



The Dow Chemical Company
Midland, Michigan 48674

December 6, 1995

Dr. Hasmukh C. Shah
Manager, Vinyl Chloride Panel
Chemical Manufacturers Association
2501 M Street, NW
Washington, DC 20037

Dear Dr. Shah:

I am submitting a technical and cost proposal to conduct a Vinyl Chloride Combined Inhalation Two-Generation Reproduction and Developmental Toxicity Study in CD rats as per your request dated November, 15, 1995. We are very interested in conducting this study at the Dow Chemical Company, and we appreciate the opportunity to submit a proposal.

We are experienced in reproductive and developmental toxicology via the inhalation route of exposure, and our facility is well staffed scientifically to conduct a study of this magnitude and scope. Please find enclosed the curricula vitae of Drs. Richard Corely and Timothy Landry who specialize in inhalation toxicology, Drs. William Breslin and Edward Carney who specialize in reproductive and developmental toxicology, and Drs. Richard Kociba, Barry Yano, and Kenneth Stebbins three of the pathologists in our toxicology laboratory.

I estimate that we could conduct the study as per the enclosed protocol beginning approximately April of 1996 with a final report issued no later than September of 1997. A more detailed list of milestones and an approximate timeline for the study is enclosed. Although we have tentatively scheduled the developmental exposures to coincide with the pre-breeding exposures of the P₂ animals, we could conduct the developmental segment at any time during the reproductive segment of the study. The cost for the study would be \$650,000. Compositional analysis of the test material for the active ingredient and impurities >0.1% could be conducted in our analytical laboratory pre-study, post-study and once approximately mid way through the study for an additional \$10,000. This analysis would include an infrared structural analysis on the pre- and post-study samples. If there are any specific impurities of interest that consist of less than 0.1%, an additional charge would be necessary. Please feel free to contact me if you are interested in an additional quote.

Please feel free to contact me directly if you have any questions or need additional information. We look forward to the opportunity to do business with CMA again.

Sincerely,

Toni K. Jeffries
Toxicology Laboratory

Enclosures

R&S147319



The Dow Chemical Company
Midland, Michigan 48674

Milestones/Proposed Timeline

Vinyl Chloride Inhalation Two-Generation Reproduction and Developmental Toxicity Study in CD Rats

Reproductive Segment	
P ₁ Generation Begin	April 1996
P ₁ Generation Begin	June 1996
P ₁ Generation Necropsy	August 1996
P ₂ Generation Begin	August 1996
P ₂ Generation Begin	November 1996
P ₂ Generation Necropsy	Jan 1997
Developmental Segment	
Begin Exposure	August 1996
Finish C-Sections	September 1996
Final Report	July to August 1997

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Preliminary Copy X

Final Copy —

HEALTH AND ENVIRONMENTAL SCIENCES
THE DOW CHEMICAL COMPANY

PROTOCOL

THE TOXICOLOGY RESEARCH LABORATORY,
1803 BUILDING, MIDLAND, MICHIGAN 48674

TITLE: VINYL CHLORIDE: COMBINED INHALATION TWO-GENERATION
REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

DATE:

FILE NUMBER:

PROPOSED EXPERIMENTAL
START DATE:

PROJECT NUMBER:

TASK NUMBER:

PROPOSED EXPERIMENTAL
TERMINATION DATE:

OSD NUMBER:

COST CENTER:

ESTIMATED DATE
FINAL REPORT:

SPONSOR:

CAS NUMBER:

SIGNATURES:

STUDY DIRECTOR:

/DATE

COINVESTIGATOR(S):

/DATE

INHALATION SPECIALIST:

/DATE

STUDY PATHOLOGIST:

/DATE

APPROVAL(S):

/DATE

SPONSOR:

/DATE

DISTRIBUTION -- SEE ATTACHED LIST

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INTRODUCTION

Objective.

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).

Statement of GLP Compliance.

This study 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.

In addition, in response to the Final Rules amending the U.S. Animal Welfare Act that were promulgated by the U.S. Department of Agriculture effective October 30, 1989, the Animal Care and Use Activity (ACUA) that is required for the conduct of this study has been reviewed and given full approval by the Institutional Animal Care and Use Committee (IACUC). The IACUC has determined that the proposed Activity is in full accordance with these Final Rules. The IACUC has assigned Activity No(s). Reproductive Toxicology 01 and 02 to this Animal Care and Use Activity.

MATERIALS AND METHODS

The test material used for this study will be obtained from a commercial supplier and identified by lot number. The purity of the test material will be determined and reported. A sample of the test material will be taken and stored in a manner consistent with the reference sample retention policy of this laboratory. The test material will be reanalyzed at approximately 6-month intervals to confirm purity and stability.

The test substance has the following properties:

Chemical Name:	Vinyl chloride
Synonyms:	Monochloroethylene, VC, VCM, vinyl chloride monomer
Molecular Formula:	C_2H_3Cl
Molecular Weight:	62.5
Structures:	$CH_2=CHCl$
Appearance:	Colorless gas
Vapor Pressure:	2,530 mm Hg at 20 °C
Saturated Atmosphere:	Gas at room temperature
Vapor Density:	2.16
Flash Point:	-77.75 °C (open cup)
Boiling Point:	-13.6 °C
Specific Gravity:	0.9121
Conversion Factors:	1 ppm = 2.60 mg/m ³ in air 1 mg/mm ³ = 0.39 ppm in air

Test Species and Husbandry.

Male and female CD rats (Charles River Breeding Laboratory, Kingston, NY or Portage, MI) approximately four weeks of age will be purchased for the reproduction phase of this study. An additional group of adult female time-mated CD rats (Charles River Breeding Laboratory, Kingston, NY or Portage, MI) approximately ten weeks of age will be purchased for the developmental portion of this study. Animals will be ordered to ensure that a sufficient

number of animals of acceptable health and weight are available to conduct the study as designed. This strain of rat has been selected because of its general acceptance and suitability for toxicity testing and the availability of a reliable commercial source. Upon arrival at the laboratory¹, all rats will be examined for health status by a veterinarian and acclimated to the laboratory environment (approximately two weeks for the reproduction study; 5 days for the developmental study), according to the Standard Operating Procedures of the Reproductive Toxicology Group. The animals will be randomly assigned by weight to the treatment groups to increase the probability of uniform group mean weights and standard deviations at the initiation of the study. Rats not placed on test will be removed from the test room and the disposition of these animals will be documented in the study file.

Identification of all rats on test will be accomplished by inserting a uniquely coded alphanumeric metal tag in one ear of each rat. In the event that an ear tag becomes dislodged during the course of the study, it will be replaced with one having the same alphanumeric code (i.e., a new alphanumeric code will not be assigned) and noted in the study file.

Rats will be housed singly in wire mesh, stainless steel cages in racks provided with cage board to minimize odor and aid in maintaining a clean environment. Prior to and following daily exposures during late gestation and throughout lactation, females will be housed in plastic nesting boxes provided with ground corn cob nesting material (further details provided in experimental design section). The animal rooms of the facility are designed to maintain humidity at approximately 40-60%, temperature at approximately 22 °C, photoperiod at 12 hrs light:12 hrs dark and air flow at 12-15 changes/hour. A feed crock and a pressure-activated stainless steel water nipple will be components of all cages. A basal diet of Purina Certified Rodent Chow No. 5002 (Purina Mills Inc., St. Louis, MO) will be provided *ad libitum* except during the six hour per day exposures, at which time feed will be withheld. Municipal drinking water will be available *ad libitum*.

¹Fully accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC).

throughout the prestudy and study periods. Analysis of the chow will be performed by Purina Mills Inc. to confirm that the diet provides adequate nutrition, and to quantify the levels of selected contaminants associated with the formulation process. Drinking water obtained from the City of Midland, MI will be analyzed for chemical parameters and biological contaminants by the City of Midland Water Department. In addition, specific analyses for chemical contaminants will be conducted at periodic intervals as stated in the Standard Operating Procedures of The Toxicology Research Laboratory, The Dow Chemical Company.

Exposure Chamber.

Animals will be housed and exposed to test material vapors in a 14.5 m³ chamber (2.4 m wide x 2.4 m high x 2.4 m deep with a pyramidal top) under dynamic airflow conditions. Chamber airflows will be maintained at approximately 2900 liters/minute, which is sufficient to provide the normal concentration of oxygen to the animals.

Vapor Generating System.

The various concentrations of test material will be generated using a glass J-tube method (Miller et al., 1980). Liquid test material will be metered into a glass J-tube assembly and vaporized by a preheated stream of compressed air (up to 100 l/min) passing through the J-tube. Compressed air will be heated to the minimum extent necessary to facilitate complete vaporization of the test material. The compressed air and test material vapors will be diluted and mixed with room air to achieve the desired concentration of test material vapors at a total flow rate of 2900 l/min.

Chamber Monitoring.

The concentration of the test material in each chamber will be measured at least once per hour using a MIRAN 1A infrared spectrophotometer (Foxboro Analytical, Norwalk, CT). Analytical equipment will be calibrated using standards having a known test material vapor concentration contained in 90 liter SARAN* film gas bags prior to the first exposure and at least monthly

* Trademark of The Dow Chemical Company

thereafter. Daily checks of the analytical equipment will be performed prior to each exposure period using a single test material standard concentration. In addition, the amount of test material used each day will be recorded and the nominal concentrations (amount of the test material used/total chamber airflow) of test material will be calculated. Prior to the start of the study, each of the chambers to be used will be checked to ensure that a uniform distribution of vapors occurs within the breathing zone according to Standard Operating Procedures.

Airflow through each chamber will be determined at hourly intervals using a differential pressure transducer (Model C264, Setra Systems, Inc., Acton, MA) or a Universal Venturi tube (Series 180, BIF, 345 Harris Ave., Providence, RI). The manometer and differential pressure transducer will be calibrated with a gas meter (Singer Aluminum Diaphragm Meter, Model AL-1400, American Meter Division, Philadelphia, PA) prior to the start of the study. The Universal Venturi tubes have been calibrated at the factory.

Chamber temperatures will be measured with a thermometer or resistance temperature device (RTD) and relative humidities will be measured with relative humidity gauges or humidity sensors (HMP 112A, Vaisala, Helsinki, Finland) at least once each hour. Calibration of the hygrometers, RTD's and humidity sensors will be documented in the study file. The temperature and relative humidity in each chamber will be controlled by a system designed to maintain temperature at approximately $22\pm 2^{\circ}\text{C}$ and relative humidity at approximately 40-60%.

Output from the differential pressure transducer, RTD, humidity sensor and infrared spectrophotometer will be collected by the CAMILE* Data Acquisition and Control System.

Exposure Concentrations.

Rats will be exposed to target concentrations of 0, 10, 100 or 1100 ppm of the test material. These exposure levels correspond to oral equivalent doses of

* Trademark of SAGIAN Indianapolis, Indiana.

approximately 0, 9.2, 92 and 1012 mg/kg/day assuming ventilation rates of 1 l/min/kg, 100 percent absorption and a 6 hour/day exposure. The high concentration of vinyl chloride was selected based on the oral equivalent of the limit dose of 1000 mg/kg body weight/day. The high exposure of 1100 ppm is also expected to produce effects on the liver and other organ systems (ATSDR, 1993). The middle and low exposure levels were selected to provide a dose response for the observed effects and a no-observed-effect level, respectively. The calculations used to convert ppm to an oral dose equivalent are as follows:

$$\text{Dose (mg/kg/day)} = \text{exposure concentration (mg/l)} \times \text{minute volume/kg body wt} \times \text{minutes of exposure} \times \text{absorbed dose}$$

$$\text{Exposure concentration (mg/l)} = (\text{ppm} \times \text{molecular wt})/24,450$$

$$\text{Dose (mg/kg/day)} = \text{ppm} \times \text{molecular wt} \times 1/24,450 \times \text{minute volume/kg body wt (1 l/min/kg)} \times \text{minutes of exposure} \times \text{absorbed dose}$$

Where:

Dose = 1012, 92 or 9.2 mg/kg/day

Minute volume/kg body wt = 1 liter/min

Minutes of exposure/day = 360

Molecular wt = 62.5

Proportion absorbed = 100%

Conversion factor used in converting mg/l to ppm = 1/24,450

Example: $1012 \text{ mg/kg/day} = 1100 \text{ ppm} \times 62.5 \text{ (molecular wt.)} \times 1/24,450 \times 1 \text{ l/min/kg body wt} \times 360 \text{ min} \times 100\% \text{ absorption}$

Reproduction - Experimental Design.

Groups of 30 male and 30 female rats will be exposed to 0, 10, 100 or 1100 ppm of the test material via inhalation, for 6 hours/day, 5 days/week prior to mating and 6 hours/day, 7 days/week during mating, gestation and lactation. The overall chronology of events and study design for this study are depicted in Tables 1 and 2, respectively. The treatment of the first generation parental (P1) rats will begin at approximately 6 weeks of age. After approximately 10

weeks of exposure (5 days/week, excluding holidays), P1 rats will be mated (one male to one female of the respective treatment group) to produce the F1 litters. Following weaning (3 weeks of age) of the F1 litters, 30 males and 30 females from each treatment group will be randomly selected and assigned to the respective treatment group to become the second generation parents (P2). After approximately 10 weeks of treatment following weaning of the last F1 litter, the P2 adults will be bred to produce the F2 litters. Exposures of P1 and P2 adults rats to the test material will continue until the adults are sent to necropsy. All rats will be housed continuously in exposure chambers following the initial exposure to the test material, except during late gestation and throughout lactation periods, when female rats will be housed outside of the exposure chambers during non-exposure periods. Maternal rats will not be exposed to the test material after day 20 of gestation (as calculated from day 0 of gestation via sperm-positive vaginal lavage) through the fourth day postpartum, in order to allow for parturition and initiation of lactation. During the lactation period, pups will not be placed in the exposure chambers, but will remain in the nesting boxes separated from the dam for approximately 7 hours/day on lactation days 5 through 21.

Reproduction - Breeding Procedure

Breeding of the P1 and P2 adults will commence after approximately 10 weeks of treatment. Each female will be placed with a single male from the same dose level (1:1 mating) until pregnancy occurs or two weeks have elapsed. During each breeding period, daily vaginal lavage samples will be evaluated for the presence of sperm as an indication of mating. The day on which sperm are detected or a vaginal plug is observed *in situ* will be considered day 0 of gestation. Sperm- and plug-positive females will then be separated and placed back into wire mesh, stainless steel cages. If mating has not occurred after two weeks, the animals will be separated without further opportunity for mating. For the P2 mating, cohabitation of male and female litter mates will be avoided.

Reproduction - Culling and Weaning

To reduce the variation in the growth of the pups, the F1 and F2 litters with a total number of pups exceeding eight will be culled on day 4 postpartum. Culled litters will be reduced to a total of eight pups, four males and four females, if possible. Pups to be culled will be selected using a computer generated randomization procedure. Litters with eight or fewer pups will not be culled. Preferential culling of runts will not be performed. Culled pups will be examined grossly for abnormalities and euthanized by the deposition of sodium pentobarbital (Succumb Butler, Columbus, OH) into the oral cavity. Weaning of all litters will be done on lactation day 21. Weanlings not held for prospective generations or selected for necropsy will be examined grossly for abnormalities and euthanized by CO₂ inhalation.

Reproduction - Physical Observations

Each rat on study will be observed twice daily (a.m. and p.m.) for mortality, morbidity and moribundity as well as availability of feed and water. Changes in behavior or demeanor and indications of overt toxicity will be evaluated during the a.m. or p.m. observation. In addition, a thorough clinical examination will be conducted on all animals prior to the start of the study and weekly thereafter. This examination will include thorough evaluations of the skin and fur, mucous membranes, respiration, nervous system and behavior pattern. All adult rats found dead or in moribund condition will be submitted for a gross pathologic examination. Adult rats found dead after normal working hours will be refrigerated until a necropsy can be performed. All pups found dead or pups that are euthanized in moribund condition will be examined to the extent possible for defects and/or cause of death and preserved in neutral, phosphate-buffered 10% formalin. Cannibalized pups will be examined to the extent possible and discarded.

Reproduction - Body Weights and Feed Consumption

All P1 animals will have body weights and feed consumption (optional) recorded weekly during the 10-week pre-breeding treatment period, beginning on or before the first week of the study. Body weights for males will be recorded weekly throughout the course of the study. Sperm and plug positive

females will be weighed on Days 0, 7, 14 and 21 of gestation. Females that deliver litters will be weighed on Days 1, 4, 7, 14, and 21 of lactation. During breeding, feed consumption will not be measured in males or females due to cohousing. Following completion of the breeding periods, weekly feed consumption again will be measured in males. During gestation, feed consumption will be measured at weekly intervals in sperm and plug positive females. After parturition, feed consumption will be measured twice during the first and second week of lactation and at 2 - 3 day intervals during the last week of lactation. A similar schedule will be followed for the P2 generation.

Reproduction - Litter Data

All litters will be examined as soon as possible after delivery. The following parameters will be recorded for each litter: total litter size on the day of parturition (day 0), the number of live and dead pups on days 0, 1, 4, 7, 14, and 21 postpartum, and the sex and the weight of each pup on days 1, 4 (before and after culling), 7, 14, and 21 of lactation. Any visible physical abnormalities or demeanor changes in the neonates will be recorded during the lactation period.

Reproduction - Physical Maturation Landmarks

All F1 weanlings selected for mating will be observed daily for vaginal opening beginning on postnatal day 30 (Adams *et al.*, 1985) or preputial separation beginning on day 35 (Korenbrodt *et al.*, 1977). If there is a treatment-related effect observed on the F1 sex ratio, age of vaginal opening or age of preputial separation, then anogenital distance will be measured on post natal day 4 for all F2 pups.

Reproduction - Estrous Cycling

Estrous cycle length and normality will be evaluated daily by vaginal lavage (Cooper *et al.*, 1993) on the first 15 P1 and P2 females starting three weeks prior to mating and continuing throughout cohabitation.

Reproduction - Pathology - Adult Rats

A complete necropsy will be conducted by a team of trained individuals under the direct supervision of a veterinary pathologist on all P1 and P2 adults. The scheduled necropsy will be performed after the last litter of the respective generation has been weaned. Adult males will be fasted overnight, anesthetized with methoxyflurane and euthanized. Adult females will be necropsied on day 2 of diestrus whenever possible. This will be accomplished by monitoring (by vaginal lavage) for the occurrence of at least one estrous cycle after which time females found to be in day one of diestrus will be fasted overnight and necropsied on the following morning. The expected, subsequent stage of the estrous cycle (day 2 of diestrus) will be confirmed by vaginal lavage on the day of necropsy, prior to euthanasia. Based upon the results of these smears, exclusion of appropriate data parameters used for statistics will be performed for females not found to be in the appropriate stage of the estrous cycle (day 2 of diestrus) on the day of necropsy. The fasted females will be euthanized as described for the males. The eyes of both males and females will be examined *in situ* by gently pressing a moistened glass slide against the cornea and observing the eyes under fluorescent light. The uteri of all cohabited females will be examined for the presence and number of implantation sites. Tissues routinely collected (Table 3) will be saved from these rats and preserved in neutral, phosphate-buffered 10% formalin, with the following exceptions. The testes and epididymides will be preserved in Bouin's fixative. The lungs will be infused with formalin to their approximate normal inspiratory volume. The nasal cavity will be flushed with formalin via the pharyngeal duct to ensure rapid fixation of the tissue. Moribund rats and those dying spontaneously will be necropsied in a similar manner. However, body and organ weights will not be recorded.

Reproduction - Organ Weights - Adult Rats

The following organs on the first 15 P1 and P2 parental animals will be weighed at the scheduled terminal necropsy: uterus, ovaries, testes, single epididymis (total and cauda), seminal vesicles (with coagulating glands and their fluids), prostate, brain, liver, kidneys, lungs, adrenal glands, spleen, and thymus, and the organ-to-body weight ratios calculated.

Reproduction - Histology - Adult Rats

Histologic examination of potential target organs and reproductive tissues (Table 3) will be performed on the control and high dose groups.

Examination of tissues from the low and middle dose groups will be limited to those tissues that demonstrate treatment-related histologic changes in the high dose group. Only the right ovary will be routinely processed for standard microscopic examination. The left ovary will be saved for possible oocyte quantification. If deemed necessary by the study sponsor, oocyte quantification will include evaluation of a minimum of ten sections, randomly selected from one completely sectioned ovary per female of the high-dose and control groups. Ovarian follicles will be placed into one of three categories as described by Plowchalk et al., (1993). The total number of follicles and the number of follicles in each of the three categories will be evaluated. Ovaries from the low and middle dose groups may be evaluated if treatment-related changes are observed in the high dose group. A complete set of tissues (excluding the left ovary for females), encompassing all organs listed in Table 3, will be prepared from all rats dying spontaneously or euthanized in a moribund condition and examined in an attempt to determine cause of death.

Reproduction - Sperm Count, Motility and Morphology

For the first 15 P1 and P2 males at termination, samples of sperm from the distal cauda epididymis will be collected for evaluation of percent progressively motile sperm and possible evaluation of sperm morphology. The entire right cauda epididymis will be weighed and then minced in saline to enumerate the total number of sperm (cauda reserves). Sperm motility and count will be determined with the use of the Hamilton-Thorn (HTM) Integrated Visual Optical System (IVOS) motility analyzer (Hamilton-Thorn Research, Beverly, Massachusetts). All samples for motility analyses will be video recorded or recorded digitally on disk and the recording kept as raw data. Sperm samples will be prepared for morphological evaluation and saved, but will not be evaluated unless deemed necessary by the study sponsor.

Reproduction - Pathology - Weanling Rats

At the time of weaning, 1 pup/sex/litter/dose from the F1 and F2 litters will be randomly selected for a complete necropsy by a team of trained individuals under the direct supervision of a veterinary pathologist. In order to control for variation in body and organ weight, all F1 and F2 pups selected for a complete necropsy will be euthanized at the same age. Pups will be anesthetized with methoxyflurane and euthanized. Terminal body weights will be recorded. Gross pathologic examination and preservation of tissue samples (Table 3) will be performed as described above for adults.

Reproduction - Organ Weights - Weanling Rats

For the first 15 male and female F1 and F2 pups that are examined macroscopically (one/sex/litter), the following organs will be weighed: ovaries, testes, brain, liver, kidneys, adrenal glands, spleen and thymus.

Reproduction - Histology - Weanling Rats

Organs that demonstrate treatment-related effects in weanlings will be examined microscopically in the control and high dose groups. Examination of tissues from the low and middle dose groups will be limited to those tissues which demonstrate treatment-related histologic changes in the high dose group. Microscopic examination will also be made of all tissues showing gross pathologic changes.

Developmental - Experimental Design.

Groups of 25 adult time-mated female rats will be exposed to 0, 10, 100 or 1100 ppm of the test material via inhalation, for 6 hours/day, on gestation days 6 through 20. These exposure levels correspond to oral equivalent doses of approximately 0, 9.2, 92 and 1012 mg/kg/day assuming ventilation rates of 1 l/min/kg, 100 percent absorption and a 6 hour/day exposure. The high concentration of vinyl chloride was selected based on the oral equivalent of the limit dose of 1,000 mg/kg body weight/day. For further discussion of dose level selection refer to the "Exposure Concentrations" section of this protocol.

The overall chronology and study design for the developmental portion of this study is depicted in Tables 1 and 2, respectively.

Developmental - Breeding Procedure

Sexually mature, adult virgin females, approximately 10 weeks of age and weighing approximately 200 - 250 grams, will be naturally mated with male rats (one male/female) of the same strain at the Charles River Breeding Laboratory. Females will be checked for plugs the following morning and those found with a vaginal plug will be removed from the male's cage. The day on which a vaginal plug is detected will be considered Day 0 of gestation. Day 0 body weights will be provided by Charles River Breeding Laboratory, and maintained in the study record. Rats will be shipped on Day 0 or 1 of gestation and will arrive at our laboratory on Day 1 or 2 of gestation.

Developmental - Maternal Observations

All animals will be observed daily during the study for alterations in behavior or demeanor as previously described under the Reproduction Study "Physical Observation" section, with the exception that a thorough weekly clinical examination will not be conducted. Any animal which dies, appears moribund or shows indications of early termination of pregnancy will be submitted for a complete necropsy as described for the Reproduction Study. Body weights will be recorded on gestation days 0, 6, 14 and 21.

On Day 21 of gestation, all surviving animals assigned to the developmental study will be euthanized by carbon dioxide inhalation and given a limited necropsy. Any obvious structural or pathologic changes noted in the adult will be recorded and the weight of the liver, kidneys and gravid uteri will be recorded. Liver, kidneys and gross lesions will be preserved in neutral, phosphate-buffered 10% formalin, but microscopic examination of tissues will not be conducted unless deemed necessary to interpret other observations made during the study or requested by the sponsors.

Developmental - Fetal Observations

At necropsy, the uterine horns will be exteriorized through an abdominal incision and the following data recorded: 1) the number and position of fetuses *in utero*, 2) the number of live and dead fetuses, 3) the number and position of resorptions, 4) the number of corpora lutea, 5) the sex and body weight of each fetus, and 6) any gross external alteration. The uteri of apparently non-pregnant animals will be stained with an aqueous 10% solution of sodium sulfide (Kopf et al., 1964) and examined for evidence of early resorptions. Corpora lutea will not be recorded for females that are not visibly pregnant at C-section or for females that are submitted for necropsy prior to Day 21. At least one-half of the fetuses in each litter, selected using a table of random numbers, will be examined immediately by dissection under a low power stereo-microscope for evidence of visceral alterations (Staples, 1974). The heads of rat fetuses examined by dissection will be removed, placed in Bouin's fixative and examined by the serial sectioning technique of Wilson (1965). All fetuses will then be preserved in alcohol, eviscerated and stained with alizarin red-S (Dawson, 1926). Skeletal examination will be conducted on all fetuses that were not given visceral examinations.

Statistical Evaluation.

Descriptive statistics (means and standard deviations) will be reported for feed consumption. Body weights, gestation/lactation body weight gains, organ weights, and sperm count per gram cauda epididymis and percent motile sperm will first be evaluated by Bartlett's test for equality of variances. Based upon the outcome of Bartlett's test, either a parametric or nonparametric analysis of variance (ANOVA) will be performed. If the ANOVA is significant, a Dunnett's test or the Wilcoxon Rank-Sum test with Bonferroni's correction will be performed.

Gestation length, average time to mating, number of corpora lutea, number of implants, litter size, age at vaginal opening and age at preputial separation will be analyzed using a nonparametric ANOVA. If the ANOVA is significant, the Wilcoxon Rank-Sum test with Bonferroni's correction will be performed. Statistical outliers will be identified by the method of Grubbs

(1969) and will be routinely excluded from analysis for feed consumption only. Outliers for other endpoints will only be excluded from analysis for documented, scientifically sound reasons. Fertility indices and pregnancy rate will be analyzed by the Fisher exact probability test and Bonferroni's correction will be used for multiple testing of groups in comparison to a single control. Evaluation of the neonatal sex ratio will be performed by the binomial distribution test. Survival indices will be analyzed using the litter as the experimental unit by the Wilcoxon test as modified by Haseman and Hoel (1974). Statistical evaluation of the frequency of pre-implantation loss, resorptions and fetal alterations among litters and the fetal population will be performed using a censored Wilcoxon test with Bonferroni's correction. Nonpregnant females, females pregnant following staining or females having totally resorbed litters will be excluded from the appropriate analyses.

The nominal alpha levels to be used are as follows:

Bartlett's Test (Winer, 1971)	$\alpha=0.01$
Parametric ANOVA (Steel and Torrie, 1960)	$\alpha=0.10$
Nonparametric ANOVA (Hollander and Wolfe, 1973)	$\alpha=0.10$
Dunnett's Test (Winer, 1971)	$\alpha=0.05$, two-sided
Wilcoxon Rank-Sum Test (Hollander and Wolfe, 1973)	$\alpha=0.05$, two-sided with Bonferroni correction (Miller, 1966)
Fisher's Test (Siegel, 1956)	$\alpha=0.05$, two-sided
Censored Wilcoxon Test (Haseman and Hoel, 1974)	$\alpha=0.05$, two-sided
Outlier Test (Grubbs, 1969)	$\alpha=0.02$, two-sided
Binomial Distribution Test (Steel and Torrie, 1960)	$\alpha=0.05$, two-sided

Because numerous measurements are statistically compared in the same group of animals, the overall false positive rate (Type I errors) will be much greater than the cited alpha levels would suggest. Thus, the final

interpretation of numerical data will consider statistical analyses along with other factors such as dose-response relationships and whether the results are significant in the light of other biologic and pathologic findings.

Safety Precautions.

Standard safety precautions will be followed during the conduct of this study.

Quality Assurance.

Permanent records of all data generated during the course of this study, the protocol, any addenda to the protocol, and the final report will be available for inspection by the Quality Assurance Unit. All data generated including the protocol, addenda, and final report will be archived at Health and Environmental Sciences, The Dow Chemical Company, Midland, Michigan.

December 7, 1995

DRAFT

R&S 147338

REFERENCES

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TABLE 1

VINYL CHLORIDE: COMBINED INHALATION TWO-GENERATION REPRODUCTION
AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

CHRONOLOGY OF EVENTS

WEEKS ON STUDY	P1/Developmental	F1/P2	F2
1-10	Exposure of P1 males and females prior to first mating. Exposure (gestation days 6-20) of the dams for developmental toxicity evaluation Necropsy of developmental toxicity dams and fetal evaluations		
11-12	P1 mating period for F1 litters.		
14-15		F1 born and litters culled on day 4 post-partum to 8 pups each.	
17-18		F1 litters weaned on day 21 post-partum; offspring selected for P2 adults; 1 F1 pup/sex/dose/litter selected for necropsy; remaining pups euthanized.	
19-28	Necropsy P1 adults.	Exposure of P2 males and females prior to first mating.	
29-30		Mating period of P2 for F2 litters.	
32-33			F2 born and litters culled on day 4 post-partum to 8 pups each.
35-36			F2 litters weaned on day 21 post-partum; 1 F2 pup/sex/dose/litter selected for necropsy; remaining pups euthanized.
37		Necropsy P2 adults.	

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TABLE 2

VINYL CHLORIDE: COMBINED INHALATION TWO-GENERATION
REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

STUDY DESIGN

<u>EXPOSURE LEVELS (PPM)</u>	<u>NO. NO. MALES</u>	<u>NO. FEMALES</u>
0	30	30 Reproductive 25 Development
10	30	30 Reproductive 25 Development
100	30	30 Reproductive 25 Development
1100	30	30 Reproductive 25 Development
TOTAL=		120 220

PARAMETERS

REPRODUCTION STUDY

Animal Observations
Body Weights (parental and neonatal)
Feed Consumption (optional)
Necropsy (parental and weanlings)
Organ Weights (parental and weanlings)
Gross Pathology (parental and weanlings)
Histopathology (parental and weanling)
Fertility Indices
Estrous Cycling and Sperm Analyses
Developmental Landmarks
Neonatal Survival

DEVELOPMENTAL STUDY

Animal Observations
Body Weights (maternal and fetal)
Feed Consumption (optional)
Necropsy
Limited Organ Weights
Gross Pathology
Uterine Examination
External, Visceral and Skeletal Examination

TABLE 3

VINYL CHLORIDE: COMBINED INHALATION TWO-GENERATION REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY
IN CD RATS

TISSUES COLLECTED AND PRESERVED AT NECROPSY

ADRENALS	KIDNEYS*	PROSTATE*
AORTA	LACRIMAL/HARDERIAN GLANDS	RECTUM
AUDITORY SEBACEOUS GLANDS	LARYNX	SALIVARY GLANDS
BONE (INCLUDING JOINT)	LIVER*	SEMINAL VESICLES*
BONE MARROW	LUNGS*	SKELETAL MUSCLE
BRAIN (CEREBRUM, BRAINSTEM, CEREBELLUM)	MAMMARY GLAND*	SKIN
CECUM	MEDIASTINAL LYMPH NODE	SPINAL CORD (CERVICAL, THORACIC, LUMBAR)
CERVIX*	MEDIASTINAL TISSUES	SPLEEN
COAGULATING GLANDS*	MESENTERIC LYMPH NODE	STOMACH
COLON	MESENTERIC TISSUES	TESTES*
DUODENUM	NASAL TISSUES*	THYMUS
EPIDIDYMIDES*	ORAL TISSUES	THYROID GLAND
ESOPHAGUS	OVARIES*	TONGUE
EYES	OVIDUCTS*	TRACHEA*
GROSS LESIONS*	PANCREAS	URINARY BLADDER
HEART	PARATHYROID GLANDS	UTERUS*
ILEUM	PERIPHERAL NERVE	VAGINA*
JEJUNUM	PITUITARY*	

*TISSUE SELECTED FOR HISTOPATHOLOGIC EVALUATION.

December 7, 1995

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RICHARD ALLEN CORLEY, Ph.D.

TITLE: Research Associate

PRESENT POSITION: Technology Leader of The Inhalation Toxicology
Research Laboratory

BUSINESS ADDRESS: The Toxicology Research Laboratory
The Dow Chemical Company
1803 Building
Midland, Michigan 48674

TELEPHONE NUMBER: 517-636-1318

DATE OF BIRTH: 21 March 1957

MARITAL STATUS: Married

CHILDREN: Two

EDUCATION

Ph.D. (1985) University of Illinois at Urbana-Champaign. Major:
Environmental Toxicology. Minor: Analytical Chemistry

Doctoral Thesis: The Metabolic Fate of Tritium-Labeled T-2
Toxin, a Trichothecene Mycotoxin, in Swine

B.A. (1979) University of Missouri at Columbia.
Major: Biology. Minor: Chemistry.

PROFESSIONAL AFFILIATIONS

American Association for the Advancement of Science, Student Member (1983-1985).

American Chemical Society, Student Member (1983-1986).

Michigan Chapter of The Society of Toxicology (1993-Present).

Society of Toxicology, Full Member (1992-Present).

12/04/95

AWARDS AND RECOGNITION

Special Recognition Award (Dow) (March, 1987)

1994 Health and Environmental Sciences (Dow) Excellence in Science Award (Nov., 1994)

EMPLOYMENT

- 12/95-Present Research Associate. The Toxicology Research Laboratory, The Dow Chemical Company, Midland, Michigan 48674.
- Consulting toxicologist for the Chemicals and Performance Products (C&PP) businesses. Responsible for coordinating C&PP activities within the Health and Environmental Sciences department, respond to issues related to toxicology and interact with product stewards, business and product management teams, customers, trade associations and regulatory agencies as the toxicology representative of the business. Laboratory leader in the development and application of physiologically-based pharmacokinetic (PB-PK) models in risk assessment. Also responsible for scientific activities and strategic direction of the inhalation toxicology laboratory as well as mentoring and developing scientific expertise within the laboratory. Principle study director and scientific reviewer for R & D reports. Supervisor: J.S. Bus.
- 7/93-12/95 Research Leader. The Toxicology Research Laboratory, The Dow Chemical Company, Midland, Michigan 48674.
- Job description: same as above.
- 5/91-7/93 Research Leader. The Toxicology Research Laboratory, The Dow Chemical Company, Midland, Michigan 48674.
- Group Leader of The Inhalation Toxicology Research Laboratory. Responsible for planning and budgeting research activities, personnel development, strategic direction and laboratory operations. Principle study director and scientific reviewer for R & D reports. Additional responsibilities included scientific input into toxicology-related issues and development of physiologically-based pharmacokinetic models. Supervisor: J.S. Bus.

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12/90-5/91

Project Leader. The Toxicology Research Laboratory, The Dow Chemical Company, Midland, Michigan 48674.

Job description: same as above.

4/89-12/90

Project Leader. The Toxicology Research Laboratory, The Dow Chemical Company, Midland, Michigan 48674.

Group Leader of the Chronic Toxicology Research Laboratory. Responsible for planning and budgeting research activities, personnel development and laboratory operations. Also involved in the design and conduct of studies, data analysis, development of physiologically-based pharmacokinetic models, report writing and scientific reviewer for R & D reports. Additional responsibilities for scientific input into toxicology-related issues for the Chemicals and Performance Products department. Supervisor: P.G. Watanabe.

12/88-4/89

Project Leader. The Toxicology Research Laboratory, The Dow Chemical Company, Midland, Michigan 48674.

Research toxicologist in the inhalation/dermal toxicology research group. Responsible for protocol design, study implementation, data analysis, report writing and quality assurance in support of discovery stage compounds and product registration. Experience in state-of-the-art inhalation equipment, atmospheric analyses, computer monitoring, metabolism studies, dermal studies and physiologically-based pharmacokinetic modeling. Competent in HPLC, GLC, LSC and IR techniques and the use of computers for data acquisition and analysis. Additional responsibilities as toxicology consultant for the Chemicals and Performance Products department. Supervisors: T.D. Landry and P.G. Watanabe.

6/87-12/88

Senior Research Toxicologist. The Toxicology Research Laboratory, The Dow Chemical Company, Midland, Michigan 48674.

Job description: same as above.

10/85-6/87:

Post-Doctoral Fellow. The Toxicology Research Laboratory, The Dow Chemical Company, Midland, Michigan 48674.

Position as research toxicologist in the inhalation/dermal research group. Designed and conducted studies on the mechanism of action of organo-metallics and halogenated solvents, in addition to inhalation, dermal and physiologically-based pharmacokinetic studies in support of product registration. Supervisors: R.R. Miller and P.G. Watanabe.

12/04/95

8/80-10/85: Graduate Research Assistant in Environmental Toxicology. Department of Veterinary Biosciences, College of Veterinary Medicine, University of Illinois, Urbana, Illinois 61801.

Graduate education emphasizing the areas of environmental, veterinary and natural products toxicology. Specific research interests in metabolism and kinetics of trichothecene mycotoxins in domestic animals. Experience with radiotracers, fungal culture, GLC, TLC, HPLC, GPC and spectroscopic techniques. Supervisors: W. B. Buck and S. P. Swanson.

8/79-8/80: Student Technician. Analytical Toxicology, Veterinary Medical Diagnostic Laboratory, University of Missouri, Columbia, Missouri 65201.

Responsible for the analysis of animal feeds, tissues and environmental samples for chemicals and metals in support of the Diagnostic Laboratory. Experience with UV, IR, GLC, HPLC, TLC and AAS techniques. Supervisors: G.D. Osweiler and G.E. Rottinghaus.

PROFESSIONAL EXPERIENCE

MANAGEMENT OF TOXICOLOGY RESEARCH. Supervisor of the subchronic/chronic dietary toxicology laboratory (1989-1990) and the inhalation toxicology laboratory (1990-1993). Technical Leader of the inhalation toxicology laboratory (1993-present).

TECHNICAL R&D REPORTS. Authored or co-authored over 20 reports including: subchronic dermal toxicity studies, acute-to-subchronic inhalation studies, inhalation teratology studies, subacute-to-chronic dietary toxicity/oncogenicity studies, metabolism studies and physiologically-based pharmacokinetic studies. Species studied include: mice, rats, humans, rabbits and dogs.

ONGOING RESEARCH. Chronic rat and mouse inhalation studies, mechanistic (enzyme kinetics, cell proliferation, etc.) and physiologically-based pharmacokinetic and pharmacodynamic model development.

CONSULTING. Toxicology Consultant, Organic Chemicals, The Dow Chemical Company (1988-1990; 1993-Present). Member of the Toxicology Research Task Group, Ethylene Glycol Ethers Panel, Chemical Manufacturers Association (1988-1990; 1993-Present); Toxicology Research Task Group, Propylene Glycol Ethers Panel,

12/04/95

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Chemical Manufacturers Association (1993-Present); Ethylene Oxide Industry Council, Chemical Manufacturers Association (1989-1990); Water Quality Technical Committee of the ILSI Health and Environmental Sciences Institute (1995-Present).

INVITED WORKSHOPS AND ADVISORY PANELS

1. EPA/ILSI Workshop: Principles of Route-to-Route Extrapolations for Risk Assessment. March 20, 1990. Hilton Head, SC. (Speaker).
2. ATSDR Decision Support Methodologies for Hazard Identification/Risk Assessment of Toxic Substances. Atlanta, GA. October 18-20, 1993. (Expert Panelist).
3. EPA/AIHC/ILSI Workshop: Human Variability. October 16-17, 1995. Washington, D.C. (Participant).
4. EPA/CMA Working Group: IRIS RfC/RfD Process for Ethylene Glycol n-Butyl Ether and Diethylene Glycol n-Butyl Ether. September, 1995 - Present. (Participant).
5. CIIT Technical Advisory Panel: MTBE Research Program. September, 1995 - Present. (Participant).

PUBLICATIONS

1. Gas Chromatographic Method for the Determination of Diacetoxyscirpenol in Swine Plasma and Urine. S.P. Swanson, L. Terwell, R.A. Corley. *J. Chromatog.* 248: 456-460, 1982.
2. Apparent Blue-Green Algae Poisoning in Swine Subsequent to Ingestion of a Bloom Dominated by *Anabaena Spiroides*. V.R. Beasley, R.W. Coppock, J. Simon, R. Ely, W.B. Buck, R.A. Corley, D.M. Carlson, P.R. Gorham. *JAVMA* 182(4): 413-414, 1983.
3. Rapid Thin-Layer Chromatographic Method for the Determination of Zearalenone and Zearalenol in Grains and Animal Feeds. S.P. Swanson, R.A. Corley, D.G. White, W.B. Buck. *JAOC* 67(3): 580-582, 1984.
4. Glucuronide Conjugates of T-2 Toxin and Metabolites in Swine Bile and Urine. R.A. Corley, S.P. Swanson, W.B. Buck. *J. Agric. Fd. Chem.* 33: 1085-1089, 1986.

5. Pharmacokinetics of the Trichothecene Mycotoxin, T-2 Toxin, in Swine and Cattle. V.R. Beasley, S.P. Swanson, R.A. Corley, W.B., Buck, G.D. Koritz, H.R. Burmeister. *Toxicon*. 24(1): 13-23, 1986.
6. Disposition of T-2 Toxin, a Trichothecene Mycotoxin, in Intravascularly-Dosed Swine. R.A. Corley, S.P. Swanson, G.J. Gullo, L. Johnson, V.R. Beasley, W.B. Buck. *J. Agric. Fd. Chem.* 34: 868-875, 1986.
7. Disposition of Trichothecene Mycotoxins. S.P. Swanson, R.A. Corley. In "Trichothecene Mycotoxicosis: Pathophysiologic Effects". V.R. Beasley, Ed. CRC Press, Inc. 1988.
8. Chlorpyrifos: A 13-Week Nose-Only Vapor Inhalation Study in Fischer 344 Rats. R.A. Corley, L.L. Calhoun, D.A. Dittenber, L.G. Lomax, T.D. Landry. *Fund. Appl. Toxicol.* 13, 616-618, 1989.
9. Development of a Physiologically-Based Pharmacokinetic Model for Chloroform. R.A. Corley, A.L. Mendrala, F.A. Smith, M.L. Gargas, D.A. Staats, R.B. Conolly, M.E. Andersen, and R.H. Reitz. *Toxicol. Appl. Pharmacol.* 103, 512-527, 1990.
10. Estimating the Risk of Liver Cancer Associated With Human Exposures to Chloroform. R.H. Reitz, A.L. Mendrala, R.A. Corley, J.F. Quast, M.L. Gargas, M.E. Andersen, D.A. Staats, and R.B. Conolly. *Toxicol. Appl. Pharmacol.* 105, 443-459, 1990.
11. Dose-Route Extrapolations in Quantitative Toxicology: Physiologically-Based Pharmacokinetics and Pharmacodynamics of Chloroform. R.A. Corley and R.H. Reitz. In "Principles of Route-to-Route Extrapolation". T.R. Gerity and C.J. Henry, Eds. Elsevier, NY. 1990.
12. Physiologically-Based Pharmacokinetics of 2-Butoxyethanol and its Major Metabolite, Butoxyacetic Acid, in Rats and Humans. R.A. Corley, G.A. Bormett and B.I. Ghanayem. *Toxicol. Appl. Pharmacol.* 129, 61-79, 1994.
13. Multiple Endpoints: Integrated Strategies and Contemporary Issues In Animal Assays for Existing Chemicals. N.D. Krivanek and R.A. Corley. In "Screening and Testing Chemicals in Commerce". U.S. Congress, Office of Technology Assessment, OTA-BP-ENV-166. September, 1995.
14. Adaptive Metabolic and Pathologic Changes Following Chronic Inhalation of Propylene Glycol Monomethyl Ether in Rats and Mice. R.A. Corley, J.W. Crissman, J.R. Redmond, R.J. McGuirk, F.S. Cieszlak and W.T. Stott. *Occ. Hyg.* In press.

15. Evaluation of the Developmental Toxicity of Inhaled Dipropylene Glycol Monomethyl Ether (DPGME) in Rabbits and Rats. W.J. Breslin, F.S. Cieszlak, C.L. Zablotny, R.A. Corley, H.G. Verschuuren and B.L. Yano. *Occ. Hyg.* In press.
16. Toxicology of Diethylene Glycol Butyl Ether: Exposure and Risk Assessment. R. Gingell, R.J. Boatman, R.A. Corley, J.B. Knaak, K.A. Rosica, R.C. Wise. *Occ. Hyg.* In press.
17. Assessing the Risk of Hemolysis in Humans Exposed to 2-Butoxyethanol Using a Physiologically-Based Pharmacokinetic Model R.A. Corley. *Occ. Hyg.* In press.
18. Subchronic Oral and Dermal Toxicity/Neurotoxicity of Triethylene Glycol Monomethyl Ether in Rats. *Manuscript in preparation.*
19. Physiologically-Based Pharmacokinetics of the Dermal Absorption of 2-Butoxyethanol Vapors in Humans. *Manuscript in preparation.*

ABSTRACTS AND PROCEEDINGS

1. Rapid Thin-Layer Chromatographic Method for the Determination of Zearalenone and Zearalenol in Corn. R.A. Corley, S.P. Swanson, D.G. White, W.B. Buck. Abst. #190. 95th An. Meeting Assoc. of Official Anal. Chem. October, 1981. Washington, D.C.
2. Toxicokinetics and Toxicodynamics of T-2 Toxin in Swine and Cattle. V.R. Beasley, W.B. Buck, S.P. Swanson, J.R. Szabo, R.A. Corley. Abst. #18. 16th An. Meeting Amer. Chem. Soc., Great Lakes Region. June, 1982. Normal, IL.
3. Gas Chromatographic Method for the Determination of Deoxynivalenol (Vomitoxin) in Swine Plasma and Urine. S.P. Swanson, R.A. Corley, R.F. Vesonder, W.B. Buck. Proceed. 96th An. Meeting Assoc. of Official Anal. Chem. October, 1982. Washington, D.C.
4. Current Status of Toxicokinetics and Residue Detection of Trichothecene Mycotoxins in Swine, Cattle and Feedstuffs. V.R. Beasley, S.P. Swanson, J.D. Reynolds, R.W. Coppock, R.A. Corley, L.M. Cote, W.B. Buck. Proceed. 86th An. Meeting U.S. Animal Health Assoc. November, 1982. Nashville, TN
5. Analysis of Deoxynivalenol (Vomitoxin) in Plasma and Urine. S.P. Swanson, R.A. Corley, R.F. Vesonder, J.D. Reynolds, L.M. Cote, R.W. Coppock, W.B. Buck. Abst. #3. 25th An. Meeting Amer. Assoc. of Vet. Lab. Diagnosticians. November, 1982. Nashville TN.

6. Metabolism of T-2 Toxin in Swine. R.A. Corley, S.P. Swanson, R.H. Poppenga, W.B. Buck. Abst. #42. 187th Nat. Meeting Amer. Chem. Soc. April, 1984. St. Louis, MO.
7. Metabolism and Distribution of Tritium-Labeled T-2 Toxin in Swine. R.A. Corley, S.P. Swanson, W.B. Buck. Conference on Toxicity and Therapy of Trichothecene Mycotoxicosis. FASEB Summer Research Conferences. June, 1984. Saxtons River, VT.
8. Chlorpyrifos: 13-Week Nose-Only Vapor Inhalation Study In Fischer 344 Rats. R.A. Corley, T.D. Landry, L.L. Calhoun, D.A. Dittenber, L.G. Lomax. Abst. #190. 26th An. Society of Toxicology Meeting. February, 1987. Washington, D.C.
9. A Physiologically-Based Pharmacokinetic Model for Chloroform. R.A. Corley, A.L. Mendrala, F.A. Smith, M.L. Gargas, R.B. Conolly, M.E. Andersen, and R.H. Reitz. Abst #948. 28th An. Society of Toxicology Meeting. February, 1989. Atlanta, GA.
10. Developmental Toxicity of Inhaled Dipropylene Glycol Monomethyl Ether (DPGME) in Rabbits and Rats. W.J. Breslin, F.S. Cieszlak, C.L. Zablony, R.A. Corley, B.L. Yano and H.G. Verschuuren. Abst. #154. 29th An. Society of Toxicology Meeting. February, 1990. Miami, FL.
11. A PB-PK Risk Assessment for Chloroform. R.H. Reitz, R.A. Corley, A.L. Mendrala, J.F. Quast, M.E. Andersen, M.L. Gargas, R.B. Conolly and D.A. Staats. Abst. #285. 29th An. Society of Toxicology Meeting. February, 1990. Miami, FL.
12. Descriptive Toxicology. In: "Mammalian and Environmental Toxicology - An Overview". J.M. Waechter, R.A. Corley and M.A. Mayes. Abst. #72-75. American Chemical Society, Central Region. June, 1990. University Center, MI.
13. Toxicology of Diethylene Glycol Butyl Ether: 1. Exposure and Risk Assessments. R. Gingell, W.J. Krasavage, T.R. Tyler, J.B. Knaak, R.A. Corley, J.H. Sayler and C.A. Stack. Abst. # 1223. 30th An. Society of Toxicology Meeting. February, 1991. Dallas, TX.
14. Rat and Mouse Liver and Kidney Response to Inhaled Propylene Glycol Monomethyl Ether (PGME). J.S. Bus, J.W. Crissman, T.R. Fox, J.M. Redmond, F.S. Cieszlak, R.A. Corley and W.T. Stott. Abst. #871. 31st An. Society of Toxicology Meeting. February, 1992, Seattle, WA.

15. The Subchronic Toxicity of Triethylene Glycol Monomethyl Ether (TGME) in Dermally-Exposed Sprague-Dawley Rats. R.A. Corley, F.S. Cieszlak, W.J. Breslin, L.G. Lomax and C.R. Stack. Abst. #868. 31st An. Society of Toxicology Meeting. February, 1992, Seattle, WA.
16. Triethylene Glycol Monomethyl Ether (TGME): Ninety-Day Subchronic Drinking Water Inclusion Neurotoxicity Study in Rats. P.E. Losco, M.W. Gill, J. P. Maurissen, R.A. Corley, R. Gingell and C.R. Stack. Abst. #869. 31st An. Society of Toxicology Meeting. February, 1992, Seattle, WA.
17. Subchronic Dietary Toxicity of 2,4-D Acid, 2,4-D Amine Salts and 2,4-D Esters in Rats. B.L. Yano, G.E. Schultze, J.R. Szabo, R.A. Corley, P.F. Cosse and L.H. Billups. Abst. #404. 31st An. Society of Toxicology Meeting. February, 1992, Seattle, WA.
18. A Physiologically-Based Pharmacokinetic Model for 2-Butoxyethanol and its Metabolite, Butoxyacetic Acid. R.A. Corley, G.A. Bormett, B.J. Markley and C.R. Stack. Abst. #1387. 32nd An. Society of Toxicology Meeting. March, 1993, New Orleans, LA.
19. Adaptive Metabolic and Pathologic Changes Following Chronic Inhalation of Propylene Glycol Monomethyl Ether in Rats and Mice. R.A. Corley, J.W. Crissman, J.R. Redmond, R.J. McGuirk, F.S. Cieszlak and W.T. Stott. International Symposium on Health Hazards of Glycol Ethers. Nancy, France. April 19-22, 1994.
20. Evaluation of the Developmental Toxicity of Inhaled Dipropylene Glycol Monomethyl Ether (DPGME) in Rabbits and Rats. W.J. Breslin, F.S. Cieszlak, C.L. Zablotny, R.A. Corley, H.G. Verschuuren and B.L. Yano. International Symposium on Health Hazards of Glycol Ethers. Nancy, France. April 19-22, 1994.
21. Toxicology of Diethylene Glycol Butyl Ether: Exposure and Risk Assessment. R. Gingell, R.J. Boatman, R.A. Corley, J.B. Knaak, K.A. Rosica, R.C. Wise. International Symposium on Health Hazards of Glycol Ethers. Nancy, France. April 19-22, 1994.
22. Physiologically-Based Pharmacokinetics of the Dermal Absorption of 2-Butoxyethanol Vapors in Humans. R.A. Corley, D.A. Markham, C. Banks, P. Delorme, A. Masterman, J.M. Houle and K.A. Rosica. Abst. #255. 34th An. Society of Toxicology Meeting. Baltimore, MD. March, 1995.
23. Analysis of 2-Butoxyethanol and Metabolites in Human Urine by GC & ESI/MS. D.A. Markham, M.J. Bartels, R.A. Corley, and A.W. Rettenmeier. Abst. #WPG

170. 43rd ASMS Conference on Mass Spectrometry and Allied Topics. Atlanta, GA. May 21-26, 1995.
24. A Physiologically-Based Pharmacokinetic (PBPK) Model for 2-Butoxyethanol and its Hemolytic Metabolite, 2-Butoxyacetic Acid. K.M. Lee, R.D. Stenner, R.A. Corley, and K.D. Thrall. Abst. #63-PF-2. VII International Congress of Toxicology. Seattle, WA. July 2-6, 1995.
24. Multiple 2-Butoxyethanol Intoxications in the Same Patient: Clinical Findings, Pharmacokinetics and Therapy. J. Gualtieri, C. Harris, R. Roy, R. Corley and C. Manderfield. North American Congress of Clinical Toxicology. Rochester, NY. September 16-19, 1995.
25. Chronic Toxicity, Oncogenicity and Mechanistic Studies with Propylene Glycol Monomethyl Ether (PGME). R.A. Corley, J.W. Crissman, F.S. Cieszlak and W.T. Stott. Abst. #. 35th An. Society of Toxicology Meeting. Anaheim, CA. March 10-14, 1996.

INVITED PRESENTATIONS

1. Short and Long Range Effects of Pesticides in Agriculture. R.A. Corley. Quad Cities Chapter, Amer. Soc. of Agric. Eng. November 3, 1983. Moline, IL. .
2. The Toxicology of Glycols. R.A. Corley. Society of Automotive Engineers. August 17, 1989. Tulsa, OK..
3. A Physiologically-Based Pharmacokinetic Model for Chloroform/Chloroform Risk Estimations using PB-PK Models. R.A. Corley and R.H. Reitz. Interagency Pharmacokinetics Group. October 17, 1989. Washington, D.C.
4. A Physiologically-Based Pharmacokinetic Model for Chloroform/Chloroform Risk Estimations using PB-PK Models. R.A. Corley and R.H. Reitz. American Industrial Health Council. October 17, 1989. Washington, D.C.
5. Dose-Route Extrapolations in Quantitative Toxicology: Physiologically-Based Pharmacokinetics and Pharmacodynamics of Chloroform. R.A. Corley. EPA/ILSI Workshop: Principles of Route-to-Route Extrapolations for Risk Assessment. March 20, 1990. Hilton Head, S.C.
6. Physiologically-Based Pharmacodynamic Models in Cancer Risk Assessment. R.A. Corley. U.S.C. Biomedical Simulations Resource Short Course on "Advanced Modeling Methodologies in Pharmacokinetics and Pharmacodynamics". May 17, 1991. Los Angeles, CA.

7. Physiologically-Based Pharmacodynamic Models in Cancer Risk Assessment. R.A. Corley. University of Pittsburgh Graduate School of Public Health Seminar Series. July 24, 1991. Pittsburgh, PA.
8. Using Physiologically-Based Pharmacokinetic Modeling in Risk Assessments. R.H. Reitz and R.A. Corley. Short Course for the State of Michigan Department of Natural Resources. September 12, 1991. Lansing, MI.
9. Improvements in Health Risk Assessment: Biologically-Based Models for Tissue Dosimetry. R.A. Corley. ACS Symposium: "The Role of Mechanistic Data in Regulatory Decisions". 204th National Meeting, American Chemical Society. August 25, 1992. Washington, D.C.
10. A Physiologically-Based Pharmacokinetic Model for 2-Butoxyethanol and its Metabolite, Butoxyacetic Acid. R.A. Corley. Chemical Manufacturers Association, Glycol Ethers Toxicology Research Task Group. October 14, 1992. Washington, D.C.
11. A Physiologically-Based Pharmacokinetic Model for 2-Butoxyethanol and its Metabolite, Butoxyacetic Acid. R.A. Corley. U.S.E.P.A. RfC Work Group. February 12, 1993. Research Triangle Park, NC.
12. Improvements in Health Risk Assessment: Biologically-Based Models for Tissue Dosimetry. R.A. Corley. University of Kentucky Graduate Center for Toxicology Seminar Series. April 5, 1993.
13. Toxicology in the Chemical Industry. R.A. Corley. University of Kentucky Graduate Center for Toxicology (TOX 680 Advanced Toxicology). April 6, 1993.
14. Improving Health Risk Assessments Using Biologically-Based Models for Tissue Dosimetry. R.A. Corley. Michigan Society for Risk Analysis. Dearborn, MI. October, 26, 1993.
15. Improving Health Risk Assessments Using Biologically-Based Models for Tissue Dosimetry. R.A. Corley. Pharmacokinetics (U.K.). Birmingham, U.K. November 12, 1993.
16. A Physiologically-Based Pharmacokinetic Model for 2-Butoxyethanol and its Metabolite, Butoxyacetic Acid, in Rats and Humans. R.A. Corley. International Symposium on Health Hazards of Glycol Ethers. Nancy, France. April 19-22, 1994.

17. Multiple Endpoints. N. Krivanek and R.A. Corley. Office of Technology Assessment Workshop on Testing and Screening Technologies for Review of Chemicals in Commerce. Washington, D.C. April 24-25, 1995.
18. Physiologically Based Pharmacokinetics of 2-Butoxyethanol: Biological Basis for an Occupational Exposure Limit. R.A. Corley. ACGIH TLV Committee. San Antonio, TX. October 14, 1995.
19. Use of Physiologically-Based Pharmacokinetic Modeling as an Approach to Risk Assessment of 2-Butoxyethanol. R.A. Corley. 1995 Fall Mtg. of the MI Chapter of the Society of Toxicology. Novi, MI. October 20, 1995.
20. Physiologically-Based Pharmacokinetics and the Dermal Absorption of 2-Butoxyethanol Vapors by Humans. R.A. Corley. Pacific Northwest National Laboratory. Richland, WA. November 30, 1995.

CURRICULUM VITAE

TIMOTHY DAVID LANDRY

- OBJECTIVES:** Contribute industrial and inhalation toxicology skills to practical and research applications. Improve my knowledge/expertise in broad aspects of toxicology.
- EMPLOYMENT:**
- 1990 - present - The Dow Chemical Company, Toxicology Research Laboratory, Health and Environmental Sciences, Midland, MI (Research Associate)
 - 1989 - 1990 - The Dow Chemical Company, Health and Environmental Sciences, (Group Leader)
 - 1987 - 1989 - The Dow Chemical Company, Health and Environmental Sciences, (Research Leader)
 - 1983 - 1987 - The Dow Chemical Company, Health and Environmental Sciences (Project Leader)
 - 1981 - 1983 - The Dow Chemical Company, Health and Environmental Sciences, Midland, MI (Senior Research Toxicologist)
 - 1979 - 1980 - The Dow Chemical Company, Health and Environmental Sciences (Postdoctoral Fellow)
 - 1975 - 1977 - University of Rochester, Laboratory Instructor in Biology (part-time)
- JOB DESCRIPTION:** Direct studies and review technical reports within the Inhalation Toxicology Group at the Dow Chemical Company's Toxicology Research Laboratory. An extensive range of studies are conducted from acute to chronic duration, teratology and reproduction studies, and more specialized research. Provide technological expertise to Dow Chemical relating to inhalation, industrial, metals, hydrogenated fluorocarbons, fibers, exposure modeling and combustion toxicology. Member of Dow's Emergency Response Planning Guideline Committee. Liaison from Toxicology/Health & Environmental Sciences to the Polyurethanes, Polyolefins and STYROFOAM* Products departments. In conjunction with this, I am a member of the

Society of the Plastics Industry Polyurethane Toxicology Committee, the International Isocyanate Institute Americas Med-Tox Committee, and the International Isocyanate Institute Occupational Asthma Task Force.

CITIZENSHIP: Canadian (U.S. immigrant visa)

EDUCATION: 1974 - 1979 - University of Rochester, Rochester, NY. (NIH Predoctoral Trainee: Ph.D., Toxicology). Thesis: "Developmental Changes in Mouse: Mercury Retention, Metabolism, and Excretion after Methylmercuric Chloride Administration"

1973 - 1974 - Dalhousie University, Halifax, Nova Scotia (Special student in Pharmacology)

1969 - 1973 - Colby College, Waterville, Maine (A.B., Biology)

PROFESSIONAL SOCIETIES: American Board of Toxicology - Diplomate, 1982
American Industrial Hygiene Association - member, 1981
Sigma Xi - member, 1983 (Midland Chapter: Treasurer, 1994 - 1996, President-elect, 1995 - 1996)
Society of Toxicology - member, 1983
SOT Michigan Regional Chapter (Secretary/Treasurer, 1992 - 1994)
SOT Inhalation Specialty Section

COMMUNITY ACTIVITIES: Kiwanis Club - member, 1990; committee chair, 1992, 1995; Board of Directors, 1993-1996
March of Dimes - Chairman of Midland fund raising, 1993 - 1994, Mid-Michigan Board of Directors, 1995 - 1996.
Sylvan Pines Condo. Assoc. - President, 1994

REFERENCES: on request

PUBLICATIONS

1. Von Burg, R. and Landry, T. D. (1975). Methylmercury induced neuromuscular dysfunction in the rat. Neuroscience Letters **1**, 169-172.
2. Von Burg, R. and Landry, T. D. (1976). Methylmercury and the skeletal muscle receptor. Journal of Pharmacy and Pharmacology **28**, 548-551.
3. Doherty, R. A., Gates, A. H. and Landry, T. D. (1977). Methylmercury excretion: Developmental changes in mouse and man. Pediatrics Research **11**, 416 (abstract).
4. Landry, T. D., Doherty, R. A. and Gates, A. H. (1978). Dietary effects on mercury elimination after administration of CH₃HgCl or HgCl₂. Pediatrics Research **12**, 406 (abstract).
5. Landry, T. D., Doherty, R. A. and Gates, A. H. (1978). Effects of three diets on Hg excretion after methylmercury administration. Bulletin of Environmental Contamination and Toxicology **22**, 22, 151-158.
6. Waechter, J. M., Ramsey, J. C., Kropscott, B. E., Quast, J. F., Landry, T. D. and Braun, W. H. (1982). Allyl chloride: Pharmacokinetics and metabolism following administration to CDF-Fischer 344 rats by three routes, The Toxicologist **2**, 31 (abstract).
7. Landry, T. D., Ayres, J. A., Johnson, K. A. and Wall, J. M. (1982). Ethyl chloride: A two-week inhalation toxicity study in rats and dogs. Fundam. Appl. Toxicol. **2**, 230-234.
8. Landry, T. D., Miller, R. R., McKenna, M. J., Ramsey, J. C. and Watanabe, P. G. (1983). Application of pharmacokinetic principles to problems in inhalation toxicology, in Modeling the Uptake, Metabolism, and Elimination of Some Inhalation Vapors and Gases **2**, V. Thomas (ed.), CRC Press, Inc., Boca Raton, Florida.
9. Rowland, I. R., Robinson, R. D., Doherty, R. A. and Landry, T. D. (1983). Are developmental changes in methylmercury metabolism and excretion mediated by the intestinal microflora? Reproductive and Developmental Toxicity of Metals, T. W. Clarkson, G. F. Nordberg and P. R. Sager (eds.), Plenum Press, New York.
10. Landry, T. D., Gushow, T. S., Langvardt, P. W., Wall, J. M. and McKenna, M. J. (1983). Metabolism and pharmacokinetics of inhaled methyl chloride in the rat and dog. Toxicol. Appl. Pharmacol. **68**, 473-486.

11. Landry, T. D., Gushow, T. S. and Yano, B. L. (1983). Propylene glycol monomethyl ether: A 13-week inhalation toxicity study in rats and rabbits. Fundam. Appl. Toxicol. 3, 627-630.
12. Landry, T. D., Ramsey, J. C. and McKenna, M. J. (1983). Pulmonary physiology and inhalation dosimetry in rats: Development of a method and two examples. Toxicol. Appl. Pharmacol. 71, 72-83.
13. Landry, T. D. and Yano, B. L. (1984). Dipropylene glycol monomethyl ether: A 13-week inhalation toxicity study in rats and rabbits. Fundam. Appl. Toxicol. 4, 612-617.
14. Miller, R. R., Herman, E. A., Young, J. T., Landry, T. D. and Calhoun, L. L. (1984). Ethylene glycol monomethyl ether and propylene - series glycol ether metabolism, disposition, and subchronic inhalation studies. Environ. Health Persp. 57, 233-239.
15. Landry, T. D., Quast, J. F., Gushow, T. S. and Mattsson, J. L. (1985). Neurotoxicity of methyl chloride in continuously versus intermittently exposed female C57BL/6 mice. Fundam. Appl. Toxicol. 5, 87-98.
16. Nolan, R. J., Rick, D. L., Landry, T. D., McCarty, L. P., Agin, G. L. and Saunders, J. H. (1985). Pharmacokinetics of inhaled methyl chloride (CH₃Cl) in human volunteers, Fundam. Appl. Toxicol. 5, 361-369.
17. Johnson, K. A., Landry, T. D., Gorzinski, S. J., Cieszlak, F. S., Kropscott, B. E. and Wolfe, E. A. (1986). Picloram: A two-year chronic toxicity and oncogenicity study in Fischer 344 rats. The Toxicologist 6 abstract #331.
18. Gorzinski, S. J., Johnson, K. A., Campbell, R. A. and Landry, T. D. (1987). Dietary toxicity of picloram herbicide in rats. J. Toxicol. Environ. Health, 20:367-377.
19. Corley, R. A., Calhoun, L. L., Dittenber, D. A., Lomax, L. G. and Landry, T. D. (1989). Chlorpyrifos: 13-week nose-only vapor inhalation study in Fischer 344 rats. Fundam Appl Toxicol. 13, 616-618.
20. Landry, T. D., Johnson, K. A., Phillips, J. E. and Weiss, S. K. (1989). Ethyl Chloride: 11-day continuous exposure inhalation toxicity study in B6C3F1 mice. Fundam Appl Toxicol. 13, 516-522.
21. Stott, W. T., Johnson, K. A., Landry, T. D., Gorzinski, S. J. and Cieszlak, F. S. (1990). Chronic toxicity and oncogenicity of picloram in fischer 344 rats. J. Toxicol. Envir. Health 30, 91-104.

22. Pottenger, L.H., Landry, T.D. and Bus,, J.S. (1991). Species-specific and dose-dependent non-protein sulfhydryls (NPSH) depletion in female mice and rats after inhalation exposure to ethyl chloride. The Toxicologist 11, 1368 (abstract).
23. Landry, T.D. and Steffens, C.A. (1992). "Industrial Toxicology of Reaction Polymers" in Reaction Polymers 746-770, Carl Hanser Verlag, Munich.
24. Landry, T.D. (1993). Polyurethane Dust - Inhalation Toxicology, section written for Patty's Industrial Hygiene and Toxicology (in preparation), Wiley Interscience)

PRESENTATIONS

1. Annual Society of Toxicology (SOT) Meeting (1978). "Effects of certain diets on mercury excretion after methylmercury administration." Abstract: Toxicol. Appl. Pharmacol. 45, 350.
2. Annual SOT Meeting. (1979). "Age differences in mouse methylmercury retention and demethylation." Abstract: Toxicol. Appl. Pharmacol. 48, 116.
3. Annual SOT Meeting. (1981). "Pharmacokinetics and metabolism of inhaled methyl chloride in the rat." Abstract: The Toxicologist 1, 6.
4. Annual SOT Meeting. (1982). "Parent compound pharmacokinetics of inhaled methyl chloride in the rat and dog." Abstract: The Toxicologist 2, 168.
5. Michigan SOT Meeting. (1982). "Pulmonary physiology and inhalation dosimetry in rats: Development of a method with two examples."
6. Annual SOT Meeting (1984). "Neurotoxicity of methyl chloride in continuously versus intermittently exposed female C57BL/6 Mice." Abstract: The Toxicologist 4, 181.
7. Michigan Macromolecular Institute (1984). "Combustion product toxicity: current research and testing procedures."
8. American Chemical Society - Midland Chapter. Fall Scientific Meeting (1984). "Applications of respiratory physiology and inhalation dosimetry to toxicology."
9. Annual SOT Meeting (1985). "Triclopyr: 13-week dietary toxicity study and 4-week pharmacokinetic study in Fischer 344 rats." Abstract: The Toxicologist 5, 1.

10. Annual SOT Meeting (1987). Ethyl Chloride (EtCl): 11-day continuous inhalation exposure study in B6C3F1 mice. The Toxicologist 7, 756.
11. Annual SOT Meeting (1991). 1,3-Dioxolane 13-week vapor inhalation study in Fischer 344 Rats. The Toxicologist 11, 1236.

CIRRICULUM VITAE

William J. Breslin

EDUCATION

- Ph.D. Michigan State University, 1984. Dual degree in Environmental Toxicology (College of Veterinary Medicine) and Animal Science (College of Agriculture and Natural Resources).
- M.S. Michigan State University, 1982. Major: Poultry Science/Toxicology.
- B.S. Michigan State University, 1980. Major: Wildlife Management.

EMPLOYMENT

- 1993- Present Research Associate. Toxicology Research Laboratory, The Dow Chemical Company, 1803 Building, Midland, MI 48674. (517) 636-1311. Toxicology Consultant: Responsibilities include providing toxicology expertise to the product departments and representing the company as a toxicology expert on various intra-company, industry-wide and government panels. Technical leader: Reproductive and Developmental Toxicology. Responsible for overall design, conduct and interpretation of reproductive and developmental toxicity studies, managing and auditing studies placed in contract laboratories and mentorship of less senior doctoral and non-doctoral staff.
- 1989- 1993 Research Leader. Toxicology Research Laboratory, The Dow Chemical Company. Manager: Reproductive and Developmental Toxicology. Primary responsibilities included managing/supervising all group personnel and research activities. The Reproductive and Developmental Toxicology group is responsible for providing specialized testing, research services and technical expertise for the manufacturing divisions, product departments and research facilities of the Company. Professional staff (B.S., M.S., Ph.D.) of nine full-time and one half-time employees. Research budget \$2.0-2.5 million. Primary Investigator/Study Director: Design, conduct, interpret, and report developmental, reproductive and subchronic toxicity studies; independent and cooperative investigative research; monitoring contract research and cooperation with product departments in developing testing strategies.
- 1987- 1989 Project Leader. Toxicology Research Laboratory, The Dow Chemical Company. Primary Investigator/Study Director.

EMPLOYMENT (Continued)

- 1986-1987 **Senior Research Biologist.** Toxicology Research Laboratory, The Dow Chemical Company. Primary Investigator/Study Director.
- 1984-1986 **Post-doctoral Fellow.** Toxicology Research Laboratory, Reproductive and Developmental Toxicology, The Dow Chemical Company. Evaluation of a neonatal neurobehavioral test battery; chemical effects on the endocrine system and associated toxicity; acute organophosphate toxicity and therapeutic treatment in mice; hemolytic investigations in rabbits and rats; 2-generation inhalation and dietary reproduction studies in rats; developmental toxicity studies in rats and rabbits.
- 1984-1980 **Graduate Research Assistant.** Department of Animal Science, Michigan State University, East Lansing, MI 48824. Conducted subacute avian toxicity tests, chronic avian reproductive toxicity tests, placental and mammary transfer and excretion of ^{14}C -labeled compounds in the European ferret, and distribution and excretion of ^{14}C -labeled compounds in bobwhite quail. Additional experience in single generation mammalian reproductive toxicity assays, radioimmunoassays for hormones and assays for the induction of hepatic microsomal mixed function oxidases.
- 1979-1980 **Research Assistant.** Department of Poultry Science, Michigan State University, East Lansing, MI 48824. Conducted subacute and reproductive avian toxicity studies.

PUBLICATIONS

Scientific Journals

Carney, E.W., Liberacki, A. Bartels, M. and Breslin, W. J. (1996). Identification of proximate toxicant for ethylene glycol developmental toxicity using rat whole embryo culture. *Teratology*. (Accepted)

Breslin W.J., Dittenber D.A. and Quast J.F. (1996). Evaluation of the developmental and reproductive toxicity of chlorpyrifos in the rat. *Fundam. Appl. Toxicol.* (Accepted)

Breslin W.J., Ciezlak F.S. Zablotny C.L. Corley R.A., Verschuuren H.G. and Yano, B.L. (1996). Evaluation of the developmental toxicity of inhaled dipropylene glycol monomethyl ether in rabbits and rats. *Occupational Hygiene*. (Accepted)

PUBLICATIONS (Continued)

Scientific Journals

Kirk, H. D., Berdasco, N. M., Breslin, W. J. and Hanley, T. R. (1995). Developmental Toxicity of 1,2-dichloropropane (PDC) in rats and rabbits following oral gavage. *Fundam. Appl. Toxicol.* 28, 18-26

Liberacki, A. B., Neepser-Bradley, T., Breslin, W. J. and Zielke, G. J. (1995). Teratologic evaluation of dermally applied monoethanolamine in rats and rabbits. *Fundam. Appl. Toxicol.* (Accepted)

Daston G.P., Gooch J.W., Breslin W.J., Shuey D.L., Nikiforov A.L., Fico T.A. and Gorsuch J. (1995). Environmental estrogens and reproductive health: a review of the human and environmental data. *Reproductive Toxicology*. (In preparation)

Carney, E.W., Breslin, W.J., Pottenger, L.H., Johnson, K.A. and Corley, R.A., 1995. Comparative developmental toxicity of the ethylene glycol ether metabolite, methoxyacetic acid, and the propylene glycol ether metabolite, methoxypropionic acid, in New Zealand White rabbits. (In preparation)

Breslin, W. J., Phillips, J. E., Lomax, L. G., Bartels, M. J., Dittenber, D. A., Calhoun, L. L. and Miller, R. R. (1991). Hemolytic activity of ethylene glycol phenyl ether (EGPE) in rabbits. *Fundam. Appl. Toxicol.* 17, 466-481.

Breslin, W. J., Kirk, H. D. and Zimmer, M. A. (1989). Teratogenic evaluation of a polybrominated diphenyl oxide (PBDPO) mixture in New Zealand white rabbits following oral exposure. *Fundam. Appl. Toxicol.* 12, 151-157.

Breslin, W. J., Kirk, H. D., Streeter, C. M., Quast, J. F. and Szabo, J. R. (1989). 1,3-dichloropropene (DCPT): two-generation inhalation reproduction study in Fischer 344 rats. *Fundam. Appl. Toxicol.* 12, 129-143.

Albee, R. R., Mattsson, J. L., Kirk, H. D., Johnson, K. A. and Breslin, W. J. (1989). Neurological consequences of congenital hypothyroidism in Fischer 344 rats. *Neurotox. Teratol.* 11, 171-183.

Breslin, W. J., Kirk, H. D. and Johnson, K. A. (1988). Teratogenic evaluation of diglycidyl ether of bisphenol A (DGEBA) in New Zealand white rabbits following dermal exposure. *Fundam. Appl. Toxicol.* 10, 736-743.

Rao, K. S., Breslin W. J. and Waechter, J. M. (1987). Letter to the editor. *Toxicol. Appl. Pharmacol.* 83, 153-155.

PUBLICATIONS (Continued)

Scientific Journals

Aulerich, R. J., Bursian, S. J., Breslin, W. J., Olson, B. A. and Ringer, R. K. (1985). Toxicological manifestations of 2,4,5,2',4',5'-, 2,3,6,2',3',6'-, and 3,4,5,3',4',5'-hexachlorobiphenyl and Aroclor 1254 in mink. *J. Toxicol. Environ. Health* 15, 63-79.

Bleavins, M. R., Breslin, W. J., Aulerich, R. J. and Ringer, R. K. (1984). Placental and mammary transfer of a polychlorinated biphenyl mixture (Aroclor 1254) in the European ferret (Mustela putorius furo). *J Environ. Toxicol. Chem.* 3, 637-644.

Breslin, W. J., Bleavins, M. R. and Ringer, R. K. (1983). Distribution and excretion of hexachlorobenzene in bobwhite (Colinus virginianus). *J. Toxicol. Environ. Health* 11, 885-896.

Bleavins, M. R., Breslin, W. J., Aulerich, R. J. and Ringer, R. K. (1982). Excretion and placental and mammary transfer of hexachlorobenzene in the European ferret (Mustela putorius furo). *J. Toxicol. Environ. Health* 10, 929-940.

Abstracts

Breslin W. and Billington R. (1995). Evaluation of the developmental toxicology of triclopyr TEA and triclopyr BEE in rabbits. *The International Toxicologist*, 74-P-5.

Carney, E.W., Schroeder, R. and Breslin, W.J., 1995. Developmental toxicity study in rats with fluroxypyr methylheptyl ester. *Teratology* 51:P12.

Carney, E.W., Schroeder, R. and Breslin, W.J., 1995. Developmental toxicity study in rats with nitrapyrin. *Teratology* 51:P13.

Carney E., Liberacki A., Bartels M and Breslin W. (1995). Identification of proximate toxicant for ethylene glycol developmental toxicity using rat whole embryo Culture. *The Toxicologist*. Vol. 15, No. 1, 866.

Breslin, W. J., Vedula, U., Zablotty, C. L. and Stebbins, K. E. (1994). Developmental toxicity studies with picloram triisopropanolamine salt and picloram 2-ethylhexyl ester in the rabbit. *The Toxicologist* 14, 162. Abstract No. 579.

Liberacki, A. B., Zablotty, C. L., Yano, B. L. and Breslin, W. J. (1994). Developmental toxicity studies on a series of 2,4-D salts and esters in rabbits. *The Toxicologist* 14, 162. Abstract No. 580.

PUBLICATIONS (Continued)

Abstracts

Maurissen, J. P. J., Shankan, M. R., Zielke, G. J., Spencer, P. J., Breslin, W. J., Crissman, J. W. and Kirk, H. D. (1994). Lack of developmental cognitive and other neurobehavioral effects following maternal exposure to 1,1,1-trichloroethane in rats. *The Toxicologist* 14, 162. Abstract No. 584.

Breslin, W. J., Liberacki, A. B., Kirk, H. D., Bradley, G. J. and Crissman, J. W. (1993). Sulfuryl Fluoride: two-generation reproduction study in Sprague-Dawley rats. *The Toxicologist* 13, 368. Abstract No. 1439.

Quast, J. F., Liberacki, A. B. and Breslin, W. J. (1993). Chlorpyrifos insecticide: two-generation dietary reproduction study in Sprague-Dawley rats. *The Toxicologist* 13, 372. Abstract No. 1454.

Zielke, G. J., Yano, B. L. and Breslin, W. J. (1993). 2,3,5,6-Tetrachloropyridine: combined repeat-dose and reproductive/developmental toxicity screen in Sprague-Dawley rats. *The Toxicologist* 13, 77. Abstract No. 200.

Breslin, W. J., Zielke, G. J., and Stebbins, K. L. (1992). Developmental toxicity of monoethanolamine (MEA) in rats following dermal exposure. *The Toxicologist* 12, 102. Abstract No. 323.

Zablotny, C. L., Breslin, W. J. and Kociba, R. J. (1992). Developmental toxicity of orthophenylphenol (OPP) in New Zealand White rabbits. *The Toxicologist* 12, 103. Abstracts No. 327.

Kociba, R. J., Zielke, G. J., and Breslin, W. J. (1992). Picloram Herbicide: Two-generation dietary reproduction study in Sprague-Dawley rats. *The Toxicologist* 12, 120. Abstract No. 393.

Hanley, T. R., Kirk, H. D., Johnson, K. A., Bond, D. M., Stebbins, K. E. and Breslin, W. J. (1992). Propylene Dichloride (PDC): A two-generation reproduction toxicity and dominant lethal mutation study in rats. *The Toxicologist* 12, 200. Abstract No. 734.

Corley, R. A., Cieszlak, F. S., Breslin, W. J., Lomax, L. G. and Stack, C. R. (1992). The subchronic toxicity of triethylene glycol monomethyl ether (TGME) in dermally exposed Sprague-Dawley rats. *The Toxicologist* 12, 233. Abstract No. 868.

Kirk, H. D., Yano, B. L., Haut, K. T., Verschuuren, H. G. and Breslin, W. J. (1992). Tripropylene glycol N-butyl ether 13-week drinking water toxicity study in Fischer 344 rats. *The Toxicologist* 12, 233. Abstract No. 865.

PUBLICATIONS (Continued)

Abstracts

Breslin, W. J., Schroeder, R. E., and Hanley, T. R. (1991). Developmental toxicity of Picloram potassium (K) and triisopropanolamine (TIPA) salts in the rat. The Toxicologist 11, 74. Abstract No. 200.

Hanley, T. R., Schroeder, R. E., and Breslin, W. J. (1991). Developmental studies on a series of 2,4-D salts and esters in the rat. The Toxicologist 11, 72. Abstract No. 190.

Jersey, G. C., Breslin, W. J., and Zielke, G. J. (1991). Subchronic toxicity of 1,3-dichloro-2-propanol in the rat. The Toxicologist 11, Abstract No. 1387.

Breslin, W. J., Ciezlak, F. S., Zablotny, C. L., Corley, R. A., Yano, B. L. and Verschuuren, H. G. (1990). Developmental toxicity of inhaled dipropylene glycol monomethyl ether (DPGME) in rabbits and rats. The Toxicologist 10, 38. Abstract No. 154.

Breslin, W. J., Kirk, H. D., Streeter, C. M., Quast, J. F. and Szabo, J. R. (1988). TELONE® II soil fumigant: two-generation inhalation reproduction study in Fischer 344 rats. The Toxicologist 8, 239. Abstract No. 951.

Albee, R. R., Mattsson, J. L., Kirk, H.D., Johnson, K. A. and Breslin, W. J. (1988). Neurophysiological effects of perinatal methimazole administration: a positive control study. The Toxicologist 8, 227. Abstract No, 906.

Breslin, W. J., Phillips, J.E., Lomax, L. G., Calhoun, L.L., Dittenber, D. A., Bartels, M. J. and Miller, R. R. (1987). Ethylene glycol phenyl ether (EGPE): toxicological effects in rabbits and rats. The Toxicologist 7, 246. Abstract No. 906.

Bleavins, M. R., Breslin, W. J., Aulerich, R. J. and Ringer, R. K. (1984). Excretion and placental and mammary transfer of hexachlorobenzene in the European ferret (*Mustela putorius furo*). Scientifur 8, 115.

Research Reports: >75 Industry or Government Research Reports

PROFESSIONAL SOCIETIES

Teratology Society

Society of Toxicology (National and Michigan Chapter)

American Association for Laboratory Animal Science

Society of Environmental Toxicology and Chemistry (Central Great Lakes Regional Chapter)

TEACHING EXPERIENCE

Avian Physiology, Laboratory, Michigan State University, 1981-1984.
Avian Physiology, Lecture, Michigan State University, 1984.
Poultry Science and Practice, Laboratory, Michigan State University, 1981.

ORGANIZATIONS AND HONORS

Council of Graduate Students, Representative, M.S.U., 1980-1982.
Poultry Science Graduate Student Association, 1980-1984; Secretary, 1982-1984.
Fisheries and Wildlife Club, M.S.U., 1978-1984.
FarmHouse Fraternity, M.S.U., 1979-1982.
Board of Regents Scholarship, 1975-1977.
Varsity Track and Field, E.M.U., 1975-1977.

SYMPOSIUM PRESENTATIONS

Co-Chair, Poster Discussion Session: Reproductive System. International Congress of Toxicology-VII. July 2-6, 1995. Seattle, Washington, USA.

Breslin W. and Billington R. (1995). Evaluation of the developmental toxicology of triclopyr TEA and triclopyr BEE in rabbits. International Congress of Toxicology-VII. July 5, 1995. Seattle, Washington, USA.

W. J. Breslin. (1995). Dow strategy for hazard assessment of potential estrogenic chemicals. 1995 Spring Science and Technology Meeting. Midland, MI. May 17, 1995.

Breslin, W. J., Vedula, U., Zablotny, C. L. and Stebbins. (1994). Developmental toxicity studies with picloram triisopropanolamine salt and picloram 2-ethylhexyl ester in the rabbit. Society of Toxicology, 33rd Annual Meeting, Dallas, TX. March 13-18, 1994.

Liberacki, A. B., Zablotny, C. L., Yano, B. L., and Breslin, W. J. (1994). Developmental toxicity studies on a series of 2,4-D salts and esters in rabbits. Society of Toxicology, 33rd Annual Meeting, Dallas, TX. March 13-18, 1994.

Maurissen, J. P. J., Shankan, M. R., Zielke, G. J., Spencer, P. J., Breslin, W. J., Crissman, J. W., and Kirk, H. D. (1994). Lack of developmental cognitive and other neurobehavioral effects following maternal exposure to 1,1,1-trichloroethane in rats. Society of Toxicology, 33rd Annual Meeting, Dallas, TX. March 13-18, 1994.

2,3,5,6-Tetrachloropyridine: Combined Repeat-dose and Reproductive/Developmental Toxicity Screen in Sprague-Dawley Rats. Society of Toxicology, 32th Annual Meeting, New Orleans, LA. March 14-18, 1993.

SYMPOSIUM PRESENTATIONS (Continued)

Chlorpyrifos Insecticide: Two-generation Dietary Reproduction Study in Sprague-Dawley rats. Society of Toxicology, 32th Annual Meeting, New Orleans, LA. March 14-18, 1993.

Sulfuryl Fluoride: Two-generation Reproduction Study in Sprague-Dawley Rats. Society of Toxicology, 32th Annual Meeting, New Orleans, LA. March 14-18, 1993.

Developmental Toxicity of Monoethanolamine (MEA) in Rats Following Dermal Exposure. Society of Toxicology, 31th Annual Meeting, Seattle, Washington. Feb. 23-27, 1992.

Picloram Herbicide: Two-Generation Dietary Reproduction Study in Sprague-Dawley Rats. Society of Toxicology, 31th Annual Meeting, Seattle, Washington. Feb. 23-27, 1992.

Propylene Dichloride (PDC): A Two-Generation Reproduction Toxicity and Dominant Lethal Mutation Study in Rats. Society of Toxicology, 31th Annual Meeting, Seattle, Washington. Feb. 23-27, 1992.

Developmental toxicity of Picloram potassium (K) and triisopropanolamine (TIPA) salts in the rat. Society of Toxicology, 30th Annual Meeting, Dallas, Texas. Feb. 25-March 1, 1991.

Subchronic toxicity of 1,3-dichloro-2-propanol in the rat. Society of Toxicology, 30th Annual Meeting, Dallas, Texas. Feb. 25-Mar. 1, 1991.

Developmental toxicity of inhaled dipropylene glycol monomethyl ether (DPGME) in rabbits and rats. Society of Toxicology, 29th Annual Meeting. Miami Beach, Florida. Feb. 12-16, 1990.

TELONE® II soil fumigant: two-generation inhalation reproduction study in Fischer 344 rats. Society of Toxicology, 27th Annual Meeting. Dallas, Tx. Feb. 15-19, 1988.

Ethylene Glycol Phenyl Ether (EGPE): Toxicological effects in rabbits and rats. Society of Toxicology, 26th Annual Meeting. Washington D. C., Feb. 23-27, 1987.

Methylene chloride: effects on estrous cycling and serum prolactin in Sprague-Dawley rats. Michigan Regional Chapter of The Society of Toxicology. Symposium on "In Vitro Approaches for Studing Toxic Cell Injury". Western Michigan University, Kalamazoo, MI. May 23, 1986.

SYMPOSIUM PRESENTATIONS (Continued)

Methylene chloride: effects on estrous cycling and serum prolactin in Sprague-Dawley rats. 42nd Fall Scientific Meeting of the American Chemical Society. Symposium on Methylene Chloride: Carcinogenicity Risk Assessment and Regulatory Impact. Midland, MI, Nov. 8, 1986.

Toxicological manifestations of 2,4,5,2',4',5'-, 2,3,6,2',3',6'-, and 3,4,5,3',4',5'-hexachlorobiphenyl and Aroclor 1254 in mink. Michigan Regional Chapter of The Society of Toxicology. Symposium on "Mechanism of Lung Metabolism and Toxicity". General Motors Research Laboratory, Warren, MI. May 11, 1984.

SYMPOSIUMS (Participant/Attendant)

Co-Chair, Poster Discussion Session: Reproductive System. International Congress of Toxicology-VII. July 5, 1995. Seattle, Washington, USA.

International Congress of Toxicology-VII. July 2-6, 1995. Seattle, Washington, USA.

U.S. Environmental Protection Agency Health Effects Research Laboratory, Endocrine Disruptor Research Needs Workshop. Raleigh, NC. April 10-13, 1995.

Society of Toxicology. 34th Annual Meeting. Baltimore, MD. March 5-9, 1995

Michigan Regional Chapter of the Society of Toxicology, in conjunction with the Midwest Teratology Association. Symposium on Environmental Estrogens. Park-Davis Pharmaceutical Research, Ann Arbor, MI. Oct. 21, 1994.

Preventing Child Exposures to Environmental Hazards: Research and Policy Issues. The Childrens Environmental Health Network. National Symposium. Washington, D.C., March 18-19, 1994.

Society of Toxicology. 33rd Annual Meeting. Dallas, TX. March 13-17, 1994.

Sperm Quantity and Quality Measures in Male Reproductive Toxicity: EPA Human and Rodent Studies. United States Environmental Protection Agency, Washington, D.C., Crystal Mall 2, Rm. 1126. Dec. 13, 1993.

American College of Toxicology. 14th Annual Meeting, New Orleans, LA. October 3-6, 1993.

Society of Toxicology, 32nd Annual Meeting, New Orleans, LA. March 14-18, 1993.

Female Reproductive and Developmental Toxicology. Michigan Regional Chapter of the Society of Toxicology. Lansing, MI. October 23, 1992.

SYMPOSIUMS (Participant/Attendant) (Continued)

The Teratology Society, 32 Annual Meeting, Boca Raton, Florida. June 28 - July 2, 1992.

Safety Assessment for Non-cancer Endpoints: The Benchmark Dose and Other Possible Approaches. Cal/EPA, USEPA and ATSDR Workshop. Tiburon, California. May 11-12, 1992.

Society of Environmental Toxicology and Chemistry, Central Great Lakes Chapter, Biomarkers as Indicators of Contaminant Effects and Fate in Fish, Wildlife and Humans. Ann Arbor, Michigan. April 30th, 1992.

Society of Toxicology, 31st Annual Meeting, Seattle, Washington. Feb. 23-27, 1992.

The Teratology Society, 31st Annual Meeting, Boca Raton, Florida. June 22-27, 1992.

Society of Toxicology, 30th Annual Meeting, Dallas, Texas. Feb. 25-March 1, 1991.

Society of Toxicology, 29th Annual Meeting. Miami Beach, Florida. Feb. 12-16, 1990.

Gordon Research Conference. Mammalian Gametogenesis and Emgryogenesis. Plymouth State College - North. Plymouth, NH., July 18-22, 1988.

Society of Toxicology. 27th Annual Meeting. Dallas, TX., Feb. 15-19, 1988.

Michigan Regional Chapter of the Society of Toxicology. Endocrine Toxicology. Kellogg Center, East Landing, MI., May 20, 1988.

Gordon Research Conference. Hormonal Carcinogeneses. New Hampton School. New Hampton, NH., Aug. 3-7, 1987.

Society of Toxicology. 26th Annual Meeting. Washington, D. C., Feb. 23-27, 1987.

Michigan Regional Chapter of the Society of Toxicology. Toxicology of Blood and Blood Forming Organs. University of Michigan. Ann Arbor, MI., Oct. 16, 1987.

42nd Fall Scientific Meeting of the American Chemical Society. Midland, MI., Nov. 8, 1986.

Banbury Center Conference. Mechanistic Approaches to Developmental Toxicity. Banbury Center. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY., Oct. 19-22, 1986.

Michigan Regional Chapter of the Society of Toxicology. In Virto Approaches for Studying Toxic Cell Injury. Kalamazoo, MI., May 23, 1986.

SYMPOSIUMS (Participant/Attendant) (Continued)

The Eighth CIIT Conference on Toxicology. Approaches to Elucidate Mechanisms in Teratogenesis. Raleigh, N.C., April 1, 1986.

Society of Toxicology. 24th Annual Meeting. San Diego, CA., March 18-22, 1985.

Society of Toxicology. 23th Annual Meeting. Atlanta, GA., March 12-16, 1984.

Michigan Regional Chapter of the Society of Toxicology. Mechanism of Lung Metabolism and Toxicity. General Motors Research Laboratory, Warren, MI., May 11, 1984.

International Symposium on PCBs in the Great Lakes. Michigan State University Center for Environmental Toxicology. East Lansing, MI., March, 1982.

CURRICULUM VITAE

Edward W. Carney

EDUCATION & POSITIONS HELD

1994-present PROJECT LEADER, REPRODUCTIVE
AND DEVELOPMENTAL TOXICOLOGY, THE DOW
CHEMICAL COMPANY, Midland, MI

Responsibilities: (1) Conduct mechanistic research on ethylene glycol and glycol ether developmental toxicity, (2) Lead an *in vitro* teratogenicity testing program for early stage screening and for follow-up mechanistic studies (3) Serve as thesis advisor for a University of Michigan Ph.D. student conducting thesis research at Dow on the relationship between maternal and developmental toxicity, (4) Provide technical oversight and laboratory support for regulatory testing studies in developmental and reproductive toxicology (5) Act as a Dow technical consultant for issues in developmental and reproductive toxicology.

1992- 1994 SENIOR RESEARCH TOXICOLOGIST, REPRODUCTIVE
AND DEVELOPMENTAL TOXICOLOGY, THE DOW
CHEMICAL COMPANY, Midland, MI

1990-1992 POST-DOCTORAL RESEARCH FELLOW, MOUNT SINAI HOSPITAL
RESEARCH INSTITUTE, Toronto, Ontario, Canada.

Supervisors: Drs. Janet Rossant, Stephen Lye and Knox Ritchie

Research projects: (1) expression of trophoblast-specific genes during placental development: use of mRNA markers to study regulation of differentiation and analysis of cell lineage *in vivo* and *in vitro* (2) expression of angiogenic growth factors in normal and growth restricted human placentae (3) reproductive/developmental analysis of mutant mice lacking a functional colony stimulating factor-one gene.

1986-1990 Ph.D., CORNELL UNIVERSITY, Ithaca, New York.
Major: Reproductive physiology
Minors: Biochemistry and Cellular Biology

Major professor: Dr. Robert H. Foote

Thesis title: "Co-culture of rabbit preimplantation embryos with rabbit oviduct epithelial cells"

- 1984-1986 M.S., UNIVERSITY OF WISCONSIN, Madison, Wisconsin.
Major: Reproductive Biology
Major professor: Dr. Barry D. Bavister
- Thesis title: "Requirements for in vitro development of the preimplantation golden hamster embryo"
- 1982-1984 EXPERIMENT SUPERVISOR, STERLING-WINTHROP RESEARCH INSTITUTE, Rensselaer, New York.
- Duties: Supervised a staff of four technicians engaged in teratology, male and female fertility, and other GLP reproductive and developmental toxicology evaluations of experimental pharmaceuticals in rabbits and rodents
- 1981-1982 VETERINARY ASSISTANT, FAIRMOUNT ANIMAL HOSPITAL, Syracuse, New York.
- 1979-1981 B.S., CORNELL UNIVERSITY, Ithaca, New York.
Major: Animal Science
- 1977-1979 A.A.S., STATE UNIVERSITY OF NEW YORK, AGRICULTURAL AND TECHNICAL COLLEGE, Cobleskill, New York.
Major: Animal Science

HONORS

- Special Recognition Award, The Dow Chemical Company, 1993
- Gamma Sigma Delta National Academic Honor Society
- Cornell University Field of Physiology Symposium Award for Best Poster Presentation, 1988 and 1989
- Field of Physiology, Graduate Student Representative to the Faculty
- Phi Theta Kappa National Academic Honor Society
- Cobleskill College Alumni Scholarship Award for Academic Excellence and Service
- New York State Regent's Scholarship

AFFILIATIONS

- Teratology Society
- MidWest Teratology Association
- Mid-Atlantic Reproduction and Teratology Association
- Industrial In Vitro Toxicology Group

PUBLICATIONS

1. Kane, M.T., Carney, E.W. and Bavister, B.D., 1986. Vitamins and amino acids stimulate hamster blastocysts to hatch *in vitro*. *J. Exp. Zool.* 239: 429-432.
2. Carney, E.W. and Bavister, B.D., 1987. Stimulatory and inhibitory effects of amino acids on development of hamster 8-cell embryos *in vitro*. *J. In Vitro Fert. Emb. Transfer* 4: 162-167.
3. Carney, E.W. and Bavister, B.D., 1987. Regulation of hamster embryo development *in vitro* by carbon dioxide. *Biol. Reprod.* 36: 1155-1163.
4. Foote, R.H. and Carney, E.W., 1988. Factors affecting reproductive efficiency of selected laboratory animals. *Ann. N.Y. Acad. Sci.* 541: 683-696.
5. Ellington, J.E., Carney, E.W., Farrell, P.B., Simkin, M. and Foote, R.H., 1990. Bovine 1-2-cell embryo development using a simple medium in three oviduct epithelial cell coculture systems. *Biol. Reprod.* 43:97-104.
6. Carney, E.W. and Foote, R.H., 1990. Effects of superovulation, embryo recovery, culture system and embryo transfer on development of rabbit embryos *in vivo* and *in vitro*. *J. Reprod. Fert.* 89:543-551.
7. Carney, E.W., Tobback, C., and Foote, R.H., 1990. Co-culture of rabbit one-cell embryos with rabbit oviduct epithelial cells. *J. in Vitro Cell. Dev. Biol.* 26:629-635.
8. Carney, E.W., Tobback, C., Ellington, J.E., and Foote, R.H., 1990. Co-culture of rabbit 2-cell embryos with rabbit oviduct epithelial or other somatic cells. *Molec. Reprod. Dev.* 27:209-215.
9. Carney, E.W. and Foote, R.H., 1991. Improved development of rabbit one-cell embryos to the hatching blastocyst stage in a defined, protein-free culture medium. *J. Reprod. Fert.* 91:113-123.
10. Hallden, K., Li, J., Carney, E.W. and Foote, R.H., 1992. Increasing carbon dioxide from five to ten percent improves rabbit blastocyst development from cultured zygotes. *Molec. Reprod. Dev.* 33:276-280.
11. Carney, E.W., Lye, S.J. and Ritchie, J.W.K., 1992. Cellular localization of basic fibroblast growth factor within human placenta throughout gestation. *Society for Gynecological Investigation, 39th Annual Meeting*, p. 375.
12. Ellington, J.E., Farrell, E.W., Carney, E.W., Simkin, M.S., and Foote, R.H., 1992. *In vitro* developmental potential of bovine zygotes in oviduct epithelial cell co-culture systems. *Theriogenology*

13. Kane, M.T., Carney, E.W. and Ellington, J.E., 1992. The role of nutrients, peptide growth factors and co-culture cells in development of preimplantation embryos *in vitro*. *Theriogenology* August.
14. Carney, E.W., Prideaux, V., Lye, S.J. and Rossant, J., 1993. Progressive expression of trophoblast-specific genes during formation of mouse trophectoderm giant cells *in vitro*. *Molec. Reprod. Devel.* 34:357-368.
15. Carney, E.W., 1994. An integrated perspective on the developmental toxicity of ethylene glycol. *Reproductive Toxicology* 8:99-113.
16. Jackson, M.R., Carney, E.W., Lye, S.J. and Ritchie, J.W.K., 1994. Immunolocalisation of two angiogenic factors (PDEC GF and VEGF) in human placentae throughout gestation. *Placenta* 15: 341-353.
17. Kamrin, M.A., Carney, E.W., Chou, K., Cummings, A., Dostal, L.A., Harris, C., Henck, J.W., Loch-Caruso, R., and Miller, R.K., 1994. Female reproductive and developmental toxicology: overview and current approaches. *Toxicology Letters* 74:99-119.
18. Carney, E.W., Schroeder, R. and Breslin, W.J., 1995. Developmental toxicity study in rats with fluroxypyr methylheptyl ester. *Teratology* 51:P12.
19. Carney, E.W., Schroeder, R. and Breslin, W.J., 1995. Developmental toxicity study in rats with nitrapyrin. *Teratology* 51:P13.
20. Carney, E.W., Liberacki, A. Bartels, M. and Breslin, W.J. Identification of proximate toxicant for ethylene glycol developmental toxicity using rat whole embryo culture. *Teratology* (in press)..
21. Carney, E.W. Maternal physiological disruption. In: *Handbook of Experimental Pharmacology: Drug Toxicity in Embryonic Development*. Daston, G. and R. Kavlock, eds. Springer-Verlag (in press).
22. Carney, E.W. Preimplantation Embryogenesis. In: *Comprehensive Toxicology*. Sipes, I.G., McQueen, C.A. and Gandolfi, A.J., eds. Pergamon, Oxford (in press).
23. Carney, E.W., Breslin, W.J., Pottenger, L.H., Johnson, K.A. and Corley, R.A., 1995. Comparative developmental toxicity of the ethylene glycol ether metabolite, methoxyacetic acid, and the propylene glycol ether metabolite, methoxypropionic acid, in New Zealand White rabbits. (In preparation)

WORKSHOPS/SYMPOSIA

Member of Expert Panel for Ethylene Glycol: Institute for the Evaluation of Health Risks (IEHR) Pilot Evaluative Process for Assessing Human Developmental and Reproductive Toxicity of Agents. January, 1993, Williamsburg, VA. Published in: *Reprod. Toxicol* 9: 61-95 (1995); *Reprod. Toxicol.* 9: 175-210 (1995).

CURRICULUM VITAE

NAME: RICHARD JOSEPH KOCIBA

CURRENT JOB TITLE: Research Scientist

EDUCATION: 1953-1957 - Our Lady of Lake Huron High School , Harbor Beach, MI.

1959-1966 - B.S. and Doctor of Veterinary Medicine (D.V.M.), Michigan State University, East Lansing, MI, U.S.A.

1967-1969 - M.S. Pathology Major, Michigan State University, East Lansing, MI, U.S.A.

1969-1970 - Ph.D. Pathology, Michigan State University, East Lansing, MI, U.S.A. Thesis: "Cancer Chemotherapeutic Properties and Toxicologic Effects of Cis-Platinum II Diamminodichloride"

EMPLOYMENT: 1957-1958 - U. S. Army

1966-1967 - Veterinary Medicine Private Practice, Indiana

1967-1968 - Faculty, College of Veterinary Medicine, NIH Postdoctoral Fellow, Pathology Department, Michigan State University

1970-1974 - Senior Research Specialist, Pathology Department, The Dow Chemical Company, Chemical Biology Research, Toxicology Section

1974-1977 - Group Leader, Pathology Section, Toxicology Research Laboratory, Health and Environmental Research, Dow Chemical U.S.A., (Restructured from Chemical Biology Research)

1977-1981 - Associate Scientist, Dow Chemical U.S.A., Toxicology Research Laboratory, Health and Environmental Sciences, (Restructured from Health and Environmental Research), Pathology Group

EMPLOYMENT (Cont.): 1981 - Senior Associate Scientist, Dow Chemical U.S.A., Toxicology Research Laboratory, Health and Environmental Sciences

1986 - Research Scientist, The Dow Chemical Company, Mammalian and Environmental Toxicology Research Laboratory, Health and Environmental Sciences.

MEMBERSHIPS: Phi-Zeta, Veterinary Medicine, Honorary Society
Sigma Xi, Scientific Research, Honorary Society
Michigan Veterinary Medical Association
American Association of Laboratory Animal Sciences
American Veterinary Medical Association
American College of Veterinary Pathologists
Society of Toxicology
American Board of Toxicology
Board of Trustees, Elsa U. Pardee Cancer Foundation

CERTIFICATIONS: Diplomate, American College of Veterinary Pathologists - 1972
Diplomate, American Board of Toxicology - 1981

APPOINTMENTS: Medical Review Committee, Elsa U. Pardee Cancer Research Foundation
BioMedical Scientific Review Board, Midland Macromolecular Institute
External Reviewer, NIOSH Criteria Document on Chlorinated Benzenes, Dr. David West, National Institute of Occupational Safety and Health
External Consultant, NIEHS Toxicology Program, National Institutes of Environmental Health Sciences
Program Committee, Society of Toxicology Annual Meetings
External Consultant, World Health Organization, Health Document on Chlorine and Hydrogen Chloride
External Consultant, EPA Criteria Document on Dibenzofurans
Member, Division of Medical Sciences Committee, National Research Council, National Academy of Sciences
Adjunct Clinical Professor of Pathology, Michigan State University, East Lansing, Michigan
Editorial Board, Veterinary Pathology Journal

**APPOINTMENTS
(Cont.):**

Council Member, Society of Toxicology Michigan
Chapter
External Consultant, EPA Multimedia Criteria
Documents for Chlorinated Dioxins, 1983.
Member, National Toxicology Program Technical
Reports Review Subcommittee of Board of
Scientific Counselors, 1983
Editorial Board, Fundamental and Applied
Toxicology.
Editorial Board, Chemosphere Journal

PUBLICATIONS: See Attached.

PRESENTATIONS: See Attached.

Reviewed/Revised: _____ Date: _____

PUBLICATIONS

1. Kociba, R. J. Nitrite Toxicosis in the Ascorbic Acid-Deficient Guinea Pig. M. S. Thesis, Pathology Department, Michigan State University, 1969.
2. Kociba, R. J. and Sleight, S. D. Nitrite Toxicosis in the Ascorbic Acid-Deficient Guinea Pig. *Toxicol. Appl. Pharmacol.* 16:424-429, 1970.
3. Kociba, R. J., Sleight, S. D., and Rosenberg, B. Inhibition of Dunning Asitic Leukemia and Walker 256 Carcinosarcoma with Cis-Diamminedichloro-platinum (NSC-119875). *Cancer Chemotherapy Reports* 54:325-329, 1970.
4. Kociba, R. J. Cancer Chemotherapeutic Properties and Toxicologic Effects of Cis-Platinum (II) Diamminochloride. Ph.D. Thesis, Pathology Department, Michigan State University, 1970.
5. Kociba, R. J. and Sleight, S. D. Acute Toxicologic and Pathologic Effects of Cis-Diamminedichloroplatinum (NSC-119875) in the male rat. *Cancer Chemotherapy Reports* 55:1-8, 1971.
6. Kociba, R. J., Gehring, P. J., Humiston, C. G., and Sparschu, G. L. Toxicological Study of Female Rats Administered Hexachlorobutadiene or Hexachlorobenzene for Thirty Days. A Special Release of The Dow Chemical Company, August 1971.
7. Spencer, H. C., McCollister, S. B., Kociba, R. J., Humiston, C. G. Toxicological Studies on a Beryllium Containing Exhaust Product. Published in the Proceedings of the Third Conference on Environmental Toxicology, October 25-27, 1972. Sponsored by SysMed Corporation under Contract No. F3361-5-70-C-1046 with the Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, Ohio.
8. Spencer, H. C., McCollister, S. B., Kociba, R. J., Humiston, C. G., and Sparschu, G. L. Toxicological Evaluation of a Beryllium Motor Exhaust Product Document AMRL-TR-72-118, 95 pages, Contract No. F3361-5-C-1046 with the Aerospace Medical Research Laboratory, Aerospace Medical Division, Air Force Systems Command, Wright-Patterson Air Force Base, Ohio, 1972.
9. Kociba, R. J., Sparschu, G. L., Leong, B.K.J., and Gehring, P. J. Tissue Response to Ceramic Foam Dust Following Intratracheal and Intraperitoneal Administration. *Toxicol. Appl. Pharmacol.* 25:145-151, 1973.
10. McCollister, S. B., Kociba, R. J., and McCollister, D. D. Dietary Feeding Studies of Methylcellulose and Hydroxypropylmethylcellulose in Rats and Dogs. *Food and Cosmetics Toxicol.* 11:943-953, 1973.

PUBLICATIONS (Cont.)

11. Johnson, R. L., Gehring, P. J., Kociba, R. J., and Schwetz, B. A. Chlorinated Dibenzodioxins and Pentachlorophenol. *Environmental Health Perspectives, Experimental Issue* 5:171-175, 1973.
12. Norris, J. M., Kociba, R. J., Schwetz, B. A., Rose, J. Q., Humiston, C. G., and Gehring, P. J. Toxicological Evaluation of Fire Retardant Chemicals: Fall Meeting Am. Soc. Pharmacol. Exp. Therap. *The Pharmacologist* 15:394, 1973.
13. Norris, J. M., Ehrmantraut, J. W., Gibbons, C. L., Kociba, R. J., Schwetz, B. A., Rose, J. Q., Humiston, C. G., Jewett, G. L., Crummett, W. B., Gehring, P. J., Tirsell, J. B., and Brosier, J. S. Toxicological and Environmental Factors Involved in the Selection of Decabromodiphenyl Oxide as a Fire Retardant Chemical. *Appl. Polymer Symposium No. 22*, 195-219, 1973.
14. Norris, J. M., Ehrmantraut, J. W., Gibbons, C. L., Kociba, R. J., Schwetz, B. A., Rose, J. Q., Humiston, C. G., Jewett, G. L., Crummett, W. B., Gehring, P. J., Tirsell, J. B., and Brosier, J. S. Toxicological and Environmental Factors Involved in the Selection of Decabromodiphenyl Oxide as a Fire Retardant Chemical. *J. Fire and Flammability/Combustion Toxicology* 1:52-57, February 1974.
15. Kociba, R. J., McCollister, S. B., Park, C. N., Torkelson, T. R., and Gehring, P. J. 1,4-Dioxane: (I) Results of Two-Year Ingestion Studies in Rats. *Toxicol. Appl. Pharmacol.* 30:275-286, 1974.
16. Torkelson, T. R., Leong, B.K.J., Kociba, R. J., Richter, W. A., and Gehring, P. J. 1,4-Dioxane: (II) Results of a Two-Year Inhalation Study in Rats. *Toxicol. Appl. Pharmacol.* 30:287-298, 1974.
17. McCollister, S. B., Kociba, R. J., and Gehring, P. J. Studies on the Acute and Chronic Oral Toxicity of O,O-diethyl-O-(3,5,6-trichloro-2-pyridyl) Phosphorothioate. *Food and Cosmetics Toxicol.* 12:45-61, 1974.
18. Schwetz, B. A., Norris, J. M., Kociba, R. J., Keeler, P. A., Cornier, R. F., and Gehring, P. J. Reproduction Study in Japanese Quail Fed Hexachloro-butadiene for 90 Days. *Toxicol. Appl. Pharmacol.* 30:255-266, 1974.
19. Kociba, R. J., Leong, B.K.J., Jersey, G. C., Quast, J. F., and Gehring, P. J. Induction of Esthesioneuroepitheliomas in Rats Exposed to Bis(chloromethyl)ether. *Lab. Invest.* 32:12, 1975.

PUBLICATIONS (Cont.)

20. Kociba, R. J., Torkelson, T. R., Young, J. D., and Gehring, P. J. 1,4-Dioxane: Correlation of the Results of Chronic Ingestion and Inhalation Studies With Its Dose-Dependent Fate in Rats. Proceedings of the Sixth Conference on Environmental Toxicology, AMRL-TR-75-125, 345-354, Dayton, Ohio, 1975.
21. Norris, J. M., Kociba, R. J., Schwetz, B. A., Rose, J. Q., Humiston, C. G., Jewett, G. L., Gehring, P. J., and Mailhes, J. B. Toxicology of Octobromobiphenyl and Decabromodiphenyl Oxide. Environ. Health Perspectives 11:153-161, 1975.
22. Kociba, R. J., Frauson, L. O., Humiston, C. G., Norris, J. M., Wade, C. E., Lisowe, R. W., Quast, J. F., Jersey, G. C., and Jewett, G. L. Results of a Two-Year Dietary Feeding Study with Decabromodiphenyl Oxide (DBDPO) in Rats. Combustion Toxicology 2:267-285, 1975.
23. Hefner, R. E., Jr., Leong, B.K.J., Kociba, R. J., and Gehring, P. J. Repeated Inhalation Toxicology of Diphenyl Oxide in Experimental Animals. Toxicol. Appl. Pharmacol 33:78-86, 1975.
24. Fishbeck, W. A., Langner, R. R., and Kociba, R. J. Elevated Urinary Phenol Levels Not Related to Benzene Exposure. Journal of the American Industrial Hygiene Association 36:820-824, 1975.
25. Kociba, R. J., Keeler, P. A., Park, C. N., and Gehring, P. J. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD): Results of a 13-Week Oral Toxicity Study in Rats. Toxicol. Appl. Pharmacol. 35:553-574, 1976.
26. Kociba, R. J., Kalnins, R. V., Wade, C. E., Garfield, E. L., and Fishbeck, W. A. Elevated Urinary Phenol Levels in Dogs Treated with Salol. Journal of the American Industrial Hygiene Association, 37:183-191, 1976.
27. Schwetz, B. A., Humiston, C. G., Kociba, R. J., and Jersey, G. C. Results of Subchronic Toxicity Studies on HCl-Tailored Hydroxypropyl Methyl Cellulose in Rats and Dogs. Amer. Chem. Soc., Div. of Polymer Chemicals, Series 17, 1:6-11, 1976.
28. Kociba, R. J., Keyes, D. G., Jersey, G. C., Ballard, J. J., Dittenber, D. A., Quast, J. F., Wade, C. E., Humiston, C. G., and Schwetz, B. A. Results of a Two-Year Chronic Toxicity Study with Hexachlorobutadiene in Rats. J. American Industrial Hygiene Association 38:589-602, 1977.
29. Kociba, R. J., Schwetz, B. A., Keyes, D. G., Jersey, G. C., Ballard, J. J., Dittenber, D. A., Quast, J. F., Wade, C. E., and Humiston, C. G. Chronic Toxicity and Reproduction Studies of Hexachlorobutadiene in Rats. Environ. Hlth. Perspectives 21:49-53, 1977.

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14. Kociba, R. J. Toxicity of Vinyl Chloride. Presented at the 1975 Spring Seminar of the Midwest Veterinary Pathologists Meeting, Indianapolis, February 28, 1975.
15. Kociba, R. J. Toxicologic Pathology. Presented at the Armed Forces Institute of Pathology Course on Pathology of Laboratory Animals, Washington, DC, September 15-19, 1975.
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23. Braun, W. H., Sung, L. Y., Keyes, D. G., and Kociba, R. J. Pharmacokinetics and Toxicologic Evaluation of Dogs Fed 1,2,4,5-Tetrachlorobenzene in the Diet for Two Years.
24. Kociba, R. J. The Toxicology of TCDD. Presented at the Winter Meeting of the Midwest Association of Veterinary Pathologists, Purdue University, March 1977.
25. Kociba, R. J., Schwetz, B. A., Keyes, D. G., Jersey, G. C., Ballard, J. J., Dittenber, D. A., Quast, J. F., Wade, C. E., and Humiston, C. G. Chronic Toxicity and Reproduction Studies of Hexachlorobutadiene in Rats. Presented at a Symposium on Compounds Similar to Vinyl Chloride, National Institute of Environmental Health Sciences, Bethesda, MD, May 1977.

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27. Smith, F. A., Schwetz, B. A., Murray, F. J., Crawford, A. A., John, J. A., Kociba, R. J., and Humiston, C. G. Three-Generation Reproduction Study of Rats Ingesting 2,4,5-Trichlorophenoxyacetic Acid in the Diet.
28. Kociba, R. J., Keyes, D. G., Carreon, R. M., Wade, C. E., Dittenber, D. A., Kalnins, R. P., Frauson, L. E., Park, C. N., Hummel, R. A., and Humiston, C. G. Results of a Two-Year Chronic Toxicity and Oncogenicity Study of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) in Rats.

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36. Watanabe, P. G., Kociba, R. J., Keyes, D. G., Carreon, R. M., and Yakel, H. O. Acute and Subchronic Toxicity of α -Picoline in Rats.
37. Gorzinski, S. J., Nolan, R. J., Kociba, R. J., Karbowski, R. J., Wade, C. E., Morden, D. C., and Hermann, E. A. Results of a Subchronic Dietary Study of Hexachloroethane in Rats with Preliminary Data on Clearance from Selected Tissues.
38. Kociba, R. J., Keyes, D. G., Wade, C. E., Kalnins, R. P., Lisowe, R. W., and Dittenber, D. A. A Two-Year Chronic Toxicity and Oncogenic Study of 2,4,5-Trichlorophenoxyacetic Acid (2,4,5-T) in Rats.

PRESENTATIONS (Cont.)

The following two papers were presented at the 19th Annual Meeting of the Society of Toxicology, Washington, DC, March 10-13, 1980.

39. Nitschke, K. D., Keyes, D. G., Kociba, R. J. A Ninety-Day Inhalation Toxicity Study of 2-Methyl-3-Butyn-2-ol in Rats and Mice.
40. Keyes, D. G., Kociba, R. J., Schwetz, R. W., Wade, C. E., Dittenber, D. A., Gorzinski, S. J., Quinn, T., Kalnins, R. P., Hermann, E. A., Momany, J. J., and Schwetz, B. A. Results of a Two-Year Chronic Toxicity and Oncogenic Study of Rats Ingesting Diets Containing Dibromoneopentyl Glycol (FR-1138).

The following two papers were presented at the 20th Annual Meeting of the Society of Toxicology, San Diego, CA, March 1-5, 1981.

41. Nitschke, K. D., Kociba, R. J., Keyes, D. G., and McKenna, M. J. A Thirteen- Week Inhalation Toxicity Study of Ethylene Dibromide in Rats.
42. Gorzinski, S. J., Kociba, R. J., Wade, C. E., Morden, D. C., Keyes, D. G., and Schwetz, B. A. 2,4-D((2,4-Dichlorophenoxy) Acetic Acid): Results of a 13-Week Feeding Study in CDF Fischer 344 Rats.
43. Kociba, R. J. The Toxicity of Dioxin Compounds. Presented at the 1981 Spring Meeting of the Central States Association of Food and Drug Officials, Grand Rapids, MI, May 5-7, 1981.
44. Nitschke, K. D., Kociba, R. J., Keyes, D. G. Thirteen-Week Repeated Inhalation Study of Ethylene Dibromide in Male and Female Rats. Presented at the Dow Spring Scientific Meeting, April 1980.
45. Keyes, D. G., Kociba, R. J., Henck, J. W., Blogg, C. D., Schuetz, D. J. Methyl Chloroacetate (MCAC): Results of an Eleven-Day Repeated Inhalation Toxicity Study in Rats. Poster presentation given at Michigan State University, East Lansing, MI, May, 1981.
46. Kociba, R. J. and Schwetz, B. A. A Review of the Toxicity of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) with a Comparison to the Toxicity of Other Chlorinated Dioxin Isomers. Spring, 1981 Meeting of Central States Association of Food and Drug Officials, Grand Rapids, Michigan, 1981.
47. Kociba, R. J., and Schwetz, B. A. Toxicity of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD). Presentation at Symposium entitled "Metabolism and Pharmacokinetics of Environmental Chemicals in Man". Sarasota, FL, June 7-12, 1981.

PRESENTATIONS (Cont.)

48. Kociba, R. J. Laboratory Studies on the Identification of Environmental Causes of Cancer. Presentation at 1981 Annual Meeting of United Cancer Council, Midland, MI, October 22-24, 1981.
49. Kociba, R. J. Toxicological Studies of TCDD and Related Dioxin Isomers. International Symposium on Chlorinated Dioxins and Related Compounds. Arlington, VA, October 25-29, 1981.
50. Gorzinski, S. J., Jersey, G. C., Wade, C. E., Hermann, E. A., McCollister, S. B., and Kociba, R. J. Butyl and Methyl Acrylate: 13-Week Oral Toxicity Studies in CDF Fischer 344 Rats. Presented at 21st Annual Meeting of the Society of Toxicology, Boston, MA, February 22-26, 1982.
51. Keyes, D. G., Kociba, R. J., Henck, J. W. Nasal Mucosal Response Induced by a Respiratory Irritant. Presented at the 21st Annual Meeting of the Society of Toxicology, Boston, MA, February 22-26, 1982.
52. Kociba, R. J. Career Opportunities In Toxicologic Pathology. Michigan State University, Department of Pathology, Lansing, Michigan, February 16, 1982.
53. Kociba, R. J. Establishment of Adequate Margin of Safety for Chemical Carcinogens. Midwest Air Pollution Control Association Meeting, Southfield, Michigan, April 7, 1982.
54. Kociba, R. J. Carcinogenesis Testing in Toxicology. Midwest American Chemical Society Short Course, Northwood Institute, Midland, Michigan, June 14 and 15, 1982.
55. Kociba, R. J. Overview of the Animal Data Available for Assessment of Carcinogenic Potential of TCDD and Other Chlorinated Dioxins. Rockefeller University Symposium, New York, October 19 and 20, 1983.
56. Kociba, R. J. Pathologic Lesions Encountered During the Conduct of Long-Term Mammalian Toxicity Studies. University of Illinois, October, 1983.
57. Kociba, R. J. Evaluation of the Carcinogenic and Mutagenic Potential of 2,3,7,8-Tetrachlorodibenzo-p-dioxin and Other Chlorinated Dioxins. Banbury Conference Center, Cold Spring Harbor, New York, April 2-4, 1984.
58. Kociba, R. J. Overview of the Animal Toxicity Data on Chlorinated Dioxins. Ohio State University, April 24, 1984.

PRESENTATIONS (Cont.)

59. Kociba, R. J. Laboratory Studies for the Detection of Carcinogenic Potential. Medical Education Conference, August 29, 1984. Midland Hospital Center, Midland, Michigan.
60. Kociba, R. J. Critique of Proposed Methodology for Assessment of Target Organ Toxicity (Human Health Effects). EPA Workshop. December 3-4, 1984, Cincinnati, Ohio.
61. Kociba, R. J. and Cabey, O. Comparative Toxicity and Biologic Activity of Chlorinated Dioxins and Furans Relative to 2,3,7,8-TCDD. 4th International Symposium on Dioxins, Ottawa, Canada, September, 1984.
62. Kociba, R. J. Concluding Summary on Aspects of Dioxin Issue-Toxicology and Epidemiology. 4th International Symposium on Dioxins. Ottawa, Canada, September, 1984.
63. Kociba, R. J. Evaluation of Global Literature for Definition of Dose-Response Relationship for Hexachlorobenzene Toxicity. International Agency for Research on Cancer. June, 1985.
64. Kociba, R. J. Review of the Toxicology of 2,3,7,8-TCDD and Related Compounds. 5th International Symposium on Dioxin. Bayreuth, FRG. September, 1985.
65. Kociba, R. J. Case Examples of Morphological and Mechanistic Studies of Hepatic and Renal Carcinogenesis. Workshop on Toxicity, Tumor Promotion and Carcinogenesis. Aspen, Colorado. July, 1985.
66. Kociba, R. J. Review of the Toxicology of 2,3,7,8-TCDD and Related Compounds. 5th International Symposium on Chlorinated Dioxins. Bayreuth, FRG, September, 1985.
67. Kociba, R. J. Analysis of the Animal Toxicity Studies of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) Used in Derivation of Lifetime Exposure Control Limit Recommendations for Humans. ACS Annual Meeting, New York, NY. April, 1985.
68. Kociba, R. J. Overview of the toxicity of the Chlorodibenzo-p-dioxins/Furans and the Basis for Extrapolation from Animals to Man. National Council for Air and Stream Improvements. Chicago, IL May, 1986.
69. Kociba, R. J. Overview of the toxicity of the Chlorodibenzo-p-dioxins/Furans and the Basis for Extrapolation from Animals to Man. Canadian Paper & Pulp Association. Toronto, Ontario, Canada. September, 1986.

PRESENTATIONS (Cont.)

70. Bond, D. M., Kociba, R. J., Keyes, D. G., Wall, J. M. and S. K. Weiss. Results of a One-Year Dietary Toxicity Study in Beagle Dogs Administered Cyhexatin. The 26th Annual Meeting of the Society of Toxicology. Washington, DC. Feb, 1987.
71. Kociba, R. J. Historical Perspectives on the Rationale for Selection of the Maximum Tolerated Dose (MTD) for Chronic Animal Studies. The 26th Annual Meeting of the Society of Toxicology, Washington, DC. Feb, 1987.
72. Kociba, R. J. Key Factors in the Interpretation and Extrapolation of Data Derived from Chronic Organ Toxicity Studies in Laboratory Animals. Spring 1987 Meeting of the American Conference of Chemical Labeling. Washington, DC. March, 1987.
73. Kociba, R. J. Toxicity of Combustion Products from Plastics Containing Brominated Flame Retardants Relative to the Toxicity of Brominated Dioxins and Furans. U.S. Industry User's Meetings. Washington, DC. 1987.
74. Kociba, R. J. Toxicity of Combustion Products from Plastics Containing Brominated Flame Retardants Relative to the Toxicity of Brominated Dioxins and Furans. VCI Industry User's Meeting. Frankfurt, Federal Republic of Germany, 1987.
75. Kociba, R. J. Selection of the MTD for Chronic Bioassays. Natural Institutes of Environ. Health Sciences Meeting. Research Triangle Park, NC, 1987.
76. Kociba, R. J. Application of Risk Assessment to Toxicologic Data. Toxicology Information Roundtable. Annual Meeting, Midland, MI, 1987.
77. Pinkerton, M., Kociba, R. J., Petrella, R. et al. Investigation of the Comparative Toxicity of Combustion Products of High Impact Polystyrene (HIPS) With and Without Decabromodiphenyl Oxide/Antimony Trioxide (DBDPO/Sb₂O₃) as a Flame Retardant Using 2,3,7,8-TBDD and 2,3,7,8-TBDF as Positive Controls. Dioxin '87 Meeting, Las Vegas, Nev., 1987.
78. Betso., J. and R. J. Kociba. Hazard Communication: The Case for Category IV" Cancer Information" 27th Annual Meeting of the Society of Toxicology, Dallas, Texas, 1988.
79. Pinkerton, M., Kociba, R. J., Petrella, R. et al. The Comparative Toxicity of Combustion Products of HIPS With and Without Decabromodiphenyl Oxide/Antimony Trioxide (DBDPO/Sb₂O₃) as a Flame Retardant Using 2,3,7,8-TBDD and 2,3,7,8-TBDF as Positive Controls. 27th Annual Meeting of the Society of Toxicology, Dallas, Texas, 1988.

CURRICULUM VITAE

BARRY LESTER YANO

EDUCATION:

1965-1970 -University of Minnesota,
St. Paul, Minnesota- B.S.

1968-1972 - University of Minnesota,
St. Paul, Minnesota - D.V.M.

1975-1981 - University of Minnesota,
St. Paul, Minnesota - Ph.D.

EMPLOYMENT:

1972-1973 - Intern, Department of Small
Animal Medicine, University of Minnesota
St. Paul, Minnesota.

1973-1975 - United States Air Force,
Base Veterinarian

1975-1980 - Veterinary Medical Associate,
Department of Veterinary Pathobiology,
College of Veterinary Medicine, University of
Minnesota, St. Paul, Minnesota.

1980-1984 - Project Leader - Pathology, Health and
Environmental Sciences, Toxicology Research
Laboratory, Dow Chemical, U.S.A., Midland,
Michigan.

1984-1989- Research Leader - Department of
Pathology, Mammalian and Environmental
Toxicology Research Laboratory, Health and
Environmental Sciences, Dow Chemical
Company, Midland, Michigan.

1989-present- Research Associate- Department of
Pathology, Mammalian and Environmental
Toxicology Research Laboratory, Health and
Environmental Sciences, Dow Chemical Company,
Midland, Michigan.

JOB DESCRIPTION: Provides professional expertise in the areas of pathology, clinical pathology, and toxicology as needed to design, conduct, interpret, and report safety assessment studies conducted by the Mammalian and Environmental Toxicology Research Laboratory.

MEMBERSHIPS: American College of Veterinary Pathology
Society of Toxicologic Pathologists
Phi Zeta (Veterinary Honor Society)

CERTIFICATION: 1982 American College of Veterinary Pathologists

AWARDS: 1972 - Outstanding Achievement in Small Animal Medicine

1972 - Outstanding Achievement in Small Animal Surgery

1972 - Minnesota A.V.M.A., Outstanding Senior

1978 - Charles Louis Davis, D.V.M. Foundation Scholarship Award in Veterinary Pathology

PUBLICATIONS

Gray, G. W.; Yano, B. L.; A Study of the Actions of Methamprone and of a Commercial Intestinal Extract Preparation on Intestinal Motility. Am J Vet Res 36(2):201-208, 1975.

Osborne, C. A.; Engen, M. H.; Yano, B. L.; Brasmer, T. H.; Jessen, C. R.; Blevins, W. E.: Congenital Urethrorectal Fistula in Two Dogs. JAVMA 166(10):999-1002, 1975.

Osborne, C. A.; Hammer, R. D.; Resnick, J.; Stevens, J.; Yano, B. L.; Vernier, R. L.: Natural Remission of Nephrotic Syndrome in a Dog with Immune-Complex Glomerular Disease. JAVMA 168(2):129-137, 1976.

Johnston, G. R.; Osborne, C. A.; Wilson, J. W.; Yano, B. L.: Familial Urethral Ectopia in the Dog. JAAHA 13:168-170, 1977.

Osborne, C. A.; Stevens, J. B.; Yano, B. L.: Hypercalcemic Nephropathy, Spontaneous Animal Models of Human Disease, Vol. 2, pp. 290-292, Academic Press, Inc., New York, NY, 1979.

Segedy, A. K.; Yano, B. L.; Jeraj, K.: Sacral Spinal Cord Agenesis in a Kitten. JAVMA 174(5):510-512, 1979.

Jeraj, K.; Ogburn, P.; Johnston, G.; Edwards, W.; Yano, B.; Brunson, D.; Wallace, L.; McGrath, C.: Atrial Spetal Defect (Sinus Venosus Type) in a Dog. JAVMA 177(4):342-346, 1980.

Yano, B. L.: Feline Insular Amyloid. Ph.D. Thesis, 1981.

Yano, B. L.; Johnson, K. H.; Hayden, D. W.: Feline Insular Amyloid: Histochemical Distinction from Secondary Systemic Amyloid. Vet Path 18(2):181-187, 1981.

Yano, B. L.; Hayden, D. W.; Johnson, K. H.: Feline Insular Amyloid: Incidence in Adult Cats with No Clinicopathologic Evidence of Overt Diabetes Mellitus. Vet Path 18(3):310-315, 1981.

Yano, B. L.; Hayden, D. W.; Johnson, K. H.: Feline Insular Amyloid: Association with Diabetes Mellitus. Vet Path 18(5):621-627, 1981.

Yano, B. L.; Hayden, D. W.; Johnson, K. H.: Feline Insular Amyloid Ultrastructural Evidence for Intracellular Formation by nonendocrine Cells. Lab Invest 45(2):149-156, 1981.

Jeraj, K.; Yano, B.; Osborne, C. A.; Wallace, L. J.; Stevens, J. B.: Primary Hepatic Osteosarcoma in a Dog. JAVMA 197(10):1000-1003, 1981.

O'Brien, T. D.; Osborne, C. A.; Yano, B. L.: Clinicopathologic Manifestations of Progressive Renal Disease in Lhasa and Shih Tzu Dogs. JAVMA 180(6):658-664, 1982.

Yano, B. L., Hayden, D. W.; Johnson, K. H.: Occurrence of Secondary Systemic Amyloid in the Pancreatic Islets of a Cat. AJVR 44(2):338-339, 1983.

Landry, T. D.; Gushow, T. S.; Yano, B. L.: Propylene Glycol Monomethyl Ether: A 13-Week Inhalation Study in Rats and Rabbits. Fundam. Appl. Toxicol. 3:627-630, 1983.

Hanley, T. R., Jr.; Calhoun, L. L.; Yano, B. L.; Rao, K. S.: Teratologic Evaluation of Inhaled Propylene Glycol Monomethyl Ether in Rats and Rabbits. Fundam. Appl. Toxicol. 4(5):784-794, 1984.

Hanley, T. R., Jr.; Yano, B. L.; Nitschke, K. D.; John, J. A.: Comparison of the Teratogenic Potential of Inhaled Ethylene Glycol Monomethyl Ether in Rats, Mice and Rabbits. *Toxicol. Appl. Pharmacol.* 75:409-422, 1984.

Landry, T. D.; Yano, B. L.: Dipropylene Glycol Monomethyl Ether: A 13-Week Inhalation Study in Rats and Rabbits. *Fundam. Appl. Toxicol.* 4:612-617, 1984.

Lomax, L. G., Stott, W. T. Johnson, K. A., Calhoun, L. L., Yano, B. L. and Quast, J. F: The Chronic Toxicity and Oncogenicity of Inhaled Technical-Grade 1,3-Dichloropropene in Rats and Mice. *Fundam. Appl. Toxicol.* 12:418-431, 1989.

Albee, R. R., Mattsson, J. L., Yano, B. L. and Chang, L. W. Neurobehavioral Effects of Dietary Restriction in Rats. *Neurotics and Terat* 9:203-211, 1987.

Fox, T. R., Schumann, A. M., Watanabe, P. G., Yano, B. L., Maher, V. M. and McCormick, J. J. Mutational Analysis Of The H-ras Oncogene In Spontaneous C57BL/6 X CH3/He Mouse Liver Tumors and Tumors Induced With Genotoxic and Nongenotoxic Hepatocarcinogens. *Cancer Research* 50: 4014-4019, 1990.

Yano, B.L., Dittenber, D.A., Albee, R.R. and Mattsson, J.L. Abnormal Auditory Brainstem Responses and Cochlear Pathology in Rats Induced by an Exaggerated Styrene Exposure Regimen. *Toxicologic Pathology* 20 (1): 1-6, 1992.

Stott, W.T., Yano, B.L., Williams, D.M., Barnard, S.D., Hannah, M.A., Cieszlak, F.S., and Herman, J.R. Species-Dependent Induction of Peroxisome Proliferation by Haloxyfop, an Arloxyphenoxy Herbicide. *Fundamental and Applied Toxicology* 28: 71-79, 1995.

ABSTRACTS AND ORAL PRESENTATIONS

Yano, B. L. Effects of Two Veterinary Drugs on Intestinal Motility. (1970). The 51st Congress of Research Workers in Animal Diseases, Chicago, IL.

Yano, B. L., Campbell, R. A., Cieszlak, F. S., Barna-Lloyd, T., and Battjes, J. E. (1990). Dietary Chronic Toxicity And Oncogenicity OF Haloxyfop Herbicide In Dogs, Rats and Mice. Society of Toxicology, Miami Beach, FL.

Quast, J. F., Yano, B. L., Dietz, F. K., Marler, R. M. and Hayes, W. C. (1990). Subchronic And Reproductive Toxicity And Teratology Of Haloxyfop Herbicide. Society of Toxicology, Miami Beach, FL.

Breslin, W. J., Cieszlak, F. S., Zablotny, C. L., Corley, R. A., Yano, B. L. and Verschuuren, H. G. (1990). Developmental Toxicity Of Inhaled Dipropylene Glycol Monomethyl Ether (DPGME) In Rabbits And Rats. Society of Toxicology, Miami Beach, FL.

Stott, W. T., Yano, B. L., Williams, D. M., Barnard, S. D., Hannah, M. A. and Cieszlak, F. S. (1990). Species Dependent Induction Of Peroxisome Proliferation By Haloxyfop, A New Herbicide. Society of Toxicology, Miami Beach, FL.

Fox, T. R., Schumman, A. M., Yano, B. L., Watanabe, P. G., Maher, V. M. and McCormick, J. J. (1990). Mutational Analysis Of The H-ras Gene In B6C3F1 Mouse Liver Tumors Induced With Nongenotoxic Hepatocarcinogens. Society of Toxicology, Miami Beach, FL.

Yano, B.L., Schultze, G.E., J R Szabo, J.R., Corley, R.A., Cosse, P.F. and Billups, L.H. (1991). Subchronic Dietary Toxicity Of 2,4-D Acid, 2,4-D Amine Salts And 2,4-D Esters In Rats. Society of Toxicology, Seattle, WA.

Richardson, R. J., Yano, B. L., Kayyali, U. S. and Randall, J. C. (1992). Potentiation of Organophosphate Neuropathy: Preliminary Histopathology and Demonstration of Clinical Potentiation by an Organophosphinate. Society of Toxicology, Seattle, WA.

Kirk, H. D., Yano, B. L., Haut, K. T., Verschuuren, H. and Breslin, W. J. (1992). Tripropylene Glycol N-Butyl Ether 13-Week Drinking Water Study in Fischer 344 Rats. Society of Toxicology, Seattle, WA.

Crissman, J. W., Long, P. H., Yano, B. L. and Everitt, J. I. (1992). Spontaneous Renal Tubular Tumors and Atypical Hyperplasia in Two Strains of Rats on 90-Day Studies; Comparison to Hereditary Renal Carcinomas in the Eker Rat. Society of Toxicologic Pathologists, Phoenix, Arizona.

Yano, B. L. and Mattsson, J. L. (1992). Tissues Selection for TSCA/FIFRA Neurotoxicity Guideline Studies. American College of Veterinary Pathologists, San Diego, CA. Vet Path 29:5, 445, 1992.

Zielke, G. J., Yano, B. L. and Breslin, W.J. (1993). 2,3,5,6-Tetrachloropyridine: Combined Repeat Dose an

Reproductive/Developmental Toxicity Screen in Sprague-Dawley Rats.
Society of Toxicology, New Orleans, LA.

Albee, R. R., Mattsson, J. L., Yano, B. L., Beekman, M. J. and Spencer, P. J. (1993). Ototoxicologic and Neurotoxicologic Evaluation of Rats Exposed to Styrene. Society of Toxicology, New Orleans, LA.

Mattsson, J. L., Albee, R. R., Yano, B. L., Bradley, G. J., and Spenser, P. J. (1995). Neurotoxicologic Examination of Rats Exposed to 1,1,2,2-Tetrachloroethylene (Perchloroethylene) Vapor for 13 Weeks. Society of Toxicology, Baltimore, MD.

Yano, B. L., Mattsson, J. L., and Jeffries, T. K. (1995). 2,4-D Herbicide (2,4-Dichlorophenoxyacetic Acid): One-Year Oral Neurotoxicity Study in Fischer 344 Rats. Society of Toxicology, Baltimore, MD.

Jeffries, T.K., Yano, B.L., Stott, W.T., Ormond, J.E., Battjes, J.E., Charles, J.M., Cunny, H.C., Wilson, R.D., and Bus, J.S. (1996). Dietary Chronic Toxicity /Oncogenicity of 2,4-Dichlorophenoxyacetic Acid (2,4-D) in Rats. Society of Toxicology, Annaheim, CA.

CURRICULUM VITAE

NAME: KENNETH EDWARD STEBBINS

CURRENT JOB TITLE: Research Leader

EDUCATION: 1980 - B. S. Medical Technology - Michigan State University

1984 - D.V.M. - Michigan State University

1987-88 - Pathology Residency, University of Pennsylvania, School of Veterinary Medicine

1976 - Byron Center High School, Byron Center, Michigan

EMPLOYMENT: 1984-85 - Pet Veterinary Clinic, Grandville, Michigan - veterinarian in private small animal practice

1989-present - Project Leader - Pathology Section, The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company

INDUSTRIAL PATHOLOGY TRAINING: 1988 - Three month externship at E. I. du Pont de Nemours and Co., Inc., Haskell Laboratory for Toxicology and Industrial Medicine, Newark, Delaware

RESEARCH EXPERIENCE: Co-Investigator in the project entitled "Ultrasonographic Evaluation of Tendon and Ligament Injuries in the Horse: Correlation with Gross and Histopathologic Findings". Supported by a grant from the Grayson Foundation

TEACHING EXPERIENCE: 1985-88 - University of Pennsylvania. Assistance with laboratory teaching of Core Pathology. Assistance with instruction of senior veterinary students on large and small animal necropsy rotations.

**TEACHING
EXPERIENCE (Cont.):**

1987-88 - Philadelphia College of Pharmacy and Science. Lectures to undergraduate toxicology students in "Principles of Pathobiology" course. Upper and lower digestive systems, bone and connective tissue.

1988-89 - Cornell University. Instruction of veterinary pathology residents in diagnostic pathology

**HONORS AND
HONORARY
SOCIETIES:**

C. L. Davis Foundation Scholarship in Veterinary Pathology, November, 1987

Merck Award (for highest GPA in my freshman veterinary class) Michigan State University, 1981

Membership in Society of Phi Zeta, the National Honor Society of Veterinary Medicine, for ranking in the top ten of my junior veterinary class, Michigan State University, 1983.

**PROFESSIONAL
SOCIETIES:**

American Veterinary Medical Association
American College of Veterinary Pathologists
Charles Davis Foundation

CERTIFICATIONS:

American College of Veterinary Pathologists - 1988

PUBLICATIONS:

See Attached

ABSTRACT:

See Attached

Reviewed/Revised:

Kenneth E. Stebbins

Date: 15 March 1995

PUBLICATIONS

- 1) deMadron, E., Helfand, S. C., Stebbins, K. E. Use of Chemotherapy for Treatment of Cardiac Hemangiosarcoma in a Dog. JAVMA 190 (7):887-891 (1987).
- 2) Stebbins, K. E. and McGrath, J. T. Meningio-angiomatosis in a Dog. Veterinary Pathology 25 (2):167-168 (1988).
- 3) Stebbins, K. E. Polycystic Kidney and Liver Disease in an Adult Persian Cat. Journal of Comparative Pathology 100:327-330 (1989).
- 4) Foodman, M., Giger, U., and Stebbins, K. E. Immotile Cilia Syndrome in a Dog. Journal of Small Animal Practice (1989).
- 5) Stebbins, K. E., Morse, C. C., and Goldschmidt, M. H. Feline Oral Neoplasia: A Ten Year Survey. Veterinary Pathology 26 (2):121-128 (1989).
- 6) Sweeney, C. R., Stebbins, K. E., Schelling, C. G., Beech, J., and Schilling, D. A. Hypertrophic Osteopathy in a Pony with a Pituitary Adenoma. JAVMA 195 (1):103-105 (1989).
- 7) Rowland, P. H., Valentine, B. A., Stebbins, K. E., and Smith, C. A. Cutaneous Plasmacytomas with Amyloid in Six Dogs. Veterinary Pathology 28 (2):125-130 (1991).

ABSTRACTS

Breslin, W. J., Zielke, G. J., and Stebbins, K. E. (1992). Developmental toxicity of monoethanolamine (MEA) in rats following dermal exposure. The Toxicologist 12, 102. Abstract No. 323.