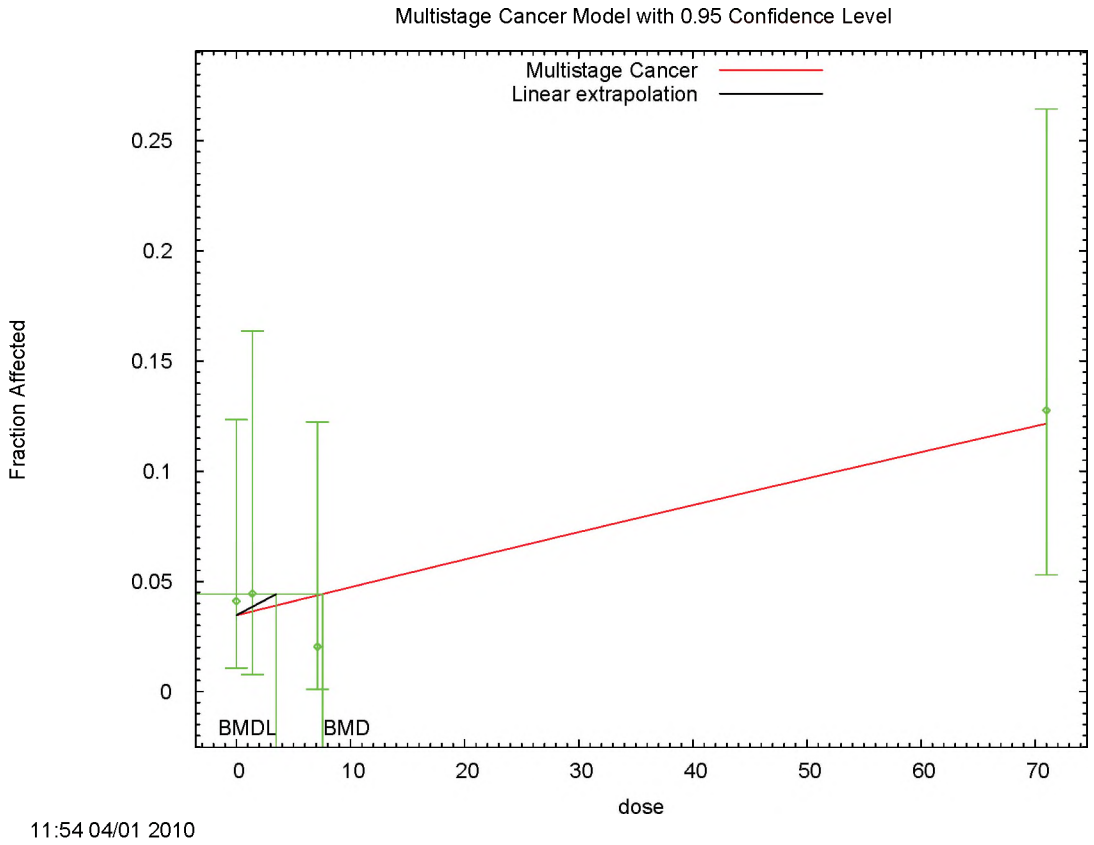
BMDL = 3.48815

BMDU = 964541

Taken together, (3.48815, 964541) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00286685

F.2.10.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



National Toxicology Program, 1982: Thyroid: Follicular-Cell Adenoma

F.2.11. National Toxicology Program, 1982: Liver: Neoplastic Nodule or Hepatocellular Carcinoma

F.2.11.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**2**	**0.398**	**133.832**	**2.554E+00**	**1.600E+00**	
Multistage Cancer, 2-Degree	2	0.503	133.436	1.334E+01	1.652E+00	
Multistage Cancer, 3-Degree	2	0.503	133.436	1.334E+01	1.652E+00	final ß=0

[a] Best-fitting model, BMDS output presented in this appendix

F.2.11.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

National Toxicology Program, 1982: Liver: Neoplastic Nodule or Hepatocellular Carcinoma

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Canc\11_msc1_1Perc_liver_nod.(d)
         Gnuplot Plotting File:  C:\Canc\11_msc1_1Perc_liver_nod.plt
                                                Thu Apr 01 12:55:05 2010
 ======================================================================

 Source - Table 9
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =  0.000900399
```

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Beta(1)
Beta(1)	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0.000775683	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-11.3484	4			
Fitted model	-11.6976	1	0.698469	3	0.8736
Reduced model	-15.9189	1	9.14109	3	0.02747

AIC: 25.3952

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	74	0.000
1.4000	0.0011	0.054	0.000	50	-0.233
7.1000	0.0055	0.275	0.000	50	-0.525
71.0000	0.0536	2.679	3.000	50	0.201

Chi^2 = 0.37 d.f. = 3 P-value = 0.9462

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 12.9568

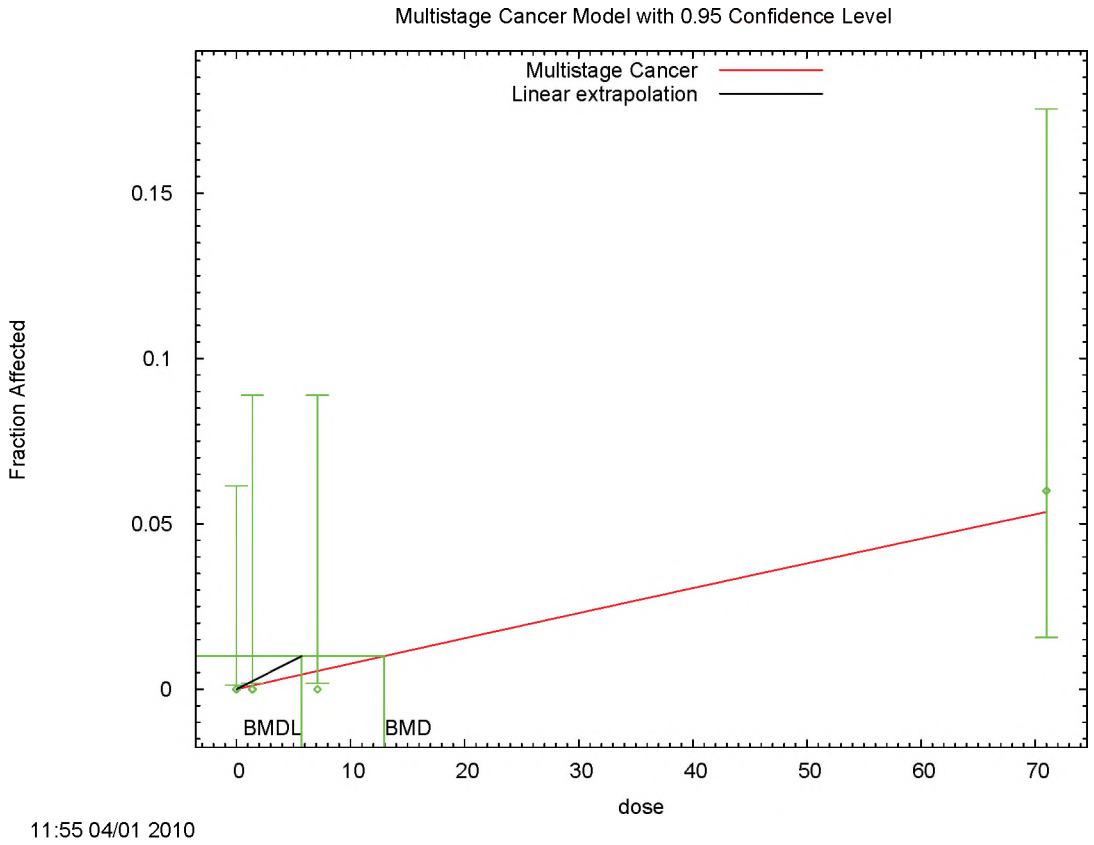
BMDL = 5.70369

BMDU = 39.9878

Taken together, (5.70369, 39.9878) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00175325

F.2.11.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



National Toxicology Program, 1982: Liver: Neoplastic Nodule or Hepatocellular Carcinoma

F.2.12. National Toxicology Program, 1982: Thyroid: Follicular-Cell Adenoma or Carcinoma

F.2.12.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**2**	**0.028**	**151.224**	**3.521E+00**	**1.916E+00**	
Multistage Cancer, 2-Degree	2	0.028	151.224	3.521E+00	1.916E+00	final ß=0
Multistage Cancer, 3-Degree	2	0.028	151.224	3.521E+00	1.916E+00	final ß=0

[a] Best-fitting model, BMDS output presented in this appendix

F.2.12.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

National Toxicology Program, 1982: Thyroid: Follicular-Cell Adenoma or Carcinoma

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Canc\12_msc1_1Perc_thyroid.(d)
         Gnuplot Plotting File:  C:\Canc\12_msc1_1Perc_thyroid.plt
                                                Thu Apr 01 12:55:38 2010
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 Source - Table 9
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =    0.0867382
                        Beta(1) =   0.00232055
```

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.53
Beta(1)	-0.53	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0704713	*	*	*
Beta(1)	0.00285481	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-69.5946	4			
Fitted model	-73.6119	2	8.03468	2	0.018
Reduced model	-77.5267	1	15.8643	3	0.001209

AIC: 151.224

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0705	4.863	1.000	69	-1.817
1.4000	0.0742	3.561	5.000	48	0.793
7.1000	0.0891	4.456	8.000	50	1.759
71.0000	0.2410	12.051	11.000	50	-0.347

Chi^2 = 7.14 d.f. = 2 P-value = 0.0281

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 3.5205

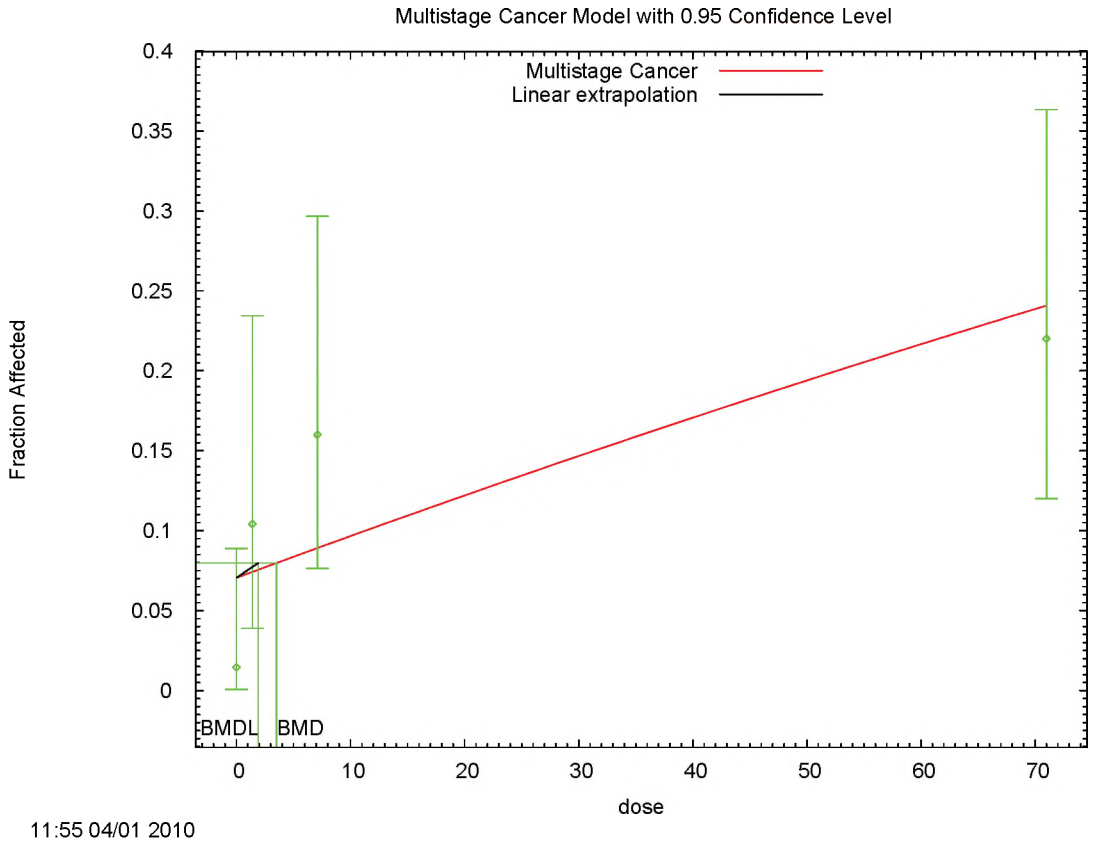
BMDL = 1.91558

BMDU = 9.76663

Taken together, (1.91558, 9.76663) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00522034

F.2.12.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



National Toxicology Program, 1982: Thyroid: Follicular-Cell Adenoma or Carcinoma

F.2.13. National Toxicology Program, 1982: Adrenal cortex: Adenoma

F.2.13.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**2**	**0.054**	**199.672**	**1.400E+01**	**3.444E+00**	
Multistage Cancer, 2-Degree	2	0.054	199.672	1.400E+01	3.444E+00	final ß=0
Multistage Cancer, 3-Degree	2	0.054	199.672	1.400E+01	3.444E+00	final ß=0

[a] Best-fitting model, BMDS output presented in this appendix

F.2.13.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

National Toxicology Program, 1982: Adrenal cortex: Adenoma

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Canc\13_msc1_1Perc_adre_cort.(d)
         Gnuplot Plotting File:  C:\Canc\13_msc1_1Perc_adre_cort.plt
                                                Thu Apr 01 12:56:10 2010
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 Source - Table 9
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =     0.168444
                        Beta(1) =  0.000395949
```

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.53
Beta(1)	-0.53	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.153096	*	*	*
Beta(1)	0.000718012	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-94.8672	4			
Fitted model	-97.8359	2	5.93732	2	0.05137
Reduced model	-98.0432	1	6.35197	3	0.09569

AIC: 199.672

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1531	11.023	6.000	72	-1.644
1.4000	0.1539	7.697	9.000	50	0.510
7.1000	0.1574	7.713	12.000	49	1.682
71.0000	0.1952	9.564	9.000	49	-0.203

Chi^2 = 5.83 d.f. = 2 P-value = 0.0541

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

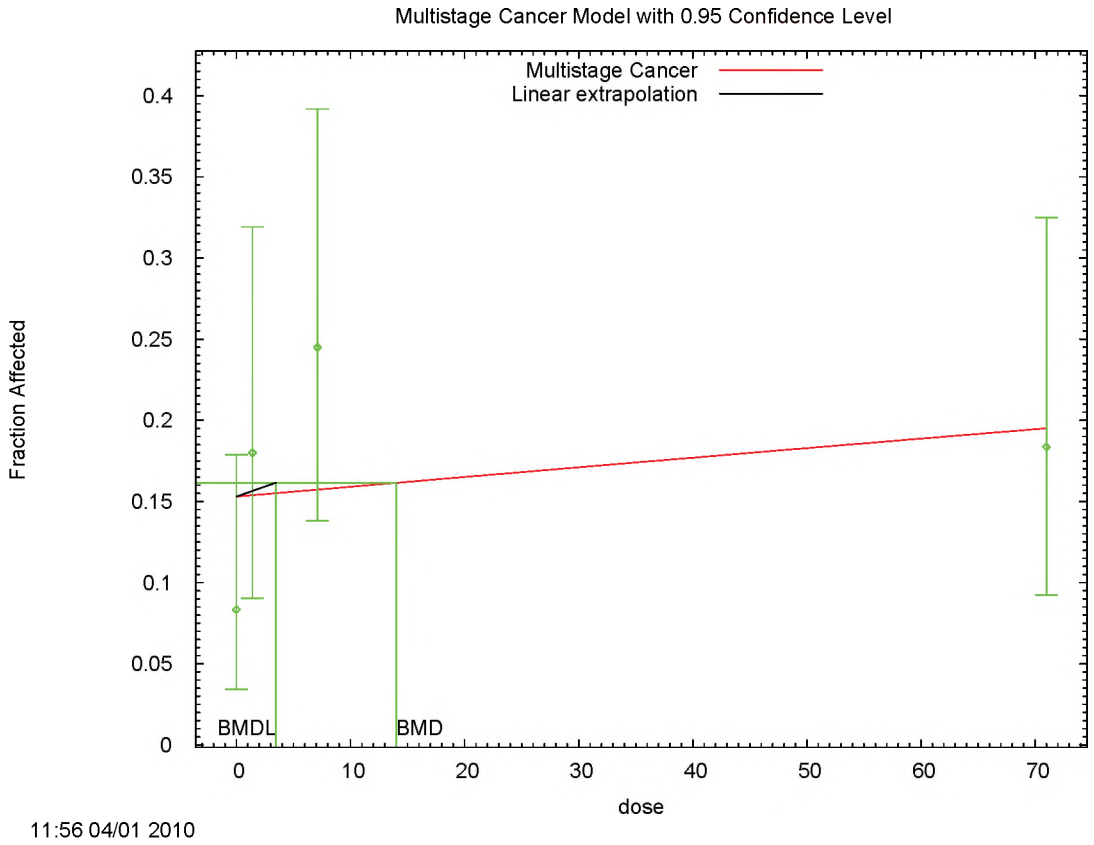
Confidence level = 0.95

BMD = 13.9974

BMDL = 3.4443

BMDU did not converge for BMR = 0.010000
BMDU calculation failed
BMDU = Inf

F.2.13.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



National Toxicology Program, 1982: Adrenal cortex: Adenoma

F.2.14. National Toxicology Program, 1982: Subcutaneous Tissue: Fibrosarcoma

F.2.14.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**2**	**0.146**	**76.377**	**9.761E+00**	**3.964E+00**	
Multistage Cancer, 2-Degree	2	0.146	76.377	9.761E+00	3.964E+00	final ß=0
Multistage Cancer, 3-Degree	2	0.146	76.377	9.761E+00	3.964E+00	final ß=0

[a] Best-fitting model, BMDS output presented in this appendix

F.2.14.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

National Toxicology Program, 1982: Subcutaneous Tissue: Fibrosarcoma

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Canc\14_msc1_1Perc_subcu_fibro.(d)
         Gnuplot Plotting File:  C:\Canc\14_msc1_1Perc_subcu_fibro.plt
                                                 Thu Apr 01 12:56:41 2010
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =    0.0143554
                        Beta(1) =  0.000341874
```

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.5
Beta(1)	-0.5	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0145028	*	*	*
Beta(1)	0.000338561	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-30.9876	4			
Fitted model	-31.0199	2	0.0645971	2	0.9682
Reduced model	-34.3291	1	6.68308	3	0.08272

AIC: 66.0397

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0145	1.073	1.000	74	-0.071
5.7000	0.0164	0.820	1.000	50	0.200
28.6000	0.0240	1.152	1.000	48	-0.143
286.0000	0.1055	4.956	5.000	47	0.021

Chi^2 = 0.07 d.f. = 2 P-value = 0.9675

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 29.6855

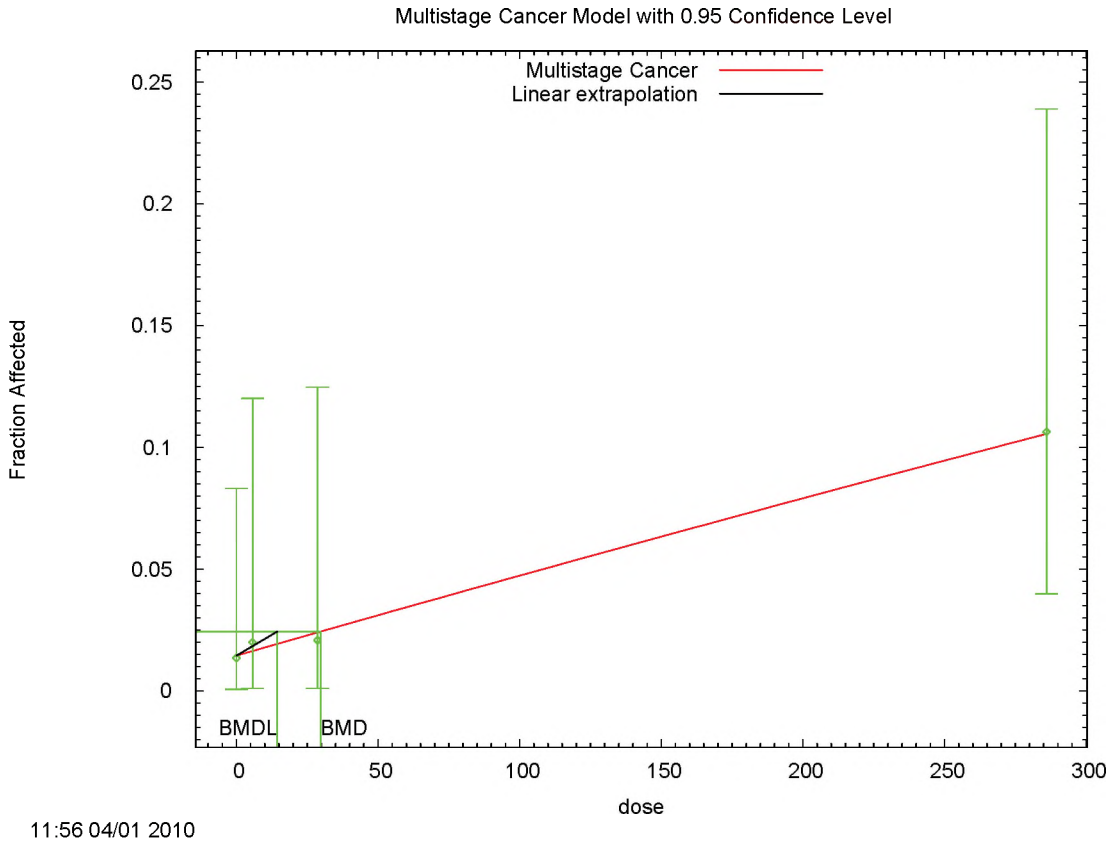
BMDL = 14.3524

BMDU = 100.382

Taken together, (14.3524, 100.382) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.000696747

F.2.14.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



National Toxicology Program, 1982: Subcutaneous Tissue: Fibrosarcoma

F.2.15. National Toxicology Program, 1982: Hematopoietio System: Lymphoma or Leukemia

F.2.15.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**2**	**0.987**	**261.425**	**1.034E+01**	**5.456E+00**	
Multistage Cancer, 2-Degree	2	0.987	261.425	1.034E+01	5.456E+00	final ß=0
Multistage Cancer, 3-Degree	2	0.987	261.425	1.034E+01	5.456E+00	final ß=0

[a] Best-fitting model, BMDS output presented in this appendix

F.2.15.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

National Toxicology Program, 1982: Hematopoietio System: Lymphoma or Leukemia

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         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Canc\15_msc1_1Perc_mice_f_lymphoma.(d)
         Gnuplot Plotting File:  C:\Canc\15_msc1_1Perc_mice_f_lymphoma.plt
                                                Thu Apr 01 12:57:14 2010
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 Table 15 page 64 Hematopoietic System Lymphoma or Leukemia
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =     0.242959
                        Beta(1) =  0.000967723
```

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.48
Beta(1)	-0.48	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.242712	*	*	*
Beta(1)	0.000971954	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-128.699	4			
Fitted model	-128.712	2	0.0264819	2	0.9868
Reduced model	-131.412	1	5.42487	3	0.1432
AIC:	261.425				

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.2427	17.961	18.000	74	0.011
5.7000	0.2469	12.345	12.000	50	-0.113
28.6000	0.2635	12.647	13.000	48	0.116
286.0000	0.4265	20.045	20.000	47	-0.013

Chi^2 = 0.03 d.f. = 2 P-value = 0.9868

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 10.3403

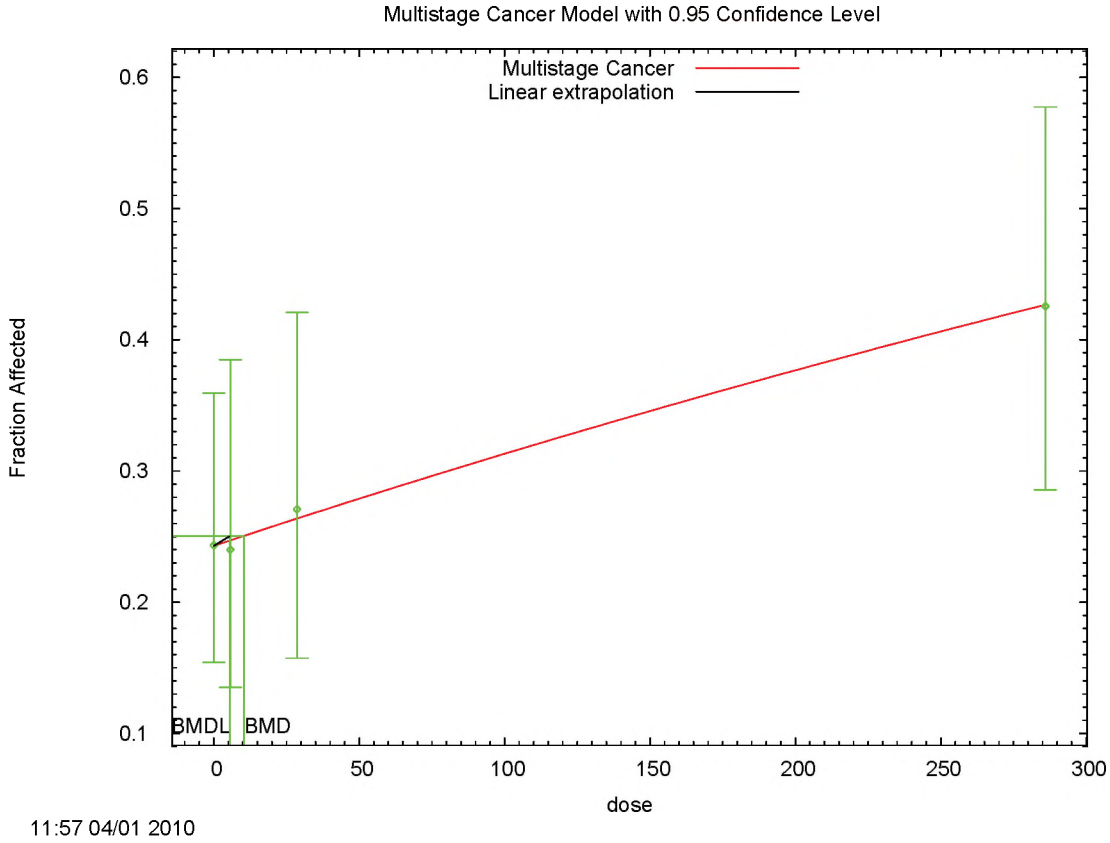
BMDL = 5.45599

BMDU = 38.9139

Taken together, (5.45599, 38.9139) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00183285

F.2.15.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



National Toxicology Program, 1982: Hematopoietio System: Lymphoma or Leukemia

F.2.16. National Toxicology Program, 1982: Liver: Hepatooellular Adenoma or Carcinoma

F.2.16.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**2**	**0.244**	**156.001**	**1.458E+01**	**7.829E+00**	
Multistage Cancer, 2-Degree	2	0.244	156.001	1.458E+01	7.829E+00	final ß=0
Multistage Cancer, 3-Degree	2	0.244	156.001	1.458E+01	7.829E+00	final ß=0

[a] Best-fitting model, BMDS output presented in this appendix

F.2.16.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

National Toxicology Program, 1982: Liver: Hepatooellular Adenoma or Carcinoma

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         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Canc\16_msc1_1Perc_mice_f_liv_aden_carc.(d)
         Gnuplot Plotting File:  C:\Canc\16_msc1_1Perc_mice_f_liv_aden_carc.plt
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =    0.0888873
                        Beta(1) =  0.000616931
```

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.5
Beta(1)	-0.5	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0788077	*	*	*
Beta(1)	0.000689385	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-74.5177	4			
Fitted model	-76.0006	2	2.96597	2	0.227
Reduced model	-79.6703	1	10.3053	3	0.01614

AIC: 156.001

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0788	5.753	3.000	73	-1.196
5.7000	0.0824	4.121	6.000	50	0.966
28.6000	0.0968	4.646	6.000	48	0.661
286.0000	0.2436	11.452	11.000	47	-0.153

Chi^2 = 2.82 d.f. = 2 P-value = 0.2436

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 14.5787

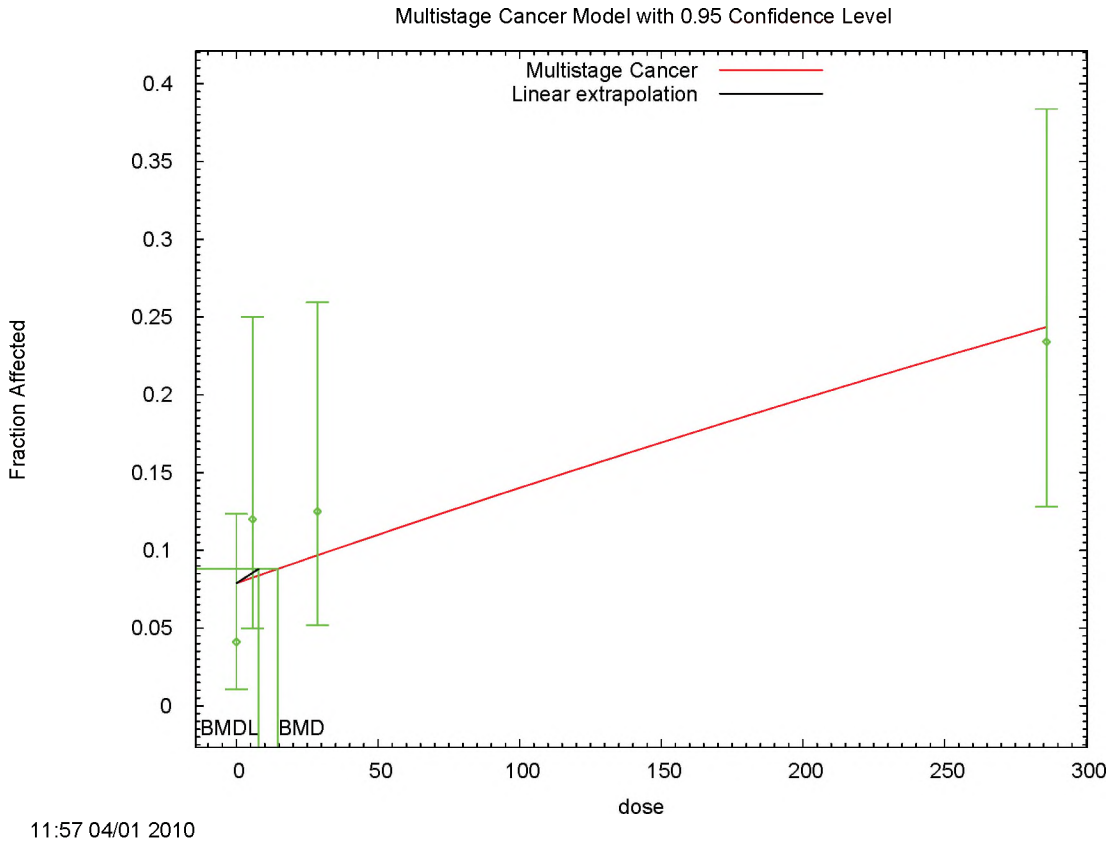
BMDL = 7.82902

BMDU = 42.4536

Taken together, (7.82902, 42.4536) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0012773

F.2.16.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



National Toxicology Program, 1982: Liver: Hepatooellular Adenoma or Carcinoma

F.2.17. National Toxicology Program, 1982: Subcutaneous Tissue: Fibrosarcoma

F.2.17.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**2**	**0.146**	**76.377**	**9.761E+00**	**3.964E+00**	
Multistage Cancer, 2-Degree	2	0.146	76.377	9.761E+00	3.964E+00	final ß=0
Multistage Cancer, 3-Degree	2	0.146	76.377	9.761E+00	3.964E+00	final ß=0

[a] Best-fitting model, BMDS output presented in this appendix

F.2.17.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

National Toxicology Program, 1982: Subcutaneous Tissue: Fibrosarcoma

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 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Canc\17_msc1_1Perc_mice_f_thyroid_aden.(d)
         Gnuplot Plotting File:  C:\Canc\17_msc1_1Perc_mice_f_thyroid_aden.plt
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =      0.02405
                        Beta(1) =  0.000315564
```

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.51
Beta(1)	-0.51	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0207192	*	*	*
Beta(1)	0.000331835	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-32.0017	4			
Fitted model	-34.6122	2	5.22112	2	0.07349
Reduced model	-37.2405	1	10.4776	3	0.01491

AIC: 73.2245

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0207	1.430	0.000	69	-1.208
5.7000	0.0226	1.128	3.000	50	1.782
28.6000	0.0300	1.409	1.000	47	-0.350
286.0000	0.1094	5.032	5.000	46	-0.015

Chi^2 = 4.76 d.f. = 2 P-value = 0.0927

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 30.2871

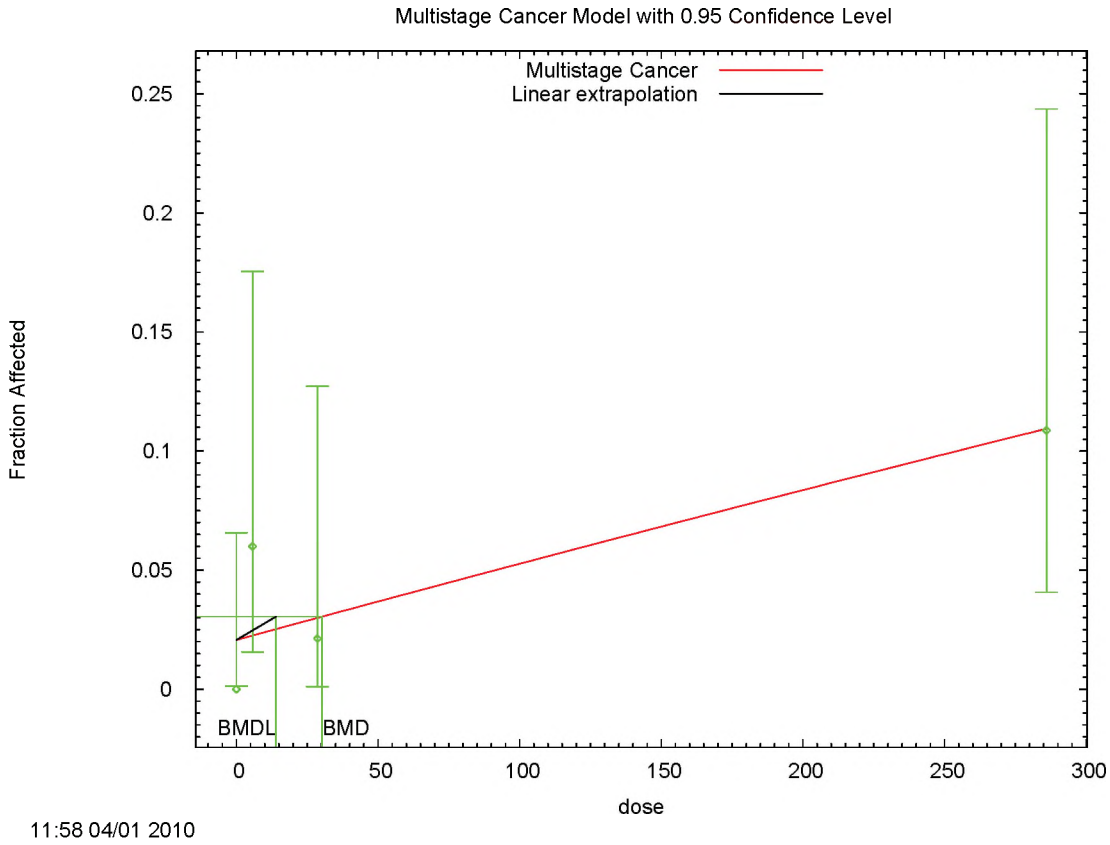
BMDL = 13.993

BMDU = 130.014

Taken together, (13.993 , 130.014) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.000714641

F.2.17.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



National Toxicology Program, 1982: Subcutaneous Tissue: Fibrosarcoma

F.2.18. National Toxicology Program, 1982: Lung: Alveolar/Bronchiolar Adenoma or Carcinoma

F.2.18.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree	2	0.138	167.341	3.706E+00	2.026E+00	
Multistage Cancer, 2-Degree [a]	**2**	**0.181**	**166.805**	**1.590E+01**	**2.139E+00**	
Multistage Cancer, 3-Degree	2	0.185	166.777	2.618E+01	2.145E+00	

[a] Best-fitting model, BMDS output presented in this appendix

F.2.18.2. *Output for Selected Model: Multistage Cancer, 2-Degree*

National Toxicology Program, 1982: Lung: Alveolar/Bronchiolar Adenoma or Carcinoma

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 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Canc\18_msc2_1Perc_lung_aden_carc.(d)
         Gnuplot Plotting File:  C:\Canc\18_msc2_1Perc_lung_aden_carc.plt
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =    0.0889033
                        Beta(1) =            0
```

Beta(2) = 4.12413e-005

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Beta(1)
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Background	Beta(2)
Background	1	-0.45
Beta(2)	-0.45	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0953987	*	*	*
Beta(1)	0	*	*	*
Beta(2)	3.97322e-005	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-79.5959	4			
Fitted model	-81.4024	2	3.61287	2	0.1642
Reduced model	-85.3351	1	11.4782	3	0.009402

AIC: 166.805

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0954	6.773	10.000	71	1.304
1.4000	0.0955	4.583	2.000	48	-1.268
7.1000	0.0972	4.666	4.000	48	-0.325
71.0000	0.2596	12.979	13.000	50	0.007

Chi^2 = 3.41 d.f. = 2 P-value = 0.1814

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 15.9045

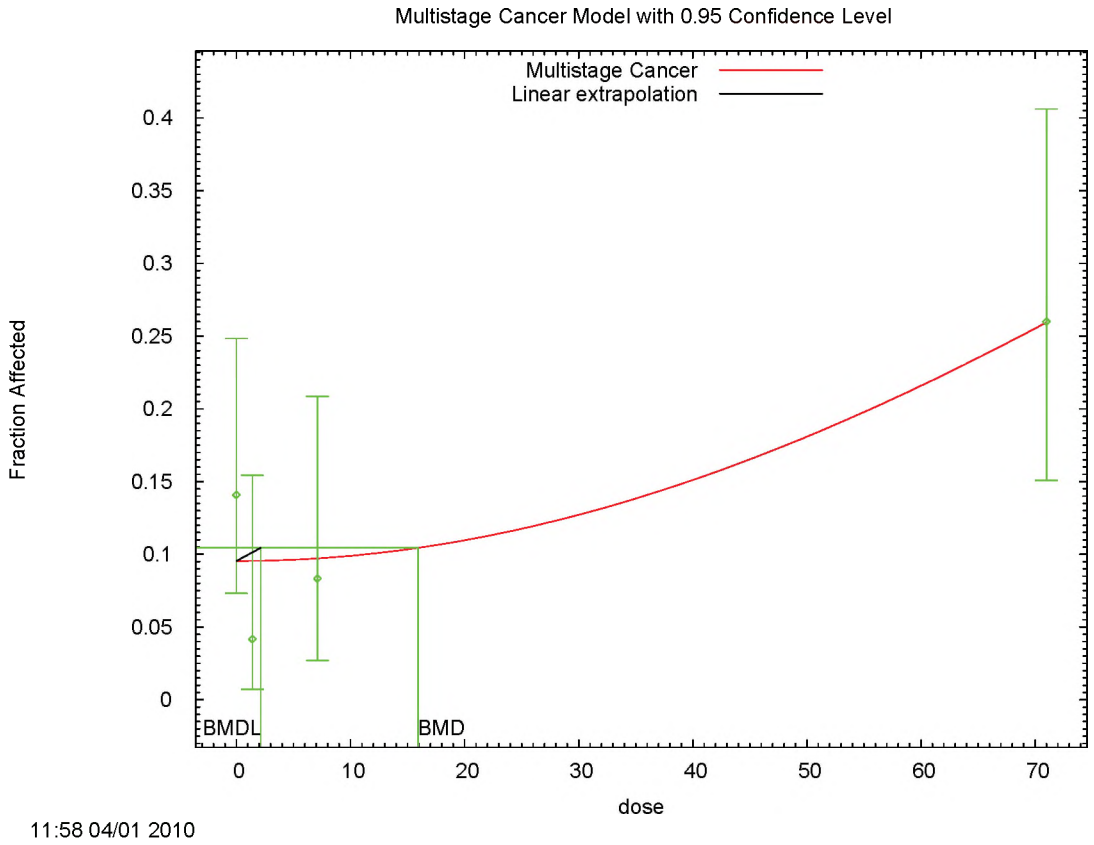
BMDL = 2.1388

BMDU = 26.2712

Taken together, (2.1388 , 26.2712) is a 90 % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor = 0.00467551

F.2.18.3. *Figure for Selected Model: Multistage Cancer, 2-Degree*



National Toxicology Program, 1982: Lung: Alveolar/Bronchiolar Adenoma or Carcinoma

F.2.19. National Toxicology Program, 1982: Liver: Hepatocellular Adenoma or Carcinoma

F.2.19.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**2**	**0.916**	**258.572**	**1.338E+00**	**8.620E-01**	
Multistage Cancer, 2-Degree	2	0.916	258.572	1.338E+00	8.620E-01	final ß=0
Multistage Cancer, 3-Degree	2	0.916	258.572	1.338E+00	8.620E-01	final ß=0

[a] Best-fitting model, BMDS output presented in this appendix

F.2.19.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

National Toxicology Program, 1982: Liver: Hepatocellular Adenoma or Carcinoma

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         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Canc\19_msc1_1Perc_mice_m_liver_aden_carc.(d)
         Gnuplot Plotting File:  C:\Canc\19_msc1_1Perc_mice_m_liver_aden_carc.plt
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =      0.22264
                        Beta(1) =    0.0074005
```

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.46
Beta(1)	-0.46	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.219315	*	*	*
Beta(1)	0.00750879	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-127.199	4			
Fitted model	-127.286	2	0.174343	2	0.9165
Reduced model	-135.589	1	16.7801	3	0.0007843

AIC: 258.572

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.2193	16.010	15.000	73	-0.286
1.4000	0.2275	11.146	12.000	49	0.291
7.1000	0.2598	12.732	13.000	49	0.087
71.0000	0.5419	27.096	27.000	50	-0.027

Chi^2 = 0.17 d.f. = 2 P-value = 0.9164

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 1.33848

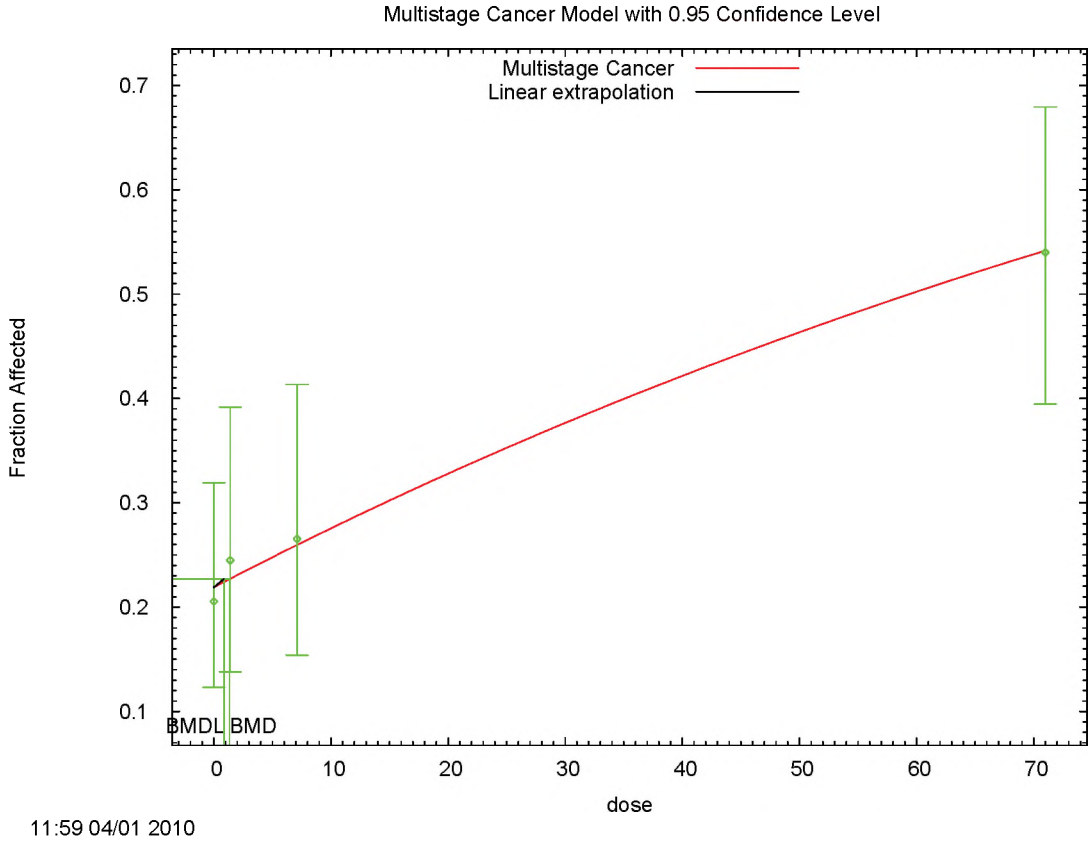
BMDL = 0.861975

BMDU = 2.4671

Taken together, (0.861975, 2.4671) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0116013

F.2.19.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



National Toxicology Program, 1982: Liver: Hepatocellular Adenoma or Carcinoma

F.2.20. National Toxicology Program, 2006: Liver: Cholangiocarcinoma

F.2.20.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree	5	0.024	129.070	1.872E+00	1.404E+00	
Multistage Cancer, 2-Degree	5	0.947	114.349	9.440E+00	5.290E+00	
Multistage Cancer, 3-Degree [a]	**4**	**0.995**	**115.158**	**1.310E+01**	**4.468E+00**	

[a] Best-fitting model, BMDS output presented in this appendix

F.2.20.2. *Output for Selected Model: Multistage Cancer, 3-Degree*

National Toxicology Program, 2006: Liver: Cholangiocarcinoma

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 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Canc\20_msc3_1Perc_liv_cho-carc.(d)
         Gnuplot Plotting File:  C:\Canc\20_msc3_1Perc_liv_cho-carc.plt
                                                 Thu Apr 01 13:00:03 2010
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 4
 Total number of specified parameters = 0
 Degree of polynomial = 3


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =  0.000561481
                        Beta(2) = 1.74365e-005
                        Beta(3) = 1.40248e-006
```

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background -Beta(1)
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Beta(2)	Beta(3)
Beta(2)	1	-0.99
Beta(3)	-0.99	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0	*	*	*
Beta(2)	4.35927e-005	*	*	*
Beta(3)	1.14186e-006	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-55.408	6			
Fitted model	-55.5789	2	0.34181	4	0.987
Reduced model	-96.9934	1	83.1708	5	<.0001

AIC: 115.158

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	49	0.000
2.1400	0.0002	0.010	0.000	48	-0.101
7.1400	0.0026	0.121	0.000	46	-0.349
15.7000	0.0150	0.752	1.000	50	0.288
32.9000	0.0841	4.121	4.000	49	-0.062
71.4000	0.4716	24.994	25.000	53	0.002

Chi^2 = 0.22 d.f. = 4 P-value = 0.9945

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 13.1014

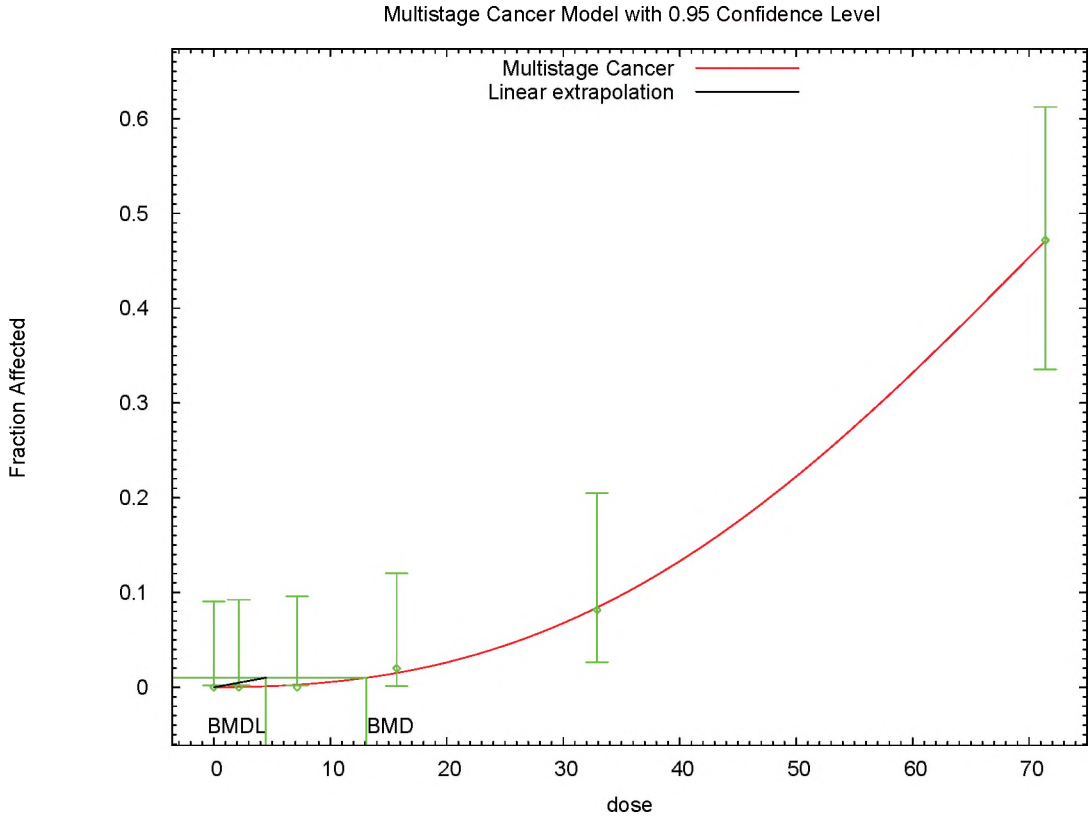
BMDL = 4.46755

BMDU = 19.1783

Taken together, (4.46755, 19.1783) is a 90 % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor = 0.00223836

F.2.20.3. *Figure for Selected Model: Multistage Cancer, 3-Degree*



National Toxicology Program, 2006: Liver: Cholangiocarcinoma

F.2.21. National Toxicology Program, 2006: Liver: Hepatocellular adenoma

F.2.21.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree	5	0.131	82.310	4.393E+00	2.915E+00	
Multistage Cancer, 2-Degree	5	0.857	73.656	1.475E+01	8.618E+00	
Multistage Cancer, 3-Degree [a]	**5**	**0.999**	**71.216**	**2.379E+01**	**1.153E+01**	

[a] Best-fitting model, BMDS output presented in this appendix

F.2.21.2. *Output for Selected Model: Multistage Cancer, 3-Degree*

National Toxicology Program, 2006: Liver: Hepatocellular adenoma

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Canc\21_msc3_1Perc_liv_hepat_ad.(d)
         Gnuplot Plotting File:  C:\Canc\21_msc3_1Perc_liv_hepat_ad.plt
                                                 Thu Apr 01 13:00:36 2010
 ================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 4
 Total number of specified parameters = 0
 Degree of polynomial = 3


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =            0
                        Beta(2) =            0
                        Beta(3) = 7.77141e-007
```

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background -Beta(1) -Beta(2)
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Beta(3)
Beta(3)	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0	*	*	*
Beta(3)	7.46408e-007	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-34.4075	6			
Fitted model	-34.6078	1	0.40065	5	0.9953
Reduced model	-56.3333	1	43.8515	5	<.0001

AIC: 71.2156

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	49	0.000
2.1400	0.0000	0.000	0.000	48	-0.019
7.1400	0.0003	0.012	0.000	46	-0.112
15.7000	0.0029	0.144	0.000	50	-0.380
32.9000	0.0262	1.285	1.000	49	-0.255
71.4000	0.2379	12.609	13.000	53	0.126

Chi^2 = 0.24 d.f. = 5 P-value = 0.9986

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 23.7904

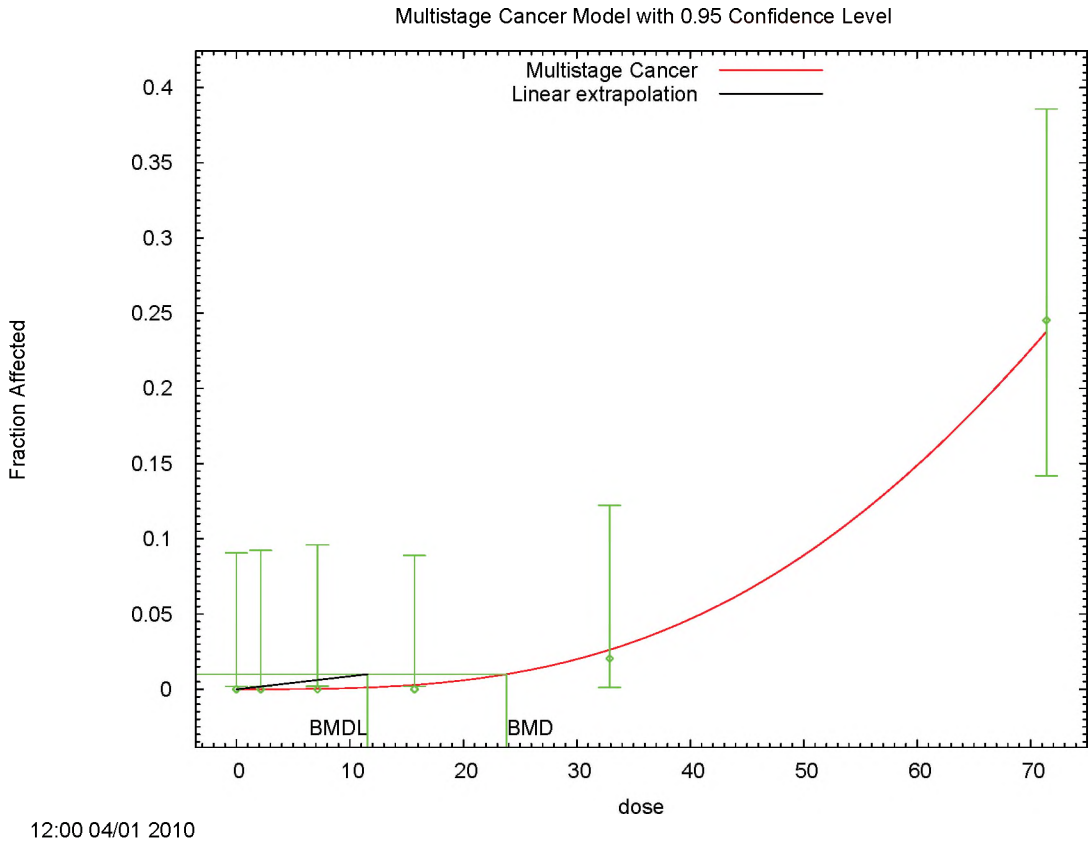
BMDL = 11.5343

BMDU = 27.8755

Taken together, (11.5343, 27.8755) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.000866978

F.2.21.3. *Figure for Selected Model: Multistage Cancer, 3-Degree*



National Toxicology Program, 2006: Liver: Hepatocellular adenoma

F.2.22. National Toxicology Program, 2006: Oral mucosa: squamous cell carcinoma

F.2.22.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**4**	**0.386**	**125.484**	**4.751E+00**	**2.956E+00**	
Multistage Cancer, 2-Degree	4	0.587	123.245	1.635E+01	3.845E+00	
Multistage Cancer, 3-Degree	4	0.587	123.245	1.635E+01	3.844E+00	final ß=0

[a] Best-fitting model, BMDS output presented in this appendix

F.2.22.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

National Toxicology Program, 2006: Oral mucosa: squamous cell carcinoma

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Canc\22_msc1_1Perc_oral_carc.(d)
         Gnuplot Plotting File:  C:\Canc\22_msc1_1Perc_oral_carc.plt
                                                 Thu Apr 01 13:01:11 2010
 ======================================================================

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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                     Background =   0.00607545
                        Beta(1) =   0.00265195
```

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.6
Beta(1)	-0.6	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0171416	*	*	*
Beta(1)	0.00211536	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-57.5353	6			
Fitted model	-60.7418	2	6.41293	4	0.1704
Reduced model	-67.7782	1	20.4858	5	0.001013

AIC: 125.484

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0171	0.840	1.000	49	0.176
2.1400	0.0216	1.036	2.000	48	0.958
7.1400	0.0319	1.466	1.000	46	-0.391
15.7000	0.0492	2.462	0.000	50	-1.609
32.9000	0.0832	4.078	4.000	49	-0.040
71.4000	0.1549	8.211	10.000	53	0.679

Chi^2 = 4.15 d.f. = 4 P-value = 0.3855

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 4.75111

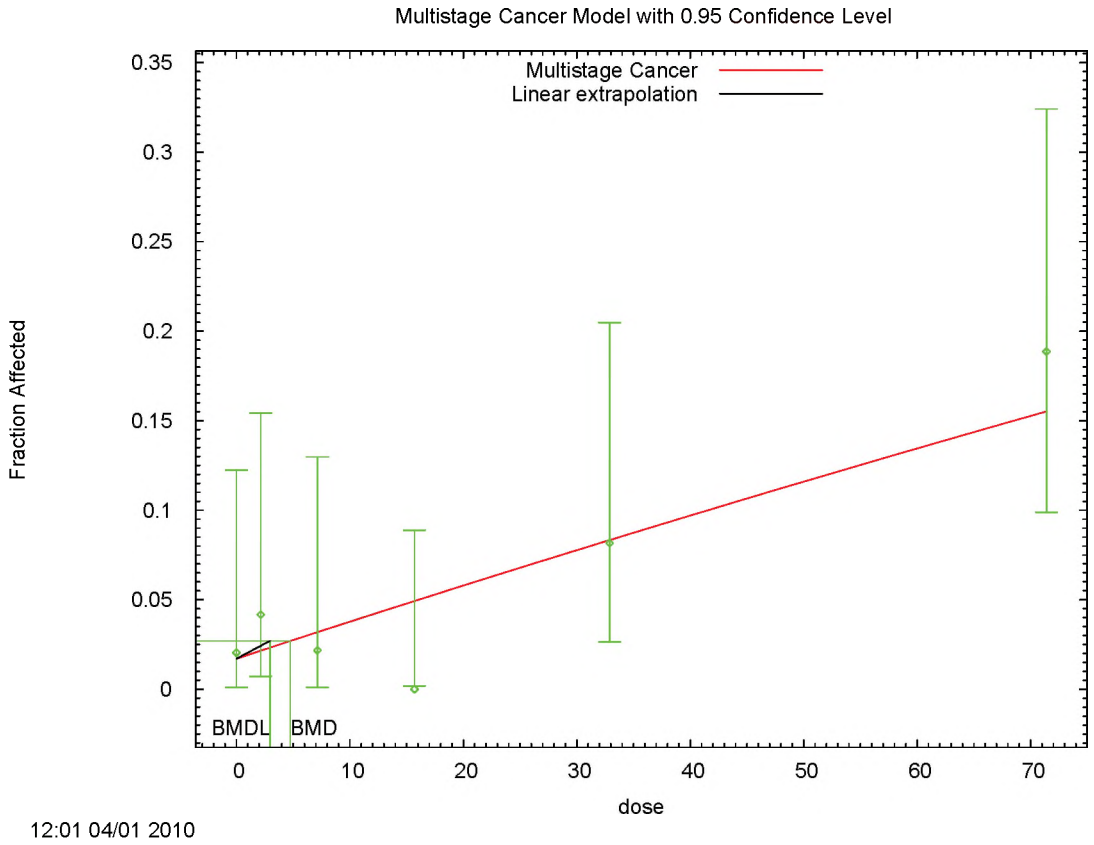
BMDL = 2.9556

BMDU = 9.19454

Taken together, (2.9556 , 9.19454) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0033834

F.2.22.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



National Toxicology Program, 2006: Oral mucosa: squamous cell carcinoma

F.2.23. National Toxicology Program, 2006: Pancreas: adenoma or carcinoma

F.2.23.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**5**	**0.796**	**28.316**	**2.120E+01**	**9.335E+00**	
Multistage Cancer, 2-Degree	5	0.977	26.230	3.270E+01	1.389E+01	
Multistage Cancer, 3-Degree	5	0.997	25.427	4.057E+01	1.755E+01	

[a] Best-fitting model, BMDS output presented in this appendix

F.2.23.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

National Toxicology Program, 2006: Pancreas: adenoma or carcinoma

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Canc\23_msc1_1Perc_panc_ad_carc.(d)
         Gnuplot Plotting File:  C:\Canc\23_msc1_1Perc_panc_ad_carc.plt
                                                 Thu Apr 01 13:01:43 2010
 ================================================================

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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =  0.000817541


           Asymptotic Correlation Matrix of Parameter Estimates
```

(*** The model parameter(s) -Background
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

Beta(1)

Beta(1) 1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0.000474004	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-11.4096	6			
Fitted model	-13.1581	1	3.49702	5	0.6238
Reduced model	-16.7086	1	10.598	5	0.05996

AIC: 28.3163

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	48	0.000
2.1400	0.0010	0.049	0.000	48	-0.221
7.1400	0.0034	0.155	0.000	46	-0.395
15.7000	0.0074	0.371	0.000	50	-0.611
32.9000	0.0155	0.743	0.000	48	-0.869
71.4000	0.0333	1.697	3.000	51	1.017

Chi^2 = 2.37 d.f. = 5 P-value = 0.7964

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 21.2031

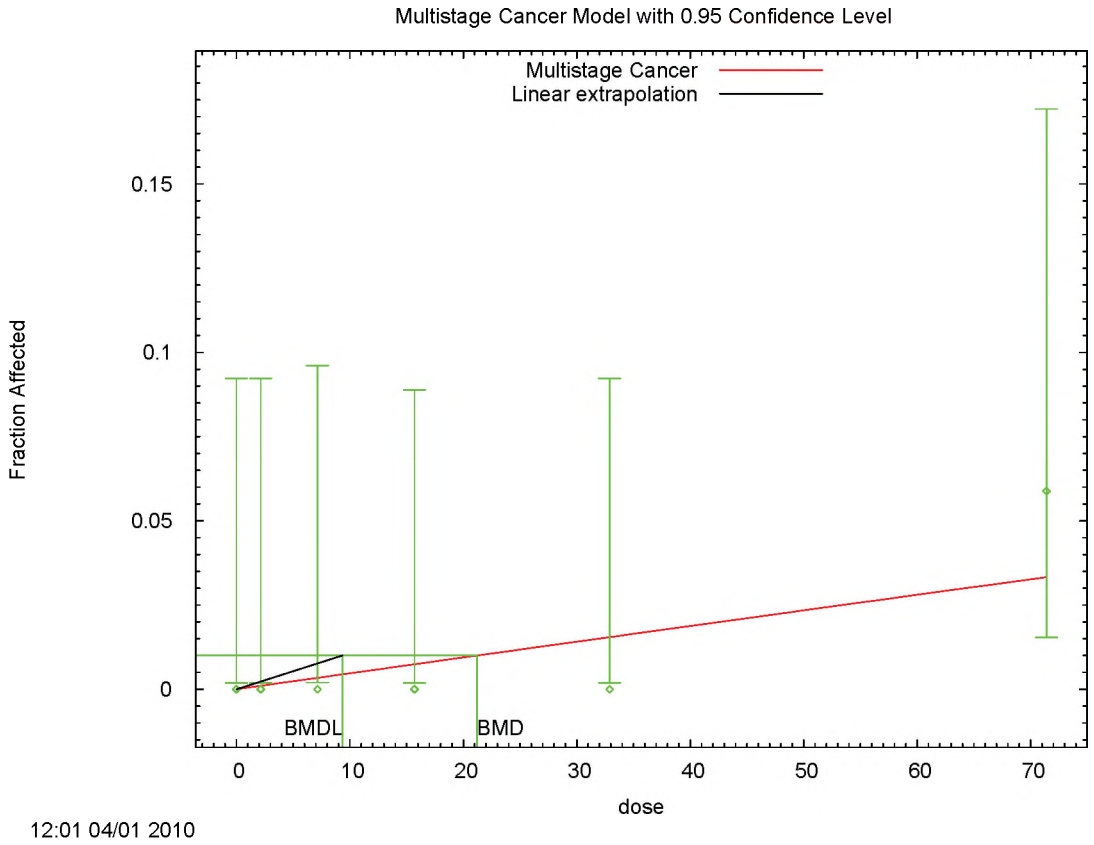
BMDL = 9.33481

BMDU = 65.4351

Taken together, (9.33481, 65.4351) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00107126

F.2.23.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



National Toxicology Program, 2006: Pancreas: adenoma or carcinoma

F.2.24. National Toxicology Program, 2006: Lung: Cystic keratinizing epithelioma

F.2.24.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree	5	0.192	60.806	6.922E+00	4.187E+00	
Multistage Cancer, 2-Degree [a]	**5**	**0.771**	**54.363**	**1.858E+01**	**1.069E+01**	
Multistage Cancer, 3-Degree	5	0.961	51.847	2.778E+01	1.556E+01	

[a] Best-fitting model, BMDS output presented in this appendix

F.2.24.2. *Output for Selected Model: Multistage Cancer, 2-Degree*

National Toxicology Program, 2006: Lung: Cystic keratinizing epithelioma

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Canc\24_msc2_1Perc_lung_epith.(d)
         Gnuplot Plotting File:  C:\Canc\24_msc2_1Perc_lung_epith.plt
                                                 Thu Apr 01 13:02:19 2010
 ================================================================

 0
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =           0
                        Beta(1) =           0
                        Beta(2) = 3.77591e-005
```

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background -Beta(1)
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Beta(2)
Beta(2)	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0	*	*	*
Beta(2)	2.91011e-005	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-23.958	6			
Fitted model	-26.1815	1	4.44693	5	0.487
Reduced model	-40.2069	1	32.4976	5	<.0001

AIC: 54.363

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	49	0.000
2.1400	0.0001	0.006	0.000	48	-0.080
7.1400	0.0015	0.068	0.000	46	-0.261
15.7000	0.0071	0.350	0.000	49	-0.594
32.9000	0.0310	1.519	0.000	49	-1.252
71.4000	0.1379	7.170	9.000	52	0.736

Chi^2 = 2.54 d.f. = 5 P-value = 0.7708

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 18.5839

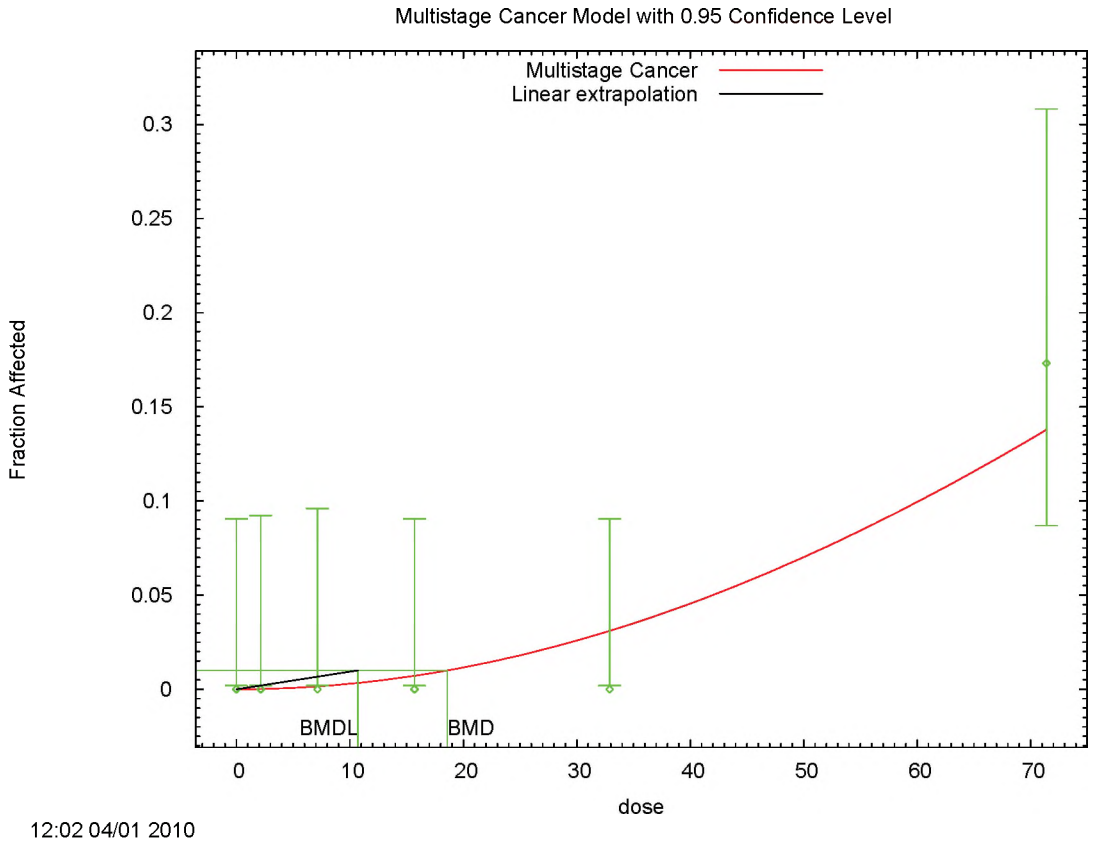
BMDL = 10.6878

BMDU = 25.1324

Taken together, (10.6878, 25.1324) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.000935646

F.2.24.3. *Figure for Selected Model: Multistage Cancer, 2-Degree*



National Toxicology Program, 2006: Lung: Cystic keratinizing epithelioma

F.2.25. Toth et al., 1979: Liver: Tumors

F.2.25.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**1**	**0.254**	**155.946**	**2.689E+00**	**1.522E+00**	
Multistage Cancer, 2-Degree	1	0.254	155.946	2.689E+00	1.522E+00	final ß=0

[a] Best-fitting model, BMDS output presented in this appendix

F.2.25.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

Toth et al., 1979: Liver: Tumors

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Canc\25_msc1_1Perc_adr_cor_1yr.(d)
         Gnuplot Plotting File:  C:\Canc\25_msc1_1Perc_adr_cor_1yr.plt
                                                Thu Apr 01 13:10:25 2010
 ======================================================================

 Table 1
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Mean
   Independent variable = Dose

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =     0.240176
                        Beta(1) =   0.00374745


            Asymptotic Correlation Matrix of Parameter Estimates

              Background      Beta(1)
```

Background	1	-0.53
Beta(1)	-0.53	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.2418	*	*	*
Beta(1)	0.00373791	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-75.3127	3			
Fitted model	-75.9728	2	1.3201	1	0.2506
Reduced model	-79.4897	1	8.35401	2	0.01534
AIC:	155.946				

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.2418	9.188	7.000	38	-0.829
1.0000	0.2446	10.764	13.000	44	0.784
100.0000	0.4783	21.044	21.000	44	-0.013

Chi^2 = 1.30 d.f. = 1 P-value = 0.2537

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 2.68876

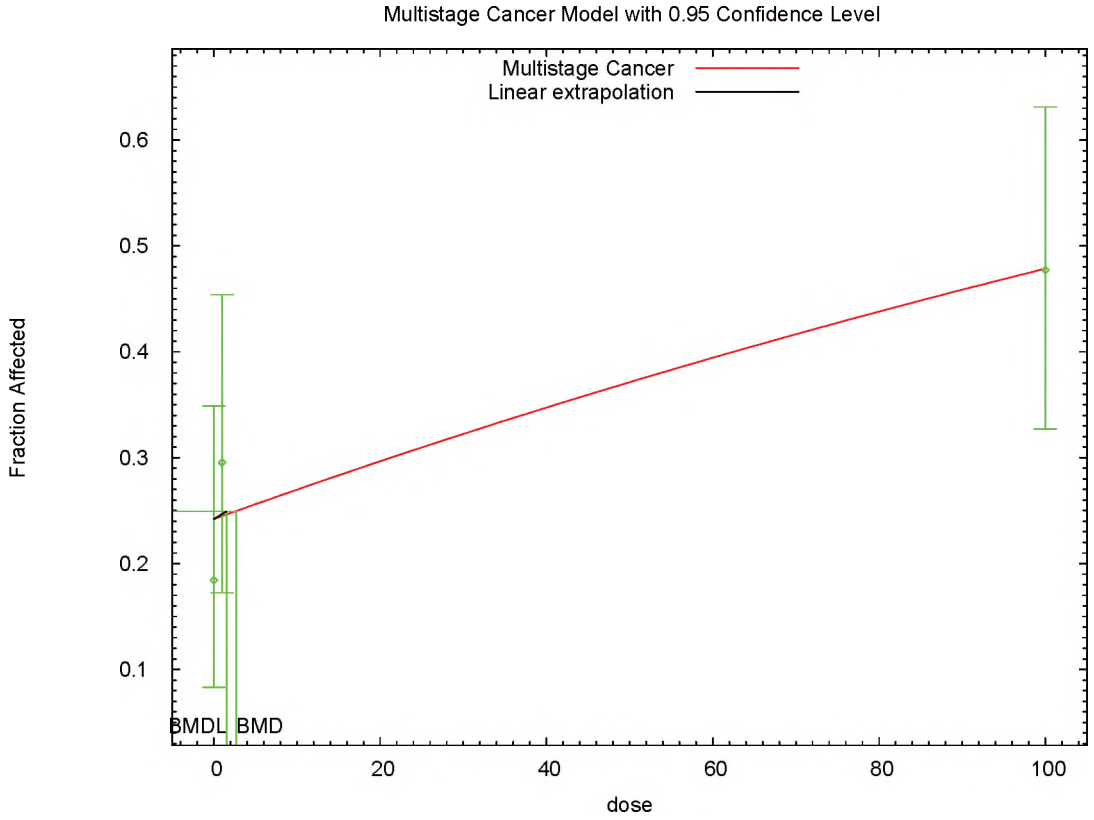
BMDL = 1.52183

BMDU = 7.54263

Taken together, (1.52183, 7.54263) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00657103

F.2.25.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



Toth et al., 1979: Liver: Tumors

F.2.26. Della Porta et al., 1987: Table 4, B6C3 mice, male, hepatocellular carcinoma

F.2.26.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree	1	0.073	164.110	9.255E+00	6.946E+00	
Multistage Cancer, 2-Degree [a]	**1**	**0.899**	**160.823**	**7.359E+01**	**9.825E+00**	

[a] Best-fitting model, BMDS output presented in this appendix

F.2.26.2. *Output for Selected Model: Multistage Cancer, 2-Degree*

Della Porta et al., 1987: Table 4, B6C3 mice, male, hepatocellular carcinoma

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\1\94_DPorta_1987_Male_Hep_Carc_MultiCanc2_1.(d)
         Gnuplot Plotting File:  C:\1\94_DPorta_1987_Male_Hep_Carc_MultiCanc2_1.plt
                                                 Fri Apr 02 13:58:02 2010
 ======================================================================

 Table 4, B6C3 mice, Male, Hepatocellular carcinoma
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =     0.110507
                        Beta(1) =            0
                        Beta(2) = 1.88069e-006


            Asymptotic Correlation Matrix of Parameter Estimates
```

(*** The model parameter(s) -Beta(1)
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Background	Beta(2)
Background	1	-0.62
Beta(2)	-0.62	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.114031	*	*	*
Beta(1)	0	*	*	*
Beta(2)	1.8559e-006	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-78.4036	3			
Fitted model	-78.4116	2	0.0160146	1	0.8993
Reduced model	-94.7394	1	32.6717	2	<.0001

AIC: 160.823

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1140	4.903	5.000	43	0.046
357.1429	0.3008	15.340	15.000	51	-0.104
714.2857	0.6563	32.815	33.000	50	0.055

Chi^2 = 0.02 d.f. = 1 P-value = 0.8994

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 73.5891

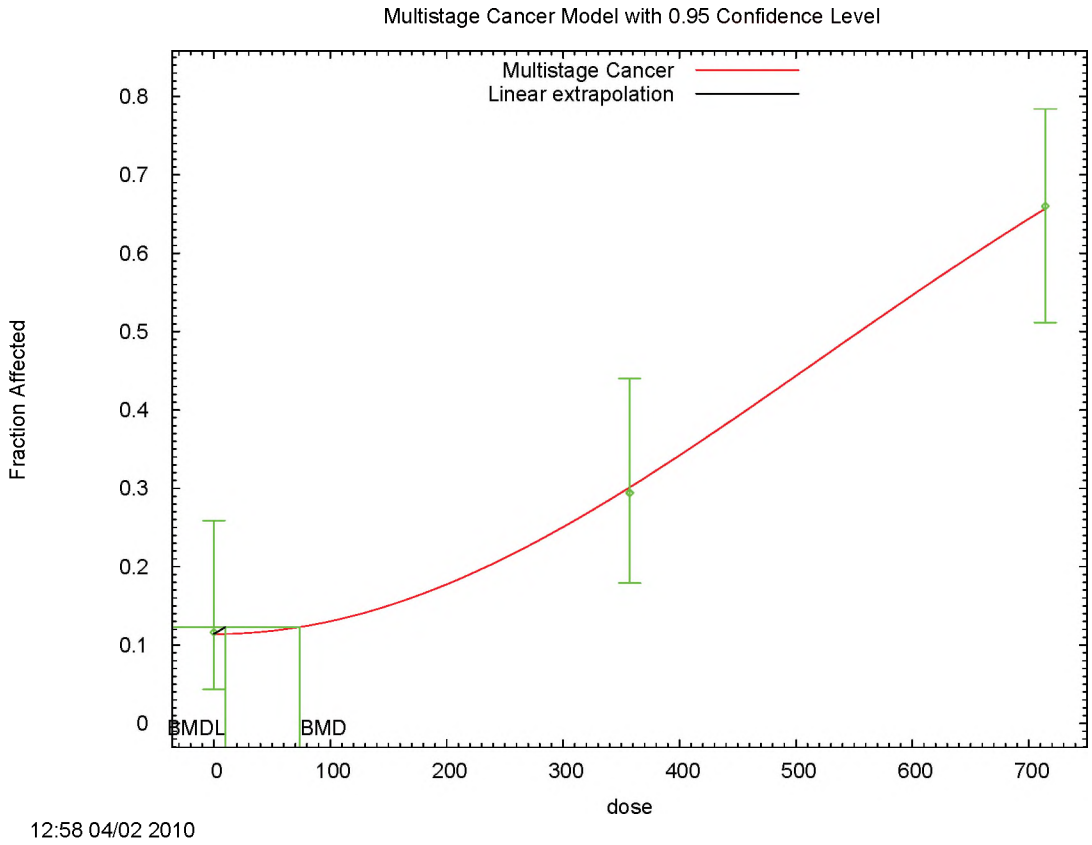
BMDL = 9.82517

BMDU = 88.9247

Taken together, (9.82517, 88.9247) is a 90 % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor = 0.00101779

F.2.26.3. *Figure for Selected Model: Multistage Cancer, 2-Degree*



Della Porta et al., 1987: Table 4, B6C3 mice, male, hepatocellular carcinoma

F.2.27. Della Porta et al., 1987: Table 4, B6C3 mice, female, hepatocellular adenoma

F.2.27.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**1**	**0.468**	**99.355**	**3.695E+01**	**2.245E+01**	
Multistage Cancer, 2-Degree	0	NA	100.803	1.345E+02	2.353E+01	

[a] Best-fitting model, BMDS output presented in this appendix

F.2.27.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

Della Porta et al., 1987: Table 4, B6C3 mice, female, hepatocellular adenoma

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\1\95_DPorta_1987_Female_Hep_Aden_MultiCanc1_1.(d)
         Gnuplot Plotting File:  C:\1\95_DPorta_1987_Female_Hep_Aden_MultiCanc1_1.plt
                                                 Fri Apr 02 13:58:32 2010
 ======================================================================

 Table 4, B6C3 mice, Female, Hepatocellular adenoma
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =    0.0244051
                        Beta(1) =  0.000306055


            Asymptotic Correlation Matrix of Parameter Estimates

              Background      Beta(1)
```

```
Background            1        -0.72

   Beta(1)        -0.72            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background        0.0369416            *               *                   *
        Beta(1)      0.000272012            *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -47.4015         3
    Fitted model       -47.6775         2      0.552146      1          0.4574
   Reduced model       -51.6367         1       8.47042      2         0.01448

           AIC:         99.3551


                                Goodness  of  Fit
                                                                      Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------------
    0.0000     0.0369         1.810     2.000          49        0.144
  357.1429     0.1261         5.296     4.000          42       -0.602
  714.2857     0.2070         9.936    11.000          48        0.379

 Chi^2 = 0.53      d.f. = 1        P-value = 0.4677


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        36.9482

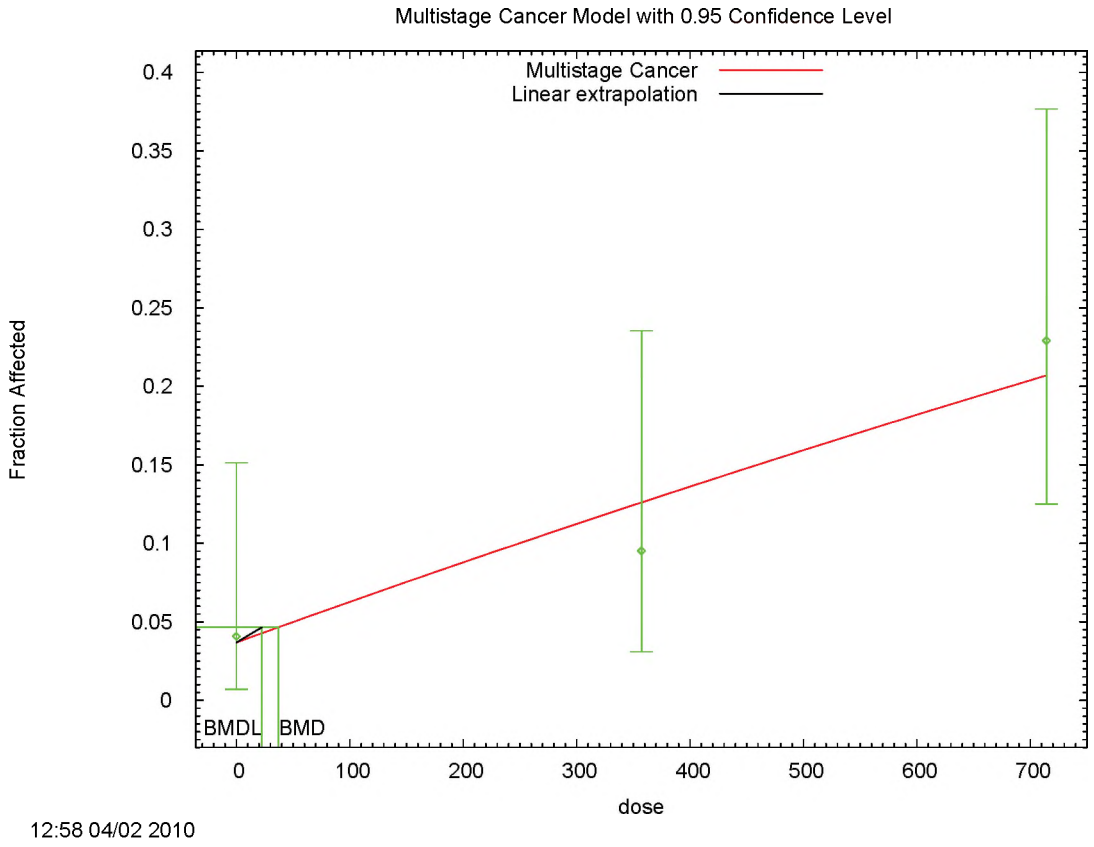
             BMDL =        22.4477

             BMDU =        86.1826

Taken together, (22.4477, 86.1826) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =   0.000445481
```

F.2.27.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



Della Porta et al., 1987: Table 4, B6C3 mice, female, hepatocellular adenoma

F.2.28. Della Porta et al., 1987: Table 4, B6C3 mice, female, hepatocellular carcinoma

F.2.28.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
Multistage Cancer, 1-Degree [a]	**1**	**0.010**	**116.588**	**2.425E+01**	**1.605E+01**	
Multistage Cancer, 2-Degree	1	0.010	116.588	2.425E+01	1.605E+01	final ß=0

[a] Best-fitting model, BMDS output presented in this appendix

F.2.28.2. *Output for Selected Model: Multistage Cancer, 1-Degree*

Della Porta et al., 1987: Table 4, B6C3 mice, female, hepatocellular carcinoma

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\1\96_DPorta_1987_Female_Hep_Carc_MultiCanc1_1.(d)
         Gnuplot Plotting File:  C:\1\96_DPorta_1987_Female_Hep_Carc_MultiCanc1_1.plt
                                                 Fri Apr 02 13:59:01 2010
 ======================================================================

 Table 4, B6C3 mice, Female, Hepatocellular carcinoma
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =    0.0903848
                        Beta(1) =  0.000261828


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)
```

Background	1	-0.8
Beta(1)	-0.8	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0300271	*	*	*
Beta(1)	0.000414523	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-53.1726	3			
Fitted model	-56.2941	2	6.24292	1	0.01247
Reduced model	-60.7146	1	15.084	2	0.0005303

AIC: 116.588

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0300	1.471	1.000	49	-0.395
357.1429	0.1635	6.867	12.000	42	2.142
714.2857	0.2786	13.373	9.000	48	-1.408

Chi^2 = 6.72 d.f. = 1 P-value = 0.0095

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 24.2455

BMDL = 16.0512

BMDU = 49.7176

Taken together, (16.0512, 49.7176) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.000623007

F.2.28.3. *Figure for Selected Model: Multistage Cancer, 1-Degree*



Della Porta et al., 1987: Table 4, B6C3 mice, female, hepatocellular carcinoma

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APPENDIX G

Endpoints Excluded From Reference Dose Derivation Based on Toxicological Relevance

NOTICE

THIS DOCUMENT IS AN EXTERNAL REVIEW DRAFT. It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH

APPENDIX G. ENDPOINTS EXCLUDED FROM REFERENCE DOSE DERIVATION BASED ON TOXICOLOGICAL RELEVANCE

The National Academy of Sciences (NAS) committee commented on the low dose model predictions and the need to discuss the biological significance of the noncancer health effects modeled in the 2003 Reassessment. In selecting point of departure (POD) candidates from the animal bioassays for derivation of the reference dose (RfD), U.S. Environmental Protection Agency (EPA) had to consider the toxicological relevance of the identified endpoint(s) from any given study. Often endpoints/effects may be sensitive, but lack general toxicological significance due to not being clearly adverse (defined in the Integrated Risk Information System (IRIS) glossary as a biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism, or reduces an organism's ability to respond to an additional environmental challenge), being an adaptive response, or not being clearly linked to downstream functional or pathological alterations. It is standard EPA RfD derivation policy not to base a reference value on endpoints that are not adverse or not obvious precursors to an adverse effect. For select studies, a rationale for lack of toxicological relevance of particular endpoints reported is listed here. These endpoints were not considered for derivation of the RfD.

Kitchin and Woods (1979) administered female Sprague-Dawley rats a single gavage dose of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and measured cytochrome P450 levels and benzo(a)pyrene hydroxylase (BPH) activity as a marker of hepatic microsomal cytochrome P448-mediated enzyme activity. They found a statistically significant increase in BPH at doses $\geq$2 ng/kg and a significant increase in cytochrome P450 levels at doses $\geq$600 ng/kg. Aryl hydrocarbon hydrolase and EROD were both significantly increased 3 months after exposure; however the elevation did not maintain statistical significance at 6 months. No other indicators of hepatic effects were analyzed. CYP induction alone is not considered a significant toxicologically adverse effect given that CYPs are induced as a means of hepatic processing of xenobiotic agents. Additionally, the role of CYP induction in hepatotoxicity and carcinogenicity of TCDD is unknown, and CYP induction is not considered a relevant POD without obvious pathological significance.

In multiple studies by Hassoun et al. (1998, 2000, 2002, 2003), various indicators of oxidative stress were measured in hepatic and brain tissue of female B6C3F1 mice and Sprague-

Dawley rats following 13 or 30 weeks of TCDD gavage dosing (5 days a week). Biomarkers for oxidative stress included production superoxide anion, lipid peroxidation, and DNA single-strand breaks. The authors report a statistically significant effect on several oxidative stress markers as a result of TCDD exposure, the lowest dose producing an effect being 0.32 ng/kg-day (Hassoun et al., 1998). In this study, all oxidative stress markers were significantly effected, but no other indicators of brain pathology were assessed. Thus, it is impracticable to link the markers of oxidative stress to a toxicological outcome in the brain, and this study and its endpoints are not considered relevant POD candidates.

Burleson et al. (1996) analyzed the effect of a TCDD on viral host resistance following a single gavage dose of TCDD by measuring mortality mediated by influenza virus challenge in B6C3F1 female mice. The study authors found that TCDD at ≥10 ng/kg-day increased influenza-induced mortality. The experimental design calls for a 30% mortality in untreated animals (15% was achieved); mortality, itself, is not a direct result of TCDD exposure. None of the other immunologically-relevant measures were affected by TCDD treatment in this study, and no other effects were reported. The interpretation of these results with respect to humans is problematic. Furthermore, the findings were not reproduced by Nohara et al. (2002) using the same experimental design (see Section 2.4.2). Therefore, this endpoint is not considered relevant as a POD candidate.

To examine the central nervous system response to TCDD, Kuchiiwa et al (2002) analyzed the effect of in utero and lactational TCDD exposure on the serotonergic system in the brainstem of male ddY mice. Female mice were administered TCDD by oral gavage once a week for 8 weeks prior to pregnancy and, using an immunocytochemical detection method, the raphe nuclei in the brainstem of male offspring was monitored for serotogergic neurons. TCDD at 0.7 ng/kg-day caused a 25−50% reduction in the immunostaining of serotonin, however there were no differences in external morphology, birth or postnatal body weights between TCDD-exposed and control offspring. The authors suggest that these findings may indicate that TCDD acts as a neuroteratogen by mediating long-term alterations in neuronal serotonin synthesis and serotonergic function. However, no other relevant neurotoxicity endpoints were examined or reported. Thus, reduced serotonin is not an adverse endpoint of toxicological significance in and of itself, and this study is deemed unsuitable as a POD candidate.

Mally and Chipman (2002) evaluated the effect of TCDD on gap junctions, hypothesizing that as a nongenotoxic carcinogen, TCDD may induce tumor formation by disturbing tissue homeostasis. Female F344 rats were dosed with TCDD by oral gavage for either 3 consecutive days or 2 days a week for 28 days. Gap junction connexin (Cx) plaque expression and hepatocyte proliferation was measured. The study authors report a decrease in Cx32 plaque number and area in the liver of rats exposed to 0.7 ng/kg-day and higher, however they did not find an associated increase in hepatocyte proliferation. No clinical signs of toxicity were observed, and histological examination of the liver revealed no abnormalities. In the absence of additional indicators of hepatotoxicity, a decrease in Cx32 plaque formation is not clearly linked to TCDD-mediated hepatotoxicity or hepatocarcinogenicty, nor is it considered an adverse effect. This endpoint is not considered a toxicologically relevant POD.

Vanden Heuvel et al. (1994) analyzed changes in hepatic mRNA following a single administration of TCDD to female Sprague-Dawley rats by oral gavage. Four days after treatment, animals were sacrificed and livers were excised. Using reverse transcriptase-polymerase chain reaction (RT-PCR) on hepatic RNA, they compared levels of "dioxin responsive" mRNA's (CYP1A1, UDP-glucuronosyltransferase I, plasminogen activator inhibitor 2, and transforming growth factor α) at various doses of TCDD and at control (baseline) levels. They determined that CYP1A1 elicited the most sensitive response to TCDD, with a statistically significant increase (3-fold) in mRNA from rat livers exposed to 1 ng/kg-day TCDD. Induction of CYP1A1 expression is not considered an adverse effect, as the role of CYP1A1 in TCDD-mediated carcinogenicity is unsettled. Therefore, in the absence of other indicators of hepatoxicity, increases in liver CYP1A1 cannot be considered toxicologically relevant for a POD candidate.

Devito et al. (1994) assessed the activity of CYP1A1 and CYP1A2, the amount of phosphorylation of phosphotyrosyl proteins (pp32, pp34, and pp38), and the levels of estrogen receptor in the liver, uterus, lung and skin tissue of female B6C3F1 mice administered TCDD for 5 days a week for 13 weeks. The authors hypothesized that these measurements may be sensitive biomarkers for exposure to TCDD. Body weights were also recorded weekly. Induction of CY1A1 and CYP1A2, as well as increased phosphorylated forms of pp32, pp34, and pp38 were sensitive indicators of TCDD exposure, with statistically significant changes seen at 1.07 ng/kg-day. EROD activity in the ling, skin, and liver was also observed with significant

increases at this dose. However, the authors did not find a change in rat body or terminal organ weights, nor did they note any pathology in the animals at this dose level. The role of CYPs and phosphorylated pp32, pp34, and pp38 in TCDD-mediated toxicity is unknown, and changes in the activity or function of these proteins are not considered adverse. Therefore, these endpoints are not considered suitable as PODs.

Because TCDD had been detected in the soil of contaminated locations, determining the bioavailability of TCDD from ingested soil may be important to the calculation of safe exposure levels. Lucier et al. (1986) fed adult female Sprague-Dawley rats TCDD contaminated soil or gave them TCDD in corn oil at various doses and compared the effects of TCDD on biochemical parameters from liver tissue. They found that equivalent doses of TCDD in corn oil and soil produced similar increases in hepatic aryl hydrocarbon hydroxylase activity (AHH) and UDP glucuronyltransferase activity. They determined that AHH was statistically induced 1.8-fold at 15 ng/kg in corn oil and 40 ng/kg in soil. Cytochrome P450 was significantly increased at higher doses. No clinical signs of acute toxicity or changes in body weight were observed. The association between AHH activity and TCDD-mediated hepatotoxicity is unknown and no adverse endpoints were measured. Thus, this endpoint is not suitable as a POD candidate.

Sugita-Konishi et al. (2003) investigated the change in host resistance of mice offspring lactationally exposed to TCDD. Pregnant C57BL/6NCji mice were administered TCDD via drinking water from parturition to weaning of the offspring (17 days). One group of offspring was then infected with *Listeria monocytogenes* and blood and spleen samples were collected various time points post infection. Uninfected, TCDD exposed offspring were weighed and their spleens and thymuses removed for assay of cellular content and protein expression. TCDD exposure caused a statistically-significant decrease in relative spleen weight and a statistically-significant increase in thymic CD4+ cells in the high-dose group (11.3 ng/kg-day). Offspring infected with *Listeria* following TCDD exposure exhibited a statistically significant increase in serum tumor necrosis factor alpha (TNF-α) 2 days after infection in both sexes in the low- (1.14 ng/kg-day) and high-dose groups. The authors conclude that exposure to TCDD disrupted the host resistance of the offspring at the lowest dose tested, despite the primary immune parameters being unaffected. Without an obvious association between TCDD and immune function, however, this endpoint is not suitable for identification of a LOAEL. Thus, the LOAEL for this study is 11.3 ng/kg-day, and the NOAEL is 1.14 ng/kg-day.

Sewall et al. (1993) investigated alterations in the epidermal growth factor receptor (EGFR) pathway in a two-stage initiation promotion model of TCDD hepatic cancer. EGFR signaling has been implicated in the altered cell growth induction by tumor promoters. Female Sprague-Dawley rats were administered TCDD biweekly by oral gavage for 30 weeks following initiation by a single dose of diethylnitrosamine (DEN). A group also received TCDD without prior DEN initiation. Livers were harvested and fixed from sacrificed animals and sections tested for EGFR binding, autophosphorylation, immunolocalization, and hepatic cell proliferation. The authors report a significant dose-dependent decrease in plasma membrane EGFR maximum binding capacity in TCDD-exposed rats beginning at 3.5 ng/kg-day. However, at this same dose, the authors note a statistically significant decrease in cell proliferation (as measured by DNA replication labeling), with increases in proliferation only occurring at higher doses (125 ng/kg-day). No other indicators of hepatic toxicity or tumorigenicity were assessed. The role of EGFR in TCDD-mediated hepatotoxicity and hepatocarcinogenicity is unknown, and as such, this endpoint cannot be unequivocally linked to TCDD-induced hepatic effects nor labeled as adverse. Thus, it is not suitable as a POD candidate.

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APPENDIX H

Cancer Precursor Benchmark Dose Modeling

NOTICE

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National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH

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APPENDIX H. CANCER PRECURSOR BENCHMARK DOSE MODELING

H.1. BMDS INPUT TABLES

H.1.1. Hassoun et al. (2000)

Endpoint	Administered Dose (ng/kg-day)					
	0	3	10	22	46	100
	Internal Dose (ng/kg blood) [a]					
	0	1.94	4.61	8.15	14.01	25.34
	n = 6	n = 6	n = 6	n = 6	n = 6	n = 6
Cytochrome C reductase [d]	0.15 ± 0.07	0.18 ± 0.05 [b]	0.19 ± 0.06	0.27 ± 0.06 [c]	0.39 ± 0.06 [c]	0.44 ± 0.11 [c]
DNA single-strand breaks [f]	7.41 ± 1.54	10.78 ± 1.25 [b,c]	13.6 ± 1.69 [c]	15.3 ± 1.71 [c]	20.4 ± 2.25 [c]	23.5 ± 1.37 [c]
TBARs [e]	1.47 ± 0.29	1.55 ± 0.54 [b]	2.15 ± 0.36 [c]	2.28 ± 0.25 [c]	2.62 ± 0.52 [c]	2.29 ± 0.49 [c]

[a]From the Emond PBPK model described in 3.3.
[b]LOEL for selected endpoint.
[c]Statistically significant as compared to control ($p < 0.05$).
[d]Values are the mean ± SD. Data obtained from Table 1 in Hassoun et al. 2000.
[e]Values are the mean ± SD. Data obtained from Table 2 in Hassoun et al. 2000.
[f]Values are the mean ± SD. Data obtained from Table 3 in Hassoun et al. 2000.

H.1.2. Kitchin and Woods (1979)

Endpoint	Administered Dose (ng/kg-day)					
	0	0.6	2	4	20	60
	Internal Dose (ng/kg blood) [a]					
	0	0.06	0.20	0.38	1.61	4.15
	n = 9	n = 4	n = 4	n = 4	n = 4	n = 4
BaP hydroxylase activity [f] (continued on next line)	4.9 ± 0.37	4.9 ± 0.59 [b]	6.7 ± 0.70 [c,d]	7.2 ± 0.90 [d]	8.3 ± 0.13 [e]	14 ± 2.5 [e]
	Administered Dose (ng/kg-day)					
	200	600	2000	5000	20,000	
	Internal Dose (ng/kg blood) [a]					
	11.59	30.26	90.90	218.02	863.18	
	n = 4	n = 4	n = 4	n = 4	n = 4	
BaP hydroxylase activity [f] (continued)	59 ± 3.4 [e]	96 ± 23 [e]	155 ± 8.2 [e]	182 ± 13 [e]	189 ± 13 [e]	

[a]From the Emond PBPK model described in 3.3.
[b]NOEL for selected endpoint.
[c]LOEL for selected endpoint.
[d]Statistically significant as compared to control ($p < 0.05$).
[e]Statistically significant as compared to control ($p < 0.001$).
[f]Values are the mean ± SE. Data obtained from Table 3 in Kitchin and Woods 1979.

H.1.3. National Toxicology Program (2006), 31 Week Exposure

Endpoint	Administered Dose (ng/kg-day)					
	0	2.14	7.14	15.7	32.9	71.4
	Internal Dose (ng/kg blood) [a]					
	0	2.33	5.32	9.21	15.66	28.13
	n = 9	n = 10	n = 10	n = 10	n = 10	n = 10
Labeling Index ,week 31 [c]	0.33 ± 0.0.06	0.85 ± 0.21 [b]	0.96 ± 0.23 [b]	0.79 ± 0.15 [b]	1.33 ± 0.36 [b]	3.85 ± 0.97 [b]

[a]From the Emond PBPK model described in 3.3.
[b]Statistically significant as compared to control ($p < 0.05$).
[c]Values are the mean ± SE. Data obtained from Table 11 in NTP 2006.

H.1.4. National Toxicology Program (2006), 53 Week Exposure

Endpoint	Administered Dose (ng/kg-day)					
	0	2.14	7.14	15.7	32.9	71.4
	Internal Dose (ng/kg blood) [a]					
	0.00	2.46	5.53	9.54	16.18	29.04
	n = 8	n = 8	n = 8	n = 8	n = 8	n = 8
Liver EROD, week 53 [c]	30.22 ± 1.59	569.38 ± 24.62 [b]	1280.00 ± 95.30 [b]	1551.16 ± 112.36 [b]	1726.81 ± 107.58 [b]	1871.47 ± 109.14 [b]
Lung EROD, week 53 [c]	3.01 ± 0.56	27.15 ± 1.87 [b]	42.85 ± 3.94 [b]	36.57 ± 4.59 [b]	43.75 ± 6.56 [b]	43.71 ± 2.24 [b]

[a]From the Emond PBPK model described in 3.3.
[b]Statistically significant as compared to control ($p < 0.01$).
[c]Values are the mean ± SE. Data obtained from Table 12 in NTP 2006.

H.1.5. Vanden Heuvel et al. (1994)

Endpoint	Administered Dose (ng/kg-day)						
	0	0.1	1	10	100	1,000	10,000
	Internal Dose (ng/kg blood) [a]						
	0.00	0.01	0.11	0.88	6.45	48.32	434.50
	n = 13	n = 5	n = 12	n = 7	n = 7	n = 11	n = 5
Hepatic CYP1A1 mRNA Expression [c]	5.4 ± 1.0	7.2 ± 2.5	14.8 ± 4.3 [b]	12.8 ± 1.7 [b]	536 ± 121 [b]	18000 ± 4590 [b]	36700 ± 9900 [b]

[a]From the Emond PBPK model described in 3.3.
[b]Statistically significant as compared to control ($p < 0.05$).
[c]Values are the mean ± SE. Data obtained from Table 2 in vanden Heuvel 1994.

H.2. ALTERNATE DOSE: WHOLE BLOOD BMDS RESULTS

H.2.1. Hassoun et al., 2000: Cytochrome C Reductase

H.2.1.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	4	0.016	-143.333	9.274E+00	7.737E+00	
exponential (M3)	4	0.016	-143.333	9.274E+00	7.737E+00	power hit bound (d = 1)
exponential (M4)	3	0.339	-150.139	3.364E+00	2.170E+00	
exponential (M5) [b]	2	0.788	-151.027	5.913E+00	3.102E+00	
Hill	2	0.743	-150.910	6.208E+00	3.190E+00	
linear	4	0.170	-149.086	5.613E+00	4.429E+00	
polynomial, 5-degree	4	0.170	-149.086	5.613E+00	4.429E+00	
power	4	0.170	-149.086	5.613E+00	4.429E+00	power bound hit (power = 1)

[a] Constant variance model selected ($p = 0.3871$)

[b] Best-fitting model, BMDS output presented in this appendix

H.2.1.2. *Output for Selected Model: Exponential (M5)*

Hassoun et al., 2000: Cytochrome C reductase

```
 ======================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\5\Blood\17_Has_2000_CytCLiv_ExpCV_1.(d)
         Gnuplot Plotting File:
                                                Fri Apr 30 14:14:34 2010
 ======================================================================

 TBARs, liver only (Table 2)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
```

```
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


               Initial Parameter Values

               Variable          Model 5
               --------          --------
                 lnalpha            -5.48625
                     rho(S)                0
                       a              0.1387
                       b           0.0225296
                       c             6.40231
                       d                   1

  (S) = Specified


                  Parameter Estimates

                Variable          Model 5
                --------          -------
                 lnalpha          -5.47298
                     rho                0
                       a          0.156024
                       b         0.0891513
                       c           2.85355
                       d           2.14235


         Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0      6         0.146       0.06614
  1.938      6         0.177       0.05389
  4.614      6         0.191       0.05634
  8.147      6         0.271       0.05634
  14.01      6         0.388       0.06369
  25.34      6         0.444        0.1102


               Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
      0         0.156       0.0648          -0.3789
  1.938        0.1627       0.0648           0.5416
  4.614        0.1961       0.0648          -0.1919
  8.147        0.2705       0.0648          0.01769
  14.01        0.3874       0.0648          0.02224
  25.34        0.4443       0.0648          -0.0107


Other models for which likelihoods are calculated:

  Model A1:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma^2
```

```
  Model A2:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
              Var{e(ij)} = Sigma^2


                            Likelihoods of Interest

                 Model      Log(likelihood)      DF         AIC
                -------    -----------------    ----   ------------
                    A1        80.75258           7     -147.5052
                    A2        83.37355          12     -142.7471
                    A3        80.75258           7     -147.5052
                     R        55.82002           2       -107.64
                     5        80.51364           5     -151.0273


Additive constant for all log-likelihoods =     -33.08.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.


                              Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)

Test 7a: Does Model 5 fit the data? (A3 vs 5)


                          Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                      55.11            10           < 0.0001
  Test 2                      5.242             5             0.3871
  Test 3                      5.242             5             0.3871
 Test 7a                     0.4779             2             0.7875


  The p-value for Test 1 is less than .05.  There appears to be a
  difference between response and/or variances among the dose
  levels, it seems appropriate to model the data.

  The p-value for Test 2 is greater than .1.  A homogeneous
  variance model appears to be appropriate here.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 7a is greater than .1.  Model 5 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 1.000000

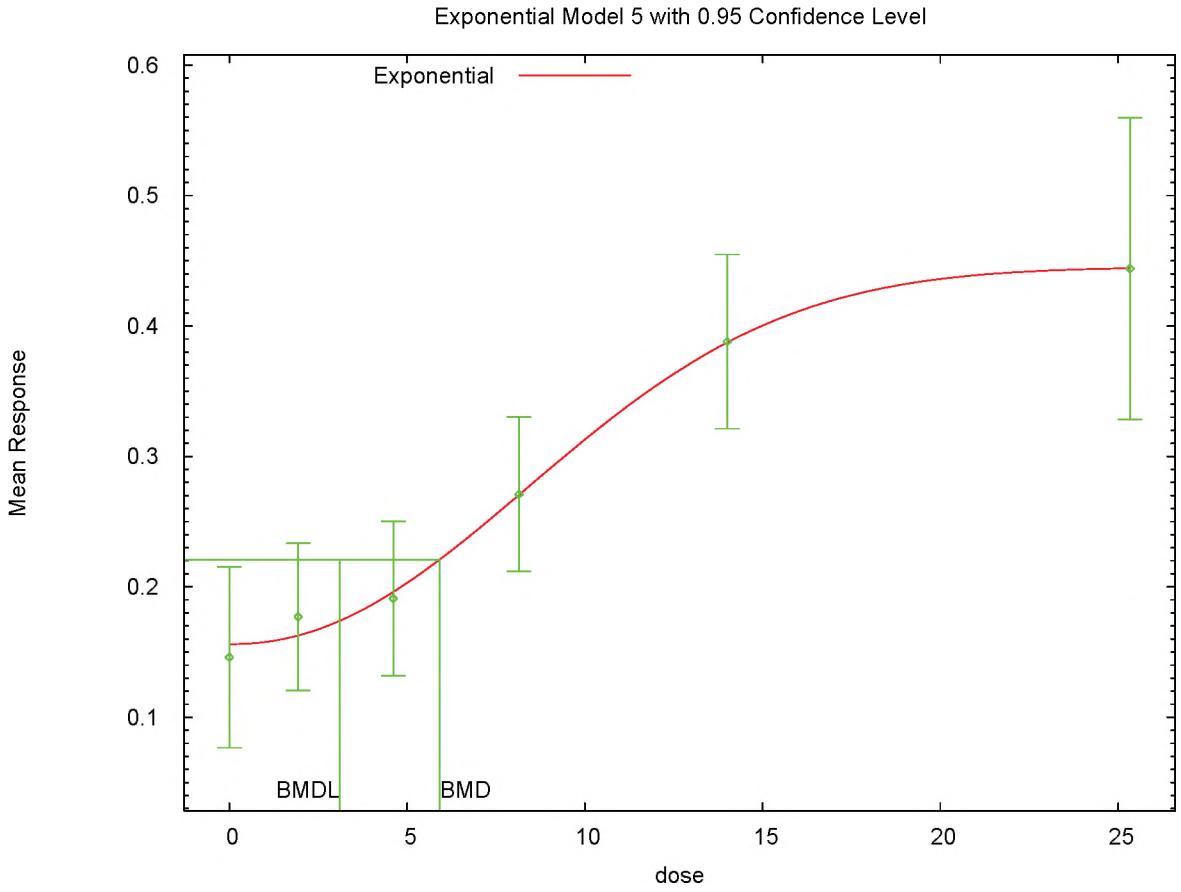
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

              BMD =      5.91298

             BMDL =      3.10234
```

H.2.1.3. *Figure for Selected Model: Exponential (M5)*



H.2.2. Hassoun et al., 2000: DNA Single-Strand Breaks

H.2.2.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	4	<0.0001	111.134	6.551E+00	5.472E+00	
exponential (M3)	4	<0.0001	111.134	6.551E+00	5.472E+00	power hit bound (d = 1)
exponential (M4) [b]	3	0.231	78.588	1.207E+00	9.165E-01	
exponential (M5)	3	0.231	78.588	1.207E+00	9.165E-01	power hit bound (d = 1)
Hill	3	0.230	78.590	1.097E+00	7.966E-01	n lower bound hit (n = 1)
linear	4	<.0001	97.616	3.552E+00	2.890E+00	
polynomial, 5-degree	4	<.0001	97.616	3.552E+00	2.890E+00	
power	4	<.0001	97.616	3.552E+00	2.890E+00	power bound hit (power = 1)
power, unrestricted [c]	3	0.132	79.893	4.522E-01	2.027E-01	unrestricted (power = 0.576)

[a] Constant variance model selected ($p = 0.7521$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

H.2.2.2. *Output for Selected Model: Exponential (M4)*

Hassoun et al., 2000: DNA single-strand breaks

```
 ================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\5\Blood\18_Has_2000_SSB_ExpCV_1.(d)
         Gnuplot Plotting File:
                                                Fri Apr 30 14:15:16 2010
 ================================================================

 DNA single-strand breaks, liver only (Table 3)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.
```

Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	0.841244
rho(S)	0
a	7.0395
b	0.103521
c	3.50522
d	1

(S) = Specified

Parameter Estimates

Variable	Model 4
lnalpha	0.960789
rho	0
a	7.7528
b	0.075429
c	3.39665
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	6	7.41	1.543
1.938	6	10.78	1.249
4.614	6	13.6	1.69
8.147	6	15.3	1.715
14.01	6	20.4	2.254
25.34	6	23.5	1.372

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	7.753	1.617	-0.5194
1.938	10.28	1.617	0.7575
4.614	13.21	1.617	0.5853
8.147	16.28	1.617	-1.49
14.01	19.87	1.617	0.7958
25.34	23.59	1.617	-0.1293

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij)

```
            Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
            Var{e(ij)} = Sigma^2


                              Likelihoods of Interest

                   Model      Log(likelihood)      DF         AIC
                  -------    -----------------    ----   ------------
                      A1       -33.14239           7      80.28478
                      A2       -31.81197          12      87.62394
                      A3       -33.14239           7      80.28478
                       R       -80.44209           2      164.8842
                       4       -35.29421           4      78.58842


Additive constant for all log-likelihoods =     -33.08.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.

                               Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)


                           Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                        97.26          10            < 0.0001
  Test 2                        2.661           5              0.7521
  Test 3                        2.661           5              0.7521
 Test 6a                        4.304           3              0.2305


  The p-value for Test 1 is less than .05.  There appears to be a
  difference between response and/or variances among the dose
  levels, it seems appropriate to model the data.

  The p-value for Test 2 is greater than .1.  A homogeneous
  variance model appears to be appropriate here.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 6a is greater than .1.  Model 4 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 1.000000

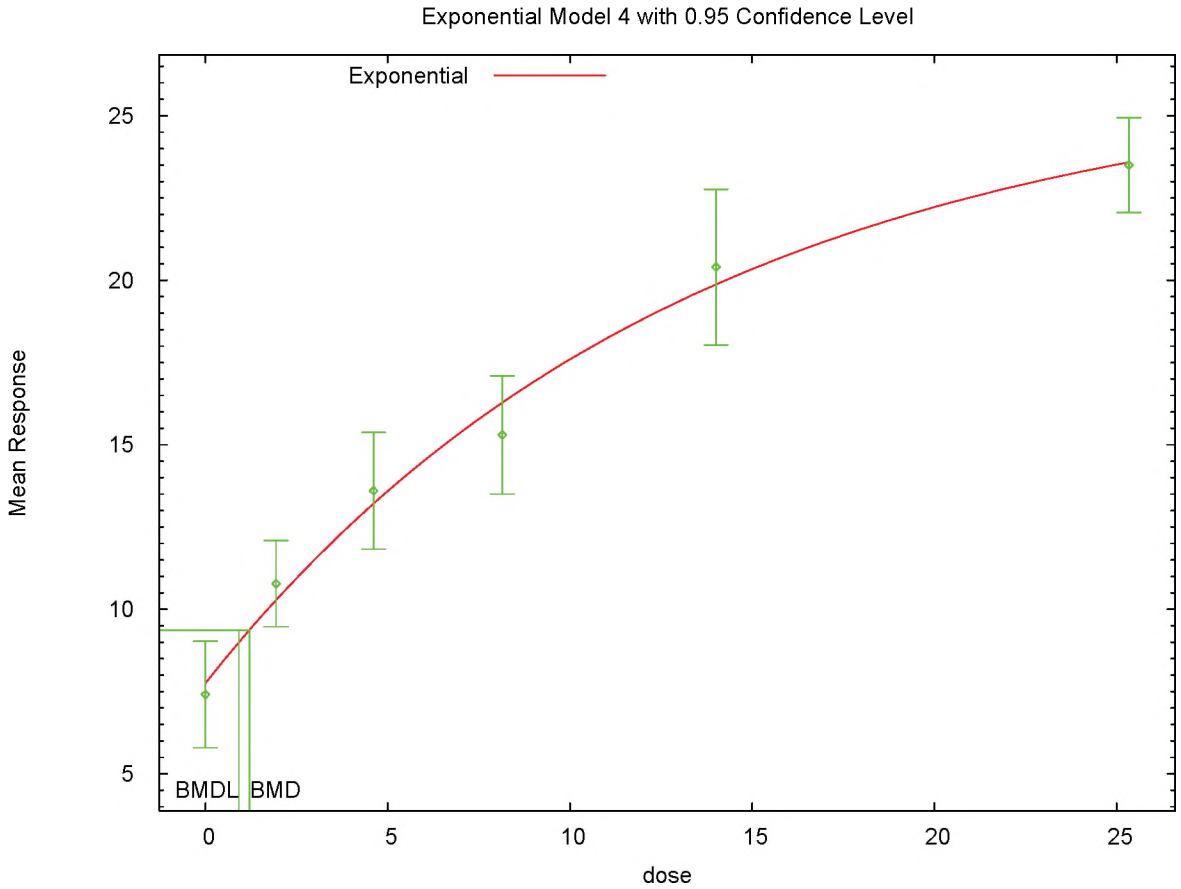
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD =      1.20684

              BMDL =     0.916526
```

H.2.2.3. *Figure for Selected Model: Exponential (M4)*



H.2.2.4. *Output for Additional Model Presented: Power, Unrestricted*

Hassoun et al., 2000: DNA single-strand breaks

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\5\Blood\18_Has_2000_SSB_PwrCV_U_1.(d)
         Gnuplot Plotting File:  C:\5\Blood\18_Has_2000_SSB_PwrCV_U_1.plt
                                              Fri Apr 30 14:15:20 2010
 ================================================================

 DNA single-strand breaks, liver only (Table 3)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   The power is not restricted
   A constant variance model is fit

   Total number of dose groups = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                         alpha =       2.7831
                           rho =            0   Specified
                       control =         7.41
                         slope =      2.16848
                         power =     0.620048


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been specified by the user,
                and do not appear in the correlation matrix )

                  alpha      control        slope        power

    alpha             1     2.5e-009    -4.6e-009     5.7e-009

  control     2.5e-009            1        -0.79         0.66

    slope    -4.6e-009        -0.79            1        -0.97

    power     5.7e-009         0.66        -0.97            1


                               Parameter Estimates

                                                      95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         alpha          2.71022         0.638804             1.45818             3.96225
       control          7.26415         0.644159             6.00163             8.52668
         slope          2.60017         0.530762             1.55989             3.64044
         power         0.575946        0.0589669            0.460373            0.691519


      Table of Data and Estimated Values of Interest
```

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	6	7.41	7.26	1.54	1.65	0.217
1.938	6	10.8	11.1	1.25	1.65	-0.432
4.614	6	13.6	13.5	1.69	1.65	0.094
8.147	6	15.3	16	1.71	1.65	-0.993
14.01	6	20.4	19.2	2.25	1.65	1.85
25.34	6	23.5	24	1.37	1.65	-0.735

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that
were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-33.142389	7	80.284779
A2	-31.811970	12	87.623940
A3	-33.142389	7	80.284779
fitted	-35.946504	4	79.893008
R	-80.442086	2	164.884172

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	97.2602	10	<.0001
Test 2	2.66084	5	0.7521
Test 3	2.66084	5	0.7521
Test 4	5.60823	3	0.1323

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance
model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears
to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems

```
to adequately describe the data


                Benchmark Dose Computation

Specified effect =             1

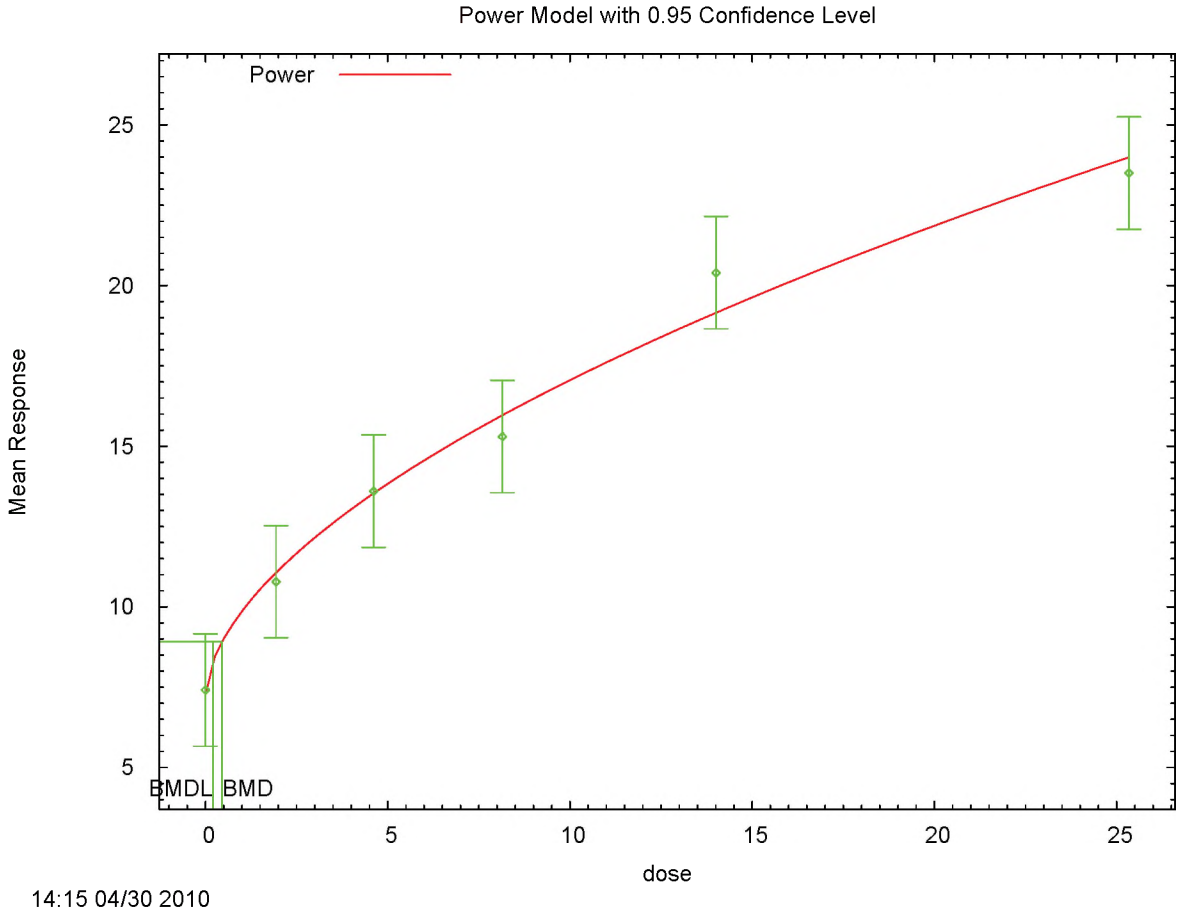
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

              BMD = 0.452221


             BMDL = 0.202688
```

H.2.2.5. *Figure for Additional Model Presented: Power, Unrestricted*



H.2.3. Hassoun et al., 2000: TBARS

H.2.3.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	4	0.001	-8.517	1.736E+01	1.223E+01	
exponential (M3)	4	0.001	-8.517	1.736E+01	1.223E+01	power hit bound (d = 1)
exponential (M4)	3	0.188	-19.755	2.189E+00	1.151E+00	
exponential (M5)	2	0.240	-19.681	3.470E+00	1.525E+00	
Hill [b]	2	0.272	-19.935	3.292E+00	1.737E+00	
linear	4	0.002	-9.793	1.444E+01	9.622E+00	
polynomial, 5-degree	4	0.002	-9.793	1.444E+01	9.622E+00	
power	4	0.002	-9.793	1.444E+01	9.622E+00	power bound hit (power = 1)

[a] Constant variance model selected ($p = 0.3348$)

[b] Best-fitting model, BMDS output presented in this appendix

H.2.3.2. *Output for Selected Model: Hill*

Hassoun et al., 2000: TBARS

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\5\Blood\19_Has_2000_TBARsLiv_HillCV_1.(d)
         Gnuplot Plotting File:  C:\5\Blood\19_Has_2000_TBARsLiv_HillCV_1.plt
                                          Fri Apr 30 14:16:02 2010
 ================================================================

 TBARs, liver only (Table 2)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter restricted to be greater than 1
   A constant variance model is fit

   Total number of dose groups = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values

alpha =	0.178788	
rho =	0	Specified
intercept =	1.469	
v =	1.15	
n =	1.2785	
k =	5.08547	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	intercept	v	n	k
alpha	1	2.8e-008	-4.4e-008	4.9e-008	-1.5e-008
intercept	2.8e-008	1	-0.82	0.48	0.52
v	-4.4e-008	-0.82	1	-0.61	-0.22
n	4.9e-008	0.48	-0.61	1	0.29
k	-1.5e-008	0.52	-0.22	0.29	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	0.16017	0.0377523	0.0861764	0.234163
intercept	1.46138	0.152797	1.1619	1.76086
v	0.963033	0.20228	0.566571	1.3595
n	3.44642	2.43468	-1.32547	8.21832
k	3.63417	1.02019	1.63464	5.6337

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	6	1.47	1.46	0.291	0.4	0.0466
1.938	6	1.55	1.56	0.539	0.4	-0.0696
4.614	6	2.15	2.13	0.363	0.4	0.12
8.147	6	2.28	2.37	0.247	0.4	-0.54
14.01	6	2.62	2.42	0.517	0.4	1.25
25.34	6	2.29	2.42	0.487	0.4	-0.803

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that
were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	16.269770	7	-18.539539
A2	19.127827	12	-14.255654
A3	16.269770	7	-18.539539
fitted	14.967391	5	-19.934782
R	2.442940	2	-0.885880

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	33.3698	10	0.000236
Test 2	5.71611	5	0.3348
Test 3	5.71611	5	0.3348
Test 4	2.60476	2	0.2719

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance
model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears
to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems
to adequately describe the data

Benchmark Dose Computation

Specified effect = 1

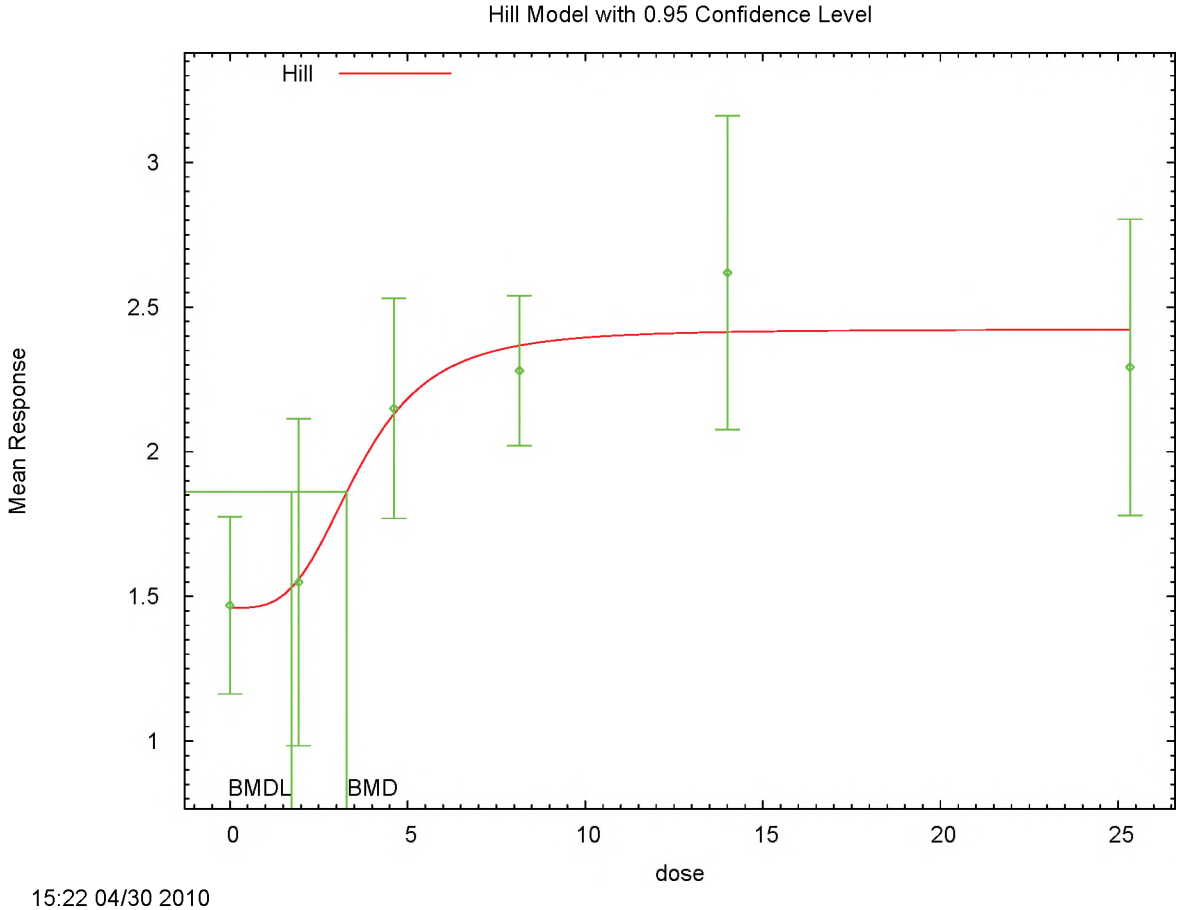
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 3.29185

BMDL = 1.73738

H.2.3.3. *Figure for Selected Model: Hill*



15:22 04/30 2010

H.2.4. Kitchin and Woods, 1979: Bap Hydroxylase Activity

H.2.4.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	9	<0.0001	452.100	2.960E+02	1.446E+02	
exponential (M3)	9	<0.0001	452.100	2.960E+02	1.446E+02	power hit bound (d = 1)
exponential (M4)	8	0.002	232.110	3.182E-01	2.373E-01	
exponential (M5) [b]	7	0.015	227.004	9.321E-01	4.900E-01	
Hill	8	<.0001	479.250	5.340E+00	4.528E+00	
linear	9	<.0001	291.380	4.552E-01	3.303E-01	
polynomial, 8-degree	6	<.0001	468.198	1.012E+03	7.899E-01	
power	9	<.0001	291.380	4.552E-01	3.303E-01	power bound hit (power = 1)

[a] Non-constant variance model selected (p = <0.0001)

[b] Best-fitting model, BMDS output presented in this appendix

H.2.4.2. *Output for Selected Model: Exponential (M5)*

Kitchin and Woods, 1979: BaP Hydroxylase Activity

```
 ======================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\5\Blood\27_Kitchin_1979_Hydrolase_Exp_1.(d)
         Gnuplot Plotting File:
                                                  Fri Apr 30 14:17:28 2010
 ======================================================================

 Kitchin 1979, Tbl3, BaP hydrolase activity
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
```

The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 11
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 5
lnalpha	-3.27793
rho	1.92227
a	4.655
b	0.0041206
c	42.6316
d	1

Parameter Estimates

Variable	Model 5
lnalpha	-2.64071
rho	1.94046
a	5.46248
b	0.0382278
c	30.9208
d	1.42906

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	9	4.9	1.11
0.0645	4	4.9	1.18
0.2023	4	6.7	1.4
0.3839	4	7.2	1.8
1.613	4	8.3	0.26
4.146	4	14	5
11.59	4	59	6.8
30.26	4	96	46
90.9	4	155	16.4
218	4	182	26
863.2	4	189	26

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	5.462	1.387	-1.217
0.0645	5.493	1.394	-0.8507
0.2023	5.619	1.425	1.516
0.3839	5.854	1.483	1.815
1.613	8.483	2.126	-0.1723
4.146	16.8	4.125	-1.358
11.59	49.32	11.73	1.65
30.26	121.2	28.06	-1.796
90.9	168.5	38.62	-0.6975
218	168.9	38.72	0.6765
863.2	168.9	38.72	1.038

Other models for which likelihoods are calculated:

```
  Model A1:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
             Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-158.1306	12	340.2613
A2	-84.80028	22	213.6006
A3	-98.82189	13	223.6438
R	-234.6252	2	473.2504
5	-107.5022	6	227.0044

Additive constant for all log-likelihoods = -45.03. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 7a: Does Model 5 fit the data? (A3 vs 5)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	299.6	20	< 0.0001
Test 2	146.7	10	< 0.0001
Test 3	28.04	9	0.0009381
Test 7a	17.36	7	0.01521

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

The p-value for Test 3 is less than .1. You may want to consider a different variance model.

The p-value for Test 7a is less than .1. Model 5 may not adequately describe the data; you may want to consider another model.

Benchmark Dose Computations:

Specified Effect = 1.000000

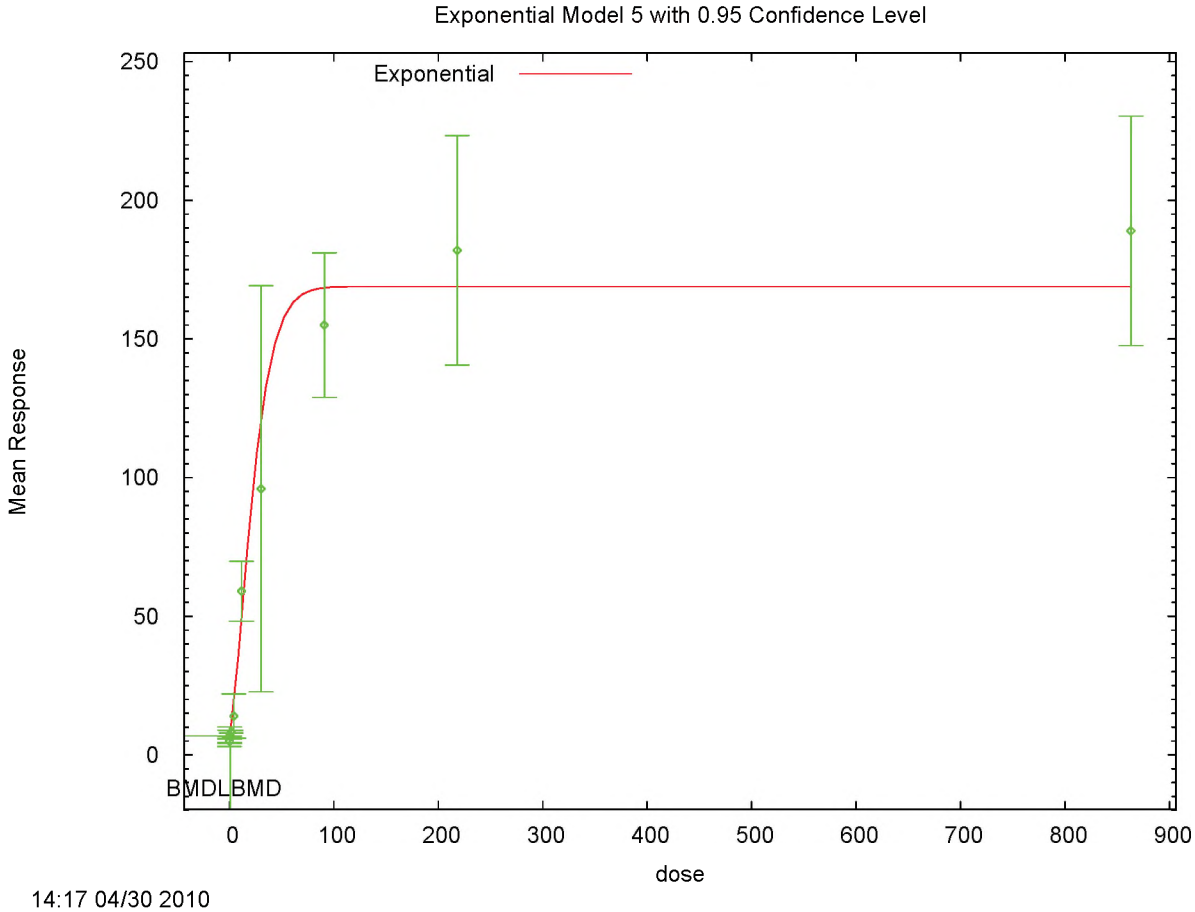
Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 0.9321

BMDL = 0.490004

H.2.4.3. *Figure for Selected Model: Exponential (M5)*



14:17 04/30 2010

H.2.5. National Toxicology Program, 2006: Liver EROD 53 Weeks

H.2.5.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	4	<0.0001	648.094	2.011E+01	1.464E+01	
exponential (M3)	4	<0.0001	648.094	2.011E+01	1.464E+01	power hit bound (d = 1)
exponential (M4)	3	0.015	521.251	1.430E-02	9.808E-03	
exponential (M5)	2	0.354	514.812	7.656E-02	3.202E-02	
Hill [b]	2	0.760	513.286	1.853E-01	9.351E-02	
linear	4	<.0001	639.841	1.034E+01	6.557E-03	
polynomial, 5-degree	1	<.0001	14.000	error	error	
power	4	<.0001	592.889	2.254E-02	1.527E-02	power bound hit (power = 1)

[a] Non-constant variance model selected (*p* = <.0001)

[b] Best-fitting model, BMDS output presented in this appendix

H.2.5.2. *Output for Selected Model: Hill*

National Toxicology Program, 2006: Liver EROD 53 Weeks

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\5\Blood\46_NTP_2006_ERODliv53_Hill_1.(d)
         Gnuplot Plotting File:  C:\5\Blood\46_NTP_2006_ERODliv53_Hill_1.plt
                                              Sun May 02 15:34:21 2010
 ================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   Power parameter restricted to be greater than 1
   The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

   Total number of dose groups = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
```

lalpha =	11.0197
rho =	0
intercept =	30.215
v =	1841.26
n =	7.0105
k =	6.95814

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	intercept	v	n	k
lalpha	1	-0.97	-0.18	0.065	-0.025	0.046
rho	-0.97	1	0.17	-0.093	0.025	-0.048
intercept	-0.18	0.17	1	-0.022	0.011	0.00084
v	0.065	-0.093	-0.022	1	-0.73	0.87
n	-0.025	0.025	0.011	-0.73	1	-0.83
k	0.046	-0.048	0.00084	0.87	-0.83	1

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
lalpha	-4.47504	0.923978	-6.286	-2.66407
rho	2.12799	0.137849	1.85781	2.39817
intercept	30.2685	1.41935	27.4866	33.0504
v	1813.88	100.554	1616.8	2010.96
n	2.02516	0.29717	1.44272	2.6076
k	3.78554	0.349266	3.101	4.47009

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	30.2	30.3	4.5	4.02	-0.0377
2.458	8	569	564	69.6	90.3	0.17
5.533	8	1.28e+003	1.27e+003	270	214	0.137
9.543	8	1.55e+003	1.6e+003	318	274	-0.529
16.18	8	1.73e+003	1.75e+003	304	302	-0.248
29.04	8	1.87e+003	1.82e+003	309	313	0.507

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-285.269096	7	584.538193
A2	-249.237836	12	522.475671
A3	-250.368300	8	516.736600
fitted	-250.643212	6	513.286424
R	-338.451300	2	680.902600

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	178.427	10	<.0001
Test 2	72.0625	5	<.0001
Test 3	2.26093	4	0.6879
Test 4	0.549824	2	0.7596

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

Benchmark Dose Computation

Specified effect = 1

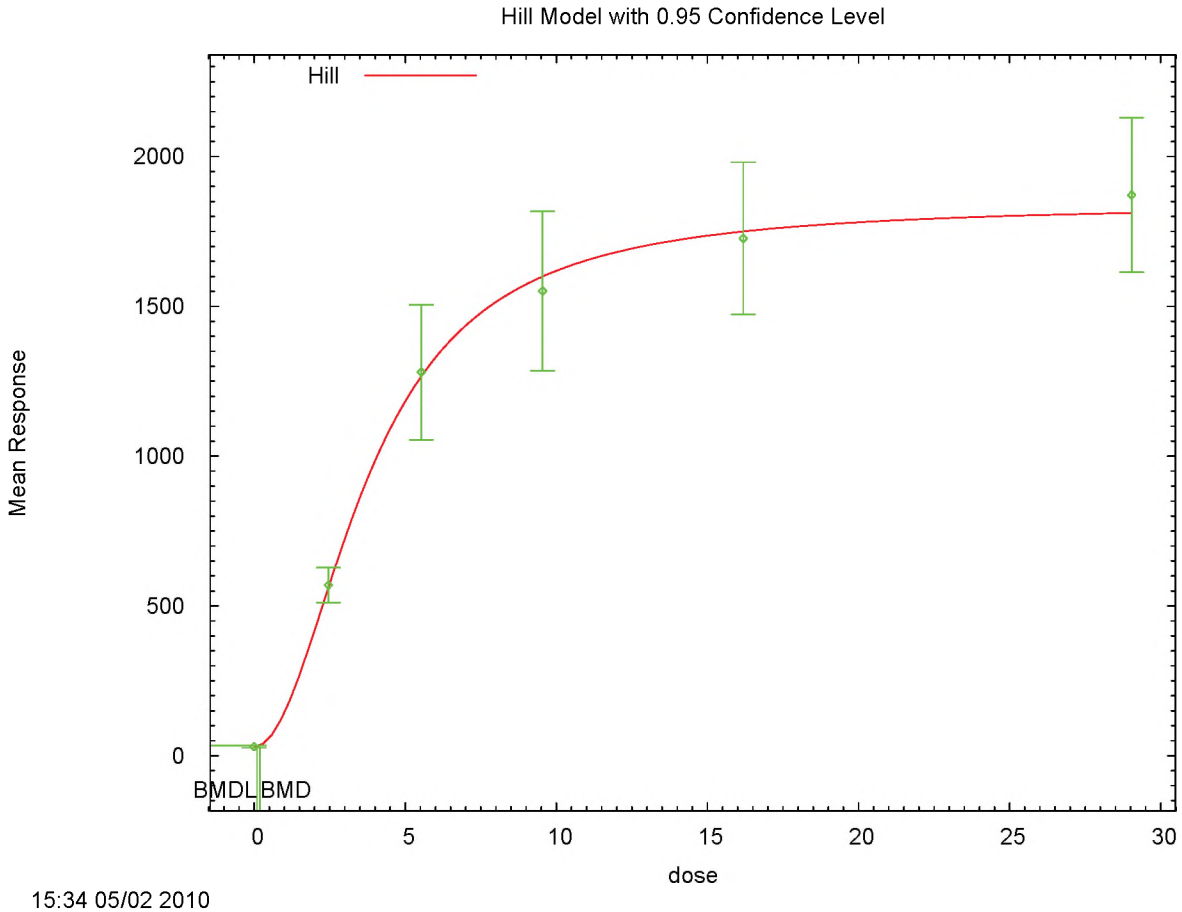
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 0.185269

BMDL = 0.0935065

H.2.5.3. *Figure for Selected Model: Hill*



H.2.6. National Toxicology Program, 2006: Lung Erod 53 Weeks

H.2.6.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	4	<0.0001	314.332	3.281E+01	2.047E+01	
exponential (M3)	4	<0.0001	555.061	5.210E+00	8.194E-01	power hit bound (d = 1)
exponential (M4) [b]	3	0.302	255.955	9.586E-02	5.907E-02	
exponential (M5)	2	0.276	256.882	1.044E+00	6.588E-02	
Hill	2	0.275	256.882	1.903E+00	3.469E-01	
linear	4	<.0001	313.237	2.662E+01	1.251E+01	
polynomial, 5-degree	5	<.0001	330.180	error	2.718E+01	
power	4	<.0001	313.237	2.662E+01	1.251E+01	power bound hit (power = 1)
power, unrestricted [c]	3	0.032	261.083	1.875E-07	1.875E-07	unrestricted (power = 0.18)

[a] Non-constant variance model selected (p = <0.0001)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

H.2.6.2. *Output for Selected Model: Exponential (M4)*

National Toxicology Program, 2006: Lung EROD 53 Weeks

```
 ========================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\5\Blood\52_NTP_2006_LungEROD53_Exp_1.(d)
         Gnuplot Plotting File:
                                                 Fri Apr 30 14:20:27 2010
 ========================================================================

 Tbl 12, Week 53, Lung Microsomes EROD
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

     Note: Y[dose] is the median response for exposure = dose;
           sign = +1 for increasing trend in data;
           sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.
```

Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	-0.80064
rho	1.47683
a	2.86045
b	0.134268
c	16.0581
d	1

Parameter Estimates

Variable	Model 4
lnalpha	-1.14455
rho	1.63458
a	3.06102
b	0.371249
c	14.1551
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	8	3.011	1.584
2.458	8	27.15	5.269
5.533	8	42.85	11.15
9.543	8	36.57	12.99
16.18	8	43.75	18.55
29.04	8	43.71	6.322

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	3.061	1.408	-0.1005
2.458	27.16	8.383	-0.003073
5.533	38.17	11.07	1.196
9.543	42.16	12.01	-1.318
16.18	43.23	12.26	0.1191
29.04	43.33	12.28	0.08864

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

```
  Model A2:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
              Var{e(ij)} = Sigma^2


                              Likelihoods of Interest

                    Model      Log(likelihood)      DF         AIC
                    -------    -----------------    ----   ------------
                       A1       -135.2677           7      284.5353
                       A2       -115.6885          12      255.3771
                       A3       -121.1517           8      258.3034
                        R       -162.0902           2      328.1805
                        4       -122.9773           5      255.9546


Additive constant for all log-likelihoods =     -44.11.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.


                                Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)


                           Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                         92.8           10           < 0.0001
  Test 2                        39.16            5           < 0.0001
  Test 3                        10.93            4             0.0274
 Test 6a                        3.651            3             0.3017


  The p-value for Test 1 is less than .05.  There appears to be a
  difference between response and/or variances among the dose
  levels, it seems appropriate to model the data.

  The p-value for Test 2 is less than .1.  A non-homogeneous
  variance model appears to be appropriate.

  The p-value for Test 3 is less than .1.  You may want to
  consider a different variance model.

  The p-value for Test 6a is greater than .1.  Model 4 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 1.000000

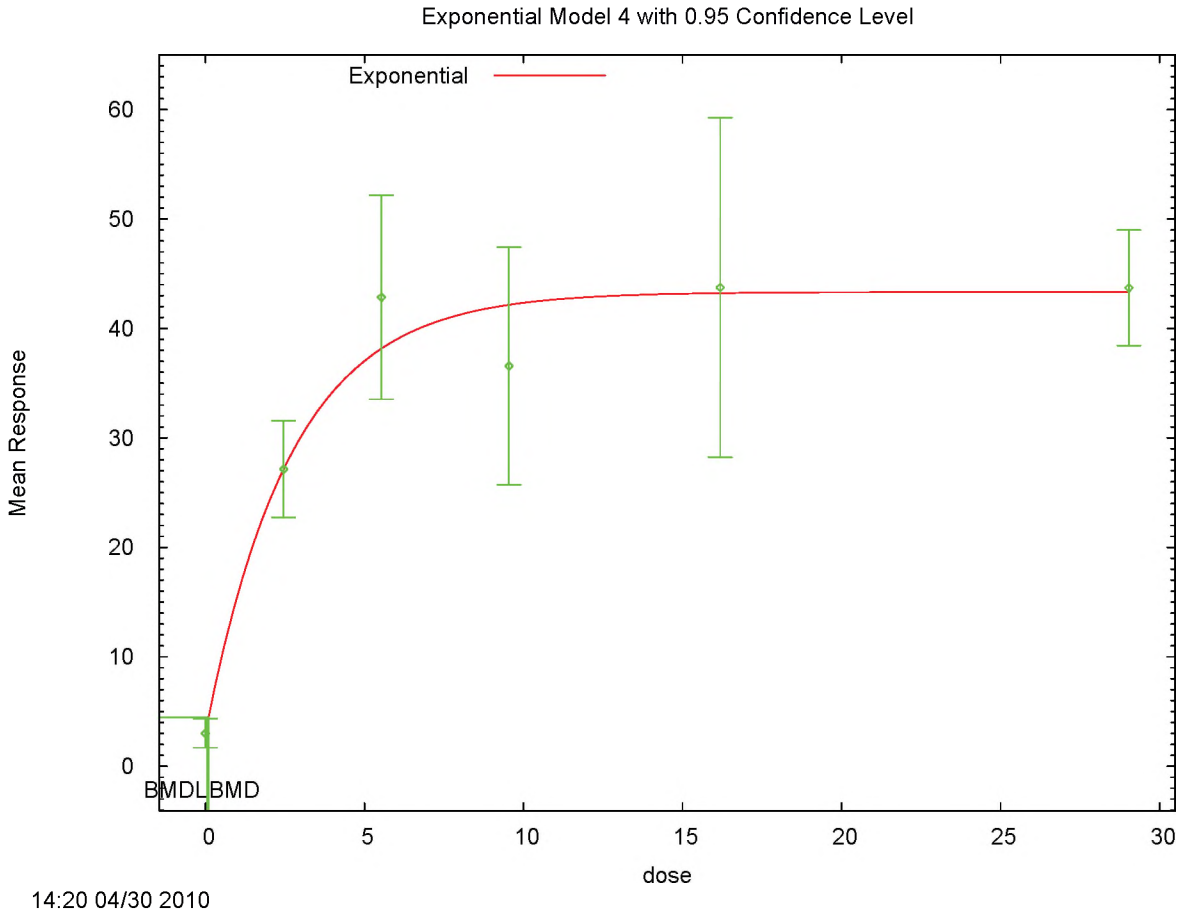
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD =      0.09586

              BMDL =    0.0590734
```

H.2.6.3. *Figure for Selected Model: Exponential (M4)*



14:20 04/30 2010

H.2.6.4. *Output for Additional Model Presented: Power, Unrestricted*

National Toxicology Program, 2006: Lung EROD 53 Weeks

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\5\Blood\52_NTP_2006_LungEROD53_Pwr_U_1.(d)
         Gnuplot Plotting File:  C:\5\Blood\52_NTP_2006_LungEROD53_Pwr_U_1.plt
                                              Fri Apr 30 14:20:33 2010
 ================================================================

 Tbl 12, Week 53, Lung Microsomes EROD
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   The power is not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                Default Initial Parameter Values
                       lalpha =      4.76968
                          rho =            0
                      control =        3.011
                        slope =      23.2411
                        power =     0.187468


           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho      control        slope        power

    lalpha            1        -0.96        -0.49          0.1       -0.045

       rho        -0.96            1         0.45        -0.13         0.05

   control        -0.49         0.45            1        -0.14        0.048

     slope          0.1        -0.13        -0.14            1        -0.94

     power       -0.045         0.05        0.048        -0.94            1


                                Parameter Estimates

                                                      95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha         -1.02668         0.818488           -2.63088            0.577531
            rho          1.63033          0.24056            1.15884             2.10182
        control          3.01543         0.519355            1.99751             4.03335
          slope          23.8167          3.70401            16.5569             31.0764
          power         0.179731        0.0639681           0.054356            0.305106


      Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
```

```
------     ---   --------     --------   -----------  -----------   ----------

     0     8       3.01         3.02         1.58         1.47       -0.00851
 2.458     8       27.1           31         5.27         9.84          -1.11
 5.533     8       42.8         35.4         11.2           11           1.92
 9.543     8       36.6         38.7           13         11.8          -0.52
 16.18     8       43.7         42.3         18.5         12.7          0.323
 29.04     8       43.7         46.6         6.32         13.7         -0.605


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
      Model A3 uses any fixed variance parameters that
      were specified by the user

 Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
              A1         -135.267662          7     284.535325
              A2         -115.688533         12     255.377067
              A3         -121.151707          8     258.303413
          fitted         -125.541690          5     261.083380
               R         -162.090242          2     328.180484


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              92.8034         10          <.0001
   Test 2              39.1583          5          <.0001
   Test 3              10.9263          4          0.0274
   Test 4              8.77997          3         0.03236

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

The p-value for Test 4 is less than .1.  You may want to try a different
model
```

```
                Benchmark Dose Computation

Specified effect =             1

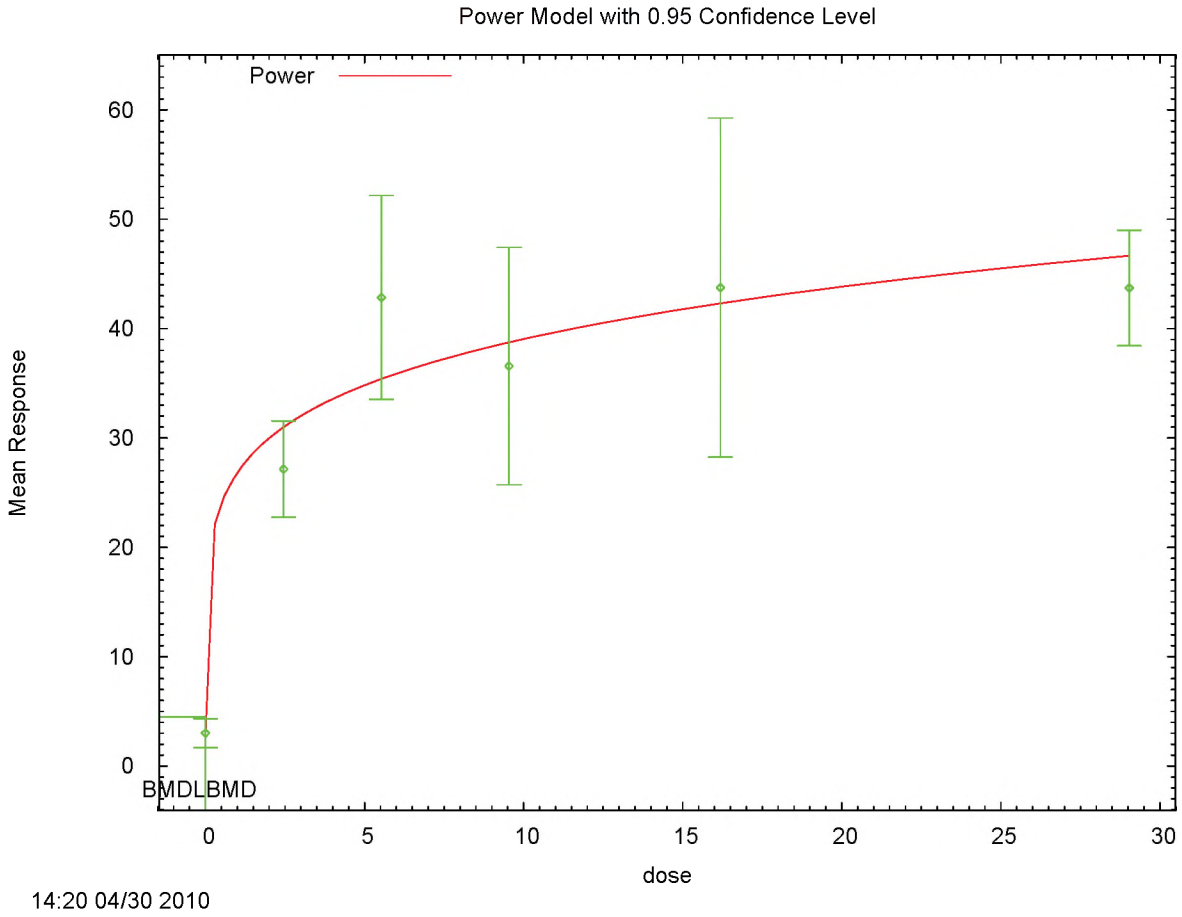
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

              BMD = 1.8745e-007


             BMDL = 1.8745e-007
```

H.2.6.5. *Figure for Additional Model Presented: Power, Unrestricted*



H.2.7. National Toxicology Program, 2006: Labeling Index 31 Weeks

H.2.7.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	4	0.000	46.547	8.660E+00	6.926E+00	
exponential (M3)	4	0.000	46.547	8.660E+00	6.926E+00	power hit bound (d = 1)
exponential (M4)	3	<0.0001	50.958	3.151E+00	1.865E+00	
exponential (M5)	3	<0.0001	50.958	3.151E+00	1.864E+00	power hit bound (d = 1)
Hill	3	<.0001	50.963	3.145E+00	error	n lower bound hit (n = 1)
linear	4	0.000	48.958	3.151E+00	1.865E+00	
polynomial, 5-degree [b]	3	0.000	46.230	7.607E+00	3.125E+00	
power	4	0.000	48.958	3.151E+00	1.865E+00	power bound hit (power = 1)

[a] Non-constant variance model selected (*p* = <.0001)

[b] Best-fitting model, BMDS output presented in this appendix

H.2.7.2. *Output for Selected Model: Polynomial, 5-degree*

National Toxicology Program, 2006: Labeling Index 31 Weeks

```
 ======================================================================
          Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
          Input Data File: C:\5\Blood\38_NTP_2006_HepIndex_Poly5_1.(d)
          Gnuplot Plotting File:  C:\5\Blood\38_NTP_2006_HepIndex_Poly5_1.plt
                                                 Fri Apr 30 14:21:16 2010
 ======================================================================

 Tbl 11, 31wk, Hep Cell Proliferation Labeling Index
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   The polynomial coefficients are restricted to be positive
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
```

```
                          lalpha =     0.708431
                             rho =            0
                          beta_0 =        0.327
                          beta_1 =            0
                          beta_2 =            0
                          beta_3 =            0
                          beta_4 =            0
                          beta_5 =            0


            Asymptotic Correlation Matrix of Parameter Estimates

            ( *** The model parameter(s)  -beta_2    -beta_3    -beta_4
                  have been estimated at a boundary point, or have been specified by the user,
                  and do not appear in the correlation matrix )

                  lalpha          rho       beta_0       beta_1       beta_5

    lalpha             1       -0.086        0.012       -0.032        0.043

       rho       -0.086            1      -0.0027       -0.011        0.076

    beta_0        0.012      -0.0027            1         -0.6         0.23

    beta_1       -0.032       -0.011         -0.6            1        -0.53

    beta_5        0.043        0.076         0.23        -0.53            1


                                 Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha        -0.501559         0.185039          -0.864229           -0.138889
            rho          1.90452         0.272948            1.36955             2.43948
         beta_0         0.500197         0.102837           0.298641            0.701753
         beta_1        0.0525247        0.0192967          0.0147038           0.0903456
         beta_2     8.00068e-025               NA
         beta_3                0               NA
         beta_4                0               NA
         beta_5     1.08658e-007     6.10451e-008       -1.09879e-008        2.28305e-007

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.



     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     9      0.327          0.5        0.189        0.402          -1.29
2.331    10      0.852        0.623        0.651        0.496           1.46
5.315    10      0.956         0.78        0.737        0.614          0.907
9.207    10      0.792        0.991        0.462        0.772         -0.816
15.66    10       1.33         1.42         1.12         1.09         -0.266
28.13    10       3.85         3.89         3.08         2.84        -0.0523


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2
```

```
Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1          -47.234977            7     108.469953
             A2           -8.679256           12      41.358512
             A3           -8.980651            8      33.961301
         fitted          -18.115050            5      46.230101
              R          -63.448285            2     130.896571


                   Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value

  Test 1              109.538         10          <.0001
  Test 2              77.1114          5          <.0001
  Test 3              0.60279          4          0.9628
  Test 4              18.2688          3       0.0003871

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1.  You may want to try a different
model


             Benchmark Dose Computation

Specified effect =             1

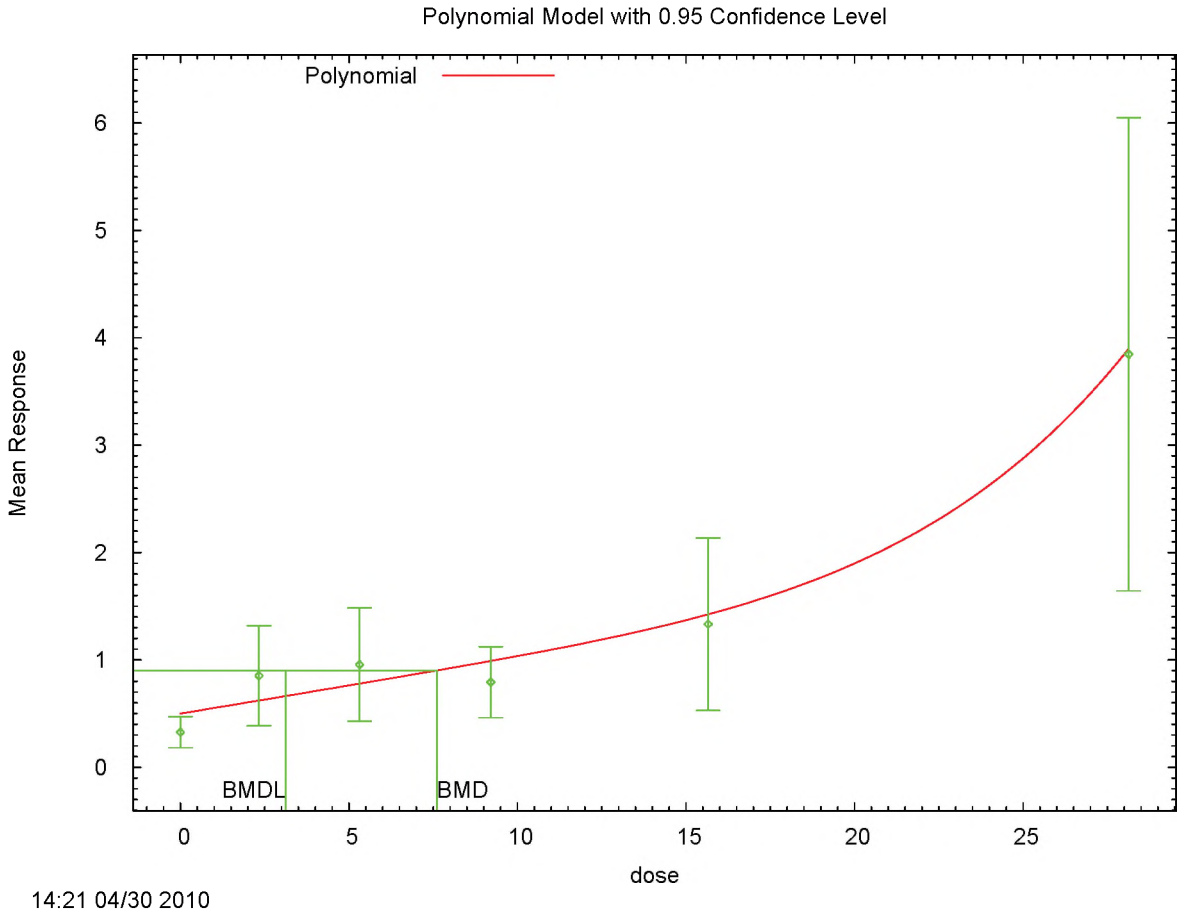
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =         7.6073


             BMDL =        3.12526
```

H.2.7.3. *Figure for Selected Model: Polynomial, 5-degree*



H.2.8. Vanden Heuvel et al., 1994: Hepatic CYP1A1 Mrna Expression

H.2.8.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
exponential (M2)	5	<0.0001	1147.626	1.769E+01	1.257E+01	
exponential (M3)	4	<0.0001	1149.626	1.769E+01	1.257E+01	power hit bound (d = 1)
exponential (M4)	4	<0.0001	666.337	6.104E-02	2.871E-02	
exponential (M5)	3	<0.0001	635.591	1.252E+00	9.089E-01	
Hill [b]	3	<.0001	664.418	2.429E-01	1.679E-01	
linear	5	<.0001	673.777	4.546E-02	2.487E-02	
polynomial, 6-degree	6	<.0001	1213.329	error	1.301E+03	
power	4	<.0001	673.418	6.269E-02	3.196E-02	

[a] Non-constant variance model selected (p = <0.0001)

[b] Best-fitting model, BMDS output presented in this appendix

H.2.8.2. *Output for Selected Model: Hill*

Vanden Heuvel et al., 1994: Hepatic CYP1A1 mRNA Expression

```
================================================================
          Hill Model. (Version: 2.14;  Date: 06/26/2008)
          Input Data File: C:\Usepa\BMDS21\Data\hil_Vanden_mRNA_Setting.(d)
          Gnuplot Plotting File:  C:\Usepa\BMDS21\Data\hil_Vanden_mRNA_Setting.plt
                                                Tue May 18 05:24:48 2010
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = mRNA_mean
   Independent variable = blood_conc
   Power parameter is not restricted
   The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

   Total number of dose groups = 7
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  User Inputs Initial Parameter Values
```

```
                          lalpha =           1
                             rho =         1.9
                       intercept =           6
                               v =       36000
                               n =           1
                               k =        1000


            Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha          rho    intercept            v            n            k

     lalpha            1        -0.89        -0.43         0.27         0.68        -0.18

        rho        -0.89            1         0.31        -0.42        -0.72         0.22

  intercept        -0.43         0.31            1       -0.093         0.14        -0.04

          v         0.27        -0.42       -0.093            1        0.075          0.7

          n         0.68        -0.72         0.14        0.075            1        -0.52

          k        -0.18         0.22        -0.04          0.7        -0.52            1


                                  Parameter Estimates

                                                                95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
          lalpha        -0.191631         0.711681            -1.5865             1.20324
             rho           2.0275         0.132551            1.76771             2.28729
       intercept            5.416          1.16292            3.13672             7.69529
               v          41657.2          16561.5            9197.25             74117.2
               n          1.29154         0.100513            1.09454             1.48854
               k          97.8648          41.0376            17.4325             178.297


       Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0    13         5.4         5.42         3.61         5.04        -0.0115
0.0113     5         7.2         5.76         5.59         5.36          0.602
0.106     12        14.8         11.6         14.9         10.9           1.03
0.8828     7        12.8          100          4.5         97.2          -2.38
 6.46      7         536    1.21e+003          320    1.22e+003          -1.48
48.32     11    1.8e+004    1.19e+004    1.52e+004    1.24e+004           1.62
434.5      5   3.67e+004    3.64e+004    2.21e+004    3.82e+004         0.0199


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
      Model A3 uses any fixed variance parameters that
      were specified by the user

 Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-572.470944	8	1160.941889
A2	-290.799287	14	609.598575
A3	-293.809342	9	605.618684
fitted	-326.209186	6	664.418372
R	-603.663396	2	1211.326792

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	625.728	12	<.0001
Test 2	563.343	6	<.0001
Test 3	6.02011	5	0.3043
Test 4	64.7997	3	<.0001

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

Specified effect = 24

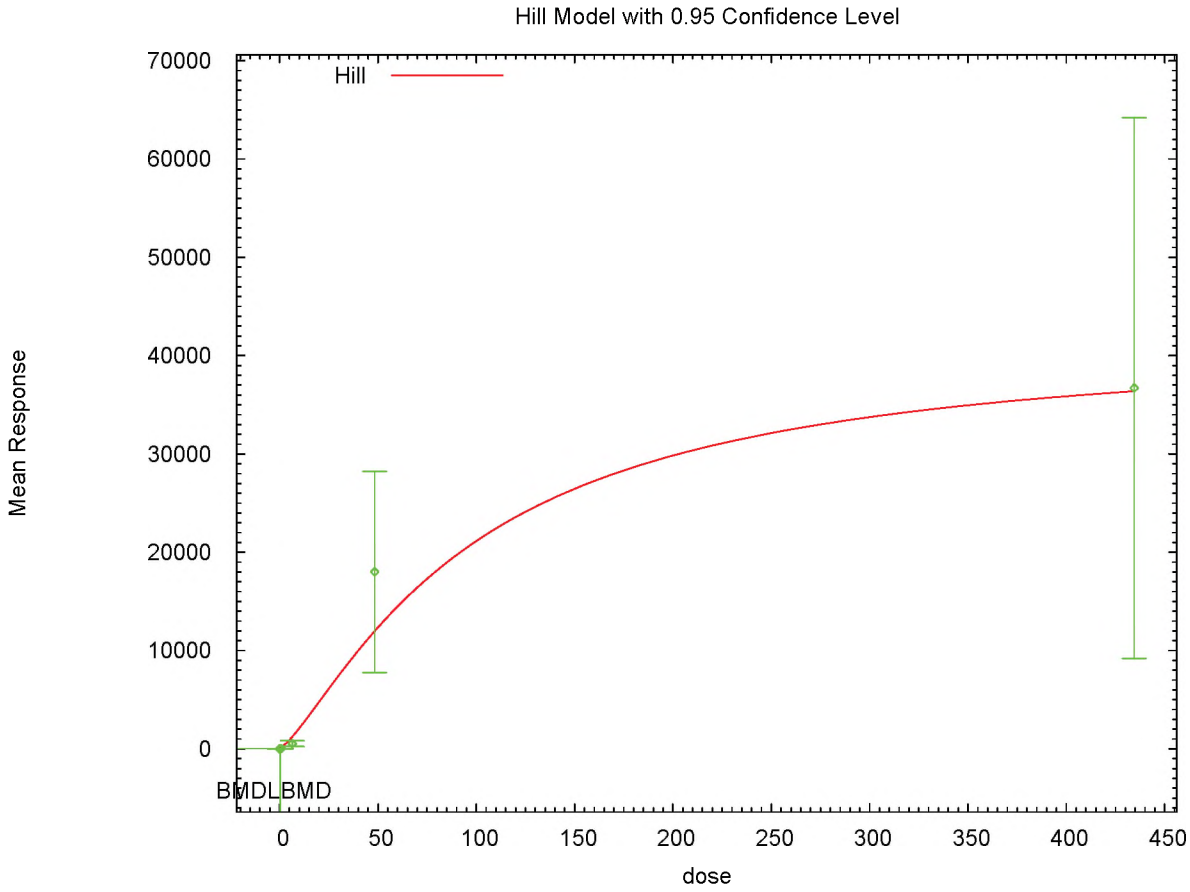
Risk Type = Point risk

Confidence level = 0.95

BMD = 0.249203

BMDL = 0.167897

H.2.8.3. *Figure for Selected Model: Hill*



05:24 05/18 2010

H.3. ADMINISTERED DOSE BMDS RESULTS

H.3.1. Hassoun et al., 2000: Cytochrome C Reductase

H.3.1.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2)	4	0.002	-139.075	3.939E+01	3.254E+01	
exponential (M3)	4	0.002	-139.075	3.939E+01	3.254E+01	power hit bound (d = 1)
exponential (M4) [b]	3	0.637	-151.807	9.085E+00	5.886E+00	
exponential (M5)	2	0.786	-151.023	1.420E+01	6.537E+00	
Hill	2	0.741	-150.905	1.513E+01	6.277E+00	
linear	4	0.032	-144.946	2.470E+01	1.933E+01	
polynomial, 5-degree	4	0.032	-144.946	2.470E+01	1.933E+01	
power	4	0.032	-144.946	2.470E+01	1.933E+01	power bound hit (power = 1)
power, unrestricted [c]	3	0.211	-148.989	6.573E+00	1.966E+00	unrestricted (power = 0.574)

[a] Constant variance model selected ($p = 0.3871$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

H.3.1.2. *Output for Selected Model: Exponential (M4)*

Hassoun et al., 2000: Cytochrome C reductase

```
 ========================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\5\17_Has_2000_CytCLiv_ExpCV_1.(d)
         Gnuplot Plotting File:
                                                Fri Apr 30 21:15:20 2010
 ========================================================================

 TBARs, liver only (Table 2)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
```

Model 4 is nested within Model 5.

Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	-5.48625
rho(S)	0
a	0.1387
b	0.027423
c	3.36121
d	1

(S) = Specified

Parameter Estimates

Variable	Model 4
lnalpha	-5.43908
rho	0
a	0.141259
b	0.0235562
c	3.42165
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	6	0.146	0.06614
3	6	0.177	0.05389
10	6	0.191	0.05634
22	6	0.271	0.05634
46	6	0.388	0.06369
100	6	0.444	0.1102

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.1413	0.06591	0.1762
3	0.1646	0.06591	0.4609
10	0.2131	0.06591	-0.8196
22	0.2796	0.06591	-0.3199
46	0.3676	0.06591	0.7587
100	0.4509	0.06591	-0.2564

Other models for which likelihoods are calculated:

```
  Model A1:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
             Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	80.75258	7	-147.5052
A2	83.37355	12	-142.7471
A3	80.75258	7	-147.5052
R	55.82002	2	-107.64
4	79.90337	4	-151.8067

Additive constant for all log-likelihoods = -33.08. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	55.11	10	< 0.0001
Test 2	5.242	5	0.3871
Test 3	5.242	5	0.3871
Test 6a	1.698	3	0.6373

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data.

Benchmark Dose Computations:

```
  Specified Effect = 1.000000

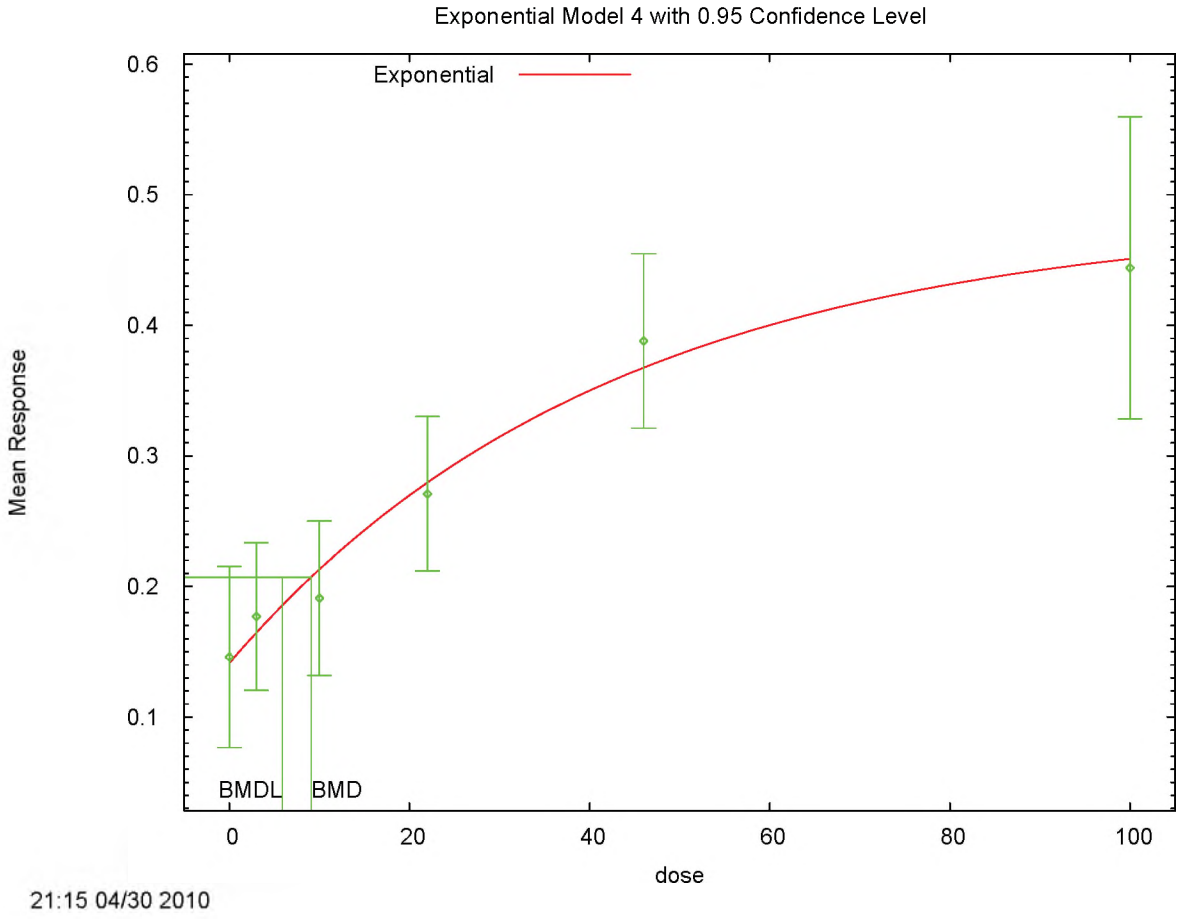
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000
```

```
BMD =        9.0851

BMDL =       5.88612
```

H.3.1.3. *Figure for Selected Model: Exponential (M4)*



H.3.1.4. *Output for Additional Model Presented: Power, Unrestricted*

Hassoun et al., 2000: Cytochrome C reductase

```
================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\5\17_Has_2000_CytCLiv_PwrCV_U_1.(d)
        Gnuplot Plotting File:  C:\5\17_Has_2000_CytCLiv_PwrCV_U_1.plt
                                          Fri Apr 30 21:15:26 2010
================================================================

TBARs, liver only (Table 2)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the response function is:

  Y[dose] = control + slope * dose^power


  Dependent variable = Mean
  Independent variable = Dose
  rho is set to 0
  The power is not restricted
  A constant variance model is fit
```

Total number of dose groups = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

alpha =	0.004972	
rho =	0	Specified
control =	0.146	
slope =	0.0109242	
power =	0.717914	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	control	slope	power
alpha	1	-8.8e-010	-3.8e-009	4.5e-009
control	-8.8e-010	1	-0.77	0.68
slope	-3.8e-009	-0.77	1	-0.98
power	4.5e-009	0.68	-0.98	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	0.00469717	0.00110713	0.00252723	0.00686711
control	0.135495	0.0246289	0.0872229	0.183766
slope	0.0232652	0.013381	-0.00296103	0.0494915
power	0.573772	0.119032	0.340474	0.80707

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	6	0.146	0.135	0.0661	0.0685	0.375
3	6	0.177	0.179	0.0539	0.0685	-0.0784
10	6	0.191	0.223	0.0563	0.0685	-1.13
22	6	0.271	0.273	0.0563	0.0685	-0.056
46	6	0.388	0.345	0.0637	0.0685	1.54
100	6	0.444	0.462	0.11	0.0685	-0.653

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

```
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
              A1          80.752584            7    -147.505168
              A2          83.373547           12    -142.747094
              A3          80.752584            7    -147.505168
          fitted          78.494318            4    -148.988637
               R          55.820023            2    -107.640047


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1               55.107         10          <.0001
   Test 2              5.24193          5          0.3871
   Test 3              5.24193          5          0.3871
   Test 4              4.51653          3          0.2108

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


               Benchmark Dose Computation

Specified effect =             1

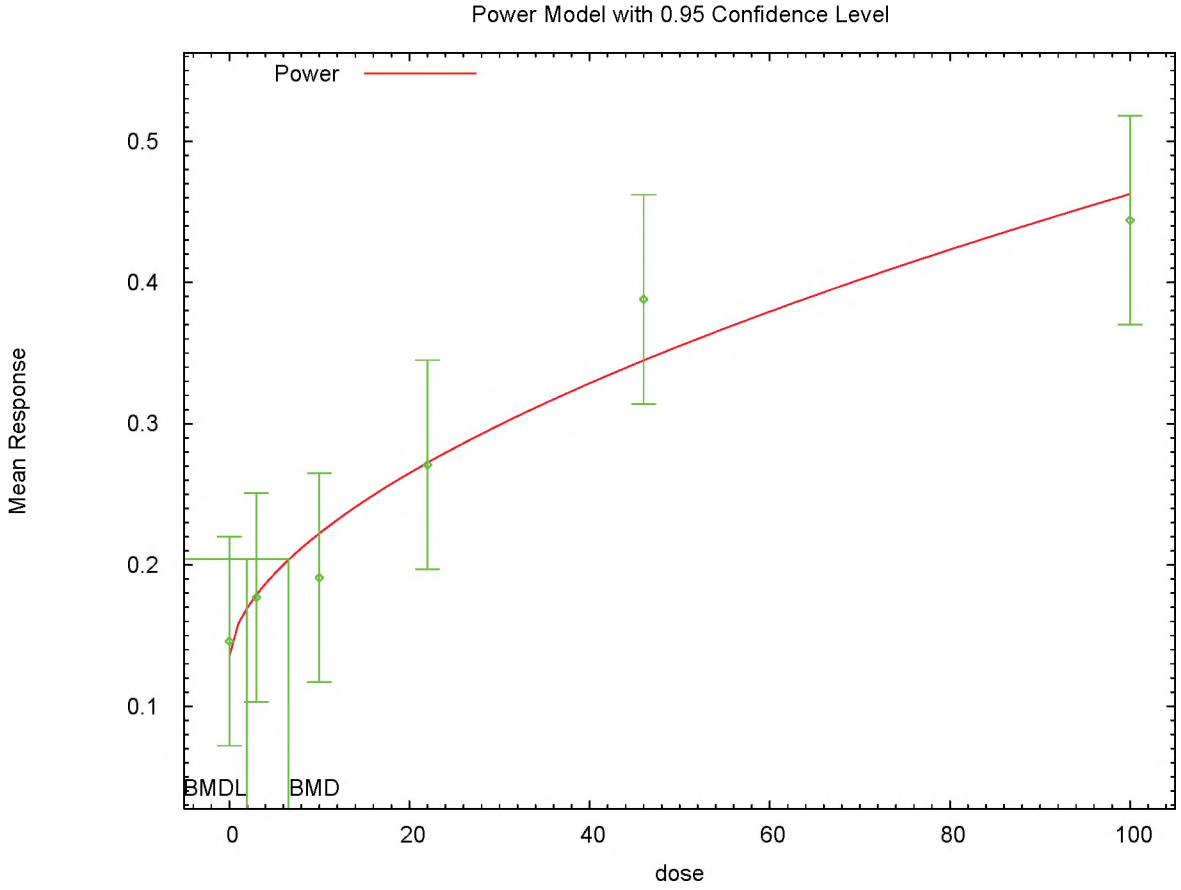
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 6.57302


            BMDL = 1.96558
```

H.3.1.5. *Figure for Additional Model Presented: Power, Unrestricted*



H.3.2. Hassoun et al., 2000: DNA Single-Strand Breaks

H.3.2.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2)	4	<0.0001	120.828	3.006E+01	2.491E+01	
exponential (M3)	4	<0.0001	120.828	3.006E+01	2.491E+01	power hit bound (d = 1)
exponential (M4)	3	0.036	82.814	3.734E+00	2.783E+00	
exponential (M5)	3	0.036	82.814	3.734E+00	2.783E+00	power hit bound (d = 1)
Hill [b]	3	0.068	81.407	2.890E+00	2.007E+00	n lower bound hit (n = 1)
linear	4	<.0001	111.165	1.807E+01	1.452E+01	
polynomial, 5-degree	4	<.0001	111.165	1.807E+01	1.452E+01	
power	4	<.0001	111.165	1.807E+01	1.452E+01	power bound hit (power = 1)
Hill, unrestricted [c]	2	0.133	80.318	9.618E-01	2.114E-01	unrestricted (n = 0.613)

[a] Constant variance model selected ($p = 0.7521$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

H.3.2.2. *Output for Selected Model: Hill*

Hassoun et al., 2000: DNA single-strand breaks

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\5\18_Has_2000_SSB_HillCV_1.(d)
         Gnuplot Plotting File:  C:\5\18_Has_2000_SSB_HillCV_1.plt
                                          Fri Apr 30 21:16:28 2010
 ================================================================

 DNA single-strand breaks, liver only (Table 3)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter restricted to be greater than 1
   A constant variance model is fit

   Total number of dose groups = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
```

Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

alpha =	2.7831	
rho =	0	Specified
intercept =	7.41	
v =	16.09	
n =	0.174831	
k =	69.2706	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho -n
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	intercept	v	k
alpha	1	1.1e-007	1.9e-007	1.9e-007
intercept	1.1e-007	1	0.099	0.61
v	1.9e-007	0.099	1	0.79
k	1.9e-007	0.61	0.79	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	2.82659	0.666233	1.5208	4.13238
intercept	8.16404	0.581043	7.02522	9.30286
v	20.1253	1.69013	16.8127	23.4379
n	1	NA		
k	31.702	8.35815	15.3203	48.0836

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	6	7.41	8.16	1.54	1.68	-1.1
3	6	10.8	9.9	1.25	1.68	1.28
10	6	13.6	13	1.69	1.68	0.889
22	6	15.3	16.4	1.71	1.68	-1.62
46	6	20.4	20.1	2.25	1.68	0.469
100	6	23.5	23.4	1.37	1.68	0.0802

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

```
Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                       Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
              A1          -33.142389           7      80.284779
              A2          -31.811970          12      87.623940
              A3          -33.142389           7      80.284779
          fitted          -36.703273           4      81.406545
               R          -80.442086           2     164.884172


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              97.2602         10          <.0001
   Test 2              2.66084          5          0.7521
   Test 3              2.66084          5          0.7521
   Test 4              7.12177          3         0.06812

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1.  You may want to try a different
model


        Benchmark Dose Computation

Specified effect =             1

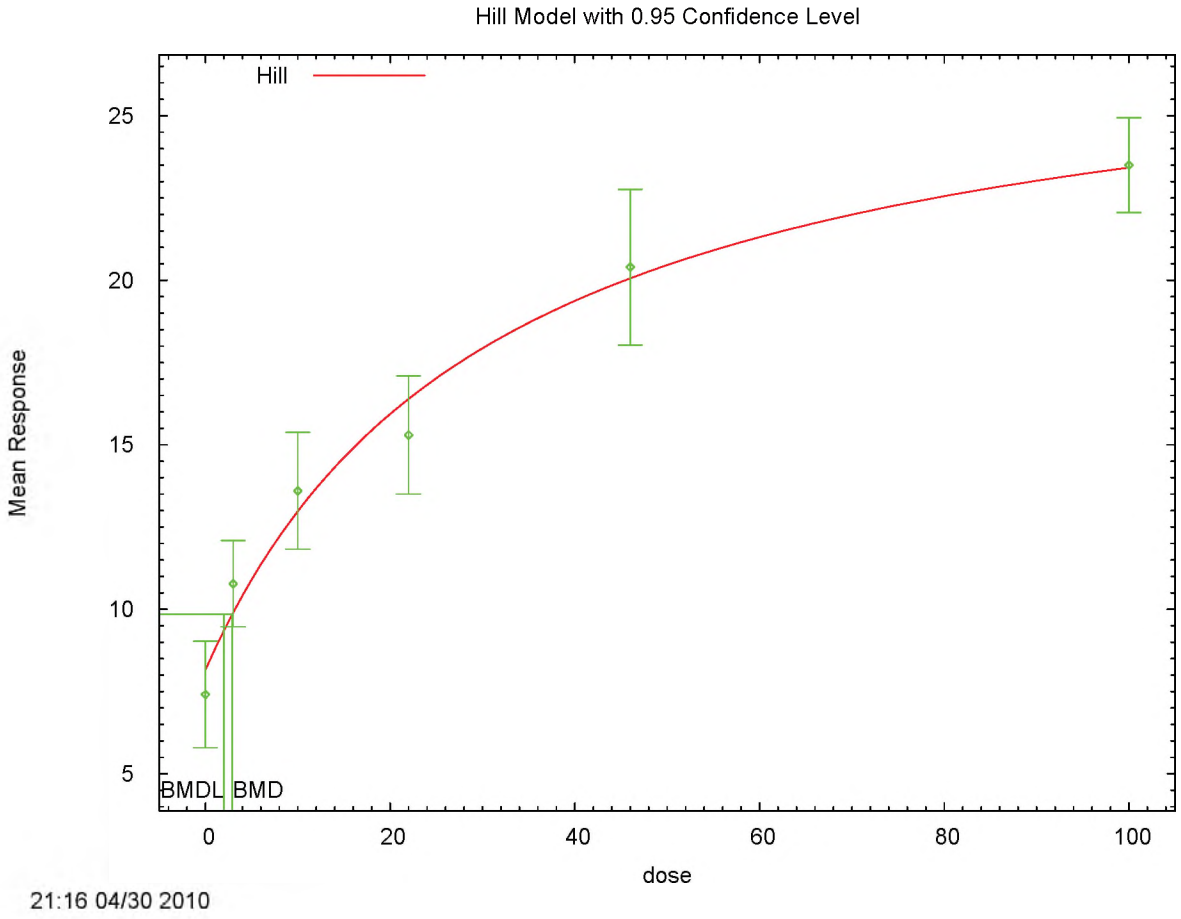
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =        2.88976

            BMDL =       2.00669
```

H.3.2.3. *Figure for Selected Model: Hill*



H.3.2.4. *Output for Additional Model Presented: Hill, Unrestricted*

Hassoun et al., 2000: DNA single-strand breaks

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\5\18_Has_2000_SSB_HillCV_U_1.(d)
         Gnuplot Plotting File:  C:\5\18_Has_2000_SSB_HillCV_U_1.plt
                                              Fri Apr 30 21:16:30 2010
 ================================================================

 DNA single-strand breaks, liver only (Table 3)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter is not restricted
   A constant variance model is fit

   Total number of dose groups = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
```

Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

alpha =	2.7831	
rho =	0	Specified
intercept =	7.41	
v =	16.09	
n =	0.174831	
k =	69.2706	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	intercept	v	n	k
alpha	1	-2.2e-008	-4.6e-008	8.4e-009	-4.3e-008
intercept	-2.2e-008	1	-0.33	0.47	-0.29
v	-4.6e-008	-0.33	1	-0.95	1
n	8.4e-009	0.47	-0.95	1	-0.96
k	-4.3e-008	-0.29	1	-0.96	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	2.5942	0.611459	1.39576	3.79264
intercept	7.47627	0.665055	6.17278	8.77975
v	36.9014	25.5466	-13.1689	86.9718
n	0.612877	0.190055	0.240376	0.985377
k	148.104	303.532	-446.809	743.016

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	6	7.41	7.48	1.54	1.61	-0.101
3	6	10.8	10.6	1.25	1.61	0.313
10	6	13.6	13.4	1.69	1.61	0.286
22	6	15.3	16.2	1.71	1.61	-1.41
46	6	20.4	19.6	2.25	1.61	1.24
100	6	23.5	23.7	1.37	1.61	-0.33

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

```
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
              A1          -33.142389           7      80.284779
              A2          -31.811970          12      87.623940
              A3          -33.142389           7      80.284779
          fitted          -35.159023           5      80.318046
               R          -80.442086           2     164.884172


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              97.2602         10          <.0001
   Test 2              2.66084          5          0.7521
   Test 3              2.66084          5          0.7521
   Test 4              4.03327          2          0.1331

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =             1

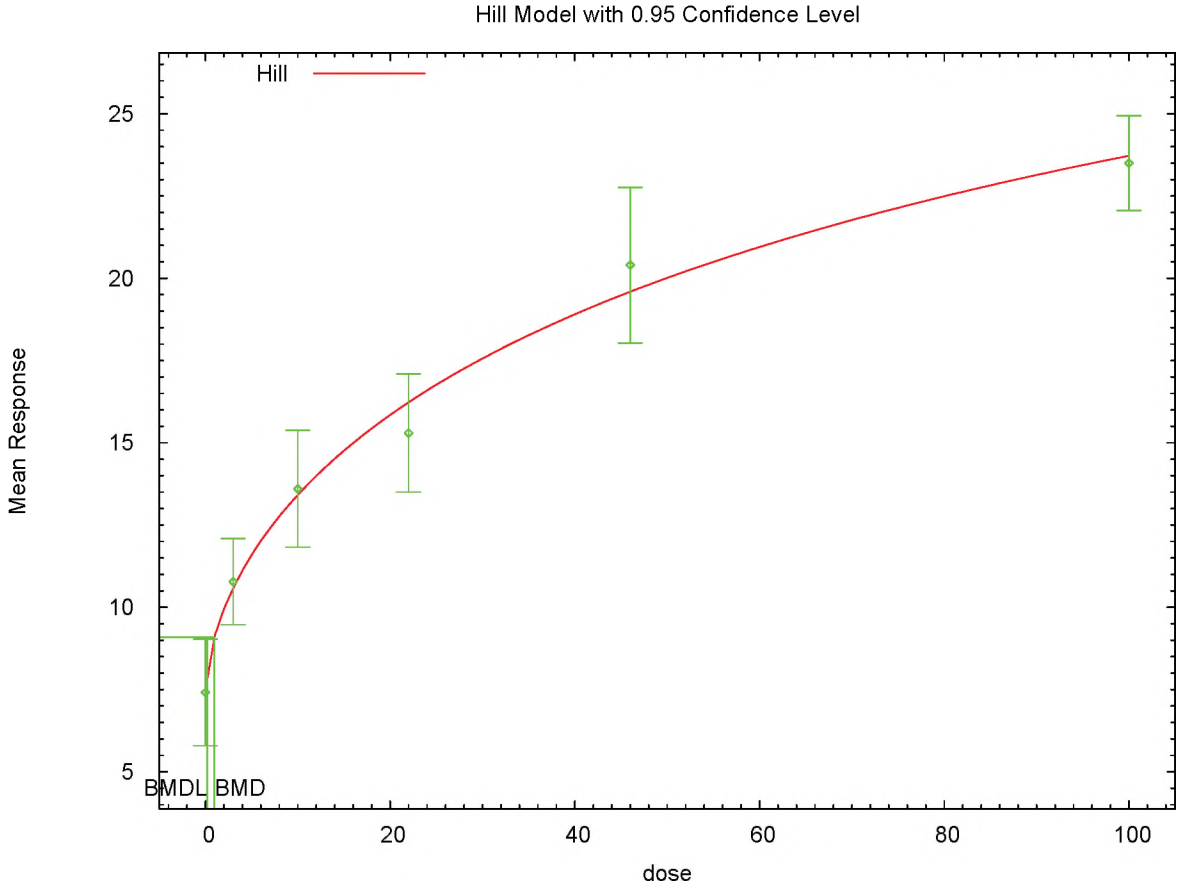
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =       0.961789

            BMDL =      0.211403
```

H.3.2.5. *Figure for Additional Model Presented: Hill, Unrestricted*



H.3.3. Hassoun et al., 2000: TBARS

H.3.3.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2)	4	0.000	-6.143	7.977E+01	5.344E+01	
exponential (M3)	4	0.000	-6.143	7.977E+01	5.344E+01	power hit bound (d = 1)
exponential (M4) [b]	3	0.340	-21.181	4.916E+00	2.300E+00	
exponential (M5)	2	0.240	-19.681	6.732E+00	2.470E+00	
Hill	2	0.272	-19.932	6.261E+00	2.575E+00	
linear	4	0.001	-7.019	6.904E+01	4.373E+01	
polynomial, 5-degree	4	0.001	-7.019	6.904E+01	4.373E+01	
power	4	0.001	-7.019	6.904E+01	4.373E+01	power bound hit (power = 1)
power, unrestricted [c]	3	0.023	-14.993	2.902E+00	6.150E-02	unrestricted (power = 0.263)

[a] Constant variance model selected ($p = 0.3348$)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

H.3.3.2. *Output for Selected Model: Exponential (M4)*

Hassoun et al., 2000: TBARS

```
 ======================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\5\19_Has_2000_TBARsLiv_ExpCV_1.(d)
         Gnuplot Plotting File:
                                                Fri Apr 30 21:17:17 2010
 ======================================================================

 TBARs, liver only (Table 2)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.
```

Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	-1.90388
rho(S)	0
a	1.39555
b	0.0194898
c	1.97051
d	1

(S) = Specified

Parameter Estimates

Variable	Model 4
lnalpha	-1.81059
rho	0
a	1.40436
b	0.0996859
c	1.74329
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	6	1.469	0.2915
3	6	1.549	0.5389
10	6	2.15	0.3625
22	6	2.28	0.2474
46	6	2.619	0.5168
100	6	2.292	0.4874

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	1.404	0.4044	0.3915
3	1.674	0.4044	-0.7582
10	2.063	0.4044	0.527
22	2.332	0.4044	-0.3134
46	2.438	0.4044	1.099
100	2.448	0.4044	-0.9458

Other models for which likelihoods are calculated:

```
  Model A1:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
              Var{e(ij)} = Sigma^2


                              Likelihoods of Interest

                    Model      Log(likelihood)      DF         AIC
                    -------    -----------------    ----   ------------
                       A1        16.26977            7     -18.53954
                       A2        19.12783           12     -14.25565
                       A3        16.26977            7     -18.53954
                        R         2.44294            2    -0.8858799
                        4          14.5907           4     -21.18141


Additive constant for all log-likelihoods =     -33.08.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.


                               Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)


                           Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                         33.37          10            0.000236
  Test 2                         5.716           5              0.3348
  Test 3                         5.716           5              0.3348
 Test 6a                         3.358           3              0.3396


  The p-value for Test 1 is less than .05.  There appears to be a
  difference between response and/or variances among the dose
  levels, it seems appropriate to model the data.

  The p-value for Test 2 is greater than .1.  A homogeneous
  variance model appears to be appropriate here.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 6a is greater than .1.  Model 4 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 1.000000

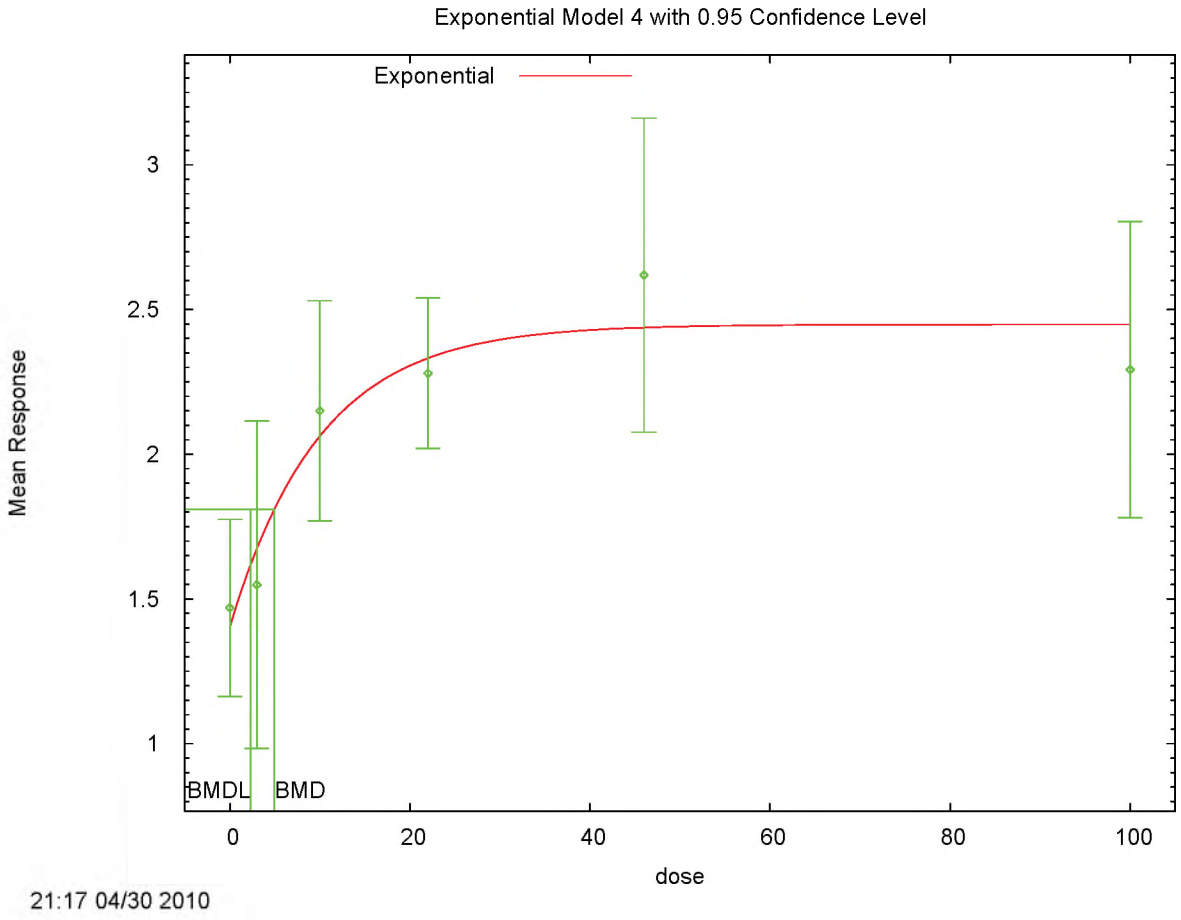
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

              BMD =      4.91639
```

BMDL = 2.29952

H.3.3.3. *Figure for Selected Model: Exponential (M4)*



H.3.3.4. *Output for Additional Model Presented: Power, Unrestricted*

Hassoun et al., 2000: TBARS

```
================================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\5\19_Has_2000_TBARsLiv_PwrCV_U_1.(d)
        Gnuplot Plotting File:  C:\5\19_Has_2000_TBARsLiv_PwrCV_U_1.plt
                                                Fri Apr 30 21:17:21 2010
================================================================================

TBARs, liver only (Table 2)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the response function is:

  Y[dose] = control + slope * dose^power


  Dependent variable = Mean
  Independent variable = Dose
  rho is set to 0
  The power is not restricted
  A constant variance model is fit

  Total number of dose groups = 6
```

```
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                          alpha =     0.178788
                            rho =            0   Specified
                        control =        1.469
                          slope =    0.0756538
                          power =     0.652114


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -rho
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

                    alpha      control        slope        power

      alpha             1     1.1e-008    -1.1e-009    -1.5e-008

    control     1.1e-008            1        -0.75         0.47

      slope    -1.1e-009        -0.75            1        -0.91

      power    -1.5e-008         0.47        -0.91            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
           alpha         0.194232        0.0457809           0.104503            0.283961
         control          1.42104         0.171077            1.08573             1.75634
           slope         0.333105         0.166768         0.00624603            0.659963
           power         0.262735        0.0983956          0.0698836            0.455587


      Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0       6       1.47         1.42        0.291        0.441          0.267
    3       6       1.55         1.87        0.539        0.441          -1.76
   10       6       2.15         2.03        0.363        0.441          0.661
   22       6       2.28         2.17        0.247        0.441          0.603
   46       6       2.62         2.33        0.517        0.441            1.6
  100       6       2.29         2.54        0.487        0.441          -1.37


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
      Model A3 uses any fixed variance parameters that
      were specified by the user
```

```
Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                       Likelihoods of Interest

           Model      Log(likelihood)   # Param's      AIC
            A1           16.269770           7     -18.539539
            A2           19.127827          12     -14.255654
            A3           16.269770           7     -18.539539
         fitted          11.496634           4     -14.993268
             R            2.442940           2      -0.885880


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              33.3698         10        0.000236
   Test 2              5.71611          5          0.3348
   Test 3              5.71611          5          0.3348
   Test 4              9.54627          3         0.02284

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1.  You may want to try a different
model


               Benchmark Dose Computation

Specified effect =             1

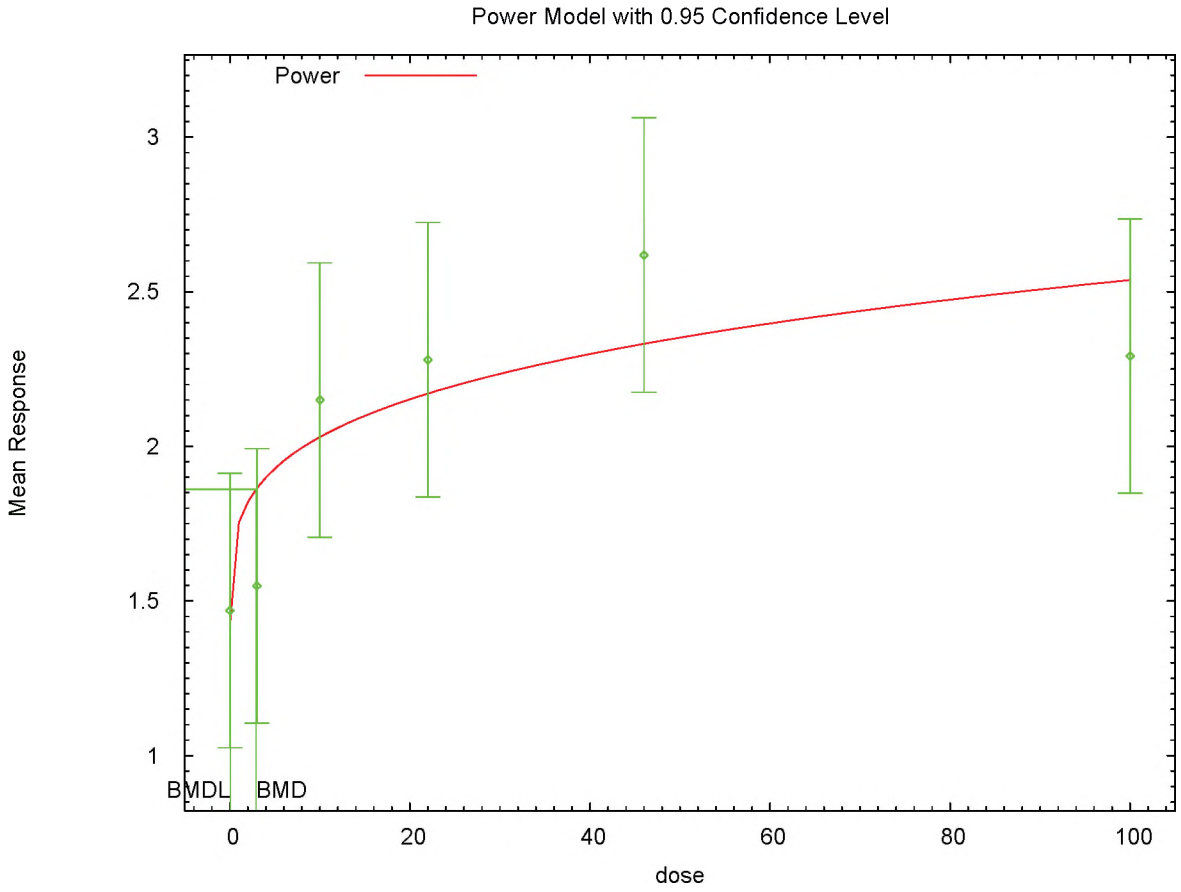
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 2.90232


            BMDL = 0.0614971
```

H.3.3.5. *Figure for Additional Model Presented: Power, Unrestricted*



21:17 04/30 2010

H.3.4. Kitchin and Woods, 1979: Bap Hydroxylase Activity

H.3.4.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2)	9	<0.0001	452.693	7.939E+03	3.663E+03	
exponential (M3)	9	<0.0001	452.693	7.939E+03	3.663E+03	power hit bound (d = 1)
exponential (M4)	8	0.015	226.600	5.458E+00	4.099E+00	
exponential (M5) [b]	7	0.019	226.401	1.022E+01	4.807E+00	
Hill	8	<.0001	504.527	error	error	n upper bound hit (n = 18)
linear	9	<.0001	299.732	8.276E+00	5.945E+00	
polynomial, 8-degree	3	<.0001	20.000	error	error	
power	9	<.0001	299.732	8.276E+00	5.945E+00	power bound hit (power = 1)

[a] Non-constant variance model selected (*p* = <0.0001)

[b] Best-fitting model, BMDS output presented in this appendix

H.3.4.2. *Output for Selected Model: Exponential (M5)*

Kitchin and Woods, 1979: BaP Hydroxylase Activity

```
 ======================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\5\27_Kitchin_1979_Hydrolase_Exp_1.(d)
         Gnuplot Plotting File:
                                                 Fri Apr 30 21:18:04 2010
 ======================================================================

 Kitchin 1979, Tbl3, BaP hydrolase activity
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
```

The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 11
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 5
lnalpha	-3.27793
rho	1.92227
a	4.655
b	0.000177432
c	42.6316
d	1

Parameter Estimates

Variable	Model 5
lnalpha	-2.64304
rho	1.93753
a	5.43423
b	0.00191658
c	31.2033
d	1.21503

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	9	4.9	1.11
0.6	4	4.9	1.18
2	4	6.7	1.4
4	4	7.2	1.8
20	4	8.3	0.26
60	4	14	5
200	4	59	6.8
600	4	96	46
2000	4	155	16.4
5000	4	182	26
2e+004	4	189	26

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	5.434	1.375	-1.166
0.6	5.478	1.386	-0.8347
2	5.624	1.421	1.514
4	5.875	1.483	1.787
20	8.525	2.127	-0.2115
60	16.87	4.12	-1.394
200	49.41	11.67	1.643
600	119.4	27.43	-1.705
2000	168.6	38.31	-0.7091
5000	169.6	38.53	0.6454
2e+004	169.6	38.53	1.009

Other models for which likelihoods are calculated:

```
  Model A1:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
             Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-158.1306	12	340.2613
A2	-84.80028	22	213.6006
A3	-98.82189	13	223.6438
R	-234.6252	2	473.2504
5	-107.2005	6	226.4011

Additive constant for all log-likelihoods = -45.03. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 7a: Does Model 5 fit the data? (A3 vs 5)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	299.6	20	< 0.0001
Test 2	146.7	10	< 0.0001
Test 3	28.04	9	0.0009381
Test 7a	16.76	7	0.01903

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

The p-value for Test 3 is less than .1. You may want to consider a different variance model.

The p-value for Test 7a is less than .1. Model 5 may not adequately describe the data; you may want to consider another model.

Benchmark Dose Computations:

Specified Effect = 1.000000

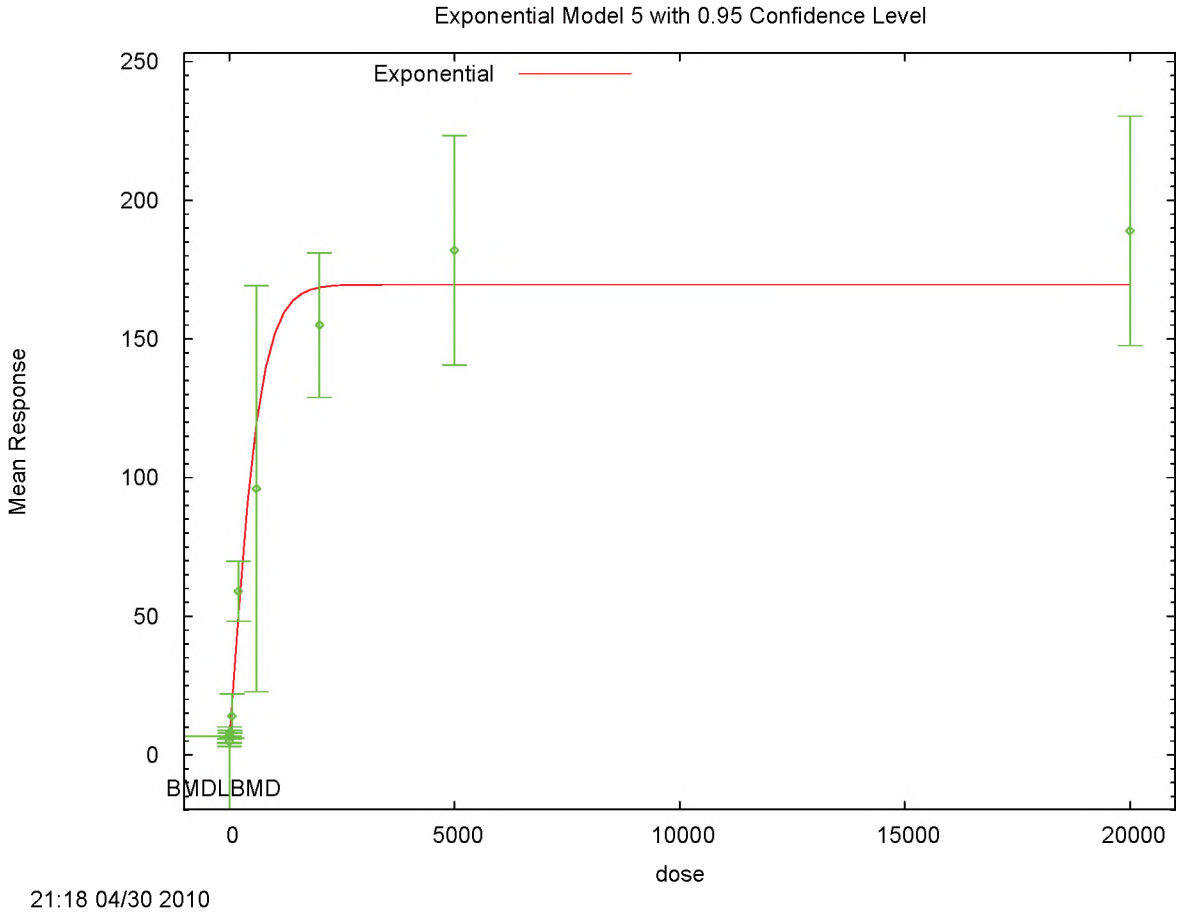
Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 10.2235

BMDL = 4.80673

H.3.4.3. *Figure for Selected Model: Exponential (M5)*



H.3.5. National Toxicology Program, 2006: Liver EROD 53 Weeks

H.3.5.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2)	4	<0.0001	210.749	4.068E+01	2.856E+01	
exponential (M3)	4	<0.0001	210.749	4.068E+01	2.856E+01	power hit bound (d = 1)
exponential (M4)	3	0.071	98.835	1.912E-01	1.384E-01	
exponential (M5)	2	0.040	100.232	2.394E-01	1.433E-01	
Hill [b]	2	0.219	96.847	3.823E-01	2.336E-01	
linear	4	<.0001	203.577	2.076E+01	8.128E+00	
polynomial, 5-degree	4	<.0001	203.577	2.076E+01	8.128E+00	
power	4	<.0001	203.577	2.076E+01	8.128E+00	power bound hit (power = 1)

[a] Non-constant variance model selected (*p* = <.0001)

[b] Best-fitting model, BMDS output presented in this appendix

H.3.5.2. *Output for Selected Model: Hill*

National Toxicology Program, 2006: Liver EROD 53 Weeks

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\5\46_NTP_2006_ERODliv53_Hill_1.(d)
         Gnuplot Plotting File:  C:\5\46_NTP_2006_ERODliv53_Hill_1.plt
                                          Sun May 02 15:05:02 2010
 ================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   Power parameter restricted to be greater than 1
   The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

   Total number of dose groups = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
```

```
                          lalpha =      1.59547
                             rho =            0
                       intercept =        3.614
                               v =       17.599
                               n =      1.38542
                               k =      8.70663


            Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha          rho    intercept            v            n            k

     lalpha            1        -0.96        -0.16        0.086       -0.057        0.041

        rho        -0.96            1         0.14        -0.11        0.059       -0.045

  intercept        -0.16         0.14            1        -0.18         0.13        0.069

          v        0.086        -0.11        -0.18            1        -0.72         0.84

          n       -0.057        0.059         0.13        -0.72            1        -0.79

          k        0.041       -0.045        0.069         0.84        -0.79            1


                                  Parameter Estimates

                                                                 95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha         -4.86522         0.741624           -6.31878            -3.41167
            rho          2.26949         0.287245             1.7065             2.83248
      intercept          3.62909         0.133823             3.3668             3.89138
              v          17.9802         0.989132            16.0416             19.9189
              n           1.4314         0.162447            1.11301             1.74979
              k          5.58259         0.717084            4.17713             6.98805


    Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0       8       3.61         3.63        0.486        0.379         -0.113
 2.14       8       7.27         7.27        0.557        0.833         0.0203
 7.14       8       14.8         14.2         1.61         1.78          0.911
 15.7       8       17.3         18.3         1.59         2.37          -1.19
 32.9       8       20.6         20.3         3.05         2.67          0.304
 71.4       8       21.2         21.2         3.82          2.8         0.0606


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-59.086537	7	132.173073
A2	-37.515858	12	99.031716
A3	-40.906180	8	97.812359
fitted	-42.423278	6	96.846556
R	-116.710291	2	237.420582

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	158.389	10	<.0001
Test 2	43.1414	5	<.0001
Test 3	6.78064	4	0.1479
Test 4	3.0342	2	0.2193

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears
to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems
to adequately describe the data

Benchmark Dose Computation

Specified effect = 1

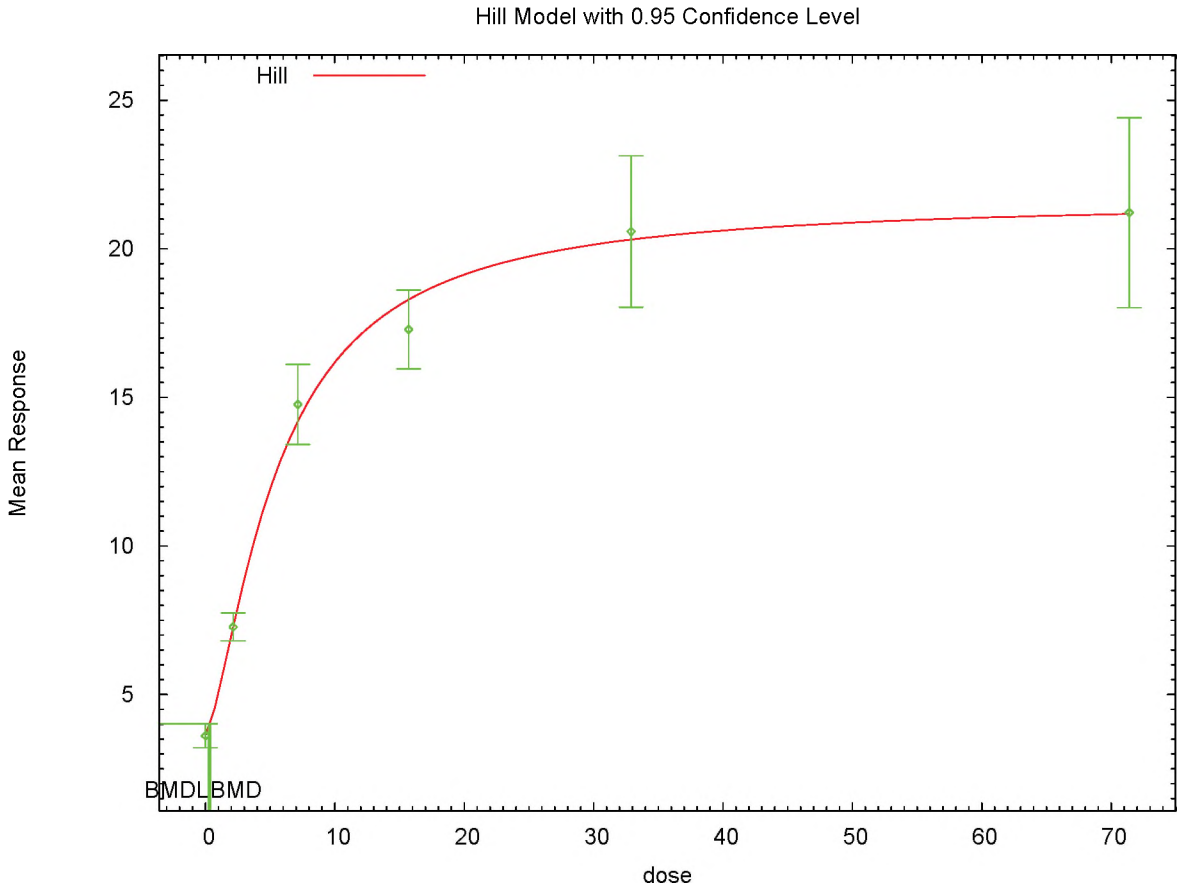
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 0.382287

BMDL = 0.233611

H.3.5.3. *Figure for Selected Model: Hill*



15:05 05/02 2010

H.3.6. National Toxicology Program, 2006: Lung Erod 53 Weeks

H.3.6.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2)	4	<0.0001	316.324	8.979E+01	5.757E+01	
exponential (M3)	4	<0.0001	316.324	8.979E+01	5.757E+01	power hit bound (d = 1)
exponential (M4) [b]	3	0.421	255.120	8.746E-02	5.370E-02	
exponential (M5)	2	0.276	256.882	6.769E-01	5.491E-02	
Hill	2	0.275	256.882	1.454E+00	1.138E-01	
linear	4	<.0001	315.961	8.550E+01	4.502E+01	
polynomial, 5-degree	4	<.0001	315.961	8.550E+01	4.502E+01	
power	4	<.0001	315.961	8.550E+01	4.502E+01	power bound hit (power = 1)
power, unrestricted [c]	3	0.037	260.794	2.688E-10	2.688E-10	unrestricted (power = 0.129)

[a] Non-constant variance model selected (p = <0.0001)

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

H.3.6.2. *Output for Selected Model: Exponential (M4)*

National Toxicology Program, 2006: Lung EROD 53 Weeks

```
 ========================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\5\52_NTP_2006_LungEROD53_Exp_1.(d)
         Gnuplot Plotting File:
                                                Fri Apr 30 21:22:36 2010
 ========================================================================

 Tbl 12, Week 53, Lung Microsomes EROD
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

     Note: Y[dose] is the median response for exposure = dose;
           sign = +1 for increasing trend in data;
           sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.
```

Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	-0.80064
rho	1.47683
a	2.86045
b	0.054659
c	16.0581
d	1

Parameter Estimates

Variable	Model 4
lnalpha	-1.15021
rho	1.63127
a	3.06838
b	0.414677
c	13.847
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	8	3.011	1.584
2.14	8	27.15	5.269
7.14	8	42.85	11.15
15.7	8	36.57	12.99
32.9	8	43.75	18.55
71.4	8	43.71	6.322

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	3.068	1.404	-0.1156
2.14	26.26	8.088	0.3116
7.14	40.45	11.5	0.5901
15.7	42.43	11.96	-1.386
32.9	42.49	11.98	0.2972
71.4	42.49	11.98	0.2894

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

```
  Model A2:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
              Var{e(ij)} = Sigma^2


                              Likelihoods of Interest

                    Model      Log(likelihood)      DF         AIC
                    -------    -----------------    ----   ------------
                       A1       -135.2677           7      284.5353
                       A2       -115.6885          12      255.3771
                       A3       -121.1517           8      258.3034
                        R       -162.0902           2      328.1805
                        4       -122.5601           5      255.1202


Additive constant for all log-likelihoods =     -44.11.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.


                               Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)


                           Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                         92.8           10           < 0.0001
  Test 2                        39.16            5           < 0.0001
  Test 3                        10.93            4             0.0274
 Test 6a                        2.817            3             0.4207


  The p-value for Test 1 is less than .05.  There appears to be a
  difference between response and/or variances among the dose
  levels, it seems appropriate to model the data.

  The p-value for Test 2 is less than .1.  A non-homogeneous
  variance model appears to be appropriate.

  The p-value for Test 3 is less than .1.  You may want to
  consider a different variance model.

  The p-value for Test 6a is greater than .1.  Model 4 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 1.000000

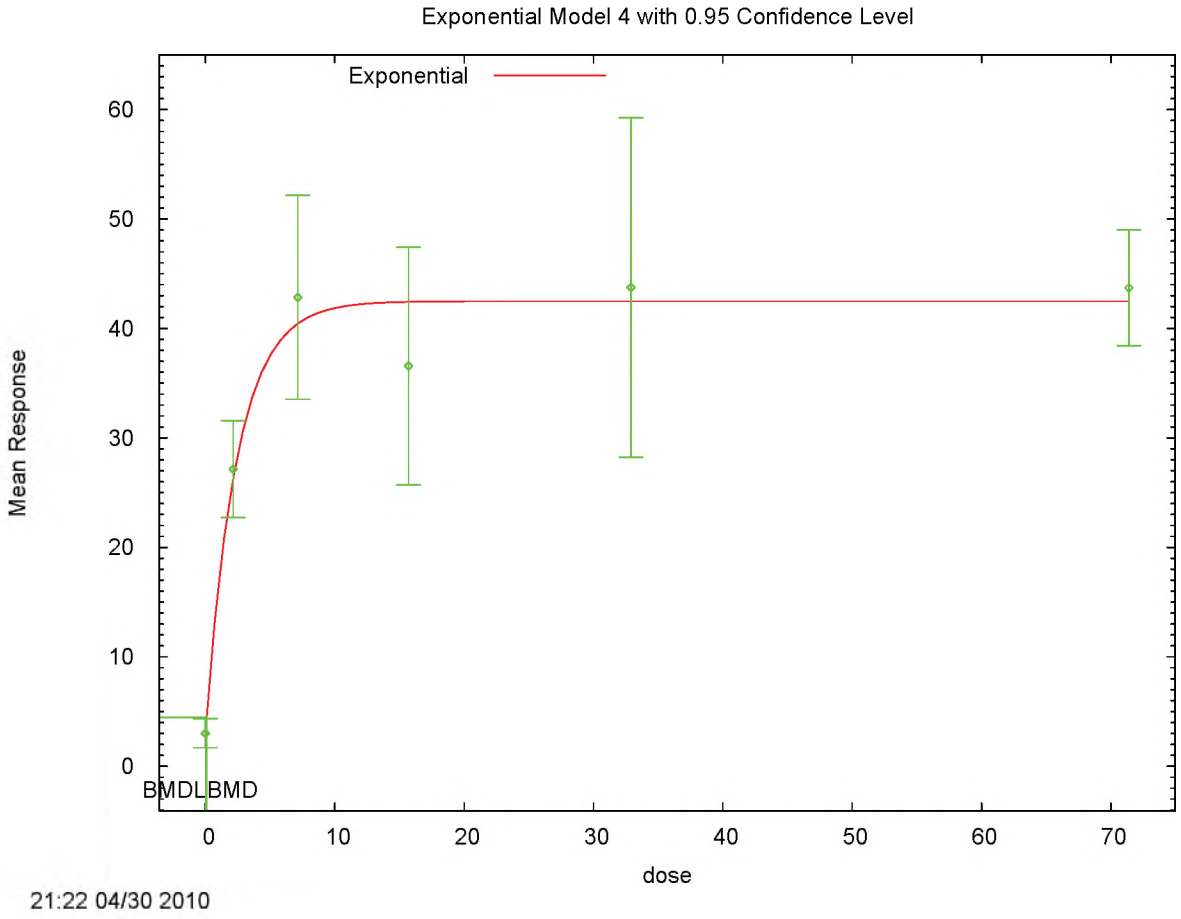
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD =    0.0874595

              BMDL =    0.0537035
```

H.3.6.3. *Figure for Selected Model: Exponential (M4)*



H.3.6.4. *Output for Additional Model Presented: Power, Unrestricted*

National Toxicology Program, 2006: Lung EROD 53 Weeks

```
 ========================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\5\52_NTP_2006_LungEROD53_Pwr_U_1.(d)
         Gnuplot Plotting File:  C:\5\52_NTP_2006_LungEROD53_Pwr_U_1.plt
                                                Fri Apr 30 21:22:40 2010
 ========================================================================

 Tbl 12, Week 53, Lung Microsomes EROD
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   The power is not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
```

Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	4.76968
rho =	0
control =	3.011
slope =	24.7003
power =	0.132996

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	control	slope	power
lalpha	1	-0.96	-0.48	0.11	-0.048
rho	-0.96	1	0.45	-0.15	0.053
control	-0.48	0.45	1	-0.15	0.05
slope	0.11	-0.15	-0.15	1	-0.92
power	-0.048	0.053	0.05	-0.92	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-1.03242	0.815871	-2.6315	0.566654
rho	1.63031	0.239764	1.16038	2.10024
control	3.01793	0.518146	2.00238	4.03348
slope	25.144	3.39289	18.494	31.7939
power	0.128894	0.0448391	0.041011	0.216777

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	3.01	3.02	1.58	1.47	-0.0133
2.14	8	27.1	30.8	5.27	9.74	-1.05
7.14	8	42.8	35.4	11.2	10.9	1.92
15.7	8	36.6	38.9	13	11.8	-0.553
32.9	8	43.7	42.5	18.5	12.7	0.286
71.4	8	43.7	46.6	6.32	13.7	-0.598

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-135.267662	7	284.535325
A2	-115.688533	12	255.377067
A3	-121.151707	8	258.303413
fitted	-125.397022	5	260.794043
R	-162.090242	2	328.180484

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	92.8034	10	<.0001
Test 2	39.1583	5	<.0001
Test 3	10.9263	4	0.0274
Test 4	8.49063	3	0.03689

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is less than .1. You may want to consider a different variance model

The p-value for Test 4 is less than .1. You may want to try a different model

Benchmark Dose Computation

Specified effect = 1

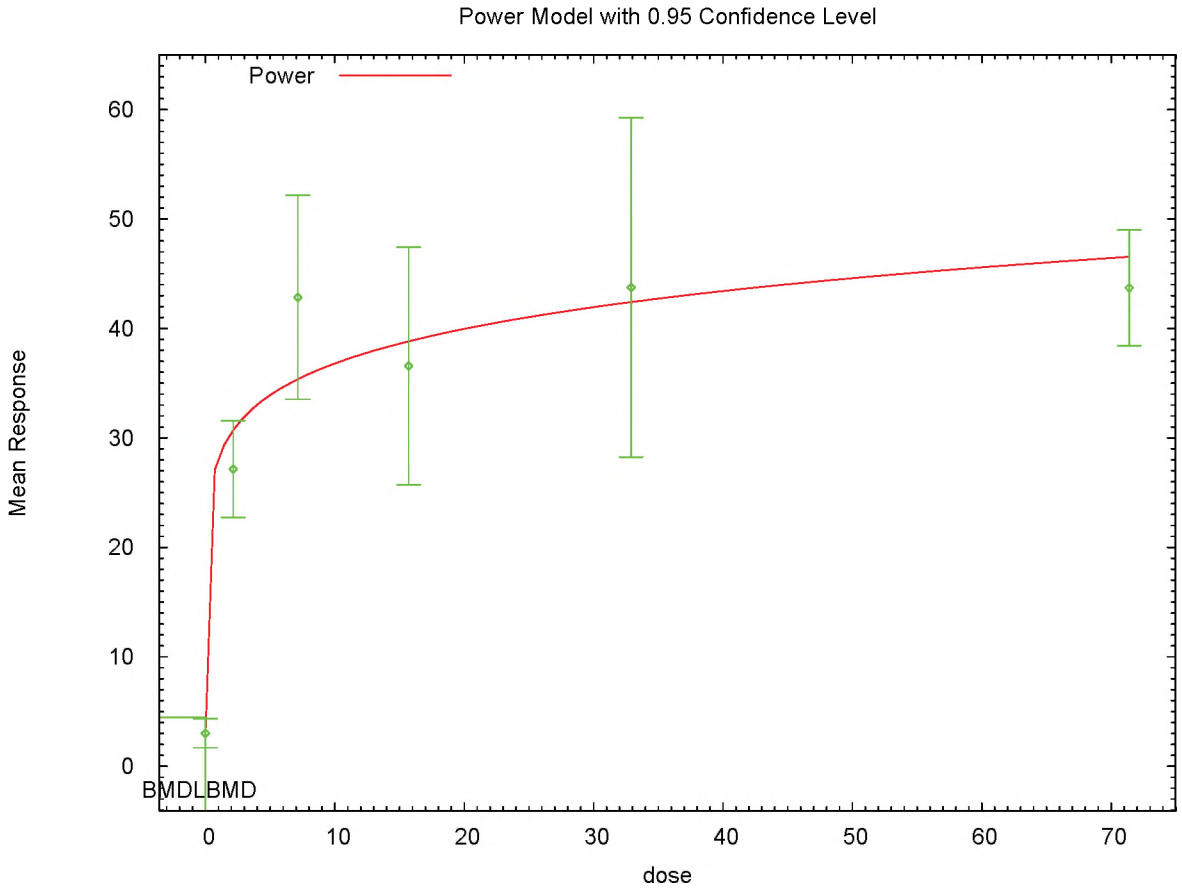
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 2.68823e-010

BMDL = 2.68823e-010

H.3.6.5. *Figure for Additional Model Presented: Power, Unrestricted*



H.3.7. National Toxicology Program, 2006: Labeling Index 31 Weeks

H.3.7.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2) [b]	4	0.000	47.304	2.336E+01	1.867E+01	
exponential (M3)	4	0.000	47.304	2.336E+01	1.867E+01	power hit bound (d = 1)
exponential (M4)	3	<0.0001	53.331	1.233E+01	7.562E+00	
exponential (M5)	2	<0.0001	51.057	3.279E+01	2.055E+01	
Hill	3	0.000	49.057	3.277E+01	error	n upper bound hit (n = 18)
linear	4	<.0001	51.331	1.233E+01	7.563E+00	
polynomial, 5-degree	3	0.000	48.698	2.510E+01	1.192E+01	
power	3	<.0001	49.826	3.238E+01	1.723E+01	

[a] Non-constant variance model selected (*p* = <0.0001)

[b] Best-fitting model, BMDS output presented in this appendix

H.3.7.2. *Output for Selected Model: Exponential (M2)*

National Toxicology Program, 2006: Labeling Index 31 Weeks

```
 ======================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\5\38_NTP_2006_HepIndex_Exp_1.(d)
         Gnuplot Plotting File:
                                                  Fri Apr 30 21:23:28 2010
 ======================================================================

 Tbl 11, 31wk, Hep Cell Proliferation Labeling Index
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
```

The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 2
lnalpha	-0.674004
rho	2.29189
a	0.576363
b	0.0266174
c	0
d	1

Parameter Estimates

Variable	Model 2
lnalpha	-0.471424
rho	1.90298
a	0.616539
b	0.0253715
c	0
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	9	0.327	0.189
2.14	10	0.852	0.6514
7.14	10	0.956	0.7368
15.7	10	0.792	0.4617
32.9	10	1.333	1.123
71.4	10	3.846	3.08

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.6165	0.4986	-1.742
2.14	0.6509	0.5251	1.211
7.14	0.739	0.5924	1.158
15.7	0.9182	0.7284	-0.548
32.9	1.421	1.103	-0.2511
71.4	3.773	2.795	0.08251

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

```
  Model  R:        Yij = Mu + e(i)
            Var{e(ij)} = Sigma^2


                              Likelihoods of Interest

                    Model      Log(likelihood)      DF         AIC
                    -------    -----------------    ----   ------------
                       A1       -47.23498           7        108.47
                       A2       -8.679256          12       41.35851
                       A3       -8.980651           8        33.9613
                        R       -63.44829           2       130.8966
                        2       -19.65195           4       47.30389


Additive constant for all log-likelihoods =     -54.22.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.


                               Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does Model 2 fit the data? (A3 vs. 2)


                           Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                         109.5          10           < 0.0001
  Test 2                         77.11           5           < 0.0001
  Test 3                        0.6028           4             0.9628
  Test 4                         21.34           4          0.0002708


  The p-value for Test 1 is less than .05.  There appears to be a
  difference between response and/or variances among the dose
  levels, it seems appropriate to model the data.

  The p-value for Test 2 is less than .1.  A non-homogeneous
  variance model appears to be appropriate.

  The p-value for Test 3 is greater than .1.  The modeled
  variance appears to be appropriate here.

  The p-value for Test 4 is less than .1.  Model 2 may not adequately
  describe the data; you may want to consider another model.


Benchmark Dose Computations:

  Specified Effect = 1.000000

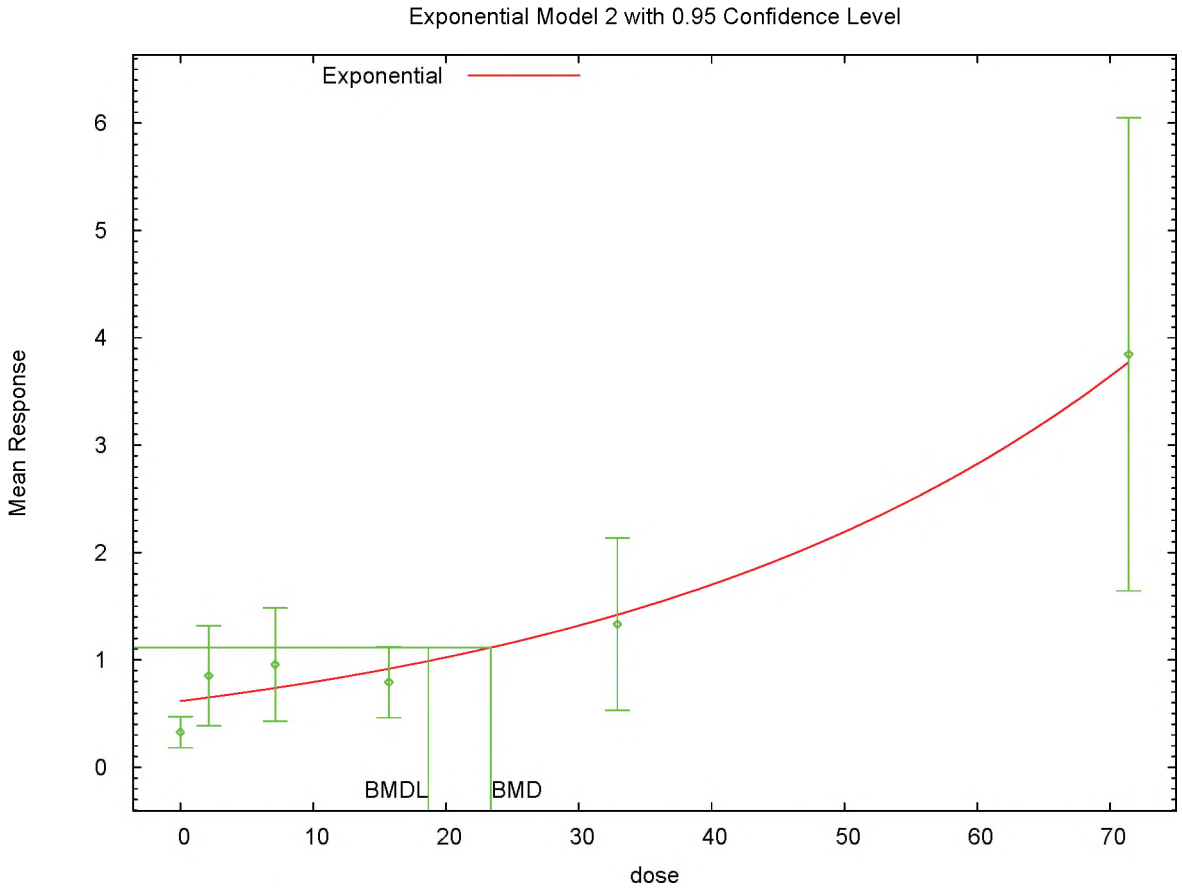
         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD =      23.3586

              BMDL =      18.6683
```

H.3.7.3. *Figure for Selected Model: Exponential (M2)*



21:23 04/30 2010

H.3.8. Vanden Heuvel et al., 1994: Hepatic CYP1A1 Mrna Expression

H.3.8.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p*-Value	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Notes
exponential (M2)	5	<0.0001	1164.377	4.699E+03	1.729E+03	
exponential (M3)	5	<0.0001	1164.377	4.699E+03	1.729E+03	power hit bound (d = 1)
exponential (M4)	4	<0.0001	661.006	4.550E-01	2.643E-01	
exponential (M5)	3	<0.0001	635.327	1.516E+01	1.046E+01	
Hill [b]	3	<.0001	662.251	8.091E-01	4.844E-01	
linear	5	<.0001	667.554	4.953E-01	3.093E-01	
polynomial, 6-degree	1	<.0001	715.412	5.774E+03	1.204E+01	
power	4	<.0001	669.441	5.571E-01	3.204E-01	

[a] Non-constant variance model selected (*p* = <0.0001)

[b] Best-fitting model, BMDS output presented in this appendix

H.3.8.2. *Output for Selected Model: Hill*

Vanden Heuvel et al., 1994: Hepatic CYP1A1 mRNA Expression

```
================================================================
          Hill Model. (Version: 2.14;  Date: 06/26/2008)
          Input Data File: C:\Usepa\BMDS21\Data\hil_Vanden_mRNA_Setting.(d)
          Gnuplot Plotting File:  C:\Usepa\BMDS21\Data\hil_Vanden_mRNA_Setting.plt
                                                Wed May 19 14:25:06 2010
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = mRNA_mean
   Independent variable = d
   Power parameter is not restricted
   The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

   Total number of dose groups = 7
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
```

```
                          lalpha =      18.2064
                             rho =            0
                       intercept =          5.4
                               v =      36694.6
                               n =     0.720907
                               k =      18830.3


            Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha          rho    intercept            v            n            k

     lalpha            1        -0.89        -0.41         0.37          0.7         -0.2

        rho        -0.89            1         0.29        -0.54        -0.75         0.24

  intercept        -0.41         0.29            1        -0.11         0.13       -0.034

          v         0.37        -0.54        -0.11            1         0.21         0.57

          n          0.7        -0.75         0.13         0.21            1        -0.53

          k         -0.2         0.24       -0.034         0.57        -0.53            1


                                  Parameter Estimates

                                                                 95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha         -0.28219         0.733221           -1.71928              1.1549
            rho          2.05171         0.146654            1.76427             2.33915
      intercept           5.4299          1.14997            3.17599             7.68381
              v          36598.9          13930.2            9296.23             63901.7
              n          1.13992        0.0919476           0.959705             1.32013
              k          2012.71           881.73            284.554             3740.87


      Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0    13        5.4          5.43         3.61         4.93        -0.0219
  0.1     5        7.2          5.88         5.59         5.35           0.55
    1    12       14.8          11.7         14.9         10.8          0.991
   10     7       12.8          91.8          4.5         89.6          -2.33
  100     7        536     1.16e+003          320     1.21e+003          -1.37
 1000    11   1.8e+004     1.14e+004     1.52e+004     1.26e+004           1.75
1e+004     5  3.67e+004     3.15e+004     2.21e+004     3.58e+004          0.323


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
      Model A3 uses any fixed variance parameters that
      were specified by the user

 Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-572.470944	8	1160.941889
A2	-290.799287	14	609.598575
A3	-293.809342	9	605.618684
fitted	-325.125462	6	662.250924
R	-603.663396	2	1211.326792

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	625.728	12	<.0001
Test 2	563.343	6	<.0001
Test 3	6.02011	5	0.3043
Test 4	62.6322	3	<.0001

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears
to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different
model

Benchmark Dose Computation

Specified effect = 1

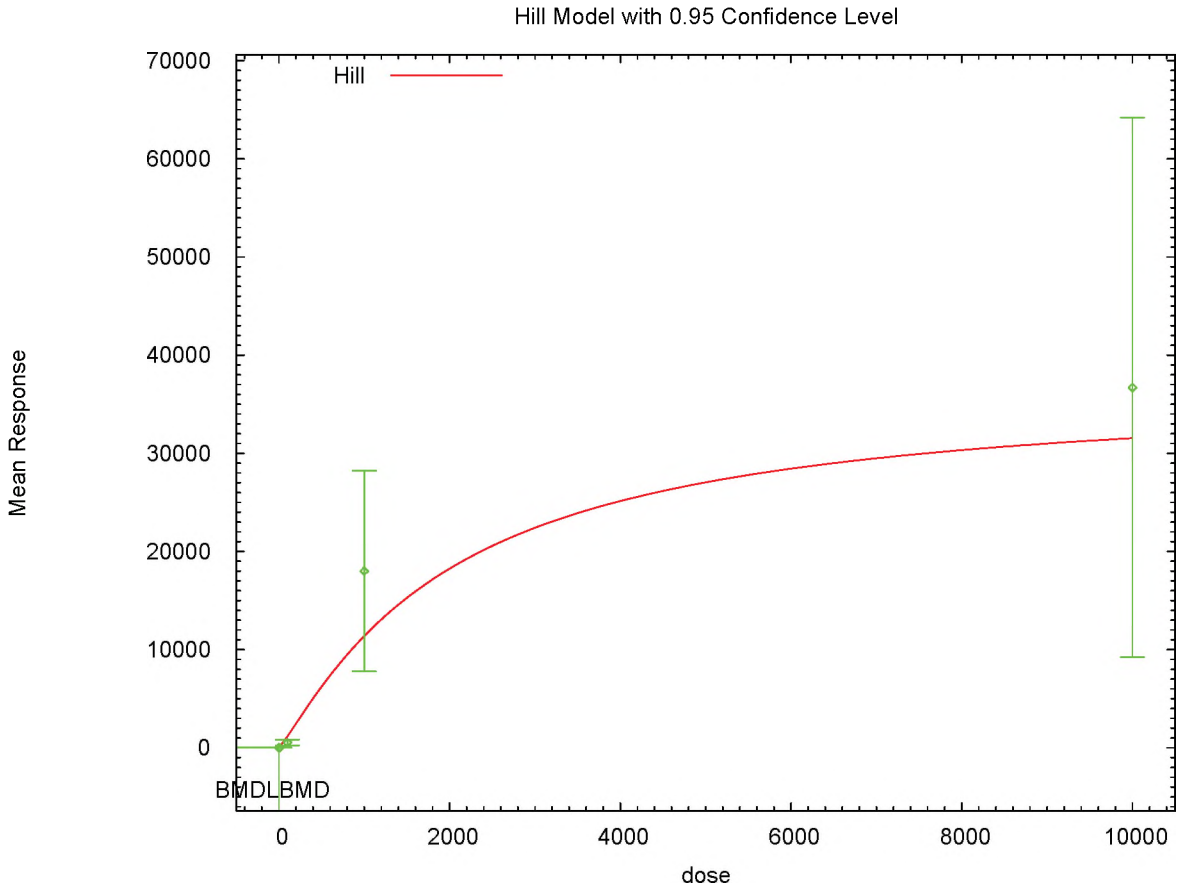
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 0.809125

BMDL = 0.484455

H.3.8.3. *Figure for Selected Model: Exponential (M5)*



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APPENDIX I

Effect of Background Exposure on Benchmark-Dose Modeling

NOTICE

THIS DOCUMENT IS AN EXTERNAL REVIEW DRAFT. It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH

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APPENDIX I. EFFECT OF BACKGROUND EXPOSURE ON BENCHMARK-DOSE MODELING

I.1. NTP, 2006 (CHOLANGIOCARCINOMAS): UNADJUSTED BLOOD CONCENTRATIONS

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Usepa\BMDS21\Data\msc_NTP_2006_carcin_Setting.(d)
         Gnuplot Plotting File:  C:\Usepa\BMDS21\Data\msc_NTP_2006_carcin_Setting.plt
                                              Wed Apr 14 12:59:57 2010
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive


   Dependent variable = cholang
   Independent variable = bl_nom

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 4
 Total number of specified parameters = 0
 Degree of polynomial = 3


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =            0
                        Beta(2) =            0
                        Beta(3) = 2.44609e-005


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(1)    -Beta(2)
                 have been estimated at a boundary point, or have been specified by
the user,
                 and do not appear in the correlation matrix )

                Beta(3)

   Beta(3)           1
```

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0	*	*	*
Beta(3)	2.30992e-005	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-55.408	6			
Fitted model	-55.7584	1	0.700706	5	0.9829
Reduced model	-96.9934	1	83.1708	5	<.0001

AIC: 113.517

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	49	0.000
2.5600	0.0004	0.019	0.000	48	-0.136
5.6900	0.0042	0.195	0.000	46	-0.443
9.7900	0.0214	1.072	1.000	50	-0.070
16.6000	0.1003	4.913	4.000	49	-0.434
29.7000	0.4540	24.063	25.000	53	0.259

Chi^2 = 0.48 d.f. = 5 P-value = 0.9930

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 7.57754

BMDL = 4.13907

BMDU = 8.42931

Taken together, (4.13907, 8.42931) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.002416

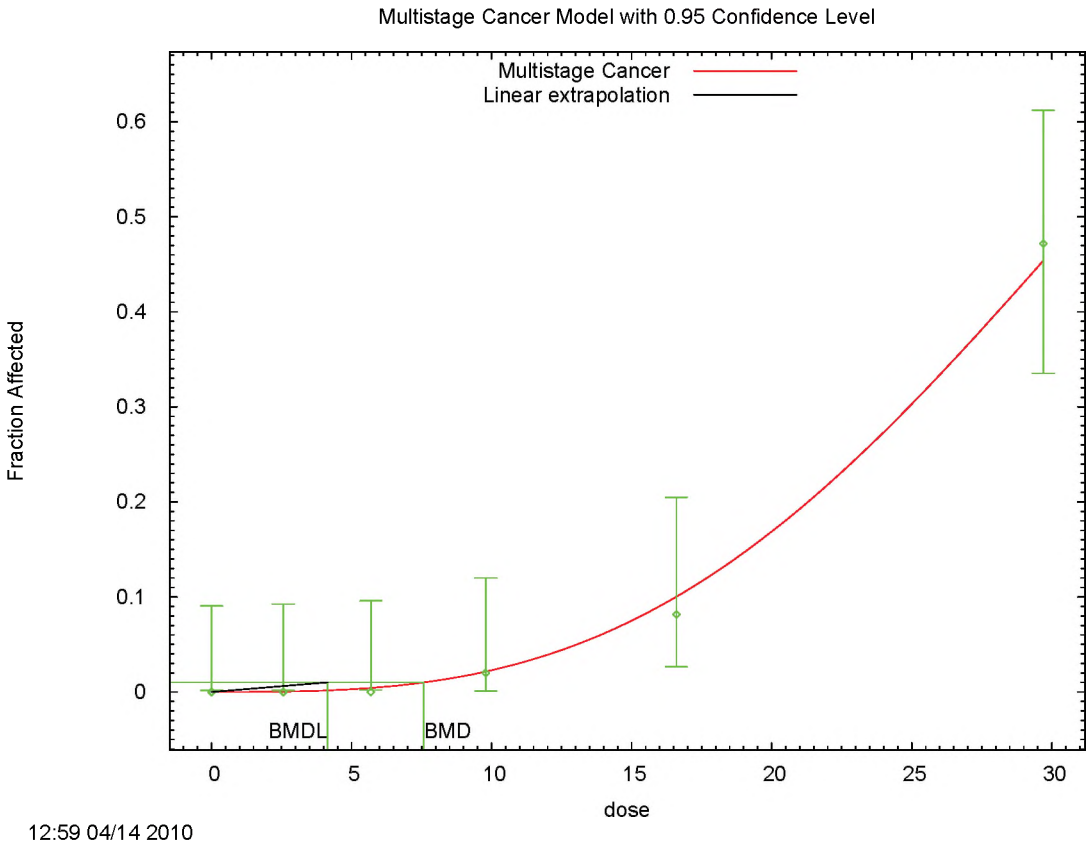


Figure I-1. NTP, 2006: Unadjusted blood concentrations (cholangiocarcinomas).

I.2. NTP, 2006 (CHOLANGIOCARCINOMAS): BACKGROUND DOSE = MEASURED TCDD CONCENTRATION ONLY

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Usepa\BMDS21\Data\msc_NTP_2006_carcin_Setting.(d)
         Gnuplot Plotting File:  C:\Usepa\BMDS21\Data\msc_NTP_2006_carcin_Setting.plt
                                              Fri Apr 16 15:47:08 2010
 ================================================================

 BMDS Model Run
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive


   Dependent variable = cholang
   Independent variable = bl_TCDDadj

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 4
 Total number of specified parameters = 0
 Degree of polynomial = 3


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =            0
                        Beta(2) =            0
                        Beta(3) = 2.43074e-005


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(1)    -Beta(2)
                 have been estimated at a boundary point, or have been specified by
the user,
                 and do not appear in the correlation matrix )

                Beta(3)

   Beta(3)            1



                                Parameter Estimates
```

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0	*	*	*
Beta(3)	2.29144e-005	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-55.408	6			
Fitted model	-55.771	1	0.726	5	0.9815
Reduced model	-96.9934	1	83.1708	5	<.0001

AIC: 113.542

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0640	0.0000	0.000	0.000	49	-0.001
2.6240	0.0004	0.020	0.000	48	-0.141
5.7540	0.0044	0.200	0.000	46	-0.449
9.8540	0.0217	1.084	1.000	50	-0.082
16.6640	0.1006	4.930	4.000	49	-0.442
29.7640	0.4535	24.035	25.000	53	0.266

Chi^2 = 0.49 d.f. = 5 P-value = 0.9924

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 7.59785

BMDL = 4.19355

BMDU = 8.45188

Taken together, (4.19355, 8.45188) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00238461

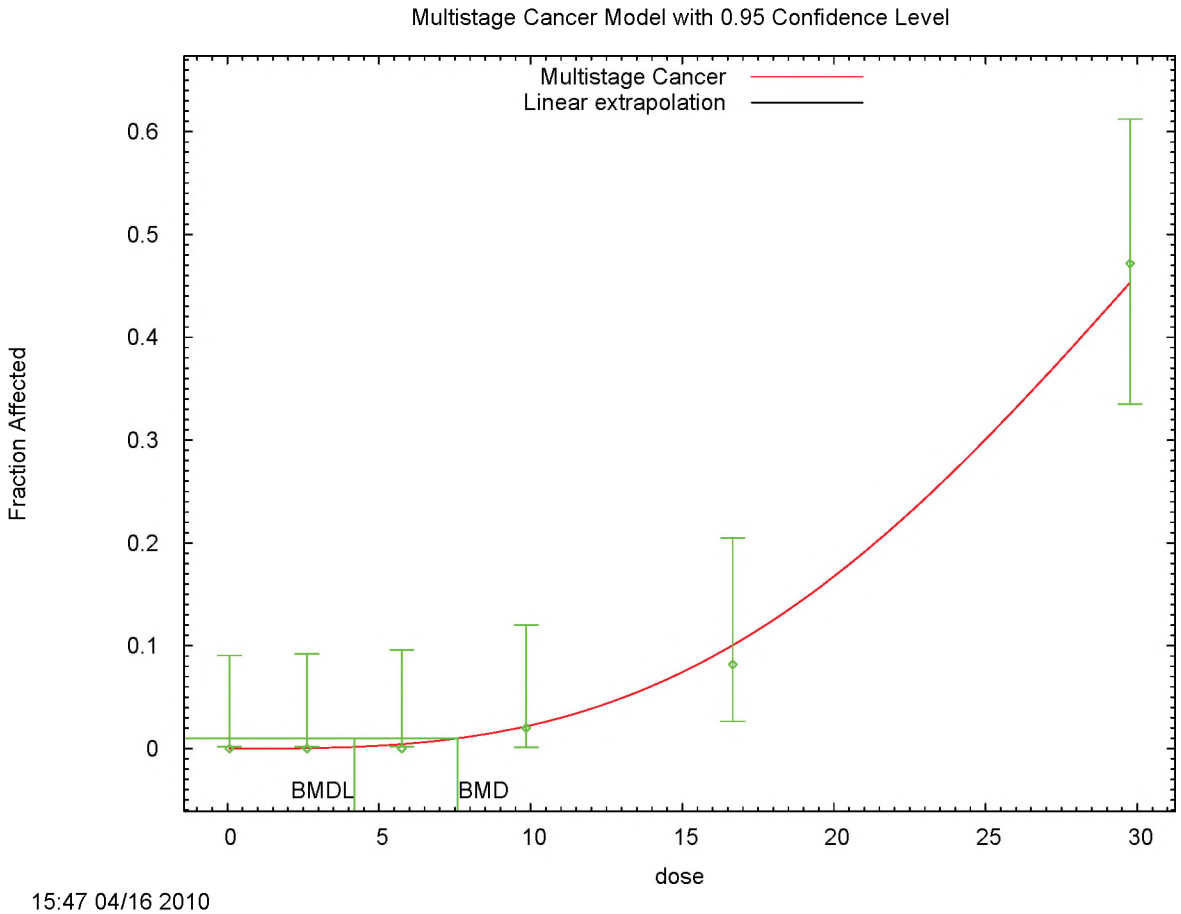


Figure I-2. NTP, 2006 (cholangiocarcinomas): Background dose = measured TCDD concentration only.

I.3. NTP, 2006 (CHOLANGIOCARCINOMAS): BACKGROUND DOSE = MEASURED TEQ CONCENTRATION (TCDD, PECDF, AND PCB-126)

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Usepa\BMDS21\Data\msc_NTP_2006_carcin_Setting.(d)
         Gnuplot Plotting File:  C:\Usepa\BMDS21\Data\msc_NTP_2006_carcin_Setting.plt
                                              Fri Apr 16 15:50:00 2010
 ================================================================

 BMDS Model Run
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive


   Dependent variable = cholang
   Independent variable = bl_TEQadj

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 4
 Total number of specified parameters = 0
 Degree of polynomial = 3


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =            0
                        Beta(2) =            0
                        Beta(3) = 2.40088e-005


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(1)    -Beta(2)
                 have been estimated at a boundary point, or have been specified by
the user,
                 and do not appear in the correlation matrix )

                Beta(3)

   Beta(3)            1



                                Parameter Estimates
```

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0	*	*	*
Beta(3)	2.25556e-005	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-55.408	6			
Fitted model	-55.7969	1	0.777718	5	0.9784
Reduced model	-96.9934	1	83.1708	5	<.0001

AIC: 113.594

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.1900	0.0000	0.000	0.000	49	-0.003
2.7500	0.0005	0.023	0.000	48	-0.150
5.8800	0.0046	0.210	0.000	46	-0.460
9.9800	0.0222	1.109	1.000	50	-0.104
16.7900	0.1013	4.962	4.000	49	-0.455
29.8900	0.4525	23.981	25.000	53	0.281

Chi^2 = 0.53 d.f. = 5 P-value = 0.9909

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 7.63793

BMDL = 4.29872

BMDU = 8.4964

Taken together, (4.29872, 8.4964) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00232627

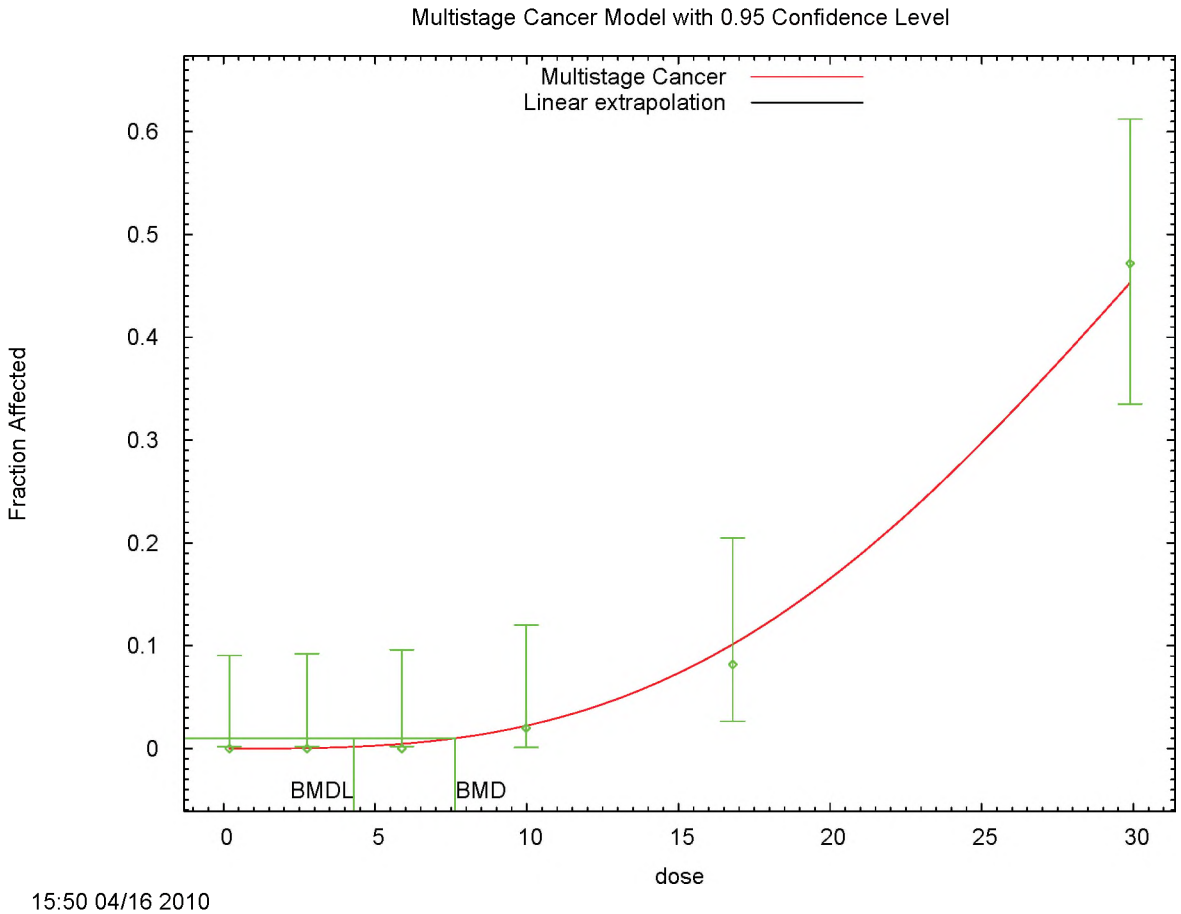


Figure I-3. NTP, 2006 (cholangiocarcinomas): Background dose = measured TEQ concentration (TCDD, PeCDF, and PCB-126).

I.4. NTP, 2006 (CHOLANGIOCARCINOMAS): BACKGROUND DOSE = 2× MEASURED TEQ CONCENTRATION (TCDD, PECDF, AND PCB-126)

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Usepa\BMDS21\Data\msc_NTP_2006_carcin_Setting.(d)
         Gnuplot Plotting File:  C:\Usepa\BMDS21\Data\msc_NTP_2006_carcin_Setting.plt
                                              Fri Apr 16 15:51:30 2010
 ================================================================

 BMDS Model Run
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive


   Dependent variable = cholang
   Independent variable = bl_TEQ2x

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 4
 Total number of specified parameters = 0
 Degree of polynomial = 3


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =            0
                        Beta(2) =            0
                        Beta(3) =  2.3568e-005


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(1)    -Beta(2)
                 have been estimated at a boundary point, or have been specified by
the user,
                 and do not appear in the correlation matrix )

                Beta(3)

   Beta(3)            1



                                Parameter Estimates
```

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0	*	*	*
Beta(3)	2.20268e-005	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-55.408	6			
Fitted model	-55.8382	1	0.860456	5	0.973
Reduced model	-96.9934	1	83.1708	5	<.0001

AIC: 113.676

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.3800	0.0000	0.000	0.000	49	-0.008
2.9400	0.0006	0.027	0.000	48	-0.164
6.0700	0.0049	0.226	0.000	46	-0.477
10.1700	0.0229	1.145	1.000	50	-0.137
16.9800	0.1022	5.009	4.000	49	-0.476
30.0800	0.4509	23.898	25.000	53	0.304

Chi^2 = 0.59 d.f. = 5 P-value = 0.9884

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 7.69856

BMDL = 4.45212

BMDU = 8.56376

Taken together, (4.45212, 8.56376) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00224612

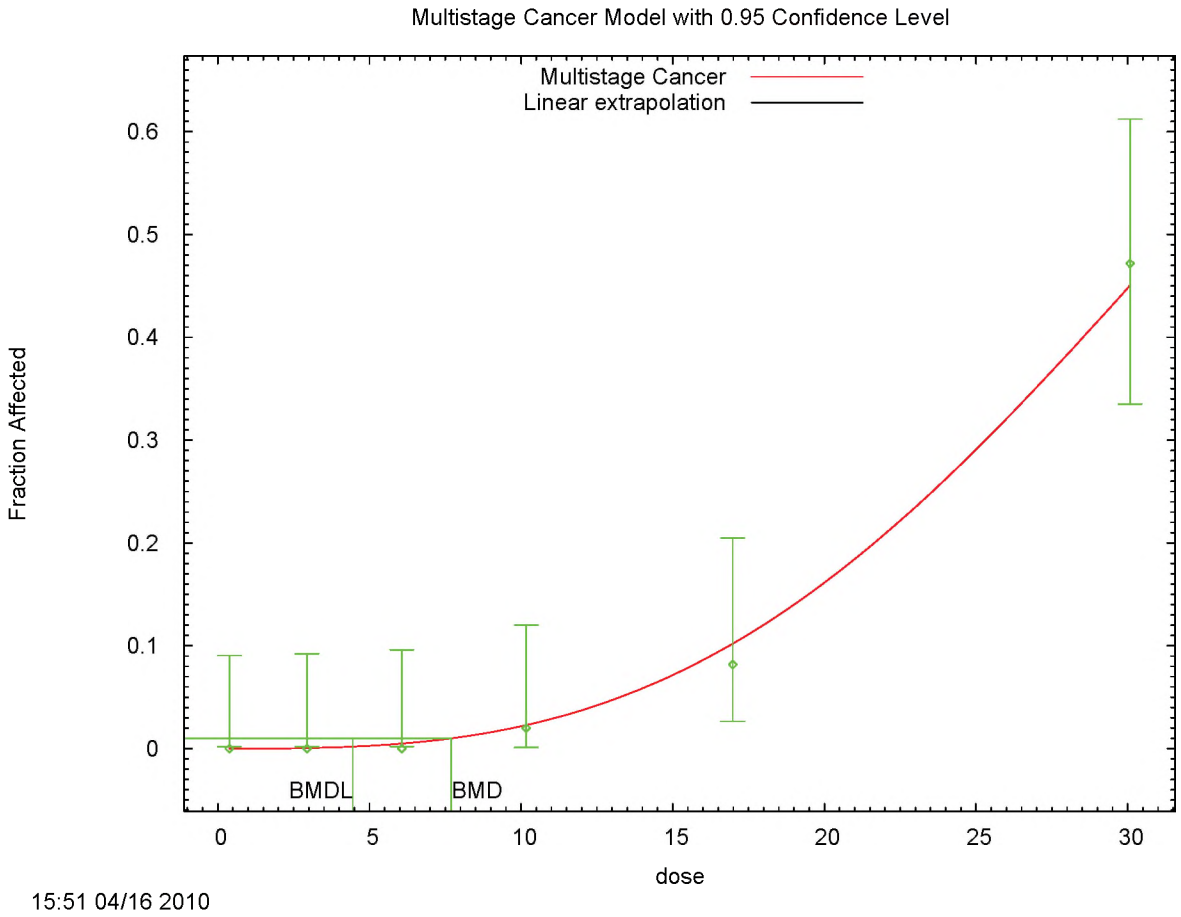


Figure I-4. NTP, 2006 (cholangiocarcinomas): Background dose = 2× measured TEQ concentration (TCDD, PeCDF, and PCB-126).

I.5. NTP, 2006 (CHOLANGIOCARCINOMAS): BACKGROUND DOSE = 10× MEASURED TCDD CONCENTRATION

```
 ================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File: C:\Usepa\BMDS21\Data\msc_NTP_2006_carcin_Setting.(d)
        Gnuplot Plotting File:  C:\Usepa\BMDS21\Data\msc_NTP_2006_carcin_Setting.plt
                                            Fri Apr 16 15:55:37 2010
 ================================================================

 BMDS Model Run
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive


   Dependent variable = cholang
   Independent variable = bl_TEQmax

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 4
 Total number of specified parameters = 0
 Degree of polynomial = 3


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =            0
                        Beta(2) =            0
                        Beta(3) = 2.29823e-005


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(1)    -Beta(2)
                 have been estimated at a boundary point, or have been specified by
the user,
                 and do not appear in the correlation matrix )

                Beta(3)

   Beta(3)            1



                                Parameter Estimates
```

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0	*	*	*
Beta(3)	2.13264e-005	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-55.408	6			
Fitted model	-55.8994	1	0.982747	5	0.9639
Reduced model	-96.9934	1	83.1708	5	<.0001

AIC: 113.799

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.6400	0.0000	0.000	0.000	49	-0.017
3.2000	0.0007	0.034	0.000	48	-0.183
6.3300	0.0054	0.248	0.000	46	-0.499
10.4300	0.0239	1.195	1.000	50	-0.181
17.2400	0.1035	5.072	4.000	49	-0.503
30.3400	0.4488	23.785	25.000	53	0.336

Chi^2 = 0.68 d.f. = 5 P-value = 0.9840

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 7.78193

BMDL = 4.65224

BMDU = 8.65638

Taken together, (4.65224, 8.65638) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0021495

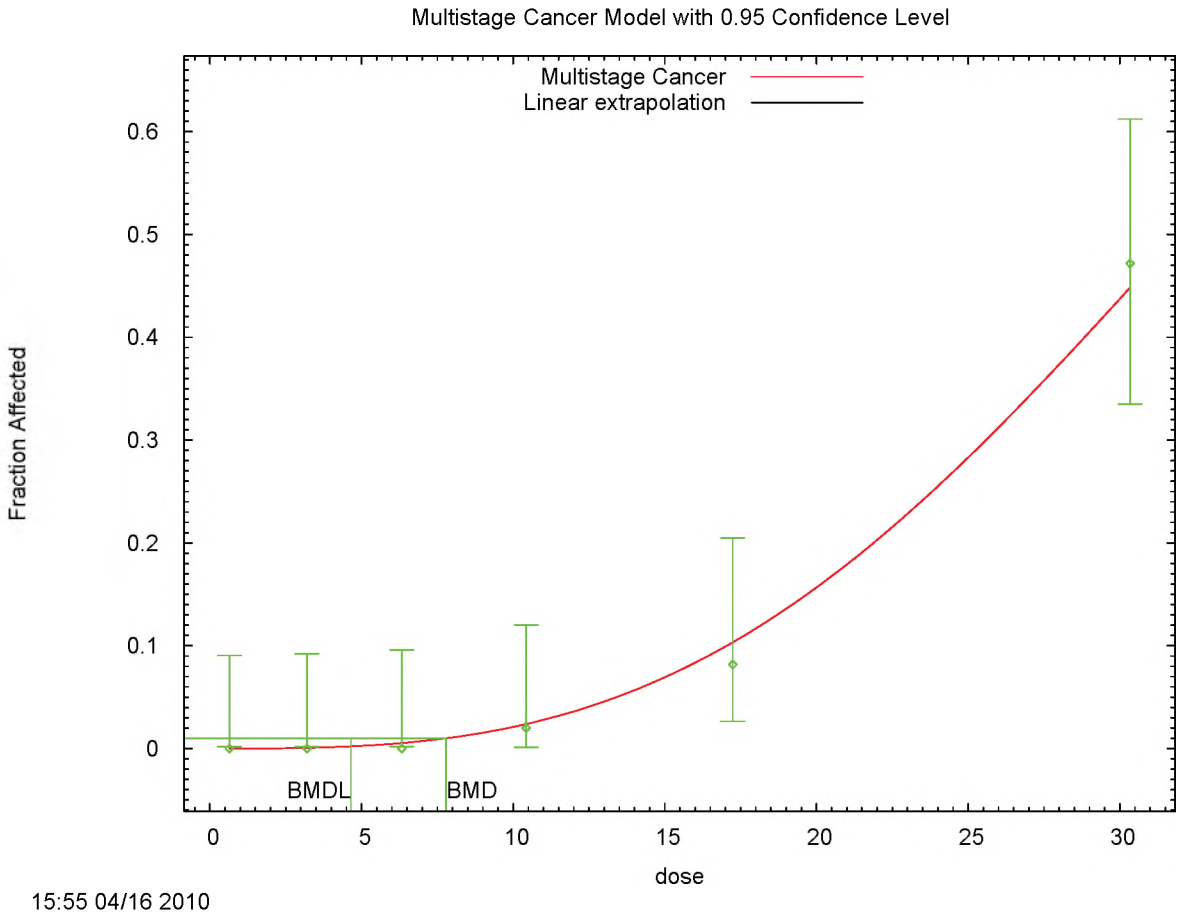


Figure I-5. NTP, 2006 (cholangiocarcinomas): Background dose = 10× measured TCDD concentration.

I.6. REFERENCE

NTP (National Toxicology Program). (2006a) NTP technical report on the toxicology and carcinogenesis studies of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (CAS No. 1746-01-6) in female Harlan Sprague-Dawley rats (Gavage Studies). Natl Toxicol ProgramTech Rep 521. Public Health Service, National Institute of Health, U.S. Department of Health and Human Services, Research Triangle Park, NC.