CHEMICAL MANUFACTURERS ASSOCIATION

May 2, 1996

Ms. Joan Dollarhyde
Integrated Risk Information System (IRIS) Submission Desk
NCEA (MS-190)
U.S. Environmental Protection Agency (EPA)
26 Martin Luther King Drive
Cincinnati, OH 45268

Dear Ms. Dollarhyde:

In accordance with the Federal Register notice of Tuesday, April 4, 1996, this is to inform you of our intent to submit information about Vinyl Chloride (CAS. NO. 75-01-4) for the IRIS Pilot Project. The purpose of our submission is to identify cancer and non-cancer risk assessment materials which may not be readily accessible to EPA's internal and external peer review groups. Specifically, we intend to submit information on the following:

- Reitz, R.H.,et al, "Predicting Cancer Risk from Vinyl Chloride Exposure with a Physiologically Based harmacokinetic Model." *Toxicology and Applied Pharmacology* 137, 253-267 (1996)

- Clewell, H.J., et al, "Considering Pharmacokinetic and Mechanistic Information in Cancer Risk Assessments for Environmental Contaminants: Examples with Vinyl Chloride and Trichloroethylene." In Press.

In addition, through a Memorandum of Understanding with the Agency for Toxic Substances and Disease Registry , CMA is conducting a combined inhalation two-generation reproductive and developmental toxicity study of Vinyl Chloride in rats. The results of this study also will be made available to EPA for the IRIS Pilot Project.

CMA's interest in the IRIS Pilot Project represents the concern of its Vinyl Chloride Health Committee which is composed of representatives from all U.S. manufacturers of Vinyl Chloride. The Committee also will be gathering information on Vinyl Chloride in the near future which may not be easily accessible to EPA.

We believe that the organization of this material is of key importance to a comprehensive characterization of Vinyl Chloride risk assessment. We look forward to working with EPA on this issue. Any questions about this material should be referred to me at 703/741-5639.

Sincerely,

Robert A. Venezia

Robert A. Venezia, Dr.P.H.
Manager, CHEMSTAR

1300 WILSON BOULEVARD, ARLINGTON, VA 22209 • TELEPHONE 703-741-5000 • FAX 703-741-6000

Responsible Care® A Public Commitment

SL 110315

PROPOSAL TO IMPACT THE RE-EVALUATION OF VINYL CHLORIDE (VCl) CARCINOGENICITY

April 29, 1996

Prepared for:

Dr. Hazmukh Shah
Chemical Manufacturers Association
1300 Wilson Blvd.
Arlington, VA 22209

Prepared by:

ChemRisk®
Division of McLaren/Hart
29225 Chagrin Boulevard
Cleveland, OH 44122

Proposal Number CL96-0059

PROPRIETARY NOTICE:

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1.0 INTRODUCTION

The ChemRisk® Division of McLaren/Hart (ChemRisk®) and RHR Toxicology Consulting are pleased to respond to a verbal request for proposal (RFP) from Drs. Shah and Venezia of the Chemical Manufacturers Association (CMA) during a meeting held at the CMA offices in Arlington, Virginia on April 4, 1996. It is our understanding that the CMA is concerned with the Federal Register Notice of Tuesday, April 2, 1996 (Vol. 61, No. 64) entitled: "Integrated Risk Information System (IRIS); An Announcement of Pilot Program; Request for Information" in that vinyl chloride (VCl) is listed as one of the Pilot Substances for evaluation in the program. The concern of CMA is with the potential cancer slope factor (SF) that may be developed and put into the IRIS database for VCl under this USEPA Pilot Program. USEPA has indicated that the pilot program for reevaluating the "demonstration" chemicals will consist of several steps including (a) identifying and collecting all pertinent material dealing with the specific chemicals, (b) evaluating this information within USEPA and developing draft IRIS summaries based on the updated information, (c) having an internal (to USEPA) peer-review of the summaries, (d) having an "appropriate" outside peer review of the IRIS drafts, and then, if appropriate, updating the IRIS database.

ChemRisk® notes that step (d) above is of critical importance in deciding whether or not the current IRIS numbers should be modified. USEPA (and many other Federal Agencies) are currently operating under rather strict financial limitations, and this will undoubtedly affect the nature of the external peer review process. The Agency notes that:

> "Depending upon the complexity of the scientific information and other factors the form of the peer review will either be via mail, forums of experts, or formal federal advisory committees."

Thus it is possible that outside peer review conducted by the Agency may be limited in scope because financial resources (and/or time) available to the Agency may not be sufficient to fully address the many complex issues that exist in the VCl database. Therefore we propose that CMA sponsor a scientific workshop on the topic: "Updating the IRIS cancer guidelines for Vinyl Chloride". The purpose of this workshop would be to develop a consensus document to be submitted for publication in the peer-review literature at the earliest opportunity.

ChemRisk® has extensive experience in the organization of such workshops. More importantly, ChemRisk® has the experience to ensure that a useful product (consensus document) will be obtained from the workshop. Without proper guidance, the output from scientific workshops frequently become just a recommendation for "more research", and this type of recommendation is not particularly useful in supporting the revision of existing standards! We believe that if the organization of this workshop is properly coordinated with the Agency, it would be well accepted by them and would ensure that a comprehensive and balanced review does take place. ChemRisk® would work closely with CMA to achieve these objectives.

2.0 SCOPE OF WORK

To meet the goal of this project as stated above, the following tasks are proposed:

Task 1: Submit Initial List to USEPA

Task 2: Identify Review Materials/Prepare Instructions

Task 3: Identify Expert Panel Participants

Task 4: Organize Meeting

Task 5: Conduct and Participate in Expert Panel Meeting/Prepare Synopsis

Task 6: Prepare Manuscript

Task 7: Submission to USEPA

The work to be performed in each of the tasks is described in more detail below.

2.1 Task 1: Submit Initial List to USEPA

The purpose of this task is to identify materials for the EPA (as requested in the Federal Register notice of April 2, 1996) that may not be readily accessible to the internal and external peer review groups, and when appropriate, to provide those less accessible materials to the Agency.

In particular, ChemRisk® personnel have, in collaboration with RHR Toxicology Consulting, developed a new approach for utilizing Physiologically Based Pharmacokinetic (PBPK) modeling to modify the risk assessment for VCl. ChemRisk® activities in this task would be:

- Identify the recent publication in Toxicology and Applied Pharmacology where the new VCl risk assessment is summarized.
- Assemble all the source code and command procedures necessary for the Agency to reproduce the modeling of VCl disposition in rodents and humans.
- Assemble (and provide to the Agency when requested) all the support materials employed in development of the PBPK model for VCl.
- Interact directly with Agency personnel to ensure that they are able to do the modeling themselves (have and can run the computer programs)

Schedule

It is anticipated the list for submittal to the Agency will be prepared for CMA review within 2 weeks of project authorization. The submittal will be accomplished within 3 working days of gaining CMA approval of the list. The timing for on-going interactions with the USEPA cannot

be accurately described currently, although we anticipate it should only require a 1-day trip by Dr. Reitz to aid the USEPA in running the model.

2.2 Task 2: Identify Review Materials/Prepare Instructions

The purpose of this task will be to identify all materials that will be made available for review by the Expert Panel and to prepare instructions for the panel members as well as the terms and agreements regarding participation on the panel. ChemRisk® activities will be:

- Conduct literature search
- Assemble list of review documents
- Prepare instructions to Expert Panel members
- Prepare agreements
- Distribute to CMA for approval/edits
- Send final versions to CMA

Schedule:

It is anticipated that the list for initial submittal to USEPA, and the review list and other documents for the Expert Panel will be delivered to the CMA within 4 weeks of authorization to proceed on the project. A final version of the list and documents for Expert Panel review will be provided within one week of receiving CMA comments.

2.3 Task 3: Identify Participants

The purpose of this task is to identify potential candidates for participation on the Expert Panel and to gain approval of final selection from the CMA. ChemRisk® proposes to provide the CMA with the names and resumes of at least two candidates from each of the following disciplines:

- Risk Assessment Methodology
- Genotoxic Cancer Mechanisms
- PBPK Modeling
- Epidemiology

It will be strongly preferred that each expert have some experience with VCl.

Specific ChemRisk® activities will be:

- Contact each potential candidate to discuss the project, compensation, and their willingness to be considered as a possible participant
- Send instructions and list of documents for review to willing candidates
- Obtain resumes (or C.V.'s) of potential candidates
- Assemble resumes and list of candidates for review by CMA
- Obtain final selections from CMA
- Notify selected candidates and obtain a signed "Statement of Participation"
- Distribute all review materials to participants
- Arrange payment of all stipends

Schedule:

Following completion of Task 2 above, it is anticipated that it will require 4 weeks to identify, interview, and obtain resumes of the potential candidates and provide the list of potential candidates to the CMA. Following final selection by the CMA and notification of the selections to ChemRisk®, two weeks will be required to obtain signed agreements and to disseminate all review materials to the panel members.

2.4 Task 4: Organize Meeting

The purpose of this task is to organize, coordinate, and arrange the Expert Panel Meeting. It is anticipated that in addition to the four Expert Panel members, there will be two ChemRisk® and one RHR Toxicology Consulting staff members and approximately six CMA members present at this meeting (~13 participants total). It is proposed that this meeting be held at a hotel in the Washington, DC area that has conference facilities or possibly at the CMA. The meeting agenda will be prepared by ChemRisk® for CMA review and suggestions, but is anticipated that the meeting will require a one night stay and meeting activities will cover one and one-half days. It is proposed that all meeting attendees arrive in the afternoon of day 1 and participate in a group dinner. The meeting will commence following the dinner with brief presentations and will continue to the end of day 2 (5 p.m.).

Specific ChemRisk® activities will be:

- Prepare and distribute draft agenda to the CMA
- Prepare final agenda and distribute to the CMA and Expert Panel
- Coordinate meeting dates with the CMA and Expert Panel
- Arrange for conference facilities
  - Dinner on Day 1
  - Conference Room
  - Catered breakfast and lunch on Day 2
  - Mid-afternoon break

Schedule:

The draft meeting agenda (less specific dates) will be prepared and delivered to the CMA within three weeks of completion of Task 2. Coordination of meeting dates and arrangement of

conference facilities are anticipated to take approximately 2 weeks following selection of Expert Panel members (see Task 3).

2.5 Task 5: Expert Panel Meeting/Prepare Synopsis

It is proposed that Dr. Gargas of ChemRisk® chair the Expert Panel Meeting and that the meeting also be attended by Betsy Brien of ChemRisk® and Dr. Reitz of RHR Toxicology Consulting. Dr. Reitz will serve as an Expert Panel Member. As chairperson, Dr. Gargas will:

- Coordinate all presentations and discussions during the meeting
- Keep the meeting on schedule according to the agenda
- In conjunction with Dr. Reitz and Ms. Brien, prepare a synopsis of the meeting for distribution to all participants for approval and edits (meeting notes to be taken by Betsy Brien)

The meeting synopsis will be important to judge the positions taken by various panel members and will prove valuable when preparing the first draft of the manuscript. ChemRisk® and RHR Toxicology Consulting will be responsible for calculating the SF for VCl following Panel discussions and recommendations.

Schedule:

The preparation and distribution to the Panel and the CMA of a draft meeting synopsis (including SF determination) will be completed within 3 weeks following the meeting. Edits from these groups will be requested within one week of delivery of the draft and a final version of the synopsis will be prepared and distributed one week following receipt of all comments.

2.6 Task 6: Prepare and Submit Manuscript

The purpose of this task is to prepare a manuscript that describes the findings, recommendations, and SF determination of the Expert Panel. It is anticipated the paper will be co-authored by ChemRisk® staff, RHR Toxicology Consulting, and the Expert Panel members. It is proposed that Dr. Gargas coordinate input from all co-authors and it that the resulting manuscript be submitted to a journal such as *Risk Analysis* (or another journal deemed suitable by the CMA). The meeting synopsis prepared for the CMA by ChemRisk® should serve as a good starting point for the first draft of this manuscript.

Schedule:
It is anticipated it will require 8 weeks following the finalization of the meeting synopsis for ChemRisk® and the panel members to prepare the "draft" manuscript for CMA review. Following receipt of the CMA comments, it is anticipated that 2 more weeks will be needed to finalize the manuscript for submittal to a journal for peer review.

NOTE: For all deliverables sent to the CMA, only one set of documents will be provided for review to one designated member of the CMA. All input from CMA members should be directed through that designated member and one set of comments from the CMA returned to ChemRisk®.

2.7 Task 7: Submission to USEPA

The purpose of this task is to prepare a formal submission of the Expert Panel findings, recommendations, and evaluations to the USEPA committee responsible for evaluating VCl in the Pilot Program. This submittal could be the manuscript prepared by the Expert Panel or, if

timing permits, a reprint of the published paper. ChemRisk® will coordinate this submittal with the CMA.

ChemRisk® activities will include:

- Prepare all necessary forms and the manuscript
- Send to the CMA for review and approval
- Submit appropriate/required documents to the USEPA

Schedule:

The preparation of documents for submittal to USEPA is anticipated to take 2 weeks from the availability of the manuscript or the published paper. Formal submission will occur within 1 week of receiving the CMA edits/approval.

3.0 APPROXIMATE TOTAL PROJECT SCHEDULE

Based on the tasks described above and depending on the Expert Panel member schedules, etc., as well as CMA authorization, it is anticipated that the initial list of documents could be submitted to the USEPA as early as late May, 1996. The Expert Panel meeting could be organized and conducted (Tasks 2-4) by early September with the meeting synopsis completed by the end of September. The manuscript (Task 6) should then be ready to submit to a journal by early to mid December, 1996. This schedule is only an estimate and should be considered as a "Best Case" scenario for CMA planning purposes and will be largely dependent on Expert Panel Member schedules.

4.0 PROJECT TEAM

Based on our current understanding of this project, the following team is proposed. Complete resumes can be found in Appendix A.

Michael L. Gargas, Ph.D.: Dr. Gargas is a Principal Health Scientist and will serve as Project Manager on this project. He will coordinate and direct all activities in the project tasks. He will be the chairperson of the Expert Panel and will coordinate preparation of the meeting synopsis and the manuscript. Dr. Gargas has over 18 years of experience in human health risk assessment and in biochemical toxicology research. He has conducted toxicology research on numerous volatile organic compounds (VOCs) including benzene, toluene, styrene, xylenes, furan, ethylene oxide, butadiene, acrylonitrile, all the halogenated methanes, ethanes, and ethylenes, as well as 2,3,7,8-tetrachlorodibenzo-p-dioxin, chromium, and Pb. Dr. Gargas has co-authored several papers on VCl toxicokinetics and carcinogenicity and has been involved in several Expert Panels.

Richard H. Reitz, Ph.D. DABT: Dr. Reitz will serve as an Expert Panel member on this project. His major input will include participation on the panel, preparation of the meeting synopsis, and co-author of the manuscript.

Dr. Reitz has 29 years of experience in the biological sciences including work in the discovery and development of new drugs for central nervous system or immunological disorders, use of enzymes from microorganisms for chemical synthesis, identification of the mechanisms by which industrial chemicals produce genotoxic and/or carcinogenic effects in mammals, pharmacokinetic modeling, development of computerized systems for data acquisition, and development of risk assessments using PBPK models. In recent years he has conducted research aimed at understanding the potential hazard for humans exposed to methylene chloride,

perchlorethylene, trichloroethylene, dichloroethane, vinylidene chloride, vinyl chloride, orthophenylphenol, chloroform, and 1,4-dioxane.

Dr. Reitz has served on the USEPA Scientific Advisory Board and as an Associate Editor for both *Toxicology Letters* and *Toxicology and Applied Pharmacology*.

Betsy A. Brien M.S.: Ms. Brien is an Assistant Health Scientist and will participate in organizing and carrying out the above mentioned tasks as directed by the Project Manager.

Ms. Brien recently received her masters degree in environmental health/ toxicology. In graduate school, she was a laboratory research assistant; and as part of her master's thesis, she organized and directed a two year experimental study. Ms. Brien's undergraduate degree is in biology, with an emphasis in the biomedical sciences, which strengthens her background for human health risk assessment. Her work experience includes a toxicology internship in which she reviewed and summarized human health and ecotoxicology data, and she has also maintained positions working in environmental testing facilities.

5.0 COST

The costs for this project are described below and include both firm costs and estimated costs. The firm costs cover the professional time of ChemRisk® staff members and their subcontractor, Dr. Reitz, as well as all preparation, reproduction and distribution charges associated with project documents, deliverables, and correspondence. Estimated costs are dependent on agreements reached with Expert Panel participants (*i.e.*, stipends) as well as Expert Panel Member travel costs. Another estimated cost is that associated with the conference facilities for the Expert Panel Meeting. It is not possible to get a firm costs for these facilities until the meeting is actually scheduled. The estimated costs are provided in this proposal so the CMA

has an approximate total amount to plan for. The meeting costs could be significantly reduced if CMA decides to hold the meeting at their facilities in Arlington, VA. A summary of the firm and estimated costs are broken out below and ChemRisk® emphasizes to the CMA that the estimated costs are subject to change. Detailed pricing sheets for the firm and estimated costs follow this summary.

It is proposed that the firm costs associated with this project be on a Time and Materials basis and that the estimated costs be paid based on final agreements with Expert Panel Members and the conference facilities.

Note: Estimated costs are in parentheses

Task 1: *Submit Initial List to USEPA*		
Firm Costs	=	$ 6,046
Total Firm and Estimated Costs for Task	=	**$ 6,046**
Task 2: *Identify-Review Materials/Prepare Instructions*		
Firm Costs	=	$10,455
Total Firm and Estimated Costs for Task	=	**$10,455**
Task 3: *Identify Participants*		
Firm Costs	=	$ 9,187
Estimated Costs	=	($ 6,000)
(Assuming $1500 stipend for each Expert Panel Member		
Total Firm and Estimated Costs for Task	=	**$15,187**
Task 4: *Organize Meeting*		
Firm Costs	=	$12,577
Estimated Costs (Conference Facilities)	=	($ 2,000)
Total Firm and Estimated Costs for Task	=	**$14,577**
Task 5: *Conduct and Participate in Expert Panel Meeting*		
Firm Costs	=	$ 16,556
Travel Costs (2 ChemRisk® Staff/$1200 each)	=	$ 2,400
Travel Costs (1 RHR Toxicology Consulting/$1200)	=	$ 1,200
Estimated Costs	=	($ 4,800)
(Travel for 4 Expert Panel Members/$1200 each)		
Total firm and Estimated Costs for Task	=	**$ 24,956**
Task 6: *Prepare and Submit Manuscript*		
Firm Costs	=	$ 33,458
Total Firm and Estimated Costs for Task	=	**$ 33,458**
Task 7: *Submission to USEPA*		
Firm Costs	=	$ 4,415
Total Firm and Estimated Costs for Task	=	**$ 4,415**
Total Firm Costs for Project	=	**$90,248**
Total Estimated Costs for Project	=	**$(12,800)**
TOTAL FIRM AND ESTIMATED COSTS FOR PROJECT	=	**$103,048**

N:\GARGAS\PROPOSAL\PANVCL

APPENDIX A

RESUMES

MICHAEL L. GARGAS, Ph.D.

Principal Health Scientist

Education

Ph.D. Biomedical Sciences (Toxicology Specialty), Wright State University, 1988
B.S. Biology, Wright State University, 1984
A.S. Medical Laboratory Technology, George Washington University, 1979

Capabilities

Toxicology
Human Health Risk Assessments
Physiologically Based Pharmacokinetic (PBPK) Model Development and Applications

Experience Summary

Dr. Gargas is a Principal Health Scientist with the ChemRisk® Division of McLaren/Hart in the Cleveland, Ohio office. Dr. Gargas manages the ChemRisk® group in Cleveland and has technical oversight and administrative responsibilities for the group. Dr. Gargas oversees and prepares human health risk assessments, conducts toxic tort support investigations and addresses various toxicological issues through applied research on behalf of clients. He has over 18 years of experience in human health risk assessment and in biochemical toxicology research with emphasis in the areas of inhalation toxicology, chemical metabolism, PBPK modeling, and chemical dosimetry, with specific application of these approaches to risk assessments. Dr. Gargas has conducted toxicology research on numerous volatile organic compounds (VOCs) including benzene, toluene, styrene, xylenes, furan, ethylene oxide, butadiene, acrylonitrile, the halogenated methanes, ethanes, and ethylenes, as well as 2,3,7,8-tetrachlorodibenzo-p-dioxin, chromium, and Pb.

Key Projects

McLaren/Hart: May 1992 - Present

- Currently serving as a member of a steering committee on behalf of the CMA in which industry representatives and USEPA staff are re-evaluating the reference dose (RfD) for ethylene glycol-n-butyl ether. A PBPK modeling approach is being used in this study. This pilot program may serve as a template for evaluating and setting regulatory criteria in the future.

- Currently serving as a member of the "Generic Numeric Cleanup Standards and Risk Assessment Procedures" subcommittee of the Ohio Voluntary Action Program (S.B. 221; Brownsfield). This group is charged with writing the rules associated with generic standards and risk assessment procedures in this Ohio Program.

- Currently Project Manager for a work in which ChemRisk® is writing the risk assessment guidance for site-specific risk assessments in the Czech Republic. This work is being conducted in cooperation with a Czech based consulting firm (AQUATEST). This project is funded by the National Property Fund of the Czech Republic through AUTOPAL (a company now owned by Ford Motor Company). In addition to writing the guidance, ChemRisk® is providing oversight to AQUATEST in preparing risk assessments on four AUTOPAL sites.

- Prepared a position paper on the oral and inhalation cancer slope factors (SFs) for acrylonitrile on behalf of BP Chemicals. The current SFs were found to be outdated and a PBPK approach has been recommended.

- Project manager for a refined cancer risk assessment for butadiene for the Chemical Manufacturers Association. This project involves developing a state-of-the-science PBPK model for butadiene to predict relevant internal dose measures for use in a Decision Analysis approach for estimating human risk. The intent is to provide the USEPA with the most current knowledge regarding the cancer risks posed to humans by exposure to butadiene.

- Project manager for a re-evaluation of the cancer potency of trichlorethylene using advanced PBPK approaches for the Department of Energy. The project combines PBPK, sensitivity analyses, and Monte Carlo simulations to produce a refined estimate of the cancer risk to humans exposed to trichloroethylene. The intent is to provide the USEPA with an alternate risk assessment for their consideration when the agency re-evaluates this chemical in the near future.

- Manager for a joint project between the Halogenated Solvents Industry Alliance (HSIA) and the ATSDR. A PBPK model for methylene chloride (MeCl) is being used to fill data gaps identified by ATSDR. The model is being used to conduct dose route extrapolation (i.e., inhalation to oral, etc.) as a replacement for costly animal testing. If successful, this project will serve as a prototype for filling data gaps in exposure assessment with other chemicals.

- Project manager for review of a USEPA proposed hazardous waste listing on behalf of a confidential client. The risk assessments conducted by the USEPA were reviewed and critiqued. Many inconsistencies and errors were discovered during this review which were described in a written report to the submitted to the USEPA. Expert witness and public meeting support are also anticipated for this project. The final outcome is pending.

- Project manager for a review and critique of the USEPA's Exposure Assessment and Health Assessment Documents on 2, 3, 7, 8- tetrachloro-p-dibenodioxin (TCDD). The entire Exposure Assessment Document (over 1300 pages) and several chapters of the Health Assessment Document were reviewed and comments were provided to the Chemical Manufacturers Association's Chlorine

Chemistry Council. All comments were sent to the USEPA for their consideration. Numerous inconsistencies in interpretation of toxicity and exposure data as well as numerous data gaps were identified and suggestions for improvement were provided.

- Conducted a review for a pump manufacturer on the acute toxicity of Pb and performed Pb modeling (IEUBK and PBPK) to demonstrate the Pb leaching from pumps used in domestic wells were not of a health concern. Based on this assessment the manufacturer has decided to continue sales of these pumps. Potential toxic tort litigation support may follow.

- Challenged the Pb clean-up level chosen by USEPA for a Superfund site in Region V. Dr. Gargas conducted an extensive review of the Pb toxicology and modeling literature and the review and resulting report became part of the basis for challenging the ROD. Dr. Gargas also served as one of 3 experts on a Blue Ribbon Panel representing the PRPs during a series of meetings with USEPA representatives. The final decision regarding the clean-up level is under court review.

- Prepared a risk-based approach for determining cleanup goals for soils contaminated by waste oils from overfilling of a UST at a site in Ohio. The risk assessment to be performed at this site in Ohio will represent one of only several risk assessments submitted to Ohio BUSTR.

- Designed and implemented a human biomonitoring study in which urinary excretion of chromium was monitored following ingestion of soils that contain chromium. This work identified the proper sampling regimen to follow to optimize biomonitoring and demonstrated the shortcomings of a urine surveillance program designed by a State Regulatory Agency.

- Applied a PBPK model of chromium kinetics in rodents to extrapolate data from a sub-chronic study to determine an equivalent chronic dose. Also used the model to derive estimates of the bioavailability of chromium salts. The findings of this work are under consideration by USEPA in their effort to establish new RfDs for chromium compounds.

- Provided expert witness testimony on the dose/response characteristics of methylene chloride with regards to neurotoxicity for a workers compensation case in the State of Michigan. Based on the report of my findings and my expert witness testimony, the court found in favor of our client.

- Provided review and comment on the use of PBPK models in risk assessments involving chloroform in the State of California. These comments were incorporated into a document prepared by the International Life Sciences Institute

(ILSI) to address issues raised concerning approaches proposed by California's Department of Health Sciences.

Chemical Industry Institute of Toxicology (CIIT): August, 1989 - May, 1992 (Biochemical Toxicologist)

- Conducted basic toxicology research in the development of PBPK dosimetry models and their application in human risk assessments for a variety of industrial compounds, including acrylonitrile, 1,3-butadiene, ethylene oxide, chloroform, 2,3,7,8-TCDD, and methylene chloride.

- Supervised various research teams consisting of 1-3 technical staff and up to 3 post-doctoral fellows in the day-to-day conduct of the research programs at the Institute.

Toxic Hazards Division - Wright-Patterson AFB, Dayton, Ohio: April, 1981 - August, 1989 (Research Chemist)

- Conducted inhalation toxicology, chemical metabolism, tissue solubility, and dosimetry research. Co-authored the first two papers demonstrating the use of PBPK models in establishing more scientifically defensible dose-tumor response relationships for methylene chloride and chloroform in rodents and their application in establishing human risk from drinking water and from inhalation exposures.

Professional Memberships

Society of Toxicology (1989 - Present)
- Inhalation Specialty Section (1989-1992)
- Risk Assessment Specialty Section (1993 - Present)

North Carolina Chapter of the Society of Toxicology (1990-1992)

Allegheny - Erie Chapter of the Society of Toxicology (1993 - Present)

Society for Risk Analysis (1993 - Present)

Awards

Frank R. Blood Award - Society of Toxicology - 1982 (best paper published in Toxicology and Applied Pharmacology for the period June 1980 - May 1981).

Department of the Air Force Invention/Patent Award (Co-Inventor), November 23, 1983, for an In Vivo Dermal Absorption System for Rats, Invention No. 15, 859 (U.S. Patent Number: 4,582,055).

Outstanding Technical Civilian of the Year Award, 1983, Air Force Aerospace Medical Research Laboratory.

Editorial Board Appointments

Toxicology and Applied Pharmacology

External Referee for:

Toxicology and Applied Pharmacology
Fundamental and Applied Toxicology
Cancer Research
Archives of Toxicology
Canadian Journal of Physiology and Pharmacology
Journal of Exposure Analysis and Environmental Epidemiology
Nutrition
Drug Metabolism and Disposition

Peer-Reviewed Publications:

Andersen, M. E., French, J. E., Gargas, M. L., Jones, R. A., and Jenkins, L. J., Jr. (1979). Saturable metabolism and the acute toxicity of 1,1-dichloroethylene. Toxicol. Appl. Pharmacol., **47**, 385-393.

Andersen, M. E., Gargas, M. L., Jones, R. A. and Jenkins, L. J., Jr. (1979). The use of inhalation techniques to assess the kinetic constants of 1,1-dichloroethylene metabolism. Toxicol. Appl. Pharmacol., **47**, 395-409.

Andersen, M. E., Gargas, M. L., Jones, R. A., and Jenkins, L. J., Jr. (1980). Determination of the kinetic constants of metabolism of inhaled toxicants in vivo based on gas uptake measurements. Toxicol. Appl. Pharmacol., **54**, 100-116.

Gargas, M. L., and Andersen, M. E. (1980). Closed atmosphere gas uptake studies and their validation by direct metabolite determination. Proceedings of the 10th Annual Conference on Environmental Toxicology, Dayton, Ohio, November 1979. AFAMRL-TR-79-121, 74-92.

Andersen, M. E., Thomas, O. E., Gargas, M. L., Jones, R. A., and Jenkins, L. J., Jr. (1980). The significance of multiple detoxification pathways for reactive metabolites in the toxicity of 1,1-dichloroethylene. Toxicol. Appl. Pharmacol., **52**, 422-432.

Gargas, M. L., and Andersen, M. E. (1982). Metabolism of inhaled brominated hydrocarbons: Validation of gas uptake by determination of a stable metabolite. Toxicol. Appl. Pharmacol., **66**, 55-68.

Andersen, M. E., Gargas, M. L., and Ramsey, J. C. (1984). Inhalation pharmacokinetics: evaluating systemic extraction, total in vivo metabolism, and the time course of induction for inhaled styrene based on steady-state blood gas concentration ratios. Toxicol. Appl. Pharmacol., **73**, 176-187.

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(PBPK) model. Toxicologist, 12, Paper No. 1352. Presented at the 31st Annual Meeting of the Society of Toxicology, Feb. 23-27, 1992, Seattle, WA.

Larson, J. L., Wolf, D. C., Gargas, M. L., and Butterworth, B. E. (1992). Acute hepato- and nephrotoxicity of chloroform (CHCl3) in male F344 rats. Toxicologist, 12, Paper No. 800. Presented at the 31st Annual Meeting of the Society of Toxicology, Feb. 23-27, 1992, Seattle, WA.

Burnette, W. B., Gargas, M. L., Murphy, J. E., and Andersen, M. E. (1992). In vivo metabolic and gastrointestinal (GI) absorption rates of chloroform (CHCl3) in the female F-344 rat. Toxicologist, 12, Paper No.1663. Presented at the 31st Annual Meeting of the Society of Toxicology, Feb. 23-27, 1992, Seattle, WA.

Larson, J. L., Wolf, D. C., Gargas, M. L., and Butterworth, B. E. (1992). Acute hepatotoxicity of chloroform (CHCl3) in female B6C3F1 mice. Presented at the 83rd Annual Meeting of the American Association for Cancer Research, May 20-23, 1992, San Diego, CA.

Kim, C. S., Gargas, M. L., and Andersen, M. E. (1992). Development of a physiologically based pharmacokinetic (PBPK) model of 2,4-dichlorophenoxyacetic acid (2,4-D) levels in the brain following single dose administration. Presented at the conference on, "Applications of Advances in Toxicology to Risk Assessment", May 19-21, 1992, Wright-Patterson AFB, Ohio.

Andersen, M. E., Mills, J. J., and Gargas, M. L. (1992). Biologically-motivated risk assessments for dioxin. Presented at the conference on, "Applications of Advances in Toxicology to Risk Assessment", May 19-21, 1992, Wright-Patterson AFB, Ohio.

Borghoff, S. J., Gargas, M. L., Andersen, M. E., and Conolly, R. B. (1993). Quantitative evaluation of 2,4,4-trimethyl-2-penanol (TMP-2-OH)-induced α 2 μ-globulin ($\alpha 2\mu$) accumulation in male rat. Toxicologist, 13, Paper no. 623. Presented at the 32nd Annual Meeting of the Society of Toxicology, March 14-18, 1993, New Orleans, LA.

Gargas, M. L., Bono, M. A., Scott, P. K., Finley, B. L., and Paustenbach, D. J. (1993). Approaches to assessing human exposure to soil contaminants at wood preserving facilities. Toxicologist, 13, Paper no. 1045. Presented at the 32nd Annual Meeting of the Society of Toxicology, March 14-18, 1993, New Orleans, LA.

Kim, C. S., Slikker, W., Binienda, Z., Gargas, M. L., and Andersen, M. E. (1993). Development of a physiologically based pharmacokinetic (PBPK) model for 2,4-dichlorophenoxy acetic acid (2,4-D) dosimetry in discrete areas of the brain following a single intraperitoneal dose. Presented at the Annual Meeting of the Society for Neuroscience, November 7-12, 1993, Washington, DC.

Kim, C. S., Slikker, W., Binienda, Z., Gargas, M. L., and Andersen, M. E. (1993). Physiologically based pharmacokinetic (PBPK) modeling of sodium 2,4-dichlorophenoxy acetic acid

(NA-2,4-D) dosimetry in different regions of the brain following a single intravenous dose. Presented at the meeting of Pharmacology 93, ASPET, San Francisco, CA.

Kedderis, G., Held, S. D., and Gargas, M. L. (1993). Prediction of chemical pharmacokinetics in vivo using freshly isolated hepatocytes in vitro. Presented at the Fifth North American ISSX Meeting, October 17-21, 1993, Tucson, Arizona.

Gargas, M.L., Finely, B.L., Norton, R.L., Proctor, D.M., and Paustenbach, D.J. (1994). Biomonitoring of chromium (Cr) exposure by urinary excretion: bioavailability and sampling design. Toxicologist, 14, Paper no. 383. Presented at the 1994 Society of Toxicology meeting, Dallas, Texas.

Kedderis, G.L., Teo, S.K.O., Batra, R., and Gargas, M.L. (1994). Refinement and validation of a physiologically-based dosimetry description for acrylonitrile and 2-cyanoethylene oxide in F-344 rats. Toxicologist, 14, Paper no. 76. Presented at the 1994 Society of Toxicology meeting, Dallas, Texas.

Krishnan, K., Filser, J.G., and Gargas, M.L. (1994). Physiologically-based pharmacokinetic (PBPK) modeling of ethylene in rats and humans. Toxicologist, 14, Paper no. 81. Presented at the 1994 Society of Toxicology meeting, Dallas, Texas.

Kerger, B.D., Walker, L.B., Gargas, M.L., Paustenbach, D.J., and Reitz, R.H. (1994). Perspective on risks of chloroform in tap water: implications of physiologically-based pharmacokinetic modeling on regulatory toxicity criteria. Toxicologist, 14, Paper no. 542. Presented at the 1994 Society of Toxicology meeting, Dallas, Texas.

Fehling, K., Scott, P., Bono, M., and Gargas, M. (1994). A comparison of two biokinetic models for lead to determine health based soil standards for residential and industrial sites. Toxicologist, 14, Paper no. 56. Presented at the 1994 Society of Toxicology meeting, Dallas, Texas.

Held, S. D., Gargas, M. L., and Kedderis, G. L. (1994). Kinetics of chloroform biotransformation determined in freshly isolated male and female hepatocytes. Presented at the Sixth North American ISSX Meeting, October 23-27, 1994, Raleigh, NC, paper no. 168.

Finley, B. L., Norton, R. L., and Gargas, M. L. (1995). Urinary chromium concentrations in humans following ingestion of safe doses of hexavalent and trivalent chromium: Implications for biomonitoring. Toxicologist, 15, Paper No. 1036. Presented at the 34th Annual Meeting of the Society of Toxicology, Baltimore, Maryland.

O'Flaherty, E. J., Reitz, R. H., and Gargas, M. L. (1995). Chromium(III) and Cr(VI) kinetics in the rat: A physiologically-based model. Toxicologist, 15, Paper No. 1452. Presented at the 34th Annual Meeting of the Society of Toxicology, Baltimore, Maryland.

Gargas, M. L. and Dourson, M. L. (1995). Techniques for quantifying uncertainty in risk assessment. Toxicologist, 15, Paper No. 1746. Presented at the 34th Annual Meeting of the Society of Toxicology, Baltimore, Maryland.

Invited Presentations/Lectures/Symposia:

Gargas, M. L. (1988). Physiological modeling of the uptake and elimination of pulmonary toxicants. Presented at the Military Medical Pulmonary Research Review and Analyses, September 20-22, 1988, Fitzsimmons Army Medical Center, Denver, Colorado.

Gargas, M. L. (1989). Determining the kinetic constants for metabolism of volatile chemicals, in vivo. Presented at the Chemical Defense Establishment, Porton Down, Salisbury, England, April 27, 1989 and at the NIEHS, Research Triangle Park, North Carolina, March 15, 1989.

Gargas, M. L. (1990). Gas uptake and exhaled breath techniques for assessing in vivo metabolism of volatiles. Presented at the E.I. DuPont DeNemours and Co., Haskell Laboratory, August 9, 1990.

Gargas, M. L. (1990). Incorporating metabolism into pharmacokinetic models. Presented as part of a mini-course on "Physiological Pharmacokinetic Modeling", held at CIIT, Jan./Feb. 1990.

Gargas, M. L. (1990). Evaluating metabolic and G.I. uptake parameters through the use of PBPK models. Presented as part of a workshop entitled, "Physiologically-Based Pharmacokinetic Models: Principles and Implementation", November 13-15, 1990, Research Triangle Park, N.C.

Gargas, M. L. (1991). Evaluating metabolic and G.I. uptake parameters through the use of PBPK models. Presented as part of a workshop entitled, "Physiologically-Based Pharmacokinetic Models: Principles and Implementation", March 12-14, 1991, Research Triangle Park, N.C.

Gargas, M. L. (1991). Estimating in vivo metabolic parameters using a PB-PK model. Presented as part of a continuing education course entitled, "Implementing Physiologically-Based Pharmacokinetic Models" at the 30th Annual Meeting of the Society of Toxicology, Feb. 25- March 1, 1991, Dallas, Texas.

Gargas, M. L. (1991). In vivo metabolic assessment of volatile organic chemicals. Presented at College of Pharmacy, University of Georgia, April 15, 1991.

Gargas, M. L. (1991). Development of a physiologically-based pharmacokinetic model for ethylene oxide in the rat. Presented at the Institute fur Toxikologie, GSF, Neuherberg, FRG, Oct. 16, 1991.

Gargas, M. L. (1992). In vivo metabolism, biochemical mechanisms, and PBPK modeling. Presented at the "International Workshop on Physiologically Based Pharmacokinetic Modeling and Risk Assessment," Colorado State University, Fort Collins, CO., August 3-21, 1992.

Gargas, M. L. (1992). Determination of in vivo rate constants of metabolism for volatile chemicals using PBPK models (Computer Session). Presented at the "International Workshop on Physiologically Based Pharmacokinetic Modeling and Risk Assessment," Colorado State University, Fort Collins, CO., August 3-21, 1992.

Clewell, H. J., III, Gargas, M. L. and Andersen, M. E. (1992). Physiologically-based pharmacokinetic (PB-PK) modeling of mixtures. The Toxicologist, 12, Paper No. 10. Presented as part of a Symposium entitled," Risk assessment of chemical mixtures: Biologic and toxicologic issues", at the 31st Annual Meeting of the Society of Toxicology, Feb. 23-27, 1992, Seattle, Washington.

Gargas, M. L. (1992). Estimating in vivo metabolic parameters using a PB-PK model. Presented as part of a continuing education course entitled, "Implementing Physiologically-Based Pharmacokinetic Models" at the 31st Annual Meeting of the Society of Toxicology, Feb. 23-27, 1992, Seattle, Washington.

Andersen, M. E., Krishnan, K., and Gargas, M. L. (1992). In vitro toxicology and risk assessment. Presented at the Tenth Anniversary Symposium of the Center For Alternatives To Animal Testing, April 14-16, 1992, Baltimore, Md.

Bond, J. A., Csanady, G. A., Leavens, T., Gargas, M. L., Medinsky, M.A., and Recio, L. (1992). 1,3-Butadiene: Linking metabolism, dosimetry, and mutation induction. Presented at the IV European ISSX Meeting, July 3-6, 1992, Bologna, Italy.

Gargas, M. L. (1993). The basics of risk assessment. Presented to the Cuyahoga County Planning Commission's "Brownfields Working Group". March 1, 1993, Cleveland, Ohio.

Gargas, M. L. and Paustenbach, D. J. (1993). Risk assessment in Industrial Hygiene: What's New? Presented at the 8th Annual Professional Conference on Industrial Hygiene, Cincinnati, Ohio, October 25, 1993.

Gargas, M. L. (1993). Risk Assessment: Advantages, Refinements, And Use In Setting Remediation Goals. Presented at a Breakfast Seminar entitled, "Recycling Industrial Properties: Balancing the Environmental Risks", Pittsburgh, Pa., October 28, 1993.

Gargas, M. L. (1993). The historical practice of health risk assessment in the United States: How that experience can benefit Brownfield Initiatives. Presented as testimony to the Environmental Resources and Energy and Community and Economic Development Committees of the Pennsylvania Senate, Harrisburg, Pa., November 23, 1993.

Gargas, M. L. (1993). The historical practice of health risk assessment in the United States: How that experience can benefit Brownfield Initiatives. Presented at a seminar sponsored by McLaren/Hart and Baker & Hostetler law offices entitled "Revitalizing Urban Industrial/Commercial

Property: The Ohio Brownfields Initiative," The Forum Conference Center, Cleveland, Ohio, December 2, 1993.

Gargas, M. L., and Malsch, P. A. (1994). Progress in improving the risk assessment process. Presented at the "1994 Squire, Sanders & Dempsey Environmental Law Update for Clients," March 24, 1994, Columbus, Ohio.

Gargas, M. L., Scott, P. K., Finley, B. L., and Reitz, R. H. (1994). Refinements in the exposure assessment process. Presented at the "Conference on Temporal Aspects in Risk Assessment for Non-Cancer Endpoints," April 18-20, 1994, Wright-Patterson, AFB, Ohio.

Gargas, M. L. (1994). In vivo metabolism, biochemical mechanisms, and PBPK modeling. Presented at the "International Workshop on Physiologically Based Pharmacokinetic Modeling and Risk Assessment," Colorado State University, Fort Collins, CO., August 1-13, 1994.

Gargas, M. L. (1994). Determination of in vivo rate constants of metabolism for volatile chemicals using PBPK models (Computer Session). Presented at the "International Workshop on Physiologically Based Pharmacokinetic Modeling and Risk Assessment," Colorado State University, Fort Collins, CO., August 1-13, 1994.

Gargas, M. L. (1994). The role of risk assessment in Brownfield Initiatives. Presented at The Liquid and Solid Industrial Control Association (LICA) Conference, September 6-7, Detroit, MI.

Gargas, M. L. (1994). Progress in improving the risk assessment process. Presented at a conference entitled, "Environmental Remediation in Ohio", September 28, Cleveland, Ohio, presented by the Institute of Business Law.

Gargas, M. L. (1994). Progress in improving the risk assessment process: Applications for the CPMA. Presented to the Color Pigments Manufacturers Association (CPMA) Members Luncheon Meeting on October 19, Cincinnati, Ohio.

Gargas, M. L. (1994). Incorporating metabolism into PBPK models - in vivo experiments and model prediction. Presented at the International Society for the Study of Xenobiotics (ISSX) 6th North American Meeting, October 23-27, Raleigh, NC.

Gargas, M. L. (1995). Risk Assessment in Industrial Hygiene and Safety: What's New? Presented at the Industrial Health Foundation 60th Anniversary Annual Scientific Meeting, Pittsburgh, Pennsylvania.

Gargas, M. L. (1995). Risk Assessment - Methods and Applications. Presented at the AWMA Spring Meetings, Kent, Ohio.

Gargas, M. L. (1995). An historical perspective of risk assessment in the United States: Lessons learned, Presented at an International Workshop entitled, "Methods of Determination of Target

Concentration Limits and Risk Assessment for Contaminated Sites", Prague, Czech Republic, September 14-15, 1995.

Gargas, M. L. (1995). PBPK Modeling: Is a Human Simply a 70 kg Rat?, Presented at a seminar entitled, "Risk, Regulation, & Reason", Hudson, Ohio, December 8, 1995.

Gargas, M. L., Hays, S. M., and Reitz, R. H. (1995). The application of physiologically-based pharmacokinetic (PBPK) models in risk assessment. Presented at a risk assessment workshop entitled, "State of Practice of Risk Assessment in Human Health and Environmental Decision-Making", Tallahassee, Florida, December 13-14, 1995.

Gargas, M. L. (1996). The application of PBPK models in risk assessment, or (Is a Human Simply a 70 kg Rat?), presented at the January meeting of the North East Ohio Chapter of the AIHA, Independence, Ohio, January 16, 1996.

RICHARD H. REITZ, Ph.D.

Principal Health Scientist

Education

Ph.D. Biochemistry (Microbiology Minor), Northwestern University, 1966
B.S. Chemistry (Mathematics Minor), DePauw University, 1962

Capabilities

Genetic Toxicology & Cancer Mechanisms
Microbiology
Physiologically-based Pharmacokinetic (PB-PK) Modeling
Human Health Risk Assessment
Computer Programming

Experience Summary

Dr. Reitz is a Principal Health Scientist with the ChemRisk Division of McLaren/Hart in the Cleveland, Ohio office. He has 27 years of experience in the biological sciences including work in the discovery and development of new drugs for central nervous system or immunological disorders, use of enzymes from microorganisms for chemical synthesis, identification of the mechanisms by which industrial chemicals produce genotoxic and/or carcinogenic effects in mammals, pharmacokinetic modeling, development of computerized systems for data acquisition, and development of risk assessments using PB-PK models. In recent years he has conducted research aimed at establishing the potential hazard for humans exposed to methylene chloride, perchloroethylene, trichloroethylene, dichloroethane, vinylidene chloride, vinyl chloride, orthophenylphenol, chloroform, and 1,4-dioxane.

Key Projects

McLaren/Hart ChemRisk - Cleveland Office

- Joined Office September 7, 1993 as Principal Health Scientist

U. S. E. P. A. Science Advisory Board: September 1992 - Present

- Member: Drinking Water Advisory Subcommittee
- Review Research Programs EPA's Health Effects Research Laboratories
- Critical Review of Drinking Water Standards for Arsenic, Radon, Chloroform.

SL 110354

- Review Ambient Water Quality Criteria

- Review Carcinogen Risk Assessment Guidelines

Dow Chemical Company: September 1966 - August 1993

- Conducted research to discover and evaluate new drugs (antidepressants, asthma and hypersensitivity drugs).

- Conducted pharmacokinetic studies with Investigational New Drugs.

- Isolated microorganisms from soil capable of carrying out stereospecific biosynthetic reactions.

- Prepared enzymes from these organisms to evaluate their potential for use in immobilized enzyme systems.

- Evaluated procedures for reducing heat lability of enzymes to be used in industrial processes.

- Developed in vivo procedures for evaluating DNA alkylation, DNA repair, and cellular division in rodents.

- Conducted studies to determine biochemical mechanisms of carcinogenicity.

- Wrote the first quantitative risk assessment which used PB-PK modeling for high dose/low dose, dose route, and interspecies extrapolations (methylene chloride) in collaboration with Drs. Mel Andersen, Michael Gargas, and Colonel Harvey Clewell.

- With Mel Andersen, presented PB-PK risk assessment to Federal Agencies, identified their concerns, and conducted studies to address those concerns (e.g. in vitro measurements of methylene chloride metabolism in human tissue samples).

- With Dr. Richard Corley, wrote the first risk assessment to use cellular replication following cytotoxicity as a quantitative dose metric.

Chemical Industry Institute of Toxicology: September 1989 - June 1990

Visiting Scientist in Toxicology (Sabbatical leave from Dow)

SL 110355

- Drafted the protocol for the Institute's ongoing program in chloroform research.

Nat. Acad. of Sci. Committee on Risk Assessment Methodology: 1989 - 1993

- Conducted Workshops on use of MTD, Environmental Risk Assessment, Two Stage Growth Modeling, Exposure Assessment, Reproductive Risk Assessment.

- Co-authored Academy reports on MTD, Environmental Risk Assessment, Two Stage Modeling.

Specialized Training and Certifications

Society of Toxicology
- Risk Assessment Specialty Section

American Association for Advancement of Science

American Society of Microbiology

American Chemical Society

Awards

Annual Best Paper Award: Midland Chapter of Sigma Xi, 1988.

Certifications

Certified by the American Board of Toxicology

Associate Editor for Professional Journals

Toxicology Letters (1988 to 1990)
Toxicology & Applied Pharmacology (1990 to 1992)

External Referee for:

Toxicology & Applied Pharmacology
Fundamental & Applied Toxicology
Archives of Toxicology
Biochemistry
Cancer Research

Risk Analysis
Biochemical Pharmacology

Publications/Presentations

Reitz, R. H., Slade, H. D., and Neuhaus, F. D. (1966). The Biochemical Mechanisms of D-Cycloserine Resistance. Federation Proceedings Abstracts, 25, 355.

Reitz, R. H. The Biochemical Mechanisms of Resistance to the Antibiotics D-cycloserine and O-Carbamyl-D-Serine. Submitted to the Graduate School (Northwestern University) in partial fulfillment of the requirements for the degree Doctor of Philosophy (June, 1967).

Reitz, R. H., Slade, H. D., and Neuhaus, F. C. (1967). Biochemical Mechanisms of Resistance by Streptococci to the Antibiotics D-Cycloserine and O-Carbamyl-D-Serine. Biochemistry, 6(8), 2561.

Reitz, R. H. and Riley, W. H. (1970). Another Simple Equilibrium Dialysis Apparatus. Analytical Biochemistry, 36, 535.

Reitz, R. H., Bocknik, S. E., and Kulkarni, A. S. (1972). A Comparison of MG Pemoline and (+) Amphetamine Effects upon Avoidance Behaviour and the Amine Pump. Journal Pharmacy and Pharmacology, 24, 830.

Reitz, R. H., Abdallah, A. H., Roby, D. M., Krauss, J.A. and Marshall, F. N. (1973). Selective Antagonism of Central Nervous System Depressants by DH-524: A Comparative Study with Bemegride. Proc. Soc. Expt. Biol. Med., 144, 291.

Dorman, L. C., Reitz, R. H., Krauss, J. A., Cheng, R. C., and Lewis, J. E. (1975). N,N'-Diprotected-Aminoalkanlyl-Lysine Dipeptide Bronchodilators. Peptides: Chemistry, Structure, and Biology, Roderich Walter, ed. Ann Arbor Science Publishers, Woburn, MA, pp 579-582.

Kern, B. A. and Reitz, R. H. (1978). A General Method for Preparation of the D or L Stereoisomers of 5 Substituted Hydatoins. Agricultural and Biological Chemistry Japan, 42, 1275-1278.

Reitz, R. H., Park, C. N., and Gehring, P. J. (1978). Carcinogenic Risk Estimation for Chloroform: An Alternative to EPA's Procedures. Food. Cosmet. Toxicol. 16, 511-514.

Reitz, R. H., Quast, J. F., Watanabe, P. G., and Gehring, P. J. (1979). Chemical Carcinogens: Estimating the Risk, Science, 205, 1206-1208.

Reitz, R. H., Schumann, A. M., Watanabe, P. G., and Gehring, P. J. (1979). An Experimental Approach for Evaluating Genetic and Epigenetic Contributions to Chemical Carcinogenesis. Proceedings Amer. Assoc. Cancer Res., 20, 266.

Reitz, R. H., Quast, J. F., Schumann, A. M., Watanabe, P. G., and Gehring, P. J. (1980). Nonlinear Pharmacokinetic Parameters Need to be Considered in High Dose/Low Dose Extrapolation. Archives of Toxicology, Supplement, 3, 79-94. "Quantitative Aspects of Risk Assessment in Chemical Carcinogenesis" (Eds. Kramer, Henschler, Oesch) Springer-Verlag, Heidelberg, Germany.

Reitz, R. H., Watanabe, P. G., McKenna, M. J., Quast, J. F., and Gehring, P. J. (1980). Effects of Vinylidene Chloride on DNA Synthesis and DNA Repair in the Rat and Mouse: A Comparative Study with Dimethylnitrosamine. Toxicol. Appl. Pharmacol., 52, 357-370.

Reitz, R. H., Quast, J. F., Stott, W. T., Watanabe, P.G., and Gehring, P. J. (1980). Pharmacokinetics and Macromolecular Effects of Chloroform in Rats and Mice: Implications for Carcinogenic Risk Estimation. Water Chlorination: Environmental Impact and Health Effects, (Vol III), 983-993. Ed. Jolley, Brungs & Cummins, Ann Arbor Science Publishers, Woburn, MA.

Reitz, R. H., Fox, T. R., Domoradzki, J. Y., Quast, J. F., Langvardt, P., and Watanabe, P. G. (1980). Pharmacokinetics and Macromolecular Interactions of Ethylene Dichloride; Comparison of Oral and Inhalation Exposures. Banbury Report #5, "Ethylene Dichloride: Economic Importance and Potential Health Risks", Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.

Watanabe, P. G., Reitz, R. H., Schumann, A. M., McKenna, M. J., Quast, J. F., and Gehring, P. J. (1980). Implications of the Mechanisms of Tumorigenicity for Risk Assessment in The Scientific Basis of Toxicity Assessment, 69-89, Ed. H. R. Witschi, Elsevier/North Holland Biomedical Press, Amsterdam, The Netherlands.

Reitz, R. H., and Gehring, P. J. (1980). Pharmacokinetic Models in Handbook of Environmental Chemistry, Vol. 1, "The Environment, Composition and Reactions: Ed. O. Hutzinger, Springer-Verlag, Amsterdam, The Netherlands.

Ramsey, J. C., and Reitz, R. H. (1981). Pharmacokinetics and Threshold Concepts, In THE PESTICIDE CHEMIST AND MODERN TOXICOLOGY, (S. K. Bandal, G. J. Marco, L. Golberg, and M. L. Leng, eds.), American Chemical Society, Washington, D.C.

Stott, W. T., Reitz, R. H., Schumann, A. M., and Watanabe, P. G. (1981). Genetic and Nongenetic Events in Neoplasia. Fd. Cosmet. Toxicol., 19, 567-576.

Reitz, R. H., Fox, T. R., Ramsey, J. C., Langvardt, P. W., and Watanabe, P. G. (1982). Pharmacokinetics and Macromolecular Interactions of Ethylene Dichloride in Rats After Inhalation or Gavage, Toxicol. Appl. Pharm., 62, 190-204.

Reitz, R. H., Fox, T. R., and Quast, J. F. (1982). Mechanistic Considerations for Carcinogenic Risk Estimation - Example: Chloroform, Environmental Health Perspectives, 46, 163-168.

Schumann, A. M., Watanabe, P. G., Reitz, R. H., and Gehring, P. J. (1982). The Importance of Pharmacokinetic and Macromolecular Events as they Relate to Mechanisms of Tumorigenicity and Risk Assessment. In: "Toxicology of the Liver" (Plaa and Hewitt, eds.), Raven Press, New York, NY. pp. 311-331.

Reitz, R. H., Schumann, A. M., Watanabe, P. G., and Gehring, P. J. (1982). Genetic vs. Nongenetic Chemical Carcinogenesis and Risk Assessment. In: "Toxicology, An Agricultural Perspective" (R. A. Fleck, ed.), Plenum Press, New York, NY. pp. 425-438.

Reitz, R. H., Schumann, A. M., Watanabe, P. G., and Gehring, P. J. (1982). Genetic Versus Nongenetic Chemical Carcinogenesis and Risk Assessment. Genetic Toxicol., pp 425-438, ed R. A. Fleck and A. Hollander, Plenum Publ. Corp.

Dietz, F. K., Reitz, R. H., Watanabe, P. G., and Gehring, P. J. (1982). Translation of Pharmacokinetic/biochemical Data Into Risk Assessment. Biological Reactive Intermediates-II. Part B pp 1399-1424, ed Synder, Park, Kocsis, Jollow, Gibson, and Witmer, Plenum Publ. Corp.

Livesey, J. C., Anders, M. W., Langvardt, P. W., Putzig, C. L., and Reitz, R. H. (1982). Stereochemistry of the Glutathione-dependent Biotransformation of Vicinal-Dihaloalkanes to Alkenes. Drug Metabol. & Dispos., 10, 201-204.

Reitz, R. H., Fox, T. R., Quast, J. F., Hermann, E. A., and Watanabe, P. G. (1983). Molecular Mechanisms Involved in the Toxicity of Orthophenylphenol and its Sodium Salt. Chem. Biol. Interact. 43, 99-119.

Reitz, R. H., and Watanabe, P. G. (1983). Importance of Non-genetic Mechanisms in Carcinogenicity. Dev. Toxicol. Environ. Sci., 11, 163-172.

Reitz, R. H., and Watanabe, P. G. (1983), Importance of Non-genetic Mechanisms in Carcinogenicity., In: Developments in the Science and Practice of Toxicology, A. W. Hayes, R. C. Schnell, and T. S. Miya, eds, Elsevier Science Publishers, B. V., pp 163-171.

Reitz, R. H., Fox, T. R., Quast, J. F., Hermann, E. A., and Watanabe, P. G. (1984). Biochemical Factors Involved in the Effects of Orthophenylphenol (OPP) and Sodium Orthophenylphenol (SOPP) on the Urinary Tract of Male F344 Rats. Toxicol. Appl. Pharmacol. 73, 345-349.

Fox, T. R., Reitz, R. H., and Watanabe, P. G. (1984). Evaluation of the Genotoxic Potential of Picloram Herbicide in F344 Rats. The Toxicologist, 4, 40.

Reitz, R. H. (1985). Mechanistic Considerations in the Formulation of Risk Estimations, in "Risk Quantitation and Regulatory Policy", Banbury Report 19, 241-247.

Reitz, R. H., Fox, T. R., and Watanabe, P. G. (1986). The Role of Pharmacokinetic in Risk Assessment in "Mechanisms of DNA Damage & Repair", (Simic et al. eds). Plenum Press.

Reitz, R. H., Schumann, A. M., Osborne, D. W., and Nolan, R. J. (1985). Pharmacokinetics of 1,1,1-trichloroethane in Humans, Rats, and Mice After Inhalation or Drinking Water Administration. The Toxicologist, 5, 110.

Reitz, R. H., Smith, F. A., Gargas, M. L., Clewell, H. J., and Andersen, M. E. (1986). Physiological Modeling and Risk Assessments: Example, Methylene Chloride. The Toxicologist, 6, 7.

Eisenbrandt, D. L., and Reitz, R. H. (1986). Acute Toxicity of Methylene Chloride: Tumorigenic Implications for B6C3F1 Mice. The Toxicologist, 6, 164.

Reitz, R. H., Smith, F. A., and Andersen, M. E. (1986). In Vivo Metabolism of ^{14}C-Methylene Chloride (MEC). The Toxicologist, 6, 260.

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Reitz, R. H., Fox, T. R., and Watanabe. (1986). The Role of Pharmacokinetics in Risk Assessment. Basic Life Sci., 38, 499-507.

Reitz, R. H. (1987). The Role of Cytotoxicity in the Carcinogenic Process. In Banbury Report 25, "Nongenotoxic Mechanisms in Carcinogenesis", B. Butterworth and T. Slaga, eds., Cold Spring Harbor Press, Cold Spring Harbor, NY.

Reitz, R. H., Conolly, R. B and Andersen, M. E. (1987). Pharmacokinetic Models for Indirect Carcinogens. The Toxicologist, 7, 236.

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BETSY A. BRIEN

Assistant Health Scientist

Education

M.S., Environmental Health/Toxicology, Colorado State University, 1995
B.S., Biology, Nicholls State University, 1992

Capabilities

Toxicology
Physiology
Human Health Risk Assessment
Physiologically-Based Pharmacokinetic/Pharmacodynamic Modeling

Experience Summary

Betsy Brien is an Assistant Health Scientist with ChemRisk Division of McLaren/Hart in the Cleveland, OH office. Ms. Brien's primary responsibilities are to provide knowledge in the areas of human health risk assessment and physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) modeling. Ms. Brien has three years of toxicology research experience, in which time she organized and directed a laboratory study. Ms. Brien's previous work experience includes a toxicology internship in which she reviewed and summarized human health and ecotoxicology data, and she also has experience working in environmental testing facilities.

Key Projects

McLaren/Hart

- Conducting review of pertinent scientific literature to evaluate the cancer potency factor (CPF) for acrylonitrile (ACN). The goal of this project is to identify scientific literature that can be used to alter the current CPFs, identify current data gaps, and determine methods to improve the existing CPFs.

- Aiding in the development of a PBPK model of methylene chloride ($MeCl_2$) for the Halogenated Solvents Industrial Alliance (HSIA) and the Agency for Toxic Substances and Disease Registry (ATSDR). The PBPK model is to be used to conduct dose route extrapolations (i.e., inhalation to oral) as an alternative to expensive testing methods as a means of filling data gaps identified by the ATSDR.

Colorado State University

- Responsible for conducting metabolism experiment of aflatoxin B_1 (AFB_1) evaluating stain difference in a resistant and non-resistant strain of broiler chickens.

Professional Affiliations

Society of Toxicology, Mountain West Chapter (9/94 - present)
Society of Environmental Toxicology and Chemistry (10/94 - present)

APPENDIX B

AUTHORIZATION TO PROCEED FORM
AND
TERMS AND CONDITIONS

CHEMRISK DIVISION OF McLAREN/HART

PROJECT AUTHORIZATION FORM

ChemRisk® Division of McLaren/Hart (ChemRisk®) is hereby authorized to provide professional services as defined in ChemRisk's® Proposal Number CL96-0059, dated April 29, 1996. All work will be completed in accordance with the scope of work as defined in that proposal and the Contract Terms and Conditions provided as an attachment to the proposal.

Time and Material Price (Firm Costs):	$90,248
Estimated Costs (Subject to Change)	$12,800

AUTHORIZATION TO PROCEED:

_____
Name (please print)

_____
Title

_____
Representing

_____
Address

_____
City, State

_____
Date

_____
Signature

McLaren Hart
ENVIRONMENTAL ENGINEERING CORPORATION

Contract Terms and Conditions

Proposal: CL96-0059
Date: April 29, 1996

1. **INTRODUCTION:** All McLAREN/HART proposals are submitted on the condition that the following Terms and Conditions will establish the general scope of liability and responsibility that governs the contract and/or work authorizations resulting therefrom. The contract prices and terms are established hereunder in good faith and are not subject to renegotiation except with the mutual agreement of both principal parties.

2. **PROPOSAL TERM:** Unless otherwise stated in the proposal, this offer shall remain valid for a period not-to-exceed sixty (60) calendar days.

3. **PAYMENT TERMS:** Invoices, submitted in accordance with paragraph 4 herein, are due and payable to McLAREN/HART within 30 days of receipt. CLIENT shall notify McLAREN/HART of any invoice discrepancies and agrees to pay all amounts not in dispute within the terms specified herein. Non-payment within the terms and conditions specified herein will be considered a material breach of this contract.

   CLIENT's payments hereunder shall not be delayed or extended due to CLIENT's failure to secure reimbursement from any third party. Payment in accordance with the terms hereunder shall not be delayed or reduced as a result of any current or future litigation or other efforts by CLIENT to recover damages or costs from third parties. McLAREN/HART may, after giving seven (7) days written notice, suspend all services and withhold reports and data, without further liability until all past due amounts are paid in full. CLIENTs without established credit with McLAREN/HART may be required to submit advance payments.

4. INVOICING - Time-and-Materials: CLIENT recognizes that McLAREN/HART's proposal is an estimate of probable cost only. The cost and schedule may vary significantly based on conditions encountered at the Site and/or during review of relevant project data and historical records. Invoices will be issued monthly in McLAREN/HART format which will itemize labor expended by skill category, individual and hourly rate, along with the material, equipment, supplies, subcontracted services, travel and other expenses incurred by McLAREN/HART directly in the performance of the services provided. All labor and expenses incurred shall be invoiced and reimbursed as set forth in the attached McLAREN/HART Rate Schedule unless otherwise stated in the proposal. Any special project summary reporting or special invoicing requirements must be conveyed by CLIENT prior to project commencement to allow McLAREN/HART to evaluate the cost impact, if any. McLAREN/HART will be under no obligation to exceed the authorized contract amount to complete the work.

   Lump Sum/Fixed-Price: All projects exceeding thirty (30) days in duration will be invoiced monthly based upon the percent of completion or total units completed, as applicable. Projects less than 30 days in duration will be invoiced on a lump sum basis at completion. No cost element detail is provided on fixed-price or lump sum projects.

5. **TAXES:** Prices, Rates, and Estimates provided hereunder are exclusive of any federal, state, local or municipal sales, use, or excise taxes on the services or equipment delivered hereunder, which if applicable will be invoiced separately.

6. **CLIENT INFORMATION:** CLIENT acknowledges that McLAREN/HART is not liable for the accuracy and completeness of information, (including, but not limited to, specifications, drawings, maps, surveys, reports, historical land usage and operations, results of previous Site investigations and surface or subsurface conditions affecting the Site), supplied by CLIENT or its agents to McLAREN/HART and acknowledges that McLAREN/HART is relying upon such information or data in the preparation of this proposal and the performance of the work without further verification by McLAREN/HART as to its accuracy or completeness.

7. **EXISTING SITE CONDITION AND ACCESS:** CLIENT grants to McLAREN/HART and its subcontractors ACCESS and authority to enter the property ("Site") to fulfill the scope of services called for by this Agreement. CLIENT acknowledges that McLAREN/HART did not create any hazardous waste, pollution sources, nuisance, or chemical or industrial disposal problem, if any, which may exist at the Site. The responsibility for making any disclosures or reports to any third party and for taking corrective, remedial or mitigative action, including disposal of any drums, shall be solely that of the CLIENT and/or OWNER. McLAREN/HART will take reasonable precautions to minimize damage to the Site and adjoining properties.

8. **INSURANCE:** McLAREN/HART maintains workers' compensation and employer's liability insurance of a form and in an amount as required by the state in which the Services are being performed; other coverages include: commercial general liability (including contractual and products), automobile liability (including owned, non-owned and hired), professional liability, and pollution liability insurance with policy limits of one million dollars ($1,000,000). Certificates f insurance to provide evidence of the above coverage will be provided upon request and award of contract.

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9. INDEMNITY: McLAREN/HART shall hold harmless and indemnify CLIENT from and against liability, including reasonable counsel fees, arising out of McLAREN/HART's willful misconduct or negligent performance of the work, provided however, that such indemnification shall not apply to the extent any losses, damages, liabilities, or expenses result from, are attributable to, or arise out of (a) any negligence or willful misconduct of CLIENT or its agents or subcontractors; (b) any delay attributable to CLIENT's conduct; (c) any breach by CLIENT of any warranties or other provisions hereunder; (d) claims arising out of, as a result of, or in connection with pre-existing conditions unknown to McLAREN/HART prior to the date of this Agreement, and not addressed in the contract work scope; or (e) CLIENT's and/or Site Owner's non-compliance with Environmental Laws.

   CLIENT agrees to indemnify and hold harmless McLAREN/HART from and against liability, including reasonable counsel fees, arising out of (a) any negligence or willful misconduct of CLIENT; (b) any breach by CLIENT of any warranties or other obligations hereunder; (c) all waste removal assistance rendered by McLAREN/HART to the extent McLAREN/HART followed, or provided a subcontractor to follow, the current established waste removal practices applicable in the locality in which the services are being rendered; (d) any condition existing at the Site prior to the arrival of McLAREN/HART of which McLAREN/HART had no actual knowledge or over which McLAREN/HART had no control; or (e) any misrepresentations by CLIENT that result in the improper disposition of a hazardous substance.

10. LIMITATION OF LIABILITY: **Notwithstanding any other language in this contract, in no event will the total and aggregate liability of McLAREN/HART exceed: (1) one and a half times the contract amount, or (2) $1,000,000, whichever is less. CLIENT acknowledges that McLAREN/HART reports may contain additional limitations with regard to re-use and reliance on the stated results and conclusions. Neither party shall be liable to the other for incidental, special, exemplary, punitive or consequential damages, including, but not limited to, loss of profits or revenue, interference with business operations, or loss of tenants, lenders, investors or buyers or inability to use the property.**

11. STANDARD OF SERVICES AND WARRANTY: Services performed by McLAREN/HART under this Agreement shall be conducted in a manner consistent with that level of care and skill ordinarily exercised by members of the same profession currently practicing in the same locality under similar conditions. McLAREN/HART warrants that if any of its completed products or services fail to conform to the above professional standard, McLAREN/HART will, at its own expense, perform corrective services of the type originally performed as may be reasonably required to correct such defects, of which McLAREN/HART is notified in writing within six months of the substantial completion of services or delivery of product. No other representation, express or implied, and no warranty or guarantee is included or intended in this Agreement, or in any report, opinion, document or otherwise.

12. NON-DISCLOSURE AGREEMENT: McLAREN/HART will keep confidential all CLIENT furnished data and reports generated hereunder and will not disclose such information to any third parties without CLIENT authorization. CLIENT acknowledges that dissemination or reuse of McLAREN/HART reports or data outside the scope and intent of this Agreement will be at CLIENT's sole risk and liability. The technical and pricing information contained in any proposal submitted by McLAREN/HART hereunder, or any addendum thereto, is to be considered confidential and proprietary, and shall not be released, disclosed, or otherwise made available to any third party without the express written consent of McLAREN/HART.

13. RIGHTS IN DATA: Any reports, documents or findings that are presented or delivered to CLIENT in complete or partial fulfillment of this agreement shall become the property of CLIENT. CLIENT agrees that any patentable or copyrightable concepts, data or software developed by McLAREN/HART as a direct or indirect consequence of services rendered hereunder are the sole and exclusive property of McLAREN/HART. CLIENT shall have unlimited rights and use of all data or software developed under contract to CLIENT.

14. CHANGES: The CLIENT may at any time, by written order, and within the general scope of this contract, make changes to the Services called for hereunder. If any such change causes an increase or decrease in the cost of, or the time required for, the performance of any part of the work under this Agreement, an equitable adjustment shall be made in the contract price or delivery schedule, or both, and the Agreement shall be modified in writing accordingly. In addition, McLAREN/HART shall be entitled to an equitable adjustment for any changed conditions, delays, or directions by the CLIENT which cause an increase to the cost of or the time required for the performance of any part of the work under this contract, whether or not directed in writing by the CLIENT. McLAREN/HART will endeavor to submit a claim for adjustment under this clause within thirty (30) days from the date the change notification was received from CLIENT or from the date McLAREN/HART first had knowledge of the change. McLAREN/HART shall have no obligation to perform the changed work until a mutually agreeable adjustment is reached and executed in writing by both parties. Commencement by McLAREN/HART of changed work with the knowledge of the CLIENT prior to a mutual agreement on an equitable adjustment shall not prejudice McLAREN/HART's rights to an equitable adjustment for such work. Failure to reach a mutual agreement on any adjustment hereunder after good faith efforts to do so shall constitute a dispute under Paragraph 17 of these Terms and Conditions.

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15. **DELAYS/FORCE MAJEURE:** Neither party shall be deemed in default of this Agreement to the extent that any delay or failure in the performance of its obligations (other than payment obligations for services rendered) results from any causes beyond its reasonable control and without its fault or negligence. Examples of such causes include, but are not limited to (1) Acts of God or the public enemy, (2) Acts of the Government in either its sovereign or contractual capacity, (3) fires, (4) floods, (5) epidemics, (6) quarantine restrictions, (7) strikes, (8) embargoes, (9) earthquakes and (10) unusually severe weather.

16. **TERMINATION:** Either CLIENT or McLAREN/HART may terminate this Agreement without cause and for its own convenience given seven (7) days written notice. CLIENT will be liable, regardless of contract type, for all costs expended by McLAREN/HART through the date such written termination notice is received by McLAREN/HART, (as well as any excess costs to copy and deliver finished or partially finished data to CLIENT, and all costs of implementing the termination and arriving at settlement thereof, with CLIENT, including all costs of settling and paying claims arising out of subcontracts hereunder), along with associated administrative burden and profit.

    Any termination of this Agreement by CLIENT for a material failure to perform may be exercised only if McLAREN/HART does not initiate corrective action within thirty (30) days (or more if authorized in writing by the CLIENT) after receipt of the notice from the CLIENT specifying the failure. McLAREN/HART's liability shall be limited to the reasonable costs incurred by the CLIENT in excess of the contract price (as that price stood at the time f termination) for completion of the scope of work in effect at the time of the termination. In the event of termination for any reason the parties shall enter into good faith negotiations to arrive at a fair and reasonable quantification of the liabilities set forth in this paragraph. Failure to agree on such a quantification of liability shall be deemed a dispute under Paragraph 17 of these Terms and Conditions.

17. **DISPUTES:** All claims, disputes, and other matters in question between the parties arising out of or relating to this Agreement or the breach thereof, shall be addressed in the following manner. The parties shall enter into good faith negotiations to reach an equitable settlement. If a good faith settlement cannot be reached, the parties may agree to select a method of dispute resolution other than litigation, such as, arbitration, mediation, mini trial, or other cost effective methods of alternative dispute resolution. In the event that the parties are unable to agree on a method of dispute resolution other than litigation, suit may be brought in a court located nearest the applicable McLAREN/HART office involved with the dispute. Should it be necessary for either party to initiate legal proceedings to resolve disputes under this Agreement, the prevailing party shall be entitled to all costs and expenses, including reasonable attorneys' fees, incurred in such proceedings. Should McLAREN/HART initiate collection proceedings to collect amounts owed hereunder, the added costs of such collection shall be paid by CLIENT.

18. **INDEPENDENT CONTRACTOR:** McLAREN/HART is and shall perform its services under this Agreement as an independent contractor and not as the CLIENT's agent, partner, or joint venture. McLAREN/HART is employed to render professional services only, and any payments made by CLIENT are compensation solely for such services rendered. McLAREN/HART cannot sign waste manifests on behalf of CLIENT and only CLIENT can direct the disposition of CLIENT's hazardous waste. McLAREN/HART's review or supervision of work prepared or performed by other individuals or firms employed by CLIENT shall not relieve those individuals or firms of complete responsibility for the adequacy of their work.

19. **CONFORMANCE WITH LAW:** The validity, performance and construction of this Agreement shall be governed and interpreted in accordance with the laws of the state where the majority of the services are being provided.

20. **ASSIGNMENT:** There shall be no assignment of the rights or obligations in this agreement by either party without the written consent of the other party and any assignment absent such consent shall be null and void, and shall render the corresponding duties and obligations of the other party null and void.

21. **ENTIRE AGREEMENT:** This Agreement along with McLAREN/HART's proposal, referenced above, contains the entire agreement and understanding between the parties hereto with respect to the subject services and shall not be varied in its terms by any previous communications, negotiations and agreements, whether oral or written, between the parties with respect to such subject matter, and no addition to or modification or waiver of any provision of this Agreement shall be binding on either party unless made in writing and executed by McLAREN/HART and a duly authorized agent of CLIENT. If any portion of this agreement is held invalid or unenforceable, any remaining portion shall continue in full force and effect.

22. **ACCEPTANCE:** This proposal becomes a binding contract on the terms set forth herein when accepted by CLIENT by giving McLAREN/HART formal written acknowledgment hereof. **IT IS A CONDITION OF THIS PROPOSAL THAT ANY PROVISIONS, WRITTEN OR OTHERWISE, CONTAINED IN ANY ACKNOWLEDGEMENT HEREOF, WHICH ARE INCONSISTENT WITH OR IN ADDITION TO THE TERMS AND CONDITIONS HEREIN CONTAINED, AND ANY ALTERATIONS HERETO, SHALL HAVE NO FORCE OR EFFECT, AND THAT CLIENT BY SUCH ACCEPTANCE THEREBY AGREES THAT ANY SUCH PROVISIONS OR ANY SUCH ALTERATIONS SHALL NOT CONSTITUTE ANY PART OF THE CONTRACT RESULTING FROM ITS ACCEPTANCE OF THIS PROPOSAL, UNLESS A MUTUALLY AGREEABLE REVISION TO THESE TERMS IS AGREED TO BY THE PARTIES.**

[END]

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