

Chemical Industry Institute of Toxicology



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President**

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December 7, 1995

Dr. Hashmukh C. Shah
Manager, Vinyl Chloride Panel
Chemical Manufacturers Association
2501 M Street, N.W.
Washington, DC 20037

Dear Dr. Shah:

The Chemical Industry Institute of Toxicology (CIIT) with our partner, Research Triangle Institute (RTI), is pleased to provide one original and one bound copy of a technical and cost proposal in response to the Chemical Manufacturer Association's (CMA) request addressed on November 15, 1995 to Dr. Rochelle Tyl at the Research Triangle Institute. Our bid is for a Vinyl Chloride Combined Inhalation Two-Generation Reproduction and Developmental Toxicity Study in CD Rats.

Our study proposals related to the developmental toxicity of vinyl chloride in rats and reproductive toxicity of vinyl chloride in rats represent a joint partnership with our colleagues at the Research Triangle Institute (RTI). RTI will serve as the CIIT Subcontractor for these two studies. These two research proposals build upon the respective strengths of both organizations. We are confident that high quality data sets will emerge from the partnership between CIIT and RTI. For the submitted research proposals CIIT should be considered to be the Contractor.

CIIT has carefully considered the costs associated with the conduct of these studies. The lump sum, fixed price for the project is \$520,824.

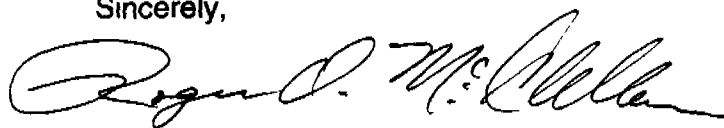
In closing, let me note that my colleagues at both CIIT and RTI are very enthusiastic about the opportunity to carry out this important research for CMA. The proposed vinyl chloride work is closely related to CIIT's ongoing research in inhalation developmental and reproductive toxicology. Dr. Frank Welsch, the proposed study director, has extensive experience in developmental toxicology. Dr. Rochelle Tyl, the co-study director who is now at RTI, has had extensive experience conducting inhalation studies concerned with developmental/reproduction/fertility effects. Dr. Brian Wong, who will be responsible for overseeing the inhalation exposures, is an experienced inhalation toxicologist. We are confident that this team of experienced investigators at CIIT and RTI will carry out the proposed research in an exemplary manner.

CMA 119914

Dr. Hasmukh C. Shah
December 7, 1995
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If you should have questions on any of the submitted technical and cost proposals, please call me at (919) 558-1202, or Dr. James Bond at (919) 558-1327. My colleagues and I appreciate the opportunity to present this proposal and look forward to carrying out a meritorious research effort on behalf of the CMA.

Sincerely,

A handwritten signature in black ink, appearing to read "Roger O. McClellan". The signature is fluid and cursive, with the first name "Roger" being more prominent.

Roger O. McClellan, D.V.M.
President

FW:ROM:ksm

Enclosures: Two (2) Technical and Cost Proposals

cc: Dr. James Bond
Dr. Fred Miller
Mr. Dave Althaus

CMA 119915

**CHEMICAL INDUSTRY INSTITUTE OF TOXICOLOGY
RESPONSE TO REQUEST FOR PROPOSAL FROM
THE CHEMICAL MANUFACTURERS ASSOCIATION
FOR
A VINYL CHLORIDE COMBINED INHALATION
REPRODUCTION AND DEVELOPMENTAL TOXICITY
STUDY IN CD RATS**

Submitted on behalf of the Chemical Industry Institute of Toxicology



Roger O. McClellan, D.V.M.
President

12/7/95
Date

Restricted Distribution and Use

CMA 119916

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1.0 SUBJECT

The Chemical Manufacturers Association has requested a technical and cost proposal to conduct an inhalation toxicology study with vinyl chloride (monochloroethylene; vinyl chloride monomer). There are two purposes of the proposed studies. One is to conduct a developmental toxicity study in CD rats. The second objective is to perform a Two-Generation Reproduction and Fertility Effects Study in CD rats. Both studies will be conducted in accordance with the Food and Drug Administration (FDA) Good Laboratory Practice Regulations for NonClinical Studies (FDA, 1988), the EPA TSCA Good Laboratory Practice Standards (EPA, 1990), the OECD Good Laboratory Practice Procedures (OECD, 1982), and the Standard Operating Procedures of The Toxicology Research Laboratory of The Dow Chemical Company.

Test protocols will follow the new draft EPA Health Effects Test Guidelines OPPTS 870.3700 (Developmental toxicity study) and EPA Health Effects Test Guidelines OPPTS 870.3800 (Reproduction and fertility effects) and will be conducted in accordance with EPA's Good Laboratory Practice Regulations (40 CFR Part 792) and quality control procedures to ensure valid test data of high quality. For each animal test, well-accepted approaches will be used to quarantine and screen animals prior to testing, uniquely identify animals placed on test, and randomly assign animals to test groups.

The inhalation exposures will be conducted at CIIT, and all test animals will be housed at CIIT throughout the duration of the in-life portions of the studies. All animals test protocols will be reviewed by both the CIIT and RTI Institutional Animal Care and Use Committees. All studies involving animals are conducted in AAALAC accredited facilities.

However, all studies will be done in very close collaboration and task sharing with the scientific and support staff at the Center for Life Sciences and Toxicology of the Research Triangle Institute (RTI) that is located in close proximity to CIIT. A complete description of the evaluations to be conducted by RTI can be found in the Appendix #1.

In each study, animals will be exposed to vinyl chloride gas in inhalation chambers of appropriate aerodynamic design to sustain a dynamic air flow of 12 to 15 air changes per hour to ensure an oxygen content of 19 percent and to deliver an evenly distributed exposure atmosphere. Studies for chamber uniformity of vinyl chloride concentration will be performed prior to the initiation of animal exposures. The cage placement pattern will be changed weekly in a predetermined manner within each chamber to compensate for possible, but undetected, variations in chamber exposure conditions. Chamber temperature and relative humidity will be maintained at $22 \pm 2^{\circ}\text{C}$ and 40 to 60 percent, respectively. During the exposure period, vinyl chloride concentrations will be verified at least hourly by sweeping breathing zone air to an infrared spectrophotometer calibrated for vinyl chloride measurement. During non-exposure

periods, water and food will be available to the animals ad libitum. Food and water will be withheld during the 6-hour exposure periods.

2.0 VINYL CHLORIDE INHALATION DEVELOPMENTAL TOXICITY STUDY: WORK PLAN

2.1 Objectives

The objectives of the combined inhalation two-generation reproduction and developmental toxicity study outlined in this protocol are to evaluate the effects of the test material on parental toxicity, reproductive capability, *in utero* development, and neonatal growth and survival in rats. This study will be conducted to meet the requirements of the Environmental Protection Agency (EPA): TSCA Test Guidelines (EPA, 1985), the Organisation for Economic Co-Operation and Development (OECD), Guidelines, for Testing of Chemicals, Section 4: Health Effects, (OECD, 1981), and the European Economic Community (EEC), Methods for the Determination of Toxicity (EEC, 1988).

2.2 Research Tasks

Test protocols will follow the new draft EPA OPPTS Health Effects Test Guidelines. For each animal test, well accepted approaches will be used to quarantine and screen animals prior to testing.

The time frame during which the definitive developmental toxicity study will be conducted and the task sharing between CIIT and RTI staff are described in the Proposed Experiment Schedule as well as in Figure 1 and Table 1, respectively (Appendix #5). This study will be conducted while the inhalation exposures for the Two-Generation Reproductive Toxicity are ongoing in the first prebreeding exposure phase (Figure 1, Appendix #5).

2.3 Data Treatment

Data will be recorded, condensed, tabulated, summarized and statistically processed according to standard procedures. Final reports will document the test design, exposure conditions, measurement parameters, in-life study results, necropsy results (e.g., gross lesions), and fetal evaluations. Reports will describe the results in terms of statistical and apparent biological significance, and they will attempt to identify causative mechanisms for the compound-related effects found.

The biological and statistical analyses of all the data generated during the course of the proposed studies will be performed with the Teratology Standard Operating Procedures of RTI (Appendix #3).

3.0 VINYL CHLORIDE INHALATION REPRODUCTIVE TOXICITY STUDY: WORK PLAN

3.1 Objectives

The objectives of this study will be to conduct an inhalation study in rats of both sexes; three (3) concentrations of vinyl chloride and a control group will be evaluated.

3.2 Research Tasks

Test protocols will follow the EPA OPPS Health Effects Test Guidelines. For each animal shipment standardized tests on sentinel animals and well accepted approaches will be used to quarantine and screen animals prior to testing.

The time frame for the definitive reproductive toxicity study (July 1996 - November 1997) is described in the Proposed Experiment Schedule and also in Figure 1 (Appendix #5). The task sharing between CIIT and RTI staff is detailed in Table 2 (Appendix #5). The definitive reproduction/fertility study will require about 18 months to complete and is projected to start with purchase of the animals in July 1996 and actual inhalation exposure beginning immediately after quarantine as shown in Figure 1 (Appendix #5). The task sharing for this study is described in Table 2 (Appendix #5).

3.3 Data Treatment

Data will be recorded, condensed, tabulated, summarized and statistically processed according to standard procedures. Final reports will document the test design, exposure conditions, measurement parameters, in-life study results, necropsy results (e.g., gross lesions), and histopathology findings definitive study. Reports will describe the results in terms of statistical and apparent biological significance, and they will attempt to identify causative mechanisms for the compound-related effects found.

The biological and statistical analyses of all the data generated during the course of the proposed studies will be performed with the Teratology Standard Operating Procedures of RTI (Appendix #3).

4.0 MANPOWER REQUIREMENTS

4.1 Manpower CIIT

Key Personnel	Labor Category
Scientist	
Frank Welsch	Developmental Toxicologist
Brian Wong	Inhalation Scientist
Jeff Everitt	Pathologist/Lab Animal Veterinarian
Paul Ross	Animal Care Supervisor
Technical	
TBA	Animal Care Technician
TBA	Inhalation Technician

4.2 Manpower RTI

Key Personnel	Labor Category
Scientist	
Rochelle Tyl	Developmental Toxicologist
Patricia Fail	Reproductive Endocrinologist
John Seely	Veterinary Pathologist
Technical	
Melissa Marr	Reproductive and Developmental Toxicology Lab. Supervisor
Christina Myers	Reproductive and Developmental Toxicology Specialist
Tsai-Ying Chang	Histotechnologist
TBA	Animal Care Technicians
Stephanie Taulbee	Quality Assurance

5.0 PROGRAM DURATION

5.1 Proposed Experimental Schedule

5.1.A. Definitive Developmental Toxicity Study in Rats

The Definitive Developmental Toxicity Study in Rats will be conducted as illustrated in the Proposed Experiment Schedule below and in Figure 1 (Appendix #5). Rats will be purchased in August 1996 and mated as soon as the quarantine is completed. Three different inhalation exposures concentrations will be used, 10, 100, 1100 ppm and a chamber air control. The inhalation phase will be completed in September 1996.

5.1.B. Definitive Reproductive Toxicity Study in Rats

The Definitive Reproductive Toxicity Study in Rats will start with quarantine of the test animals in July 1996 as illustrated in the Proposed Experimental Schedule below. The in life phase will require 41 weeks (Figure 1, Appendix #5).

The proposed experimental sequence is described in the schedule below:

VINYL CHLORIDE INHALATION DEVELOPMENTAL AND REPRODUCTION/FERTILITY PROPOSAL

Proposed Experimental Schedule

DATE		
Year	Month	Event
1. Definitive Developmental Toxicity Study In Rats		
1996	April	Protocol to Sponsor
	July/August	Order Animals
	August	Initiate Exposures
	September	Complete In-Life Phase
1997	January	Submission of Draft Report
	March	Final Report
2. Definitive Reproductive Toxicity Study In Rats		
1996	April	Protocol to Sponsor
	July	Order Animals
	August	Initiate Exposures
1997	April	Complete In-Life Phase
	September	Submission of Draft Final Report
	November	Final Report

The study designs proposed by RTI and CIIT are as follows:

5.2 Definitive Developmental Toxicity Study in Rats

A total of 170 virgin female rats will be purchased and mated 1:1 to the males in the CIIT breeding colony. The date of insemination (dropped copulation plug, vaginal sperm or vaginal copulation plug) will be designated gestational day (gd) 0. A total of 100 sperm-positive female rats ("dams") will be employed in four groups (three chemical and one vehicle control groups), 25 dams per group. The rats will be exposed to vinyl chloride by inhalation six hours per day, on gd 6 through 19 at exposure concentrations of 0, 10, 100 and 1100 ppm (as provided in Dow's protocol). These exposures will occur during the first prebreed exposure period of F0 animals in the two-generation study. Clinical observations will be documented daily (twice daily during the exposure period), and dams will be weighed on gd 0, 6, 9, 12, 15, 18, 19 and 20. Feed consumption will be documented on individually housed dams on a schedule corresponding to times of maternal body weight collection. At scheduled sacrifice on gd 20 at RTI, dams will be weighed and maternal liver and gravid uterine weights will be recorded. Maternal gross lesions will be retained in fixative. Ovarian corpora lutea will be counted and the status of uterine implantation sites will be recorded (live fetuses, dead fetuses, early and late resorptions). Any apparently nonpregnant uteri or uteri with apparent single horn pregnancies will be stained with ammonium sulfide to confirm pregnancy status and identify any early postimplantation pregnancy losses. All live fetuses will be counted, sexed, weighed and examined externally for malformations (including cleft palate) and variations; approximately 50% of the fetuses in each litter will be examined for visceral alterations, and decapitated and the heads fixed and decalcified for soft tissue craniofacial examinations (including the fetal brain). All fetuses will be eviscerated, cleared and stained with alizarin red S (for ossified bone) and alcian blue (for cartilaginous bone); intact fetuses (50% per litter) will be examined for skeletal malformations and variations. Placental weights will be recorded. A draft report will be submitted within four months of the last sacrifice date.

5.3 Definitive Reproductive Toxicity Study

This study is designed to conform to new draft OPPTS Testing Guidelines as requested. Route of administration will be inhalation exposure, six hours/day, five days/week during the F0 and F1 10-week prebreed exposure periods, and seven days/week during mating, gestation and lactation of F0 and F1 parental animals; exposure may also occur to F1 and F2 offspring during gestation via transplacental processes and/or during lactation by translactational transfer.

One hundred forty (140) weanling (4-5 week old) CD® (Sprague-Dawley) male and female rats will be ordered. During the two-week quarantine, 5/sex will be evaluated for serum viral antibody titers and parasites; all will be examined by the CIIT veterinarian. At study start, 120 rats per sex, designated the F0 generation, will be distributed by randomization procedures stratified by body weight into four groups, 30 animals/sex/group (with exposure concentrations of 0, 10, 100 and 1100 ppm as specified in the Dow protocol). Animals will be exposed by inhalation, six hours per day, five days/week for 10 weeks. The 10 weeks (70 days) corresponds to one complete spermatogenic cycle and allows for any bioaccumulation. Animals will be weighed weekly. Feed consumption will also be measured weekly; clinical observations will be recorded twice daily, morning and afternoon.

Seven weeks into the 10-week F0 prebreed exposure period, the F0 females will be subjected to daily vaginal lavages for three weeks to determine estrous cyclicity. The three weeks correspond to at least three complete estrous cycles (which last 4-5 days in rats). They will be weighed, and feed consumption and clinical observations documented as described above for males.

At the end of the 10 week F0 prebreed exposure period, animals will be cohabited 1:1 (one male:one female) within groups for two weeks (as specified by OPPTS; re-pairing unsuccessful animals within groups after one week of cohabitation will not be done.) Exposures for both sexes will continue now at seven days/week; body weights will be taken weekly in males and weekly until insemination occurs in females. Feed consumption will not be recorded during cohabitation. Females will be checked daily for dropped or vaginal copulation plug and/or vaginal sperm by lavage and for estrous cyclicity during the two-week mating period or until evidence of insemination. The date of evidence of copulation will be designated gd 0. F0 males will be necropsied at the end of the gestation period with reproductive organs, liver, kidneys (2), spleen, thymus, adrenal glands (2), brain, and pituitary weighed and retained (one testis per male will be frozen for spermatid head counts, one testis will be fixed for histopathologic examination), and any gross lesions retained in fixative. Sperm assessments (number, morphology and motility) will be done from the cauda epididymis and homogenization-resistant testicular sperm will be evaluated from the testis from all F0 males at necropsy. Presumed pregnant females (dams) will be weighed and feed consumption measured on gd 0, 7, 14, and 20.

Dams usually litter on gd 22 or 23; the date of parturition will be designated as postnatal day (pnd) 0. Offspring of F0 parents will be designated the F1 generation. Pregnant females will not be exposed on gd 20 through pnd 4, with exposure to the dams resuming on pnd 5. Dams and their litters will be weighed and feed consumption measured on pnd 0, 4, 7, 14, and 21. Pups will be counted, sexed, weighed individually and examined externally also on pnd 0, 4, 7, 14 and 21. Anogenital distance will be recorded for all pups on pnd 0. On pnd 4, litters will be randomly

culled to eight pups with as equal a sex ratio as possible; natural litters of eight or less pups will not be culled. On pnd 21, each litter will be weaned; the F0 dams will then be necropsied (with stage of estrus at sacrifice documented) with reproductive tract, liver, kidneys (2), spleen, thymus, adrenal glands (2), brain, and pituitary weighed and retained, and any gross lesions retained in fixative. A total of 30 F1 weanlings per sex per group will be randomly selected from the maximum number of litters as F1 parents for the next generation. They will be exposed to vinyl chloride by inhalation, five days/week, beginning on pnd 22 (the day after weaning); when the last litter is weaned, the formal 10-week prebreed exposure period for the F1 animals will begin (the youngest pups will be 13 weeks old at the end of this exposure period). In addition, three F1 weanlings/sex/litter will be necropsied with reproductive organs, liver, kidneys (2), spleen, thymus, adrenal glands (2), brain, and pituitary weighed and retained, and any gross lesions retained in fixative. Remaining non-selected F1 weanlings will be examined externally and euthanized with the concurrence of the Sponsor. The date of acquisition of vaginal patency in females (pnd 28-45) and of preputial separation (pnd 35-50) in males will be recorded in the F1 pups selected as parents until all available pups have reached criterion.

At the end of the F1 10-week prebreed exposure period (with a three-week evaluation of F1 females for estrous cyclicity), mating, gestation and lactation (with pairing of non-sibling animals within groups) will be performed as described above for F0 animals. Necropsy of F1 parental animals will occur as described above for F0 parents. Offspring of F1 parents will be designated the F2 generation. At weaning of F2 litters, three F2 weanlings/sex/litter will be necropsied as described above for F1 weanlings; remaining unselected F2 weanlings will be examined externally and euthanized with concurrence of the Sponsor. Organs of F0 and F1 parental animals to be weighed (all groups) include ovaries (2), uterus, testes (2), epididymides (2), seminal vesicles (2) with coagulating glands, prostate, spleen, kidneys (2), liver, adrenal glands (2), thymus, brain and pituitary. Organs of these animals to be retained in fixative include the above (one testis per male will be frozen for homogenization-resistant spermatid head count), plus cervix and vagina in females. Organs of the top dose and control group parental animals, plus any animals in mid and low dose groups which die on study or were not reproductively successful, will be examined histologically. Ovaries from F0 and F1 parental females (high dose and control) will have five (5) sections taken at least 100 μ m apart from the inner third of each ovary with enumeration of the total number of primordial follicles from these 10 sections per female. F0 and F1 parental males (all doses) will have sperm assessments (number, morphology, motility) performed from the cauda epididymis and homogenization-resistant spermatid head counts performed from the testis. Organs of F1 and F2 weanlings will be retained in fixative for possible subsequent histopathologic assessment if gross examination and/or organ weights indicate possible treatment-related effects. A draft final report will be submitted within five months of the last necropsy date.

5.4. Quality Assurance Schedule

**SCHEDULE FOR QUALITY ASSURANCE AUDITS AND INSPECTIONS
ON PROPOSED VINYL CHLORIDE INHALATION DEVELOPMENTAL TOXICITY AND
REPRODUCTION/FERTILITY STUDY**

AUDIT/INSPECTION* OF	TENTATIVE QUALITY ASSURANCE UNIT ACTIVITIES PROPOSED TO OCCUR DURING MONTH(s)
1. Definitive Developmental Toxicity Study In Rats	
Protocols	April, 1996
In-Life Critical Phases	August/September, 1996
Review Raw Data/Draft Report	January 1997
Final Report	March, 1997
2. Reproduction/Fertility Definitive Study In Rats	
Protocol	April, 1996
In-Life Critical Phases	July 1996 - April 1997
Review Raw Data/Draft Report	September, 1997
Final Report	November, 1997

* In-Life Critical Phases will be identified from the written protocols

5.5 Proposed Payment Schedule

Projected Date	Project Benchmarks	Payment Schedule
4/30/96	Submission of protocol for developmental toxicity and reproduction studies	5%
11/1/96	Completion of in-life portion of developmental toxicity study	10%
11/15/96	Completion of 20 weeks of in-life portion of reproductive/fertility study	20%
1/17/97	Submission of draft final report on developmental toxicity study	5%
3/31/97	Submission of final report on developmental toxicity study	5%
4/30/97	Completion of in-life portion of reproductive/fertility study	25%
9/15/97	Submission of draft final report on reproductive/fertility study	25%
11/30/97	Submission of final report for reproductive/fertility study	5%

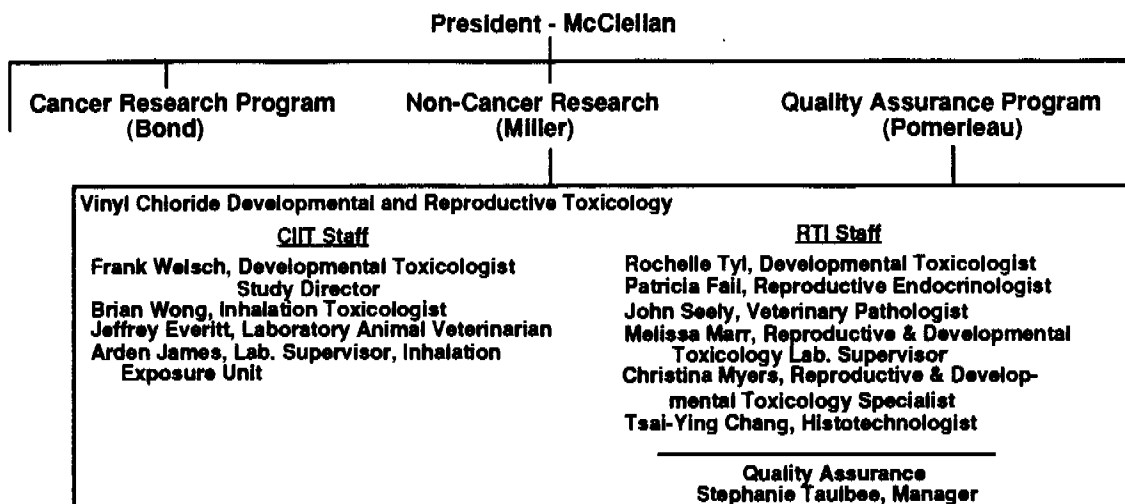
6.0 COST

6.1 Projected Budget

CIIT proposes to conduct an inhalation developmental toxicity study in rats with vinyl chloride and an inhalation reproductive/fertility study in rats with vinyl chloride for a total lump sum price of \$520,824.

7.0 PROJECT ADMINISTRATION

7.1 Internal Organization Chart



7.2 Biographical Sketches of Key CIIT Personnel

Frank Welsch

Brian Wong

Jeffrey Everitt

Patricia O'Brien Pomerleau

FRANK WELSCH

Senior Scientist, Chemical Industry Institute of Toxicology

EDUCATION:

1959	Graduation from High School (Gymnasium) in Berlin
1959-64	Veterinary student at the Veterinary Schools in Munich, Vienna and Berlin
1964	State Board examination and graduation as veterinarian in Berlin
1965	Licensed veterinarian after fulfillment of internship requirements
1965	Promotion to Doctor of Veterinary Medicine (Dr. med. vet.) after presentation of doctoral thesis to the Veterinary School of Freie Universität, Berlin

PROFESSIONAL LICENSURE AND CERTIFICATION:

American Board of Toxicology, Diplomate

EXPERIENCE:

1993-present	Senior Scientist, Head of the Teratology Laboratory, Chemical Industry Institute of Toxicology, Research Triangle Park, North Carolina
1982-1992	Scientist, Department of Experimental Pathology and Toxicology, Head of the Teratology Laboratory, Chemical Industry Institute of Toxicology, Research Triangle Park, North Carolina
1971-82	Instructor to Full Professor, Department of Pharmacology and Toxicology, Michigan State University, East Lansing, Michigan
1977-78	Visiting Scientist, Institute of Toxicology and Embryopharmacology, Freie Universität Berlin, Berlin, Germany (Sabbatical leave)
1968-71	Research Associate, Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee
1967-68	Research Associate, Laboratory of Neurochemistry, Columbia University College of Physicians and Surgeons, New York City
1964-67	Research Associate, Department of Veterinary Pharmacology and Toxicology, School of Veterinary Medicine, Freie Universität Berlin

ACADEMIC AFFILIATIONS:

1982-present	Adjunct Professor, School of Veterinary Medicine, North Carolina State University, Raleigh, NC
1982-present	Adjunct Associate Professor, Curriculum in Toxicology, University of North Carolina, Chapel Hill, NC
1992-present	Adjunct Professor, Integrated Toxicology Program, Duke University, Durham, NC

ADVISORY APPOINTMENTS:

1986-1992	Member, Science Review Panel for Health Research, Environmental Protection Agency
1987-1991	Member, Review Committee on Health Effects - Electric Power Research Institute

Welsch, Frank

1987-1991	Member, Developmental Toxicity Profile Organizing Committee, Environmental Protection Agency
1987-1992	Member, Reproductive and Developmental Toxicology Program Review Subcommittee of the National Toxicology Program Board of Scientific Counselors
1994	Ad Hoc Reviewer for NIH Grants, NIH Toxicology Study Section, Subcommittee 2, Bethesda, MD, February 16-18.
1994	Member of the Scientific Organizing Committee, International Symposium on Glycol Ethers, Nancy, France, April 19-22.

EDITORIAL APPOINTMENTS:

1982-86	Associate Editor, Teratology
1989-94	Member, Editorial Board for Fundamental and Applied Toxicology
1989-	Associate Editor, Teratogenesis, Carcinogenesis, and Mutagenesis
1989-	Member, Editorial Board for Archives of Toxicology
1992-	Member, Editorial Board for Toxicology
1995-	Section Editor, Teratology

PROFESSIONAL AFFILIATIONS:

Society of Toxicology
American Society for Pharmacology and Experimental Therapeutics
The Teratology Society
American Association for the Advancement of Science
German Society for Pharmacology and Toxicology
European Teratology Society

AWARDS AND HONORS:

1977-78	Alexander von Humboldt Foundation Research Fellowship Award (sabbatical leave)
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AREAS OF INTEREST

Placenta function; placental drug transfer and metabolism, effect of drugs on placenta and fetus.
Effects of pregnancy on pharmacokinetics and pharmacodynamics, physiologically based pharmacokinetics; extrapolation between species and to humans, risk assessment.
Role of chemical metabolism for the expression of embryotoxicity/teratogenicity and to explain species differences in embryotoxic response.
Teratology including manifestations of the effects of prenatal exposure to chemicals at the gross structural, micromorphological and biochemical/functional level.
Development of new testing methods to predict developmental toxicity hazard.
Application of in vitro methods involving embryo organ culture and whole embryo culture to study mechanisms of teratogenesis.

SELECTED PUBLICATIONS:

Dr. Welsch is author or co-author of more than 70 peer-reviewed publications. Among recent publications are:

Welsch, Frank

Sleet, R.B., J.A. John-Greene and F. Welsch: "The Relationship of Embryotoxicity to Disposition of 2-Methoxyethanol in Mice," Toxicol. Appl. Pharmacol. **93**: 195-207 (1988).

Stedman, D.B. and F. Welsch: "Inhibition of DNA Synthesis in Whole Embryo Culture by 2-Methoxyacetic Acid and Attenuation of the Effects by Simple Physiological Compounds," Toxicol. Lett. **45**: 111-117 (1989).

Mebus, C.A. and F. Welsch: "The Possible Role of One-Carbon Moieties in 2-Methoxyethanol and 2-Methoxyacetic Acid-Induced Developmental Toxicity," Toxicol. Appl. Pharmacol. **99**: 98-109 (1989).

Mebus, C.A., F. Welsch and P.K. Working: "Attenuation of 2-Methoxyethanol-Induced Testicular Toxicity by Simple Physiological Compounds," Toxicol. Appl. Pharmacol. **99**: 110-121 (1989).

Kavlock, R.J., J.A. Greene, G.L. Kimmell, R.E. Morrissey, E. Owens, J.M. Rogers, T.W. Sadler, H.F. Stack, M.D. Waters, and F. Welsch: "Activity Profiles of Developmental Toxicity: Design Considerations and Pilot Implementation," Teratology **33**: 159-185 (1991).

Schwetz, B.A., R.E. Morrissey, F. Welsch, and R.A. Kavlock: "In Vitro Teratology," Environ. Health Perspect. **94**: 265-268.

Mebus, C.A., D.O. Clarke, D.B. Stedman, and F. Welsch: "2-Methoxyethanol Metabolism in Pregnant CD-1 Mice and Embryos," Toxicol. Appl. Pharmacol. **112**: 87-94 (1992).

Clarke, D.O., J.M. Duignan, and F. Welsch: "2-Methoxyacetic Acid Dosimetry-Teratogenicity Relationships in CD-1 Mice Exposed to 2-Methoxyethanol," Toxicol. Appl. Pharmacol. **114**: 77-87 (1992).

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Clarke, D.O., B.A. Elswick, F. Welsch, and R. Conolly: "Pharmacokinetics of 2-Methoxyethanol and 2-Methoxyacetic Acid in the Pregnant Mouse: A Physiologically-Based Mathematical Model," Toxicol. Appl. Pharmacol. **121**: 239-252 (1993).

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Terry, K.K., B.A. Elswick, F. Welsch, and R.B. Conolly: "A Physiologically-Based Pharmacokinetic Model Describing 2-Methoxyacetic Acid in the Pregnant Mouse," Proceedings of International Symposium on Health Hazards of Glycol Ethers, Nancy, France, Occup. Hyg., in press (1995).

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BOOK CHAPTERS (selected from 9 book chapters)

Welsch, F.: "Disruption of Cell-Cell Channels as an Event Common to the Potential Mechanism of Action of Some Chemicals with Activity in Teratogenesis and Carcinogenesis," In Progress in Cancer Research and Therapy, Vol. 34, "Tumor Promoters: Biological Approaches for Mechanistic Studies and Assay Systems" (R. Langenbach, J.C. Barrett, and E. Elmore, eds.), Raven Press, pp. 113-130 (1988).

Welsch, F.: "Teratogens and Cell-to-Cell Communication," In "Cell Intercommunication" (W.C. De Mello, ed.), CRC Press, pp. 133-160 (1990).

Welsch, F.: "Short Term Methods of Assessing Developmental Toxicity Hazard: Status and Critical Evaluation," In: "Issues and Reviews in Teratology", Vol. 5 (H. Kalter, ed.), Plenum Press, pp. 115-153 (1990).

BRIAN A. WONG

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EDUCATION:

Ph.D., Environmental Engineering Science, California Institute of Technology, Pasadena, CA.
1991.

M.S., Environmental Engineering Science, California Institute of Technology, Pasadena, CA,
1984.

B.S., Chemistry, Harvey Mudd College, Claremont, CA, 1974.

EXPERIENCE:

1991-present Scientist I, Chemical Industry Institute of Toxicology, Research Triangle
Park, NC.

1983-1991 Research Assistant, California Institute of Technology, Pasadena, CA.

1979-1983 Senior Research Technologist, Inhalation Toxicology Research Institute,
Albuquerque, NM.

1974-1979 Laboratory Technologist, Inhalation Toxicology Research Institute,
Albuquerque, NM.

PROFESSIONAL AFFILIATIONS:

American Association for the Advancement of Science
Association for the Advancement of Aerosol Research

AREAS OF INTEREST:

Aerosols - physical, optical, thermodynamic properties. Combustion - kinetics and chemistry of coal combustion and fly ash formation. Inhalation Toxicology - biological effects of air pollution, hazardous wastes. Atmospheric Chemistry - air pollution formation, abatement. Cleanroom Technology - application of aerosol science to cleanrooms.

PEER REVIEWED PUBLICATIONS:

1. G. J. Moser, B. A. Wong, D. C. Wolf, O. R. Moss and T. L. Goldsworthy (1995). Comparative short-term effects of methyl tertiary butyl ether and unleaded gasoline vapor in female B6C3F1 mice. Toxicol. Appl. Pharmacol., submitted as of 4/95.
2. R. J. Han, O. R. Moss and B. A. Wong (1995). Application of an analytic solution of the mass transfer equation to the case of forced convective flow around a cylindrical and a spherical particle. J. Aerosol Sci., in press.
3. T. R. Gelzleichter, E. Bermudez, J. B. Mangum, B. A. Wong, O. R. Moss, and J. I. Everitt. (1995). Pulmonary and pleural responses in Fischer-344 rats following short-term inhalation of a carcinogenic synthetic vitreous fiber. II. Pathobiologic responses. Fundam. Appl. Toxicol., in press.
4. T. R. Gelzleichter, E. Bermudez, J. B. Mangum, B. A. Wong, J. I. Everitt, and O. R. Moss (1995). Quantitation of pulmonary and pleural fiber burdens in Fischer-344 rats following short-term inhalation of a carcinogenic synthetic vitreous fiber. Fundam. Appl. Toxicol., in press.

Wong, Brian A.

5. D. C. Dorman, B. Bolon, M. F. Struve, K. M. D. LaPerle, B. A. Wong, B. Elswick, and F. Welsch (1995). The role of formate in methanol-induced exencephaly in CD-1 mice. *Teratology* 52: 30-40.
6. D. C. Dorman, B. A. Wong, M. F. Struve, R. A. James, K. M. D. LaPerle, M. W. Marshall, and B. Bolon (1995). Development of a mouse whole-body exposure system from a directed-flow, rat nose-only system. *Inhalation Toxicol.*, in press as of 5/95.
7. C. D. Brown, B. A. Wong, and T. R. Fennell (1995). In vivo and in vitro kinetics of ethylene oxide metabolism in rats and mice. *Toxicol. Appl. Pharmacol.*, Submitted as of 8/94.
8. B. A. Wong, G. R. Gavalas, and R. C. Flagan (1995). The effect of char formation temperature on the densification of a bituminous coal char during gasification. *Energy and Fuels* 9: 493-499.
9. B. A. Wong, G. R. Gavalas, and R. C. Flagan (1995). Laser ignition of levitated char particles. *Energy and Fuels* 9: 484-492.
10. A. A. J. J. L. Rutten, E. Bermudez, J. B. Mangum, B. A. Wong, O. R. Moss, and J. I. Everitt (1994). Mesothelial cell proliferation induced by intrapleural instillation of man-made fibers in rats and hamsters. *Fundam. Appl. Toxicol.* 23: 107-116.
11. R. J. Han, O. R. Moss, and B. A. Wong (1994). Airborne fiber separation by electrophoresis and dielectrophoresis. *Aerosol Sci. Technol.* 21: 241-258.
12. J. I. Everitt, E. Bermudez, J. B. Mangum, B. A. Wong, O. R. Moss, D. Janszen, and A. A. J. J. L. Rutten (1994). Pleural lesions in Syrian hamsters and Fischer-344 rats following intrapleural instillation of man-made ceramic or glass fibers. *Toxicol. Pathol.* 22: 229-236.

BOOK CHAPTERS, MONOGRAPHS AND PROCEEDINGS:

1. B. A. Wong (1995). Generation and characterization of gases and vapors. In: *Concepts in Inhalation Toxicology*, R. O. McClellan and R. Henderson, eds., Taylor and Francis, Washington, DC, in press as of 2-95.
2. T. R. Gelzleichter, J. B. Mangum, E. Bermudez, B. A. Wong, O. R. Moss and J. I. Everitt (1995). Pulmonary and pleural leukocytes from F344 rats produce elevated levels of fibronectin following inhalation of refractory ceramic fibers. *Proceedings, 5th International Inhalation Symposium, Hannover, Germany, February 19-24, 1995.*
3. O. R. Moss, B. A. Wong, and B. Asgharian. (1994). Bimodal bivariate log-normal distributions in the application of inhalation toxicology specific to the measurement of fiber and particle dosimetry. In: *Toxic and Carcinogenic Effects of Solid Particles in the Respiratory Tract.*, U. Mohr, D. L. Dungworth, J. L. Mauderly, and G. Oberdoerster, eds., ILSI Press, Washington, DC, p. 623-628.
4. F. J. Miller, S. Anjilvel, B. Asgharian, J. S. Kimbell, E. Bermudez, M. N. Godo, T. R. Gelzleichter, B. A. Wong, and O. R. Moss (1994). A strategy for combining experimental, large-scale, and site-specific models to determine fiber deposition in animals and humans. In: *Toxic and Carcinogenic Effects of Solid Particles in the Respiratory Tract.*, U. Mohr, D. L. Dungworth, J. L. Mauderly, and G. Oberdoerster, eds., ILSI Press, Washington, DC, p. 619-622.

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5. J. I. Everitt, E. Bermudez, J. Mangum, B. Wong, F. Miller and O. Moss (1994). Acute pleural response of hamsters and rats to inhaled ceramic fibers. In: Toxic and Carcinogenic Effects of Solid Particles in the Respiratory Tract., U. Mohr, D. L. Dungworth, J. L. Mauderly, and G. Oberdoerster, eds., ILSI Press, Washington, DC, p. 599-602.
6. A. Rutten, E. Bermudez, J. Mangum, B. Wong, O. Moss and J. Everitt (1994). Pleural pathology in hamsters and rats exposed to instilled man-made vitreous fibers. In: Toxic and Carcinogenic Effects of Solid Particles in the Respiratory Tract., U. Mohr, D. L. Dungworth, J. L. Mauderly, and G. Oberdoerster, eds., ILSI Press, Washington, DC, p. 595-598.

JEFFREY EVERITT

Scientist II, Chemical Industry Institute of Toxicology

EDUCATION:

Biological Science, Cornell University, Ithaca, NY, 1973

D.V.M., Veterinary Medicine, Cornell University, Ithaca, NY, 1977

Certificate of Residency, Veterinary Pathology, University of Pennsylvania, Philadelphia, PA, 1980

PROFESSIONAL LICENSES AND SPECIALTY CERTIFICATIONS:

Licensed to practice veterinary medicine in NY, PA, and NC

American College of Veterinary Pathologists, Diplomate, 1982

American College of Laboratory Animal Medicine, Diplomate, 1988

EXPERIENCE:

1993-present	Scientist II, Department of Experimental Pathology and Toxicology, Chemical Industry Institute of Toxicology, Research Triangle Park, NC
1985-1993	Scientist I, Department of Experimental Pathology and Toxicology, Chemical Industry Institute of Toxicology, Research Triangle Park, NC
1981-1985	Teaching Associate, Department of Pathobiology, College of Veterinary Medicine, University of Illinois, Urbana, IL
1980-1981	Lecturer in Pathology, University of Pennsylvania School of Veterinary Medicine, New Bolton Center, Kennett Square, PA
1977-1980	Resident in Pathology, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA

ACADEMIC AFFILIATIONS:

1987-Present Adjunct Assistant Professor of Pathology, School of Veterinary Medicine, North Carolina State University, Raleigh, NC

ADVISORY POSITIONS:

Member, Pathology Working Groups, National Toxicology Program, NIEHS, Research Triangle Park, NC (1985 -)

Member, NIH DRG Special Study Section (1992, 1993)

Ad hoc consultant in laboratory animal medicine for the American Association for the Accreditation of Laboratory Animal Care (AAALAC) (1990-present)

Ad hoc consultant in laboratory animal medicine, Veterans Administration, Department of Defense (1994-present)

Everitt, Jeff

PROFESSIONAL AFFILIATIONS:

American Veterinary Medical Association
American College of Veterinary Pathologists
Co-chairperson Pulmonary Specialty Group, 1991; Chairman, 1992
United States and Canadian Academy of Pathology
American Association for Laboratory Animal Science
Committee on Public Policy, 1987-1990; Chairman, 1991
Abstract Review Committee, 1989
District IV Meeting Chairman, 1989-1990
American Society of Laboratory Animal Practitioners
Society of Toxicologic Pathologists
American College of Laboratory Animal Medicine
North Carolina Chapter of the Society of Toxicology
North Carolina Academy of Laboratory Animal Medicine
Board of Directors, 1989-1990
President-elect, 1992; President, 1993
Association of Primate Veterinarians
Association of American Pathologists

HONORS:

NSF Undergraduate Research Program, Jackson Laboratory, 1972
Anna Olafson Sussex Pathology Award, Cornell University, 1976
Co-Author 1992 Research Paper of the Year published in Fundam. Appl. Toxicol.

AREAS OF INTEREST:

Comparative Medicine (Laboratory animal issues in toxicology studies)
Toxicologic Pathology (Lung and kidney carcinogenesis)
Pulmonary Toxicology (Pathobiology of fiber-induced disease)

SELECTED PUBLICATIONS:

Dr. Everitt is the author or co-author of more than 60 publications.

Hesterberg, T.W., Boreiko, C.J., Maness, S.C., Iglehart, J.D., Mangum, J.B. Everitt, J.I.: Carcinogen-induced unscheduled DNA synthesis (UDS) in xenotransplanted human tracheobronchial epithelium: Comparison with rat tracheal epithelium. *Carcinogenesis* 9:467-472, 1988.

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Monticello, T.M., Morgan, K.T., Everitt, J.I., Popp, J.A.: Effects of formaldehyde gas on the respiratory tract of rhesus monkeys: Pathology and cell proliferation. *Am. J. Pathol.* 134:515-527, 1989.

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Casanova, M., Morgan, K.T., Steinhagen, W.H., Everitt, J.I., Popp, J.A., Heck, H.A.: Covalent binding of inhaled formaldehyde to DNA in the respiratory tract of rhesus monkeys: pharmacokinetics, rat-to-monkey interspecies scaling and extrapolation to man. *Fundam. Appl. Tox.* **17**:409-428, 1991.

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Funaki, K., Everitt, J., Bermudez, E., Walker, C.: Trisomy of rat chromosome 1 associated with mesothelial cell transformation. *Cancer Res.* **51**:4059-4066, 1991.

Kinnula, V.L., Everitt, J.I., Whorton, A.R., Crapo, J.D.: Hydrogen peroxide production by freshly isolated alveolar type II cells, alveolar macrophages and cultured endothelial cells. *Am. J. Physiol.* **261**:L84-91, 1991.

Walker, C., Funaki, K., Knudson, A.G., and Everitt, J.: The Eker rat: A model for hereditary renal cell carcinoma. In, Advances in Gene Technology: The Molecular Biology of Human Genetic Disease, Vol. 1, F. Ahmed, H. Bialy, S. Black, R. Howell, et al., Miami Bio/Technology Winter Symposia, 1990, 103, 1991.

Walker, C., Everitt, J., Freed, J.J., Knudson, Jr., A.G., Whiteley, L.O.: Altered expression of rat TGF-alpha in hereditary renal cell carcinoma. *Cancer Res.* **51**:2973-2978, 1991.

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Farris, G.M., Everitt, J.I., Irons, R.D., Popp, J.A.: Carcinogenicity of inhaled benzene in CBA mice. *Fundam. Appl. Toxicol.* 20:503-507, 1993.

Cattley, R.C., Everitt, J.I., Gross, E.A., Moss, O.R., Hamm, T.E., Jr., and Popp, J.A.: Carcinogenicity and toxicity of inhaled nitrobenzene in B6C3F1 mice and F344 and CD rats. *Fundam. Appl. Toxicol.* 22:328-340, 1994.

Walker, C., Rutten, F., Yuan, C., Pass, H., Mew, D.M., and Everitt, J.: Wilms' tumor suppressor gene expression in rat and human mesothelioma. *Cancer Res.* 54:3101-3106, 1994.

Everitt, J.I., Bermudez, E., Mangum, J.B., Wong, B., Moss, O.R., Janszen, D., and Rutten, A.A.J.L.: Pleural lesions in Syrian hamsters and Fischer-344 rats following intrapleural instillation of man-made fibers. *Toxicol. Pathol.* 22(3):229-236, 1994.

Rutten, A.A.J.J.L., Bermudez, E., Mangum, J.B., Wong, B., Moss, O.R., and Everitt, J.I.: Mesothelial cell proliferation induced by intrapleural instillation of man-made fibers in rats and hamsters. *Fundam. Appl. Toxicol.* 23:107-116, 1994.

Hard, G.C., Long, P.H., Crissman, J.W., Everitt, J.I., Yano, B.L., and Bertram, T.A.: Atypical tubule hyperplasia and renal tubule tumors in conventional rats on 90-day toxicity studies. *Toxicol. Pathol.* (in press).

Everitt, Jeff

Horesovsky, G., Ginsler, J., Everitt, J., and Walker, C.: Increased susceptibility to in vitro transformation of cells carrying the Eker susceptibility mutation. Carcinogenesis (in press).

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EDUCATION:

Bachelor of Science, Biology, Marymount College, Tarrytown, NY, 1964.

Master of Science, Cellular Biology, Magna Cum Laude, Fairleigh Dickinson University, Teaneck, NJ, 1967.

EXPERIENCE:

1990-present	Quality Assurance Manager, Chemical Industry Institute of Toxicology, Research Triangle Park, NC
1986-1990	Manager, Quality Assurance, Rhône-Poulenc Rorer Pharmaceuticals Inc., Rhône-Poulenc Rorer Central Research, Horsham, PA
1971-1986	Revlon Health Care Group (acquired by Rorer Pharmaceuticals, Inc. in 1985), USV Laboratories, Tuckahoe, NY
1983-1986	Manager, Quality Assurance Unit, [FDA Good Laboratory Practice (GLP) regulations]
1979-1983	Head, Quality Assurance Unit, [FDA Good Laboratory Practice (GLP) regulations]
1974-1979	Senior Biochemist and Assistant Radiation Safety Officer
1971-1974	Biochemist and Assistant Radiation Safety Officer
1970-1971	Chemical Technician in Cancer Research, Farbenfabriken Bayer Research Center, Wuppertal, Germany
1968-1970	Research Associate in Cancer Research, Yale Medical School, Department of Pharmacology and Medicine, New Haven, CT
1964-1968	Research Assistant in Viral Oncology, Charles Pfizer and Company, Inc., The John L. Smith Memorial for Cancer Research, Maywood, NJ

ADVISORY APPOINTMENTS:

Member of Scientific Review Panel for Proposals submitted to the National Institute of Health, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC. Reviewed (8/94) proposals submitted to NIEHS for conduct of studies of the toxic and carcinogenic potential of selected chemicals in laboratory animals.

Member of Scientific Review Panel for Proposals submitted to the National Institute of Health, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC. Reviewed (4/94) proposal submitted to NIEHS for the Archives for the National Toxicology Program (NTP).

Member of Scientific Review Panel for Proposals submitted to the National Institute of Health, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC. Reviewed proposals (5/92) submitted to NIEHS for conduct of studies of the toxic and carcinogenic potential of selected chemicals in laboratory animals.

Member of Scientific Review Group for National Toxicology Program Proposals submitted to the National Institute of Health, National Institute of Environmental Health Sciences, Research Triangle Park, NC. Reviewed proposals (8/86) for scientific and technical merit in response to "Good Laboratory Practice Compliance and Data Auditing Support Resource" program.

Pomerleau, Patricia

EDITORIAL APPOINTMENTS:

Member, Board of Publications, Society of Quality Assurance (1990-1993)
Society of Quality Assurance Newsletter, Editor-in-Chief (1992-1993)

PROFESSIONAL AFFILIATIONS:

North Carolina Society of Toxicology (1994-present)
North Carolina Quality Assurance Discussion Group (NCQADG)
 Past President (1994)
 President (1991 - 1993)
 QA in Basic Research Committee (1991 - present)
Society of Quality Assurance (SQA)
 President (1994-1995)
 Vice President (1993-1994) and Chairperson 1994 SQA Annual Meeting Planning Committee
 Board of Publications, Chairperson (1993, appointed; member, 1990-1993)
 Regulatory Review Committee (1992 - present)
 Total Quality Specialty Section (1993 - present)
 Historical Committee (1991 - present)
 Articles of Incorporation and By-Laws Committee (1989 - 1991)
 Education Committee (1989 - 1990)
 Nominating Committee (1988)
 Ethics and Membership Committee (1984 - 1986)
 Planning Committee (1983)
Carolina Society of Environmental Toxicology and Chemistry (SETAC) (1992 - present)
American Society for Quality Control (1986 - present)
Drug Information Association (1986 - present)
Pharmaceutical Manufacturer's Association, Bioresearch Monitoring Subcommittee (1988 - 1991)

AREAS OF INTEREST

Research interests include the application of Quality Assurance (QA) principles in the research environment. Ms. O'Brien Pomerleau has major expertise in Quality Assurance (QA) and Good Laboratory Practice (GLP) regulations and has planned, coordinated, and managed a QA group for auditing preclinical studies performed under the GLP regulations. Interest also includes Total Quality Management (TQM) principles, toxicology research, analytical methodology in biochemistry and drug metabolism of pharmaceuticals and their metabolites, radiation safety, cancer research, with focus on chemotherapeutic agents, and tissue culture including Rauscher and Moloney viruses and Burkett's lymphoma cells.

PUBLICATIONS:

O'Brien Pomerleau, P.: Performing Good Laboratory Practice Regulation Studies in a Traditionally Non-GLP Facility: Quality Assurance: Good Pract. Regulation Law 3(2): 149-155, 1994.

O'Brien Pomerleau, P. and Benson, B.: Looking Back - A History of Progress, Society of Quality Assurance, Qual. Assurance: Good Pract. Regulat. Law 3(1): 110-116, 1994.

O'Brien Pomerleau, P.: Total Quality Crossword Puzzle Answers, Society of QA Newsletter, QA Classifieds 4(3): 2, 1993.

Pomerleau, Patricia

O'Brien Pomerleau, P.: Quality Assurance (QA) Perspective on Compliance Education through Participational QA Programs, Qual. Assur.: Good Pract. Regulat. Law 2(2): 197-205, 1993.

O'Brien Pomerleau, P.: Total Quality Crossword Puzzle, Society of QA Newsletter 8(2): 6-7, 1993.

O'Brien Pomerleau, P., McClellan, R.O., Popp, J.: Quality Assurance at CIIT, CIIT Activities 12(2): 1-5, 1992.

O'Brien Pomerleau, P.: Who Are the Players and What Do They Bring to the Science and Compliance Teams? (American College of Toxicology and Society of Quality Assurance Joint Symposium - Science and Compliance: Study Management Through Total Quality), J. Am. Coll. Toxicol. 10(3): 377, 1991.

O'Brien Pomerleau, P.: GLP Crossword Puzzle, Society of QA Newsletter 6(2): 9, 1991.

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Grebow, P., O'Brien, P., Weinryb, I.: Stability of Tryptophan in Human Gastric Fluid, Proceedings of the Second International Meeting on Tryptophan Metabolism: Biochemistry, Pathology, and Regulation, 1977.

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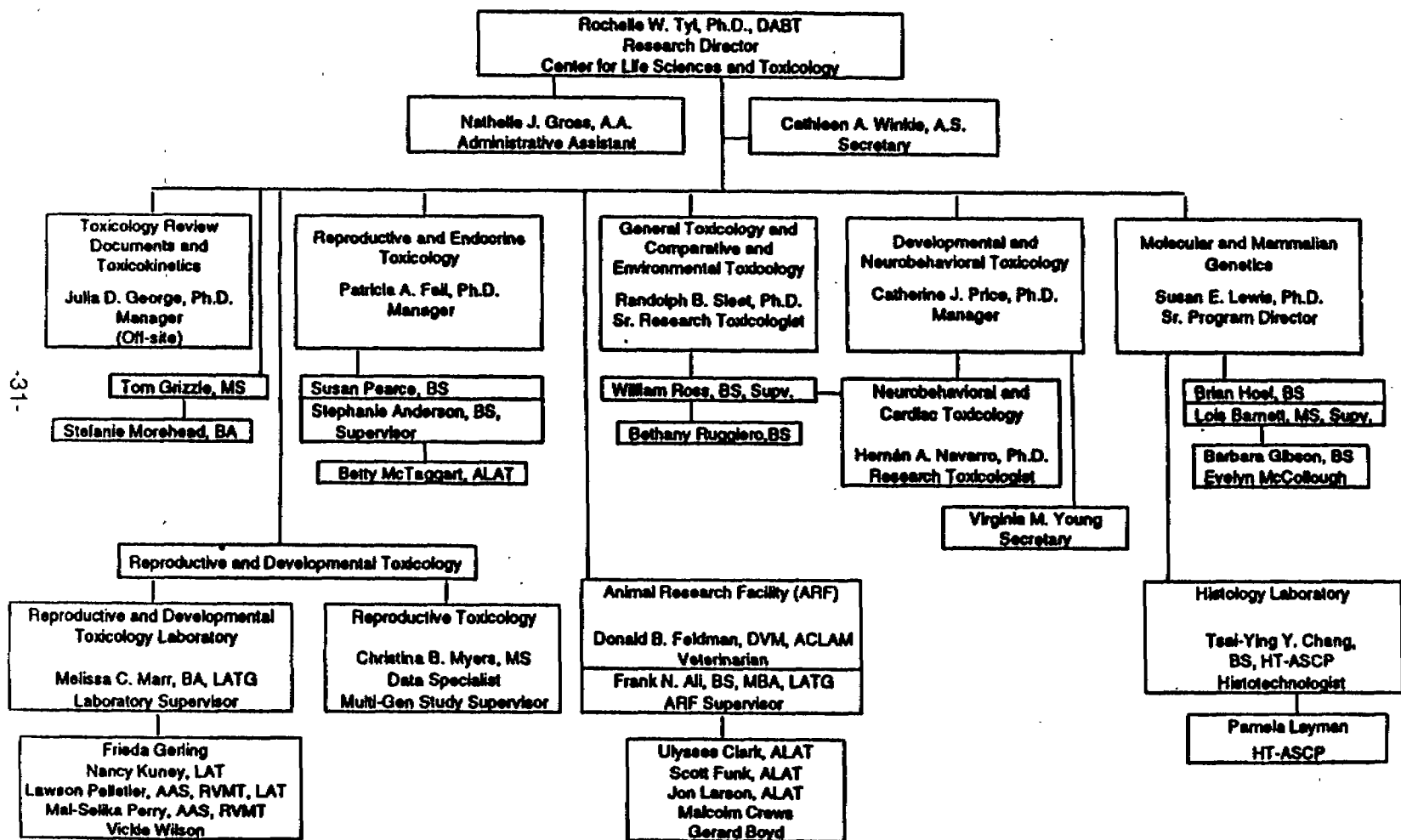
PRESENTATIONS

Ms. Pomerleau is a frequent speaker at meetings of professional societies and in workshops concerned with Quality Assurance.

CMA 119946

Organizational Structure of the Center for Life Sciences and Toxicology

7.3 Internal Organization Chart RTI



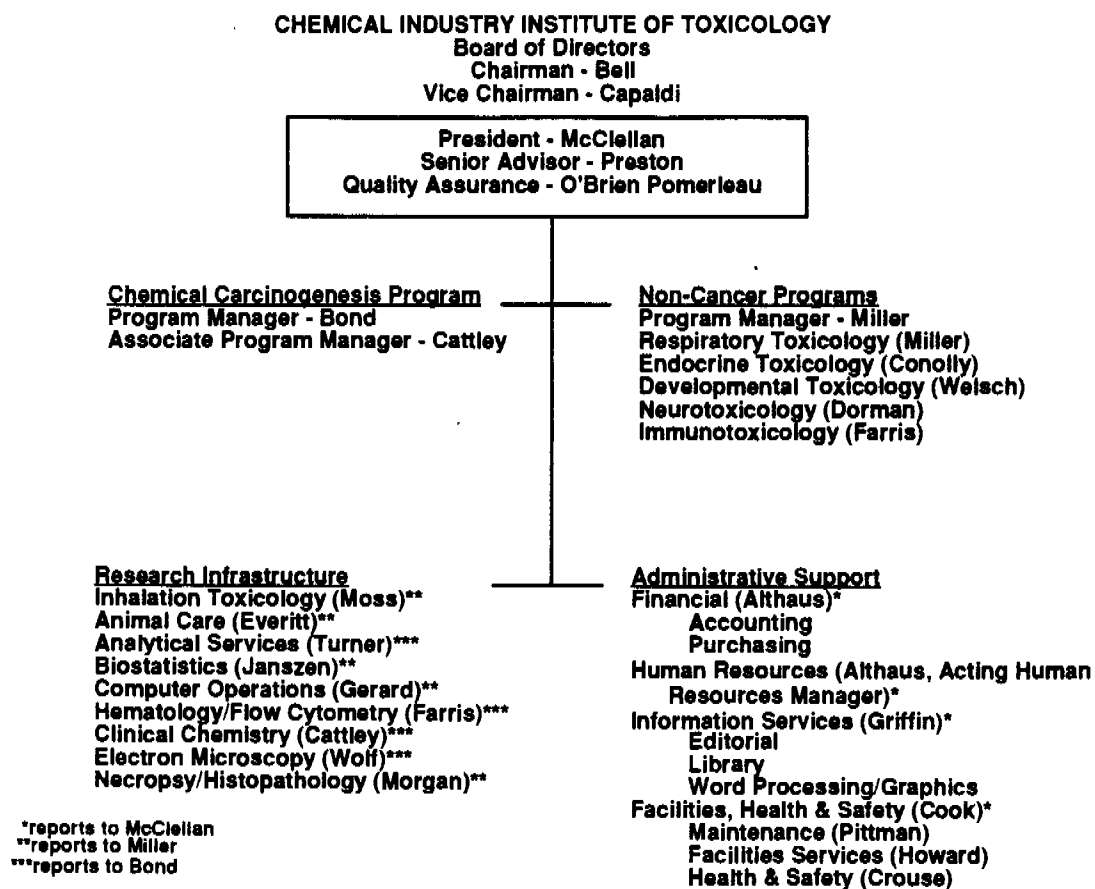
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7.4 Biographical Sketches RTI

Detailed curricula vitae can be found in Appendix #2.

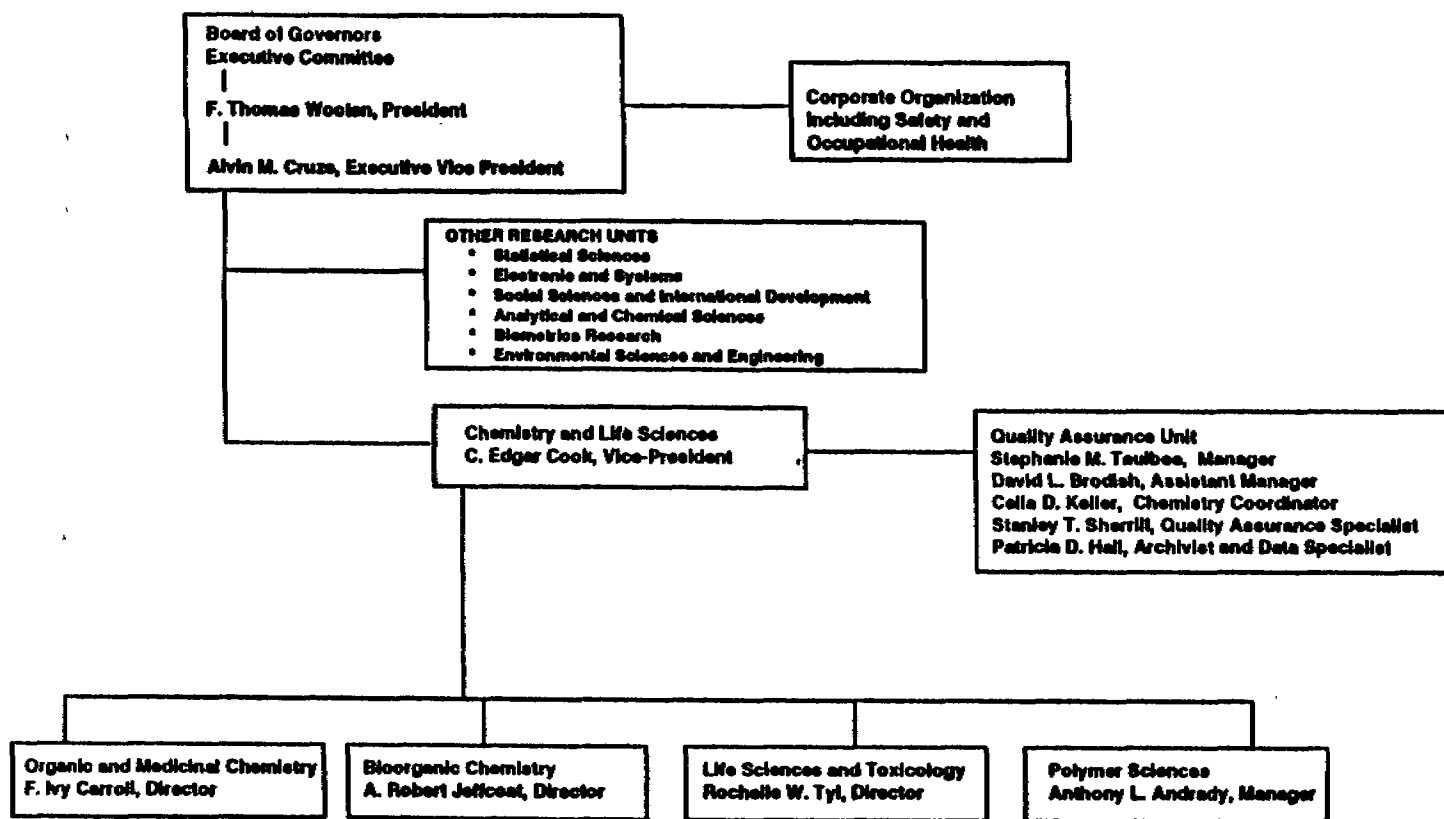
8.0 CORPORATE QUALIFICATIONS

8.1. Organization Chart CIIT



Research Triangle Institute - Research Organization

Last Update: January 18, 1995



8.3 Statement of CIIT Liability Insurance Coverage

The Chemical Industry Institute of Toxicology is insured against general liability claims by the Hartford Insurance Companies up to a limit of \$1,000,000 per each occurrence. Additional "Umbrella" coverage is in force, also provided by the Hartford, which raises the coverage an additional \$4,000,000.

8.4 Research Facilities at CIIT

General Facility

CIIT is housed in a modern 94,000 square feet laboratory and office facility that includes a molecular biology core facility, neurotoxicology laboratory, and specifically equipped facilities for electron microscopy, nuclear magnetic resonance spectroscopy, mass spectrometry, liquid and gas chromatography, radioisotope analysis, histology, necropsy, animal housing (including primates), and inhalation toxicology. An active animal care and use program supports acute and chronic studies. Complete computer capabilities including both VAX mainframe, and personal computers are available. The Institute's library provides access to multiple computer-based literature research systems.

Animal Facilities

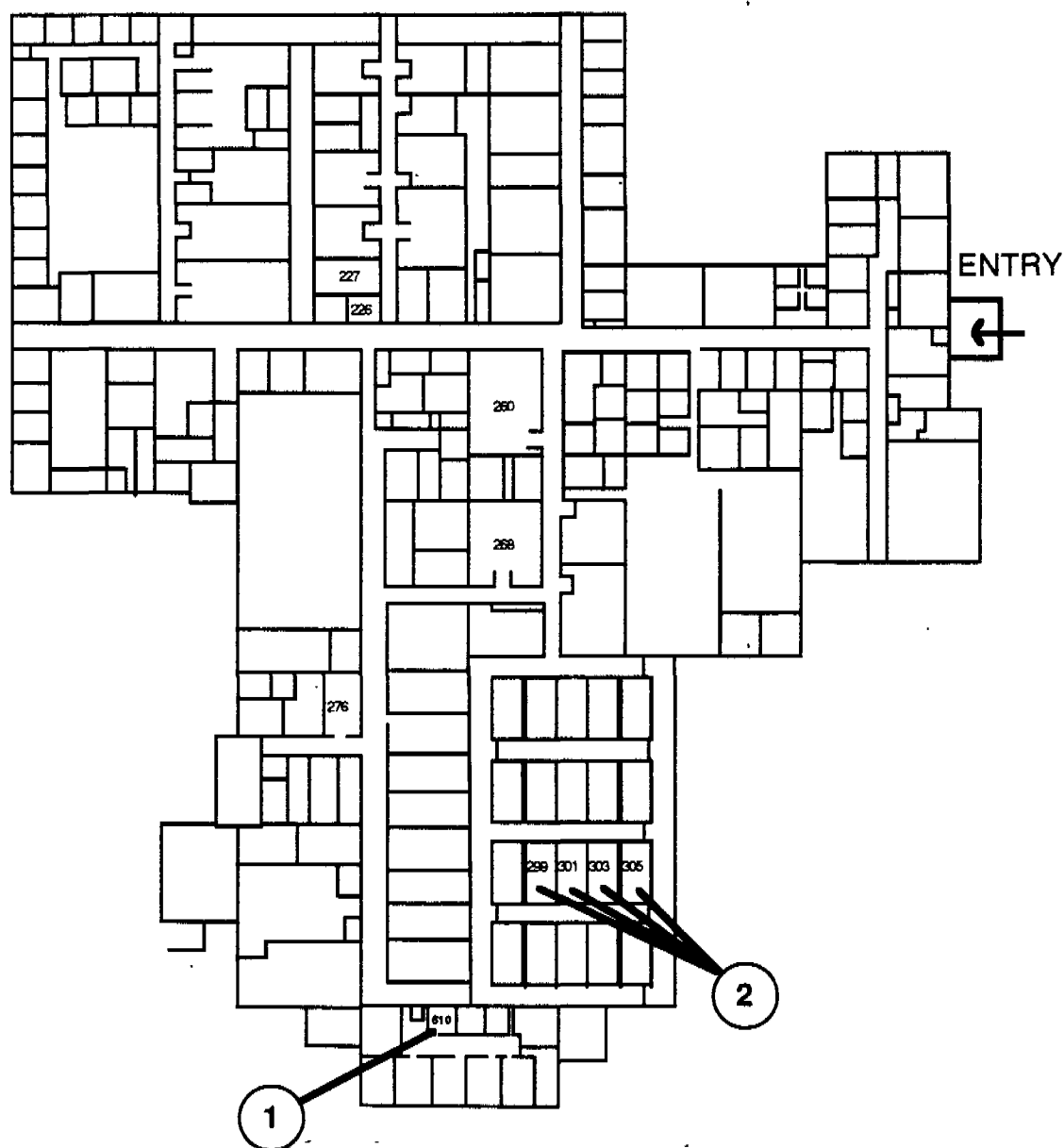
The AAALAC accredited animal facility at CIIT is supervised by a veterinarian board certified in laboratory animal medicine. The facility is a centralized barrier facility with an average daily census of several thousand rodents and a few nonhuman primates. The facility has specialized equipment and standard operating procedures which permits animal exposures to hazardous chemical agents and maintains the animals in controlled monitored environments under disease free conditions. The rodent area contains nine mass air displacement rooms (Hazleton Bioclean); 20 conventional rooms containing inhalation chambers; a metabolism room; a chemical procedures room with three chemical containment hoods; a diet preparation room with twin steel blenders with hood and glovebox containment; and typical support areas such as clean and dirty cage wash areas with two rack and one tunnel washer (Girton). There is complete redundancy in the HVAC equipment and a fully automated and computerized environmental monitoring system (Andover Infiniti-System). CIIT procures rodents from specialized vendor areas and maintains one of the most extensive surveillance programs in the laboratory animal field. All animal clinical observations are conducted by a fully certified and experienced cadre of animal care technicians. The CIIT animal care unit has experience in the conduct of acute subchronic, and long-term bioassays using a variety of stocks and strains of laboratory rodents. All clinical observations and body weights are computer recorded using PATH-TOX software (Xybion Corporation). The CIIT animal facility is a seven day/week operation.

Inhalation Exposure Facilities

CIIT's inhalation exposure facilities contain equipment capable of handling a wide variety of animal inhalation studies. These range from long-term whole body exposures to brief nose-only exposures to radioactive materials. A staff of five attends the daily operations of the facility with oversight from three doctoral-degreed scientists. Major equipment includes 20 stainless steel 8 m³ inhalation chambers with a capacity of up to 300 rats, several smaller 1 m³ exposure chambers (e.g., Lab Products H-1000 inhalation chambers with up to 96 rat capacity), multiple nose-only towers, and a variety of other specialty inhalation chambers. Environmental parameters (e.g., temperature, relative humidity, airflow, and static pressure) inside the large chambers are automatically controlled, and the data logged and reported by a building management system. Whole body exposures may be automated for increased efficiency. The staff is fully trained in the use of a variety of analytical techniques such as gas chromatography and infrared spectrometry to monitor exposures.

Schematic of CIIT Facility

- 1. Animal Acclimation
- 2. Inhalation Exposure Chambers



8.5. General Facilities at RTI

The facilities of the Reproductive and Developmental Toxicology Wing at RTI are described in Appendix #4.

8.6. Background and Related Research Capabilities

8.6.1 Quality Assurance at CIIT

It is the policy of the Chemical Industry Institute of Toxicology (CIIT) and the Research Triangle Institute (RTI) to use quality assurance procedures to assure that all data generated in research is of known, documented high quality. The on-site CIIT Quality Assurance office and archive are composed of modern office spaces equipped with two Macintosh personal computers for word processing and database capture, filing cabinets, as well as a Space Saver high-density mobile storage system and slide drawers. This space is secured through a CIIT card-access building control as well as locked authorization access into the Quality Assurance/archive area. CIIT's on-site facility is complemented by a secure off-site location for archiving. The on-site RTI Quality Assurance office is composed of modern office spaces equipped with three Macintosh personal computers for word processing and database capture, as well as locked controlled access filing cabinets. The building at RTI has locked authorization access during non-business hours.

Specific aspects of the quality assurance and archival areas that relate to the proposed studies include the following capabilities. Full-time on-site Quality Assurance at CIIT and RTI will provide support for the proposed studies through protocol reviews, critical phase inspections, as well as study data and report audits. The results of Quality Assurance inspections and audits will be reported to the Study Director and to Management to assure appropriate follow-up action, if applicable. CIIT's controlled, secure archive capabilities will be available for the proposed study materials either as the studies are on-going or at the close of the proposed studies.

Built into the process of quality data generation is the standard practice of including quality control procedures into the data collection process. The quality criteria used include reproducibility, accuracy, appropriate sampling, and standardization of data collection. Well-written SOPs, which augment the study protocol, are used to document routine, critical procedures. Data audits are performed to evaluate and report to the study director any inconsistencies between the data collection or study conduct and the required study methods as described in the protocol, SOPs, and GLPs. The report audit evaluates the completeness and consistency of the final report and the raw data. A quality assurance review of study records is augmented by peer review processes that are part of the CIIT research program (e.g., extensive internal peer review of protocols, SOPs, abstracts, manuscripts, and presentations). All scientific information disseminated from CIIT is extensively reviewed internally before release.

8.6.2 Related Research Activities

The Chemical Industry Institute of Toxicology (CIIT) was founded in 1974 by a core group of 11 chemical companies to provide the scientific data necessary for making decisions about the safe use of chemicals. Since its inception, CIIT has established itself as a premier institute for the study of toxicologic disease and has gained an international reputation in the field of toxicology. CIIT's mission is to provide an improved scientific basis for understanding and assessing the potential adverse effects of chemicals, pharmaceuticals, and consumer products on human health. The Institute has over 30 full-time doctoral level staff scientists at CIIT with diverse expertise in toxicology, neurotoxicology, biochemistry, experimental pathology, molecular biology, inhalation toxicology, developmental toxicology, chemical engineering, extrapolation modeling, and biostatistics. The Institute's professional staff is complemented by over 25 postdoctoral fellows and a technical and support staff in excess of 100 individuals.

Approximately 60% of the Institute's resources are used to study chemical carcinogenesis. CIIT is developing methods for assessing the cancer-causing potential of chemicals through the in-depth study of key mechanisms of carcinogenicity. The Institute also has a strong program in respiratory toxicology, which seeks to understand species similarities and differences in mechanisms linking exposure, dose, and response for airborne substances. Small but productive programs in neurotoxicology, developmental toxicology, and immunotoxicology round out the Institute's research efforts. The scientific data generated reduce the uncertainties in chemical-specific risk assessments and make possible the use of risk assessment models that can be generalized across classes of compounds.

CIIT has a substantial research program that is investigating the toxicity of various fuels and fuel additives (e.g., methanol, MTBE, ETBE). Included in these studies are efforts to develop improved approaches to human risk assessment by extrapolating animal developmental toxicity data including mode of action information via physiologically based pharmacokinetic models of rodent gestation.

Appendix 1
Letter from Dr. Tyl,
December 4, 1995

RESEARCH TRIANGLE INSTITUTE



Chemistry and Life Sciences
Center for Life Sciences and Toxicology

December 4, 1995

Dr. James A. Bond
Chemical Industry Institute of Toxicology
P. O. Box 12137
6 Davis Drive
Research Triangle Park, NC 27709

RE: RTI B&P No.: P606-025

Dear Dr. Bond:

In response to our discussions concerning the collaboration of Research Triangle Institute (RTI) with CIIT in a submission to Dr. H. Shah of the Chemical Manufacturers Association for reproductive and developmental toxicity studies of inhaled vinyl chloride, RTI and I are pleased to submit the enclosed cost estimates for performing a definitive developmental toxicity study of inhaled vinyl chloride in CD (Sprague-Dawley) rats, and a definitive reproductive toxicity study of inhaled vinyl chloride in CD (Sprague-Dawley) rats. Detailed descriptions of the proposed study designs are presented below, based on the Dow protocol provided by Dr. Shah and the most recent OPPTS Testing guidelines (see below). The cost estimates are presented in the attached letter from Ms. C. S. Parker, RTI Senior Contracts Administrator, and include costs for RTI's portions of the two studies following the study designs detailed below. The studies would be performed under U.S. EPA (TSCA) GLPs (Good Laboratory Practice regulations) and the most recent draft OPPTS Health Effects Test Guidelines for Prenatal Developmental Toxicity Study (OPPTS 870.3700, August 11, 1995) and for Reproduction and Fertility Effects (OPPTS 870.3800, August 11, 1995).

As we have discussed, I would be Co-Study Director for both studies and the RTI Quality Assurance Unit (along with the CIIT QAU) would oversee protocols, performance of studies and reports.

The proposed study designs are as follows:

A. Proposed Study Designs

1. Definitive Developmental Toxicity Study in Rats

A total of 170 virgin female rats will be purchased and mated 1:1 to the males in the CIIT breeding colony. The date of insemination (dropped copulation plug, vaginal sperm or vaginal copulation plug) will be designated gestational day (gd) 0. A total of 100 sperm-positive female rats ("dams") will be employed in four groups (three chemical and one vehicle control groups), 25 dams per group. The rats will be exposed to vinyl chloride by inhalation six hours per day, on gd 6 through 19 at exposure concentrations of 0, 10, 100 and 1100 ppm (as provided in Dow's protocol). These exposures will occur during the first prebreed exposure period of F0 animals in the two-generation study. Clinical observations will be documented daily (twice daily during the exposure period), and dams will be weighed on gd 0, 6, 9, 12, 15, 18, 19 and 20. Feed consumption will be documented on individually housed dams on a schedule corresponding to times of maternal body weight collection. At scheduled sacrifice on gd 20 at RTI, dams will be weighed and maternal liver and gravid uterine weights will be recorded. Maternal gross lesions will be retained in fixative. Ovarian corpora lutea will be counted and the status of uterine implantation sites will be recorded (live fetuses, dead fetuses, early and late resorptions). Any apparently nonpregnant uteri or uteri with apparent single horn pregnancies will be stained with ammonium sulfide to confirm pregnancy status and identify any early postimplantation pregnancy losses. All live fetuses will be counted, sexed, weighed and examined externally for malformations (including cleft palate) and variations; approximately 50% of the fetuses in each litter will be examined for visceral alterations, and decapitated and the heads fixed and decalcified for soft tissue

craniofacial examinations (including the fetal brain). All fetuses will be eviscerated, cleared and stained with alizarin red S (for ossified bone) and alcian blue (for cartilaginous bone); intact fetuses (50% per litter) will be examined for skeletal malformations and variations. Placental weights will be recorded. A draft report will be submitted within four months of the last sacrifice date.

2. Definitive Reproductive Toxicity Study

This study is designed to conform to new draft OPPTS Testing Guidelines as requested. Route of administration will be inhalation exposure, six hours/day, five days/week during the F0 and F1 10-week prebreed exposure periods, and seven days/week during mating, gestation and lactation of F0 and F1 parental animals; exposure may also occur to F1 and F2 offspring during gestation via transplacental processes and/or during lactation by translactational transfer.

One hundred forty (140) weanling (4-5 week old) CD® (Sprague-Dawley) male and female rats will be ordered. During the two-week quarantine, 5/sex will be evaluated for serum viral antibody titers and parasites; all will be examined by the CIIT veterinarian. At study start, 120 rats per sex, designated the F0 generation, will be distributed by randomization procedures stratified by body weight into four groups, 30 animals/sex/group (with exposure concentrations of 0, 10, 100 and 1100 ppm as specified in the Dow protocol). Animals will be exposed by inhalation, six hours per day, five days/week for 10 weeks. The 10 weeks (70 days) corresponds to one complete spermatogenic cycle and allows for any bioaccumulation. Animals will be weighed weekly. Feed consumption will also be measured weekly; clinical observations will be recorded twice daily, morning and afternoon.

Seven weeks into the 10-week F0 prebreed exposure period, the F0 females will be subjected to daily vaginal lavages for three weeks to determine estrous cyclicity. The three weeks correspond to at least three complete estrous cycles (which last 4-5 days in rats). They will be weighed, and feed consumption and clinical observations documented as described above for males.

At the end of the 10 week F0 prebreed exposure period, animals will be cohabited 1:1 (one male:one female) within groups for two weeks (as specified by OPPTS; re-pairing unsuccessful animals within groups after one week of cohabitation will not be done.) Exposures for both sexes will continue now at seven days/week; body weights will be taken weekly in males and weekly until insemination occurs in females. Feed consumption will not be recorded during cohabitation. Females will be checked daily for dropped or vaginal copulation plug and/or vaginal sperm by lavage and for estrous cyclicity during the two-week mating period or until evidence of insemination. The date of evidence of copulation will be designated gd 0. F0 males will be necropsied at the end of the gestation period with reproductive organs, liver, kidneys (2), spleen, thymus, adrenal glands (2), brain, and pituitary weighed and retained (one testis per male will be frozen for spermatid head counts, one testis will be fixed for histopathologic examination), and any gross lesions retained in fixative. Sperm assessments (number, morphology and motility) will be done from the cauda epididymis and homogenization-resistant testicular sperm will be evaluated from the testis from all F0 males at necropsy. Presumed pregnant females (dams) will be weighed and feed consumption measured on gd 0, 7, 14, and 20.

Dams usually litter on gd 22 or 23; the date of parturition will be designated as postnatal day (pnd) 0. Offspring of F0 parents will be designated the F1 generation. Pregnant females will not be exposed on gd 20 through pnd 4, with exposure to the dams resuming on pnd 5. Dams and their litters will be weighed and feed consumption measured on pnd 0, 4, 7, 14, and 21. Pups will be counted, sexed, weighed individually and examined externally also on pnd 0, 4, 7, 14 and 21. Anogenital distance will be recorded for all pups on pnd 0. On pnd 4, litters will be randomly culled to eight pups with as equal a sex ratio as possible; natural litters of eight or less pups will not be culled. On pnd 21, each litter will be weaned; the F0 dams will then be necropsied (with stage of estrus at sacrifice documented) with reproductive tract, liver, kidneys (2), spleen, thymus, adrenal glands (2), brain, and pituitary weighed and retained, and any gross lesions retained in fixative. A total of 30 F1 weanlings per sex per group will be randomly selected from the maximum number of litters as F1 parents for the next generation.

They will be exposed to vinyl chloride by inhalation, five days/week, beginning on pnd 22 (the day after weaning); when the last litter is weaned, the formal 10-week prebreed exposure period for the F1 animals will begin (the youngest pups will be 13 weeks old at the end of this exposure period). In addition, three F1 weanlings/sex/litter will be necropsied with reproductive organs, liver, kidneys (2), spleen, thymus, adrenal glands (2), brain, and pituitary weighed and retained, and any gross lesions retained in fixative. Remaining non-selected F1 weanlings will be examined externally and euthanized with the concurrence of the Sponsor. The date of acquisition of vaginal patency in females (pnd 28-45) and of preputial separation (pnd 35-50) in males will be recorded in the F1 pups selected as parents until all available pups have reached criterion.

At the end of the F1 10-week prebreed exposure period (with a three-week evaluation of F1 females for estrous cyclicity), mating, gestation and lactation (with pairing of non-sibling animals within groups) will be performed as described above for F0 animals. Necropsy of F1 parental animals will occur as described above for F0 parents. Offspring of F1 parents will be designated the F2 generation. At weaning of F2 litters, three F2 weanlings/sex/litter will be necropsied as described above for F1 weanlings; remaining unselected F2 weanlings will be examined externally and euthanized with concurrence of the Sponsor. Organs of F0 and F1 parental animals to be weighed (all groups) include ovaries (2), uterus, testes (2), epididymides (2), seminal vesicles (2) with coagulating glands, prostate, spleen, kidneys (2), liver, adrenal glands (2), thymus, brain and pituitary. Organs of these animals to be retained in fixative include the above (one testis per male will be frozen for homogenization-resistant spermatid head count), plus cervix and vagina in females. Organs of the top dose and control group parental animals, plus any animals in mid and low dose groups which die on study or were not reproductively successful, will be examined histologically. Ovaries from F0 and F1 parental females (high dose and control) will have five (5) sections taken at least 100 μ m apart from the inner third of each ovary with enumeration of the total number of primordial follicles from these 10 sections per female. F0 and F1 parental males (all doses) will have sperm assessments (number, morphology, motility) performed from the cauda epididymis and homogenization-resistant spermatid head counts performed from the testis. Organs of F1 and F2 weanlings will be retained in fixative for possible subsequent histopathologic assessment if gross examination and/or organ weights indicate possible treatment-related effects. A draft final report will be submitted within five months of the last necropsy date.

B. Proposed Time Line

1. Two-Generation Study

EVENT	DURATION	TENTATIVE DATE(S)
<u>PreStudy</u>		
Submission of Bid	---	Dec. 8, 1995
Award of Bid by CMA	---	Jan. 15, 1996 (?)
Contract, acquisition of test material (with analysis?)		
Acceptable protocol	3 months	April 15, 1996
<u>Deliverables:</u> Protocol (fully signed)		April 30, 1996
Pre-Study Inhalation work (generation and analysis of test atmospheres, etc.), order animals, study-specific equipment/supplies	2 months	June 30, 1996

EVENT	DURATION	TENTATIVE DATE(S)
<u>Study</u>		
Animals arrive for two-generation study	---	July 15, 1996
Quarantine	2 weeks	July 15-30, 1996
Prebreed exposure of F0 animals	10 weeks	July 29-Sept. 29, 1996
Mating	2 weeks	Sept.30-Oct. 14, 1996
Gestation	3 weeks	Oct. 1 (first gd 0) - Nov. 5, 1996 (last gd 22)
Necropsy F0 males	3 days	
Lactation	3 weeks	Oct. 23 (first pnd 0) - Nov. 27, 1996 (last pnd 21)
Necropsy F0 females and selected F1 offspring	Over 2 weeks as litters wean	Nov. 13-27, 1996 (pnd 21)
Euthanasia of remaining F1 offspring	1 week	Dec. 2-6, 1996
Prebreed exposure period of F1 animals	10 weeks	Nov. 25, 1996-Feb. 3, 1997
Mating	2 weeks	Feb. 3-17, 1997
Gestation	3 weeks	Feb. 4 (first gd 0) - March 11, 1997 (last gd 22)
Necropsy F1 males	3 days	
Lactation	3 weeks	Feb. 27 (first pnd 0) - April 2, 1997 (last pnd 21)
Necropsy F1 females and selected F2 offspring	over 2 weeks as litters wean	March 20 - April 2, 1997 (pnd 21)
Euthanasia of remaining F2 offspring	1 week	April 7-11, 1997
<u>Deliverables:</u>		
Draft Final Report submitted	5 months	Sept. 11, 1997
Final Report submitted within 30 days of receipt of Sponsor's comments		Nov., 1997 (?)

2. Developmental Toxicity Study

EVENT	DURATION	TENTATIVE DATE(S)
<u>PreStudy</u>	SEE TIME LINE FOR TWO-GEN STUDY	
<u>Deliverables:</u> Protocol (fully signed)		April 30, 1996

(continued)

EVENT	DURATION	TENTATIVE DATE(S)
<u>Study</u>		
Animals arrive for developmental toxicity (breeding males and study females)		Aug. 5, 1996
Quarantine	2 weeks	Aug. 5-19, 1996
Mating (100 sperm-positive females)	4-5 days (gd 0)	Aug. 20-25, 1996
*Exposures (gd 6-19)	19 days (14 days/animal with 5 breeding days)	Aug. 26 (first gd 6) - Sept. 13, 1996 (last gd 19)
Scheduled Sacrifice (gd 20)	4-5 days	Sept. 9-17, 1996
<u>Deliverables:</u>		
Draft Report submitted	4 months	Jan. 17, 1997
Final Report submitted within 30 days of receipt of Sponsor's comments		March, 1997 (?)

* NOTE: Exposure for dams in developmental toxicity study will occur in same chambers at same time as F0 animals are in the prebreed exposure period for the two-generation study.

C. Information on Proposed RTI Staff and Facilities

1. Resumés of Key RTI Personnel

RTI Quality Assurance Unit:

Ms. S. M. Taulbee, Manager

Reproductive/Developmental Toxicology:

Dr. R. W. Tyl, Co-Study Director for both studies

Ms. M. C. Marr, Laboratory Supervisor and Developmental Toxicity Study Supervisor

Ms. C. B. Myers, Data Specialist and Reproductive Toxicity Study Supervisor

Sperm Assessments:

Dr. P. A. Fail, Reproductive Endocrinologist

Histopathology:

Ms. Tsai-Ying Chang, BS, HT-ASCP

Dr. John C. Seely, DVM, ACVP, PATHCO Inc.

2. RTI Standard Operating Procedures (SOPs) For Use In These Studies

The Tables of Contents for the Reproductive and Developmental Toxicology Group, the Endocrinology Group and the Histology Group are attached.

3. Floor Plan of Proposed RTI Suite for Necropsies and Fetal Evaluations

The floor plan of the Reproductive and Developmental Toxicology Wing in the Hermann Building is attached.

D. Comments on Study Designs, Deviations from the Dow Protocol and Current OPPTS Draft Guidelines

Developmental Toxicity Study

1. The rats will be exposed according to the new draft guidelines, from gd 6 to the day before scheduled sacrifice for six hours per day for the definitive study. I have specified exposure gd 6 through 19 and sacrifice on gd 20 since this is the procedure we follow at RTI (and our historical control database is also based on a gd 20 sacrifice date). The Dow protocol exposes through gd 20 with scheduled sacrifice on gd 21. This difference should have no effect on study design, performance or interpretation.

2. The Dow protocol specifies staining of fetal preparations with alizarin red S (ossified bone) prior to skeletal evaluation. The current draft guidelines specify examination of both ossified and cartilaginous components of the skeletal system. We routinely use (and I have bid) staining with alizarin red S (for ossified bone) and with alcian blue (for cartilaginous bone) prior to skeletal evaluation, in conformance with the draft guidelines.
3. I've included placental weights in the definitive study since new harmonization guidelines are calling for more placental information, at least weight (we can retain them in fixative for possible subsequent histopathology if we see something at gross examination or in data analysis).

Reproductive Toxicity Studies

1. Proposed guidelines call for a two-week mating period (with no mention of a change in unsuccessful partners within groups and after one week) and this is included in the bid.
2. Evaluation of sperm number, motility and morphology (from the cauda epididymis), and enumeration of homogenization-resistant spermatids (from one testis) are specified in the draft guidelines for all F0 and F1 parental males, and this is included in the bid (labor intensive). The Dow protocol specifies the first 15 F0 and F1 males; this does not follow the guidelines.
3. Vaginal cytology for estrous cyclicity, as specified in the draft guidelines, is included for three weeks prior to mating, and during the two-week mating period until insemination occurs, and at sacrifice for all F0 and F1 parental females (labor intensive). The Dow protocol specifies estrous cyclicity for the first 15 F0 and F1 females; this does not follow the guideline.
4. The current draft guidelines specify rebreeding parental animals if there is evidence of reproductive problems. Therefore, I am proposing that we necropsy the F0 and F1 males after the gestation periods of their respective litters, just in case we have to breed them. F0 and F1 females will be necropsied after the weaning of their respective litters. The Dow protocol calls for sacrifice of both parents after the litter is weaned; this is unnecessary for parental males.
5. The current draft guidelines require that we identify the stage of the estrous cycle at necropsy of the F0 and F1 adult females, and I have included that in the bid. The Dow protocol specifies necropsy of F0 and F1 females at the same time in the estrous cycle; this is unnecessary.
6. Draft guidelines specify necropsy of 3 pups/sex/litter from F1 and F2 litters with organ weights and retention of selected organs. This is included in the bid. The draft guidelines indicate histopathology of weanling organs only if gross necropsy or organ weight data indicates possible treatment-related effects, so I have not bid histopathology of weanling tissues. The Dow protocol specifies necropsy and organ weights of first 15 F1 and F2 weanlings (one/sex/litter); this does not follow the guidelines.
7. The draft guidelines specify a large number of organ weights for parental and selected weanling animals at necropsy; these were included in the bid (labor intensive).
8. Draft guidelines specify evaluation of a minimum of five (5) sections taken at least 100 μ m apart from the inner third of each ovary per parental female (F0 and F1) from high dose and control groups with enumeration of the total number of primordial follicles from these 10 sections per female (labor intensive). This is included in the bid. The Dow protocol specifies processing only the right ovary (left ovary retained), with a minimum of 10 sections, randomly selected, examined from one completely sectioned ovary per female. This does not follow the guidelines.
9. New draft guidelines specify examination for vaginal patency and preputial separation for F1 pups selected for mating. Therefore, I've bid evaluation of F1 pups for vaginal patency in females and preputial separation in males (F2 pups are terminated at weaning prior to acquisition of either of these

hormonally-controlled landmarks) as time to criterion, with daily examination starting on pnd 28 for females and on pnd 35 for males based on our historical control data and experience (labor intensive).

10. Anogenital distance is incorporated for F1 and F2 offspring at birth. Draft guidelines specify this assessment only for F2 pups if there are effects on F1 sexual maturation, but the bottom line on F1 sexual maturation is, in fact, production of F2 offspring so we will not know if there are effects until after all F2 litters are born (or are not born). Therefore, I bid the parameter for both generations up front (labor intensive).
11. The Dow protocol specifies ophthalmologic examination of parental F0 and F1 animals at necropsy. In addition, the Dow protocol also specifies fasting the parental F0 and F1 males and females overnight prior to scheduled sacrifice. Neither of these activities is included in the guidelines, and these activities are therefore not included in the study design or the bid.

E. Project Bid

The costs for performing these studies are presented in the accompanying letter from Ms. C. S. Parker, RTI Senior Contracts Administrator. If you have any further questions, please do not hesitate to call me for technical aspects at (919) 541-5972, or Ms. Parker for contractual matters at (919) 541-6184.

Thank you for the opportunity to assist CIIT in its toxicologic testing needs.

Sincerely,



Rochelle W. Tyl, Ph.D., DABT
Research Director
Center for Life Sciences and Toxicology

RWT:ng

Attachments

cc: LETTER ONLY:
Dr. A. M. Cruze, EVP, RTI
Dr. F. I. Carroll, Acting VP, CLS
Dr. P. A. Fail
Dr. S. E. Lewis
Dr. J. C. Seely, PATHCO
Ms. M. C. Marr
Ms. C. B. Myers
Ms. T. Y. Chang
Ms. S. M. Taulbee, QAU
Ms. C. S. Parker, Contracts

Appendix 2
Detailed CVs of RTI Personnel

ROCHELLE W. TYL, Research Director, Center for Life Sciences and Toxicology

Professional Experience

Center for Life Sciences and Toxicology, Chemistry and Life Sciences, Research Triangle Institute, Research Triangle Park, NC.

7/15/93 - present. Research Director, Center for Life Sciences and Toxicology. Establish and implement Center goals and objectives consistent with RTI's overall financial and research strategic planning; recommend, interpret and implement RTI policies and procedures; establish guidelines and procedures for and manage allocation and utilization of Center facilities, equipment and funding; supervise senior staff of Center; initiate, plan and implement operational plans and strategies for Center direction(s) and development, and staff professional development; play a major role in establishing and implementing marketing goals and activities for the Center; maintain high level of involvement in technical efforts of the Center, including establishment and implementation of objectives, goals and procedures of projects, coordination and cooperation among senior staff in complex projects; contribute to and direct preparation and presentation of research reports to clients and the professional community.

5/1/91 - 7/14/93. Assistant Research Director, Mammalian Toxicology Program; Program Manager, Reproductive and Developmental Toxicology. Duties as described below.

5/1/90 - 4/30/91. Senior Program Director, Mammalian Toxicology Program; Program Manager, Reproductive and Developmental Toxicology. Duties as described below. In addition, supervise senior staff in general toxicology and adult and developmental neurotoxicology testing, work with higher management in policy and program development and implementation, building and renovation program for CLS.

6/15/89 - 4/30/90. Program Manager, Reproductive and Developmental Toxicology. Supervision of the staff of Developmental Toxicology, Developmental Neurotoxicology, Reproductive Toxicology and Reproductive Endocrinology. Solicit and perform reproductive and developmental toxicity evaluations for governmental, industrial and commercial clients according to appropriate governmental guidelines, FDA, EPA (FIFRA or TSCA), OECD, EPA Test Rules or FIFRA Data "Call-Ins," under Good Laboratory Practice regulations; design and implement research protocols in reproductive and developmental toxicology for various clients; plan, coordinate and direct activities in program; prepare bids, protocols, final reports and manuscripts for refereed journals; evaluate personnel performance; direct supervision of four Ph.D. staff, two senior technical supervisory staff and an Administrative Assistant. Program includes seven doctoral level staff, six supervisory staff and approximately 15 technical staff. Member of RTI Institutional Animal Care and Use Committee (IACUC), 1990 - present.

9/1/87 - 6/89. Assistant Director, Reproductive and Developmental Toxicology, Bushy Run Research Center (BRRC), Export, PA: Work with the Director and Associate Directors in planning, coordinating and directing work activities at BRRC. Prepare

equipment and personnel budgets and evaluate personnel performance. Supervise a Postdoctoral Scientist. Additional responsibilities as below.

7/1/83 - 8/31/87. Manager, Reproductive and Developmental Toxicology Section, Bushy Run Research Center (BRRRC), Export, PA: Testing for developmental and reproductive toxicity of industrial chemicals by all routes of exposure in rats, rabbits and mice for Union Carbide and other industrial clients. Supervise ten staff members, responsible for protocol development, contact with clients, writing SOPs, writing study reports and manuscripts for refereed journals, staff training, sponsor liaison for UCC teratology studies done elsewhere, work under GLPs, FDA, EPA (TSCA), EPA (FIFRA), OECD guidelines, presentation of data to various professional groups.

5/83 - 6/30/83. Manager, Teratology Section and Senior Research Teratologist I, Research Triangle Institute, Research Triangle Park, NC: Research and testing in teratogenicity and reproductive toxicity of food additives, drugs, industrial chemicals, environmental pollutants, etc., in rats, mice and rabbits for governmental and industrial clients. Supervise eight people, responsible for all facets of studies, client contact, protocol development, SOPs, writing reports and manuscripts for refereed journals, Institute and community service by lectures to professional and academic groups, work under GLPs, EPA, FDA guidelines.

7/81 - 5/83. Supervisor, Teratology Section and Senior Research Teratologist I, Research Triangle Institute, Research Triangle Park, NC: Research and testing in teratogenicity and reproductive toxicity of food additives, drugs, industrial chemicals, environmental pollutants, etc., in rats, mice and rabbits for government and industrial clients. Supervise eight people, responsible for all facets of studies, client contact, protocol development, SOPs, writing reports and manuscripts for refereed journals, Institute and community service by lectures to professional and academic groups, work under GLPs, EPA, FDA guidelines.

7/78 - 7/81. Head, Teratology Section, Chemical Industry Institute of Toxicology (CIIT), Research Triangle Park, NC: Research and testing in teratogenicity and reproductive toxicity of priority commodity chemicals, toxicokinetics and metabolism of commodity chemicals in pregnant animals, development of test battery for postnatal sequelae of in utero exposures.

9/68 - 6/78. Assistant Professor (1968-1973), Associate Professor (1973-1978), University of Connecticut, Southeastern Campus, Groton, CT: Teaching undergraduate courses in Biological Sciences, Genetics, Embryology, advising independent research students (undergraduate) and Master's thesis research students, direct own research, pre-medical student counseling, university committee memberships (tenured, 1974).

Education

A.B. cum laude, Biological Science, University of Connecticut, Storrs, CT, 1963.
Ph.D., Developmental Genetics, University of Connecticut, Storrs, CT, 1968.

Professional Societies

Teratology Society
Neurobehavioral Teratology Society
Society of Toxicology (SOT) Active Member

SOT, Reproductive and Developmental Toxicology Subsection Member
Middle Atlantic Reproduction and Teratology Association (MARTA)
North Carolina Chapter of SOT
Genotoxicity and Environmental Mutagenesis Society (GEMS, NC)
Allegheny-Erie Regional Chapter of SOT (1983-1989)

Honors

Phi Beta Kappa
Phi Kappa Phi
Sigma Xi
Gamma Sigma Delta

Certification

Diplomate, American Board of Toxicology (ABT), 1983; recertified 1988 and 1993.

Outside Current Affiliations

IRLG Workshop on Reproductive Toxicity Risk Assessment, 1981; by invitation.
Consensus Workshop on Formaldehyde, 1983.
NIOSH Symposium on "Toxic Effects of Glycol Ethers," 1983.
American Industrial Health Council (AIHC), Reproductive Effects Subcommittee, 1984-1989.
Chemical Manufacturers Association (CMA) Health Standards Task Group - Work Group on Neurobehavioral Issues, 1984-1989.
Environmental Protection Agency (EPA), "Consensus Workshop on the Evaluation of Maternal and Developmental Toxicity," May 12-14, 1986; co-chair Workshop III Modeling and Applications; by invitation.
Adjunct Assistant Professor of Human Genetics in the Graduate School of Public Health, Department of Biostatistics, University of Pittsburgh, PA, 1986-1989.
Mid-America Toxicology Course, Kansas City, MO, April 27, 1987, April 18, 1988, April 24, 1989, and April 23, 1990, Lecturer on "Teratology"; by invitation.
Editorial Board Member for Fundamental and Applied Toxicology, 1987 to present.
Manuscript Reviewer for Toxicology and Applied Pharmacology (since 1983), for Teratology (since 1984), for Laboratory Animal Science (since 1984), and for Teratogenesis, Carcinogenesis and Mutagenesis (since 1989).
Environmental Protection Agency (EPA), "Workshop on the Acceptability and Interpretation of Dermal Developmental Toxicity Studies," April 13-14, 1988; by invitation.
Environmental Protection Agency (EPA), "Workshop in Qualitative and Quantitative Comparability of Human and Animal Developmental Neurotoxicity," April 11-13, 1989; co-chair Work Group III "Weight-of-Evidence and Quantitative Evaluation of Data from Developmental Neurotoxicity Studies"; by invitation.
Lecturer in Refresher Course entitled "Foundations of Abnormal Development," Topic: NOEL, LOEL, and Dose-Response Relationships, 1989 Annual Meeting of Teratology Society, June 3-4, 1989; by invitation.
Lecturer and Discussant in workshop entitled "Risk Assessment Issues in Reproductive and Developmental Toxicology," Topic: Developmental Toxicity: Animal Endpoints (Sponsored by ILSI and EPA), Berkeley, CA, September 18-19, 1989; by invitation.
Participant, Alternative Fuels Research Strategy Peer Review (sponsored by U.S.EPA), Developmental/Reproductive Toxicology Public Health Concerns, Durham, NC, December 6-8, 1989; by invitation.

- Environmental Protection Agency (EPA)/National Institute of Environmental Health Sciences (NIEHS), Manganese/MMT Conference, Health Effects Workgroup; Reproduction and Developmental Issues Specialty Section, March 12-15, 1991; by invitation.
- Speaker at Allegheny-Erie Regional Chapter of SOT, Spring Meeting, Pittsburgh, PA, May 10, 1991, Symposium entitled: "Toxicology of the Next Generation: Reproductive and Developmental Hazards," Topic: The Developing Fetus and Possible Effects Due to Chemical Exposures; by invitation.
- Lecturer in course entitled "Fundamentals of Environmental Toxicology," Topic: Toxic Responses of the Reproductive Systems, at Georgia Tech Research Institute, Georgia Institute of Technology, June 17-21, 1991; by invitation.
- Lecturer in Continuing Education Course "Collection and Interpretation of Data for Developmental Toxicity (Teratology) Studies - 'State of the Art' Scientific Review and the Realities of the Regulatory Submission Process" sponsored by the International Federation of Teratology Societies (IFTS), Topic: Collection and Evaluation of Maternal Toxicity Data, June 25, 1991 (at the Teratology Society Annual Meeting, Boca Raton, FL); by invitation.
- Speaker at American Industrial Hygienists Association Sixth Annual Toxicology Symposium, Topic: "Issues in Reproductive and Developmental Toxicology," San Diego, CA, August 12-16, 1991; by invitation.
- Invited Participant and Presenter, Toxicology Round Table, Ocean Place, NJ, October, 1991.
- Councilor, Reproductive and Developmental Toxicity Specialty Subsection SOT, elected 1992-1994.
- Member of Council, Teratology Society, elected 1992-1995.
- Speaker at American Industrial Hygienists Association Seventh Annual Toxicology Symposium, Topic: "The Principles of Risk Assessment for Developmental Effects," San Diego, CA, August 13-16, 1992; by invitation.
- Invited Participant and Presenter, Toxicology Round Table, Hidden Valley, PA, October, 1992.
- Speaker in American College of Toxicology Annual Meeting Symposium entitled, "Current Topics in Cholinesterase Risk Assessment," Topic: Cholinesterase Determinations in Reproductive and Developmental Toxicity Studies: Implications for Risk Assessment, San Francisco, CA, October 22-24, 1992; by invitation.
- Member of IEHR (Institute for Evaluating Health Risks) Expert Committee on Reproductive and Developmental Toxicity, Williamsburg, VA, January 17-21, 1993; by invitation.
- Lecturer in Continuing Education Course "Embryology for Teratologists," Topic: "Through the Looking Glass: Possible Embryologic Models or Mechanisms of Fetal Malformations," Teratology Society Annual Meeting, Tucson, AZ, June 26-27, 1993; by invitation.
- Speaker at American Industrial Hygienists Association Eighth Annual Toxicology Symposium, Topic: "Reproductive/Developmental Toxicology," Asheville, NC, August 3-5, 1993; by invitation.
- Lecturer in UNC-CH Toxicology 207: Advanced Toxicology, Topic: "Regulatory Issues in Reproductive and Developmental Toxicology," UNC-CH, September 29, 1993; by invitation.
- Speaker at American Industrial Hygienists Association Ninth Annual Toxicology Symposium, Topic: "Genetic Toxicology, Reproductive and Developmental Toxicology," Baltimore, MD, August 15-16, 1994; by invitation.

Lecturer in UNC-CH Toxicology 207: Advanced Toxicology, Topic: "Regulatory Issues in Reproductive and Developmental Toxicology," UNC-CH, September 14, 1994 and September 13, 1995; by invitation.

Speaker at American Industrial Hygienists Association Tenth Annual Toxicology Symposium, Topic: Reproductive Toxicology: Boston, MA, August 15-16, 1995; by invitation.

Current Research Interests

Toxicokinetics and metabolism of xenobiotics in pregnant and lactating test animals; research and testing for developmental and reproductive toxicity in animal models; developmental neurotoxicology.

Publications

Effect of Actinomycin D on Early Axial Development in Chick Embryos, R. M. Wolkowski, *Teratology* 3, 389-398, 1970.

Differential Cadmium-Induced Embryotoxicity in Two In-Bred Mouse Strains. I. Analysis of Inheritance of the Response to Cadmium and of the Presence of Cadmium in Fetal and Placental Tissues, R. M. Wolkowski, *Teratology* 10, 243-262, 1974.

The Interaction of Cadmium-binding Proteins (Cd-bp) and Progesterone in Cadmium-Induced Tissue and Embryo Toxicity, R. M. Wolkowski-Tyl and S. F. Preston, *Teratology* 20, 341-352, 1979.

Perinatal Toxicity and Metabolism of n -Hexane in Fischer-344 Rats after Inhalation Exposure During Gestation. J. S. Bus, E. L. White, R. W. Tyl and C. S. Barrow, *Toxicol. Appl. Pharmacol.* 51, 295-302, 1979.

Chemical Urolithiasis. 1. Characteristics of Bladder Stone Induction by Terephthalic Acid and Dimethyl Terephthalate in Weanling Fischer-344 Rats, T. Y. Chin, R. W. Tyl, J. A. Popp and H. d'A. Heck, *Toxicol. Appl. Pharmacol.* 58, 307-321, 1981.

Animal Model of Human Disease: Urolithiasis, R. Wolkowski-Tyl, T. Y. Chin, J. A. Popp and H. d'A. Heck, *Amer. J. Pathology* 107, 419-421, 1982.

Urolithiasis, Model No. 256, R. Wolkowski-Tyl, T. Y. Chin, J. A. Popp, and H. d'A. Heck, In: Handbook: Animal Models of Human Disease. Fasc. 11, Edited by C. C. Capen, D. B. Hackel, T. C. Jones and G. Migaki, Registry of Comparative Pathology, Armed Forces Institute of Pathology, Washington, DC, 1982, 3 pages.

Chemical Urolithiasis. 3. Pharmacokinetics and Transplacental Transport of Terephthalic Acid in Fischer-344 Rats, R. Wolkowski-Tyl, T. Y. Chin and H. d'A. Heck, *Drug Metab. Disp.* 10, 486-490, 1982.

Histopathology of Acute Toxic Response in Rats and Mice Exposed to Methyl Chloride by Inhalation, K. T. Morgan, J. A. Swenberg, T. E. Hamm, Jr., R. Wolkowski-Tyl and M. Phelps, *Fundam. Appl. Toxicol.* 2, 293-299, 1982.

- Structural Teratogenicity Evaluation of Methyl Chloride in Rats and Mice after Inhalation Exposure, R. Wolkowski-Tyl, M. Phelps and J. K. Davis, *Teratology* 27, 181-195, 1983.
- Evaluation of Heart Malformations in B₆C₃F₁ Mouse Fetuses Induced by In Utero Exposure to Methyl Chloride, R. Wolkowski-Tyl, A. D. Lawton, M. Phelps and T. E. Hamm, Jr., *Teratology* 27, 197-206, 1983.
- Effects of Selected Therapeutic Agents on Urolithiasis Induced by Terephthalic Acid in the Male Weanling Fischer 344 Rat, R. Wolkowski-Tyl and T. Y. Chin, *Fundam. Appl. Toxicol.* 3(6), 552-558, 1983.
- A Teratologic Evaluation of Ethylene Glycol Monobutyl Ether in Fischer 344 Rats and New Zealand White Rabbits Following Inhalation Exposure, R. W. Tyl, G. Millicovsky, D. E. Dodd, I. M. Pritts, K. A. France and L. C. Fisher, *Environmental Health Perspectives* 57, 47-68, 1984.
- Teratologic and Postnatal Evaluation of Aniline Hydrochloride in the Fischer 344 Rat, C. J. Price, R. W. Tyl, T. A. Marks, L. L. Paschke, T. A. Ledoux, and J. R. Reel, *Toxicol. Appl. Pharmacol.* 77, 465-478, 1985.
- Reproduction in Fischer-344 Rats Exposed to Methyl Chloride by Inhalation for Two Generations, T. E. Hamm, Jr., T. H. Raynor, M. C. Phelps, C. D. Auman, W. T. Adams, J. E. Proctor and R. Wolkowski-Tyl, *Fundam. Appl. Toxicol.* 5, 568-577, 1985.
- Evaluation of a New Reproductive Toxicology Protocol using Diethylstilbestrol (DES) as a Positive Control Compound, J. R. Reel, A. D. Lawton, R. Wolkowski-Tyl, G. W. Davis and J. C. Lamb IV, *J. Amer. College of Toxicol.* 4(2), 147-162, 1985.
- The Developmental Toxicity of Ethylene Glycol In Rats and Mice, C. J. Price, C. A. Kimmel, R. W. Tyl and M. C. Marr, *Toxicol. Appl. Pharmacol.* 81(1), 113-127, 1985.
- Teratologic Evaluation of Dinitrotoluene in the Fischer 344 Rat, C. J. Price, R. W. Tyl, T. A. Marks, L. L. Paschke, T. A. Ledoux and J. R. Reel, *Fundam. Appl. Tox.* 5, 948-961, 1985.
- Letter to the Editor: Heart Malformations in B₆C₃F₁ Mouse Fetuses Induced by Methyl Chloride-Continuing Efforts to Understand the Etiology and Interpretation of an Unusual Lesion: Response to Ms. John-Green, Dr. Welsh and Dr. Bus; R. W. Tyl, *Teratology* 32, 489-492, 1985.
- Evaluation of the Teratogenicity of Bis(2-Dimethylaminoethyl)Ether After Dermal Application in New Zealand White Rabbits, R. W. Tyl, L. C. Fisher, K. A. France, R. H. Garman and B. Ballantyne, *J. of Toxicology - Cutaneous and Ocular Toxicology* 5(4), 263-284, 1986.
- The Developmental Toxicity of Orally Administered Oxytetracycline in Rats and Mice, R. E. Morrissey, R. W. Tyl, C. J. Price, T. A. Ledoux, J. R. Reel, L. L. Paschke, M. C. Marr and C. A. Kimmel, *Fundam. Appl. Toxicol.* 7(3), 434-443, 1986.

Letter to the Editor: Response to Dr. E. M. Johnson; by C. A. Kimmel, C. J. Price, M. C. Marr and R. W. Tyl, *Toxicol. Appl. Pharmacol.* 84, 196-198, 1986.

Developmental Toxicity Evaluation of Inhaled Nitrobenzene in CD® Rats, R. W. Tyl, K. A. France, L. C. Fisher, D. E. Dodd, I. M. Pritts, J. P. Lyon, F. O. O'Neal and G. Kimmerle, *Fundam. Appl. Toxicol.* 8(4), 482-492, 1987.

Reproduction and Fertility Evaluations in CD Rats Following Nitrobenzene Inhalation, D. E. Dodd, E. H. Fowler, W. M. Snellings, I. M. Pritts, R. W. Tyl, J. P. Lyon, F. O. O'Neal and G. Kimmerle, *Fundam. Appl. Toxicol.* 8(4), 493-505, 1987.

Developmental Toxicity Evaluation of Inhaled Methyl Isobutyl Ketone in Fischer 344 Rats and CD®-1 Mice, R. W. Tyl, K. A. France, L. C. Fisher, I. M. Pritts, T. R. Tyler, R. D. Phillips and E. J. Moran, *Fundam. Appl. Toxicol.* 8(3), 310-327, 1987.

The Developmental Toxicity of Bisphenol A in Rats and Mice, R. E. Morrissey, J. D. George, C. J. Price, R. W. Tyl, M. C. Marr, and C. A. Kimmel, *Fundam. Appl. Toxicol.* 8(4), 571-582, 1987.

Consensus Workshop on the Evaluation of Maternal and Developmental Toxicity Work Group III Report: Low Dose Extrapolation and Other Considerations for Risk Assessment - Models and Applications, B. A. Schwetz and R. W. Tyl, *Teratogenesis Carcinog. Mutagen.* 7(3), 321-327, 1987.

Developmental Toxicity Evaluation of Inhaled 2-Ethoxyethanol Acetate in Fischer 344 Rats and New Zealand White Rabbits, R. W. Tyl, I. M. Pritts, K. A. France, L. C. Fisher and T. R. Tyler, *Fundam. Appl. Toxicol.* 10(1), 20-39, 1988.

Developmental Toxicity Evaluation of Bendectin® in CD® Rats, R. W. Tyl, C. J. Price, M. C. Marr and C. A. Kimmel, *Teratology* 37(6), 539-552, 1988.

Developmental Toxicity Evaluation of Dietary Di(2-Ethylhexyl) Phthalate in Fischer 344 Rats and CD®-1 Mice, R. W. Tyl, C. J. Price, M. C. Marr and C. A. Kimmel, *Fundam. Appl. Toxicol.* 10(3), 395-412, 1988.

Developmental Toxicity Evaluation of Beta(3-Epoxyoctahexyl) Ethyltrimethoxysilane in Fischer 344 Rats and New Zealand White Rabbits, R. W. Tyl, K. A. France, L. C. Fisher and B. Ballantyne, *Fundam. Appl. Toxicol.* 10(3), 439-452, 1988.

Evaluation of the Developmental Toxicity of Ethylene Glycol Monohexyl Ether Vapor in Fischer 344 Rats and New Zealand White Rabbits, R. W. Tyl, B. Ballantyne, K. A. France, L. C. Fisher, D. R. Klonne, and I. M. Pritts, *Fundam. Appl. Toxicol.* 12(2), 269-280, 1989.

Dominant Lethal Assay of 2,4-Pentanedione Vapor in Fischer 344 Rats, R. W. Tyl, B. Ballantyne, L. C. Fisher, D. J. Tarasi, and D. E. Dodd, *Toxicol. Ind. Health* 5(3), 463-477, 1989.

An Evaluation of the Developmental Toxicity of 2,4-Pentanedione in the Fischer 344 Rat by Vapour Exposure, R. W. Tyl, B. Ballantyne, I. M. Pritts, R. H. Garman, L. C. Fisher, K. A. France and D. J. McNeil, *Toxicol. Ind. Health* 6, 461-474, 1990.

Proceedings of the Workshop on The Acceptability and Interpretation of Dermal Developmental Toxicity Studies. C. A. Kimmel and E. Z. Francis (R. W. Tyl, Invited Participant). *Fundam. Appl. Toxicol.* 14, 386-398, 1990.

Workshop on the Qualitative and Quantitative Comparability of Human and Animal Developmental Neurotoxicity, Workgroup III Report: Weight of Evidence and Quantitative Evaluation of Developmental Neurotoxicity Data, R. W. Tyl and William F. Sette, *Neurotoxicology and Teratology* 12(3), 275-280, 1990.

Reproductive Toxicity of Sulfamethazine in Swiss CD-1 Mice During Continuous Breeding, J. R. Reel, R. W. Tyl, A. D. Lawton and J. C. Lamb, IV, *Fundam. Appl. Toxicol.*, 18(4), 609-615, 1992.

The Developmental Toxicity of 2-Ethylhexanol (2-EH) Applied Dermally to Pregnant Fischer 344 Rats, R. W. Tyl, L. C. Fisher, M. F. Kubena, M. A. Vrbancic, R. Gingell, D. Guest, J. A. Hodgson, S. R. Murphy, T. R. Tyler and B. D. Astill, *Fundam. Appl. Toxicol.*, 19(2), 176-185, 1992.

Developmental Toxicity Evaluation of Ethylene Glycol by Gavage in New Zealand White Rabbits, R. W. Tyl, C. J. Price, M. C. Marr, C. B. Myers, J. C. Seely, J. J. Heindel and B. A. Schwetz, *Fundam. Appl. Toxicol.*, 20(4), 402-412, 1993.

Assessment of the Developmental Toxicity of 2-Ethylhexanoic Acid in Rats and Rabbits, A. G. Hendrickx, P. E. Peterson, R. W. Tyl, L. C. Fisher, L. J. Fosnight, M. F. Kubena, M. A. Vrbancic and G. Katz, *Fundam. Appl. Toxicol.*, 20, 199-209, 1993.

Developmental Toxicity Evaluation of Isopropanol by Gavage in Rats and Rabbits, R. W. Tyl, L. W. Masten, M. C. Marr, C. B. Myers, R. W. Slaughter, T. H. Gardiner, D. E. Strother, R. H. McKee and T. R. Tyler, *Fundam. Appl. Toxicol.*, 22, 139-151, 1994.

Evaluation of Exposure to Water Aerosol or Air by Nose-Only or Whole-body Inhalation Procedures for CD-1® Mice in Developmental Toxicity Studies, R. W. Tyl, B. Ballantyne, L. C. Fisher, D. L. Fait, T. A. Savine, I. M. Pritts and D. E. Dodd, *Fundam. Appl. Toxicol.*, 23(2), 251-260, 1994.

Evaluation of the Developmental Toxicity of Ethylene Glycol Aerosol in the CD Rat and CD-1 Mouse by Whole-Body Exposure, R. W. Tyl, B. Ballantyne, L. C. Fisher, D. L. Fait, T. A. Savine, D. E. Dodd, D. R. Klonne, and I. M. Pritts, *Fundam. Appl. Toxicol.*, 24, 57-75, 1995.

The evaluation of the Developmental Toxicity of Hydrochlorothiazide in Mice and Rats, J. D. George, C. J. Price, R. W. Tyl, M. C. Marr and C. A. Kimmel, *Fundam. Appl. Toxicol.*, 26, 174-180, 1995.

Evaluation of the Developmental Toxicity of Ethylene Glycol Aerosol in CD-1 Mice by Nose-Only Exposure, R. W. Tyl, B. Ballantyne, L. C. Fisher, D. L. Fait, D. E. Dodd, D. R. Klonne, I. M. Pritts, and P. E. Losco, *Fundam. Appl. Toxicol.*, 27 (1), 49-62, 1995.

Assessment of the Developmental Toxicity of Ethylene Glycol Applied Cutaneously to CD-1 Mice, R. W. Tyl, L. C. Fisher, M. F. Kubena, M. A. Vrbancic, and P. E. Losco, *Fundam. Appl. Toxicol.*, 27 (2), 155-166, 1995.

Determination of a No-Observed-Effect-Level (NOEL) for Developmental Toxicity of Ethylene Glycol Administered by Gavage to CD® Rats and CD-1® Mice, T. L. Neeper-Bradley, R. W. Tyl, L. C. Fisher, M. F. Kubena, M. A. Vrbancic, and P. E. Losco, *Fundam. Appl. Toxicol.*, 27 (1), 121-130, 1995.

Developmental Toxicity Evaluation of Methyl Tertiary-Butyl Ether (MTBE) by Inhalation in Mice and Rabbits, C. Bevan, R. W. Tyl, T. L. Neeper-Bradley, L. C. Fisher, R. D. Panson, J. F. Douglas and L. S. Andrews, *J. of Appl. Toxicol.*, in press, 1995.

Two-Generation Reproductive Toxicity Study of Methyl Tertiary-Butyl Ether (MTBE) in Rats, C. Bevan, T. L. Neeper-Bradley, R. W. Tyl, L. C. Fisher, R. D. Panson, J. J. Kneiss and L. S. Andrews. *J. of Appl. Toxicol.*, in press, 1995.

Reproductive Toxicity Assessment of Methylethyl Ketoxime by Gavage in CD® Rats, R. W. Tyl, J. M. Gerhart, C. B. Myers, M. C. Marr, D. R. Brine, A. F. Gilliam, J. C. Seely, M. J. Derelanko, and W. E. Rinehart. *Fundam. Appl. Toxicol.*, in press, 1995.

Evaluation of the Reproductive Toxicity of Dietary Tributyl Phosphate in CD® Rats, R. W. Tyl, J. M. Gerhart, C. B. Myers, M. C. Marr, D. R. Brine, and J. C. Seely, to be submitted to *Fundam. Appl. Toxicol.*, 1995.

Developmental Toxicity Evaluation of Triethylenetetramine by Occluded Cutaneous Application in New Zealand White Rabbits, R. W. Tyl, L. C. Fisher, C. M. Troup, T. A. Rebick, M. A. Vrbancic, H-W. Leung and T. R. Tyler, to be submitted to *Fundam. Appl. Toxicol.*, 1995.

Developmental Toxicity Evaluation of Aminotriazole Technical Administered by Gavage to CD® (Sprague-Dawley) Rats and New Zealand White Rabbits, R. W. Tyl, L. C. Fisher, D. L. Fait, T. A. Savine, and J. M. Charles, to be submitted to *Fundam. Appl. Toxicol.*, 1995.

Book Chapters and Monographs

Strain and Tissue Differences in Cadmium-Binding Protein (Cd-bp) in Cd-Treated Mice, R. M. Wolkowski-Tyl, Department of Energy Symposium Series 47, 568-585, 1978.

Reproductive and Teratogenic Effects: No More Thalidomides?, R. M. Wolkowski-Tyl, ACS Symposium Series: The Pesticide Chemist and Modern Toxicology 160, 115-155, 1981.

The Induction of Bladder Stones by Terephthalic Acid, Dimethyl Terephthalate and Melamine (2,4,6-Triamino-s-triazine) and Its Relevance to Risk Assessment, H. d'A. Heck and R. W. Tyl, *Regulatory Toxicology and Pharmacology* **5**, 294-313, 1985.

Chapter 8. Developmental Toxicity in Toxicology Research and Testing, R. W. Tyl, in: Perspectives in Basic and Applied Toxicology. (B. Ballantyne, Editor), John Wright and Sons, Year Book Publishers, pp. 203-238, 1987.

Chapter 25. Developmental and Reproductive Toxicity of Anticholinesterases, R. W. Tyl, in: Basic and Clinical Toxicology of Organophosphates and Carbamates. (B. Ballantyne and T. C. Marrs, Editors), John Wright and Sons, Year Book Publishers, pp. 241-257, 1992.

Chapter 16. Reproductive and Developmental Toxicity Studies by Cutaneous Administration, R. W. Tyl, R. G. York and J. L. Schardein, in: Health Risk Assessment: Dermal and Inhalation Exposure and Absorption of Toxicants. (R. G. Wang, J. B. Knaak and H. I. Maibach, Editors), CRC Press, Inc., pp. 229-261, 1993.

Chapter 44. Developmental Toxicology, R. W. Tyl, in: Textbook of General and Applied Toxicology, Vol. 2 (B. Ballantyne, T. Marrs, P. Turner, Editors), The MacMillan Press, Ltd., 1993, 1021-1046.

Chapter 7. Developmental Toxicity Testing—Methodology, R. W. Tyl and M. C. Marr, in: Handbook of Developmental Toxicology (R. D. Hood, Editor), CRC Press, Inc., in press, 1995.

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October, 1995

PATRICIA ANN FAIL (NODEN), Reproductive Biologist

PROFESSIONAL EXPERIENCE

November 1990 to date. Manager, Department of Reproductive Biology, Center for Life Sciences and Toxicology, Chemistry and Life Sciences, Research Triangle Institute, Post Office Box 12194, Research Triangle Park, NC 27709. Additional responsibilities beyond that listed below include coordination of group activities, administrative reporting, and decisions on group direction.

January 1986 to November 1990. Senior Reproductive Biologist/Toxicologist, Center for Life Sciences and Toxicology, Chemistry and Life Sciences, Research Triangle Institute, Post Office Box 12194, Research Triangle Park, NC 27709. Contract research and testing in reproductive toxicology and endocrinology for industrial, governmental, and university clients, which include: endocrinopathy after drug treatment (Principal Investigator); performing reproductive assessment by Continuous Breeding Protocol in rodents exposed to potential toxicants (Co-Principal Investigator); development of male contraceptive agents (Co-Investigator); basic research on control of sexual maturation in male deer mice; and genetic models of infertility and receptor binding and bioassay of antiprogestational activity. Collaborative research on social stimulation of testicular function in ring doves and endocrinology of reproductive function in prosimian primates. Responsible for contract administration, proposal development, protocol design, writing of Standard Operating Procedures, literature summaries, interim and final reports, and manuscripts for refereed journals, training and supervision of personnel, and supervision of chemical handling and dosage formulation. Studies conform to FDA and EPA guidelines and adhere to Good Laboratory Practices (GLP) regulations.

1987 to date. Visiting professor for minority institutions, sponsored by FASEB. Once or twice yearly, perform workshops and seminars on some aspect of reproduction or toxicology.

1984 to 1989. Research Associate, Department of Psychology, Duke University, Durham, NC. Research Consultant on reproductive endocrinology to study social stimulation of testicular function in ring doves and pubertal development of prosimian primates.

1980 to 1985. Assistant Professor of Physiology and Zoology, North Carolina State University, Raleigh, NC. Taught Veterinary Physiology, Special Topics in Physiology of Pregnancy, Histology, Comparative Physiology, and Vertebrate Physiology. Developed a research program on environmental and pituitary control of pubertal development of male rodents, hormonal regulation of prostaglandin synthesis at parturition; graduate training and undergraduate research.

1978 to 1980. Research Associate, Department of Obstetrics, Gynecology and Reproductive Biology, Michigan State University, East Lansing, MI. Planned, organized, and directed research projects in lipid metabolism in perinates of mothers with diabetes, prostaglandin-forming cyclooxygenase formation by tissues of gestation in rabbits; planned and developed blood chemistry and endocrine laboratory.

1975; 1977 to 1978. Assistant Professor and Instructor, Science Department, Lansing Community College, Lansing, MI. Taught Human Anatomy, Human Physiology, and Human Sexuality. Coordinated seven sections of Human Anatomy.

1976 to 1977. Research Associate, Kliniek Verloskunde, Gynaekologie en KI (Clinic of Veterinary Obstetrics, Gynecology and Artificial Insemination), Rijksuniversiteit te Utrecht, The Netherlands. Research on steroidogenesis in *in vitro* follicle cultures, purification of equine pituitary hormones, and induction of abortion in horses.

1970 to 1975. Research and Teaching Assistant, Department of Dairy Science and Physiology, Michigan State University, East Lansing, MI. Taught Dairy Science, Animal Reproduction, Human Physiology, and Biological Sciences Laboratories. Conducted research on ovulation control and reproductive endocrinology of horses, influence of vasoligation on sperm production in rats, radioimmunoassay development, and *in vitro* pituitary monolayer response to releasing hormones.

1966 to 1970. High School Teacher, Science Department, Sanger High School, Sanger, CA. Taught Biology, General Science, and General Mathematics.

1965 to 1966. Histological Research Technician. Experimental pathology, National Aeronautics and Space Administration, Moffett Field, CA. Performed histologic techniques (both routine and developmental) on nerve and brain tissue.

1963 to 1965. Research Assistant and Histological Technician, Zoology Department, Kansas State University, Manhattan, KS. Assisted in Human Anatomy and Embryology Laboratories; MS research on embryology of bovine heart; fixed, sectioned, and stained reproductive tissues; serial sectioned bovine and canine embryos.

EDUCATION

B.S., Kansas State University, Zoology (Embryology), 1964
M.S., Kansas State University, Zoology (Embryology), 1966
-- Fresno State University, Psychology and Biology, 1968 (teaching certificate)
Ph.D., Michigan State University, Physiology and Dairy Science, 1975

HONORS

Mary Barnes Scholarship, 1960-1962
Friedline Scholarship, 1962-1964
Kansas Heart Association Grant-in-Aid, 1964-1965
Phi Delta Gamma (Graduate Honorary), 1965
Graduate Office Scholarship Award, 1973
Excellence in Teaching Award Nominee, 1974

PROFESSIONAL SOCIETIES

American Physiological Society
American Society of Andrology
Association for Study of Animal Science
North Carolina Society of Toxicology
Sigma Xi
Society for Study of Reproduction

DISSERTATIONS

P. A. Noden, Cardiogenesis in the Bovine to 35 Somites, Masters Thesis, Kansas State University, 1965.

P. A. Noden, Estrus, Ovulation and Changes in Some Hormones During the Estrus Cycle of Mares and After Prostaglandin $F_{2\alpha}$ Ph.D. Dissertation, Michigan State University, 1975.

PUBLICATIONS

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Fail, P.A., J.D. George, T.B. Grizzle, and J.J. Heindel (in preparation). Formamide and dimethylformamide: reproductive assessment by continuous breeding in Swiss mice, *Fund. Appl. Tox.*

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Fail, P.A. (1987). Influence of 35°C and melatonin (MEL) on testosterone (T), testis, and accessory sex organs (ASO) after HCG in juvenile deer mice, *J. Andrology*, 8: P23 (Abstract 26).

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Fail, P.A., J.D. George, J.C. Seely, T.B. Grizzle, and J.J. Heindel (1989). Reproductive toxicity of boric acid (BORA) in male mice, *J. Andrology*, 10: P-45.

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Grizzle, T.B., H.R. Sauls, S.W. Dennis, and P.A. Fail (1989). Response of testis to HCG in Swiss mice (CD-1) following chronic exposure to boric acid (BORA), *Biol. Reprod.* 40 (1): 153 (Abstract 316).

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Fail, P.A., S.A. Anderson, S.W. Pearce, H.R. Sauls, and R.P. Reynolds (1994). Endocrine toxicity of nickel: effects on prolactin, thyroxine, and progesterone in rodents after subchronic exposure to nickel chloride in drinking water. Presented at Triangle Conference on Reproductive Biology, January 1994.

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Carisoprodol (CARI): Reproduction and Fertility Assessment in CD-1® Mice When Administered by Gavage in Corn Oil. J.D. George, P.A. Fail, T.B. Grizzle, J.J. Heindel, and R.E. Chapin. Final Study Report, NTP/NIEHS Contract No. N01-ES-65141, NTIS No. PB92128404, September 10, 1991.

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Ortho-Cresol (OCRE): Reproduction and Fertility in CD-1 Mice When Administered in the Feed, J.D. George, P.A. Fail, M.K. Izard, T.B. Grizzle, J.J. Heindel, and R.E. Chapin. Final Study Report, NTP/NIEHS Contract No. N01-ES-65141, NTIS No. PB92176890, March 13, 1992.

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Development and Testing of Nonsteroidal Male Contraceptive Agents. C.E. Cook, Y.W. Lee, P.A. Fail, M.C. Wani, February 6, 1991, Fifth Quarterly Report, Project No. 311U-4587/00/06Q, October 1, 1990 - December 31, 1991.

Development and Testing of Nonsteroidal Male Contraceptive Agents. C.E. Cook, Y.W. Lee, P.A. Fail, M.C. Wani, May 8, 1991, Sixth Quarterly Report, Project No. 311U-4587/00/06Q, January 1, 1991 - March 31, 1991.

Development and Testing of Nonsteroidal Male Contraceptive Agents. C.E. Cook, Y.W. Lee, P.A. Fail, M.C. Wani, September 19, 1991, Seventh Quarterly Report, Project No. 311U-4587/00/06Q, April 1, 1991 - June 30, 1991.

Development and Testing of Nonsteroidal Male Contraceptive Agents. C.E. Cook, Y.W. Lee, P.A. Fail, M.C. Wani, January 3, 1992, Eighth Quarterly Report, Project No. 311U-4587/00/06Q, July 1, 1991 - September 30, 1991.

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Two-generation study of methoxychlor administered in corn oil to Long-Evans hooded rats using the alternative reproductive test protocol, Fail, P.A., S.W. Pearce, S.A. Anderson, A Final Report issued to US EPA CR820335-01-0. 1995. (Submitted May 1994)

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Chronic Intra-atrial Cannulation and Microassay for Hormones Allows Longitudinal Study Design to Assess Endocrine Changes in Adult Female CD Rats Exposed to Dietary XXXXXX, Project B. M.K. Izard and P.A. Fail, 1990, Project No. 311C-4556-10, Submitted September 17, 1990, Confidential Client.

May 1995



JOHN CURTIS SEELY

Education: Residency in Comparative Pathology (1975-1980),
Walter Reed Army Institute of Research.
D.V.M., University of Missouri, 1975.
A.B., Zoology, University of Missouri, 1971.

Certification: Diplomate, American College of Veterinary
Pathologists, 1981.

Experience:

1985 - Present: Veterinary Pathologist, PATHCO, Inc. Duties
Include: Co-Principal Investigator of a pathology
support contract to the National Toxicology
Program: this work includes primary
histopathology, quality assessment
histopathology, necropsy supervision, serving as
Chairperson on PWGs, site visits, wet tissue
audits and special projects as assigned. Serves
additionally as a pathology consultant to the
Research Triangle Institute, the Environmental
Protection Agency, and to several other
commercial clients. Utilizes the LABCAT
histopathology computer program to generate
histopathology data. Supports training efforts
at both the professional and technical level in
Pathology and Laboratory Animal Science.

1984 - 1985 Director of Pathology, Tegeris Laboratories,
Inc., Laurel, Maryland (formerly Pharmacopathics
Research Laboratories, Inc., and Borriston
Laboratories, Inc.).

1980 - 1984 Veterinary Pathologist/Study Director, Tegeris
Laboratories, Inc. Duties included: direct
supervision of all gross necropsies and the
subsequent tissue blocking and slide preparation;
Study Director for dog studies; histopathological
interpretation of tissues and consultation with
the Study Director on the gross and
histopathological data; writing pathology reports
for in-house acute, subchronic, and chronic
studies; supervisor for histology, clinical
chemistry, and hematology departments;
contribution to TL's Standard Operating
Procedures; involvement in the study design and



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strict adherence of the SOPs regarding that portion of the study pertaining to gross and histopathology; entering of the gross and histopathology findings into the computerized LABCAT format and preparation of the pathology reports; and maintaining an active role in the continuing education of the laboratory personnel.

1975 - 1980

Staff Pathologist, (Captain, U.S. Army), Walter Reed Army Institute of Research, Washington, D.C., Department of Comparative Pathology, Division of Pathology. Duties included: Comparative Pathology residency training; gross and microscopic pathology diagnostic support involving a wide variety of laboratory animals including non-human primates. Electron microscopic support of both diagnostic cases and collaborative research projects. Active participation in training programs at WRAIR and the AFIP.

1977 - 1979

Instructor in Anatomy (1977 - 1978), Adjunct Assistant Professor (1978 - 1979) Department of Anatomy (Histology), Uniformed Services University of the Health Sciences, Bethesda, Maryland. Duties included: Primary lab instructor for the first year medical school histology course. This included weekly presentations of each organ system at both the light and ultrastructural level, test preparation and student evaluation.

Awards:

U.S. Army Health Professions Scholarship
Phi Zeta Honor Society of Veterinary Medicine

Memberships/Societies:

American Veterinary Medical Association
American College of Veterinary Pathologists
Society of Toxicologic Pathologists
American Association for Laboratory Animal Science
International Academy of Pathology
Japanese Society of Toxicologic Pathology



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Committees And Professional Activities:

Chairman, Special Presentations Group, 3rd International Symposium of the Society of Toxicologic Pathologists, May 14-16, 1984.
Local Arrangements, Society of Toxicologic Pathologists, 1985 Annual Meeting.
Ad Hoc Committee on Commercial Exhibits, American College of Veterinary Pathologists.
Editorial Advisory Board (Pathology) LAB ANIMAL, Nature Publishing Co.
Renal Specialty Group (Co-Chairperson), American College of Veterinary Pathologists, 1991 Annual Meeting.
Renal Specialty Group (Chairperson), American College of Veterinary Pathologists, 1992 Annual Meeting.
Abstract Review Committee, 1994 National AALAS meeting.

Publications:

Cox, V.S. and Seely, J.C.: A Simplified Resectioning Technique. Stain Tech. 40:329-333, 1974.

Seely, J.C., Cosenza, S.F., Montgomery, C.: Leiomyosarcoma of the Urinary Bladder in a Dog, with Metastases, JAVMA 172:1427-1429, 1978.

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Seely, J.C.: Zymbal Glands in the Rat. Lab Animal 15:25-31, 1986.

Cosenza, S.F. and Seely, J.C.: Generalized Nodular Dermatofibrosis and Renal Cystadenocarcinomas in a German Shepherd Dog. JAVMA 189: 1587-1590, 1986.



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Fail, P.A., George, J.D., Sauls, H.R., Dennis, S.W., and Seely, J.C.: Effect of Boric Acid on Reproduction and Fertility of Rodents. Adv. Contra. Deliv. Syst. 5:323-333, 1989.

Bucher, J.R., Uraih, L.C., Hildebrandt, P.K., Sauer, R.M., and Seely, J.C.: Carcinogenicity and Pulmonary Pathology Associated with a Single 2-Hour Inhalation Exposure of Laboratory Rodents to Methyl Isocyanate. JNCI 81:1586-1587, 1989.

Allis, J.W., Ward, T.R., Seely, J.C., and Simmons, J.E.: Assessment of Hepatic Indicators of Subchronic Carbon Tetrachloride Injury and Recovery in Rats. Fund. Appl. Toxicol. 15:558-570, 1990.

Dubey, J.P., Cosenza, S.F., Lipscomb, T.P., Topper, M.J., Speer, C.A., Hoban, L.D., Davis, S.W., Kincaid, A.L., Seely, J.C., Marrs, G.E.: Acute Sarcocystosis-Like Disease in a Dog. JAVMA 198:439-443, 1991.

Simmons, J.E., Allis, J.W., Grose, E.C., Seely, J.C., Robinson, B.L., and Berman, E.: Assessment of the Hepatotoxicity of Acute and Short-Term Exposure to Inhaled p-Xylene in F344 Rats. J. Toxic. Environ. Health 32:295-306, 1991.

Fail, P.A., George, J.D., Seely, J.C., Grizzle, T.B., and Heindel, J.J.: Reproductive Toxicity of Boric Acid in Swiss (CD-1) Mice: Assessment Using the Continuous Breeding Protocol. Fund. Appl. Toxicol. 17:225-239, 1991.

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House, D.E., Berman, E., Seely, J.C., and Simmons, J.E. Comparison of Open and Blind Histopathologic Evaluation of Hepatic Lesions. *Toxicology Letters*, 63:127-133, 1992.

Tyl, R.W., Price, C.J., Marr, M.C., Myers, C.B., Seely, J.C., Heindel, J.J., and Schwartz, B.A. Developmental Toxicity Evaluation of Ethylene Glycol By Gavage In New Zealand White Rabbit. *Fund. Appl. Toxicol.* 20:402-412, 1993.

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Thornton-Manning, J.R., Seely, J.C., and Pegram, R.H. Toxicology of Bromodichloromethane in Female Rats and Mice After Repeated Oral Dosing. (In Press)

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Books/Book Chapters

Feldman, D.B. and Seely, J.C.: Necropsy Guide: Rodents and the Rabbit. CRC Press, Inc., Boca Raton, FL., 1988.



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Yang, R.S.H., Huff, J., Germolec, D.R., Luster, M.I., Simmons, J.E., and Seely, J.C. Carcinogenicity and Pesticides: Biological Issues In Extrapolation. In: Carcinogenicity and Pesticides: Principles, Issues, and Relationships (N.N. Ragsdale, R.E. Menzer; eds.) ACS Symposium Series No. 414, Chapter 9, 1989.

Seely, J.C. and Hildebrandt, P.K.: Parathyroid Gland. In: Pathology of the Fischer Rat. Boorman, G.A., Eustis, S.L., Elwell, M.R., Montgomery, C.A., and MacKenzie, W.F. (eds.) Academic Press, Orlando, 1990, pp. 537-543.

Montgomery, C.A. and Seely, J.C.: Kidney. In: Pathology of the Fischer Rat. Boorman, G.A., Eustis, S.L., Elwell, M.R., Montgomery, C.A., and MacKenzie, W.F. (eds.) Academic Press, Orlando, 1990, pp. 127-153.

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Seely, J.C., Eustis, S.L. and Boorman, G.A.: Mammary Gland. In: Pathology of the B6C3F1 Mouse. Boorman, G.A., Eustis, S.L., Elwell, M.R. (eds.). Academic Press. (In Preparation)

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Study Sets

Goodman, D.G., Anver, M.R., Sauer, R.M., Seely, J.C., Strandberg, J.D., Hildebrandt, P.K., Vonderfecht, S.L., Imes, G.D., Ward, J.M., Parker, G.A., Boorman, G.A., and Uraih, L.: Experimentally Induced and Other Proliferative and Neoplastic Lesions in Mice. Registry of Veterinary Pathology, Armed Forces Institute of Pathology, Washington, D.C., 1989.

Presentations:

Cerebellar Hypoplasia in the Cat: An Ultrastructural Study. Presented at the Central States Electron Microscopic Society, March 1974, Columbia, Missouri.

Experimental Trypanosomiasis in Mice: Morphologic Pathology. Presented at the ACVP Veterinary Neuropathology Interest Group, December, 1976, Miami Beach, Florida.



John Curtis Seely

Diagnostic Electron Microscopic Pathology. Presented at the Pathology of Lab Animals Course, AFIP, 1977, 1978, 1979, 1980, Washington, D.C.

Electron Microscopy as a Technique for Diagnosis. Presented at the Wildlife Disease Meeting, August, 1978, Ft. Collins, Colorado.

Diagnostic E.M. in Veterinary Pathology. Presented at the Ultrastructural Pathology Course, NIH, October, 1977, 1978, Bethesda, Maryland.

Reptile Histology and Selected Diseases. Presented at the North Carolina Society of Histopathology Technologists Annual Meeting, May, 1986, Burlington, N.C.

Abdominal Swelling in Female Mice. Presented at the District 4 Meeting - AALAS, March 1987, Raleigh, N.C.

Diseases of the Kidney. Presented at the American Association for Laboratory Animal Science Annual Meeting, November 1987, Denver, Colorado.

Miscellaneous Skin Diseases of Laboratory Animals. Presented at the American Association for Laboratory Animal Science Annual Meeting, October 1988, Detroit, Michigan.

Diseases of the Kidney. Presented at the CIIT Pathology Minicourse, June 1990, Research Triangle Park, North Carolina.

Toxicologic Pathology of the Kidney. Presented at the College of Veterinary Medicine, NCSU as part of a graduate level course on Toxicologic Pathology, 1990, 1992, Raleigh, North Carolina.

Histopathology of the Kidney. Presented at the College of Veterinary Medicine, NCSU as part of a graduate level course on Histopathology, 1993, Raleigh, North Carolina.

Toxicologic Pathology of the Kidney and Diseases of Reptiles. Presented at the College of Veterinary Medicine, Kagoshima University, Kagoshima, Japan and at the Institute of Environmental Toxicology, Ibaraki, Japan. Nov., 1993.

Abstracts/Posters:

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**NTP Chemicals Reviewed
In Pathology Working Group Evaluations
National Toxicology Program/Technical Report Series**

<u>NTP TR NO.</u>	<u>CHEMICAL</u>
335	C. I. Acid Orange 3, Dec., 1988
338	Erythromycin Stearate, Dec., 1988
341	Nitrofurantoin, Sept., 1989
343	Benzyl Alcohol, June, 1989
344	Tetracycline Hydrochloride, Aug., 1989
357	Hydrochlorothiazide, July, 1989
368	Nalidixic Acid, Oct., 1989
369	a - Methylbenzyl Alcohol, Jan., 1990
367	Phenylbutazone, March, 1990
375	Vinyl Toluene (mixed isomers), March, 1990
378	Benzaldehyde, March, 1990
371	Toluene, Feb., 1990
382	Furfural, March, 1990
399	Titanocene Dichloride, 1991



John Curtis Seely

**NTP Chemicals Reviewed
In Pathology Working Group Evaluations
National Toxicology Program/Technical Report Series**

<u>NTP TR NO.</u>	<u>CHEMICAL</u>
406	Butyrolactone (Gamma), March, 1992
411	C.I. Pigment Red 23, Nov., 1992
402	Furan, Jan., 1993
413	Ethylene Glycol, Feb., 1993
414	Pentachloroanisole, Apr., 1993
417	p-Nitrophenol, Apr., 1993
427	Turmeric Oleoresin, Aug., 1993
398	Polybrominated Biphenyls, Aug., 1993



John Curtis Seely, D.V.M.
Diplomate, American College of Veterinary Pathologists

Summary of Experience in Carcinogenic
and Toxicologic Pathology

Dr. Seely has more than 19 years of experience in veterinary pathology. Since 1980, he has been active in toxicologic pathology. He has been responsible for all aspects of pathology including supervising histology and clinical pathology at a toxicology testing laboratory. In various capacities, he has provided pathology support to private clients and to various government scientific advisory and regulatory agencies including the National Toxicology Program (NTP) of the National Institute of Environmental Health Sciences (NIEHS), and the Environmental Protection Agency (EPA). Examples of pathology support provided to these clients include:

- . Chairing conduct of more than 85 Pathology Working Groups (PWGs) on both subacute and chronic toxicology/carcinogenicity studies conducted by NTP
- . Participating in PWGs at NTP
- . Conducting wet tissue and pathology data audits for NTP
- . Supervising and performing gross necropsies for toxicity/carcinogenicity studies
- . Conducting independent reviews of selected lesions/target organs for both private and government clients
- . Electron microscopy consultation



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John Curtis Seely, D.V.M., ACVP

- . Consulting on design of study protocols for subchronic and chronic studies
- . Performing histopathologic evaluations of microslides from numerous toxicity/carcinogenicity studies involving dogs, rats and mice for both private and government clients

CMA 120010

MELISSA C. MARR, Research Biologist II

Professional Experience

Research Triangle Institute, Center for Life Sciences and Toxicology, Chemistry and Life Sciences, Research Triangle Park, NC 27709.

June 1981 to date. Reproductive and Developmental Toxicology Laboratory Supervisor. Responsibilities include scheduling timetables for completion of all phases of studies involving mice, rats, hamsters and rabbits; direct supervision of up to nine other laboratory personnel including assignment of tasks, training and quality control, coordination of support analytical and clinical chemistry, expertise in all phases of postnatal studies including multigenerational reproductive toxicity and behavioral landmarks; development of SOPs, protocols, and preparation of study reports; design and implementation of and training of staff in procedures for research protocols in pharmacokinetics and metabolism of test agents in pregnant and lactating animals (and their offspring), and transplacental and translactational transport of test agents and/or metabolites in animal models.

1979 to 1981. Biologist I in Teratology. Teratological evaluation of compounds in laboratory animals (rats, mice, rabbits); expertise in all RTI SOPs for conventional teratology.

University of North Carolina School of Medicine, Department of Radiology, Chapel Hill, North Carolina.

1977 to 1979. Research Technician II. Used microradiological techniques to study the effects of vascular disease of the kidney in human and laboratory animals.

Bowman Gray School of Medicine, Department of Physiology, Winston-Salem, North Carolina.

1976 to 1977. Laboratory Technician II. Studied the effects of hypertension on vascular size in humans and laboratory animals.

Education

B.A., Biology (Psychology Minor), University of North Carolina at Greensboro, North Carolina, 1975.

Developmental Toxicology and Teratology, K. K. Sulik, course director, University of North Carolina at Chapel Hill (Spring, 1990).

American Association of Laboratory Animal Science—Laboratory Animal Technologist Certification course (EPA, Fall 1991)

Certification

Laboratory Animal Technologist (LATG), AALAS Certification (1992).

Professional Organizations

Society of Toxicology, NC Chapter

Teratology Society

North Carolina Association for Biomedical Research

North Carolina Quality Assurance Discussion Group

Publications

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- A Comparison of Developmental Toxicity in Fischer-344 (F-344) and CD Rats Exposed to Ethylene Glycol (EG). C. B. Myers, M. C. Marr, R. B. Sleet, *Teratology* **37**, No. 5, 479, 1988.
- Comparison of Single and Double Staining for Evaluation of Skeletal Development: The Effects of Ethylene Glycol (EG) in CD Rats. M. C. Marr, C. B. Myers, J. D. George, C. J. Price, *Teratology* **37**, No. 5, 476, 1988.
- Developmental Toxicity of Scopolamine Hydrobromide (SCOP) in Rats and Mice. J. D. George, C. J. Price, M. C. Marr, C. A. Kimmel, R. E. Morrissey and B. A. Schwetz, *The Toxicologist* **8** (1), 241, 1988.

- Teratologic Evaluation of Corn Oil (CO) or Distilled Water (DW) in CD-1 Mice and CD Rats. C. J. Price, J. D. George, B. M. Sadler, M. C. Marr, C. A. Kimmel, B. A. Schwetz, and R. E. Morrissey. *The Toxicologist* 9, 269, 1989.
- Teratologic Evaluation of Acrylamide (ACRL) in CD-1 Mice and CD Rats. E. A. Field, C. J. Price, R. B. Sleet, M. C. Marr, R. E. Morrissey, and B. A. Schwetz. *The Toxicologist* 9, 273, 1989.
- Developmental Toxicity Evaluation of Diethyl Phthalate (DEP) in CD® Rats. C. J. Price, R. B. Sleet, J. D. George, M. C. Marr, B. A. Schwetz, and R. E. Morrissey. *Teratology* 39, 473, 1989.
- Developmental Toxicity Evaluation of Dimethyl Phthalate (DMP) in CD Rats. E. A. Field, R. B. Sleet, C. J. Price, M. C. Marr, C. B. Myers, R. E. Morrissey, and B. A. Schwetz. *Teratology* 39, 452, 1989.
- Developmental Stages of the CD® Rat Skeleton. M. C. Marr, C. B. Myers, C. J. Price, R. E. Morrissey, and B. A. Schwetz. *Teratology* 39, 468, 1989.
- Developmental Toxicity of Boric Acid (BORA) in Mice and Rats. C. J. Price, E. A. Field, M. C. Marr, C. B. Myers, R. E. Morrissey and B. A. Schwetz. *The Toxicologist* 10, 39, 1990.
- Postnatal Effects of In Utero Exposure to Ethylene Glycol (EG) in the CD® Rat. H. K. Bates, C. J. Price, J. D. George, M. C. Marr, C. A. Kimmel, R. E. Morrissey and B. A. Schwetz. *The Toxicologist* 10, 38, 1990.
- Developmental Toxicity of Butyl Benzyl Phthalate (BBP) in Mice and Rats. C. J. Price, E. A. Field, M. C. Marr, C. B. Myers, R. E. Morrissey and B. A. Schwetz. *Teratology* 41, 586, 1990.
- Developmental Toxicity of Triethylene Glycol Dimethyl Ether (TGDM) in New Zealand White Rabbits. J. D. George, C. J. Price, M. C. Marr, R. E. Morrissey and B. A. Schwetz. *Teratology* 41, 560, 1990.
- Developmental Stages of the CD® Rat Skeleton after Maternal Exposure to Ethylene Glycol (EG). M. C. Marr, C. J. Price, C. B. Myers, R. E. Morrissey and B. A. Schwetz. *Teratology* 41, 576, 1990.
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March, 1995

CMA 120028

CHRISTINA B. MYERS, Research Biologist II

Professional Experience

Center for Life Sciences and Toxicology, Chemistry and Life Sciences Unit, Research Triangle Institute, Post Office Box 12194, Research Triangle Park, North Carolina 27709.

August 1987 to present. Data Specialist, Teratology Laboratory. Responsible for overseeing all data entry, statistical analysis of data for reports, SAS programming, EasyEntry Programming, dBase programming, 20/20 programming, report preparation and review. Proficiency in teratology laboratory SOPs for mice, rats and rabbits, and clinical chemistry; Involved in the development of SOPs, protocols, and preparation of study reports. Appointed Supervisor of Reproductive Toxicology Studies for commercial clients, March, 1990.

August 1984 to July 1987. Supervisor of Fertility Assessment by Continuous Breeding. Responsibilities included scheduling studies, dose preparation of test chemicals, microcomputer operation for the collection and analysis of data and necropsy procedures.

January 1984 to July 1984. Biologist I. Fertility Assessment by Continuous Breeding. Responsibilities included dosing of animals, vaginal smear analysis, sperm analysis and collection of litter data.

January 1983 to December 1983. Biologist I. Conducted metabolic studies in rats using radiolabeled xenobiotics with analysis of the biological fluids by HPLC and oxidation of the animal tissue for radioactivity determinations, *in vitro* xenobiotic metabolism, isolation of metabolites from biological fluids using reverse and normal phase HPLC.

October 1982 to December 1982. Biologist. Performed enzyme purification from various mouse tissues and *Drosophila* using affinity chromatography and isoelectric focusing.

June 1981 to September 1982. Biologist. Development of radioimmunoassays of cannabinoids.

November 1980 to May 1981. Biologist. Use of alkaline elution assay for determination of DNA damage, cloning efficiency assays of mammalian tissue culture cells, isolation of rat alveolar macrophages and their use in cytotoxicity screening, general tissue culture techniques and Ames assay for mutagenicity.

Education

B.A., Biology, West Virginia University, Morgantown, WV, 1978.

M.S., Biochemistry, West Virginia University, Morgantown, WV, 1980.

Computer Programming Courses

SAS® Program for New Computer Users

SAS® Basics

SAS® Processing

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SAS® Introduction to Statistic
SAS® Regression and ANOVA
SAS® Making the Transition to Release 6.06 of the SAS System
SAS® Macro Language
SAS® Report Writing
Introduction to 20/20 for VAX/VMS

Professional Societies

North Carolina Chapter of the Society of Toxicology
Teratology Society, Regular Member

Abstracts and Publications

Characterization and Subcellular Location of Soluble Proteins which Stimulated DNA Replication and Repair in Lysolecithin Permeabilized Animal Cells. Christina B. Myers, Pragna I. Patel and Michael R. Miller, Fed. Proc. 39 (Abstract), 1959, 1980.

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Developmental Stages of the CD® Rat Skeleton. M. C. Marr, C. B. Myers, C. J. Price, R. E. Morrissey, and B. A. Schwetz, *Teratology* 39, 468, 1989.

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Tricresyl Phosphate: Reproduction and Fertility Assessment in CD-1 Mice When Administered in the Feed. J. D. George, J. R. Reel, C. B. Myers, A. D. Lawton and J. C. Lamb IV. Final Study Report NTP/NIEHS Contract No. NO1-ES-2-5014, National Technical Information Service (NTIS) Accession No. PB86167277/AS, October 16, 1985.

Ethanol: Reproduction and Fertility Assessment in CD-1 Mice When Administered in the Drinking Water. J. D. George, J. R. Reel, C. B. Myers, A. D. Lawton and J. C. Lamb IV. Final Study Report, NTP/NIEHS Contract No. NO1-ES-2-5014, National Technical Information Service (NTIS) Accession No. PB86144979/AS, November 4, 1985.

Trichloroethylene: Reproduction and Fertility Assessment in CD-1 Mice When Administered in the Feed. J. D. George, J. R. Reel, C. B. Myers, A. D. Lawton and J. C. Lamb IV. Final Study Report, NTP/NIEHS Contract No. NO1-ES-2-5014, National Technical Information Service (NTIS) Accession No. PB86173150/AS, January 13, 1986.

Triethylene Glycol Diacetate: Reproduction and Fertility Assessment in CD-1 Mice When Administered in the Drinking Water. J. D. George, J. R. Reel, C. B. Myers, A. D. Lawton and J. C. Lamb IV. Final Study Report, NTP/NIEHS Contract No. NO1-ES-2-5014, National Technical Information Service (NTIS) Accession No. PB86161999/AS, January 13, 1986.

Methoxyacetic Acid: Reproduction and Fertility Assessment in CD-1 Mice When Administered in the Drinking Water. J. D. George, J. R. Reel, C. B. Myers, A. D. Lawton and J. C. Lamb IV. Final Study Report, NTP/NIEHS Contract No. NO1-ES-2-5014, National Technical Information Service (NTIS) Accession No. PB86164274/AS, January 17, 1986.

Trichloroethylene: Reproduction and Fertility Assessment in F-344 Rats When Administered in the Feed. J. D. George, J. R. Reel, C. B. Myers, A. D. Lawton and J. C. Lamb IV. Final Study Report, NTP/NIEHS Contract No. NO1-ES-2-5014, National Technical Information Service (NTIS) Accession No. PB86190782/AS, January 13, 1986.

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Reproduction and Fertility Evaluation of Diethylhexyl Phthalate (CAS No. 117-81-7) in CD-1 Mice Exposed During Gestation. C. J. Price, R. W. Tyl, M. C. Marr, C. B. Myers, B. M. Sadler and C. A. Kimmel. Final Study Report, NCTR/NTP Contract No. 222-80-2031(c), National Technical Information Service (NTIS) Accession No. PB88-204300/ AS, April 15, 1988.

Developmental Toxicity Evaluation of Dimethyl Phthalate (CAS No. 131-11-3) Administered to CD Rats on Gestational Days 6 through 15. E. A. Field, R. B. Sleet, C. J. Price, M. C. Marr, C. B. Myers, R. E. Morrissey and B. A. Schwetz. Final Study Report, NTP/NIEHS Contract No. NO1-ES-55080, National Technical Information Service (NTIS) Accession No. PB89-164826/AS, January, 9, 1989.

Developmental Stages of the CD Rat Skeleton: Part I: Normal Development. M. C. Marr, C. J. Price, C. B. Myers, R. E. Morrissey, and B. A. Schwetz. Final Study Report, NTP/NIEHS Contract No. NO1-ES-55080, February 10, 1989.

Developmental Toxicity Evaluation of Butyl Benzyl Phthalate (CAS No. 85-68-7) Administered in Feed to CD Rats on Gestational Days 6 to 15. E. A. Field, C. J. Price, M. C. Marr, C. B. Myers, R. E. Morrissey and B. A. Schwetz. Final Study Report, NTP/NIEHS Contract No. NO1-ES-95255, National Technical Information Service (NTIS) Accession No. PB90-115346AS, August 4, 1989.

Developmental Toxicity Evaluation of Boric Acid (CAS No. 10043-35-2) Administered in Feed to CD-1 Mice on Gestational Days 0 to 17. E. A. Field, C. J. Price, M. C. Marr, C. B. Myers, R. E. Morrissey and B. A. Schwetz. Final Study Report, NTP/NIEHS Contract No. NO1-ES-95255, August 11, 1989.

Developmental Toxicity Evaluation of Boric Acid (CAS No. 10043-35-3) Administered in Feed to CD Rats on Gestational Days 0 to 20 or 6 to 15. C. J. Price, E. A. Field, M. C. Marr, C. B. Myers, R. E. Morrissey and B. A. Schwetz. Final Study Report, NTP/NIEHS Contract NO1-ES-95255, December 20, 1989.

Developmental Stages of the CD Rat Skeleton: Part II: Development After Maternal Exposure to Ethylene Glycol (EG). M. C. Marr, C. J. Price, C. B. Myers, R. E. Morrissey, B. A. Schwetz, and J. J. Heindel. Final Study Report, NTP/NIEHS Contract No. NO1-ES-95255, January 5, 1990.

Developmental Toxicity Evaluation of Diethylene Glycol (CAS No. 111-46-6) Administered to Swiss (CD-1®) Mice on Gestational Days 6 through 15. H. K. Bates, C. J. Price, M. C. Marr, C. B. Myers, J. J. Heindel and B. A. Schwetz. Final Study Report, NTP/NIEHS Contract No. NO1-ES-95255, December 5, 1990.

Developmental Toxicity Evaluation of Mono(2-ethylhexyl) Phthalate (CAS No. 4376-20-9) Administered in Feed to Swiss (CD-1) Mice on Gestational Days 0 to 17. C. J. Price, M. C. Marr, C. B. Myers, R. E. Morrissey, J. J. Heindel, and B. A. Schwetz. Final Study Report, NTP/NIEHS Contract No. NO1-95255, December 17, 1990.

Developmental Toxicity Evaluation of Microencapsulated 2-Ethylhexanol (CAS No. 104-76-7) Administered to Swiss (CD-1®) Mice in the Feed on Gestational Days 0 to 17. R. W. Tyl, C. J. Price, M. M. Marr, C. B. Myers, J. J. Heindel and B. A. Schwetz. Final Study Report, NTP/NIEHS Contract No. NO1-ES-95255, National Technical Information Services (NTIS) Accession No. PB91185900, March 11, 1991.

Developmental Toxicity Evaluation of Ethylene Glycol (CAS No. 107-21-1) Administered to New Zealand White Rabbits by Gavage on Gestational Days 6 through 19. R. W. Tyl, C. J. Price, M. C. Marr, C. B. Myers, J. J. Heindel and B. A. Schwetz. Final Study Report, NTP/NIEHS Contract No. NO1-ES-95255, National Technical Information Services (NTIS) Accession No. PB91211219, March 15, 1991.

Developmental Toxicity Evaluation of Methacrylamide (CAS No. 79-39-0) Administered by Gavage to CD-1 Mice on Gestational Days 6 through 17. J. D. George, C. J. Price, M. C. Marr, C. B. Myers, J. J. Heindel and B. A. Schwetz. Final Study Report, NTP/NIEHS Contract No. NO1-ES-95255, NTIS Accession No. PB91208678, April 10, 1991.

Developmental Toxicity Evaluation of Boric Acid (CAS No. 10043-35-3) Administered to New Zealand White Rabbits by Gavage on Gestational Days 6 through 19. C. J. Price, M. C. Marr, C. B. Myers, J. J. Heindel, and B. A. Schwetz. Final Study Report, NTP/NIEHS Contract No. NO1-95255, NTIS Accession No. PB9212950/AS, October 30, 1991.

Developmental Toxicity Evaluation of Napthalene (CAS No. 91-20-3) Administered by Gavage to Sprague-Dawley (CD) Rats on Gestational Days 6 through 15. H. A. Navarro, C. J. Price, M. C. Marr, C. B. Myers, J. J. Heindel and B. A. Schwetz. Final Study Report, NTP/NIEHS Contract No. NO1-95255, National Technical Information Service (NTIS) Accession No. PB92135623, December 12, 1991.

Developmental Toxicity Evaluation of California Pesticide/Fertilizer Mixture Administered in the Drinking Water to Sprague-Dawley (CD) Rats on Gestational Days 6 to 20. J. D. George, C. J. Price, M. C. Marr, C. B. Myers, J. J. Heindel and B. A. Schwetz. Final Study Report, NTP/NIEHS Contract No. NO1-95255, National Technical Information Service (NTIS) Accession No. PB92170406, February 24, 1992.

Developmental Toxicity Evaluation of *d*-Camphor (CAS No. 464-49-3) Administered by Gavage to Sprague-Dawley (CD®) Rats on Gestational Days 6 Through 15. H. A. Navarro, C. J. Price, M. C. Marr, and C. B. Myers. Final Study Report, NTP/NIEHS Contract No. NO1-95255, National Technical Information Service (NTIS) Accession No. PB92170406, March 5, 1992.

Developmental Toxicity Evaluation of N,N'-Methylenebisacrylamide (CAS No. 110-26-9) Administered by Gavage to Swiss (CD-1®) Mice on Gestational Days 6 Through 17. J. D. George, C. J. Price, M. C. Marr, C. B. Myers. Final Study Report, NTP/NIEHS Contract No. NO1-95255, National Technical Information Service (NTIS) Accession No. PB92177781, March 26, 1992.

Developmental Toxicity Evaluation of Dipropylene Glycol (CAS No. 25265-71-8) Administered to Sprague-Dawley (CD®) Rats from Gestation Day 6 Through Gestation Day 15. H. K. Bates, C. J. Price, M. C. Marr, C. B. Myers. Final Study Report, NTP/NIEHS Contract No. NO1-95255, National Technical Information Service (NTIS) Accession No. PB92196179, May 26, 1992.

Developmental Toxicity Evaluation of 8-Methoxypsoralen (CAS No. 298-81-7) Administered by Gavage to Sprague-Dawley (CD®) Rats on Gestational Days 6 Through 15. H. A. Navarro, C. J. Price, M. C. Marr, C. B. Myers. Final Study Report, NTP/NIEHS Contract No. NO1-95255, National Technical Information Service (NTIS) Accession No. PB92219666, June 22, 1992.

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Developmental Toxicity Evaluation of Dipropylene Glycol (CAS No. 25265-71-8) Administered by Gavage to New Zealand White (NZW) Rabbits from Gestation Day 6 through Gestation Day 19. H. K. Bates, C. J. Price, M. C. Marr, C. B. Myers, J. J. Heindel and B. A. Schwetz. Final Study Report, NTP/NIEHS Contract No. NO1-ES-95255, National Technical Information Service (NTIS) Accession No. PB92-238294, August 28, 1992.

Developmental Toxicity Evaluation of *d*-Camphor (CAS No. 464-49-3) Administered by Gavage to New Zealand White (NZW) Rabbits on Gestational Days 6 through 15. H. A. Navarro, C. J. Price, M. C. Marr, C. B. Myers, J. J. Heindel and B. A. Schwetz. Final Study Report, NTP/NIEHS Contract No. NO1-ES-95255, National Technical Information Service (NTIS) Accession No. PB93-123784.

Developmental Toxicity Evaluation of Polyoxyethylene Sorbitan Monolaurate (CAS No. 9005-64-5) Administered by Gavage to Sprague-Dawley (CD) Rats on Gestational Days 6 through 15. C. J. Price, J. D. George, M. C. Marr, C. B. Myers, J. J. Heindel and B. A. Schwetz. Final Study Report, NTP/NIEHS Contract No. NO1-ES-95255, National Technical Information Service (NTIS) Accession No. PB93-123800, October 14, 1992.

Developmental Toxicity Evaluation of Polyoxyethylene Sorbitan Monooleate (CAS No. 9005-65-6) administered by Gavage to Sprague-Dawley (CD) Rats on Gestational Days 6 through 15. C. J. Price, J. C. George, M. C. Marr, C. B. Myers, J. J. Heindel and B. A. Schwetz. Final Study Report, NTP/NIEHS Contract No. NO1-ES-95255, National Technical Information Service (NTIS) Accession No. PB93-123826, October 14, 1992.

Developmental Toxicity Evaluation of Ethylenediamine (CAS No. 107-15-3) Administered by Gavage to New Zealand White Rabbits on Gestational Days 6 through 19. C. J. Price, J. D. George, M. C. Marr, C. B. Myers, J. J. Heindel, E. S. Hunter and B. A. Schwetz. Final Study Report, NTP/NIEHS Contract No. NO1-ES-95255, National Technical Information Service (NTIS) Accession No. PB93-190056, March 12, 1993.

Developmental Toxicity Evaluation of Methacrylonitrile (CAS No. 126-98-7) Administered to Sprague-Dawley (CD®) Rats from Gestation Day 6 through Gestation Day 15 by Gavage. J. D. George, C. J. Price, M. C. Marr, C. B. Myers, J. J. Heindel, E. S. Hunter, and B. A. Schwetz. Final Study Report, NTP/NIEHS Contract No. NO1-ES-95255, National Technical Information Service (NTIS) Accession No. PB93-190072, April 7, 1993.

Developmental Toxicity Evaluation of Methacrylonitrile (CAS No. 126-98-7) Administered by Gavage to New Zealand White (NZW) Rabbits from Gestational Day 6 through 19. J. D. George, C. J. Price, M. C. Marr, C. B. Myers, E. S. Hunter and B. A. Schwetz. Final Study Report, NTP/NIEHS Contract No. NO1-ES-95255, National Technical Information Service (NTIS) Accession No. PB93-196061, April 22, 1993.

Developmental Toxicity Evaluation of Methylene Blue Trihydrate (CAS No. 7220-79-3) Administered by Gavage to Sprague-Dawley (CD®) Rats from Gestational Days 6 through 15. H. A. Navarro, C. J. Price, M. C. Marr, C. B. Myers, J. J. Heindel, E. S. Hunter, and B. A. Schwetz. Final Study Report, NTP/NIEHS Contract No. NO1-ES-95255, National Technical Information Service (NTIS) Accession No. PB93-219574, June 14, 1993.

Developmental Toxicity Evaluation of Glyoxal Trimeric Dihydrate (CAS No. 4405-13-4) Administered by Gavage to New Zealand White (NZW) Rabbits from Gestational Days 6 through 19. J. D. George, C. J. Price, M. C. Marr, C. B. Myers, J. J. Heindel, E. S. Hunter, and B. A. Schwetz. Final Study Report, NTP/NIEHS Contract No. NO1-ES-95255, National Technical Information Service (NTIS) Accession No. PB94-104064, Final Report; National Technical Information Service (NTIS) Accession No. PB94-104072, Laboratory Supplement, August 18, 1993.

Developmental Toxicity Evaluation of Sodium Fluoride (CAS NO. 7681-49-4) Administered to New Zealand White (NZW) Rabbits from Gestational Day 6 through Gestational Day 19 in Drinking Water. H. K. Bates, C. J. Price, M. C. Marr, C. B. Myers, J. J. Heindel, E. S. Hunter, M. D. Shelby and B. A. Schwetz. Final Study Report, NTP/NIEHS Contract No. NO1-ES-95255, December 15, 1993.

Developmental Toxicity Evaluation of α -Cyclodextrin (CAS NO. 10016-20-3) Administered in the Feed to Sprague-Dawley (CD®) Rats on Gestational Days 6 to 16. H. A. Navarro, C. J. Price, M. C. Marr, C. B. Myers, E. S. Hunter, M. D. Shelby and B. A. Schwetz. Final Study Report NTP/NIEHS Contract No. NO1-ES-95255, January 10, 1994.

Developmental Toxicity Evaluation of Glyoxal Trimeric Dihydrate (CAS NO. 4405-13-4) Administered to Sprague-Dawley (CD®) Rats from Gestation Day 6 through Gestation Day 15 by Gavage. J. D. George, C. J. Price, M. C. Marr, C. B. Myers, J. J. Heindel, E. S. Hunter, M. B. Shelby and B. A. Schwetz. Final Study Report NTP/NIEHS Contract No. NO1-ES-95255, February 3, 1994.

Developmental Toxicity Evaluation of Thiophenol (CAS No. 108-98-5) Administered to Sprague-Dawley (CD®) Rats from Gestation Day 6 through Gestation Day 15 by Gavage. J. D. George, C. J. Price, M. C. Marr, C. B. Myers, E. S. Hunter, M. D. Shelby, and B. A. Schwetz. Final Study Report, NTP/NIEHS Contract No. NO1-ES-95255, February 28, 1994.

Developmental Toxicity Evaluation of α -Cyclodextrin (CAS NO. 10016-20-3) Administered in the Feed to Swiss (CD-1®) Mice on Gestational Days 6 to 16. H. A. Navarro, C. J. Price, M. C. Marr, C. B. Myers, E. S. Hunter, M. B. Shelby, and B. A. Schwetz. Final Study Report, NTP/NIEHS Contract No. N01-ES-95255, May 9, 1994.

Developmental Toxicity Evaluation of 8-Methoxypsoralen (CAS NO. 298-81-7) Administered by Gavage to New Zealand White (NZW) Rabbits from Gestational Days 6 through 19. C. J. Price, H. A. Navarro, M. C. Marr, C. B. Myers, J. J. Heindel, E. S. Hunter, M. D. Shelby and B. A. Schwetz. Final Study Report, NTP/NIEHS Contract No. N01-ES-95255, May 9, 1994.

Developmental Toxicity Evaluation of Thiophenol (CAS No. 108-98-5) Administered by Gavage to New Zealand White (NZW) Rabbits on Gestational Days 6 through 19, H. A. Navarro, C. J. Price, M. C. Marr, C. B. Myers, E. S. Hunter, III, M. D. Shelby, and B. A. Schwetz. NTP/NIEHS Contract N01-ES-95255, NTIS Nos. (to be assigned), July 29, 1994.

Developmental Toxicity Evaluation of Methylene Blue Trihydrate (CAS No. 7220-79-3) Administered by Gavage to New Zealand White (NZW) Rabbits on Gestational Days 6 through 19, H. A. Navarro, C. J. Price, M. C. Marr, C. B. Myers, J. J. Heindel, E. S. Hunter, III, M. D. Shelby, and B. A. Schwetz. NTP/NIEHS Contract N01-ES-95255, NTIS Nos. (to be assigned), August 8, 1994.

Developmental Toxicity Evaluation of Sodium Fluoride (CAS No. 7681-49-4) Administered to Sprague-Dawley (CD®) Rats from Gestation Day 6 through Gestation Day 15 in Drinking Water, H. K. Bates, C. J. Price, M. C. Marr, C. B. Myers, J. J. Heindel, E. S. Hunter, III, M. D. Shelby, and B. A. Schwetz. NTP/NIEHS Contract N01-ES-95255, NTIS Nos. (to be assigned), September 8, 1994.

Developmental Toxicity Evaluation of Diethylstilbestrol (CAS No. 56-53-1) Administered Subcutaneously to Swiss (CD-1®) Mice on Gestational Days 9 through 16, H. A. Navarro, J. D. George, C. J. Price, M. C. Marr, C. B. Myers, E. S. Hunter, III, M. D. Shelby, and B. A. Schwetz. NTP/NIEHS Contract N01-ES-95255, NTIS Nos. (to be assigned), October 5, 1994.

March, 1995

TSAI-YING YU CHANG, Research Histotechnologist 1

PROFESSIONAL EXPERIENCE

May 1992 to date. Research Histotechnologist 1, Center for Life Sciences and Toxicology, Chemistry and Life Sciences, Research Triangle Institute, Post Office Box 12194, Research Triangle Park, NC 27709. Perform all facets of work in histology laboratory, including gross trimming, embedding, cutting, staining, inventory, quality control, operating and maintenance of equipment, developing new Standard Operating Procedures (SOPs) as needed and updating existing SOPs, and performing special techniques of dissecting nervous tissue for paraffin and plastic sections. Participate in necropsies, wet tissue audits on special projects, and assist other laboratories as needed. Train and supervise laboratory personnel, communicate with project leaders and subcontractors, and provide cost estimates for proposals.

November 1990 to April 1992. Histotechnologist 2

August 1986 to October 1990. Pathologist Assistant, Roche Biomedical Laboratory, Inc., 1447 York Court, Burlington, NC 27215. Performed gross description and trimming of surgical specimens and summarized patient clinical histories.

August 1980 to July 1986. Histology Supervisor, Tegeris Research Laboratories, Inc., 9705 N. Washington Boulevard, Laurel, MD 20854. Trained and supervised histology and necropsy technicians. Performed gross trimming, processing, embedding, cutting, and staining of tissues.

August 1973 to April 1980. Histology Technician, Gillette Medical Evaluation Laboratory, 1413 Research Boulevard, Rockville, MD 20850. Supervised and trained histology technicians. Performed gross trimming, processing, embedding, cutting, and staining of tissues.

April 1972 to July 1973. Histology Technician, Columbia Hospital for Women, 24th Street, N.W., Washington, DC 20037. Performed routine histology laboratory studies (tissues, sputum, CSF).

April 1969 to August 1971. Laboratory Technician, Smithsonian Institute, 12441 Parklawn Drive, Rockville, MD 20852. Performed culture of plant materials, scoring of chromosomal aberrations, and statistical analysis of data.

EDUCATION

BS, Entomo-Phyto Pathology, Chung-Hsin University, Taichung, Taiwan, 1954

Certified Histotechnologist (HT-ASCP, #HT008134), Washington, DC, 1976.

PROFESSIONAL SOCIETIES

American Society of Clinical Pathology for Medical Technology

National Society for Histotechnologists

THESIS

Studies on Two Strains of Brown Strip Disease Pathogens (*Helminthosporum stenospilus*) of Sugarcane (BS Thesis, 1970)

PUBLICATIONS

Ma, T.-H., A. J. Snope, and T.-Y. Chang (1970). Far-red light effect of ultraviolet light induced chromatid aberrations in pollen tubes of *Tradescantia*. *Radiation Botany* 11: 39-43.

Chang, T.-Y., and R. Blakeney (1984). Precision positioning of small tissues with agar. *Laboratory Medicine*.

Chang, T.-Y., and J.L. Murdock (1985). A modified oil Red O technique. *The Maryland Micron*, Official Newsletter of the Maryland Society of Histotechnologists, July 5-6.

March 1995

STEPHANIE M. TAULBEE, Manager, Quality Assurance Unit

Professional Experience

1988 to date. Research Triangle Institute, Research Triangle Park, NC

1991 to date: Manager, Quality Assurance Unit, Research Triangle Institute, Research Triangle Park, NC 27709. Managed the Quality Assurance Unit which is responsible for assuring the compliance of ongoing nonclinical studies with 25 study directors and task leaders for the FDA, EPA and International Good Laboratory Practice (GLP) Regulations. Hosted site visitors and QA auditors from commercial and governmental sponsors. Provided training in the GLPs for study directors, laboratory personnel, and members of the QA Unit. Conducted off-site audits for private contractors and inspected laboratory subcontractors. Consulted with contractors concerning implementation of GLPs. Assisted in the development of governmental guidelines, finalization of EPA's Good Automated Laboratory Practices. Performed quality and consistency audits on Toxicological Profiles prepared by RTI staff.

1988 to 1991: Quality Assurance Specialist, Quality Assurance Unit, Research Triangle Institute, Research Triangle Park, NC 27709. Responsible for reviewing protocols, scheduling inspections of critical phases, and auditing reports and study records for the Developmental and Neurobehavioral Toxicology Laboratories to assure compliance with the FDA and EPA Good Laboratory Practice Regulations. Hosted governmental and commercial clients during site visits and their respective auditors during data and report audits. Responsible for receiving of data and specimens into the archives and maintaining the archive data base. Developed and conducts three part training seminar for study directors and laboratory staff in GLPs.

1985 to 1988: Histology Technician, Pathology Associates, Inc., Research Triangle Park, NC 27709. Conducted Quality Assurance audits for over 100 studies on NTP Retrospective Audit contract in conjunction with Argus Research Laboratories including slide/block evaluation, wet tissue review, and data auditing. Performed histological procedures including necropsy, tissue processing, embedding, cutting, staining, etc. Quality Assurance inspections and report auditing for Electron Microscopy Laboratory at Pathology Associates, Inc.

1985 to 1986. Lab Aide, Cytology Department, Wake County Medical Center, Raleigh, NC. Received, logged and numbered cytology specimens.

1979. Pathology Assistant, Carteret General Hospital, Morehead City, NC. Assisted Pathologist and Histotechnician in procedures including tissue examination and sectioning, tissue processing and embedding, staining and other special procedures.

1976 to 1978. Parapathology Supervisor, Toxic Hazards Research Unit, Dayton, OH. Duties included necropsy, description of lesions, anesthesia, euthanasia, tissue processing and embedding, stain techniques, and many special procedures relating to oncogenic studies on Rhesus monkeys, dogs, rabbits, rats, mice, hamsters, and guinea pigs. Supervised 7 lab assistants, development of new quality control procedures, writing of Standard Operating Procedure Manual, and training new technicians.

1975. Veterinary Assistant, Old Troy Pike Veterinary Clinic, Dayton, OH. Animal handling and care, assisted in clinical and operating room procedures, lab work including stool exam, urine tests, and blood tests, anesthesia, X-ray, administration of medication including injections and IV.

1974 to 1975. Media Preparation Technician, Hill Top Research, Inc., Miamiville, OH. Preparation of microbiological media and reagents, stock and inventory, assisted in testing procedures in food and product testing lab, supervised part-time assistants.

1973 to 1974. Hematology Technician, Eastern Hill/Central Laboratories, Cincinnati, OH. C.B.C or autohemolyzer, sedimentation rates, prothrombin times, pregnancy tests, type and RH factors, and urinalysis.

Education

M.S.P.H., Environmental Science and Engineering, University of North Carolina at Chapel Hill, expected completion 1995.

B.S. Health Occupations Education(Summa Cum Laude), North Carolina State University, Raleigh, NC, 1991.

Attended University of Cincinnati, Cincinnati, OH, Biology, 1972.

Attended Marshall University, Huntington, WV, Zoology, 1968-1971.

Special Training

Quality Assurance Basic Training Seminar, Society of Quality Assurance Annual Meeting, 1988.

University of California, Irvine, Wright Patterson Air Force Base, Dayton, OH. Six month training program including three months of classroom training in comparative anatomy, pathology, and laboratory procedures and three months of practical training.

Carteret Technical College, Morehead City, NC. Two classes in basic computer programming.

Professional Affiliations

The Honor Society of Phi Kappa Phi
American Society of Clinical Pathologists
Society of Quality Assurance
North Carolina Quality Assurance Discussion Group, Chairperson of Training Sub-Committee, 1991-1993.

Professional Certification

HT, American Society of Clinical Pathologists

Seminars Presented

Archive Verification, Basic Training Seminar, Society of Quality Assurance Annual Meeting, Kansas City, MO, 1991.

Walk Through the GLPs, Research Triangle Institute.

Walk through the GLPs, North Carolina Quality Assurance Discussion Group, April 1993

The Importance of Scientific Accuracy: Issues of Ethics and Integrity, February 1994, Served as Chairman of Seminar Committee and presented the Concluding Remarks.

Publications

The Good Laboratory Practices in Parallel (compiled by S. M. Taulbee), Research Triangle Institute, 1991.

International GLPs, R.S. DeWoskin and S.M. Taulbee, Interpharm Press, 1993

Taulbee's Pocket Companion: US FDA and EPA GLPs in Parallel, edited by S.M. Taulbee and R.S. DeWoskin, Interpharm Press, 1993

Taulbee's International Pocket Companion, International GLPs in Parallel, edited by S.M. Taulbee and R.S. DeWoskin, Interpharm Press, 1994

Implementation of Current Good Manufacturing Practices in a Small Research Laboratory Setting: Celia D. Keller and Stephanie M. Taulbee. Quality Assurance: Good Practice Regulation and Law 4 (1).

Abstract and Poster Presentations

FDA-EPA: So, What's the Difference? S. M. Taulbee, Society of Quality Assurance Annual Meeting, Kansas City, MO, October 1991. published in Quality Assurance: Good Practices, Regulations and Law, 1993.

Getting Started with Regulatory Compliance: How the QA Professional Can Help: S.M. Taulbee, G.D. Digsby, D.L. Brodish, C.D. Keller, and P.D Hall. Poster presented at the Society of Quality Assurance Annual Meeting, San Francisco, CA. October 1993.

Implementation of Current Good Manufacturing Practices in a Small Research Laboratory Setting: Celia D. Keller and Stephanie M. Taulbee. Poster presented at the Society of Quality Assurance Annual Meeting, New Orleans, LA, October 1994.

September 1995

Appendix 3
SOP Listings from RTI including Quality Assurance

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TERA-001	Calibration of Analytical Balances and Verification of Routine Calibration	1/28/87	11/29/95
TERA-003	Dose Formulation 1. Dose Formulation Preparation 2. Weighing of Compound 3. Preparation of a Solution 4. Preparation of a Suspension 5. Preparation of Dosed Feed 6. Preparation of Dosed Drinking Water	1/29/87	1/14/94
TERA-004	Formulation of Common Fixatives and Staining Solutions	1/29/87	1/7/94
TERA-005	Chemical Handling and Analysis 1. Receipt of Chemical, Record Keeping and Initial Processing 2. Purity and Identify of Bulk Chemical 3. Dosage Formulation and Analysis 4. Chemical-Vehicle Referee Analysis Program 5. Bulk Chemical Reanalysis	RETIRED AS OF 11/27/95 1/28/87	10/26/93
TERA-006	Peroxide Analysis	RETIRED AS OF 11/27/95 1/28/87	10/26/93
TERA-007	Weighing Granular or Pelletized Food for Determining Food Consumption for Rodents	1/28/87	1/7/94
TERA-008	Weighing Water for Determining Water Consumption	1/28/87	11/29/95
TERA-009	Blood Collection from Fetal or Neonatal Rodents	1/28/87	11/30/95
TERA-010	Blood Collection from Adult Rodents	1/28/87	1/20/94
TERA-011	Plasma Collection	1/28/87	10/26/93
TERA-012	Serum Collection	1/28/87	10/26/93
TERA-013	Necropsy Procedures for Unscheduled Deaths	1/28/87	10/26/93
TERA-014	Necropsy of Neonatal, Postweaning and Adult Rodents – Defined Ages	1/28/87	11/30/95
TERA-015	Necropsy - General Comments	1/28/87	11/30/95
TERA-016	Necropsy of Neonatal Rodents	1/28/87	10/26/93
TERA-017	Necropsy of Postweaning and Adult Rodents	6/15/89	9/21/95

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TERA-019	Collection of Urine and/or Uroliths from Rodents at Necropsy	1/28/87	11/30/95		
TERA-020	Identification of Animals	1/27/88	1/7/94		
TERA-021	Calibration and Use of Vapor Pressure Osmometer	2/16/88	RETIRED		
TERA-022	Blood Collection and Processing for Serodiagnostic Test Panel	12/20/88	1/7/94		
TERA-023	Preparing Specimens and Data to be Sent to the Research Triangle Institute Archives and the National Toxicology Program (NTP) Archives	10/12/89	4/8/94		
TERA-024	Staining Implantation Sites in Formalin-Fixed Uteri with Potassium Ferricyanide	5/14/90	11/1/93		
TERA-025	Skeletal Staining with the Sakura EBS-400B Teratology Processor	5/24/90	11/5/93		
TERA-026	Determination of Estrous Cyclicity and Cycle Length in Rodents	3/8/91	11/5/93		
TERA-027	External Determination of Fetal or Neonatal Sex in Rodents	4/15/91	11/10/93		
TERA-028	Collection of Amniotic Fluid	4/2/92	11/8/93		
TERA-029	Identification of Neonatal Rodents	3/10/93	11/8/93		
TERA-030	Evaluation of Postnatal Rodent Heads	4/13/93	11/8/93		
TERA-031	External Exam of Neonatal Rodents	10/15/93			
TERA-032	Necropsy of the Rodent Dominant Lethal Females	1/24/94			
TERA-033	Transferring Animals Into and Out of Inhalation Exposure Chambers	1/24/94			
TERA-034	Administration of Test Chemical by Cutaneous Application	2/8/94			
TERA-035	Descriptions of Findings During Teratological Evaluations (Glossary)	10/24/94			
TERA-036	Obtaining Random Numbers for Use in Reproductive Toxicity Studies	10/25/94			
TERA-037	Transfer of Live Study Rodents from Another Facility to RTI	10/13/95			
TERA-038	Measuring Anogenital Distance in Perinatal Rodents	8/28/95			

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TERA-039	Unscheduled Deaths When the In-Life Portions of a Study are Conducted at Another Facility	10/16/95	
TERA-040	Calibration of Liquid in Glass Laboratory Thermometers	11/16/95	

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SPECIES-SPECIFIC STANDARD OPERATING PROCEDURES RAT: TERA-100 SERIES					
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TERA-100	Teratological Evaluation in Rats	1/29/87	---		
TERA-101	Weighing Rats 1. Weighing Mature Rats 2. Weighing Neonatal Rats	1/30/87	7/26/93		
TERA-102	Breeding Rats	1/29/87	8/1/95		
TERA-103	Examination of Vaginal Cytology in Rats	1/30/87	8/1/95		
TERA-104	Vaginal Smears: Detection of Sperm - Positive Females	1/29/87	8/1/95		
TERA-105	Assignment of Female Rats to Dose Groups Using Stratified Randomization Procedures	1/29/87	9/18/95		
TERA-106	Compound Administration 1. General Remarks 2. Intravenous Injection (iv) 3. Intraperitoneal Injection (ip) 4. Subcutaneous Injection (sc) 5. Gavage (po) 6. Administration of Test Chemical by Drinking Water 7. Administration of Test Chemical by Feed 8. Clinical Signs	1/30/87	2/28/95		
TERA-109	Teratological Evaluation 1. Station I 2. Station II 3. Station III 4. Station IV	1/30/87	8/1/95		
TERA-110	Determining Fetal Crown-Rump Length	1/29/87	8/2/95		
TERA-111	Detailed Examination of Diaphragm and Removal of Diaphragm and Heart from Rodent Fetuses	1/29/87	8/1/95		
TERA-112	Examination and Storage of Fetal Rat Heads	1/30/87	8/1/95		
TERA-113	Staining the Rat Skeleton with Alizarin Red S.	1/29/87	10/22/95		
TERA-114	Examination of Alizarin Red S Stained Skeletons	1/30/87	10/22/93		

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<u>SOP Number</u>	<u>Subject</u>	<u>Effective Date</u>	<u>Review or Revision Date</u>
TERA-115	Staining the Rat Skeleton with Alcian Blue/Alizarin Red S	1/30/87	11/20/95
TERA-116	Examination of Alcian Blue/Alizarin Red S Stained Rat Skeletons	1/30/87	12/1/95
TERA-117	Preparation of Rat Skeletons for Storage	1/29/87	11/20/95
TERA-118	Milk Collection from Lactating Rats	2/16/88	11/20/95
TERA-119	Pup Fluid Deprivation	2/16/88	11/20/95
	RETIRED 10/21/93		
TERA-120	Culling Postnatal Litters	3/16/89	11/20/95
TERA-121	Orbital Bleeding of Rodents	7/19/89	11/20/95
TERA-122	Selection of Fetuses for External, Visceral, Craniofacial and Skeletal Examinations During a Definitive Developmental Toxicity Study	10/17/89	10/22/93
TERA-123	Documentation of Postnatal Day 0, of Culling of Litters, of Pup Body Weights, and of Pup Selections for Multigeneration Studies	6/5/90	11/20/95
TERA-124	Administering Dosing Formulations by Gavage or Parenteral Routes to Females During Delivery of their Litters	9/19/90	11/20/95

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<u>SOP Number</u>	<u>Subject</u>	<u>Effective Date</u>	<u>Review or Revision Date</u>
TERA-200	Teratological Evaluation in Mice	1/28/87	7/13/95
TERA-201	Weighing Mice 1. Weighing Mature Mice 2. Weighing Neonatal Mice	1/28/87	9/6/96
TERA-202	Breeding Mice	1/29/87	9/6/96
TERA-203	Copulation Plugs in Mice	1/28/87	9/6/96
TERA-204	Assignment of Female Mice to Dose Groups Using Stratified Randomization Procedures	1/28/87	9/6/96
TERA-205	Compound Administration to Mice 1. General Remarks 2. Intravenous Injection (iv) 3. Intraperitoneal Injection (ip) 4. Subcutaneous Injection (sc) 5. Gavage (po) 6. Administration of Test Chemical in Drinking Water 7. Administration of Test Chemical by Feed 8. Clinical Signs	1/28/87	9/6/96
TERA-209	Teratological Evaluation 1. Station I 2. Station II 3. Station III 4. Station IV	1/30/87	10/3/95
TERA-210	Examination and Storage of Fetal Mouse Heads	1/30/87	9/6/96
TERA-211	Staining the Mouse Skeleton with Alizarin Red S	1/28/87	7/18/90
TERA-212	Examination of Alizarin Red S Stained Skeletons	1/30/87	7/18/90
TERA-213	Staining the Mouse Skeleton with Alcian Blue/Alizarin Red S	1/28/87	10/3/95
TERA-214	Examination of Alcian Blue/Alizarin Red S Stained Mouse Skeletons	2/2/87	7/13/93
TERA-215	Preparation of the Mouse Skeleton for Storage	1/28/87	7/13/93
TERA-216	Selection of Fetuses for External, Visceral, Craniofacial and Skeletal Examinations During a Definitive Developmental Toxicity Study	10/17/89	9/6/96

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TERA-300	Teratological Evaluation in Rabbits	1/29/87	---
TERA-301	Weighing Rabbits 1. Weighing Mature Rabbits 2. Weighing Neonatal Rabbits	1/29/87	5/19/95
TERA-302	Artificial Insemination of the Rabbit	1/28/88	5/19/95
TERA-303	Assignment of Female Rabbits to Dose Groups Using Stratified Randomization Procedures	1/29/87	5/22/95
TERA-304	Compound Administration in Rabbits 1. General Remarks 2. Intravenous Injection (iv) 3. Subcutaneous Injection (sc) 4. Gavage (po) 5. Clinical Signs	1/29/87	5/19/95
TERA-305	Necropsy of Rabbits	7/20/89	5/19/95
TERA-307	Teratological Evaluation of Rabbit Conceptus 1. Station I 2. Station II 3. Station III 4. Station IV	1/30/87	7/31/95
TERA-308	Examination and Storage of Fetal Rabbit Heads	1/30/87	7/31/95
TERA-309	Staining the Rabbit Skeleton with Alizarin Red S	1/29/87	7/31/95
TERA-310	Examination of Alizarin Red S Stained Rabbit Fetal Skeletons	1/30/87	7/31/95
TERA-311	Staining the Rabbit Skeleton with Alcian Blue/Alizarin Red S	1/29/87	7/31/95
TERA-312	Examination of Alcian Blue/Alizarin Red S Stained Rabbit Skeletons	1/30/87	7/31/95
TERA-313	Preparation of Rabbit Skeletons for Storage	1/29/87	7/31/95
TERA-314	Arterial Blood Collection from the Central Artery of the Rabbit Ear	9/6/89	7/31/95
TERA-315	Selection of Fetuses for External, Visceral, Craniofacial and Skeletal Examinations During a Definitive Developmental Toxicity Study	RETIRED	3/93

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TERA-316	Weighing Pelletized Feed for Determining Food Consumption for Rabbits	9/26/90	7/31/95
TERA-317	Determining Fetal Crown Rump Length in Rabbits	7/14/92	3/8/95
TERA-318	Collection of Blood from the Rabbit for Coagulation Assays	11/10/92	7/31/95
TERA-319	Ordering, Receipt, Housing, Quarantine and Initial Feeding for Vendor-Mated Rabbits	11/19/93	8/14/94
TERA-320	Administration of a Test Article by Application to the Dorsal Skin of Rabbits	2/8/94	
TERA-321	Collection of Urine in Female Rabbits	1/19/95	
TERA-322	Identification of Rabbits by Microchip	3/13/95	
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(TERA-400 SERIES IS NOT CURRENTLY IN USE AND IS IN THE PROCESS OF BEING REVISED)

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TERA-400	Teratological Evaluation in Hamsters		
TERA-401	Weighing Hamsters 1. Weighing Mature Hamsters 2. Weighing Neonatal Hamsters		
TERA-402	Breeding Hamsters		
TERA-403	Assignment of Female Hamsters to Dose Groups Using Stratified Randomization Procedures		
TERA-404	Compound Administration 1. General Remarks 2. Intraperitoneal Injection (ip) 3. Subcutaneous Injection (sc) 4. Gavage (po) 5. Administration of Test Chemical by Drinking Water 6. Administration of Test Chemical by Feed 7. Clinical Signs		
TERA-407	Teratological Evaluation of Hamster Conceptus 1. Station I 2. Station II 3. Station III 4. Station IV		
TERA-408	Examination and Storage of Fetal Heads		
TERA-409	Staining the Hamster Skeleton with Alizarin Red S		
TERA-410	Examination of Alizarin Red S Stained Skeletons		
TERA-412	Examination of Alcian Blue/Alizarin Red S Stained Hamster Skeletons		
TERA-413	Preparation of the Hamster Skeleton for Storage		

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<u>SOP Number</u>	<u>Subject</u>		<u>Effective Date</u>	<u>Review or Revision Date</u>
TERA-500	Data Entry and Statistical Processing	RETIRED 8/9/95	1/29/87	-----
TERA-502	Preparation of Data for Computer Entry		1/29/87	8/9/95
TERA-504	Overview of the VAX Accounts		5/2/91	8/9/95
TERA-509	Helpful Information for Using the VAX and Submitting SAS Jobs		6/11/91	8/9/95
TERA-511	Entering Preliminary Toxicity Data and Teratology Study Data Using Easy Entry on the VAX		5/7/91	8/9/95
TERA-526	Computer Software Program Calculation of Percentage of Fetuses Affected with Malformations or Variations		7/5/90	8/9/95
TERA-527	Collecting, Collating and Summarizing Clinical Observations		12/12/90	8/9/95
TERA-528	Logging Onto the VAX Using the VT 320 or VT 420		5/7/91	8/9/95
TERA-529	Generation of Study-Specific Codebook		5/2/91	8/9/95
TERA-530	Creating SAS Files from Raw Teratology Data		5/7/91	8/9/95
TERA-531	Bartlett Test		5/7/91	8/9/95
TERA-532	Analysis of Variance - ANOVA		6/4/91	8/9/95
TERA-533	Dunnett's Test		5/31/91	8/9/95
TERA-534	Williams' Test		6/11/91	8/9/95
TERA-535	Linear Trends Test		6/4/91	8/9/95
TERA-536	Chi-Square Test		5/31/91	8/9/95
TERA-537	Fisher's Exact Test		6/4/91	8/9/95
TERA-538	Linear Trend on Proportions		5/31/91	8/9/95
TERA-539	Repeated Measures ANOVA		6/12/91	8/9/95
TERA-540	Kruskal-Wallis Test		6/11/92	8/9/95

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TERA-541	Mann-Whitney U Test	6/11/91	8/9/95
TERA-542	Jonckheere's Test	6/11/91	8/9/95
TERA-543	Generating a Table of Defects	6/12/91	8/9/95
TERA-544	Generating the Embryo/Fetal Table	6/11/91	8/9/95
TERA-545	Generating Individual Data Tables	6/11/91	8/9/95
TERA-546	Generating Summary Data Tables	6/11/91	8/9/95
TERA-547	Entry of Non-Standard Teratology Data and Generation of SAS Datasets	6/11/91	8/9/95
TERA-548	Validation of Statistical Analysis Programs	6/11/91	9/27/95
TERA-549	Determination of Data Outliers	6/11/91	8/9/95
TERA-550	Summarizing Clinical Observations for Report Tables	6/12/92	8/9/95
TERA-551	Cochran-Armitage Test	10/26/92	8/9/95
TERA-552	Weighted Analysis of Covariance	10/26/92	8/9/95
TERA-553	Multiplicity-Adjusted Fisher Test	10/26/92	8/9/95
TERA-554	Normality Test	10/26/92	8/9/95
TERA-555	Weighted ANOVA	10/26/92	8/9/95
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TERA-601	Role and Responsibilities of a Study Director for Nongovernmental Clients	<u>10/26/93</u>
TERA-602	Recording Handwritten Raw Data	<u>10/26/93</u>
TERA-603	Archiving Study Records	<u>3/23/94</u>
TERA-604	Preparation and Revision of a Standard Operating Procedure	<u>3/11/94</u>
TERA-605	Disposition and Fate of Animals for Data Summarization and Analyses in Preparation for Final Reports for Developmental and Reproductive Toxicity Studies	<u>10/24/94</u>
TERA-606	Assignment of 5-Digit Rx Code and Color Code For Dose Groups Within a Study	<u>4/20/95</u>
TERA-607	Training Reproductive and Developmental Toxicology Staff	<u>5/23/95</u>
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LORET-002	Chemicals	Handling, Storage, and Disposal of the Test Chemical Formulations
LORET-003	Chemicals	Preparation of Methyl Cellulose as Vehicle for Gavage Studies
LORET-004 - 009	Chemicals	RESERVED
LORET-010	Formulation	Preparation of Test Chemical by Gavage
LORET-011	Formulation	RETIRED
LORET-012 - 019	Formulation	RESERVED
LORET-020	Animals	Purchasing, Receipt, and Quarantine of Animals
LORET-021	Animals	Eartagging
LORET-022	Animals	Randomization Procedures for Assignment of Rodents to Groups
LORET-023	Animals	Weighing Rodents
LORET-024	Animals	Weighing Granular or Pelletized Feed for Determining Feed Consumption for Rodents
LORET-025	Animals	Weighing Water for Determining Water Consumption
LORET-026	Animals	Collection, Preparation, and Examination of Vaginal Cytology in Rodents
LORET-027	Animals	Examination of Animals Having Unscheduled Deaths
LORET-028	Animals	Necropsy of Rodents
LORET-029	Animals	Intra-atrial Cannulation and Blood Collection of Rats
LORET-030	Animals	Pair Feeding - Group Average Method
LORET-031	Animals	Sacrifice of Animals to Minimize Release of Stress Hormone
LORET-032	Animals	Breeding Rats
LORET-033	Animals	Vaginal Smears: Detection of Sperm/Plug-Positive Females
LORET-034	Animals	Culling Postnatal Litters
LORET-035	Animals	Castration of the Rat

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LORET-036	Animals	Measuring Anogenital Distance in Prepubertal Rodents
LORET-037	Animals	Counting Nipples on Rodents
LORET-038	Animals	Oral and Parenteral Dosing of Rodents
LORET-039	Animals	Observation of Clinical Signs
LORET-040	Animals	Disposition and Fate of Animals for Data Summarization and Analyses in Preparation for Final Reports of Reproductive and Endocrine Toxicity Studies
LORET-041 - 049	Animals	RESERVED
LORET-050	Andrology	Estimating Sperm Motility With a Microscope
LORET-051	Andrology	Performing Epididymal Sperm Analyses - Rats
LORET-052	Andrology	Sperm Head Counts in Rats
LORET-053	Andrology	Obtaining Ejaculated Sperm Counts in Rats
LORET-054	Andrology	Evaluation of Spermatogenic Potency Using the Spermatogenic Index
LORET-055	Andrology	Staging of the Spermatogenic Cycle in Rodents
LORET-056	Andrology	Intratesticular Hormone Assay: Sample Homogenization, Storage, and Preparation
LORET-057 - 059	Andrology	RESERVED
LORET-060	Gynecology	Conducting Oocyte Counts in Ovarian Sections From Rodents or Rabbits
LORET-061 - 079	Gynecology	RESERVED
LORET-080	<i>In Vitro</i> Culture	Testicular <i>In Vitro</i> Incubation
LORET-081 - 100	<i>In Vitro</i> Culture	RESERVED
LORET-101	Endocrinology	Mouse Prolactin Radioimmunoassay
LORE-102	Endocrinology	Rat Prolactin Radioimmunoassay
LORET-103 - 200	Endocrinology	RESERVED
LORET-201	Endocrinology	RETIRED
LORET-202	Endocrinology	RETIRED

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LORET-203	Endocrinology	RETIRED
LORET-204	Endocrinology	Rat Luteinizing Hormone Mini-Radioimmunoassay
LORET-205 - 300	Endocrinology	RESERVED
LORET-301	Endocrinology	RETIRED
LORET-302	Endocrinology	RETIRED
LORET-303	Endocrinology	RETIRED
LORE-304	Endocrinology	Rat Follicle Stimulating Hormone Mini-Radioimmunoassay
LORET-305 - 399	Endocrinology	RESERVED
LORET-400	Endocrinology	Validation of Immunoassays
LORET-401	Endocrinology	RETIRED
LORET-402	Endocrinology	RETIRED
LORET-402R	Endocrinology	RETIRED
LORET-403	Endocrinology	Estradiol Radioimmunoassay
LORET-404	Endocrinology	RETIRED
LORET-405	Endocrinology	Testosterone Coat-A-Count Assay
LORE-406	Endocrinology	Total Thyroxine Coat-A-Count Assay
LORE-407	Endocrinology	Progesterone Coat-A-Count Assay
LORE-408	Endocrinology	Rat Growth Hormone Mini-Radioimmunoassay
LORE-409	Endocrinology	Estradiol Double Antibody Radioimmunoassay
LORE-410	Endocrinology	Rat Corticosterone Coat-A-Count Assay
LORE-411	Endocrinology	ACTH Double Antibody Radioimmunoassay
LORE-412	Endocrinology	Rat Thyroid Stimulating Hormone Mini-Radioimmunoassay
LORE-413	Endocrinology	Triiodothyronine Coat-A-Count Assay
LORET-414	Endocrinology	Aldosterone Coated-Tube Assay
LORET-415-449	Endocrinology	RESERVED

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LORET-450	Endocrinology	Protein Hormone Iodination
LORET-451 - 500	Endocrinology	RESERVED
LORET-501	Endocrinology	Enzyme Immunoassay for Progesterone
LORET-502	Endocrinology	Enzyme Immunoassay for Estradiol
LORET-503 - 549	Endocrinology	RESERVED
LORET-550	Receptors	Androgen Receptor Competitive Binding Assay and Androgen Scatchard Analysis
LORET-551 - 600	Receptors	RESERVED
LORET-601	Challenge Test	Hormone Challenge Tests
LORET-602 - 649	Challenge Test	RESERVED
LORE-650	Hormone Assessments	Summarizing Hormone Secretory Patterns
LORET-651 - 699	Hormone Assessments	RESERVED
LORET-700	Miscellaneous	Other Related SOPs Used by LORET
LORET-701 - 799	Miscellaneous	RESERVED
LORET-800	Statistics	Logging on and off VAX using the VT220, VT320, or VT420
LORET-801	Statistics	Organization of VAX Accounts and Subdirectories
LORET-802	Statistics	Submitting SAS Jobs on the VAX
LORET-803	Statistics	Entering Data on the VAX Using EasyEntry
LORET-804	Statistics	Putting Isodata Files From Diskette into Microsoft Word
LORET-805 - 899	Statistics	RESERVED
LORE-900	Equipment	Operation of TJ-6 Centrifuge
LORET-901	Equipment	RETIRED
LORET-902	Equipment	Operation of Toploading Balance
LORET-903	Equipment	Calibration of Toploading Electronic Balances

STANDARD OPERATING PROCEDURES (Continued)

SOP NO.	KEY WORD	TITLE
LORET-904	Equipment	RETIRED
LORET-905	Equipment	Operation of Beta Scintillation Counter
LORET-906	Equipment	RETIRED
LORET-907	Equipment	Maintenance of Refrigerator and Freezer Units
LORET-908	Equipment	Verification of Pipetman® Calibration (Gravimetric Method)
LORET-909	Equipment	Use and Calibration of ICN Apex 10/600 Gamma Counter
LORET-910	Equipment	Use of Isodata Software
LORET-911	Equipment	Operation and Maintenance of the CADD-1® Computerized Ambulatory Infusion Pump
LORET-912	Equipment	Operation of Corning 340 pH Meter
LORET-913	Equipment	Operating and Cleaning Microscope (Zeiss or Other)
LORET-914	Equipment	Operation and Maintenance of the Water-Jacketed CO ₂ Incubator

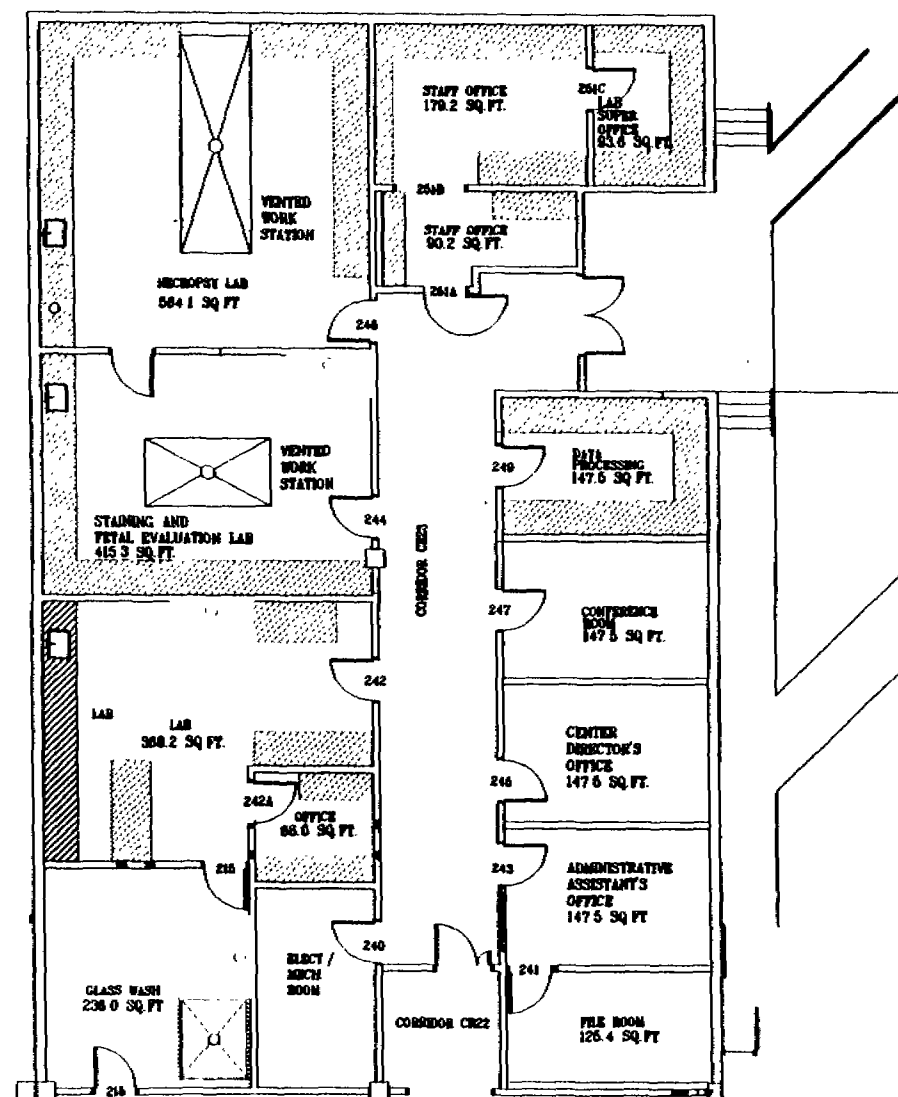
HISTOLOGY STANDARD OPERATING PROCEDURES

TABLE OF CONTENTS

SOP No.	TITLE	EFFECTIVE DATE
HIST-001	Receiving Wet Tissues and Logging in Specimens	October 8, 1992
HIST-002	Tissue Trimming	October 21, 1992
HIST-003	Tissue Processing	October 8, 1992
HIST-004	Tissue Embedding	October 21, 1992
HIST-005	Microtomy	October 21, 1992
HIST-006	Staining: Hematoxylin and Eosin	October 21, 1992
HIST-007	Coverslipping and Labeling Slides	October 8, 1992
HIST-008	Tissue/Slide/Block Checkout-Quality Control	October 21, 1992
HIST-009	Bagging of Trimmed Tissue	October 8, 1992
HIST-010	Delivery and Storage	October 21, 1992
HIST-011	Equipment Maintenance	October 21, 1992
HIST-012	Balance Calibration	October 21, 1992
HIST-013	Laboratory Safety	October 8, 1992
HIST-014	Personnel Training File	October 20, 1992
HIST-015	Necropsy	October 8, 1992
HIST-016	Decalcification	October 21, 1992
HIST-017	Processing the Eye	October 20, 1992
HIST-018	Fine Dissection of Central and Peripheral Nervous System	October 21, 1992
HIST-019	Special Stains	October 21, 1992
HIST-020	Glycol Methacrylate Procedure (GMA)	November 30, 1994

Appendix 4
RTI Reproductive and Developmental Toxicology Wing

CMA 120064



REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY WING

1,021 SQUARE FEET OF USABLE OFFICE SPACE
1,387.6 SQUARE FEET OF USABLE LAB SPACE
2,388.6 SQUARE FEET OF USABLE SPACE
3,537.81 SQUARE FEET OF BUILDING OCCUPIED

 BUILT IN
WORK SURFACES

	DATE	NAME	LOCATION	SCALE	1"=12'-0"
OWN	10/5/92	OB&A	MAD CAMPUS	REV	
APP		SSJ		FILENAME	MISSY DWG
REV	5/29/95	CCT3	HERMANN BUILDING (PARTIAL)		

Appendix 5

CIIT Experimental Design Figure and CIIT/RTI Task Sharing Tables

Figure 1

Reproduction/Fertility with Added on Developmental Toxicity Study in Rats

The study takes ~ 18 months to completion

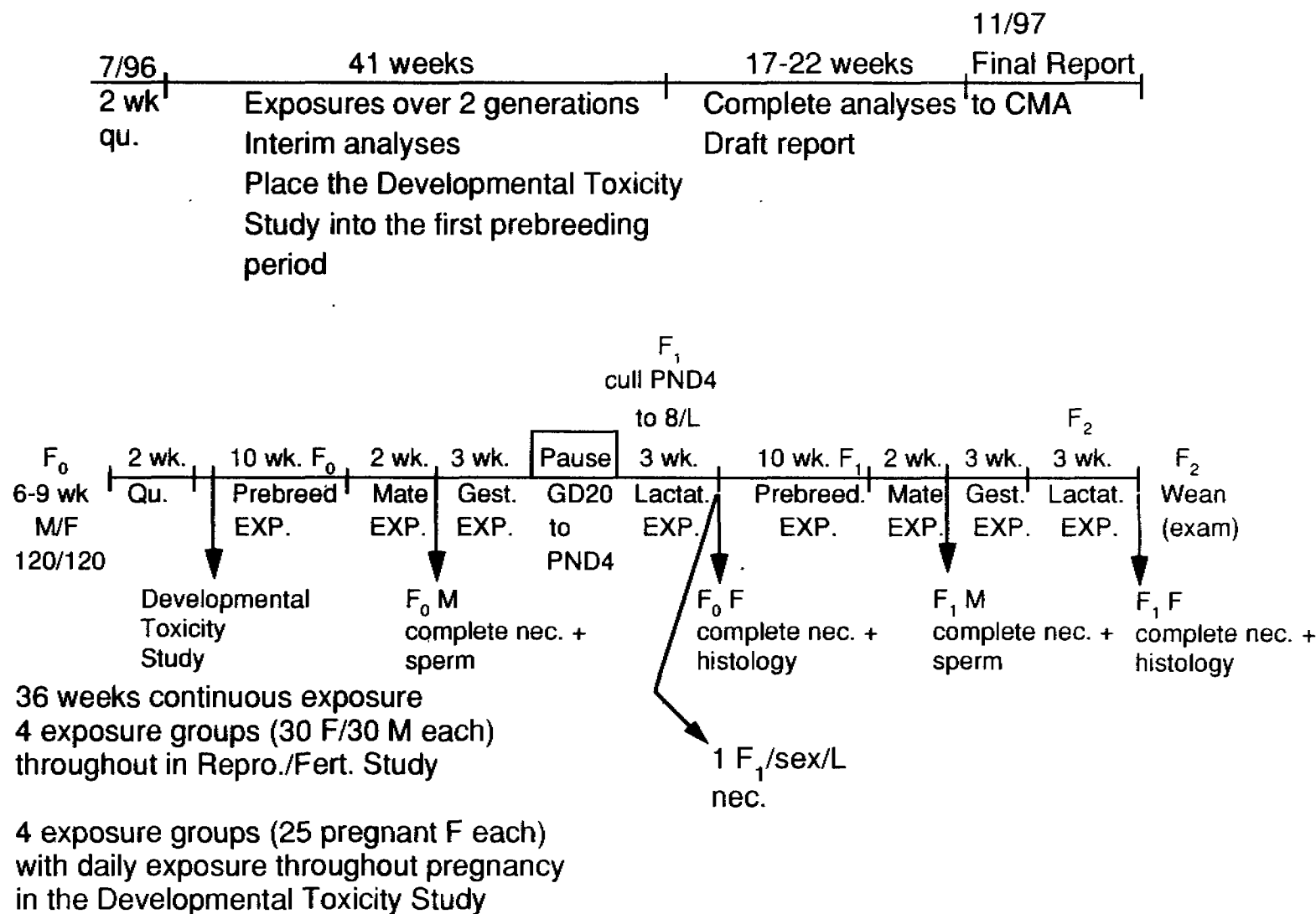


Table 1
Definitive Developmental Toxicity Study in Rats

Task Sharing	RTI	CIIT
Purchase		√
Receipt		√
Quarantine		√
Mating	√	
Group Assignment	√	
Exposure	√	√
Daily observation		√
Food consumption/body weight	√	√
Remove for necropsy	√	√
Complete necropsy ^a	√	
Fetal evaluation	√	
Report Preparation		
- Draft	√	√
- Final	√	√
Quality Assurance	√	√

^aThe sequence of task sharing for the range finding study in rats and mice is the same up to this task.

Table 2
Definitive Reproduction/Fertility Study in Rats

Task Sharing	RTI	CIIT
Purchase		✓
Receipt		✓
Quarantine		✓
Assign to Study (6-9 wks only)		✓
Pre Breed. exposure (10 weeks)		✓
Daily observation		✓
Vaginal cyclicity (last 3 weeks)	✓	
2 week mating		✓
Vaginal smears/vaginal cyclicity	✓	
Sperm detection GD 0	✓	
F ₀ male removal; necropsy; sperm analysis; retain tissues	✓	
Gestation 3 weeks	✓	
Food consumption to GD 19	✓	
Exposure stop GD20 through PND 4	✓	
PND 0 → anogenital distance	✓	
Cull to 8 pups on PND 4	✓	
Dams back into chambers on PND 5	✓	✓
Exposure during lactation 3 weeks		✓
Wean PND 21	✓	
F ₀ females; 3 wk postweaning vaginal cyclicity	✓	
F ₀ females removed; necropsy; retain tissues	✓	
Necropsy of selected F ₁ offspring; one/sex/litter	✓	
F ₁ Pre Breed. exposure (10 weeks)		✓
Vaginal cyclicity (last 3 weeks)	✓	
2 week mating	✓	
F ₁ male removal; necropsy; sperm analysis	✓	
Gestation 3 weeks	✓	
Food consumption to GD 19	✓	
Exposure stop GD 20 to PND 4	✓	
Gestation, litter GD 22 F ₂ offspring	✓	
PND 0 → anogenital distance	✓	
Cull to 8 pups on PND 4	✓	
Dams back into chambers PND 5	✓	✓
Exposure during 3 weeks of lactation	✓	
Wean PND 21	✓	
F ₁ females 3 weeks postweaning vaginal cyclicity	✓	
F ₁ females removed; necropsy; retain tissues	✓	
Necropsy of selected F ₂ weanlings (one/sex/litter)	✓	
Histology		
-F ₀	✓	
-F ₁	✓	

Table 2 (cont'd)
Definitive Reproduction/Fertility Study in Rats

Task Sharing	RTI	CIIT
-F2	√	
Data analysis	√	√
Report		
-Draft	√	√
-Final	√	√
Quality Assurance	√	√