NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 300

TOXICOLOGY AND CARCINOGENESIS STUDIES OF 3-CHLORO-2-METHYLPROPENE

(Technical grade containing 5% dimethylvinyl chloride)

(CAS NO. 563-47-3)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

NATIONAL TOXICOLOGY PROGRAM

The National Toxicology Program (NTP), established in 1978, develops and evaluates scientific information about potentially toxic and hazardous chemicals. This knowledge can be used for protecting the health of the American people and for the primary prevention of disease. By bringing together the relevant programs, staff, and resources from the U.S. Public Health Service, DHHS, the National Toxicology Program has centralized and strengthened activities relating to toxicology research, testing and test development/validation efforts, and the dissemination of toxicological information to the public and scientific communities and to the research and regulatory agencies.

The NTP is made up of four charter DHHS agencies: the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS.

NTP TECHNICAL REPORT

ON THE

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NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

June 1986

NTP TR 300

NIH Publication No. 86-2556

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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NOTE TO THE READER

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for testing in the NTP Carcinogenesis Program are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection per se is not an indicator of a chemical's carcinogenic potential. Negative results, in which the test animals do not have a greater incidence of cancer than control animals, do not necessarily mean that a test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical has the potential for hazard to humans. The determination of the risk to humans from chemicals found to be carcinogenic in animals requires a wider analysis which extends beyond the purview of this study.

Five categories of interpretative conclusions were adopted for use in June 1983 in the Technical Reports series to specifically emphasize consistency and the concept of actual evidence of carcinogenicity. For each definitive study result (male rats, female rats, male mice, female mice), one of the following quintet will be selected to describe the findings. These categories refer to the strength of the experimental evidence and not to either potency or mechanism.

- **Clear Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of malignant neoplasms, studies that exhibit a substantially increased incidence of benign neoplasms, or studies that exhibit an increased incidence of a combination of malignant and benign neoplasms where each increases with dose.
- **Some Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of benign neoplasms, studies that exhibit marginal increases in neoplasms of several organs/tissues, or studies that exhibit a slight increase in uncommon malignant or benign neoplasms.
- **Equivocal Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related marginal increase of neoplasms.
- **No Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.
- **Inadequate Study of Carcinogenicity** demonstrates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as valid for showing either the presence or absence of a carcinogenic effect.

Additionally, the following concepts (as patterned from the International Agency for Research on Cancer Monographs) have been adopted by the NTP to give further clarification of these issues:

> The term *chemical carcinogenesis* generally means the induction by chemicals of neoplasms not usually observed, the earlier induction by chemicals of neoplasms that are commonly observed, or the induction by chemicals of more neoplasms than are generally found. Different mechanisms may be involved in these situations. Etymologically, the term *carcinogenesis* means induction of cancer, that is, of malignant neoplasms; however, the commonly accepted meaning is the induction of various types of neoplasms or of a combination of malignant and benign neoplasms. In the Technical Reports, the words *tumor* and *neoplasm* are used interchangeably.

This study was initiated by the National Cancer Institute's Carcinogenesis Bioassay Program, now part of the National Institute of Environmental Health Sciences, National Toxicology Program. The studies described in this Technical Report have been conducted in compliance with NTP chemical health and safety requirements and must meet or exceed all applicable Federal, state, and local health and safety regulations. All NTP toxicology and carcinogenesis studies are subjected to a data audit before being presented for peer review.

Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to identify any mistakes so that corrective action may be taken. Further, anyone who is aware of related ongoing or published studies not mentioned in this report is encouraged to make this information known to the NTP. Comments and questions about the National Toxicology Program Technical Reports on Toxicology and Carcinogenesis Studies should be directed to Dr. J.E. Huff, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709 (919-541-3780).

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Technical Report are available without charge (and while supplies last) from the NTP Public Information Office, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709.

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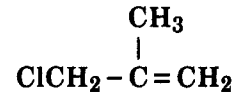

3-CHLORO-2-METHYLPROPENE

CAS No. 563-47-3

C_4H_7Cl Molecular weight: 90.55

Synonyms:

2-Methallyl chloride	**Isobutenyl chloride**
Methyl allyl chloride	**3-Chloro-2-methyl-1-propene**
β-methallyl chloride	**2-Methyl-2-propenyl chloride**
γ-chloroisobutylene	

ABSTRACT

Toxicology and carcinogenesis studies of technical-grade 3-chloro-2-methylpropene (containing 5% dimethylvinyl chloride), a widely used insecticide and chemical intermediate, were performed on F344/N rats and B6C3F$_1$ mice. In the 13-week studies, 50%-100% mortality occurred in groups of male and female rats receiving 400 mg/kg, male rats receiving 300 mg/kg, and male and female mice receiving 500-1,250 mg/kg. Inflammation and necrosis of the liver were seen in rats and mice, and necrosis of cortical tubules of the kidney was seen in mice. Based on these observations, groups of 50 male and 50 female rats were administered 3-chloro-2-methylpropene in corn oil by gavage at doses of 0, 75, or 150 mg/kg body weight, 5 days per week for 103 weeks, and groups of 50 male and 50 female mice received 3-chloro-2-methylpropene at 0, 100, or 200 mg/kg on the same schedule.

In the 2-year studies, the mean body weight of high dose male rats was consistently 10%-15% lower than that of the vehicle control group, and late in the study there was a marginal reduction in survival of high dose male rats. Mean body weights and survival in low dose male rats and in both dosed groups of female rats were comparable to those of their vehicle control groups. Mean body weights of high dose male mice and of both dosed groups of female mice were slightly (5%-9%) lower than those of the vehicle controls, whereas survival in both male and female mice was not affected by 3-chloro-2-methylpropene administration.

Dose-related increases in the incidence of forestomach inflammation were observed in male and female mice (male: vehicle control, 0/49; low dose, 9/49; high dose, 7/49; female: vehicle control, 2/50; low dose, 3/48; high dose, 9/44). Increased incidences of forestomach basal cell hyperplasia were observed in rats and mice of each sex. 3-Chloro-2-methylpropene induced forestomach squamous cell papillomas and squamous cell carcinomas in rats and mice as shown in the table. Invasion or metastasis of the squamous cell carcinomas to other organs was observed in two low dose male, three high dose male, and one high dose female mice.

Renal tubular cell adenocarcinomas (1/49), renal transitional cell carcinomas (1/49), and transitional cell papillomas (1/46) of the urinary bladder were observed in high dose male rats, and renal tubular cell adenomas (1/50) and renal tubular cell adenocarcinomas (1/50) were seen in low dose male rats. These urinary tract neoplasms were not observed in vehicle controls.

The incidences of inflammation of the nasal cavity and of nephropathy/nephrosis were greater in the two dosed groups than in the vehicle control groups of rats and mice of each sex.

INCIDENCES OF FORESTOMACH LESIONS IN RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE

	Basal Cell or Epithelial Hyperplasia			Squamous Cell Papilloma			Squamous Cell Carcinoma		
RATS	Vehicle Control	75 mg/kg	150 mg/kg	Vehicle Control	75 mg/kg	150 mg/kg	Vehicle Control	75 mg/kg	150 mg/kg
Male	19/50	41/50	44/48	1/50	5/50	30/48	0/50	0/50	2/48
Female	24/50	42/50	45/50	1/50	1/50	10/50	0/50	0/50	0/50
MICE	Vehicle Control	100 mg/kg	200 mg/kg	Vehicle Control	100 mg/kg	200 mg/kg	Vehicle Control	100 mg/kg	200 mg/kg
Male	0/49	14/49	15/49	3/49	19/49	30/49	0/49	5/49	7/49
Female	4/50	6/48	13/44	0/50	15/48	29/44	0/50	1/48	2/44

Negative trends or lower incidences of pheochromocytomas of the adrenal gland and C-cell adenomas or carcinomas (combined) of the thyroid gland were observed in dosed male rats. Negative trends were observed in the incidences of hepatocellular adenomas or carcinomas (combined) in dosed male mice and of hemangiomas or hemangiosarcomas (combined) in dosed female mice.

3-Chloro-2-methylpropene was weakly mutagenic in *Salmonella typhimurium* strain TA1537 with 10% rat liver S9; results in strain TA100 with 10% Syrian hamster liver S9 or with 10% or 30% rat liver S9 were judged equivocal. Mutagenicity tests with *S. typhimurium* strains TA1535 and TA98 were negative with or without metabolic activation. 3-Chloro-2-methylpropene was mutagenic in the mouse lymphoma L5178Y/TK$^{+/-}$ forward mutation assay without exogenous metabolic activation. Cytogenetics tests with cultured Chinese hamster ovary cells were positive for induction of chromosomal aberrations and sister-chromatid exchanges (SCE's) in the absence of rat liver S9. With metabolic activation, SCE levels remained significantly elevated, but the number of chromosomal aberrations was reduced.

An audit of the experimental data was conducted for these 2-year carcinogenesis studies on 3-chloro-2-methylpropene. No data discrepancies were found that influenced the final interpretations.

Under the conditions of these 2-year gavage studies, there was *clear evidence of carcinogenicity** for 3-chloro-2-methylpropene as shown by the increased incidences of squamous cell neoplasms in the forestomach of male and female F344/N rats and of male and female B6C3F$_1$ mice.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2. The public discussion regarding the interpretative conclusions is summarized on page 14.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of 3-Chloro-2-methylpropene is based on the 13-week studies that began in September 1978 and ended in December 1978 and the 2-year studies that began in August 1980 and ended in August 1982 at Litton Bionetics, Inc.

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The members of the Peer Review Panel who evaluated the draft Technical Report on 3-chloro-2-methylpropene on November 2, 1984, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF 3-CHLORO-2-METHYLPROPENE

On November 2, 1984, the draft Technical Report on the toxicology and carcinogenesis studies of 3-chloro-2-methylpropene received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held in the Conference Center, Building 101, South Campus, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. P. Chan, NTP, began the discussion with a summary of the study design, results and proposed conclusions (clear evidence of carcinogenicity in rats and mice of each sex). Dr. Slaga, a principal reviewer, agreed with the conclusions. As a second principal reviewer, Dr. Jones agreed with the conclusions, but he felt that the forestomach neoplasms might be more accurately described as "squamous cell papillomas or carcinomas (combined)." He asked what effects the contaminant dimethylvinyl chloride (up to 5% of the 3-chloro-2-methylpropene) may have had on the stomach lesions, since preliminary findings from the NTP indicated that it is a carcinogen for the forestomach. Dr. Jones also asked whether there might be a correlation between the poor survival of high dose male rats and the negative tumor trends, especially for thyroid gland C-cell adenomas and carcinomas.

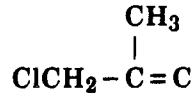
As a third principal reviewer, Dr. Friess did not agree with the composite conclusion for both sexes of both species. Because of the lack of dose response for squamous cell papillomas in rats and no significant increases in carcinomas alone in rats and female mice, he thought the category should be some evidence of carcinogenicity. He agreed with the category of clear evidence of carcinogenicity for male mice. Dr. Kociba concurred. Dr. Friess questioned whether the estimated maximum tolerated doses (EMTD's) had been achieved, except for the doses for male rats. Dr. Swenberg said that the issue of whether an EMTD was reached becomes an important point only with a negative study. Dr. Hook asked that more discussion of how doses were selected be in the report. [See page 56.] Dr. Friess asked for further discussion in the text on (1) the potential contributions of dimethylvinyl chloride to the carcinogenic process in the forestomach and (2) the finding of renal tubular cell adenomas and carcinomas, albeit at low incidences, in male rats, and whether this may be an effect related to low-molecular-weight chlorinated hydrocarbons in male rats. Dr. Chan commented that the 3-chloro-2-methylpropene (containing about 5% dimethylvinyl chloride) was the material commercially available and the formulation to which humans are exposed. Dr. B. Schwetz, NTP, reported that completed NTP 2-year gavage studies with dimethylvinyl chloride in rats and mice showed a spectrum of neoplastic responses not seen in this study, including those of the nasal passage, oral cavities, and esophagus. Dr. Kociba and Dr. Swenberg asked that either the presence of the dimethylvinyl chloride be given in the title of the report or the designation "technical grade" be inserted. Dr. Hook added that the composition should be given more prominence in the abstract.

Considerable discussion ensued as to (1) whether there was some evidence of carcinogenicity or clear evidence of carcinogenicity in rats and female mice and (2) whether the species and sexes should be separated in the conclusions. Dr. J. Huff, NTP, explained that the clear evidence of carcinogenicity category allowed for a substantial increase in benign neoplasms and, further, that the affected organ in each of those four experiments was the same. Hence, the single category seemed appropriate. Dr. Friess said he could agree to the conclusions as explained. Dr. Swenberg and Dr. Slaga agreed that the single categorization for all made the most scientific sense, since there were only small differences between benign and malignant neoplasms of the forestomach, since these are known to progress, and since all groups had the same lesions.

Dr. Jones moved that the Technical Report on the toxicology and carcinogenesis studies of 3-chloro-2-methylpropene be accepted with the conclusion as stated, with some additional discussion on certain mentioned items and with the addition of "technical grade" to the title of the report and to the Abstract to indicate the presence of 5% dimethylvinyl chloride. Mr. Beliczky seconded the motion, and the report was approved by nine affirmative votes. There was one negative vote (Dr. Kociba).

I. INTRODUCTION

I. INTRODUCTION



3-CHLORO-2-METHYLPROPENE

CAS No. 563-47-3

C_4H_7Cl Molecular weight: 90.55

Synonyms:

2-Methallyl chloride
Methyl allyl chloride
β-methallyl chloride
γ-chloroisobutylene
Isobutenyl chloride
3-Chloro-2-methyl-1-propene
2-Methyl-2-propenyl chloride

3-Chloro-2-methylpropene is a colorless, volatile liquid with a pungent odor. It has a specific gravity of 0.92 at 15° C, a boiling point of 71°-72° C, a vapor pressure of 101.7 mm Hg at 20° C, and a refractive index of 1.4318 at 15° C. 3-Chloro-2-methylpropene is insoluble in water but is soluble in chloroform, acetone, alcohol, ether, and benzene. It is flammable with a flash point of −12° C (closed cup). Its explosive limit in air is 2.3%-9.3% (Merck Index, 1983; Hawley, 1977). 3-Chloro-2-methylpropene is relatively stable at room temperature but is unstable at high temperature. It reacts vigorously with oxidizing materials and during decomposition emits toxic fumes of chlorine and hydrochloric acid (Sax, 1979).

3-Chloro-2-methylpropene is produced by substitutive chlorination of isobutylene (Melnikov, 1971). The annual production of 3-chloro-2-methylpropene in the United States is 12-24 million pounds; less than 500 pounds was imported in 1984 (I.M. Kipnis, personal communication to NTP, January 1985).

3-Chloro-2-methylpropene is used as an intermediate for the production of plastics, pharmaceuticals, and other organic chemicals and as an insecticide and fumigant for grains, tobacco, and soil (Merck Index, 1983; Hawley, 1977). According to the manufacturer, approximately 97.5% of the 3-chloro-2-methylpropene produced in the United States is used as a site-limited intermediate in the synthesis of agricultural chemicals, 1.8% as a textile additive, 0.6% as a perfume additive, and 0.2% for other purposes. The material is not registered for use as a pesticide in the United States; it may be used for that purpose in other countries (I.M. Kipnis, personal communication to NTP, January 1985).

3-Chloro-2-methylpropene at concentrations as high as 400 $\mu g/m^3$ has been detected in the ambient air near Curtis Bay in Maryland (Pellizzari, 1982). Residual 3-chloro-2-methylpropene has also been detected in maize fumigated with the chemical (Taylor, 1975).

3-Chloro-2-methylpropene is toxic when inhaled, applied to the skin, or ingested and irritates the eyes and respiratory tract. The LC_{50} values of 3-chloro-2-methylpropene are 34,000 mg/m^3 for 30 minutes or 2,000 mg/m^3 for 24 hours for rats and 91,000 mg/m^3 for 10 minutes for mice (Sax, 1979). Inhalation studies in mice showed that 3-chloro-2-methylpropene caused respiratory failure and induced pulmonary tissue damage (Silverman and Abreu, 1938).

Investigations of the genetic toxicity of allylic chloride compounds (Neudecker et al., 1980; Eder et al., 1980, 1982) showed 3-chloro-2-methylpropene to be weakly mutagenic to *Salmonella typhimurium* strain TA100 without exogenous metabolic activation. Like the majority of allyl chlorides, this chemical is considered to be a direct-acting alkylating agent whose mutagenic potential is destroyed by activation. In contrast, the NTP-sponsored tests showed weak mutagenic activity in *S. typhimurium* strain TA1537 only in the presence of S9 from Aroclor 1254-induced male Sprague-Dawley rat livers;

activity was considered equivocal in strain TA100 with S9 from Aroclor 1254-induced male Syrian hamster and Sprague-Dawley rat livers (Appendix L, Table L1). 3-Chloro-2-methylpropene was also mutagenic in the L5178Y/TK$^{+/-}$ mouse lymphoma assay in the absence of S9 (Table L2); it was not tested in the presence of S9. The chemical induced sister-chromatid exchanges (SCE's) and chromosomal aberrations in cultured Chinese hamster ovary cells without metabolic activiation. With Aroclor-1254-induced male Sprague-Dawley rat liver S9, SCE's remained significantly elevated. However, exogenous metabolic activation greatly reduced the strength of the mutagenic response as measured by chromosomal aberrations (Table L3 and L4). In addition, 3-chloro-2-methylpropene induced unscheduled DNA synthesis in HeLa cells (Schiffmann et al., 1983). No information was found in the literature on the pharmacokinetics, reproductive toxicity, or carcinogenicity of 3-chloro-2-methylpropene.

Workers may be exposed to 3-chloro-2-methylpropene while using it as a gaseous insecticide or as an intermediate in organic synthesis. The U.S. Environmental Protection Agency nominated 3-chloro-2-methylpropene for carcinogenicity testing because of its presence in ambient air and its structural relationship to vinyl chloride, a recognized animal and human carcinogen. The gavage route of administration was chosen because the chemical is volatile and flammable.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF 3-CHLORO-2-METHYLPROPENE

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

SINGLE-ADMINISTRATION STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Study Design

Source and Specifications of Animals

Animal Maintenance

Clinical Examinations and Pathology

Statistical Methods

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF 3-CHLORO-2-METHYLPROPENE

3-Chloro-2-methylpropene (manufactured by FMC Corporation) was obtained in two different lots (Table 1). Purity, identity, and stability analyses were conducted at Midwest Research Institute. Both lots of chemical were identified as 3-chloro-2-methylpropene by spectroscopy. Infrared, ultraviolet/visible, and nuclear magnetic resonance spectra were all consistent with the literature spectra and the structure of 3-chloro-2-methylpropene (Appendix G).

Cumulative data on lot no. 110967 indicated a purity of approximately 93%. The results of elemental analysis agreed with theoretical values. Titration of acidic components indicated the presence of 34 ppm hydrochloric acid. Gas chromatography analysis by two systems showed the study material to be approximately 93% pure and to contain two major impurities with areas of 3% and 6% relative to the major component. The retention time of the 6% relative impurity was consistent with that of dimethylvinyl chloride. The nuclear magnetic resonance spectrum contained five peaks attributed to impurities. Two of these could be assigned to dimethylvinyl chloride; integration ratios indicated a concentration of 5% for the dimethylvinyl chloride. Therefore it was concluded that lot no. 11067 of the study material contained approximately 5% dimethylvinyl chloride as an impurity.

Lot no. P091781 was determined to have a purity of greater than 95% based on the following data. Results of elemental analysis were consistent with theoretical values. Titration of acidic components indicated the presence of 159 ppm hydrochloric acid. Gas chromatographic analysis by two systems showed the study material to be greater than 95% pure and to contain a 3.6% impurity that was identified as dimethylvinyl chloride.

The bulk chemical was stable when stored for 2 weeks at −20° to 60° C (Appendix G). The study laboratory stored several portions at −20° C as reference samples, and the remainder was stored at room temperature. Results of periodic reanalysis of the study and reference samples at the study laboratory by infrared spectroscopy and gas chromatography indicated that no notable deterioration of the study chemical occurred over the course of the studies.

TABLE 1. IDENTITY AND SOURCE OF LOTS USED IN THE GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE

	Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Lot Numbers	110967	110967	110967	110967 and P091781
Date of Initial Use of Each Lot	N/A	N/A	N/A	8/81
Supplier	Lot no. 110967--Aldrich Chemical Co. (Milwaukee, WI)	Same as single administration studies	Same as single administration studies	Lot no. 110967--Aldrich Chemical Co. (Milwaukee, WI); lot no. P091781--Pfaltz and Bauer (Stamford, CT)

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

3-Chloro-2-methylpropene and corn oil were mixed to yield the desired concentrations (Table 2; Appendix H). 3-Chloro-2-methylpropene (2.25% w/v) in corn oil was found to be stable (within the limits of detection) when stored at room temperature for 7 days. In the 2-year studies, mixtures of 3-chloro-2-methylpropene in corn oil were stored at room temperature for no longer than 7 days. Periodic analyses for 3-chloro-2-methylpropene were performed by the study and analytical chemistry laboratories to confirm that correct concentrations were administered to the animals (Appendix I). The analytical method included a methanol extraction followed by gas chromatographic analysis. The analytical results are presented in Appendix J and are summarized in Table 3. Because 53/62 samples analyzed were within ± 10% of target concentrations, it is estimated that dosing mixtures were formulated within specifications 85% of the time.

TABLE 2. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE

	Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation	3-Chloro-2-methylpropene was mixed with the appropriate volume of corn oil.	Same as single-administration studies	Same as single-administration studies	3-chloro-2-methylpropene was added to a graduated cylinder, diluted with corn oil, and mixed by inversion.
Maximum Storage Time	N/A	7 d	7 d	7 d
Storage Conditions	N/A	Refrigerated	Refrigerated	Room temperature

TABLE 3. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIESOF 3-CHLORO-2-METHYLPROPENE

	Concentration of 3-Chloro-2-methylpropene in Corn Oil for Target Concentration (mg/ml)			
	10	15	20	30
Mean (mg/ml)	10.7	15.5	20.0	31.2
Standard deviation	0.77	0.70	4.80	1.50
Coefficient of variation (percent)	7.2	4.5	24.0	4.8
Range (mg/ml)	9.8-12.5	14.0-16.4	(a) 2.8-24.2	29.6-34.9
Number of samples	15	16	16	15

(a) The 2.8 mg/ml dose mixture was not used.

II. MATERIALS AND METHODS

SINGLE-ADMINISTRATION STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Harlan Industries and observed for 2 weeks before the studies began. Groups of five rats of each sex were administered a single dose of 100, 316, 1,000, 3,160, or 10,000 mg/kg 3-chloro-2-methylpropene in corn oil by gavage. Groups of five mice of each sex were administered 31.6, 100, 316, 1,000, or 3,160 mg/kg. The selection of doses was based on available data in the literature. Rats and mice were observed daily and were killed 14 days after the dose was administered. A necropsy was performed on all animals. Details of animal maintenance are given in Table 4.

FOURTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Harlan Industries and held for 6 weeks (rats) or 3 or 4 weeks (mice) before the studies began. Groups of five rats of each sex were administered 0, 89, 158, 281, 500, or 750 mg/kg 3-chloro-2-methylpropene in corn oil by gavage for 14 consecutive days. Groups of five mice of each sex were administered 0, 125, 250, 500, 750, 1,250, 1,750, or 2,500 mg/kg on the same schedule. The 125 and 250 mg/kg groups of mice were started (without matched vehicle controls) 7 days after initiation of the studies because of the large number of deaths at 750 mg/kg. Results of the 14-day studies provided information on toxic effects and affected tissues and determined doses to be used in the 13-week studies.

Animals were housed five per cage and received water and feed ad libitum. Details of animal maintenance are presented in Table 4. The rats and mice were observed once per day and were weighed on days 1 and 15. A necropsy was performed on all animals.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated administration of 3-chloro-2-methylpropene and to determine the doses to be used in the 2-year studies.

Five- to six-week-old male and female F344/N rats and 5- to 6-week-old male and female B6C3F$_1$ mice were obtained from Harlan Industries and observed for 2 weeks before the studies began. The animals were housed five per cage in polycarbonate cages. Diets consisting of Purina Lab Chow® and water (acidified with hydrochloric acid to pH 2.5 for bacterial control) were available ad libitum.

Groups of 10 rats of each sex were administered 0, 50, 100, 200, 300, or 400 mg/kg 3-chloro-2-methylpropene in corn oil by gavage, 5 days per week for 13 weeks. Groups of 10 mice of each sex received 0, 125, 250, 500, 750, or 1,250 mg/kg on the same schedule.

Animals were checked two times per day; moribund animals were killed. Clinical examinations were performed and animal weights were recorded once per week. At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined and further experimental details are listed in Table 4.

TWO-YEAR STUDIES

Study Design

Groups of 50 rats of each sex were administered 0, 75, or 150 mg/kg 3-chloro-2-methylpropene in corn oil by gavage, 5 days per week for 103 weeks. Groups of 50 mice of each sex were administered 0, 100, or 200 mg/kg on the same schedule.

Source and Specifications of Animals

The male and female F344/N rats and B6C3F$_1$ (C57BL/6N, female, × C3H/HeN MTV$^-$, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories (Kingston, NY) under a contract to the Carcinogenesis Program. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to

TABLE 4. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE

	Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN				
Study Laboratory	Litton Bionetics, Inc.	Litton Bionetics, Inc.	Litton Bionetics, Inc.	Litton Bionetics, Inc.
Size of Study Groups	5 males and 5 females of each species	Same as single-administration studies	10 males and 10 females of each species	50 males and 50 females of each species
Doses	Rats--100, 316, 1,000, 3,160, or 10,000 mg/kg 3-chloro-2-methylpropene in corn oil by gavage; dose vol--10 ml/kg; mice--31.6, 100, 316, 1,000, or 3,160 mg/kg 3-chloro-2-methylpropene in corn oil by gavage; dose vol--10 ml/kg	Rats--0, 89, 158, 281, 500, or 750 mg/kg 3-chloro-2-methylpropene in corn oil by gavage; dose vol-- 3.3 ml/kg; mice--0, 125, 250, 500, 750, 1,250, 1,750, or 2,500 mg/kg 3-chloro-2-methylpropene in corn oil by gavage; dose vol--3.3 ml/kg	Rats--0, 50, 100, 200, 300, or 400 mg/kg 3-chloro-2-methylpropene in corn oil by gavage; dose vol--10 ml/kg; mice--0, 125, 250, 500, 750, or 1,250 mg/kg 3-chloro-2-methylpropene in corn oil by gavage; dose vol--10 ml/kg	Rats--0, 75, or 150 mg/kg 3-chloro-2-methylpropene in corn oil by gavage; dose vol--5 ml/kg; mice--0, 100, or 200 mg/kg 3-chloro-2-methylpropene in corn oil by gavage; dose vol--10 ml/kg
Date of First Dose	1/19/78	Rats--3/31/78; mice--5/1/78 (5/8/78 for 125 and 250 mg/kg groups)	9/22/78	Rats--8/20/80; mice--8/13/80
Date of Last Dose	N/A	Rats--4/13/78; mice--5/14/78 (5/21/78 for 125 and 250 mg/kg groups)	Rats--12/27/78; mice--12/21/78	Rats--8/13/82; mice--8/09/82
Duration of Dosing	Single administration only	14 consecutive d	5 × wk for 13 wk	5 × wk for 103 wk
Type and Frequency of Observation	Observed 1 h and 4 h after dosing; 1 × d thereafter	Observed 1 × d; weighed on d 1 and d 15	Observed 2 × d; clinically examined 1 × wk; weighed 1 × wk	Observed 2 × d; clinically examined 1 × 4 wk; weighed 1 × wk for 13 wk, then 1 × 4 wk
Necropsy and *Histologic* Examination	Necropsy performed on all animals	Necropsy performed on all animals: tissues were not examined histologically	Necropsy performed on all animals; the following tissues were examined histologically: gross lesions and tissue masses, regional lymph nodes, mandibular or mesenteric lymph node, salivary glands, sternebrae, femur or vertebrae including marrow, thyroid gland, parathyroids, small intestine, colon, liver, prostate/testes or ovaries/uterus, lungs and mainstem bronchi, skin, gallbladder (mice), heart, esophagus,	Necropsy performed on all animals; the following tissues were examined histologically: gross lesions, tissue masses, regional lymph nodes, mandibular and mesenteric lymph nodes, colon, liver, sternebrae, femur or vertebrae including marrow, thyroid gland, parathyroids, salivary gland, urinary bladder, prostate/testes/ seminal vesicles or ovaries/uterus, lungs and mainstem bronchi, gallbladder (mice), skin, cecum, thigh muscle, costochondral junction

TABLE 4. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE (Continued)

	Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Necropsy and Histologic Examination (Continued)			stomach, brain, thymus, trachea, pancreas, spleen, kidneys, adrenal glands, urinary bladder, pituitary gland, spinal cord (if neurologic signs were present), eyes (if grossly abnormal), and mammary glands	(rib), larynx, nasal cavity, heart, esophagus, stomach, brain, thymus, trachea, pancreas, spleen, kidneys, adrenal glands, pituitary gland, spinal cord (if neurologic signs were present), eyes (if grossly abnormal), mammary glands, duodenum, jejunum, ileum, sciatic nerve, and rectum
ANIMALS AND ANIMAL MAINTENANCE				
Strain and Species	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice
Animal Source	Harlan Industries (Indianapolis, IN)	Same as single-administration studies	Same as single-administration studies	Charles River Breeding Laboratories (Kingston, NY)
Time Held Before Study	2 wk	Rats--6 wk; mice--3 wk (4 wk for 125 and 250 mg/kg groups)	2 wk	Rats--3 wk; mice--2 wk
Age When Placed on Study	8 wk	12 wk	7-8 wk	8 wk
Age When Killed	10 wk	14 wk	20-21 wk	113 wk
Necropsy Dates	2/2/78	Rats--4/14/78; mice--5/15/78 and 5/22/78	Rats--12/28/78-12/29/78; mice--12/22/78 and 12/27/78	Rats--8/23/82-8/25/82; mice--8/17/82-8/20/82
Method of Animal Distribution	At random	At random	Rats--assigned to groups according to a random numbers table; mice--assigned to groups so that cage weights for each sex were approximately equal	Assigned to cages according to a random numbers table; then cages assigned to groups according to another set of random numbers
Animal Identification	None	Ear punch and cage card	Ear punch and cage card	Ear punch, toe clip, and cage card
Feed	Purina Lab Chow® meal (Ralston Purina, St. Louis, MO); available ad libitum	Same as single-administration studies	Same as single-administration studies	NIH 07 Rat and Mouse Ration (Zeigler Bros., Gardners, PA); available ad libitum
Bedding	Ab-Sorb-Dri® heat-treated hardwood chips (Williams Feed and Bedding Corp., Gaithersburg, MD)	Same as single-administration studies	Same as single-administration studies	Ab-Sorb-Dri® heat-treated hardwood chips (Williams Feed and Bedding Corp., Gaithersburg, MD) until 9/23/81; then hardwood chip animal bedding (P.J. Murphy Forest Products Corp., Rochelle Park, NJ)

TABLE 4. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE STUDIES (Continued)

	Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Water	Acidified to pH 2.5 with hydrochloric acid, glass bottles; available ad libitum	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Cages	Polycarbonate (Lab Products, Inc., Garfield, NJ, and Rochelle Park, NJ)	Same as single-administration studies	Same as single-administration studies	Polycarbonate (Lab Products, Inc., Garfield, NJ and Rochelle Park, NJ; Hazleton Systems, Aberdeen, MD)
Cage Filters	Nonwoven filter sheets	Same as single-administration studies	Same as single-administration studies	Nonwoven polyester filter sheets (Snow Filtration Co., Cincinnati, OH)
Animals per Cage	5	5	5	5
Other Chemicals on Study in the Same Room	None	Rats--none; mice--1-chloro-2-methylpropene (dimethylvinyl chloride)	None	None
Animal Room Environment	Temp--23° ± 1°C; humidity--30%-70%; fluorescent light 12 h/d; 15 room air changes/h	Same as single-administration studies	Same as single-administration studies	Temp--23° ± 1°C; humidity--30%-70%; fluorescent light 12 h/d; 12-15 room air changes/h

barrier-maintained rooms. Animals were shipped to the study laboratory at 5 weeks of age. The animals were quarantined at the study laboratory for 2 or 3 weeks. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rodents were placed on study at 8 weeks of age. The health of the animals was monitored during the course of the study according to the protocols of the NTP Sentinel Animal Program (Appendix K).

A quality control skin grafting program has been in effect since early 1978 to monitor the genetic integrity of the inbred mice used to produce the hybrid B6C3F$_1$ study animal. In mid-1981, data were obtained that showed incompatibility between the NIH C3H reference colony and the C3H colony from a Program supplier. In August 1981, inbred parental lines of mice were further tested for genetic integrity via isozyme and protein electrophoresis profiles that demonstrate phenotype expressions of known genetic loci.

The C57BL/6 mice were homogeneous at all loci tested. Eighty-five percent of the C3H mice monitored were variant at one to three loci, indicating some heterogeneity in the C3H line from this supplier. Nevertheless, the genome of this line is more homogeneous than that of randomly bred stocks.

Male mice from the C3H colony and female mice from the C57BL/6 colony were used as parents for the hybrid B6C3F$_1$ mice used in these studies. The influence of the potential genetic nonuniformity in the hybrid mice on these results is not known, but the results of the studies are not affected because concurrent controls were included in each study.

Animal Maintenance

Rats and mice were housed five per cage in polycarbonate cages. Feed and water (acidified with hydrochloric acid to pH 2.5 for bacterial control) were available ad libitum. Details of animal maintenance are summarized in Table 4.

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded once every 4 weeks. Body weights by cage were recorded once per week for the first 13 weeks of the study and once per month thereafter. Mean body weights were calculated for each group. Moribund animals were killed, as were animals that survived to the end of the study. A necropsy was performed on all animals, including those found dead unless they were excessively autolyzed or cannibalized. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study in each group.

Examinations for grossly visible lesions were performed on major tissues or organs. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissues examined microscopically are listed in Table 4.

When the pathology examination was completed, the slides, individual animal data records, and summary tables were sent to an independent quality assurance laboratory. Individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assurance pathologist. Slides of all target tissues and those about which the original and quality assurance pathologists disagreed were submitted to the Chairperson of the Pathology Working Group (PWG) for evaluation. Representative coded slides selected by the Chairperson were reviewed by PWG pathologists, who reached a consensus and compared their findings with the original and quality assurance diagnoses. When diagnostic differences were found, the PWG sent the appropriate slides and comments to the original pathologist for review. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final diagnoses represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent evaluations, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1985).

Nonneoplastic lesions are not examined routinely by the quality assurance pathologist or PWG. Certain nonneoplastic findings are reviewed by the quality assurance pathologist and PWG if they are considered part of the toxic response to a chemical or if they are deemed of special interest.

Statistical Methods

Data Recording: Data on this experiment were recorded in the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969).

Survival Analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found dead of other than natural causes or were found to be missing; animals dying from natural causes were not censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) life table test for a dose-related trend. When significant survival differences were detected, additional analyses using these procedures were carried out to determine the time point at which significant differences in the survival curves were first detected. All reported P values for the survival analysis are two-sided.

Calculation of Incidence: The incidence of neoplastic or nonneoplastic lesions is given as the

ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators include only those animals for which the site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) prior to histologic sampling, or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Tumor Incidence: Three statistical methods are used to analyze tumor incidence data. The two that adjust for intercurrent mortality employ the classical method for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included pairwise comparisons of high dose and low dose groups with vehicle controls and tests for overall dose-response trends.

For studies in which compound administration has little effect on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death. All reported P values for tumor analyses are one-sided.

Life Table Analyses--The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and vehicle control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel method to obtain an overall P value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975). The underlying variable considered by this analysis is time to death due to tumor. If the tumor is rapidly lethal, then time to death due to tumor closely approximates time to tumor onset. In this case, the life table test also provides a comparison of the time-specific tumor incidence.

Incidental Tumor Analyses--The second method of analysis assumed that all tumors of a given type observed in animals that died before the end of the study were "incidental"; i.e., they were merely observed at necropsy in animals dying of an unrelated cause. According to this approach, the proportions of tumor-bearing animals in dosed and vehicle control groups were compared in each of five time intervals: weeks 0-52, weeks 53-78, weeks 79-92, week 93 to the week before the terminal-kill period, and the terminal-kill period. The denominators of these proportions were the number of animals actually examined for tumors during the time interval. The individual time interval comparisons were then combined by the previously described method to obtain a single overall result. (See Haseman, 1984, for the computational details of both methods.)

Unadjusted Analyses--Primarily, survival-adjusted methods are used to evaluate tumor incidence. In addition, the results of the Fisher exact test for pairwise comparisons and the Cochran-Armitage linear trend test (Armitage, 1971; Gart et al., 1979) are given in the appendix containing the analyses of primary tumor incidence. These two tests are based on the overall proportion of tumor-bearing animals and do not adjust for survival differences.

Historical Control Data: Although the concurrent control group is always the first and most appropriate control group used for evaluation, there are certain instances in which historical control data can be helpful in the overall assessment of tumor incidence. Consequently, control tumor incidences from the NTP historical control data base (Haseman et al., 1984) are included for those tumors appearing to show compound-related effects.

III. RESULTS

RATS

SINGLE-ADMINISTRATION STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

SINGLE-ADMINISTRATION STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

SINGLE-ADMINISTRATION STUDIES

Rats that received 1,000, 3,160, or 10,000 mg/kg 3-chloro-2-methylpropene died before the end of the studies (Table 5). Final body weights were not recorded. Animals that died on day 1 frequently had darkened livers, spleens, and kidneys; red lungs; and small intestines filled with red fluid. Animals that received 1,000 mg/kg and died on day 2 or 3 frequently had tan livers, darkened lungs and thymus, and gas in the stomach. No compound-related effects were observed at necropsy in animals dosed at 100 or 316 mg/kg.

TABLE 5. SURVIVAL AND INITIAL MEAN BODY WEIGHTS OF RATS IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE (a)

Dose (mg/kg)	Survival	Initial Mean Body Weights (grams)
MALE		
100	5/5	193
316	5/5	188
1,000	(b) 0/5	189
3,160	(c) 0/5	190
10,000	(c) 0/5	190
FEMALE		
100	5/5	143
316	5/5	144
1,000	(d) 0/5	143
3,160	(c) 0/5	143
10,000	(c) 0/5	144

(a) The steep survival curves precluded accurate LD_{50} calculations.
(b) Day of death: 2 (for all)
(c) Day of death: 1 (for all)
(d) Day of death: 2, 2, 2, 2, 3

FOURTEEN-DAY STUDIES

Rats that received 3-chloro-2-methylpropene at 500 or 750 mg/kg died before the end of the studies (Table 6). Male rats that received 281 mg/kg lost weight. Final mean body weights of all other dosed groups and vehicle control rats were comparable. Animals that died had yellow intestines, dark stomachs, darkened and pale areas on the liver, and/or dark fluid in the urinary bladder. Based on survival, 400 mg/kg was chosen as the highest dose for the 13-week studies.

TABLE 6. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FOURTEEN-DAY GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams)			Final Weight Relative to Vehicle Controls (percent)
		Initial	Final	Change (b)	
MALE					
0	5/5	176	199	+ 23	--
89	5/5	180	199	+ 19	0
158	5/5	184	200	+ 16	100.5
281	5/5	177	166	- 11	83.4
500	(c) 0/5	178	(d)	(d)	(d)
750	(e) 0/5	182	(d)	(d)	(d)
FEMALE					
0	5/5	119	130	+ 11	--
89	5/5	127	137	+ 10	105.4
158	5/5	119	142	+ 23	109.2
281	5/5	124	138	+ 14	106.2
500	(f) 0/5	127	(d)	(d)	(d)
750	(g) 0/5	117	(d)	(d)	(d)

(a) Number surviving/number in group
(b) Mean body weight change of the survivors
(c) Day of death: 2, 2, 2, 4, 5
(d) No data are reported due to the 100% mortality in this group.
(e) Day of death: 1, 2, 2, 2, 2
(f) Day of death: 1, 1, 2, 2, 2
(g) Day of death: 1 (for all)

III. RESULTS: RATS

THIRTEEN-WEEK STUDIES

All rats that received 3-chloro-2-methylpropene at 400 mg/kg and 5/10 males and 2/10 females that received 300 mg/kg died before the end of the studies (Table 7). The deaths of 1/10 males that received 100 mg/kg and 2/10 females that received 200 mg/kg were considered to be due to gavage injury. Final mean body weights of male rats that received 200 or 300 mg/kg were depressed 5.0% and 6.6% relative to that of the vehicle controls.

Compound-related clinical signs (primarily rough coats) were observed in 5/10 females that received 300 mg/kg and in 9/10 males and 4/10 females that received 400 mg/kg.

Histologic evidence of chronic murine pneumonia was found in 5/10 male and 6/10 female vehicle controls. Pneumonia virus of mouse (PVM) antibody titers were found in 8/10 vehicle controls, Kilham rat virus titers were found in 2/10 vehicle controls, and Sendai virus titers in 3/10 vehicle controls.

Focal areas of inflammation, which varied from acute to chronic, were observed in the livers of rats that received 300 or 400 mg/kg (Table 8). The areas of necrosis were distributed throughout the liver. In the more acute lesions, the zone of necrosis was surrounded by congestion or neutrophils. If the zone of inflammation was surrounded by a cellular infiltrate, the lesion was designated as necrotizing.

Dose Selection Rationale: Based on survival and the incidence of liver lesions, 3-chloro-2-methylpropene doses selected for rats for the 2-year studies were 0, 75, or 150 mg/kg in corn oil by gavage.

TABLE 7. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams)			Final Weight Relative to Vehicle Controls (percent)
		Initial	Final	Change (b)	
MALE					
0	10/10	119	258	+ 139	--
50	10/10	121	275	+ 154	106.6
100	(c) 9/10	124	257	+ 133	99.6
200	10/10	122	245	+ 123	95.0
300	(d) 5/10	118	241	+ 123	93.4
400	(e) 0/10	120	(f)	(f)	(f)
FEMALE					
0	10/10	99	166	+ 67	--
50	10/10	94	165	+ 71	99.4
100	10/10	99	170	+ 71	102.4
200	(c) 8/10	102	173	+ 71	104.2
300	(g) 8/10	97	166	+ 69	100.0
400	(h) 0/10	99	(f)	(f)	(f)

(a) Number surviving/number in group
(b) Mean weight change of the survivors
(c) Death (s) judged to be accidental
(d) Week of death: 10, 11, 11, 12, 12
(e) Week of death: 1, 2, 11, 11, 11, 11, 11, 11, 11, 11, 11
(f) No data are reported due to the 100% mortality in this group.
(g) Week of death: 3, 10
(h) Week of death: 1, 1, 1, 1, 7, 10, 11, 11, 11, 12

TABLE 8. NUMBERS OF RATS WITH LIVER LESIONS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE (a)

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	300 mg/kg	400 mg/kg
MALE						
Inflammation, chronic, focal	--	--	--	--	4	1
Inflammation, acute, focal	--	1	--	--	--	1
Inflammation, necrotizing, acute	--	--	--	--	--	4
Congestion	1	--	--	--	--	2
Mineralization	--	--	--	--	--	1
FEMALE						
Inflammation, chronic, focal	--	--	--	--	1	2
Inflammation, acute, focal	--	--	--	--	2	5
Inflammation, necrotizing, chronic	--	--	--	--	--	3
Congestion	--	--	--	--	--	2
Mineralization	--	--	--	--	--	3

(a) Ten animals examined per group

TWO-YEAR STUDIES

Body Weights and Clinical Signs

The mean body weights of high dose male rats were lower (by more than 10%) than those of the vehicle controls beginning at week 10 of the studies (Table 9 and Figure 1). The mean body weights of low dose male rats were slightly lower (approximately 5%) than those of the vehicle controls between week 13 and week 76. Mean body weights of high dose female rats were slightly lower (approximately 5%) than those of the vehicle controls after week 32. Mean body weights of low dose female rats were slightly greater than those of the vehicle controls throughout the studies.

TABLE 9. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE

Weeks on Study	Vehicle Control		75 mg/kg			150 mg/kg		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors
MALE								
0	141	50	144	102	50	143	101	50
1	170	49	165	97	50	169	99	50
2	202	49	199	99	50	203	100	50
3	222	49	218	98	50	210	95	50
4	239	49	233	97	50	223	93	50
5	251	49	249	99	50	237	94	50
6	269	49	264	98	50	248	92	50
7	280	49	272	97	50	256	91	50
8	286	49	278	97	50	260	91	50
9	305	49	296	97	50	276	90	50
10	313	49	302	96	50	280	89	50
11	321	49	305	95	50	286	89	49
12	328	49	320	98	50	297	91	49
13	339	49	322	95	50	300	88	49
16	358	49	339	95	50	305	85	49
20	375	49	353	94	50	319	85	49
24	392	49	370	94	50	334	85	49
28	413	49	387	94	50	348	84	49
32	426	49	398	93	50	363	85	49
36	436	48	410	94	50	372	85	48
40	441	46	417	95	50	375	85	48
44	447	45	422	94	50	379	85	48
48	452	44	429	95	50	382	85	47
52	460	44	434	94	50	389	85	46
56	463	42	437	94	50	393	85	44
60	463	41	439	95	46	391	84	44
64	465	41	443	95	45	398	86	44
68	465	40	446	96	43	398	86	44
72	466	40	448	96	43	403	86	44
76	472	39	446	94	42	406	86	42
80	465	39	445	96	41	405	87	42
84	465	38	449	97	37	394	85	39
88	456	38	444	97	36	400	88	34
92	449	38	445	99	35	397	88	34
96	453	34	452	100	30	395	87	33
100	449	32	438	98	29	386	86	30
104	442	30	443	100	25	387	88	17
FEMALE								
0	115	50	115	100	50	116	101	50
1	129	50	130	101	50	129	100	50
2	145	50	145	100	49	146	101	49
3	153	50	154	101	49	154	101	49
4	162	50	162	100	49	165	102	49
5	170	50	172	101	49	172	101	49
6	175	50	176	101	49	178	102	49
7	179	50	182	102	49	181	101	49
8	184	50	188	102	49	187	102	49
9	189	50	192	102	49	190	101	49
10	195	50	198	102	49	193	99	49
11	193	49	197	102	49	193	100	49
12	196	49	202	103	49	198	101	49
13	199	49	204	103	49	197	99	49
16	208	49	211	101	49	205	99	49
20	217	49	219	101	49	213	98	49
24	221	49	225	102	49	213	96	49
28	225	49	229	102	49	222	99	49
32	237	49	239	101	49	228	96	49
36	239	49	242	101	48	231	97	48
40	244	49	249	102	48	235	96	48
44	247	49	253	102	48	238	96	48
48	256	49	260	102	47	242	95	48
52	263	48	268	102	47	249	95	48
56	268	48	276	103	47	254	95	48
60	277	48	284	103	46	259	94	48
64	281	48	288	102	46	266	95	47
68	286	47	293	102	45	272	95	44
72	290	47	299	103	44	273	94	41
76	293	44	304	104	44	277	95	41
80	291	43	304	104	44	277	95	40
84	293	43	308	105	43	284	97	37
88	296	39	307	104	42	284	96	35
92	302	37	313	104	40	288	95	32
96	305	35	321	105	35	299	98	28
100	312	33	325	104	35	301	96	27
104	316	31	327	103	32	301	95	26

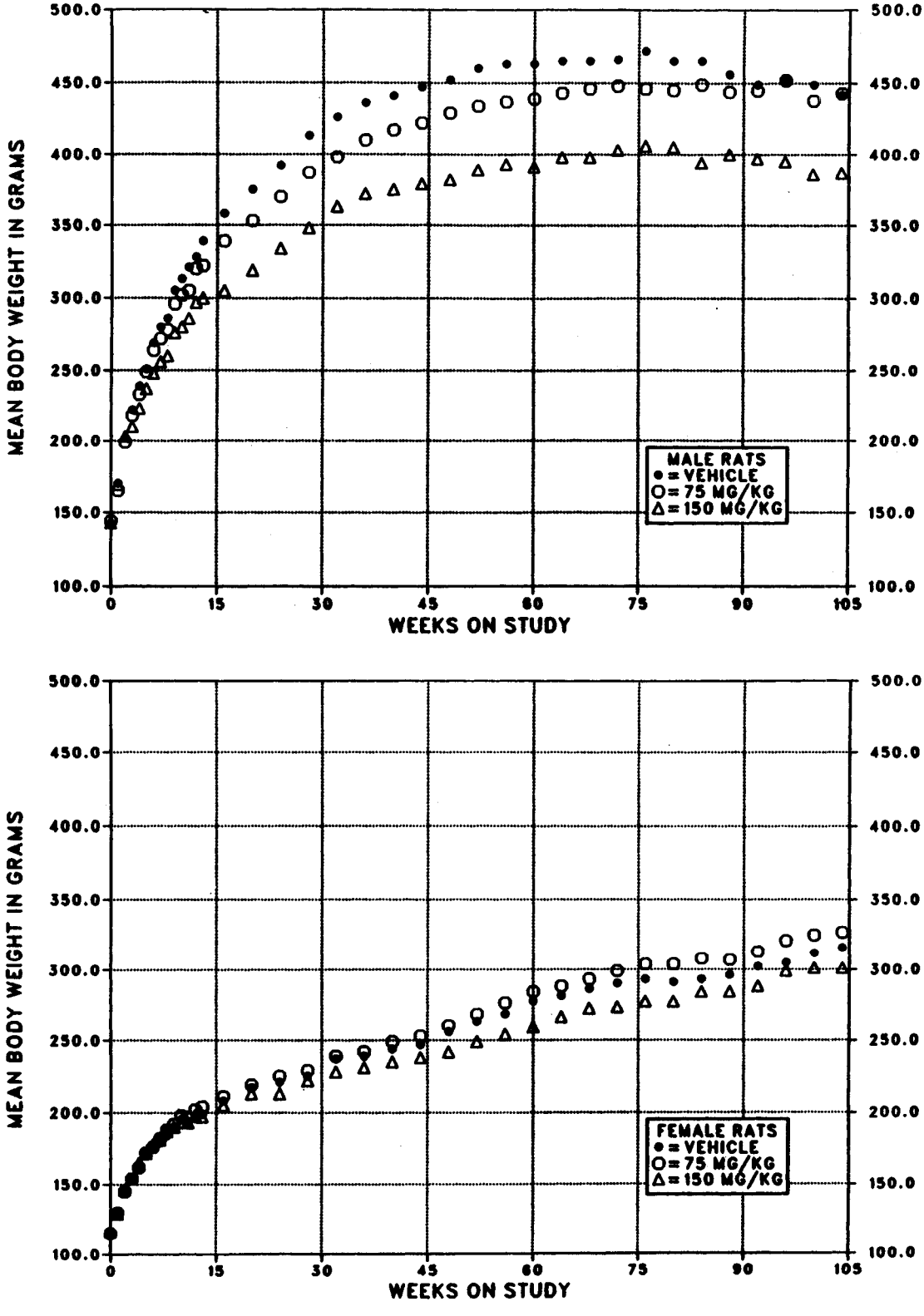


FIGURE 1. GROWTH CURVES FOR RATS ADMINISTERED 3-CHLORO-2-METHYLPROPENE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats at the doses used in these studies and for vehicle controls are shown in the Kaplan and Meier curves in Figure 2. No significant differences in survival were observed between any groups of either sex, although late in the study, survival of high dose male rats was slightly reduced (P=0.056) relative to that of the vehicle controls (Table 10).

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions in the forestomach, urinary tract, testis, integumentary system, nasal cavity, liver, adrenal gland, and thyroid gland. Histopathologic findings on neoplasms in rats are summarized in Appendix A (Tables A1 and A2); Appendix A (Tables A3 and A4) also gives the survival and tumor status for individual male and female rats. Findings on nonneoplastic lesions are summarized in Appendix C (Tables C1 and C2). Appendix E (Tables E1 and E2) contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes). Historical incidences of tumors in corn oil vehicle control animals are listed in Appendix F.

TABLE 10. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE

	Vehicle Control	75 mg/kg	150 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	19	25	32
Accidentally killed	1	0	1
Killed at termination	30	25	17
Survival P values (c)	0.053	0.419	0.056
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	19	15	22
Accidentally killed	0	3	2
Killed at termination	31	32	26
Survival P values (c)	0.456	0.561	0.509

(a) Terminal-kill period: week 105
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

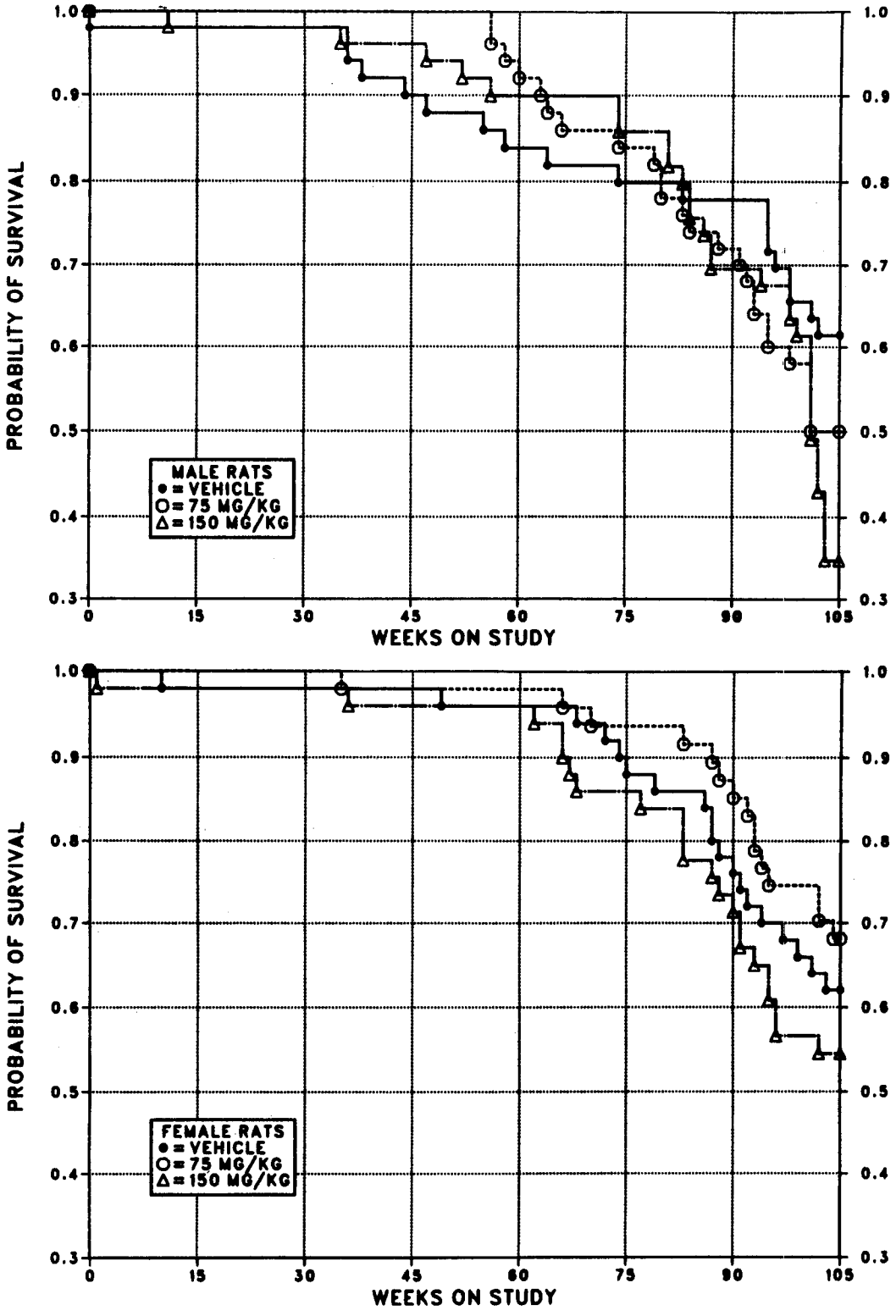


FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED 3-CHLORO-2-METHYLPROPENE IN CORN OIL BY GAVAGE FOR TWO YEARS

Forestomach: Basal cell hyperplasia was observed at increased incidences in dosed male and female rats (Table 11). Papillomas were observed at significantly increased incidences in high dose male and female rats. Squamous cell carcinomas were observed in 2/48 high dose male rats but not in any other groups. Metastasis was not observed.

Microscopically, the papillomas consisted of arborized finger-like projections from the surface. The projections had a core of fibrovascular tissue contiguous with the submucosa and were covered by hyperkeratotic squamous epithelium. In most instances, the papillomas were pedunculated and the arborized projections arose from a single stalk.

Squamous cell carcinomas were characterized by downward projecting sheets, nests, and anastomosing cords of squamous tumor cells that invaded underlying structures. The invading masses of cells originated at the base of papillomas. Keratinization at the center of a cluster of neoplastic cells resulted in concentrically arranged masses of keratin called "pearls."

TABLE 11. ANALYSIS OF FORESTOMACH LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE (a)

	Vehicle Control	75 mg/kg	150 mg/kg
MALE			
Basal Cell or Epithelial Hyperplasia			
Overall Rates	19/50 (38%)	41/50 (82%)	44/48 (90%)
Papilloma (b)			
Overall Rates	1/50 (2%)	5/50 (10%)	30/48 (63%)
Adjusted Rates	2.6%	15.5%	89.9%
Terminal Rates	0/30 (0%)	1/25 (4%)	14/17 (82%)
Life Table Tests	P<0.001	P=0.084	P<0.001
Incidental Tumor Tests	P<0.001	P=0.167	P<0.001
Squamous Cell Carcinoma			
Overall Rates	0/50 (0%)	0/50 (0%)	(c) 2/48 (4%)
FEMALE			
Basal Cell Hyperplasia			
Overall Rates	24/50 (48%)	42/50 (84%)	45/50 (90%)
Papilloma (d)			
Overall Rates	1/50 (2%)	1/50 (2%)	10/50 (20%)
Adjusted Rates	3.1%	3.1%	32.0%
Terminal Rates	0/31 (0%)	1/32 (3%)	7/26 (27%)
Life Table Tests	P<0.001	P=0.753N	P=0.003
Incidental Tumor Tests	P=0.001	P=0.720N	P=0.006

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) Historical incidence of papillomas at study laboratory (mean): 0/147; historical incidence in NTP studies: 5/1,062 (0.5%)
(c) The two animals that had squamous cell carcinomas also had squamous cell papillomas.
(d) Historical incidence of papillomas at study laboratory (mean): 1/150 (0.7%); historical incidence in NTP studies: 5/1,062 (0.5%)

Urinary Tract: The incidences of nephropathy were increased in dosed male and high dose female rats (Table 12). A renal tubular cell adenoma was observed in 1/50 low dose male rats; renal tubular cell adenocarcinomas were observed in 1/50 low dose and 1/49 high dose male rats. A renal transitional cell carcinoma was observed in 1/49 high dose male rats, and a transitional cell papilloma was observed in the urinary bladder of 1/46 high dose male rats.

Testis: Interstitial cell tumors in male rats occurred with a significant positive trend, and the incidence in the high dose group was significantly greater than that in the vehicle controls (Table 13).

TABLE 12. INCIDENCES OF URINARY TRACT LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE

	Vehicle Control	75 mg/kg	150 mg/kg
MALE			
Nephropathy			
Overall Rates	35/50 (70%)	44/50 (88%)	47/49 (96%)
Renal Tubular Cell Adenoma			
Overall Rates	0/50 (0%)	1/50 (2%)	0/49 (0%)
Renal Tubular Cell Adenocarcinoma			
Overall Rates	0/50 (0%)	1/50 (2%)	1/49 (2%)
Renal Transitional Cell Carcinoma			
Overall Rates	0/50 (0%)	0/50 (0%)	1/49 (2%)
Urinary Bladder Transitional Cell Papilloma			
Overall Rates	0/48 (0%)	0/49 (0%)	1/46 (2%)
FEMALE			
Nephropathy			
Overall Rates	17/50 (34%)	15/50 (30%)	27/50 (54%)

TABLE 13. ANALYSIS OF TESTICULAR TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE

	Vehicle Control	75 mg/kg	150 mg/kg
Interstitial Cell Tumor (a)			
Overall Rates	36/50 (72%)	43/50 (86%)	43/48 (90%)
Adjusted Rates	97.3%	100.0%	100.0%
Terminal Rates	29/30 (97%)	25/25 (100%)	17/17 (100%)
Life Table Tests	P<0.001	P=0.009	P<0.001
Incidental Tumor Tests	P=0.003	P=0.067	P=0.012

(a) Historical incidence at study laboratory (mean ± SD): 92.0% ± 6.9%; historical incidence in NTP studies: 90.4% ± 5.7%

Integumentary System: Subcutaneous fibromas in female rats occurred with a significant positive trend; the incidences of fibromas, sarcomas, or fibrosarcomas (combined) in dosed female rats were not significantly greater than that in the vehicle controls (Table 14). Keratoacanthoma in male rats occurred with a significant negative trend (skin: vehicle control, 5/50, 10%; low dose, 0/50; high dose, 0/50; integumentary system: vehicle control, 6/50, 12%; low dose, 0/50; high dose, 0/50; $P<0.02$). The incidences in the dosed groups were significantly lower than that in the vehicle controls ($P<0.05$).

Nasal Cavity: Suppurative inflammation, acute/chronic inflammation, or chronic inflammation occurred at increased incidences in high dose male and female rats (male: vehicle control, 0/50; low dose, 0/50; high dose, 26/50, 52%; female: vehicle control, 0/50; low dose, 0/50; high dose, 14/50, 28%).

Liver: Necrosis was observed in dosed male rats but not in any male vehicle controls. Centrilobular necrosis occurred in 1/50 (2%) low dose and 5/48 (10%) high dose male rats, focal necrosis was observed in 2/50 (4%) low dose and 2/48 (4%) high dose male rats, and midzonal necrosis was observed in 1/48 (2%) high dose male rats. The incidences of hepatocellular necrosis in high dose and vehicle control female rats were similar.

TABLE 14. ANALYSIS OF SUBCUTANEOUS TISSUE TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE

	Vehicle Control	75 mg/kg	150 mg/kg
Fibroma			
Overall Rates	0/50 (0%)	2/50 (4%)	4/50 (8%)
Adjusted Rates	0.0%	6.3%	13.7%
Terminal Rates	0/31 (0%)	2/32 (6%)	2/26 (8%)
Life Table Tests	P=0.024	P=0.245	P=0.047
Incidental Tumor Tests	P=0.030	P=0.245	P=0.060
Fibroma, Sarcoma, or Fibrosarcoma (a)			
Overall Rates	1/50 (2%)	3/50 (6%)	5/50 (10%)
Adjusted Rates	3.2%	9.4%	16.1%
Terminal Rates	1/31 (3%)	3/32 (9%)	2/26 (8%)
Life Table Tests	P=0.046	P=0.316	P=0.077
Incidental Tumor Tests	P=0.056	P=0.316	P=0.093

(a) Historical incidence of fibroma or fibrosarcoma at study laboratory (mean ± SD): 2.7% ± 1.2%; historical incidence in NTP studies: 1.8% ± 1.5%

Adrenal Gland: Neoplasms of the adrenal medulla (pheochromocytomas and/or malignant pheochromocytomas [combined]) in male rats occurred with a significant negative trend, and the incidences in the high dose group were significantly lower than those in the vehicle controls (Table 15). The incidences of pheochromocytomas in dosed female rats were not significantly different from that in the vehicle controls (vehicle control, 4/50, 8 %; low dose, 1/50, 2%; high dose, 4/50, 8%).

Thyroid Gland: The incidence of C-cell adenomas or carcinomas (combined) in high dose male rats was significantly lower than that in the vehicle controls (Table 16). C-cell adenomas in female rats occurred with a significant negative trend, and the incidences in the dosed groups were significantly lower than that in the vehicle controls; however, the incidences of of C-cell adenomas or carcinomas (combined) in dosed female rats were not significantly different from that in the vehicle controls.

TABLE 15. ANALYSIS OF ADRENAL GLAND TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE

	Vehicle Control	75 mg/kg	150 mg/kg
Pheochromocytoma			
Overall Rates	14/50 (28%)	8/50 (16%)	4/48 (8%)
Adjusted Rates	43.6%	30.1%	14.6%
Terminal Rates	12/30 (40%)	7/25 (28%)	1/17 (6%)
Life Table Tests	P=0.056N	P=0.216N	P=0.078N
Incidental Tumor Tests	P=0.015N	P=0.188N	P=0.015N
Malignant Pheochromocytoma			
Overall Rates	0/50 (0%)	0/50 (0%)	1/48 (2%)
Pheochromocytoma or Malignant Pheochromocytoma (a)			
Overall Rates	14/50 (28%)	8/50 (16%)	5/48 (10%)
Adjusted Rates	43.6%	30.1%	18.2%
Terminal Rates	12/30 (40%)	7/25 (28%)	1/17 (6%)
Life Table Tests	P=0.104N	P=0.216N	P=0.141N
Incidental Tumor Tests	P=0.027N	P=0.188N	P=0.026N

(a) Historical incidence at study laboratory (mean ± SD): 18% ± 12%; historical incidence in NTP studies: 18% ± 10%

TABLE 16. ANALYSIS OF THYROID GLAND TUMORS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE

	Vehicle Control	75 mg/kg	150 mg/kg
MALE			
C-Cell Adenoma			
Overall Rates	3/49 (6%)	3/48 (6%)	0/48 (0%)
Adjusted Rates	10.0%	12.0%	0.0%
Terminal Rates	3/30 (10%)	3/25 (12%)	0/17 (0%)
Life Table Tests	P=0.223N	P=0.578	P=0.236N
Incidental Tumor Tests	P=0.223N	P=0.578	P=0.236N
C-Cell Carcinoma			
Overall Rates	4/49 (8%)	5/48 (10%)	0/48 (0%)
Adjusted Rates	13.3%	18.9%	0.0%
Terminal Rates	4/30 (13%)	4/25 (16%)	0/17 (0%)
Life Table Tests	P=0.185N	P=0.391	P=0.154N
Incidental Tumor Tests	P=0.153N	P=0.406	P=0.154N
C-Cell Adenoma or Carcinoma			
Overall Rates	7/49 (14%)	8/48 (17%)	0/48 (0%)
Adjusted Rates	23.3%	30.5%	0.0%
Terminal Rates	7/30 (23%)	7/25 (28%)	0/17 (0%)
Life Table Tests	P=0.078N	P=0.349	P=0.043N
Incidental Tumor Tests	P=0.064N	P=0.360	P=0.043N
FEMALE			
C-Cell Adenoma			
Overall Rates	6/50 (12%)	1/48 (2%)	0/49 (0%)
Adjusted Rates	17.8%	3.0%	0.0%
Terminal Rates	4/31 (13%)	0/30 (0%)	0/26 (0%)
Life Table Tests	P=0.008N	P=0.063N	P=0.031N
Incidental Tumor Tests	P=0.004N	P=0.037N	P=0.020N
C-Cell Carcinoma			
Overall Rates	2/50 (4%)	5/48 (10%)	5/49 (10%)
Adjusted Rates	6.5%	16.7%	19.2%
Terminal Rates	2/31 (6%)	5/30 (17%)	5/26 (19%)
Life Table Tests	P=0.111	P=0.200	P=0.147
Incidental Tumor Tests	P=0.111	P=0.200	P=0.147
C-Cell Adenoma or Carcinoma			
Overall Rates	8/50 (16%)	6/48 (13%)	5/49 (10%)
Adjusted Rates	23.9%	19.2%	19.2%
Terminal Rates	6/31 (19%)	5/30 (17%)	5/26 (19%)
Life Table Tests	P=0.333N	P=0.400N	P=0.399N
Incidental Tumor Tests	P=0.292N	P=0.349N	P=0.355N

SINGLE-ADMINISTRATION STUDIES

All mice that received 3-chloro-2-methylpropene at 3,160 mg/kg died before the end of the studies (Table 17). Final body weights were not recorded. Yellow gelatinous intestines and pale livers, spleens, and kidneys were found in mice that died before the end of the studies. No compound-related lesions were observed in animals that survived to the end of the studies.

TABLE 17. SURVIVAL AND INITIAL MEAN BODY WEIGHTS OF MICE IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE (a)

Dose (mg/kg)	Initial Mean Body Weight (grams)	Survival
MALE		
31.6	18	5/5
100	16	5/5
316	17	5/5
1,000	16	5/5
3,160	18	(b) 0/5
FEMALE		
31.6	17	5/5
100	16	5/5
316	17	5/5
1,000	17	5/5
3,160	16	(c) 0/5

(a) The steep survival curves preclude accurate LD_{50} calculations.
(b) Day of death: 2, 2, 2, 2, 5-14
(c) Day of death: 2, 2, 2, 2, 3

III. RESULTS: MICE

FOURTEEN-DAY STUDIES

All the mice that received 3-chloro-2-methylpropene at 750, 1,250, 1,750, or 2,500 mg/kg died on day 1 (Table 18). The death of 1/5 female mice that received 3-chloro-2-methylpropene at 250 mg/kg was considered unrelated to the chemical. Male and female vehicle control animals lost weight during the studies. Animals that died during the studies had bright red or orange lungs, pale livers, or soft intestines. No gross lesions were observed at necropsy at the end of the studies, except for a pale liver in one male in the 125 mg/kg group.

TABLE 18. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FOURTEEN-DAY GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial	Final	Change (b)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	23.0	22.0	− 1.0	--
125	5/5	23.0	24.0	+ 1.0	109.1
250	5/5	23.0	25.0	+ 2.0	113.6
500	5/5	23.0	21.0	− 2.0	95.5
750	0/5	22.0	(c)	(c)	(c)
1,250	0/5	23.0	(c)	(c)	(c)
1,750	0/5	23.0	(c)	(c)	(c)
2,500	0/5	23.0	(c)	(c)	(c)
FEMALE					
0	(d) 3/5	19.0	18.0	− 1.0	--
125	5/5	18.0	20.0	+ 2.0	111.1
250	(d) 4/5	19.0	21.0	+ 2.0	116.7
500	5/5	19.0	18.0	− 1.0	100.0
750	0/5	19.0	(c)	(c)	(c)
1,250	0/5	19.0	(c)	(c)	(c)
1,750	0/5	19.0	(c)	(c)	(c)
2,500	0/5	19.0	(c)	(c)	(c)

(a) Number surviving/number in group. All compound-related deaths occurred on day 1.
(b) Mean body weight change of the survivors
(c) No data are reported due to the 100% mortality in this group.
(d) Deaths judged accidental

THIRTEEN-WEEK STUDIES

All mice that received 3-chloro-2-methylpropene at 750 or 1,250 mg/kg and 9/10 males and 5/10 females in the 500 mg/kg groups died before the end of the studies (Table 19). The deaths of 1/10 males in the 500 mg/kg group and of mice in the other groups were considered to have been due to gavage injury.

Compound-related degenerative lesions were observed in the kidney and liver (Table 20). The kidney lesions consisted of degeneration and necrosis of cortical tubules, with accumulations of cellular debris in damaged tubules. Kidney lesions varied in severity within affected dose groups. The incidence and severity were greater in males than in females. Liver lesions consisted of coagulative necrosis and/or cytoplasmic vacuolization of hepatocytes. Liver and kidney lesions often occurred in the same mice; more severe liver lesions were often associated with the more severe kidney lesions. Some animals, however, had neither lesion. Mice in all groups had lung lesions consisting of interstitial inflammation, sometimes with hyperplasia of bronchiolar epithelium and epithelialization of alveolar linings. The lesions were compatible with a viral infection. Mice in these studies had antibody titers for Sendai virus, PVM, or mouse hepatitis virus (MHV).

Dose Selection Rationale: Because of the liver lesions observed at 250 mg/kg, doses selected for mice for the 2-year studies were 0, 100, or 200 mg/kg 3-chloro-2-methylpropene in corn oil by gavage.

TABLE 19. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial	Final	Change (b)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	(c) 8/9	21	29	+ 8	--
125	(c) 9/10	21	29	+ 8	100
250	(c) 8/10	20	28	+ 8	97
500	(d) 1/10	20	30	+10	103
750	(e) 0/10	21	(f)	(f)	(f)
1,250	(g) 0/10	21	(f)	(f)	(f)
FEMALE					
0	(c) 8/10	16	23	+ 7	--
125	(c) 9/10	17	23	+ 6	100
250	10/10	16	22	+ 6	96
500	(h) 5/10	16	23	+ 7	100
750	(g) 0/10	16	(f)	(f)	(f)
1,250	(g) 0/10	16	(f)	(f)	(f)

(a) Number surviving/number in group
(b) Mean body weight change of the survivors
(c) All deaths judged accidental
(d) Week of death: 1, 1, 1, 1, 1, 1, 2, 2, 4; one accidental.
(e) Week of death: 1, 1, 1, 1, 1, 1, 1, 1, 1, 2
(f) No data are reported due to the 100% mortality in this group.
(g) Week of death: 1 (for all)
(h) Week of death: 1, 2, 2, 2, 2

TABLE 20. NUMBERS OF MICE WITH LIVER AND KIDNEY LESIONS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE (a)

	Vehicle Control	125 mg/kg	250 mg/kg	500 mg/kg	750 mg/kg	1,250 mg/kg
MALE						
Liver						
Necrosis, coagulative	--	--	--	2	3	3
Cytoplasmic vacuolization	--	--	3	4	7	8
Hemorrhage, multifocal	--	--	--	1	--	--
Sinusoidal ectasia, multifocal	--	--	1	--	--	--
Kidney						
Nephrosis	--	--	--	8	10	9
Cytoplasmic alteration, deep cortical tubules	--	--	1	--	--	--
FEMALE						
Liver						
Necrosis, coagulative	--	--	--	1	2	2
Necrosis, central	--	--	--	--	--	1
Cytoplasmic vacuolization	--	1	3	2	6	6
Mineralization	--	--	--	--	--	1
Inflammation, suppurative	--	--	--	--	1	--
Kidney						
Nephrosis	--	--	--	3	4	3
Lymphocytic inflammatory infiltrate	--	--	--	1	--	--

(a) Nine animals examined in vehicle control groups; 10 animals examined in all dosed groups.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male mice and low dose and high dose female mice were lower (by less than 10%) than those of the vehicle controls throughout most of the studies (Table 21 and Figure 3). No compound-related clinical signs were observed.

TABLE 21. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE

Weeks on Study	Vehicle Control		100 mg/kg			200 mg/kg		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors
MALE								
0	23.9	50	22.4	94	50	22.7	95	50
1	25.8	50	25.2	98	49	25.7	100	50
2	27.0	50	26.9	100	48	26.6	99	49
3	28.4	50	27.6	97	48	27.6	97	49
4	29.3	50	28.7	98	48	28.2	96	49
5	31.1	50	30.5	98	48	28.9	93	49
6	31.6	50	30.9	98	48	29.8	94	49
7	31.9	50	31.3	98	48	29.5	92	49
8	33.0	50	31.5	95	48	30.3	92	49
9	33.5	50	32.2	96	48	30.8	92	49
10	34.0	50	33.3	98	48	31.7	93	49
11	34.7	50	33.5	97	48	31.9	92	49
12	34.5	50	33.5	97	48	31.8	92	49
13	34.8	50	33.8	97	48	32.5	93	49
16	35.5	50	34.5	97	48	33.1	93	49
20	36.2	50	35.1	97	48	33.8	93	49
24	37.9	48	37.9	100	48	36.3	96	49
28	37.4	47	37.5	100	48	36.9	99	48
32	39.3	45	38.4	98	48	37.8	96	48
36	40.6	45	39.9	98	48	38.5	95	47
40	42.6	45	42.4	100	48	40.6	95	47
44	42.8	45	43.1	101	48	41.0	96	47
48	44.9	45	44.0	98	48	43.1	96	47
52	45.6	45	44.9	98	48	43.5	95	47
56	47.6	45	46.9	99	48	44.3	93	47
60	45.9	45	46.1	100	48	44.3	97	46
64	46.8	45	46.0	98	48	43.9	94	46
68	46.3	43	46.0	99	48	43.5	94	45
72	45.5	43	45.1	99	48	42.9	94	45
76	46.0	43	45.9	100	46	43.4	94	45
80	44.8	43	45.5	102	46	43.2	96	45
84	44.6	41	44.4	100	45	41.8	94	45
88	44.2	40	43.3	98	45	41.4	94	44
92	46.3	38	45.3	98	45	42.5	92	44
96	44.4	36	44.5	100	44	41.3	93	42
100	43.6	33	43.2	99	42	40.2	92	38
104	43.6	27	43.8	100	37	41.3	95	32
FEMALE								
0	18.5	50	17.7	96	50	18.3	99	50
1	20.0	50	20.3	102	50	20.4	102	50
2	20.8	50	21.4	103	50	21.4	103	50
3	21.7	50	21.9	101	50	22.3	103	50
4	22.7	50	22.6	100	50	22.9	101	50
5	24.3	50	24.1	99	50	23.8	98	50
6	24.9	50	24.2	97	50	24.7	99	50
7	25.3	50	24.4	96	50	23.9	94	45
8	25.4	50	25.1	99	50	25.0	98	45
9	26.1	50	25.1	96	50	25.1	96	44
10	26.8	50	25.8	96	50	25.6	96	44
11	26.4	49	25.6	97	50	25.7	97	43
12	26.3	49	25.5	97	50	25.4	97	43
13	26.3	49	25.4	97	50	25.4	97	43
16	27.2	49	25.9	95	48	25.6	94	42
20	28.0	49	26.6	95	48	26.6	95	42
24	29.7	49	29.0	98	48	28.7	97	42
28	29.7	49	28.8	97	48	29.2	98	42
32	31.9	49	29.7	93	48	30.0	94	42
36	33.2	49	30.9	93	48	31.2	94	42
40	33.7	49	31.9	95	48	32.6	97	42
44	35.1	49	32.9	94	48	33.1	94	42
48	35.8	49	33.8	94	48	34.9	97	42
52	36.7	48	34.3	93	48	34.7	95	41
56	38.1	48	35.6	93	48	35.3	93	41
60	38.0	48	36.3	96	48	35.8	94	41
64	38.1	48	35.6	93	48	34.9	92	41
68	37.3	48	35.1	94	48	33.9	91	37
72	36.0	48	34.0	94	47	33.2	92	36
76	37.5	47	35.2	94	46	34.2	91	35
80	37.0	46	34.8	94	46	33.5	91	35
84	36.0	46	34.4	96	45	33.3	93	34
88	36.0	46	34.6	96	44	34.0	94	34
92	37.6	45	35.8	95	44	34.2	91	33
96	36.8	45	35.4	96	44	34.2	93	33
100	37.2	39	34.5	93	43	34.2	92	29
104	38.6	37	36.1	94	43	35.1	91	27

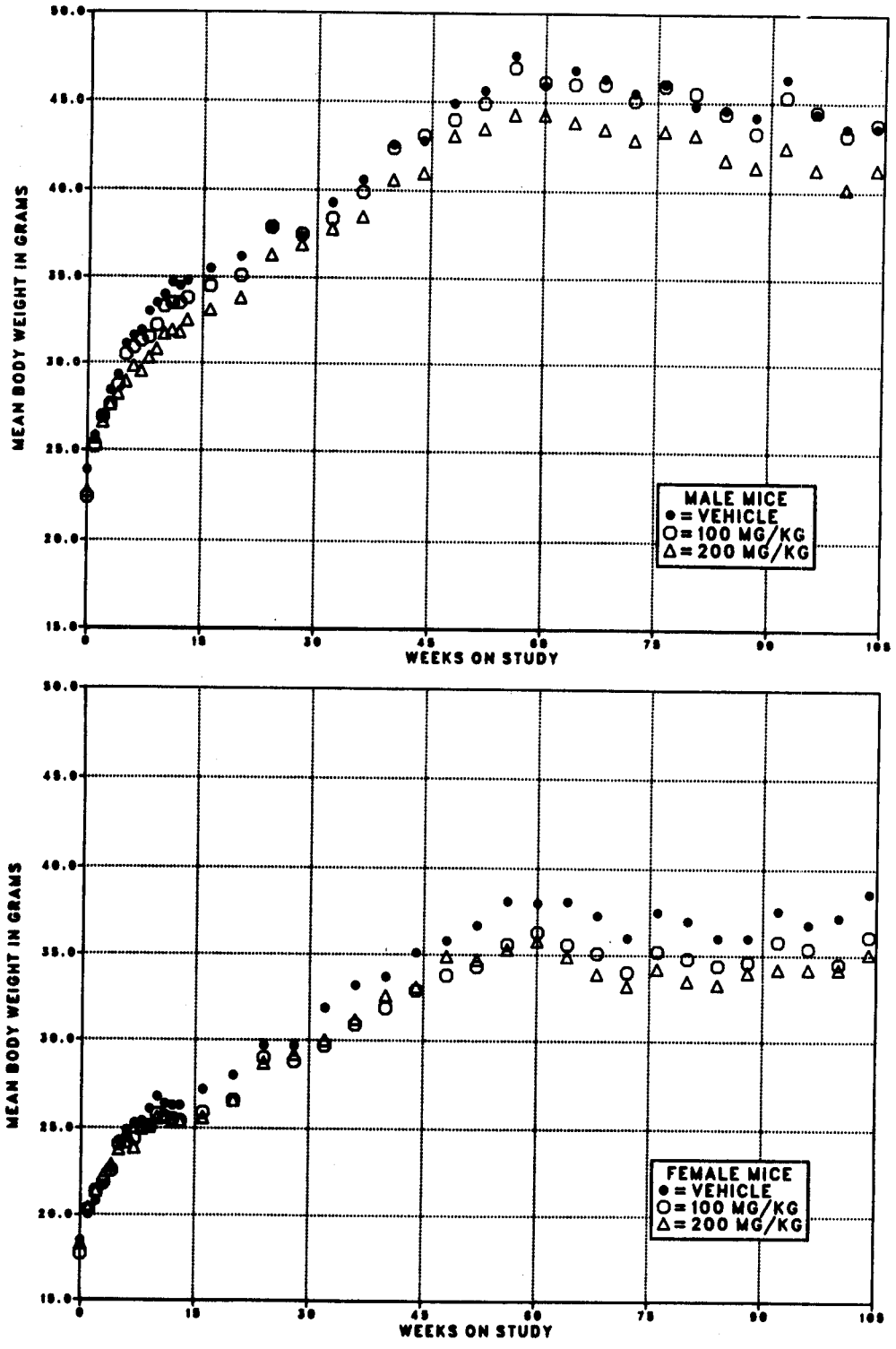


FIGURE 3. GROWTH CURVES FOR MICE ADMINISTERED 3-CHLORO-2-METHYLPROPENE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice administered 3-chloro-2-methylpropene at the doses used in these studies and for vehicle controls are shown in the Kaplan and Meier curves in Figure 4. The survival of the male vehicle control group was significantly lower than that of the low dose group (Table 22). In one of the cages of the high dose female mice, four pregnant mice were discovered and were promptly removed from the study.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions in the forestomach, nasal cavity, thyroid gland, kidney, circulatory system, and liver. Histopathologic findings on neoplasms in mice are summarized in Appendix B (Tables B1 and B2); Appendix B (Tables B3 and B4) also gives the survival and tumor status for individual male and female mice. Findings on nonneoplastic lesions are summarized in Appendix D (Tables D1 and D2). Appendix E (Tables E3 and E4) contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes). Historical incidences of tumors in corn oil vehicle control animals are listed in Appendix F.

TABLE 22. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE

	Vehicle Control	100 mg/kg	200 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	23	12	17
Accidentally killed	1	1	1
Killed at termination	26	37	32
Survival P values (c)	0.198	0.025	0.249
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	13	5	15
Accidentally killed	0	0	2
Animals missing or removed	0	2	(d) 6
Killed at termination	37	43	27
Survival P values (c)	0.343	0.091	0.368

(a) Terminal-kill period: week 105
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.
(d) Four pregnant mice in one cage were removed.

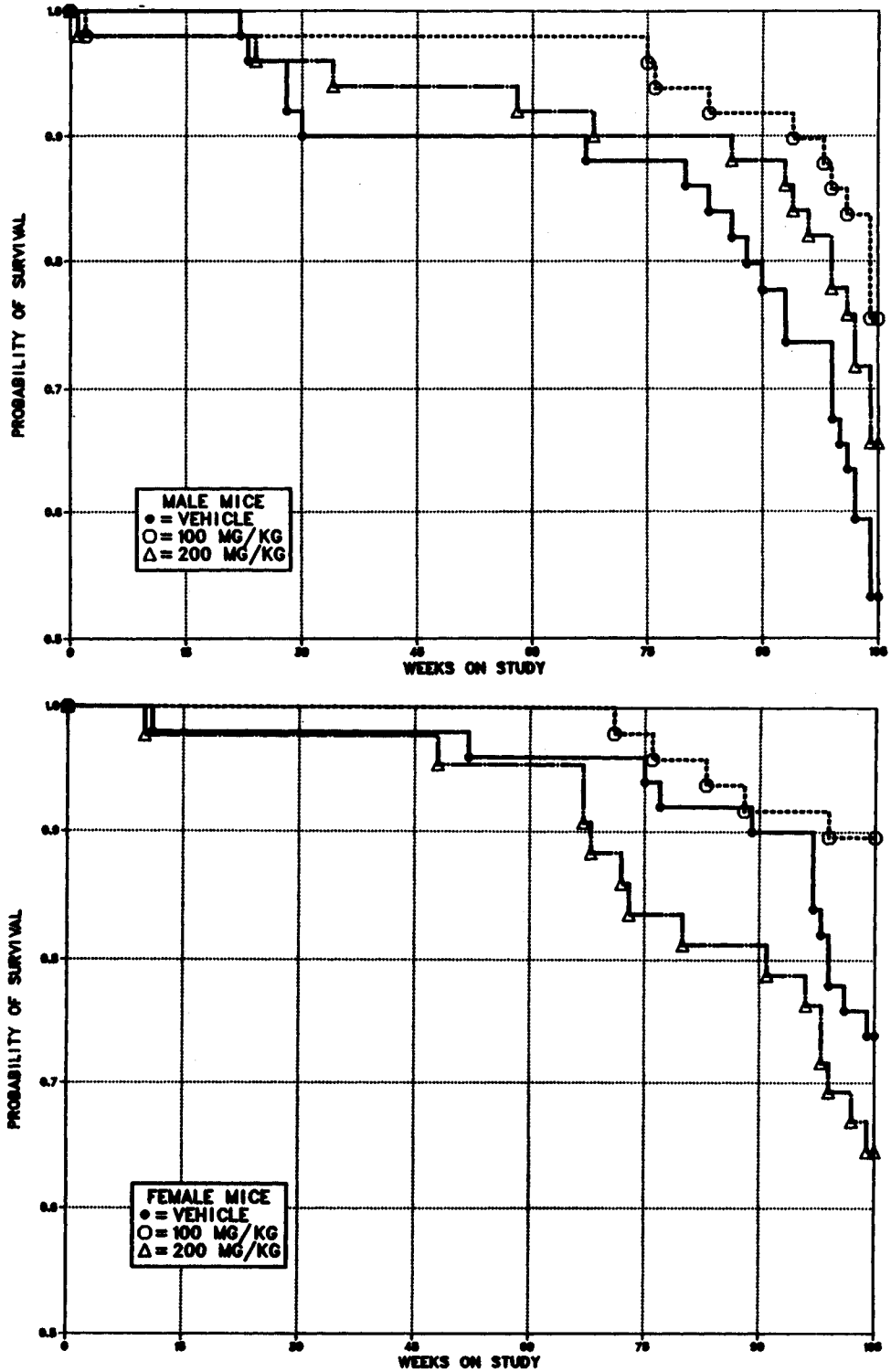


FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED 3-CHLORO-2-METHYLPROPENE IN CORN OIL BY GAVAGE FOR TWO YEARS

Forestomach: Incidences of inflammation of the forestomach were increased in dosed male and dosed female mice (male: vehicle control, 0/49; low dose, 9/49, 18%; high dose, 7/49, 14%; female: vehicle control, 2/50, 4%; low dose, 3/48, 6%; high dose, 9/44, 20%). Incidences of epithelial hyperplasia were increased in dosed male and dosed female mice (Table 23). Squamous cell papillomas in male and female mice, squamous cell carcinomas in male mice, and squamous cell papillomas or carcinomas (combined) in male and female mice occurred with significant positive trends. The incidences of papillomas in dosed male and dosed female mice, carcinomas in dosed male mice, and papillomas or carcinomas (combined) in dosed male and dosed female mice were significantly greater than those in the vehicle controls. Evidence of metastasis or invasion of other organs was observed in two low dose and three high dose male mice and in one high dose female mouse. The microscopic characteristics of squamous cell neoplasms of mice were similar to those described in rats.

Nasal Cavity: Acute inflammation of the nasal cavity was observed at increased ($P<0.05$) incidences in high dose male and female mice (male: vehicle control, 0/50; low dose, 0/50; high dose, 6/50, 12%; female: vehicle control, 0/50; low dose, 0/48; high dose, 5/44, 11%). The acute inflammation of the nasal cavity was similar histopathologically to that observed in rats.

Thyroid Gland: The incidences of follicular cysts in low dose and high dose female mice were greater than that in the vehicle controls (vehicle control, 5/44, 11%; low dose, 17/47, 36%; high dose, 8/38, 21%). Incidences of follicular cell neoplasms were not increased in dosed female mice.

Kidney: The incidence of nephrosis was increased in high dose male mice (male: vehicle control, 9/50, 18%; low dose, 10/50, 20%; high dose, 17/50, 34%; female: vehicle control, 2/50, 4%; low dose, 4/48, 8%; high dose, 5/44, 11%).

Circulatory System: Hemangiomas and hemangiomas or hemangiosarcomas (combined) in female mice occurred with significant negative trends (Table 24). The incidence of hemangiomas or hemangiosarcomas (combined) in the high dose female group was not significantly different from that in the vehicle controls. The following incidences of hemangiomas or hemangiosarcomas (combined) were observed in male mice: vehicle control, 2/50 (4%); low dose, 2/50 (4%); high dose, 3/50 (6%).

Liver: Hepatocellular carcinomas and hepatocellular adenomas or carcinomas (combined) in male mice occurred with a significant negative trend, and the incidences in the dosed groups were significantly lower than that in the vehicle controls (Table 25). In female mice, the following incidences of hepatocellular adenomas or carcinomas (combined) were observed: vehicle control, 4/50 (8%); low dose, 3/48 (6%); high dose, 1/44 (2%).

TABLE 23. ANALYSIS OF FORESTOMACH LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE (a)

	Vehicle Control	100 mg/kg	200 mg/kg
MALE			
Epithelial Hyperplasia			
Overall Rates	0/49 (0%)	14/49 (29%)	15/49 (31%)
Squamous Cell Papilloma			
Overall Rates	3/49 (6%)	19/49 (39%)	30/49 (61%)
Adjusted Rates	10.3%	46.0%	74.5%
Terminal Rates	2/26 (8%)	15/37 (41%)	22/32 (69%)
Life Table Tests	P<0.001	P=0.003	P<0.001
Incidental Tumor Tests	P<0.001	P<0.001	P<0.001
Squamous Cell Carcinoma			
Overall Rates	0/49 (0%)	5/49 (10%)	7/49 (14%)
Adjusted Rates	0.0%	11.6%	19.6%
Terminal Rates	0/26 (0%)	2/37 (5%)	5/32 (16%)
Life Table Tests	P=0.014	P=0.061	P=0.019
Incidental Tumor Tests	P=0.013	P=0.031	P=0.016
Squamous Cell Papilloma or Carcinoma (b)			
Overall Rates	3/49 (6%)	24/49 (49%)	(c) 36/49 (73%)
Adjusted Rates	10.3%	54.1%	85.5%
Terminal Rates	2/26 (8%)	17/37 (46%)	26/32 (81%)
Life Table Tests	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	P<0.001	P<0.001
FEMALE			
Epithelial Hyperplasia			
Overall Rates	4/50 (8%)	6/48 (12%)	13/44 (30%)
Squamous Cell Papilloma			
Overall Rates	0/50 (0%)	15/48 (31%)	29/44 (66%)
Adjusted Rates	0.0%	32.5%	80.2%
Terminal Rates	0/37 (0%)	12/43 (28%)	20/27 (74%)
Life Table Tests	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	P<0.001	P<0.001
Squamous Cell Carcinoma			
Overall Rates	0/50 (0%)	1/48 (2%)	2/44 (5%)
Squamous Cell Papilloma or Carcinoma (d)			
Overall Rates	0/50 (0%)	16/48 (33%)	31/44 (70%)
Adjusted Rates	0.0%	34.7%	81.5%
Terminal Rates	0/37 (0%)	13/43 (30%)	20/27 (74%)
Life Table Tests	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	P<0.001	P<0.001

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) Historical incidence of papillomas or carcinomas at study laboratory (mean): 2/147 (1.4%); historical incidence in NTP studies: 7/1,005 (0.7%)
(c) One animal had both papilloma and carcinoma.
(d) Historical incidence of papillomas or carcinomas at study laboratory (mean): 0/145; historical incidence in NTP studies: 4/1,027 (0.4%)

TABLE 24. ANALYSIS OF CIRCULATORY SYSTEM TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE

	Vehicle Control	100 mg/kg	200 mg/kg
Hemangioma			
Overall Rates	4/50 (8%)	0/48 (0%)	0/44 (0%)
Adjusted Rates	9.8%	0.0%	0.0%
Terminal Rates	2/37 (5%)	0/43 (0%)	0/27 (0%)
Life Table Tests	P=0.022N	P=0.055N	P=0.115N
Incidental Tumor Tests	P=0.036N	P=0.164N	P=0.107N
Hemangiosarcoma			
Overall Rates	1/50 (2%)	0/48 (0%)	0/44 (0%)
Hemangioma or Hemangiosarcoma (a)			
Overall Rates	5/50 (10%)	0/48 (0%)	0/44 (0%)
Adjusted Rates	12.0%	0.0%	0.0%
Terminal Rates	2/37 (5%)	0/43 (0%)	0/27 (0%)
Life Table Tests	P=0.010N	P=0.029N	P=0.072N
Incidental Tumor Tests	P=0.019N	P=0.141N	P=0.060N

(a) Historical incidence at study laboratory (mean ± SD): 4% ± 3.5%; historical incidence in NTP studies: 3% ± 2.9%

TABLE 25. ANALYSIS OF LIVER TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE

	Vehicle Control	100 mg/kg	200 mg/kg
Hepatocellular Adenoma			
Overall Rates	4/50 (8%)	7/50 (14%)	2/50 (4%)
Hepatocellular Carcinoma			
Overall Rates	19/50 (38%)	10/50 (20%)	11/50 (22%)
Adjusted Rates	49.7%	24.5%	28.9%
Terminal Rates	8/26 (31%)	7/37 (19%)	6/32 (19%)
Life Table Tests	P=0.019N	P=0.008N	P=0.031N
Incidental Tumor Tests	P=0.046N	P=0.061N	P=0.069N
Hepatocellular Adenoma or Carcinoma (a)			
Overall Rates	22/50 (44%)	16/50 (32%)	13/50 (26%)
Adjusted Rates	56.5%	39.6%	34.4%
Terminal Rates	10/26 (38%)	13/37 (35%)	8/32 (25%)
Life Table Tests	P=0.012N	P=0.025N	P=0.020N
Incidental Tumor Tests	P=0.027N	P=0.149N	P=0.042N

(a) Historical incidence at study laboratory (mean ± SD): 22% ± 8%; historical incidence in NTP studies: 31% ± 10%

IV. DISCUSSION AND CONCLUSIONS

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The discovery that vinyl chloride is carcinogenic in humans (Creech and Johnson, 1974) and animals (Maltoni, 1977) has focused attention on the potential mutagenicity and carcinogenicity of the structurally analogous aliphatic and olefinic halogenated hydrocarbons (NIEHS, 1977). Many halogenated aliphatic and olefinic hydrocarbons have since been shown to be carcinogens (Soderman, 1982). The present studies assessed the toxicity and carcinogenicity of another member of the olefinic halogenated hydrocarbon series: 3-chloro-2-methylpropene.

The toxicity and carcinogenicity of 3-chloro-2-methylpropene in F344/N rats and B6C3F$_1$ mice were evaluated in a series of short-term and 2-year studies. In the single-administration studies, rats received 100-10,000 mg/kg 3-chloro-2-methylpropene by gavage and mice received 31.6-3,160 mg/kg. In the 14-day studies, rats received 89-750 mg/kg and mice, 125-2,500 mg/kg by gavage on 14 consecutive days; vehicle control groups received corn oil on the same schedule. Rats in the 13-week gavage studies received 50-400 mg/kg and mice, 125-1,250 mg/kg; vehicle controls were administered corn oil.

In the 13-week studies, 50%-100% mortality occurred in groups of male and female rats receiving 400 mg/kg, male rats receiving 300 mg/kg, and male and female mice receiving 500, 750, or 1,250 mg/kg. Inflammation and necrosis of the liver occurred in both rats and mice administered 3-chloro-2-methylpropene for 13 weeks. Necrosis of cortical tubules of the kidneys was also observed in mice. Pathologic changes in the forestomach of dosed rats and mice were not found. Based on the histopathologic findings and the survival of the study animals in the 13-week studies, doses of 75 and 150 mg/kg for rats and 100 and 200 mg/kg for mice were selected for the 2-year studies.

Male rats receiving 150 mg/kg in the 2-year studies had reduced survival late in the study and lower mean body weights; body weight and survival were not affected in female rats or in male and female mice (see Tables 9, 10, 21, and 22; Figures 1-4).

Rats and mice administered 3-chloro-2-methylpropene by gavage in the 2-year studies had significantly increased incidences of forestomach neoplastic lesions (Table 26). For rats, these lesions were observed at 150 mg/kg. Both dosed groups of rats developed basal cell hyperplasia of the forestomach. Only a few cases of inflammation were observed. Male and female mice administered 100 or 200 mg/kg developed forestomach inflammation and forestomach epithelial hyperplasia and had significantly increased incidences of squamous cell papillomas and carcinomas of the forestomach accompanied by metastasis. The tumor data indicated that the doses of 3-chloro-2-methylpropene selected for the studies in rats and mice were appropriate for each species, even though body weight and survival were not affected in the female rats or in the male and female mice in the studies.

The forestomach of the rat and mouse is sometimes affected by chemical carcinogens, particularly when the chemical is administered by oral intubation. The squamous-lined forestomach (nonglandular stomach) is the proximal two-thirds of the stomach, immediately adjacent to the esophagus, and is sharply demarcated from the distal glandular stomach. The glandular portion of the rodent stomach is rarely a site of carcinogenesis in untreated animals or those given chemical carcinogens. The presence of mucus and/or a difference in local pH may play a role in protecting the glandular stomach from carcinogens. In the induction of malignant neoplasms in rodent forestomach by diglycidyl resorcinol ether, the earliest changes were basal cell hyperplasia. The hyperplasia progressed to papilloma and subsequently to carcinoma (NTP, 1986a). In the present studies, the pathogenesis of the forestomach neoplasm appeared to follow a similar pattern, from basal cell hyperplasia through papilloma to carcinoma.

In addition to these forestomach effects, lesions of the urinary bladder, kidney, testis, and liver were observed in dosed male rats. Although the incidence in vehicle controls was high, the incidence of nephropathy was increased in the dosed male rats (vehicle control, 35/50, 70%; low dose, 44/50, 88%; high dose, 47/49, 96%), and the

TABLE 26. NUMBERS OF RATS AND MICE WITH FORESTOMACH LESIONS IN THE TWO-YEAR GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE

RATS	Vehicle Control	75 mg/kg	150 mg/kg
Male			
Basal cell or epithelial hyperplasia	19/50 (38%)	(a) 41/50 (82%)	(a) 44/48 (90%)
Squamous cell papilloma	1/50 (2%)	5/50 (10%)	(a) 30/48 (63%)
Squamous cell carcinoma	0/50 (0%)	0/50 (0%)	2/48 (4%)
Female			
Basal cell hyperplasia	24/50 (48%)	(a) 42/50 (84%)	(a) 45/50 (90%)
Squamous cell papilloma	1/50 (2%)	1/50 (2%)	(a) 10/50 (20%)
Squamous cell carcinoma	0/50 (0%)	0/50 (0%)	0/50 (0%)
MICE	**Vehicle Control**	**100 mg/kg**	**200 mg/kg**
Male			
Epithelial hyperplasia	0/49 (0%)	(a) 14/49 (29%)	(a) 15/49 (31%)
Squamous cell papilloma	3/49 (6%)	(a) 19/49 (39%)	(a) 30/49 (61%)
Squamous cell carcinoma	0/49 (0%)	(b) 5/49 (10%)	(b) 7/49 (14%)
Female			
Epithelial hyperplasia	4/50 (8%)	6/48 (12%)	(a) 29/44 (66%)
Squamous cell papilloma	0/50 (0%)	(a) 15/48 (31%)	(a) 19/44 (43%)
Squamous cell carcinoma	0/50 (0%)	1/48 (2%)	2/44 (5%)

(a) Incidence significantly ($P<0.01$) greater than that in the vehicle controls
(b) Incidence significantly ($P<0.05$) greater than that in the vehicle controls

incidence of nephrosis was increased in male mice (vehicle control, 9/50, 18%; low dose, 10/50, 20%; high dose, 17/50, 34%). A urinary bladder transitional cell papilloma, a renal transitional cell carcinoma, and a renal tubular cell adenocarcinoma occurred in high dose male rats, and renal tubular cell adenocarcinomas or adenomas were observed in two low dose male rats; neoplasms of the urinary system were not seen in the vehicle controls. Neoplasms of the urinary bladder have not been reported previously in male F344/N rats administered corn oil by gavage in NTP studies (Appendix F, Table F7). The NTP historical incidence of renal tubular cell neoplasms in male F344/N corn oil vehicle control rats is 4/1,091 (0.4%) and that for renal transitional cell neoplasms, 1/1,091 (0.1%) (Table F6). Thus, the renal lesions might have been compound related.

Increased incidences of testicular interstitial cell tumors in male rats were dose related. This neoplasm is commonly found in aging F344/N male rats, and the incidence of testicular interstitial cell tumors in the male rats dosed with 3-chloro-2-methylpropene was within the range of historical incidence (Table F7); the development of these neoplasms was probably not chemically related. Liver necrosis, seen in rats and mice in the 13-week studies, was observed only in a few dosed male rats in the 2-year studies.

Negative trends or lower incidences were observed in dosed male rats for adrenal pheochromocytomas, C-cell adenomas or carcinomas (combined) of the thyroid gland, and keratoacanthomas of the skin. Negative trends were observed also in the incidences of liver tumors in dosed male mice and of hemangiomas or hemangiosarcomas (combined) in dosed female mice. The biologic significance of these findings is not clear. The marginally lower incidence of C-cell adenomas or carcinomas (combined) of the thyroid gland in the dosed male rats may be due to the low survival rate.

Increases were observed in the incidences of inflammation of the nasal cavity in high dose male and female rats and mice and in the incidences of follicular cysts of the thyroid gland in

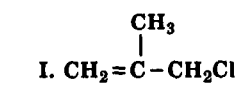
IV. DISCUSSION AND CONCLUSIONS

dosed female mice. The effects on the nasal cavity may be related to the dimethylvinyl chloride (1-chloro-2-methylpropene). Commercial 3-chloro-2-methylpropene normally contains about 5% dimethylvinyl chloride. This component is difficult to remove by distillation (Deichmann and Gerarde, 1969). The two lots of 3-chloro-2-methylpropene used in the present studies contained about 5% and 4% dimethylvinyl chloride, respectively. Thus, the male and female rats administered 75 or 150 mg/kg per day of 3-chloro-2-methylpropene received about 3 or 6 mg/kg per day of dimethylvinyl chloride, and male and female mice administered 100 or 200 mg/kg per day of 3-chloro-2-methylpropene received about 4 or 8 mg/kg per day of dimethylvinyl chloride.

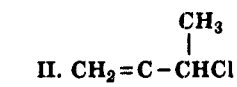
Dimethylvinyl chloride caused neoplasms in F344/N rats and $B6C3F_1$ mice (NTP, 1986b). Administered to rats at 100 or 200 mg/kg in corn oil by gavage, it induced carcinomas of the nasal cavity in male and female rats; metastasis to the brain was also observed. Squamous cell papillomas or carcinomas were found in the oral cavity, esophagus, and forestomach of dosed male and female rats. Mice administered dimethylvinyl chloride by gavage at 100 or 200 mg/kg had increased incidences of squamous cell carcinomas of the forestomach with metastasis to the lungs.

In the present studies of 3-chloro-2-methylpropene, neoplasms of the oral and nasopharyngeal areas were not observed in rats or mice; however, the high dose rats and mice developed inflammation of the nasal cavity (Tables C1, C2, D1, and D2). This inflammation may possibly be related to the effects of low doses of dimethylvinyl chloride. The presence of dimethylvinyl chloride in 3-chloro-2-methylpropene may have contributed to the development of forestomach neoplasms in rats and mice in the present studies. Future studies could help to delineate the effects of low doses of dimethylvinyl chloride on forestomach carcinogenesis in rats and mice.

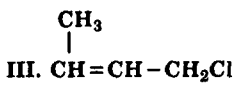
In general, studies suggest that chlorine substitution enhances the mutagenic and carcinogenic potential of propene and that monomethylation increases the alkylating potential, mutagenicity, and probably the carcinogenicity of allylic chlorides (Neudecker et al., 1980). Propene (propylene; $CH_2=CH\text{-}CH_3$) administered by inhalation was not carcinogenic in rats and mice (NTP, 1985) and was not mutagenic in *Escherichia coli* (Sandmeyer, 1981), whereas the structurally related 1-chloropropene ($CHCl=CH\text{-}CH_3$) and allyl chloride ($CH_2=CH\text{-}CH_2Cl$) administered orally induced forestomach tumors in mice (Van Duuren et al., 1979; NCI, 1978) and were mutagenic in Salmonella (McCoy et al., 1978; Eder et al., 1980; Neudecker et al., 1980). The mutagenicity of allyl chloride was enhanced by monomethylation: that is, the mutagenic potential of allyl chloride in Salmonella TA100 was less than that of 3-chloro-2-methylpropene (I); 3-chloro-1-butene (II) and 1-chloro-2-butene (III) were more potent mutagens than 3-chloro-2-methylpropene (Neudecker et al., 1980). Bimethylated allyl chlorides were slightly less mutagenic than were monomethylated allylic chlorides, and the mutagenic potencies of all of these compounds correlated well with their alkylating activities.



I. $CH_2=C(CH_3)-CH_2Cl$



II. $CH_2=C(CH_3)-CHCl$



III. $CH(CH_3)=CH-CH_2Cl$

Halogenated alkenes are thought to undergo epoxidation reactions that are catalyzed by the cytochrome P-450 dependent polysubstrate mono-oxygenase system. The resultant epoxides may react with tissue macromolecules, leading to toxicity, mutagenicity, and/or carcinogenicity (Bonse and Henschler, 1976; Anders, 1982; MacDonald, 1983). Halogenated hydrocarbons with more than two carbon atoms, such as allyl chloride, have also been postulated to be activated via the epoxidation pathway (Van Duuren, 1977).

The NTP found that 3-chloro-2-methylpropene required liver S9 to induce reverse mutation in Salmonella strains TA100 and TA1537

(Appendix L, Table L1). However, Neudecker et al. (1980) and Eder et al. (1982) reported that 3-chloro-2-methylpropene was a direct-acting mutagen in strain TA100 and that rat liver S9 greatly reduced its mutagenic effect. Results of the NTP mouse lymphoma tests (Table L2) and cytogenetic investigations (Tables L3 and L4) also suggest that 3-chloro-2-methylpropene is a direct-acting mutagen. The discrepancy between the findings of Neudecker et al. (1980) and Eder et al. (1982) and those of the NTP-sponsored tests in Salmonella may be due to differences in purity of the compound and in protocols. Taken as a whole, however, mutagenicity testing of 3-chloro-2-methylpropene indicates that it is a direct-acting mutagen in both bacterial and mammalian cells. This finding is consistent with the observation that the administration of 3-chloro-2-methylpropene by gavage to rats and mice induced neoplasms in the forestomach, the site of application.

Conclusion: Under the conditions of these 2-year gavage studies, there was *clear evidence of carcinogenicity** for 3-chloro-2-methylpropene as shown by the increased incidences of squamous cell neoplasms in the forestomach of male and female F344/N rats and male and female B6C3F$_1$ mice.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2. The public discussion regarding the interpretative conclusions is summarized on page 14.

V. REFERENCES

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
FIBROUS HISTIOCYTOMA, MALIGNANT		1 (2%)	
*SKIN	(50)	(50)	(50)
ADNEXAL ADENOMA	1 (2%)		
KERATOACANTHOMA	5 (10%)		
*SUBCUTANEOUS TISSUE	(50)	(50)	(50)
KERATOACANTHOMA	1 (2%)		
FIBROMA	1 (2%)	2 (4%)	2 (4%)
FIBROSARCOMA	3 (6%)		
FIBROUS HISTIOCYTOMA, MALIGNANT	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA			2 (4%)
SARCOMA, NOS, METASTATIC			1 (2%)
LIPOSARCOMA, METASTATIC	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS			1 (2%)
MALIG. LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
LEUKEMIA, MONONUCLEAR CELL	9 (18%)	2 (4%)	7 (14%)
#SPLEEN	(50)	(50)	(48)
FIBROMA	1 (2%)		
CIRCULATORY SYSTEM			
#SPLEEN	(50)	(50)	(48)
ANGIOSARCOMA			1 (2%)
#CARDIAC VALVE	(50)	(50)	(50)
LIPOSARCOMA	1 (2%)		
#CECUM	(49)	(49)	(47)
HEMANGIOMA	1 (2%)		
DIGESTIVE SYSTEM			
*TONGUE	(50)	(50)	(50)
PAPILLOMA, NOS			1 (2%)
#SALIVARY GLAND	(50)	(47)	(49)
SARCOMA, NOS		1 (2%)	
#LIVER	(50)	(50)	(48)
ADENOCARCINOMA, NOS, METASTATIC		1 (2%)	
NEOPLASTIC NODULE	2 (4%)		3 (6%)
HEPATOCELLULAR CARCINOMA			2 (4%)
SARCOMA, NOS, METASTATIC			1 (2%)
#PANCREAS	(50)	(50)	(48)
ACINAR-CELL ADENOMA	4 (8%)	1 (2%)	
#FORESTOMACH	(50)	(50)	(48)
PAPILLOMA, NOS	1	5	30 (63%)
SQUAMOUS CELL CARCINOMA			2 (4%)
#COLON	(49)	(49)	(47)
ADENOCARCINOMA, NOS		1 (2%)	
SARCOMA, NOS			1 (2%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(49)
TRANSITIONAL-CELL CARCINOMA			1 (2%)
TUBULAR-CELL ADENOMA		1 (2%)	
TUBULAR-CELL ADENOCARCINOMA		1 (2%)	1 (2%)
#URINARY BLADDER	(48)	(49)	(46)
TRANSITIONAL-CELL PAPILLOMA			1 (2%)
ENDOCRINE SYSTEM			
#ANTERIOR PITUITARY	(49)	(50)	(50)
ADENOMA, NOS	9 (18%)	8 (16%)	3 (6%)
#ADRENAL	(50)	(50)	(48)
CORTICAL ADENOMA	3 (6%)		1 (2%)
#ADRENAL MEDULLA	(50)	(50)	(48)
PHEOCHROMOCYTOMA	14 (28%)	8 (16%)	4 (8%)
PHEOCHROMOCYTOMA, MALIGNANT			1 (2%)
GANGLIONEUROMA		1 (2%)	
#THYROID	(49)	(48)	(48)
FOLLICULAR-CELL CARCINOMA			1 (2%)
C-CELL ADENOMA	3 (6%)	3 (6%)	
C-CELL CARCINOMA	4 (8%)	5 (10%)	
#PANCREATIC ISLETS	(50)	(50)	(48)
ISLET-CELL ADENOMA	3 (6%)	3 (6%)	2 (4%)
ISLET-CELL CARCINOMA	1 (2%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS	1 (2%)		
FIBROADENOMA		3 (6%)	1 (2%)
*PREPUTIAL GLAND	(50)	(50)	(50)
CARCINOMA, NOS	3 (6%)	4 (8%)	1 (2%)
ADENOMA, NOS	1 (2%)	1 (2%)	
#PROSTATE	(47)	(49)	(48)
ADENOMA, NOS	1 (2%)	1 (2%)	3 (6%)
#TESTIS	(50)	(50)	(48)
INTERSTITIAL-CELL TUMOR	36 (72%)	43 (86%)	43 (90%)
*SCROTUM	(50)	(50)	(50)
FIBROSARCOMA			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EAR,	(50)	(50)	(50)
NEUROFIBROSARCOMA		1 (2%)	
*ZYMBAL GLAND	(50)	(50)	(50)
CARCINOMA, NOS			1 (2%)
SQUAMOUS CELL CARCINOMA	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*BONE	(50)	(50)	(50)
OSTEOSARCOMA		1 (2%)	
*VERTEBRA	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)		

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*THORACIC CAVITY	(50)	(50)	(50)
SARCOMA, NOS		1 (2%)	
*ABDOMINAL CAVITY	(50)	(50)	(50)
LIPOMA		1 (2%)	
MESOTHELIOMA, NOS	1 (2%)	1 (2%)	
*TUNICA VAGINALIS	(50)	(50)	(50)
MESOTHELIOMA, NOS	1 (2%)	1 (2%)	2 (4%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
SARCOMA, NOS, INVASIVE		1 (2%)	
MESOTHELIOMA, NOS			1 (2%)
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	8	15	20
MORIBUND SACRIFICE	11	10	12
TERMINAL SACRIFICE	30	25	17
DOSING ACCIDENT	1		1
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	44	45	44
TOTAL PRIMARY TUMORS	115	102	120
TOTAL ANIMALS WITH BENIGN TUMORS	42	45	44
TOTAL BENIGN TUMORS	86	81	93
TOTAL ANIMALS WITH MALIGNANT TUMORS	20	16	17
TOTAL MALIGNANT TUMORS	25	19	21
TOTAL ANIMALS WITH SECONDARY TUMORS##	1	2	1
TOTAL SECONDARY TUMORS	1	2	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-- BENIGN OR MALIGNANT	3	2	6
TOTAL UNCERTAIN TUMORS	4	2	6

* NUMBER OF ANIMALS RECEIVING COMPLETE NECROPSY EXAMINATION; ALL GROSS LESIONS INCLUDING MASSES EXAMINED MICROSCOPICALLY.
** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# NUMBER OF ANIMALS EXAMINED MICROSCOPICALLY AT THIS SITE
SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
PAPILLOMA, NOS		1 (2%)	1 (2%)
*SUBCUTANEOUS TISSUE	(50)	(50)	(50)
SARCOMA, NOS			1 (2%)
FIBROMA		2 (4%)	4 (8%)
FIBROSARCOMA	1 (2%)	1 (2%)	
RHABDOMYOSARCOMA			†1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)		
C-CELL CARCINOMA, METASTATIC		1 (2%)	
SARCOMA, NOS, METASTATIC			1 (2%)
FIBROSARCOMA, METASTATIC		1 (2%)	
ENDOMETRIAL STROMAL SARCOMA, MET	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
LEUKEMIA, MONONUCLEAR CELL	16 (32%)	13 (26%)	10 (20%)
#THYMUS	(41)	(46)	(48)
SQUAMOUS CELL CARCINOMA			1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
*TONGUE	(50)	(50)	(50)
PAPILLOMA		1 (2%)	
#LIVER	(50)	(50)	(50)
NEOPLASTIC NODULE	2 (4%)	1 (2%)	
#PANCREAS	(50)	(50)	(50)
ACINAR-CELL ADENOMA	1 (2%)		2 (4%)
#FORESTOMACH	(50)	(50)	(50)
PAPILLOMA, NOS	1 (2%)	1 (2%)	10 (20%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#ANTERIOR PITUITARY	(50)	(50)	(49)
CARCINOMA, NOS	1 (2%)	1 (2%)	1 (2%)
ADENOMA, NOS	19 (38%)	21 (42%)	20 (41%)
#ADRENAL	(50)	(50)	(50)
CORTICAL ADENOMA	3 (6%)	1 (2%)	3 (6%)

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#ADRENAL MEDULLA	(50)	(50)	(50)
PHEOCHROMOCYTOMA	4 (8%)	1 (2%)	4 (8%)
#THYROID	(50)	(48)	(49)
FOLLICULAR-CELL ADENOMA		2 (4%)	2 (4%)
FOLLICULAR-CELL CARCINOMA	1 (2%)	1 (2%)	1 (2%)
C-CELL ADENOMA	6 (12%)	1 (2%)	
C-CELL CARCINOMA	2 (4%)	5 (10%)	5 (10%)
#PANCREATIC ISLETS	(50)	(50)	(50)
ISLET-CELL CARCINOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOMA, NOS	4 (8%)	2 (4%)	3 (6%)
ADENOCARCINOMA, NOS	2 (4%)	1 (2%)	1 (2%)
CYSTADENOMA, NOS	1 (2%)	1 (2%)	
FIBROADENOMA	14 (28%)	15 (30%)	10 (20%)
*CLITORAL GLAND	(50)	(50)	(50)
CARCINOMA, NOS	1 (2%)	1 (2%)	1 (2%)
CYSTADENOMA, NOS			1 (2%)
#UTERUS	(50)	(50)	(49)
ADENOCARCINOMA, NOS	1 (2%)		
ENDOMETRIAL STROMAL POLYP	7 (14%)	9 (18%)	8 (16%)
ENDOMETRIAL STROMAL SARCOMA	1 (2%)	2 (4%)	
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(49)
EPENDYMOMA	1 (2%)		
SPECIAL SENSE ORGANS			
*ZYMBAL GLAND	(50)	(50)	(50)
CARCINOMA, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	5	5	10
MORIBUND SACRIFICE	14	10	12
TERMINAL SACRIFICE	31	32	26
DOSING ACCIDENT		1	2
ACCIDENTALLY KILLED, NOS		2	

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	43	42	41
TOTAL PRIMARY TUMORS	90	85	90
TOTAL ANIMALS WITH BENIGN TUMORS	37	36	35
TOTAL BENIGN TUMORS	61	58	68
TOTAL ANIMALS WITH MALIGNANT TUMORS	23	21	20
TOTAL MALIGNANT TUMORS	28	26	22
TOTAL ANIMALS WITH SECONDARY TUMORS##	2	2	2
TOTAL SECONDARY TUMORS	2	2	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN--BENIGN OR MALIGNANT	1	1	
TOTAL UNCERTAIN TUMORS	1	1	

* NUMBER OF ANIMALS RECEIVING COMPLETE NECROPSY EXAMINATION; ALL GROSS LESIONS INCLUDING MASSES EXAMINED MICROSCOPICALLY.
** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# NUMBER OF ANIMALS EXAMINED MICROSCOPICALLY AT THIS SITE
SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN
† THE PWG DIAGNOSED THIS TUMOR AS A FIBROSARCOMA.

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE: VEHICLE CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	083	105	105	095	105	055	105	105	098	102	105	105	105	105	105	095	105	105	105	074	105				
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adnexal adenoma																							X		
Keratoacanthoma				X						X															
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																	X								
Fibroma																									
Fibrosarcoma	X																X								
Fibrous histiocytoma, malignant																							X		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liposarcoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma										X															
Lymph nodes	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	–	+	+	+	+	+	–	+	–	–	+	+	+	–	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liposarcoma																									
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule						X										X									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar-cell adenoma										X				X			X					X			
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS					X																				
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma								X																	
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS										X				X					X						
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma								X						X											
Pheochromocytoma		X	X					X	X							X									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																									
C-cell carcinoma													X			X				X					
Parathyroid	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	–	+	+	+	–	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell adenoma												X				X									
Islet-cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																						X			
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial-cell tumor	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		X
Prostate	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+
Adenoma, NOS				X																					
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS													X		X										
Adenoma, NOS							X																		
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma			X																						
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS	X																								
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell									X			X	X		X								X		

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	105	064	098	047	058	055	055	054	011	095	036	000	055	096	055	055	044	054	036	055	058	055	055	055	055	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adnexal adenoma																										1
Keratoacanthoma	X	X	X																							5
Subcutaneous tissue	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Keratoacanthoma																										1
Fibroma			X																							1
Fibrosarcoma		X																								3
Fibrous histiocytoma, malignant																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liposarcoma, metastatic									X																	1
Trachea	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	–	+	–	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liposarcoma									X																	1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar-cell adenoma																										4
Esophagus	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma, NOS																										1
Small intestine	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS							X							X	X	X	X							X		9
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma															X											3
Pheochromocytoma	X		X			X	X	X	X							X		X		X						14
Thyroid	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell adenoma													X		X								X			3
C-cell carcinoma																									X	4
Parathyroid	+	+	+	–	+	+	+	+	+	+	–	–	+	+	+	+	–	+	–	+	+	+	+	+	–	40
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet-cell adenoma									X																	3
Islet-cell carcinoma																							X			1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	N	*50
Adenocarcinoma, NOS																										1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial-cell tumor	X		X			X	X	X	X	X			X		X			X		X	X		X		X	36
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS																										1
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS									X																	3
Adenoma, NOS																					X					2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	+	N	N	N	N	N	N	+	+	N	N	N	N	+	N	+	N	N	+	N	+	N	*50
Sarcoma, NOS																										1
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, NOS						X																				1
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS						X																				1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell					X		X								X					X						9

* Animals Necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE: LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	080	101	105	093	105	101	105	105	105	105	098	101	056	074	105	058	092	105	084	080	101	066	064	088
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	N	N
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	–	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	–	+	
Sarcoma, NOS															X										
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenocarcinoma, NOS, metastatic																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Acinar-cell adenoma															X										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Papilloma, NOS											X	X													
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Large intestine	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenocarcinoma, NOS																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Tubular-cell adenoma																				X					
Tubular-cell adenocarcinoma																									
Urinary bladder	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma, NOS										X	X			X		X		X							
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Pheochromocytoma									X						X										
Ganglioneuroma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	
C-cell adenoma								X																	
C-cell carcinoma										X		X													
Parathyroid	–	+	+	+	+	+	+	+	+	–	+	+	–	+	+	–	+	+	+	–	+	–	+	–	
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Islet-cell adenoma		X						X																	
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Interstitial-cell tumor	X	X	X	X	X	X	X	X	X	X	X	X			X		X	X	X	X		X	K		X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Adenoma, NOS							X																		
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS							X			X															
Adenoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
SPECIAL SENSE ORGANS																									
Ear	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Neurofibrosarcoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	+	N	N	N	N	N	N	N	N	
Osteosarcoma																									
BODY CAVITIES																									
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Sarcoma, NOS																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Lipoma				X																					
Mesothelioma, NOS									X																
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Mesothelioma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
Sarcoma, NOS, invasive																									
Fibrous histiocytoma, malignant																					X				
Malig. lymphoma, histiocytic type				X																					
Leukemia, mononuclear cell									X																

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE
(Continued)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	091	080	083	105	105	056	105	105	105	105	105	105	095	105	105	095	105	083	105	105	093	105	105	079		TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+		*50
Fibroma									X											X						2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+		47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+		49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Thymus	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		46
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Sarcoma, NOS																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adenocarcinoma, NOS, metastatic									X																	1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Acinar-cell adenoma																										1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Papilloma, NOS	X							X													X					5
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Adenocarcinoma, NOS									X																	1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Tubular-cell adenoma																										1
Tubular-cell adenocarcinoma														X												1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adenoma, NOS	X		X																				X			8
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Pheochromocytoma								X	X	X								X				X		X		8
Ganglioneuroma													X													1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
C-cell adenoma												X												X		3
C-cell carcinoma											X		X			X										5
Parathyroid	+	–	+	+	+	+	–	+	–	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+		38
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Islet-cell adenoma											X															3
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		*50
Fibroadenoma					X										X	X										3
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Interstitial-cell tumor	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		43
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Adenoma, NOS																										1
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		*50
Carcinoma, NOS																X			X							4
Adenoma, NOS																				X						1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
SPECIAL SENSE ORGANS																										
Ear	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		*50
Neurofibrosarcoma									X																	1
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		*50
Osteosarcoma														X												1
BODY CAVITIES																										
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		*50
Sarcoma, NOS	X																									1
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		*50
Lipoma																										1
Mesothelioma, NOS																										1
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		*50
Mesothelioma, NOS					X																					1
ALL OTHER SYSTEMS																										
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		*50
Sarcoma, NOS, invasive	X																									1
Fibrous histiocytoma, malignant																										1
Malig lymphoma, histiocytic type																										1
Leukemia, mononuclear cell																								X		2

* Animals Necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE: HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	084	105	094	084	103	101	105	101	087	101	098	103	101	105	098	105	081	102	035	055	055	105	052	105	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																X									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Sarcoma, NOS, metastatic									X																
Trachea	+	+	+	–	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Angiosarcoma																									
Lymph nodes	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	–	+	+	–	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papilloma, NOS																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule			X				X									X									
Hepatocellular carcinoma								X																X	
Sarcoma, NOS, metastatic									X																
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS	X	X		X	X	X	X	X	X	X	X		X	X	X	X		X			X		X		X
Squamous cell carcinoma													X					X							
Small intestine	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS									X																
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional-cell carcinoma																									
Tubular-cell adenocarcinoma																									
Urinary bladder	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional-cell papilloma																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma								X																	
Pheochromocytoma		X				X				X															
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular-cell carcinoma																									
Parathyroid	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	–	–	+	+	+	+	+	–	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial-cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X
Prostate	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS														X											
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																						K			
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS													X												
Malignant lymphoma, NOS																	X								
Leukemia, mononuclear cell						X																	X		
Scrotum NOS																									
Fibrosarcoma			X																						

+	Tissue Examined Microscopically		No Tissue Information Submitted
–	Required Tissue Not Examined Microscopically	C	Necropsy, No Histology Due To Protocol
X	Tumor Incidence	A	Autolysis
N	Necropsy, No Autolysis, No Microscopic Examination	M	Animal Missing
S	Animal Missexed	B	No Necropsy Performed

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	086	074	099	105	047	056	026	087	052	011	011	105	074	081	011	083	105	105	105	105	105	105	103	103	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	N	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																		X								2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X					X																		2
Sarcoma, NOS, metastatic																										1
Trachea	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	45
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	48
Angiosarcoma										X																1
Lymph nodes	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	45
Thymus	–	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papilloma, NOS																				X						1
Salivary gland	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	48
Neoplastic nodule																										3
Hepatocellular carcinoma																										2
Sarcoma, NOS, metastatic																										1
Bile duct	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	48
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	46
Stomach	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	48
Papilloma, NOS			X	X		X	X			X	X						X	X	X	X	X	X				30
Squamous cell carcinoma																										2
Small intestine	+	+	+	+	+	–	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	46
Large intestine	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	47
Sarcoma, NOS																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	49
Transitional-cell carcinoma																									X	1
Tubular-cell adenocarcinoma																									X	1
Urinary bladder	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	46
Transitional-cell papilloma			X																							1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																		X	X						X	3
Adrenal	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	48
Cortical adenoma																										1
Pheochromocytoma								X																		4
Pheochromocytoma, malignant							X																			1
Thyroid	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	48
Follicular-cell carcinoma											X															1
Parathyroid	–	–	+	+	–	+	+	+	+	+	–	+	+	+	–	+	+	+	+	–	+	+	+	+	+	39
Pancreatic islets	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	48
Islet-cell adenoma																	X							X		2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	*50
Fibroadenoma																X										1
Testis	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	48
Interstitial-cell tumor	X	X	X	X		X	X		X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	43
Prostate	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS											X								X							3
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS	X																									1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS										X																1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS																					X					2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, NOS																										1
Malignant lymphoma, NOS																										1
Leukemia, mononuclear cell			X					X		X												X			X	7
Scrotum NOS																										
Fibrosarcoma																										1

* Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE: VEHICLE CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	088	105	097	072	088	101	105	105	105	105	105	105	100	105	105	105	049	105	074	105	105	105	078	105	094
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+
Fibrosarcoma																				X					
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic								X																	
Endometrial stromal sarcoma, meta																	X								
Trachea	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	–	+	+	+	+	+	–	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar-cell adenoma																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS	X	X	X					X			X	X		X	X	X							X	X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma														X					X						
Pheochromocytoma									X							X									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular-cell carcinoma																									
C-cell adenoma										X					X					X				X
C-cell carcinoma														X											
Parathyroid	+	+	+	+	+	+	+	–	+	+	+	–	–	+	+	+	–	+	+	+	+	–	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+
Adenoma, NOS										X										X					X
Adenocarcinoma, NOS																									X
Cystadenoma, NOS																									
Fibroadenoma	X					X		X								X							X	X	
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS								X																	
Endometrial stromal polyp				X		X			X																
Endometrial stromal sarcoma																	X								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ependymoma																									
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell	X		X		X	X	X	X		X						X				X					X

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0268	0327	0228	0290	0231	0232	0233	0234	0235	0236	0237	0238	0239	0240	0241	0242	0243	0244	0245	0246	0247	0248	0249	0250	TOTAL
WEEKS ON STUDY	0799	0921	1005	1005	1008	1005	0871	0877	1005	0922	1005	0905	1005	1005	0929	1005	1005	0886	1005	1005	1005	1003	1005	1005	TISSUES TUMORS
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																									1
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic																									1
Endometrial stromal sarcoma, meta																									1
Trachea	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	–	–	+	–	+	+	+	+	+	+	+	+	+	46
Thymus	+	+	–	–	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	41
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule				X			X																		2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar-cell adenoma																						X			1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma, NOS																						X			1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS						X																			1
Adenoma, NOS			X					X				X	X		X		X					X		X	19
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma						X																			3
Pheochromocytoma		X		X																					4
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular-cell carcinoma																X									1
C-cell adenoma														X	X										6
C-cell carcinoma																		X							2
Parathyroid	+	+	+	–	–	+	–	+	+	–	+	–	+	+	+	+	–	+	+	+	+	+	+	+	39
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS		X																							4
Adenocarcinoma, NOS															X										2
Cystadenoma, NOS															X										1
Fibroadenoma					X	X					X						X			X	X		X	X	14
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS			X																						1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																									1
Endometrial stromal polyp			X							X		X									X				7
Endometrial stromal sarcoma																									1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ependymoma												X													1
SPECIAL SENSE ORGANS																									
Zymbal gland	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS	X																								1
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell		X				X		X					X							X	X				16

* Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE: LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	104	105	093	105	105	105	083	102	095	035	105	105	105	105	105	105	105	090	105	070	105	086	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+
Papilloma, NOS																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+
Fibroma																									
Fibrosarcoma							X																		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell carcinoma, metastatic														X											
Fibrosarcoma, metastatic							X																		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral Cavity																									
Papilloma, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS				X																					
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS											X														
Adenoma, NOS	X	X	X				X	X	X						X	X							X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																X									
Pheochromocytoma						X																			
Thyroid	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
Follicular-cell adenoma				X																					
Follicular-cell carcinoma																X									
C-cell adenoma			X																						
C-cell carcinoma														X					X						
Parathyroid	–	–	+	+	+	–	–	+	+	+	+	+	–	–	+	+	+	–	–	+	+	–	+	+	–
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS											X														
Adenocarcinoma, NOS																									
Cystadenoma, NOS																X									
Fibrosarcoma																									
Fibroadenoma														X		X		X		X				X	
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp							X								X			X		X					
Endometrial stromal sarcoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell					X								X		X		X			X					

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	102	105	105	002	094	105	105	105	105	105	087	092	044	105	058	105	105	088	093	105	105	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	*50
Papilloma, NOS																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma								X						X												2
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell carcinoma, metastatic																										1
Fibrosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	46
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral Cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
Papilloma, NOS																								X		1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																								X		1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																										1
Adenoma, NOS		X	X		X	X	X	X						X			X		X				X	X	X	21
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																										1
Pheochromocytoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular-cell adenoma																				X						2
Follicular-cell carcinoma																										1
C-cell adenoma																										1
C-cell carcinoma						X	X														X					5
Parathyroid	–	–	+	+	+	+	–	–	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	–	+	32
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet-cell carcinoma						X																				1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS										X																2
Adenocarcinoma, NOS		X																								1
Cystadenoma, NOS																										1
Fibrosarcoma																X										1
Fibroadenoma		X				X		X	X					X		X	X			X	X				X	15
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS							X																			1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp						X										X	X					X			X	9
Endometrial stromal sarcoma			X									X														2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell	X						X	X			X	X						X			X				X	13

* Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE: HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	027	105	105	103	105	106	106	105	105	105	102	096	090	083	083	091	093	105	105	105	082	105	088	105	077
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+
Papilloma, NOS																								X	
Subcutaneous tissue	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+
Sarcoma, NOS																							X		
Fibroma											X														
Rhabdomyosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic					X																				
Sarcoma, NOS, metastatic																							X		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Thymus	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma					X																				
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar-cell adenoma																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS	X			X					X											X					
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS															X										
Adenoma, NOS			X	X		X		X		X	X		X				X	X			X			X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma		X																							
Pheochromocytoma			X																						
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular-cell adenoma																									
Follicular-cell carcinoma																									
C-cell carcinoma			X					X																	
Parathyroid	+	–	+	–	+	+	+	–	+	–	+	–	+	–	–	+	+	+	–	+	+	+	+	–	–
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS			X																						
Adenocarcinoma, NOS											X														
Fibroadenoma	X			X		X													X						
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																						X			
Cystadenoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp				X				X												X					
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell					X				X				X			X	X						X		

+ : Tissue Examined Microscopically
– : Required Tissue Not Examined Microscopically
X : Tumor Incidence
N : Necropsy, No Autolysis, No Microscopic Examination
S : Animal Missexed
: : No Tissue Information Submitted
C : Necropsy, No Histology Due To Protocol
A : Autolysis
M : Animal Missing
B : No Necropsy Performed

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	069	105	066	096	105	105	068	096	072	105	105	105	105	083	105	067	105	105	001	095	105	105	091	105		TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	N	+	N	+	+	+	N	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+		*50
Papilloma, NOS																										1
Subcutaneous tissue	N	+	N	+	+	+	N	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+		*50
Sarcoma, NOS																										1
Fibroma																				X	X		X			4
Rhabdomyosarcoma				X																						1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Squamous cell carcinoma, metastat																										1
Sarcoma, NOS, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+		49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymph nodes	+	+	+	–	+	+	+	–	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+		45
Thymus	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Squamous cell carcinoma																										1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Acinar-cell adenoma		X																		X						2
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Papilloma, NOS		X	X								X					X	X								K	10
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Large intestine	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Carcinoma, NOS																										1
Adenoma, NOS		X			X			X		X	X		X							X		X		X	20
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Cortical adenoma																				X			X			3
Pheochromocytoma					X													X		X						4
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+		49
Follicular-cell adenoma								X						X												2
Follicular-cell carcinoma																						X				1
C-cell carcinoma						X											X				X					5
Parathyroid	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	–	+	+	+	+	+		37
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+		*50
Adenoma, NOS													X												X	3
Adenocarcinoma, NOS																										1
Fibroadenoma				X	X					X		X	X							X						10
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		*50
Carcinoma, NOS																										1
Cystadenoma, NOS																				X						1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+		49
Endometrial stromal polyp										X	X			X	X					X						8
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		*50
Leukemia, mononuclear cell								X						X						X			X			10

* Animals Necropsied

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA			1 (2%)
*SUBCUTANEOUS TISSUE	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)	2 (4%)	2 (4%)
SARCOMA, NOS, INVASIVE		1 (2%)	
FIBROMA	1 (2%)		3 (6%)
LEIOMYOSARCOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(48)
HEPATOCELLULAR CARCINOMA, METAST			2 (4%)
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (6%)	4 (8%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	4 (8%)	6 (12%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	4 (8%)	2 (4%)	2 (4%)
CIRCULATORY SYSTEM			
*SUBCUTANEOUS TISSUE	(50)	(50)	(50)
HEMANGIOMA			1 (2%)
HEMANGIOSARCOMA	1 (2%)		
#SPLEEN	(48)	(46)	(50)
HEMANGIOSARCOMA		2 (4%)	2 (4%)
#HEART	(49)	(50)	(50)
HEMANGIOSARCOMA, METASTATIC			1 (2%)
#LIVER	(50)	(50)	(50)
HEMANGIOSARCOMA	1 (2%)		
HEMANGIOSARCOMA, METASTATIC		1 (2%)	1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)
HEPATOCELLULAR ADENOMA	4 (8%)	7 (14%)	2 (4%)
HEPATOCELLULAR CARCINOMA	19 (38%)	10 (20%)	11 (22%)
ALVEOLAR/BRONCHIOLAR CA, METASTA		1 (2%)	
LIPOSARCOMA		1 (2%)	
#FORESTOMACH	(49)	(49)	(49)
SQUAMOUS CELL PAPILLOMA	3 (6%)	19 (39%)	30 (61%)
SQUAMOUS CELL CARCINOMA		5 (10%)	7 (14%)
LEIOMYOSARCOMA			1 (2%)
URINARY SYSTEM			
NONE			

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(45)	(47)	(47)
ADENOMA, NOS			1 (2%)
#ADRENAL	(48)	(50)	(49)
CORTICAL ADENOMA		2 (4%)	
#ADRENAL MEDULLA	(48)	(50)	(49)
PHEOCHROMOCYTOMA		2 (4%)	
#THYROID	(45)	(47)	(47)
FOLLICULAR-CELL ADENOMA	1 (2%)		2 (4%)
FOLLICULAR-CELL CARCINOMA		1 (2%)	
#PARATHYROID	(25)	(23)	(26)
ADENOMA, NOS		1 (4%)	
#PANCREATIC ISLETS	(47)	(49)	(50)
ISLET-CELL CARCINOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
#TESTIS	(50)	(50)	(50)
INTERSTITIAL-CELL TUMOR			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)		
PAPILLARY ADENOMA		2 (4%)	3 (6%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, INVASIVE			1 (2%)
SQUAMOUS CELL CARCINOMA, METASTA		2 (4%)	1 (2%)
SARCOMA, NOS, METASTATIC		2 (4%)	
SARCOMA, NOS, UNC PRIM OR META		1 (2%)	
LEIOMYOSARCOMA, INVASIVE			1 (2%)
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	14	5	7
MORIBUND SACRIFICE	9	7	10
TERMINAL SACRIFICE	26	37	32
DOSING ACCIDENT	1		
ACCIDENTALLY KILLED, NDA			1
ACCIDENTALLY KILLED, NOS		1	

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	33	42	45
TOTAL PRIMARY TUMORS	44	68	72
TOTAL ANIMALS WITH BENIGN TUMORS	13	26	36
TOTAL BENIGN TUMORS	13	37	46
TOTAL ANIMALS WITH MALIGNANT TUMORS	28	27	23
TOTAL MALIGNANT TUMORS	31	30	26
TOTAL ANIMALS WITH SECONDARY TUMORS##		6	8
TOTAL SECONDARY TUMORS		7	8
TOTAL ANIMALS WITH TUMORS UNCERTAIN-- BENIGN OR MALIGNANT			1
TOTAL UNCERTAIN TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-- PRIMARY OR METASTATIC		1	
TOTAL UNCERTAIN TUMORS		1	

* NUMBER OF ANIMALS RECEIVING COMPLETE NECROPSY EXAMINATION; ALL GROSS LESIONS INCLUDING MASSES EXAMINED MICROSCOPICALLY.
** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# NUMBER OF ANIMALS EXAMINED MICROSCOPICALLY AT THIS SITE
SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		2	2
ANIMALS NECROPSIED	50	48	44
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	48	44
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(48)	(44)
SARCOMA, NOS			1 (2%)
*SUBCUTANEOUS TISSUE	(50)	(48)	(44)
MALIGNANT MELANOMA	1 (2%)		
SARCOMA, NOS	1 (2%)		
LIPOSARCOMA	1 (2%)		1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(48)	(43)
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (6%)	2 (4%)	3 (7%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(48)	(44)
MALIGNANT LYMPHOMA, NOS	8 (16%)	7 (15%)	6 (14%)
GRANULOCYTIC LEUKEMIA	2 (4%)		2 (5%)
#SPLEEN	(50)	(48)	(43)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
#MESENTERIC L. NODE	(39)	(32)	(28)
MALIGNANT LYMPHOMA, NOS		1 (3%)	
#CECUM	(49)	(48)	(42)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
#THYMUS	(42)	(43)	(36)
ADENOCARCINOMA, NOS, METASTATIC		1 (2%)	
CIRCULATORY SYSTEM			
*SUBCUTANEOUSANEOUS TISSUE	(50)	(48)	(44)
HEMANGIOSARCOMA, METASTATIC	1 (2%)		
#SPLEEN	(50)	(48)	(43)
HEMANGIOSARCOMA	1 (2%)		
#LIVER	(50)	(48)	(44)
HEMANGIOMA	1 (2%)		
#UTERUS	(50)	(48)	(44)
HEMANGIOMA	2 (4%)		
LYMPHANGIOMA	1 (2%)		
#OVARY	(49)	(48)	(44)
HEMANGIOMA	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(50)	(48)	(44)
HEPATOCELLULAR ADENOMA	2 (4%)	3 (6%)	1 (2%)
HEPATOCELLULAR CARCINOMA	2 (4%)		
#FORESTOMACH	(50)	(48)	(44)
SQUAMOUS CELL PAPILLOMA		15 (31%)	29 (66%)
SQUAMOUS CELL CARCINOMA		1 (2%)	2 (5%)
#CECUM	(49)	(48)	(42)
LEIOMYOSARCOMA			1 (2%)
URINARY SYSTEM			
#URINARY BLADDER	(49)	(43)	(38)
LIPOSARCOMA, INVASIVE			1 (3%)

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY INTERMEDIA	(46)	(47)	(39)
ADENOMA, NOS			1 (3%)
#ANTERIOR PITUITARY	(46)	(47)	(39)
CHROMOPHOBE ADENOMA	9 (20%)	11 (23%)	5 (13%)
#ADRENAL	(49)	(48)	(44)
CORTICAL ADENOMA	1 (2%)	1 (2%)	
#THYROID	(44)	(47)	(38)
FOLLICULAR-CELL ADENOMA	1 (2%)	1 (2%)	
#PANCREATIC ISLETS	(49)	(48)	(41)
ISLET-CELL ADENOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(48)	(44)
ADENOCARCINOMA, NOS	1 (2%)	4 (8%)	1 (2%)
#UTERUS	(50)	(48)	(44)
ADENOCARCINOMA, NOS		2 (4%)	
ENDOMETRIAL STROMAL POLYP	1 (2%)		2 (5%)
ENDOMETRIAL STROMAL SARCOMA		1 (2%)	
#OVARY	(49)	(48)	(44)
ADENOCARCINOMA, NOS, INVASIVE		1 (2%)	
LUTEOMA			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(50)	(48)	(43)
ASTROCYTOMA			1 (2%)
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(48)	(44)
PAPILLARY ADENOMA	1 (2%)		1 (2%)
MUSCULOSKELETAL SYSTEM			
*SKULL	(50)	(48)	(44)
OSTEOSARCOMA		1 (2%)	
*LUMBAR VERTEBRA	(50)	(48)	(44)
SARCOMA, NOS			1 (2%)
*RIB	(50)	(48)	(44)
OSTEOSARCOMA	1 (2%)		
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(48)	(44)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)
OSTEOSARCOMA, METASTATIC	1 (2%)	1 (2%)	

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	5	2	8
MORIBUND SACRIFICE	8	3	7
SCHEDULED SACRIFICE			4
TERMINAL SACRIFICE	37	43	27
DOSING ACCIDENT			1
ACCIDENTALLY KILLED, NDA			1
ANIMAL MISSING		2	2
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	28	32	37
TOTAL PRIMARY TUMORS	43	51	59
TOTAL ANIMALS WITH BENIGN TUMORS	17	27	32
TOTAL BENIGN TUMORS	23	34	43
TOTAL ANIMALS WITH MALIGNANT TUMORS	17	17	14
TOTAL MALIGNANT TUMORS	20	17	16
TOTAL ANIMALS WITH SECONDARY TUMORS##	1	2	2
TOTAL SECONDARY TUMORS	1	3	2

* NUMBER OF ANIMALS RECEIVING COMPLETE NECROPSY EXAMINATION; ALL GROSS LESIONS INCLUDING MASSES EXAMINED MICROSCOPICALLY.
** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# NUMBER OF ANIMALS EXAMINED MICROSCOPICALLY AT THIS SITE
SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE: VEHICLE CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	101	105	105	105	105	105	099	104	105	102	105	105	028	086	023	105	105	102	105	105	030	099	090
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Fibroma													X												
Leiomyosarcoma			X																						
Hemangiosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																			X						
Alveolar/bronchiolar carcinoma							X							X											
Trachea	+	–	–	+	+	+	+	–	+	–	–	+	+	+	–	+	–	–	–	+	+	–	+	+	–	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Lymph nodes	–	+	+	–	–	–	+	+	+	+	–	+	+	+	–	+	+	–	–	+	+	+	–	+	+	–
Thymus	–	+	+	+	+	+	+	–	–	+	+	–	–	+	+	–	+	+	+	–	+	+	+	+	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma							X	X																	
Hepatocellular carcinoma		X								X	X		X	X		X								X	
Hemangiosarcoma												X													
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	+	+	+	+	+	+	+	+	+	+	+	N	N	N	N	+	+	+	+	+	N	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma									X													X			
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	+	+	+	+	+	–	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	–	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+
Follicular-cell adenoma																									
Parathyroid	+	+	+	–	–	+	+	+	–	–	+	+	+	+	+	–	–	–	+	–	–	–	–	–	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS										X															
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS									X											X					

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	068	067	095	093	105	083	105	080	105	095	105	105	104	105	088	105	022	100	093	028	105	105	105	099	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																			X							1
Fibroma																										1
Leiomyosarcoma																										1
Hemangiosarcoma													X													1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X							X													3
Alveolar/bronchiolar carcinoma					X	X																				4
Trachea	–	–	+	–	–	–	–	+	–	–	+	–	–	+	–	–	–	–	–	+	+	–	–	–	–	21
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	48
Lymph nodes	–	+	+	+	–	+	+	+	–	+	+	–	–	+	+	–	+	+	+	–	+	+	–			32
Thymus	+	+	+	+	+	–	+	+	+	+	–	+	+	+	–	–	–	+	+	–	+	+	–	+		34
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma										X									X							4
Hepatocellular carcinoma		X		X				X		X		X	X	X	X		X				X			X	X	19
Hemangiosarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	+	N	+	N	+	N	+	+	+	+	+	+	N	+	N	+	+	+	N	+	+	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+		47
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma									X																	3
Small intestine	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	–	+	+	+	–	+		41
Large intestine	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+		45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	–	+		45
Follicular-cell adenoma					X																					1
Parathyroid	+	–	+	+	–	–	–	+	+	+	+	+	–	+	–	–	–	–	+	+	–	–	–	–	+	25
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS													X		X											4

* Animals Necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE: LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	094	105	105	105	105	105	105	105	105	105	105	105	105	105	099	100	105	105	105	076	105	105	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Sarcoma, NOS, invasive																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma		X																			X		X		
Alveolar/bronchiolar carcinoma					X		X													X					
Trachea	+	+	+	+	+	+	+	−	+	−	−	+	−	−	−	+	+	−	+	−	+	−	+	+	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Spleen	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph nodes	+	−	+	+	−	+	+	+	−	+	+	−	−	−	+	+	+	+	+	+	+	+	−	−	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	−	−	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma	X	X																		X					
Hepatocellular carcinoma	X		X							X				X									X	X	
Alveolar/bronchiolar ca, metastatic							X																		
Liposarcoma																							X		
Hemangiosarcoma, metastatic																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	N	+	+	N	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma			X	X		X		X			X		X		X				X	X			X	X	
Squamous cell carcinoma																X						X			
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	−	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma									X																
Thyroid	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular-cell carcinoma																									
Parathyroid	+	+	−	+	+	+	+	−	+	−	−	−	−	−	−	+	+	+	+	−	+	+	−	+	+
Adenoma, NOS																									
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Islet-cell carcinoma															X										
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary adenoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma, metastat																						X			
Sarcoma, NOS, metastatic																									
Sarcoma, NOS, unc prim or meta																									
Malignant lymphoma, NOS															X										X

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	105	105	078	105	105	105	101	104	105	105	105	083	105	002	098	105	105	104	105	105	104	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS								X				X														2
Sarcoma, NOS, invasive												X														1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X																				4
Alveolar/bronchiolar carcinoma		X																				X		X		6
Trachea	–	–	–	+	+	+	–	–	–	+	+	–	+	–	–	+	+	–	–	+	–	–	+	+	+	27
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Hemangiosarcoma									X													X				2
Lymph nodes	+	+	–	–	+	–	+	+	+	+	+	+	–	+	+	–	–	+	–	+	+	+	–	+	–	33
Thymus	+	+	–	+	+	+	–	+	+	+	+	–	+	+	–	+	+	+	+	+	–	–	+	+	+	40
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma						X					X					X							X			7
Hepatocellular carcinoma							X			X								X				X				10
Alveolar/bronchiolar ca, metastat																										1
Liposarcoma																										1
Hemangiosarcoma, metastatic									X																	1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	N	+	N	+	N	N	+	N	+	+	+	+	+	+	+	N	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma					X	X	X									X			X	X	X			X		19
Squamous cell carcinoma	X												X		X											5
Small intestine	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	47
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma											X					X										2
Pheochromocytoma						X																				2
Thyroid	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	47
Follicular-cell carcinoma											X															1
Parathyroid	+	–	+	–	+	+	+	–	–	–	+	–	–	–	–	+	–	–	–	–	–	–	+	–	+	23
Adenoma, NOS											X															1
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet-cell carcinoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	48
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papillary adenoma									X												X					2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma, metastat															X											2
Sarcoma, NOS, metastatic								X				X														2
Sarcoma, NOS, unc prim or meta																				X						1
Malignant lymphoma, NOS																										2

* Animals Necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE: HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	104	105	096	086	105	105	095	102	105	105	105	105	105	105	105	068	105	105	105	105	102	096	104	101	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS			X																			X			
Fibroma						X																	X		
Hemangioma																	X								
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic			X																						
Alveolar/bronchiolar adenoma														X											
Alveolar/bronchiolar carcinoma							X																		
Trachea	–	+	+	+	–	–	+	+	+	–	–	–	–	–	+	–	+	+	+	+	–	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X																					
Lymph nodes	–	+	+	+	+	+	–	+	–	+	+	–	–	–	+	+	–	–	–	–	+	+	+	+	+
Thymus	–	+	–	+	+	+	+	–	+	+	+	+	+	+	+	–	–	+	+	+	+	–	+	–	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic																									
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic															X										
Hepatocellular adenoma		X																							
Hepatocellular carcinoma			X					X	X	X										X			X		X
Hemangiosarcoma, metastatic				X																					
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	–	+	+	+	+	+	–	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma				X	X	X	X	X			X	X	X	X		X		X	X	X	X	X	X	X	X
Squamous cell carcinoma													X		X		X								
Leiomyosarcoma																								X	
Small intestine	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																X									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular-cell adenoma					X																X				
Parathyroid	–	+	+	+	–	+	+	–	–	–	+	–	–	+	–	+	–	+	+	–	+	+	+	–	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial-cell tumor																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary adenoma																								X	
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma, invasive																									
Squamous cell carcinoma, metastatic																	X								
Leiomyosarcoma, invasive																								X	
Malignant lymphoma, NOS																					X				

+ : Tissue Examined Microscopically
– : Required Tissue Not Examined Microscopically
X : Tumor Incidence
N : Necropsy, No Autolysis, No Microscopic Examination
S : Animal Missexed
No Tissue Information Submitted
C : Necropsy, No Histology Due To Protocol
A : Autolysis
M : Animal Missing
B : No Necropsy Performed

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	093	105	105	058	034	099	105	102	105	099	105	105	105	105	104	105	001	105	024	105	105	105	105	094	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma								X																		1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										2
Fibroma			X																							3
Hemangioma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular carcinoma, metasta												X														2
Alveolar/bronchiolar adenoma																									X	2
Alveolar/bronchiolar carcinoma																										1
Trachea	–	+	+	+	–	–	+	+	–	–	+	–	–	+	–	–	+	–	+	–	+	–	+	–	–	26
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																X										2
Lymph nodes	+	–	–	+	–	–	–	+	+	–	–	–	–	–	–	+	+	+	–	–	–	–	–	+	+	24
Thymus	–	+	+	+	+	–	+	+	+	+	–	–	+	+	–	+	–	+	+	+	+	+	+	–	+	36
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic																X										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastat																										1
Hepatocellular adenoma																						X				2
Hepatocellular carcinoma									X			X			X									X		11
Hemangiosarcoma, metastatic																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	45
Stomach	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma		X	X			X		X	X			X			X		X		X	X		X		X		30
Squamous cell carcinoma						X						X		X										X		7
Leiomyosarcoma																										1
Small intestine	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	46
Large intestine	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	47
Adenoma, NOS																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+		49
Thyroid	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	47
Follicular-cell adenoma																										2
Parathyroid	–	+	+	–	+	–	+	+	+	–	–	+	+	–	–	–	+	+	–	+	+	–	–	–	–	26
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial-cell tumor				X																						1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papillary adenoma														X								X				3
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma, invasive																								X		1
Squamous cell carcinoma, metastat																										1
Leiomyosarcoma, invasive																										1
Malignant lymphoma, NOS	X																									2

* Animals Necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE: VEHICLE CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	097	105	105	105	105	105	099	105	105	105	105	105	105	105	105	105	052	105	099	097	098	105	111	089	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+
Malignant melanoma																									
Sarcoma, NOS																									
Liposarcoma																									
Hemangiosarcoma, metastatic							X																		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X																					
Trachea	+	+	+	+	–	+	–	–	+	–	+	+	–	–	+	+	–	+	–	–	+	–	–	–	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma							X																		
Malignant lymphoma, NOS			X																						
Lymph nodes	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	–	+	–	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	–	–	+	+	–	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma				X																					
Hepatocellular carcinoma																									
Hemangioma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Chromophobe adenoma		X		X									X											X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Cortical adenoma				X																					
Thyroid	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+
Follicular-cell adenoma																									
Parathyroid	–	+	–	+	–	+	+	–	–	+	+	–	+	–	–	–	+	+	–	–	+	+	–	+	–
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	N	+	+
Adenocarcinoma, NOS																								X	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																									
Hemangioma																						X			
Lymphangioma																	X								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																			X						
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary adenoma											X														
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma			X																						
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma, metastatic			X																						
Malignant lymphoma, NOS	X								X			X							X		X	X			
Granulocytic leukemia																				X			X		

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	02 26	02 27	02 28	02 29	03 01	03 31	03 32	03 33	03 34	03 35	03 36	03 37	03 38	03 39	04 40	04 41	04 42	04 43	04 44	04 45	04 46	04 47	04 48	04 49	05 50	TOTAL
WEEKS ON STUDY	10 05	10 05	10 04	10 05	10 05	10 05	07 75	10 05	10 05	10 05	10 05	07 77	09 11	10 05	10 05	10 05	10 05	10 05	10 05	10 05	10 05	10 05	09 97	10 05	10 05	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Malignant melanoma																X										1
Sarcoma, NOS																							X			1
Liposarcoma																									X	1
Hemangiosarcoma, metastatic																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X																		X				3
Trachea	+	+	–	+	+	+	+	–	–	+	+	–	–	–	+	+	+	–	–	–	+	+	–	+	–	27
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Malignant lymphoma, NOS																										1
Lymph nodes	–	–	+	–	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	–	+	+	+	+	–	39
Thymus	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma															X											2
Hepatocellular carcinoma																X						X				2
Hemangioma														X												1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	N	+	+	+	+	N	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, NOS			X																							1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	46
Chromophobe adenoma				X					X						X	X		X								9
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma																										1
Thyroid	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	44
Follicular-cell adenoma																		X								1
Parathyroid	+	+	–	–	+	–	–	–	+	+	+	+	–	–	+	+	–	+	–	+	–	–	+	–	+	25
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp																					X					1
Hemangioma																							X			2
Lymphangioma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	49
Hemangioma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papillary adenoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma, metastatic																										1
Malignant lymphoma, NOS												X										X				8
Granulocytic leukemia																										2

* Animals Necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE: LOW DOSE

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0010	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025
WEEKS ON STUDY	0711	0761	0915	1005	1015	1025	1035	1058	0833	1035	1035	1035	1035	1035	1035	1035	1035	1035	1035	1035	1035	1035	1035	1035	1035
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	–	+	M	–	M	–	–	+	+	–	+	+	+	–	+	–	+	+	+	+	–	+	–	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	M	+	M	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	–	M	+	M	–	–	–	–	–	+	+	+	+	–	+	+	+	+	+	–	–	–	+	+
Malignant lymphoma, NOS																									
Thymus	+	+	M	–	M	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic																									
CIRCULATORY SYSTEM																									
Heart	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma											X						X								X
Bile duct	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma	X					X		XX		X				X	X			X							
Squamous cell carcinoma							X																		
Small intestine	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	M	–	M	+	–	+	+	–	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	M	+	M	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Chromophobe adenoma												X						X	X	X			X	X	
Adrenal	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma								X																	
Thyroid	+	+	M	+	M	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular-cell adenoma																									
Parathyroid	+	–	M	–	M	–	–	–	–	+	+	+	+	+	+	+	+	–	+	–	+	+	+	–	+
Pancreatic islets	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell adenoma				X																					
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	M	+	M	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS												X													
Uterus	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS											X														
Endometrial stromal sarcoma															X										
Ovary	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, invasive																									
NERVOUS SYSTEM																									
Brain	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	M	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma		X																							
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	M	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma, metastatic		X																							
Malignant lymphoma, NOS	X								X								X							

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	105	088	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	099	105	105	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar adenoma					X	X																				2
Trachea	+	+	–	–	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	35
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph nodes	–	–	+	+	+	+	+	–	+	+	+	+	+	+	–	+	–	+	+	+	+	–	+	+	+	32
Malignant lymphoma, NOS													X													1
Thymus	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	43
Adenocarcinoma, NOS, metastatic		X																								1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular adenoma																										3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder & common bile duct	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	*48
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell papilloma							X				X							X		X		X	X	X		15
Squamous cell carcinoma																										1
Small intestine	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Chromophobe adenoma		X				X					X											X	X			11
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cortical adenoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Follicular-cell adenoma			X																							1
Parathyroid	+	+	+	+	–	–	–	+	–	–	+	+	–	+	–	+	–	+	–	+	–	–	+	+	–	26
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet-cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*48
Adenocarcinoma, NOS										X													X	X		4
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma, NOS		X																								2
Endometrial stromal sarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma, NOS, invasive		X																								1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*48
Osteosarcoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*48
Osteosarcoma, metastatic																										1
Malignant lymphoma, NOS			X		X	X													X							7

* Animals Necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE: HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	105	105	048	105	105	099	105	010	102	105	105	098	105	068	014	072	105	105	105	067	067	104	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Sarcoma, NOS											X														
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Liposarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X											X
Trachea	–	–	+	–	+	+	–	–	+	+	+	+	+	–	+	+	M	–	–	–	–	–	+	–	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Lymph nodes	+	–	+	+	+	+	–	+	–	+	+	–	–	+	–	+	M	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	M	–	–	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Hepatocellular adenoma														X											
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	M	+	+	+	+	+	N	+	+
Pancreas	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	M	–	+	+	+	+	+	+	+
Esophagus	+	–	+	+	+	+	+	+	+	+	–	+	+	+	–	+	M	+	–	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Squamous cell papilloma	X	X		X		X	X	X	X		X	X	X			X					X		X		X
Squamous cell carcinoma														X										X	
Small intestine	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	–	+	+
Large intestine	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Urinary bladder	–	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	M	–	+	+	+	+	+	+	+
Liposarcoma, invasive																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	–	+	+	–	+	+
Adenoma, NOS				X																					
Chromophobe adenoma									X																
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	M	+	–	+	+	+	–	+	+
Parathyroid	–	–	–	+	+	–	–	–	+	–	+	–	–	–	+	M	+	–	–	–	–	–	–	–	
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS					X																				
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Endometrial stromal polyp									X										X						
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Luteoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Astrocytoma																				X					
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N
Papillary adenoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N
Sarcoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N
Squamous cell carcinoma, metastat																								X	
Malignant lymphoma, NOS								X		X				X	X			X							
Granulocytic leukemia																				X					X

+ : *Tissue Examined Microscopically*
– : Required Tissue Not Examined Microscopically
X : Tumor Incidence
N : Necropsy, No Autolysis, No Microscopic Examination
S : Animal Missexed
: *No Tissue Information Submitted*
C : Necropsy, No Histology Due To Protocol
A : Autolysis
M : Animal Missing
B : No Necropsy Performed

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	02268	02787	02889	03090	03112	03323	03340	03505	03805	04123	04263	04445	04656	04778	04899	05050	TOTAL
WEEKS ON STUDY	09191	08677	10955	10058	10573	07731	08805	10955	00707	09898	09266	10505	10505	10505	10505	10505	TISSUES TUMORS
INTEGUMENTARY SYSTEM																	
Skin	+	+	+	+	+	N	+	+	+	M	+	+	+	+	+	+	*44
Sarcoma, NOS																	1
Subcutaneous tissue	+	+	+	+	+	N	+	+	+	M	+	+	+	+	+	+	*44
Liposarcoma	X																1
RESPIRATORY SYSTEM																	
Lungs and bronchi	+	+	+	+	+	+	+	+	+	M	+	–	+	+	+	+	43
Alveolar/bronchiolar adenoma					X												3
Trachea	+	+	+	–	+	–	–	+	–	M	–	–	+	+	–	+	25
HEMATOPOIETIC SYSTEM																	
Bone marrow	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	44
Spleen	+	+	+	+	+	+	–	+	+	M	+	+	+	+	+	+	43
Lymph nodes	+	+	+	–	+	–	+	–	–	M	–	–	+	–	–	+	28
Thymus	–	+	+	+	+	+	+	+	+	M	+	–	+	+	–	–	36
CIRCULATORY SYSTEM																	
Heart	+	+	+	+	+	+	+	+	+	M	+	–	+	+	+	+	43
DIGESTIVE SYSTEM																	
Salivary gland	+	+	+	+	+	+	+	+	+	M	+	–	+	+	+	+	43
Liver	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	44
Hepatocellular adenoma																	1
Bile duct	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	44
Gallbladder & common bile duct	N	+	+	+	+	+	N	+	+	M	+	N	+	+	+	N	*44
Pancreas	+	+	+	+	+	+	–	+	+	M	+	+	+	+	+	+	41
Esophagus	+	+	+	+	+	+	+	+	+	M	+	–	+	+	+	+	39
Stomach	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	4
Squamous cell papilloma	X		X	X		X	X	X	X	X		X	X			X	X	X	X	X	29
Squamous cell carcinoma																	2
Small intestine	–	+	+	+	+	+	+	–	+	+	M	+	–	+	+	+	+	+	+	+	39
Large intestine	+	+	+	+	+	+	+	–	+	+	M	+	+	+	+	+	+	+	+	+	42
Leiomyosarcoma													X								1
URINARY SYSTEM																	
Kidney	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	44
Urinary bladder	+	+	+	+	+	–	+	+	–	+	M	+	+	+	+	+	+	+	+	+	38
Liposarcoma, invasive	X																				1
ENDOCRINE SYSTEM																	
Pituitary	–	+	+	+	+	+	–	+	+	+	M	+	–	+	+	+	+	+	+	+	39
Adenoma, NOS																					1
Chromophobe adenoma													X			X	X	X			5
Adrenal	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	44
Thyroid	+	+	+	+	–	+	+	+	–	+	M	+	–	+	+	+	+	+	+	+	38
Parathyroid	–	+	+	+	–	–	–	+	–	+	M	–	–	+	–	+	–	–	–	+	16
REPRODUCTIVE SYSTEM																	
Mammary gland	+	+	+	+	N	+	N	+	+	+	M	+	+	N	+	+	+	+	+	+	*44
Adenocarcinoma, NOS																					1
Uterus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	44
Endometrial stromal polyp																					2
Ovary	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	44
Luteoma																				X	1
NERVOUS SYSTEM																	
Brain	+	+	+	+	+	+	+	+	+	+	M	+	–	+	+	+	+	+	+	+	43
Astrocytoma																					1
SPECIAL SENSE ORGANS																	
Harderian gland	N	N	N	N	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	*44
Papillary adenoma									X												1
MUSCULOSKELETAL SYSTEM																	
Bone	N	N	N	N	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	*44
Sarcoma, NOS												X									1
ALL OTHER SYSTEMS																	
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	*44
Squamous cell carcinoma, metastat																					1
Malignant lymphoma, NOS								X													6
Granulocytic leukemia																					2

* Animals Necropsied

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
HEMORRHAGE	1 (2%)		
HYPERKERATOSIS	1 (2%)	1 (2%)	
RESPIRATORY SYSTEM			
*NASAL CAVITY	(50)	(50)	(50)
CONGESTION, NOS			1 (2%)
INFLAMMATION, SUPPURATIVE			12 (24%)
INFLAMMATION, ACUTE/CHRONIC			7 (14%)
INFLAMMATION, CHRONIC			7 (14%)
INFLAMMATION, GRANULOMATOUS			1 (2%)
HYPERPLASIA, EPITHELIAL			1 (2%)
#TRACHEA	(49)	(47)	(45)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
INFLAMMATION, CHRONIC FOCAL			2 (4%)
METAPLASIA, SQUAMOUS			1 (2%)
#LUNG	(50)	(50)	(50)
ATELECTASIS	1 (2%)	1 (2%)	1 (2%)
CONGESTION, NOS	6 (12%)	3 (6%)	7 (14%)
EDEMA, INTERSTITIAL	1 (2%)		
HEMORRHAGE	1 (2%)	1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR		3 (6%)	1 (2%)
INFLAMMATION, INTERSTITIAL			2 (4%)
ABSCESS, NOS	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
PNEUMONIA, CHRONIC MURINE	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	2 (4%)		2 (4%)
INFLAMMATION, GRANULOMATOUS FOCAL	2 (4%)	2 (4%)	
HYPERPLASIA, ADENOMATOUS			1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	2 (4%)	3 (6%)	
HISTIOCYTOSIS	1 (2%)		
#LUNG/ALVEOLI	(50)	(50)	(50)
HISTIOCYTOSIS	4 (8%)	4 (8%)	1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(50)	(49)	(50)
HYPERPLASIA, NOS		1 (2%)	
#SPLEEN	(50)	(50)	(48)
FIBROSIS	2 (4%)	1 (2%)	1 (2%)
FIBROSIS, FOCAL			2 (4%)
HEMOSIDEROSIS		3 (6%)	2 (4%)
HEMATOPOIESIS		2 (4%)	
#MANDIBULAR L. NODE	(49)	(47)	(45)
PLASMACYTOSIS		1 (2%)	
#PANCREATIC L. NODE	(49)	(47)	(45)
PIGMENTATION, NOS		1 (2%)	
#THYMUS	(41)	(46)	(41)
HEMORRHAGE	1 (2%)		3 (7%)
CIRCULATORY SYSTEM			
#MANDIBULAR L. NODE	(49)	(47)	(45)
LYMPHANGIECTASIS	3 (6%)		2 (4%)
#RENAL LYMPH NODE	(49)	(47)	(45)
LYMPHANGIECTASIS		1 (2%)	

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM (Continued)			
#LUNG	(50)	(50)	(50)
PERIVASCULITIS		1 (2%)	
#HEART	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
#HEART/ATRIUM	(50)	(50)	(50)
THROMBOSIS, NOS	1 (2%)	1 (2%)	1 (2%)
#MYOCARDIUM	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		1 (2%)
INFLAMMATION, CHRONIC	1 (2%)	1 (2%)	1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		1 (2%)
FIBROSIS			2 (4%)
DEGENERATION, NOS	34 (68%)	34 (68%)	36 (72%)
#ENDOCARDIUM	(50)	(50)	(50)
HYPERPLASIA, NOS	1 (2%)	1 (2%)	
*PULMONARY ARTERY	(50)	(50)	(50)
MINERALIZATION		1 (2%)	1 (2%)
CALCIFICATION, NOS	1 (2%)	1 (2%)	1 (2%)
CALCIFICATION, FOCAL		1 (2%)	
*CEREBRAL ARTERY	(50)	(50)	(50)
FIBROSIS	1 (2%)		
CALCIFICATION, NOS	1 (2%)		
*SUP. PANC-DUOD. ARTERY	(50)	(50)	(50)
HYPERTROPHY, NOS			1 (2%)
*PULMONARY VEIN	(50)	(50)	(50)
THROMBOSIS, NOS	1 (2%)		
#HEPATIC SINUSOID	(50)	(50)	(48)
DILATATION, NOS	1 (2%)		1 (2%)
#PANCREAS	(50)	(50)	(48)
PERIARTERITIS	1 (2%)		
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(50)	(47)	(49)
DILATATION/DUCTS			1 (2%)
RETENTION OF CONTENT			1 (2%)
CYSTIC DUCTS	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
METAPLASIA, SQUAMOUS	1 (2%)		
#LIVER	(50)	(50)	(48)
CONGESTION, NOS	2 (4%)	2 (4%)	1 (2%)
HEMORRHAGE	1 (2%)		
CHOLANGIOFIBROSIS	2 (4%)	4 (8%)	1 (2%)
DEGENERATION, HYDROPIC			1 (2%)
NECROSIS, FOCAL		2 (4%)	2 (4%)
NECROSIS, MIDZONAL			1 (2%)
INFARCT, NOS			1 (2%)
LIPOIDOSIS		1 (2%)	
BASOPHILIC CYTO CHANGE		1 (2%)	2 (4%)
GROUND-GLASS CYTO CHANGE	3 (6%)	1 (2%)	2 (4%)
FOCAL CELLULAR CHANGE	1 (2%)	1 (2%)	2 (4%)
EOSINOPHILIC CYTO CHANGE			1 (2%)
#LIVER/CENTRILOBULAR	(50)	(50)	(48)
CONGESTION, NOS			1 (2%)
DEGENERATION, GRANULAR			1 (2%)
NECROSIS, NOS		1 (2%)	5 (10%)
HYPERTROPHY, NOS			1 (2%)
#LIVER/PERIPORTAL	(50)	(50)	(48)
INFLAMMATION, NECROTIZING		1 (2%)	
#LIVER/HEPATOCYTES	(50)	(50)	(48)
CYTOPLASMIC VACUOLIZATION		1 (2%)	
HYPERPLASIA, BASAL CELL			1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#BILE DUCT	(50)	(50)	(48)
CYST, NOS			1 (2%)
HYPERPLASIA, NOS	31 (62%)	31 (62%)	6 (13%)
HYPERPLASIA, CYSTIC		1 (2%)	
#PANCREATIC ACINUS	(50)	(50)	(48)
ATROPHY, NOS	3 (6%)	3 (6%)	3 (6%)
ATROPHY, FOCAL	10 (20%)	6 (12%)	2 (4%)
HYPERPLASIA, FOCAL	10 (20%)		
#GASTRIC MUCOSA	(50)	(50)	(48)
CALCIFICATION, NOS	1 (2%)		
#GLANDULAR STOMACH	(50)	(50)	(48)
CYST, NOS	2 (4%)		1 (2%)
#GASTRIC SUBMUCOSA	(50)	(50)	(48)
EDEMA, NOS		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
#FORESTOMACH	(50)	(50)	(48)
ULCER, NOS	2 (4%)	2 (4%)	1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (2%)		1 (2%)
HYPERPLASIA, EPITHELIAL			1 (2%)
HYPERPLASIA, BASAL CELL	19 (38%)	41 (82%)	43 (90%)
HYPERKERATOSIS			3 (6%)
#DUODENUM	(48)	(50)	(46)
ULCER, NOS			1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	
#COLON	(49)	(49)	(47)
ULCER, NOS			1 (2%)
PARASITISM	1 (2%)	1 (2%)	2 (4%)
NECROSIS, FOCAL			1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(49)
CONGESTION, NOS	1 (2%)		
PYELONEPHRITIS, NOS	1 (2%)	1 (2%)	
PYELONEPHRITIS, ACUTE		1 (2%)	
NEPHROPATHY	35 (70%)	44 (88%)	47 (96%)
CALCIFICATION, FOCAL		1 (2%)	
#KIDNEY/CORTEX	(50)	(50)	(49)
CYST, NOS	1 (2%)		
PYELONEPHRITIS, NOS		2 (4%)	
PYELONEPHRITIS, FOCAL	1 (2%)		
ABSCESS, NOS	7 (14%)	5 (10%)	9 (18%)
#KIDNEY/MEDULLA	(50)	(50)	(49)
CALCIFICATION, NOS	1 (2%)		
CALCIFICATION, FOCAL	1 (2%)		
#KIDNEY/TUBULE	(50)	(50)	(49)
DILATATION, NOS	1 (2%)		
DEGENERATION, HYALINE		1 (2%)	
NECROSIS, NOS		1 (2%)	
REGENERATION, NOS		1 (2%)	
#KIDNEY/PELVIS	(50)	(50)	(49)
DILATATION, NOS		1 (2%)	
HYPERPLASIA, EPITHELIAL	1 (2%)	1 (2%)	
#URINARY BLADDER	(48)	(49)	(46)
HEMORRHAGE	1 (2%)		
INFLAMMATION, SUPPURATIVE	1 (2%)	1 (2%)	
INFLAMMATION, ACUTE			1 (2%)
HYPERPLASIA, EPITHELIAL			1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(50)	(50)
CYST, NOS			1 (2%)
HEMORRHAGE			1 (2%)
#PITUITARY INTERMEDIA	(49)	(50)	(50)
CYST, NOS			1 (2%)
PIGMENTATION, NOS		1 (2%)	
#ANTERIOR PITUITARY	(49)	(50)	(50)
CYST, NOS	6 (12%)	4 (8%)	4 (8%)
PIGMENTATION, NOS		2 (4%)	
CYTOPLASMIC VACUOLIZATION		1 (2%)	1 (2%)
HYPERPLASIA, FOCAL	16 (33%)	23 (46%)	18 (36%)
ANGIECTASIS	1 (2%)		1 (2%)
#ADRENAL	(50)	(50)	(48)
ANGIECTASIS			1 (2%)
#ADRENAL CORTEX	(50)	(50)	(48)
ACCESSORY STRUCTURE		2 (4%)	
HEMORRHAGE			1 (2%)
FIBROSIS, FOCAL		1 (2%)	
DEGENERATION, NOS			1 (2%)
DEGENERATION, LIPOID	11 (22%)	5 (10%)	11 (23%)
INFARCT, NOS		1 (2%)	
CYTOPLASMIC CHANGE, NOS	1 (2%)		
ATROPHY, FOCAL		1 (2%)	
HYPERTROPHY, FOCAL		1 (2%)	
HYPERPLASIA, FOCAL	5 (10%)	9 (18%)	11 (23%)
#ADRENAL MEDULLA	(50)	(50)	(48)
ATROPHY, FOCAL	1 (2%)		
HYPERPLASIA, FOCAL	13 (26%)	4 (8%)	8 (17%)
#THYROID	(49)	(48)	(48)
ULTIMOBRANCHIAL CYST		1 (2%)	
CYST, NOS		1 (2%)	
FOLLICULAR CYST, NOS			1 (2%)
HYPERPLASIA, C-CELL	6 (12%)	6 (13%)	4 (8%)
HYPERPLASIA, FOLLICULAR-CELL			1 (2%)
#PARATHYROID	(40)	(38)	(39)
HYPERPLASIA, NOS		1 (3%)	1 (3%)
#PANCREATIC ISLETS	(50)	(50)	(48)
HYPERPLASIA, FOCAL	3 (6%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
GALACTOCELE	3 (6%)		2 (4%)
CYSTIC DUCTS	1 (2%)		
LACTATION	4 (8%)	7 (14%)	5 (10%)
*MAMMARY LOBULE	(50)	(50)	(50)
HYPERPLASIA, NOS	1 (2%)	1 (2%)	1 (2%)
*PREPUTIAL GLAND	(50)	(50)	(50)
DILATATION/DUCTS	1 (2%)		
CYST, NOS		1 (2%)	
INFLAMMATION, ACUTE		1 (2%)	
ABSCESS, NOS	3 (6%)		
INFLAMMATION, CHRONIC	1 (2%)		
HYPERPLASIA, NOS	1 (2%)		
#PROSTATE	(47)	(49)	(48)
INFLAMMATION, SUPPURATIVE	1 (2%)	1 (2%)	2 (4%)
ABSCESS, NOS	1 (2%)	2 (4%)	1 (2%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	1 (2%)
INFLAMMATION, CHRONIC FOCAL	2 (4%)		
INFLAMMATION, GRANULOMATOUS			1 (2%)
FIBROSIS		1 (2%)	
HYPERPLASIA, EPITHELIAL	2 (4%)	6 (12%)	1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
#PROSTATE (Continued)	(47)	(49)	(48)
HYPERPLASIA, FOCAL	4 (9%)	4 (8%)	5 (10%)
*SEMINAL VESICLE	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		
ABSCESS, NOS	1 (2%)		
#TESTIS	(50)	(50)	(48)
HAMARTOMA		1 (2%)	
HYPERPLASIA, INTERSTITIAL CELL	1 (2%)		1 (2%)
#SPERMATID	(50)	(50)	(48)
CYTOMEGALY		1 (2%)	
*EPIDIDYMIS	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL			1 (2%)
NERVOUS SYSTEM			
#CEREBRAL VENTRICLE	(50)	(50)	(50)
DILATATION, NOS	1 (2%)		
#BRAIN	(50)	(50)	(50)
HEMORRHAGE	1 (2%)		
#BRAIN STEM	(50)	(50)	(50)
DEMYELINIZATION		1 (2%)	
#CEREBELLUM	(50)	(50)	(50)
CALCIFICATION, FOCAL			1 (2%)
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
ABSCESS, NOS			1 (2%)
CATARACT	5 (10%)	1 (2%)	6 (12%)
ATROPHY, NOS		2 (4%)	
*EYE/SCLERA,	(50)	(50)	(50)
CALCIFICATION, FOCAL		1 (2%)	
METAPLASIA, OSSEOUS	2 (4%)	1 (2%)	1 (2%)
*EYE/RETINA	(50)	(50)	(50)
ATROPHY, NOS	4 (8%)	3 (6%)	8 (16%)
*EYE/LACRIMAL GLAND	(50)	(50)	(50)
PORPHYRIN			1 (2%)
*NASOLACRIMAL DUCT	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
HEMORRHAGE			1 (2%)
NECROSIS, FAT	1 (2%)		
*ABDOMINAL CAVITY	(50)	(50)	(50)
NECROSIS, FAT	1 (2%)	1 (2%)	

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
NECROSIS, FAT	3		
SPECIAL MORPHOLOGY SUMMARY			
NONE			

* NUMBER OF ANIMALS RECEIVING COMPLETE NECROPSY EXAMINATION; ALL GROSS LESIONS INCLUDING MASSES EXAMINED MICROSCOPICALLY.
# NUMBER OF ANIMALS EXAMINED MICROSCOPICALLY AT THIS SITE

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(50)
HEMATOMA, NOS	1 (2%)		
RESPIRATORY SYSTEM			
*NASAL CAVITY	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE			8 (16%)
INFLAMMATION, ACUTE/CHRONIC			6 (12%)
#TRACHEA	(47)	(50)	(49)
HYPERPLASIA, EPITHELIAL	1 (2%)		
#LUNG	(50)	(50)	(50)
ATELECTASIS			1 (2%)
CONGESTION, NOS	1 (2%)	3 (6%)	1 (2%)
EDEMA, NOS		1 (2%)	
HEMORRHAGE	2 (4%)		1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
INFLAMMATION, INTERSTITIAL	1 (2%)		2 (4%)
PNEUMONIA, ASPIRATION		1 (2%)	
INFLAMMATION, SUPPURATIVE	1 (2%)		
BRONCHOPNEUMONIA, ACUTE		1 (2%)	
ABSCESS, NOS			1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
PNEUMONIA, CHRONIC MURINE		1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)	2 (4%)	1 (2%)
INFLAMMATION, GRANULOMATOUS FOCAL	3 (6%)		1 (2%)
HEMOSIDEROSIS			1 (2%)
HYPERPLASIA, ADENOMATOUS	1 (2%)		
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)	1 (2%)	
HISTIOCYTOSIS	1 (2%)		
#LUNG/ALVEOLI	(50)	(50)	(50)
HISTIOCYTOSIS	6 (12%)	3 (6%)	13 (26%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(49)	(49)	(50)
HYPOPLASIA, NOS		2 (4%)	1 (2%)
HYPERPLASIA, NOS		1 (2%)	
#SPLEEN	(49)	(50)	(50)
FIBROSIS	1 (2%)	2 (4%)	1 (2%)
INFARCT, NOS			1 (2%)
HEMOSIDEROSIS	3 (6%)	1 (2%)	8 (16%)
DEPLETION, LYMPHOID	1 (2%)		
HEMATOPOIESIS	4 (8%)	2 (4%)	1 (2%)
#LYMPH NODE	(46)	(47)	(45)
HEMORRHAGE	1 (2%)		
PLASMACYTOSIS		1 (2%)	
#MANDIBULAR L. NODE	(46)	(47)	(45)
HEMORRHAGE			1 (2%)
INFLAMMATION, GRANULOMATOUS			1 (2%)
INFLAMMATION, GRANULOMATOUS FOCAL		1 (2%)	
PLASMACYTOSIS			1 (2%)
MASTOCYTOSIS		1 (2%)	1 (2%)
#MEDIASTINAL L. NODE	(46)	(47)	(45)
INFLAMMATION, GRANULOMATOUS FOCAL	1 (2%)		
HISTIOCYTOSIS	1 (2%)		

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#LIVER	(50)	(50)	(50)
HEMATOPOIESIS			1 (2%)
#THYMUS	(41)	(46)	(48)
CYST, NOS	1 (2%)		
HEMORRHAGE		1 (2%)	3 (6%)
CIRCULATORY SYSTEM			
#RENAL LYMPH NODE	(46)	(47)	(45)
LYMPHANGIECTASIS		1 (2%)	
#HEART	(50)	(50)	(50)
CONGEN. CARDIOVASC. MALFORMATION	1 (2%)		
METAMORPHOSIS, FATTY			1 (2%)
#LEFT ATRIUM	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE		1 (2%)	
#MYOCARDIUM	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
FIBROSIS, FOCAL	2 (4%)		
DEGENERATION, NOS	27 (54%)	31 (62%)	24 (48%)
NECROSIS, NOS	1 (2%)		
*PULMONARY ARTERY	(50)	(50)	(50)
MINERALIZATION			1 (2%)
CALCIFICATION, FOCAL		2 (4%)	
*HEPATIC VEIN	(50)	(50)	(50)
HYPERPLASIA, NOS		1 (2%)	
#HEPATIC SINUSOID	(50)	(50)	(50)
DILATATION, NOS			1 (2%)
#ADRENAL CORTEX	(50)	(50)	(50)
THROMBOSIS, NOS	1 (2%)		
DIGESTIVE SYSTEM			
#TONGUE	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL			1 (2%)
#SALIVARY GLAND	(50)	(50)	(49)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
ATROPHY, NOS		1 (2%)	
#LIVER	(50)	(50)	(50)
CONGESTION, NOS			1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
INFLAMMATION, GRANULOMATOUS		1 (2%)	
GRANULOMA, NOS		1 (2%)	
INFLAMMATION, GRANULOMATOUS FOCAL	9 (18%)	8 (16%)	7 (14%)
CHOLANGIOFIBROSIS	2 (4%)	1 (2%)	2 (4%)
NECROSIS, FOCAL	2 (4%)	3 (6%)	2 (4%)
NECROSIS, DIFFUSE			1 (2%)
CYTOPLASMIC VACUOLIZATION	1 (2%)		
BASOPHILIC CYTO CHANGE	3 (6%)	1 (2%)	
GROUND-GLASS CYTO CHANGE	2 (4%)	1 (2%)	2 (4%)
FOCAL CELLULAR CHANGE		1 (2%)	1 (2%)
CLEAR-CELL CHANGE	1 (2%)		
HYPERTROPHY, FOCAL			1 (2%)
HYPERPLASIA, NOS			1 (2%)
ANGIECTASIS		1 (2%)	
#PORTAL TRACT	(50)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
PIGMENTATION, NOS			1 (2%)
#LIVER/CENTRILOBULAR	(50)	(50)	(50)
DEGENERATION, HYDROPIC		1 (2%)	
NECROSIS, NOS	1 (2%)	3 (6%)	1 (2%)
NECROSIS, COAGULATIVE	1 (2%)		

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#BILE DUCT	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
HYPERPLASIA, NOS	24 (48%)	22 (44%)	14 (28%)
#PANCREATIC ACINUS	(50)	(50)	(50)
ATROPHY, NOS	1 (2%)	2 (4%)	
ATROPHY, FOCAL	4 (8%)	1 (2%)	
#GLANDULAR STOMACH	(50)	(50)	(50)
ABSCESS, NOS			1 (2%)
FIBROSIS, FOCAL	1 (2%)		
#GASTRIC SUBMUCOSA	(50)	(50)	(50)
EDEMA, NOS			2 (4%)
#FORESTOMACH	(50)	(50)	(50)
ULCER, NOS	1 (2%)		1 (2%)
INFLAMMATION, ACUTE	1 (2%)		1 (2%)
ULCER, ACUTE	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
INFLAMMATION, CHRONIC	1 (2%)		1 (2%)
HYPERPLASIA, BASAL CELL	24 (48%)	42 (84%)	45 (90%)
HYPERKERATOSIS			1 (2%)
#JEJUNAL MUCOSA	(50)	(49)	(50)
DIVERTICULUM	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
HAMARTOMA	1 (2%)		
PYELONEPHRITIS, NOS		1 (2%)	
FIBROSIS, DIFFUSE	1 (2%)		
NEPHROPATHY	17 (34%)	15 (30%)	27 (54%)
INFARCT, NOS			1 (2%)
CALCIFICATION, FOCAL	3 (6%)	3 (6%)	2 (4%)
#KIDNEY/CORTEX	(50)	(50)	(50)
CYST, NOS	1 (2%)		
#KIDNEY/MEDULLA	(50)	(50)	(50)
MINERALIZATION			1 (2%)
CALCIFICATION, NOS	1 (2%)		1 (2%)
CALCIFICATION, FOCAL	2 (4%)	1 (2%)	1 (2%)
#RENAL PAPILLA	(50)	(50)	(50)
CALCIFICATION, FOCAL	1 (2%)		
#KIDNEY/PELVIS	(50)	(50)	(50)
CALCULUS,MICROSCOPIC EXAMINATION	1 (2%)	1 (2%)	
MINERALIZATION	1 (2%)		2 (4%)
DILATATION, NOS		1 (2%)	
CALCIFICATION, NOS	1 (2%)	3 (6%)	1 (2%)
CALCIFICATION, FOCAL	2 (4%)	7 (14%)	2 (4%)
HYPERPLASIA, EPITHELIAL	2 (4%)	3 (6%)	
#URINARY BLADDER	(49)	(49)	(50)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
HYPERPLASIA, EPITHELIAL		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(50)	(49)
CYST, NOS		1 (2%)	
DEGENERATION, NOS	1 (2%)		
#PITUITARY INTERMEDIA	(50)	(50)	(49)
CYST, NOS			2 (4%)
#ANTERIOR PITUITARY	(50)	(50)	(49)
CYST, NOS	27 (54%)	24 (48%)	23 (47%)
HEMORRHAGE			1 (2%)
HYPERPLASIA, FOCAL	20 (40%)	10 (20%)	14 (29%)
ANGIECTASIS	4 (8%)	3 (6%)	6 (12%)

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#ADRENAL	(50)	(50)	(50)
CONGESTION, NOS	1 (2%)		
ANGIECTASIS		1 (2%)	
#ADRENAL CORTEX	(50)	(50)	(50)
ACCESSORY STRUCTURE			1 (2%)
CYST, NOS			1 (2%)
CONGESTION, NOS			1 (2%)
DEGENERATION, LIPOID	18 (36%)	15 (30%)	23 (46%)
INFARCT, FOCAL	1 (2%)		
FOCAL CELLULAR CHANGE		1 (2%)	
HYPERTROPHY, FOCAL		1 (2%)	1 (2%)
HYPERTROPHY, DIFFUSE			2 (4%)
HYPERPLASIA, FOCAL	14 (28%)	10 (20%)	13 (26%)
HYPERPLASIA, DIFFUSE			1 (2%)
ANGIECTASIS		2 (4%)	1 (2%)
#ADRENAL MEDULLA	(50)	(50)	(50)
FIBROSIS, FOCAL			1 (2%)
HYPERPLASIA, FOCAL	3 (6%)	2 (4%)	4 (8%)
#THYROID	(50)	(48)	(49)
ULTIMOBRANCHIAL CYST	1 (2%)		
HYPERPLASIA, C-CELL	5 (10%)	1 (2%)	4 (8%)
HYPERPLASIA, FOLLICULAR-CELL			1 (2%)
#THYROID FOLLICLE	(50)	(48)	(49)
HYPERTROPHY, NOS			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
GALACTOCELE		2 (4%)	
LACTATION	22 (44%)	22 (44%)	21 (42%)
*MAMMARY LOBULE	(50)	(50)	(50)
HYPERPLASIA, NOS	3 (6%)	3 (6%)	3 (6%)
*PREPUTIAL GLAND	(50)	(50)	(50)
ABSCESS, NOS		1 (2%)	
*CLITORAL GLAND	(50)	(50)	(50)
DILATATION, NOS		1 (2%)	
DILATATION/DUCTS			1 (2%)
CYSTIC DUCTS		1 (2%)	
ABSCESS, NOS		2 (4%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
HYPERPLASIA, NOS		2 (4%)	
#CERVIX UTERI	(50)	(50)	(49)
CYST, NOS	1 (2%)		
ABSCESS, NOS		1 (2%)	
METAPLASIA, NOS	9 (18%)	4 (8%)	6 (12%)
#UTERUS/ENDOMETRIUM	(50)	(50)	(49)
CYST, NOS	2 (4%)		2 (4%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
FIBROSIS	2 (4%)	1 (2%)	1 (2%)
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, PAPILLARY	1 (2%)		
HYPERPLASIA, CYSTIC	2 (4%)	7 (14%)	2 (4%)
HYPERPLASIA, ADENOMATOUS	1 (2%)	1 (2%)	
HYPERPLASIA, STROMAL		1 (2%)	
#ENDOMETRIAL GLAND	(50)	(50)	(49)
HYPERPLASIA, NOS			1 (2%)
#OVARY	(50)	(50)	(50)
CYST, NOS	3 (6%)	2 (4%)	1 (2%)
HYPERPLASIA, NOS	1 (2%)		

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
#CEREBRAL VENTRICLE	(50)	(50)	(49)
DILATATION, NOS	1 (2%)		
#LATERAL VENTRICLE	(50)	(50)	(49)
DILATATION, NOS	2 (4%)		
#BRAIN	(50)	(50)	(49)
HEMORRHAGE			1 (2%)
INFARCT, HEMORRHAGIC		1 (2%)	
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
TRAUMATIC ABNORMALITY		1 (2%)	
HEMORRHAGE			1 (2%)
CATARACT	8 (16%)	9 (18%)	4 (8%)
ATROPHY, NOS	2 (4%)		
*EYE/SCLERA,	(50)	(50)	(50)
CALCIFICATION, FOCAL		1 (2%)	
METAPLASIA, OSSEOUS	1 (2%)	1 (2%)	
*EYE/CORNEA	(50)	(50)	(50)
INFLAMMATION, CHRONIC	[c]	1 (2%)	
*EYE/RETINA	(50)	(50)	(50)
ATROPHY, NOS	10 (20%)	9 (18%)	7 (14%)
*NASOLACRIMAL DUCT	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE			2 (4%)
INFLAMMATION, CHRONIC			2 (4%)
METAPLASIA, SQUAMOUS			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*THORACIC CAVITY	(50)	(50)	(50)
INFLAMMATION, FIBRINOUS		1 (2%)	
BACTERIAL SEPTICEMIA		1 (2%)	
*MEDIASTINUM	(50)	(50)	(50)
HEMORRHAGE		2 (4%)	2 (4%)
*ABDOMINAL CAVITY	(50)	(50)	(50)
NECROSIS, FAT	3 (6%)		2 (4%)
*PLEURA	(50)	(50)	(50)
ABSCESS, NOS		1 (2%)	
INFLAMMATION, ACTIVE CHRONIC		1 (2%)	
FIBROSIS, FOCAL			1 (2%)
*PERICARDIUM	(50)	(50)	(50)
INFLAMMATION, ACUTE			1 (2%)
ABSCESS, NOS			1 (2%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
GRANULOMA, FOREIGN BODY			1 (2%)
*EPICARDIUM	(50)	(50)	(50)
INFLAMMATION, ACUTE			1 (2%)
INFLAMMATION, ACUTE FIBRINOUS		1 (2%)	

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)
ADIPOSE TISSUE			
NECROSIS, FAT		1	
SPECIAL MORPHOLOGY SUMMARY			
NONE			

* NUMBER OF ANIMALS RECEIVING COMPLETE NECROPSY EXAMINATION; ALL GROSS LESIONS INCLUDING MASSES EXAMINED MICROSCOPICALLY.
# NUMBER OF ANIMALS EXAMINED MICROSCOPICALLY AT THIS SITE

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST			1 (2%)
EDEMA, NOS	1 (2%)		1 (2%)
INFLAMMATION, ACUTE/CHRONIC		2 (4%)	1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)		
RESPIRATORY SYSTEM			
*NASAL CAVITY	(50)	(50)	(50)
CONGESTION, NOS			2 (4%)
LYMPHOCYTIC INFLAMMATORY INFILTR			3 (6%)
INFLAMMATION, ACUTE			6 (12%)
#LUNG	(50)	(50)	(48)
CONGESTION, NOS	4 (8%)	2 (4%)	3 (6%)
EDEMA, NOS	1 (2%)		
HEMORRHAGE	1 (2%)	2 (4%)	1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)	2 (4%)	
INFLAMMATION, ACUTE			1 (2%)
INFLAMMATION, GRANULOMATOUS	1 (2%)		
HYPERPLASIA, ALVEOLAR EPITHELIUM			1 (2%)
HISTIOCYTOSIS	3 (6%)	3 (6%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
LEUKEMOID REACTION	1 (2%)		
PLASMACYTOSIS			1 (2%)
HYPERPLASIA, GRANULOCYTIC			1 (2%)
HYPERPLASIA, LYMPHOID	1 (2%)	1 (2%)	2 (4%)
HEMATOPOIESIS	4 (8%)		2 (4%)
MYELOPOIESIS			1 (2%)
#BONE MARROW	(50)	(46)	(50)
ANGIECTASIS		1 (2%)	
MASTOCYTOSIS			1 (2%)
#SPLEEN	(48)	(46)	(50)
ACCESSORY STRUCTURE		1 (2%)	
HEMOSIDEROSIS			1 (2%)
ANGIECTASIS			1 (2%)
HYPERPLASIA, LYMPHOID	1 (2%)	1 (2%)	4 (8%)
HEMATOPOIESIS	2 (4%)	5 (11%)	5 (10%)
#SPLENIC FOLLICLES	(48)	(46)	(50)
NECROSIS, NOS	1 (2%)		
#MANDIBULAR L. NODE	(32)	(33)	(24)
PLASMACYTOSIS		1 (3%)	
MASTOCYTOSIS		1 (3%)	
#MEDIASTINAL L. NODE	(32)	(33)	(24)
HYPERPLASIA, LYMPHOID	1 (3%)		
#MESENTERIC L. NODE	(32)	(33)	(24)
HEMORRHAGE	3 (9%)	5 (15%)	4 (17%)
INFLAMMATION, ACUTE		1 (3%)	
HYPERPLASIA, LYMPHOID	1 (3%)		
HEMATOPOIESIS	1 (3%)	1 (3%)	
#RENAL LYMPH NODE	(32)	(33)	(24)
EDEMA, NOS	1 (3%)		
#FEMORAL LYMPH NODE	(32)	(33)	(24)
PLASMACYTOSIS	1 (3%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#LIVER	(50)	(50)	(50)
MYELOPOIESIS			1 (2%)
#JEJUNUM	(41)	(46)	(46)
HYPERPLASIA, LYMPHOID			2 (4%)
#ILEUM	(41)	(46)	(46)
HYPERPLASIA, LYMPHOID			1 (2%)
#THYMUS	(34)	(40)	(36)
CYST, NOS	2 (6%)	10 (25%)	4 (11%)
MULTIPLE CYSTS	1 (3%)		
DEPLETION, LYMPHOID	1 (3%)		1 (3%)
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
PERIARTERITIS	1 (2%)		
*MEDIASTINUM	(50)	(50)	(50)
THROMBOSIS, NOS			1 (2%)
#RENAL LYMPH NODE	(32)	(33)	(24)
THROMBOSIS, NOS			1 (4%)
#LUNG	(50)	(50)	(48)
THROMBOSIS, NOS	1 (2%)		
#HEART	(49)	(50)	(50)
MINERALIZATION	1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		1 (2%)
INFLAMMATION, ACUTE	1 (2%)		
INFLAMMATION, CHRONIC			1 (2%)
FIBROSIS		1 (2%)	
#CARDIAC VALVE	(49)	(50)	(50)
PIGMENTATION, NOS	1 (2%)	5 (10%)	5 (10%)
#PROSTATE	(50)	(48)	(50)
THROMBUS, ORGANIZED	1 (2%)		
DIGESTIVE SYSTEM			
*TOOTH	(50)	(50)	(50)
INFLAMMATION, ACUTE			1 (2%)
#SALIVARY GLAND	(49)	(50)	(50)
MINERALIZATION	1 (2%)		1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
ATROPHY, NOS		1 (2%)	
#LIVER	(50)	(50)	(50)
ECTOPIA	1 (2%)		
HEMORRHAGE		1 (2%)	
INFLAMMATION, ACUTE NECROTIZING			1 (2%)
INFLAMMATION, GRANULOMATOUS		1 (2%)	
GRANULOMA, NOS		1 (2%)	
NECROSIS, NOS	1 (2%)	1 (2%)	3 (6%)
NECROSIS, FOCAL		1 (2%)	1 (2%)
NECROSIS, COAGULATIVE			1 (2%)
INFARCT, NOS			1 (2%)
NUCLEAR-SIZE ALTERATION	1 (2%)		
CYTOPLASMIC VACUOLIZATION	7 (14%)	8 (16%)	13 (26%)
BASOPHILIC CYTO CHANGE		1 (2%)	2 (4%)
CLEAR-CELL CHANGE	10 (20%)	10 (20%)	7 (14%)
HEPATOCYTOMEGALY	11 (22%)	11 (22%)	5 (10%)
ANGIECTASIS	2 (4%)	1 (2%)	
#PANCREAS	(47)	(49)	(50)
NECROSIS, NOS	1 (2%)		
NECROSIS, FAT	1 (2%)		1 (2%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#PANCREATIC ACINUS	(47)	(49)	(50)
ATROPHY, NOS	8 (17%)	6 (12%)	9 (18%)
HYPERTROPHY, FOCAL	1 (2%)	1 (2%)	
HYPERPLASIA, NOS		1 (2%)	
#ESOPHAGUS	(50)	(48)	(45)
VEGETABLE FOREIGN BODY	1 (2%)		
INFLAMMATION, CHRONIC			1 (2%)
#STOMACH	(49)	(49)	(49)
INFLAMMATION, ACUTE	1 (2%)		
#GASTRIC FUNDAL GLAND	(49)	(49)	(49)
DILATATION, NOS	1 (2%)		1 (2%)
#GLANDULAR STOMACH	(49)	(49)	(49)
INFLAMMATION, ACUTE	1 (2%)	1 (2%)	
#FORESTOMACH	(49)	(49)	(49)
ANIMAL FOREIGN BODY		1 (2%)	
CYST, NOS	1 (2%)		
ULCER, NOS			2 (4%)
INFLAMMATION, ACUTE		7 (14%)	3 (6%)
ULCER, ACUTE			1 (2%)
ABSCESS, NOS		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC		2 (4%)	4 (8%)
HYPERPLASIA, EPITHELIAL		14 (29%)	15 (31%)
#JEJUNUM	(41)	(46)	(46)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
CALCULUS,MICROSCOPIC EXAMINATION		1 (2%)	
MINERALIZATION	11 (22%)	4 (8%)	8 (16%)
HYDRONEPHROSIS	1 (2%)	1 (2%)	
CYST, NOS	2 (4%)	4 (8%)	1 (2%)
MULTIPLE CYSTS	1 (2%)		2 (4%)
HEMORRHAGE			1 (2%)
GLOMERULONEPHRITIS, NOS	2 (4%)	1 (2%)	1 (2%)
PYELONEPHRITIS, NOS	3 (6%)		
LYMPHOCYTIC INFLAMMATORY INFILTR	10 (20%)	6 (12%)	7 (14%)
INFLAMMATION, ACUTE	1 (2%)		
NEPHROSIS, NOS	9 (18%)	10 (20%)	17 (34%)
INFARCT, NOS		3 (6%)	
ATROPHY, NOS			1 (2%)
METAPLASIA, OSSEOUS	1 (2%)	2 (4%)	1 (2%)
#KIDNEY/TUBULE	(50)	(50)	(50)
DILATATION, NOS			1 (2%)
#URINARY BLADDER	(48)	(47)	(49)
CALCULUS, GROSS OBSERVATION ONLY		1 (2%)	
DILATATION, NOS	2 (4%)	1 (2%)	1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
ENDOCRINE SYSTEM			
#ANTERIOR PITUITARY	(45)	(47)	(47)
CYST, NOS			2 (4%)
#ADRENAL/CAPSULE	(48)	(50)	(49)
HYPERPLASIA, NOS	3 (6%)	3 (6%)	2 (4%)
#ADRENAL CORTEX	(48)	(50)	(49)
CYTOPLASMIC VACUOLIZATION	1 (2%)		1 (2%)
FOCAL CELLULAR CHANGE			1 (2%)
ATROPHY, BROWN			2 (4%)
HYPERTROPHY, FOCAL	3 (6%)	3 (6%)	5 (10%)
HYPERPLASIA, NODULAR	1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#ADRENAL MEDULLA	(48)	(50)	(49)
HYPERPLASIA, NOS	1 (2%)	1 (2%)	
#THYROID	(45)	(47)	(47)
FOLLICULAR CYST, NOS	4 (9%)	7 (15%)	4 (9%)
HYPERPLASIA, FOLLICULAR-CELL	4 (9%)	5 (11%)	3 (6%)
#PARATHYROID	(25)	(23)	(26)
THYROGLOSSAL DUCT CYST		1 (4%)	
#PANCREATIC ISLETS	(47)	(49)	(50)
HYPERPLASIA, NOS	1 (2%)		1 (2%)
REPRODUCTIVE SYSTEM			
*PENIS	(50)	(50)	(50)
INFLAMMATION, ACUTE	1 (2%)		1 (2%)
*PREPUCE	(50)	(50)	(50)
IMPACTION, NOS	1 (2%)		
*PREPUTIAL GLAND	(50)	(50)	(50)
DILATATION, NOS	2 (4%)	2 (4%)	2 (4%)
INFLAMMATION, ACUTE			1 (2%)
ABSCESS, NOS	1 (2%)	1 (2%)	3 (6%)
INFLAMMATION, ACUTE/CHRONIC	2 (4%)	1 (2%)	1 (2%)
INFLAMMATION, CHRONIC	1 (2%)		
#PROSTATE	(50)	(48)	(50)
HEMORRHAGE		1 (2%)	2 (4%)
INFLAMMATION, ACUTE	3 (6%)		1 (2%)
GRANULOMA, NOS	1 (2%)		
*SEMINAL VESICLE	(50)	(50)	(50)
DILATATION, NOS	3 (6%)		2 (4%)
COLLAPSE			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
PIGMENTATION, NOS			1 (2%)
*COAGULATING GLAND	(50)	(50)	(50)
DILATATION, NOS			1 (2%)
#TESTIS	(50)	(50)	(50)
MINERALIZATION	17 (34%)	9 (18%)	7 (14%)
GRANULOMA, NOS			1 (2%)
GRANULOMA, SPERMATIC		1 (2%)	
ATROPHY, NOS			1 (2%)
ASPERMATOGENESIS			1 (2%)
HYPERPLASIA, INTERSTITIAL CELL	1 (2%)	1 (2%)	
#TESTIS/TUBULE	(50)	(50)	(50)
DILATATION, NOS	1 (2%)		
MULTINUCLEATE GIANT-CELL			1 (2%)
*EPIDIDYMIS	(50)	(50)	(50)
MINERALIZATION		2 (4%)	1 (2%)
INFLAMMATION, GRANULOMATOUS		1 (2%)	
GRANULOMA, SPERMATIC	3 (6%)	2 (4%)	1 (2%)
CYTOMEGALY		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
MINERALIZATION	29 (58%)	25 (50%)	36 (72%)
CYST, NOS		1 (2%)	

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
SYNECHIA, ANTERIOR			1 (2%)
RETINOPATHY			1 (2%)
CATARACT	1 (2%)		1 (2%)
*EYE/CORNEA	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
FIBROSIS		1 (2%)	
*EYE/CONJUNCTIVA	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
VEGETABLE FOREIGN BODY		1 (2%)	
ABSCESS, NOS		1 (2%)	
*PERITONEAL CAVITY	(50)	(50)	(50)
NECROSIS, FAT		1 (2%)	1 (2%)
*EPICARDIUM	(50)	(50)	(50)
INFLAMMATION, ACUTE		1 (2%)	
*MESENTERY	(50)	(50)	(50)
NECROSIS, FAT			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
CONGESTION, NOS	2 (4%)		
HEMORRHAGE			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	21 (42%)	17 (34%)	10 (20%)
INFLAMMATION, ACUTE	3 (6%)	1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)
INFLAMMATION, GRANULOMATOUS			1 (2%)
BACTERIAL SEPTICEMIA	2 (4%)		
NECROSIS, FAT			1 (2%)
HEMOSIDEROSIS	1 (2%)		
TAIL			
INFLAMMATION, ACUTE NECROTIZING	1		
ADIPOSE TISSUE			
NECROSIS, FAT	1		
SPECIAL MORPHOLOGY SUMMARY			
NONE			

* NUMBER OF ANIMALS RECEIVING COMPLETE NECROPSY EXAMINATION; ALL GROSS LESIONS INCLUDING MASSES EXAMINED MICROSCOPICALLY.
# NUMBER OF ANIMALS EXAMINED MICROSCOPICALLY AT THIS SITE

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		2	2
ANIMALS NECROPSIED	50	48	44
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	48	44
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(48)	(44)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
RESPIRATORY SYSTEM			
*NASAL CAVITY	(50)	(48)	(44)
CONGESTION, NOS			1 (2%)
HEMORRHAGE			2 (5%)
INFLAMMATION, ACUTE			5 (11%)
#LUNG	(50)	(48)	(43)
ATELECTASIS	1 (2%)		
CONGESTION, NOS	1 (2%)		2 (5%)
HEMORRHAGE	1 (2%)	1 (2%)	1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)	1 (2%)	
INFLAMMATION, ACUTE		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	2 (4%)	1 (2%)	2 (5%)
HISTIOCYTOSIS		1 (2%)	3 (7%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(48)	(44)
LEUKEMOID REACTION			1 (2%)
HYPERPLASIA, LYMPHOID	1 (2%)	5 (10%)	3 (7%)
HEMATOPOIESIS		1 (2%)	1 (2%)
MYELOPOIESIS	1 (2%)		
#BONE MARROW	(48)	(47)	(44)
MYELOSCLEROSIS	39 (81%)	39 (83%)	26 (59%)
#SPLEEN	(50)	(48)	(43)
HEMOSIDEROSIS	7 (14%)	9 (19%)	4 (9%)
HYPERPLASIA, LYMPHOID	5 (10%)	5 (10%)	
HEMATOPOIESIS	5 (10%)	1 (2%)	3 (7%)
#LYMPH NODE	(39)	(32)	(28)
HYPERPLASIA, LYMPHOID		1 (3%)	
#MANDIBULAR L. NODE	(39)	(32)	(28)
HYPERPLASIA, LYMPHOID	1 (3%)		
#MEDIASTINAL L. NODE	(39)	(32)	(28)
PLASMACYTOSIS	1 (3%)		
HYPERPLASIA, LYMPHOID	1 (3%)		
#HEPATIC LYMPH NODE	(39)	(32)	(28)
HYPERPLASIA, LYMPHOID			1 (4%)
#MESENTERIC L. NODE	(39)	(32)	(28)
HEMORRHAGE			2 (7%)
#RENAL LYMPH NODE	(39)	(32)	(28)
HYPERPLASIA, LYMPHOID	1 (3%)		
#LIVER	(50)	(48)	(44)
HEMATOPOIESIS		3 (6%)	
#ADRENAL	(49)	(48)	(44)
HEMATOPOIESIS	1 (2%)		
#THYMUS	(42)	(43)	(36)
CYST, NOS	4 (10%)	6 (14%)	3 (8%)
MULTIPLE CYSTS		2 (5%)	
HEMORRHAGE			1 (3%)
HYPERPLASIA, LYMPHOID		1 (2%)	

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#THYMIC LYMPHOCYTES	(42)	(43)	(36)
NECROSIS, NOS	1 (2%)		
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(48)	(44)
PERIVASCULITIS		1 (2%)	
#HEART	(50)	(48)	(43)
MINERALIZATION	1 (2%)	1 (2%)	1 (2%)
HEMORRHAGE		1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)
#HEART/VENTRICLE	(50)	(48)	(43)
DEGENERATION, NOS		1 (2%)	
#CARDIAC VALVE	(50)	(48)	(43)
PIGMENTATION, NOS	4 (8%)	9 (19%)	1 (2%)
*AORTA	(50)	(48)	(44)
MINERALIZATION		1 (2%)	
#UTERUS/ENDOMETRIUM	(50)	(48)	(44)
THROMBOSIS, NOS			1 (2%)
#ADRENAL	(49)	(48)	(44)
THROMBOSIS, NOS		1 (2%)	
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(50)	(47)	(43)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
CYTOPLASMIC VACUOLIZATION			1 (2%)
#LIVER	(50)	(48)	(44)
ABNORMAL CURVATURE	1 (2%)	1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR			2 (5%)
INFLAMMATION, ACUTE	1 (2%)	2 (4%)	
GRANULOMA, NOS	1 (2%)		
CHOLANGIOFIBROSIS		1 (2%)	
NECROSIS, NOS	1 (2%)		3 (7%)
CYTOPLASMIC VACUOLIZATION	27 (54%)	38 (79%)	23 (52%)
BASOPHILIC CYTO CHANGE			2 (5%)
CLEAR-CELL CHANGE	10 (20%)	9 (19%)	6 (14%)
HEPATOCYTOMEGALY		1 (2%)	1 (2%)
ATROPHY, NOS			1 (2%)
ANGIECTASIS	1 (2%)	1 (2%)	1 (2%)
#LIVER/KUPFFER CELL	(50)	(48)	(44)
HYPERPLASIA, NOS	1 (2%)		1 (2%)
*GALLBLADDER	(50)	(48)	(44)
CYST, NOS	1 (2%)		
#BILE DUCT	(50)	(48)	(44)
DILATATION, NOS			1 (2%)
#PANCREAS	(49)	(48)	(41)
DILATATION/DUCTS	1 (2%)	1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	
#PANCREATIC ACINUS	(49)	(48)	(41)
ATROPHY, NOS	9 (18%)	3 (6%)	3 (7%)
ATROPHY, EXHAUSTION			1 (2%)
HYPERTROPHY, FOCAL	1 (2%)		2 (5%)
#ESOPHAGUS	(49)	(48)	(39)
VEGETABLE FOREIGN BODY			1 (3%)
INFLAMMATION, ACUTE			1 (3%)
#STOMACH	(50)	(48)	(44)
INFLAMMATION, ACUTE			1 (2%)
#GASTRIC FUNDAL GLAND	(50)	(48)	(44)
DILATATION, NOS	1 (2%)	1 (2%)	
DEGENERATION, BALLOONING			1 (2%)

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#GLANDULAR STOMACH	(50)	(48)	(44)
HYPERPLASIA, EPITHELIAL	1 (2%)		
#FORESTOMACH	(50)	(48)	(44)
ANIMAL FOREIGN BODY		1 (2%)	
DIVERTICULUM	1 (2%)		
INFLAMMATION, ACUTE	1 (2%)	1 (2%)	6 (14%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)	2 (4%)	3 (7%)
HYPERPLASIA, EPITHELIAL	4 (8%)	6 (13%)	13 (30%)
URINARY SYSTEM			
#KIDNEY	(50)	(48)	(44)
MINERALIZATION	2 (4%)	1 (2%)	1 (2%)
HYDRONEPHROSIS	1 (2%)	2 (4%)	
CYST, NOS			1 (2%)
GLOMERULONEPHRITIS, NOS			3 (7%)
LYMPHOCYTIC INFLAMMATORY INFILTR	4 (8%)	2 (4%)	3 (7%)
PYELONEPHRITIS, CHRONIC		1 (2%)	
DEGENERATION, HYALINE	1 (2%)		
NEPHROSIS, NOS	2 (4%)	4 (8%)	5 (11%)
INFARCT, NOS	4 (8%)	3 (6%)	
CYTOPLASMIC VACUOLIZATION			1 (2%)
METAPLASIA, OSSEOUS	2 (4%)	4 (8%)	2 (5%)
#KIDNEY/TUBULE	(50)	(48)	(44)
DILATATION, NOS	1 (2%)		
#URINARY BLADDER	(49)	(43)	(38)
MINERALIZATION		1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR	3 (6%)		3 (8%)
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(47)	(39)
CYST, NOS	1 (2%)		
CONGESTION, NOS	1 (2%)		1 (3%)
HEMORRHAGE, CHRONIC	1 (2%)		
ANGIECTASIS		1 (2%)	1 (3%)
#ANTERIOR PITUITARY	(46)	(47)	(39)
COLLOID CYST		1 (2%)	1 (3%)
MULTIPLE CYSTS		1 (2%)	
HYPERPLASIA, CHROMOPHOBE-CELL	5 (11%)	9 (19%)	6 (15%)
ANGIECTASIS	1 (2%)	2 (4%)	
#ADRENAL	(49)	(48)	(44)
ANGIECTASIS	1 (2%)		
#ADRENAL CORTEX	(49)	(48)	(44)
DEGENERATION, BALLOONING		1 (2%)	
CYTOPLASMIC VACUOLIZATION	2 (4%)		
CYTOPLASMIC AGGREGATE, NOS			1 (2%)
ATROPHY, BROWN	14 (29%)	13 (27%)	5 (11%)
HYPERTROPHY, FOCAL	2 (4%)	2 (4%)	1 (2%)
HYPERTROPHY, DIFFUSE	1 (2%)		
HYPERPLASIA, NOS		1 (2%)	
ANGIECTASIS	1 (2%)		
#ADRENAL MEDULLA	(49)	(48)	(44)
HYPERPLASIA, NOS	1 (2%)		
#THYROID	(44)	(47)	(38)
FOLLICULAR CYST, NOS	5 (11%)	17 (36%)	8 (21%)
HYPERPLASIA, FOLLICULAR-CELL	4 (9%)	5 (11%)	4 (11%)

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(48)	(44)
DILATATION/DUCTS	4 (8%)	1 (2%)	3 (7%)
HYPERPLASIA, NOS	1 (2%)	3 (6%)	2 (5%)
LACTATION	2 (4%)	1 (2%)	
*CLITORAL GLAND	(50)	(48)	(44)
DILATATION, NOS	1 (2%)		
#UTERUS	(50)	(48)	(44)
DILATATION, NOS			1 (2%)
HYDROMETRA		1 (2%)	1 (2%)
HEMORRHAGIC CYST	1 (2%)	1 (2%)	
ABSCESS, NOS			1 (2%)
ANGIECTASIS			1 (2%)
#UTERUS/ENDOMETRIUM	(50)	(48)	(44)
CYST, NOS	3 (6%)	4 (8%)	9 (20%)
INFLAMMATION, ACUTE	1 (2%)		
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, CYSTIC	36 (72%)	41 (85%)	26 (59%)
HYPERPLASIA, STROMAL			1 (2%)
METAPLASIA, SQUAMOUS			1 (2%)
#FALLOPIAN TUBE	(50)	(48)	(44)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
INFLAMMATION, ACUTE			1 (2%)
#OVARY/PAROVARIAN	(49)	(48)	(44)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
ABSCESS, NOS	1 (2%)		2 (5%)
#OVARY	(49)	(48)	(44)
MINERALIZATION			1 (2%)
CYST, NOS	19 (39%)	14 (29%)	11 (25%)
HEMORRHAGIC CYST		3 (6%)	
HYPERPLASIA, PAPILLARY	1 (2%)		
#OVARIAN LIGAMENT	(49)	(48)	(44)
ABSCESS, NOS			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(50)	(48)	(43)
MINERALIZATION	29 (58%)	28 (58%)	19 (44%)
HYDROCEPHALUS, NOS			1 (2%)
FIBROSIS			1 (2%)
CYTOPLASMIC VACUOLIZATION		3 (6%)	
SPECIAL SENSE ORGANS			
*EYE/CORNEA	(50)	(48)	(44)
INFLAMMATION, ACUTE		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
*EUSTACHIAN TUBE	(50)	(48)	(44)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MEDIASTINUM	(50)	(48)	(44)
NECROSIS, FAT	1 (2%)		

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(48)	(44)
LYMPHOCYTIC INFLAMMATORY INFILTR	24 (48%)	28 (58%)	14 (32%)
INFLAMMATION, ACUTE	1 (2%)		
BACTERIAL SEPTICEMIA			1 (2%)
NECROSIS, FAT	1 (2%)		
TAIL			
FIBROUS OSTEODYSTROPHY	1		
OMENTUM			
NECROSIS, FAT		1	
UTERINE LIGAMENT			
ABSCESS, NOS			1
SPECIAL MORPHOLOGY SUMMARY			
ANIMAL MISSING/NO NECROPSY		2	2
NO NECROPSY PERFORMED			4

* NUMBER OF ANIMALS RECEIVING COMPLETE NECROPSY EXAMINATION; ALL GROSS LESIONS INCLUDING MASSES EXAMINED MICROSCOPICALLY.
# NUMBER OF ANIMALS EXAMINED MICROSCOPICALLY AT THIS SITE

APPENDIX E

ANALYSES OF PRIMARY TUMORS IN RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE

	Vehicle Control	75 mg/kg	150 mg/kg
Skin: Keratoacanthoma			
Overall Rates (a)	5/50 (10%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	14.8%	0.0%	0.0%
Terminal Rates (c)	3/30 (10%)	0/25 (0%)	0/17 (0%)
Life Table Tests (d)	P=0.013N	P=0.046N	P=0.069N
Incidental Tumor Tests (d)	P=0.008N	P=0.033N	P=0.054N
Cochran-Armitage Trend Test (d)	P=0.006N		
Fisher Exact Test		P=0.028N	P=0.028N
Integumentary System: Keratoacanthoma			
Overall Rates (a)	6/50 (12%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	17.9%	0.0%	0.0%
Terminal Rates (c)	4/30 (13%)	0/25 (0%)	0/17 (0%)
Life Table Tests (d)	P=0.006N	P=0.027N	P=0.047N
Incidental Tumor Tests (d)	P=0.004N	P=0.019N	P=0.036N
Cochran-Armitage Trend Test (d)	P=0.003N		
Fisher Exact Test		P=0.013N	P=0.013N
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	8.1%	0.0%	0.0%
Terminal Rates (c)	1/30 (3%)	0/25 (0%)	0/17 (0%)
Life Table Tests (d)	P=0.046N	P=0.129N	P=0.150N
Incidental Tumor Tests (d)	P=0.015N	P=0.028N	P=0.058N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test		P=0.121N	P=0.121N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	10.8%	8.0%	11.8%
Terminal Rates (c)	1/30 (3%)	2/25 (8%)	2/17 (12%)
Life Table Tests (d)	P=0.390N	P=0.384N	P=0.466N
Incidental Tumor Tests (d)	P=0.283N	P=0.216N	P=0.294N
Cochran-Armitage Trend Test (d)	P=0.252N		
Fisher Exact Test		P=0.339N	P=0.339N
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	9/50 (18%)	2/50 (4%)	7/50 (14%)
Adjusted Rates (b)	26.3%	6.3%	27.7%
Terminal Rates (c)	6/30 (20%)	1/25 (4%)	3/17 (18%)
Life Table Tests (d)	P=0.548N	P=0.045N	P=0.537
Incidental Tumor Tests (d)	P=0.318N	P=0.014N	P=0.442N
Cochran-Armitage Trend Test (d)	P=0.322N		
Fisher Exact Test		P=0.026N	P=0.393N
Liver: Neoplastic Nodule			
Overall Rates (a)	2/50 (4%)	0/50 (0%)	3/48 (6%)
Adjusted Rates (b)	6.7%	0.0%	14.4%
Terminal Rates (c)	2/30 (7%)	0/25 (0%)	2/17 (12%)
Life Table Tests (d)	P=0.236	P=0.279N	P=0.291
Incidental Tumor Tests (d)	P=0.291	P=0.279N	P=0.360
Cochran-Armitage Trend Test (d)	P=0.375		
Fisher Exact Test		P=0.247N	P=0.480
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Overall Rates (a)	2/50 (4%)	0/50 (0%)	5/48 (10%)
Adjusted Rates (b)	6.7%	0.0%	20.7%
Terminal Rates (c)	2/30 (7%)	0/25 (0%)	2/17 (12%)
Life Table Tests (d)	P=0.055	P=0.279N	P=0.095
Incidental Tumor Tests (d)	P=0.119	P=0.279N	P=0.201
Cochran-Armitage Trend Test (d)	P=0.108		
Fisher Exact Test		P=0.247N	P=0.201

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	Vehicle Control	75 mg/kg	150 mg/kg
Pancreas: Acinar Cell Adenoma			
Overall Rates (a)	4/50 (8%)	1/50 (2%)	0/48 (0%)
Adjusted Rates (b)	13.3%	4.0%	0.0%
Terminal Rates (c)	4/30 (13%)	1/25 (4%)	0/17 (0%)
Life Table Tests (d)	P=0.064N	P=0.235N	P=0.154N
Incidental Tumor Tests (d)	P=0.064N	P=0.235N	P=0.154N
Cochran-Armitage Trend Test (d)	P=0.027N		
Fisher Exact Test		P=0.181N	P=0.064N
Forestomach: Papilloma			
Overall Rates (a)	1/50 (2%)	5/50 (10%)	(e) 30/48 (63%)
Adjusted Rates (b)	2.6%	15.5%	89.9%
Terminal Rates (c)	0/30 (0%)	1/25 (4%)	14/17 (82%)
Life Table Tests (d)	P<0.001	P=0.084	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.167	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test		P=0.102	P<0.001
Pituitary: Adenoma			
Overall Rates (a)	9/49 (18%)	8/50 (16%)	3/50 (6%)
Adjusted Rates (b)	24.7%	23.5%	17.6%
Terminal Rates (c)	5/30 (17%)	3/25 (12%)	3/17 (18%)
Life Table Tests (d)	P=0.159N	P=0.586N	P=0.196N
Incidental Tumor Tests (d)	P=0.050N	P=0.339N	P=0.145N
Cochran-Armitage Trend Test (d)	P=0.048N		
Fisher Exact Test		P=0.482N	P=0.056N
Adrenal: Cortical Adenoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	1/48 (2%)
Adjusted Rates (b)	10.0%	0.0%	3.3%
Terminal Rates (c)	3/30 (10%)	0/25 (0%)	0/17 (0%)
Life Table Tests (d)	P=0.276N	P=0.154N	P=0.471N
Incidental Tumor Tests (d)	P=0.218N	P=0.154N	P=0.389N
Cochran-Armitage Trend Test (d)	P=0.184N		
Fisher Exact Test		P=0.121N	P=0.324N
Adrenal: Pheochromocytoma			
Overall Rates (a)	14/50 (28%)	8/50 (16%)	4/48 (8%)
Adjusted Rates (b)	43.6%	30.1%	14.6%
Terminal Rates (c)	12/30 (40%)	7/25 (28%)	1/17 (6%)
Life Table Tests (d)	P=0.056N	P=0.216N	P=0.078N
Incidental Tumor Tests (d)	P=0.015N	P=0.188N	P=0.015N
Cochran-Armitage Trend Test (d)	P=0.008N		
Fisher Exact Test		P=0.114N	P=0.011N
Adrenal: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	14/50 (28%)	8/50 (16%)	5/48 (10%)
Adjusted Rates (b)	43.6%	30.1%	18.2%
Terminal Rates (c)	12/30 (40%)	7/25 (28%)	1/17 (6%)
Life Table Tests (d)	P=0.104N	P=0.216N	P=0.141N
Incidental Tumor Tests (d)	P=0.027N	P=0.188N	P=0.026N
Cochran-Armitage Trend Test (d)	P=0.017N		
Fisher Exact Test		P=0.114N	P=0.025N
Thyroid: C-Cell Adenoma			
Overall Rates (a)	3/49 (6%)	3/48 (6%)	0/48 (0%)
Adjusted Rates (b)	10.0%	12.0%	0.0%
Terminal Rates (c)	3/30 (10%)	3/25 (12%)	0/17 (0%)
Life Table Tests (d)	P=0.223N	P=0.578	P=0.236N
Incidental Tumor Tests (d)	P=0.223N	P=0.578	P=0.236N
Cochran-Armitage Trend Test (d)	P=0.105N		
Fisher Exact Test		P=0.651	P=0.125N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	Vehicle Control	75 mg/kg	150 mg/kg
Thyroid: C-Cell Carcinoma			
Overall Rates (a)	4/49 (8%)	5/48 (10%)	0/48 (0%)
Adjusted Rates (b)	13.3%	18.9%	0.0%
Terminal Rates (c)	4/30 (13%)	4/25 (16%)	0/17 (0%)
Life Table Tests (d)	P=0.185N	P=0.391	P=0.154N
Incidental Tumor Tests (d)	P=0.153N	P=0.406	P=0.154N
Cochran-Armitage Trend Test (d)	P=0.074N		
Fisher Exact Test		P=0.487	P=0.061N
Thyroid: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	7/49 (14%)	8/48 (17%)	0/48 (0%)
Adjusted Rates (b)	23.3%	30.5%	0.0%
Terminal Rates (c)	7/30 (23%)	7/25 (28%)	0/17 (0%)
Life Table Tests (d)	P=0.078N	P=0.349	P=0.043N
Incidental Tumor Tests (d)	P=0.064N	P=0.360	P=0.043N
Cochran-Armitage Trend Test (d)	P=0.016N		
Fisher Exact Test		P=0.482	P=0.007N
Pancreatic Islets: Islet Cell Adenoma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	2/48 (4%)
Adjusted Rates (b)	9.4%	11.2%	10.4%
Terminal Rates (c)	1/30 (3%)	2/25 (8%)	1/17 (6%)
Life Table Tests (d)	P=0.583N	P=0.586	P=0.658N
Incidental Tumor Tests (d)	P=0.351N	P=0.650	P=0.399N
Cochran-Armitage Trend Test (d)	P=0.431N		
Fisher Exact Test		P=0.661	P=0.520N
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	3/50 (6%)	2/48 (4%)
Adjusted Rates (b)	12.5%	11.2%	10.4%
Terminal Rates (c)	2/30 (7%)	2/25 (8%)	1/17 (6%)
Life Table Tests (d)	P=0.442N	P=0.587N	P=0.528N
Incidental Tumor Tests (d)	P=0.237N	P=0.530N	P=0.289N
Cochran-Armitage Trend Test (d)	P=0.280N		
Fisher Exact Test		P=0.500N	P=0.359N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	0.0%	12.0%	2.5%
Terminal Rates (c)	0/30 (0%)	3/25 (12%)	0/17 (0%)
Life Table Tests (d)	P=0.256	P=0.090	P=0.505
Incidental Tumor Tests (d)	P=0.334	P=0.090	P=0.892
Cochran-Armitage Trend Test (d)	P=0.378		
Fisher Exact Test		P=0.121	P=0.500
Preputial Gland: Carcinoma			
Overall Rates (a)	3/50 (6%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	9.6%	16.0%	2.7%
Terminal Rates (c)	2/30 (7%)	4/25 (16%)	0/17 (0%)
Life Table Tests (d)	P=0.430N	P=0.407	P=0.419N
Incidental Tumor Tests (d)	P=0.303N	P=0.424	P=0.183N
Cochran-Armitage Trend Test (d)	P=0.252N		
Fisher Exact Test		P=0.500	P=0.309N
Preputial Gland: Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	5/50 (10%)	1/50 (2%)
Adjusted Rates (b)	16.0%	20.0%	2.7%
Terminal Rates (c)	4/30 (13%)	5/25 (20%)	0/17 (0%)
Life Table Tests (d)	P=0.231N	P=0.518	P=0.214N
Incidental Tumor Tests (d)	P=0.148N	P=0.533	P=0.081N
Cochran-Armitage Trend Test (d)	P=0.090N		
Fisher Exact Test		P=0.630	P=0.102N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	Vehicle Control	75 mg/kg	150 mg/kg
Prostate: Adenoma			
Overall Rates (a)	1/47 (2%)	1/49 (2%)	3/48 (6%)
Adjusted Rates (b)	3.4%	4.0%	17.6%
Terminal Rates (c)	1/29 (3%)	1/25 (4%)	3/17 (18%)
Life Table Tests (d)	P=0.085	P=0.729	P=0.137
Incidental Tumor Tests (d)	P=0.085	P=0.729	P=0.137
Cochran-Armitage Trend Test (d)	P=0.206		
Fisher Exact Test		P=0.742N	P=0.316
Testis: Interstitial Cell Tumor			
Overall Rates (a)	36/50 (72%)	43/50 (86%)	43/48 (90%)
Adjusted Rates (b)	97.3%	100.0%	100.0%
Terminal Rates (c)	29/30 (97%)	25/25 (100%)	17/17 (100%)
Life Table Tests (d)	P<0.001	P=0.009	P<0.001
Incidental Tumor Tests (d)	P=0.003	P=0.067	P=0.012
Cochran-Armitage Trend Test (d)	P=0.015		
Fisher Exact Test		P=0.070	P=0.025
All Sites: Mesothelioma			
Overall Rates (a)	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	3.3%	8.0%	14.7%
Terminal Rates (c)	1/30 (3%)	2/25 (8%)	2/17 (12%)
Life Table Tests (d)	P=0.101	P=0.436	P=0.165
Incidental Tumor Tests (d)	P=0.130	P=0.436	P=0.217
Cochran-Armitage Trend Test (d)	P=0.222		
Fisher Exact Test		P=0.500	P=0.309

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence. A negative trend or lower incidence is indicated by (N).
(e) Two animals also had squamous cell carcinomas.

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE

	Vehicle Control	75 mg/kg	150 mg/kg
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	0/50 (0%)	2/50 (4%)	4/50 (8%)
Adjusted Rates (b)	0.0%	6.3%	13.7%
Terminal Rates (c)	0/31 (0%)	2/32 (6%)	2/26 (8%)
Life Table Tests (d)	P=0.024	P=0.245	P=0.047
Incidental Tumor Tests (d)	P=0.030	P=0.245	P=0.060
Cochran-Armitage Trend Test (d)	P=0.037		
Fisher Exact Test		P=0.247	P=0.059
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	4/50 (8%)
Adjusted Rates (b)	3.2%	9.4%	13.7%
Terminal Rates (c)	1/31 (3%)	3/32 (9%)	2/26 (8%)
Life Table Tests (d)	P=0.093	P=0.316	P=0.138
Incidental Tumor Tests (d)	P=0.106	P=0.316	P=0.162
Cochran-Armitage Trend Test (d)	P=0.133		
Fisher Exact Test		P=0.309	P=0.181
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	5/50 (10%)
Adjusted Rates (b)	3.2%	9.4%	16.1%
Terminal Rates (c)	1/31 (3%)	3/32 (9%)	2/26 (8%)
Life Table Tests (d)	P=0.046	P=0.316	P=0.077
Incidental Tumor Tests (d)	P=0.056	P=0.316	P=0.093
Cochran-Armitage Trend Test (d)			
Fisher Exact Test (d)	P=0.070	P=0.309	P=0.102
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	16/50 (32%)	13/50 (26%)	10/50 (20%)
Adjusted Rates (b)	38.8%	32.9%	26.5%
Terminal Rates (c)	7/31 (23%)	7/32 (22%)	1/26 (4%)
Life Table Tests (d)	P=0.224N	P=0.312N	P=0.263N
Incidental Tumor Tests (d)	P=0.083N	P=0.422N	P=0.087N
Cochran-Armitage Trend Test (d)	P=0.105N		
Fisher Exact Test		P=0.330N	P=0.127N
Forestomach: Papilloma			
Overall Rates (a)	1/50 (2%)	1/50 (2%)	10/50 (20%)
Adjusted Rates (b)	3.1%	3.1%	32.0%
Terminal Rates (c)	0/31 (0%)	1/32 (3%)	7/26 (27%)
Life Table Tests (d)	P<0.001	P=0.753N	P=0.003
Incidental Tumor Tests (d)	P=0.001	P=0.720N	P=0.006
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test		P=0.753N	P=0.004
Pituitary: Adenoma			
Overall Rates (a)	19/50 (38%)	21/50 (42%)	20/49 (41%)
Adjusted Rates (b)	49.3%	57.9%	65.7%
Terminal Rates (c)	12/31 (39%)	17/32 (53%)	15/25 (60%)
Life Table Tests (d)	P=0.196	P=0.470	P=0.230
Incidental Tumor Tests (d)	P=0.299	P=0.482	P=0.365
Cochran-Armitage Trend Test (d)	P=0.427		
Fisher Exact Test		P=0.419	P=0.468
Adrenal: Cortical Adenoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	9.7%	3.1%	10.4%
Terminal Rates (c)	3/31 (10%)	1/32 (3%)	2/26 (8%)
Life Table Tests (d)	P=0.525	P=0.293N	P=0.585
Incidental Tumor Tests (d)	P=0.531	P=0.293N	P=0.594
Cochran-Armitage Trend Test (d)	P=0.594		
Fisher Exact Test		P=0.309N	P=0.661

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	Vehicle Control	75 mg/kg	150 mg/kg
Adrenal: Pheochromocytoma			
Overall Rates (a)	4/50 (8%)	1/50 (2%)	4/50 (8%)
Adjusted Rates (b)	12.1%	3.1%	14.4%
Terminal Rates (c)	3/31 (10%)	1/32 (3%)	3/26 (12%)
Life Table Tests (d)	P=0.505	P=0.170N	P=0.552
Incidental Tumor Tests (d)	P=0.528	P=0.200N	P=0.582
Cochran-Armitage Trend Test (d)	P=0.583		
Fisher Exact Test		P=0.181N	P=0.643
Thyroid: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	1/50 (2%)	3/48 (6%)	3/49 (6%)
Adjusted Rates (b)	3.2%	10.0%	9.5%
Terminal Rates (c)	1/31 (3%)	3/30 (10%)	1/26 (4%)
Life Table Tests (d)	P=0.186	P=0.292	P=0.255
Incidental Tumor Tests (d)	P=0.207	P=0.292	P=0.292
Cochran-Armitage Trend Test (d)	P=0.233		
Fisher Exact Test		P=0.293	P=0.301
Thyroid: C-Cell Adenoma			
Overall Rates (a)	6/50 (12%)	1/48 (2%)	0/49 (0%)
Adjusted Rates (b)	17.8%	3.0%	0.0%
Terminal Rates (c)	4/31 (13%)	0/30 (0%)	0/26 (0%)
Life Table Tests (d)	P=0.008N	P=0.063N	P=0.031N
Incidental Tumor Tests (d)	P=0.004N	P=0.037N	P=0.020N
Cochran-Armitage Trend Test (d)	P=0.005N		
Fisher Exact Test		P=0.062N	P=0.014N
Thyroid: C-Cell Carcinoma			
Overall Rates (a)	2/50 (4%)	5/48 (10%)	5/49 (10%)
Adjusted Rates (b)	6.5%	16.7%	19.2%
Terminal Rates (c)	2/31 (6%)	5/30 (17%)	5/26 (19%)
Life Table Tests (d)	P=0.111	P=0.200	P=0.147
Incidental Tumor Tests (d)	P=0.111	P=0.200	P=0.147
Cochran-Armitage Trend Test (d)	P=0.172		
Fisher Exact Test		P=0.201	P=0.210
Thyroid: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	8/50 (16%)	6/48 (13%)	5/49 (10%)
Adjusted Rates (b)	23.9%	19.2%	19.2%
Terminal Rates (c)	6/31 (19%)	5/30 (17%)	5/26 (19%)
Life Table Tests (d)	P=0.333N	P=0.400N	P=0.399N
Incidental Tumor Tests (d)	P=0.292N	P=0.349N	P=0.355N
Cochran-Armitage Trend Test (d)	P=0.239N		
Fisher Exact Test		P=0.419N	P=0.290N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	14/50 (28%)	15/50 (30%)	10/50 (20%)
Adjusted Rates (b)	40.4%	45.0%	33.6%
Terminal Rates (c)	11/31 (35%)	14/32 (44%)	7/26 (27%)
Life Table Tests (d)	P=0.368N	P=0.537	P=0.409N
Incidental Tumor Tests (d)	P=0.284N	P=0.504	P=0.314N
Cochran-Armitage Trend Test (d)	P=0.212N		
Fisher Exact Test		P=0.500	P=0.241N
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (a)	18/50 (36%)	17/50 (34%)	12/50 (24%)
Adjusted Rates (b)	49.2%	49.5%	40.6%
Terminal Rates (c)	13/31 (42%)	15/32 (47%)	9/26 (35%)
Life Table Tests (d)	P=0.252N	P=0.457N	P=0.295N
Incidental Tumor Tests (d)	P=0.170N	P=0.483N	P=0.199N
Cochran-Armitage Trend Test (d)	P=0.118N		
Fisher Exact Test		P=0.500N	P=0.138N

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	Vehicle Control	75 mg/kg	150 mg/kg
Mammary Gland: Adenoma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	11.4%	5.8%	11.5%
Terminal Rates (c)	2/31 (6%)	1/32 (3%)	3/26 (12%)
Life Table Tests (d)	P=0.493N	P=0.325N	P=0.588N
Incidental Tumor Tests (d)	P=0.454N	P=0.314N	P=0.554N
Cochran-Armitage Trend Test (d)	P=0.417N		
Fisher Exact Test		P=0.339N	P=0.500N
Mammary Gland: Adenoma or Cystadenoma			
Overall Rates (a)	5/50 (10%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	14.0%	8.9%	11.5%
Terminal Rates (c)	2/31 (6%)	2/32 (6%)	3/26 (12%)
Life Table Tests (d)	P=0.363N	P=0.343N	P=0.454N
Incidental Tumor Tests (d)	P=0.309N	P=0.309N	P=0.392N
Cochran-Armitage Trend Test (d)	P=0.283N		
Fisher Exact Test		P=0.357N	P=0.357N
Mammary Gland: Adenoma, Cystadenoma or Adenocarcinoma			
Overall Rates (a)	5/50 (10%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	14.0%	11.9%	14.8%
Terminal Rates (c)	2/31 (6%)	3/32 (9%)	3/26 (12%)
Life Table Tests (d)	P=0.528N	P=0.480N	P=0.603N
Incidental Tumor Tests (d)	P=0.460N	P=0.451N	P=0.523N
Cochran-Armitage Trend Test (d)	P=0.429N		
Fisher Exact Test		P=0.500N	P=0.500N
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	7/50 (14%)	9/50 (18%)	8/49 (16%)
Adjusted Rates (b)	19.5%	26.8%	28.8%
Terminal Rates (c)	4/31 (13%)	8/32 (25%)	7/26 (27%)
Life Table Tests (d)	P=0.314	P=0.426	P=0.371
Incidental Tumor Tests (d)	P=0.330	P=0.313	P=0.391
Cochran-Armitage Trend Test (d)	P=0.428		
Fisher Exact Test		P=0.393	P=0.483

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence. A negative trend or lower incidence is indicated by (N).

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE

	Vehicle Control	100 mg/kg	200 mg/kg
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	3.8%	0.0%	8.9%
Terminal Rates (c)	1/26 (4%)	0/37 (0%)	2/32 (6%)
Life Table Tests (d)	P=0.209	P=0.430N	P=0.381
Incidental Tumor Tests (d)	P=0.205	P=0.430N	P=0.363
Cochran-Armitage Trend Test (d)	P=0.176		
Fisher Exact Test		P=0.500N	P=0.309
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	3/50 (6%)	4/50 (8%)	2/48 (4%)
Adjusted Rates (b)	10.9%	10.8%	6.7%
Terminal Rates (c)	2/26 (8%)	4/37 (11%)	2/30 (7%)
Life Table Tests (d)	P=0.344N	P=0.622N	P=0.431N
Incidental Tumor Tests (d)	P=0.355N	P=0.632	P=0.448N
Cochran-Armitage Trend Test (d)	P=0.436N		
Fisher Exact Test		P=0.500	P=0.520N
Lung: Alvolar/Bronchiolar Carcinoma			
Overall Rates (a)	4/50 (8%)	6/50 (12%)	1/48 (2%)
Adjusted Rates (b)	13.6%	16.2%	3.3%
Terminal Rates (c)	3/26 (12%)	6/37 (16%)	1/30 (3%)
Life Table Tests (d)	P=0.115N	P=0.583	P=0.144N
Incidental Tumor Tests (d)	P=0.167N	P=0.487	P=0.218N
Cochran-Armitage Trend Test (d)	P=0.183N		
Fisher Exact Test		P=0.370	P=0.194N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	7/50 (14%)	10/50 (20%)	3/48 (6%)
Adjusted Rates (b)	23.9%	27.0%	10.0%
Terminal Rates (c)	5/26 (19%)	10/37 (27%)	3/30 (10%)
Life Table Tests (d)	P=0.085N	P=0.591	P=0.108N
Incidental Tumor Tests (d)	P=0.122N	P=0.472	P=0.160N
Cochran-Armitage Trend Test (d)	P=0.170N		
Fisher Exact Test		P=0.298	P=0.176N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	11.8%	5.1%	4.9%
Terminal Rates (c)	1/26 (4%)	1/37 (3%)	0/32 (0%)
Life Table Tests (d)	P=0.196N	P=0.227N	P=0.275N
Incidental Tumor Tests (d)	P=0.318N	P=0.485N	P=0.423N
Cochran-Armitage Trend Test (d)	P=0.252N		
Fisher Exact Test		P=0.339N	P=0.339N
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	2/50 (4%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	6.6%	5.4%	8.3%
Terminal Rates (c)	0/26 (0%)	2/37 (5%)	2/32 (6%)
Life Table Tests (d)	P=0.480	P=0.569N	P=0.578
Incidental Tumor Tests (d)	P=0.347	P=0.689	P=0.413
Cochran-Armitage Trend Test (d)	P=0.406		
Fisher Exact Test		P=0.691N	P=0.500
Liver: Hepatocellular Adenoma			
Overall Rates (a)	4/50 (8%)	7/50 (14%)	2/50 (4%)
Adjusted Rates (b)	13.9%	18.9%	6.3%
Terminal Rates (c)	3/26 (12%)	7/37 (19%)	2/32 (6%)
Life Table Tests (d)	P=0.193N	P=0.478	P=0.251N
Incidental Tumor Tests (d)	P=0.200N	P=0.441	P=0.261N
Cochran-Armitage Trend Test (d)	P=0.297N		
Fisher Exact Test		P=0.262	P=0.339N

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	19/50 (38%)	10/50 (20%)	11/50 (22%)
Adjusted Rates (b)	49.7%	24.5%	28.9%
Terminal Rates (c)	8/26 (31%)	7/37 (19%)	6/32 (19%)
Life Table Tests (d)	P=0.019N	P=0.008N	P=0.031N
Incidental Tumor Tests (d)	P=0.046N	P=0.061N	P=0.069N
Cochran-Armitage Trend Test (d)	P=0.045N		
Fisher Exact Test		P=0.038N	P=0.063N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	22/50 (44%)	16/50 (32%)	13/50 (26%)
Adjusted Rates (b)	56.5%	39.6%	34.4%
Terminal Rates (c)	10/26 (38%)	13/37 (35%)	8/32 (25%)
Life Table Tests (d)	P=0.012N	P=0.025N	P=0.020N
Incidental Tumor Tests (d)	P=0.027N	P=0.149N	P=0.042N
Cochran-Armitage Trend Test (d)	P=0.036N		
Fisher Exact Test		P=0.151N	P=0.046N
Forestomach: Squamous Cell Papilloma			
Overall Rates (a)	3/49 (6%)	19/49 (39%)	30/49 (61%)
Adjusted Rates (b)	10.3%	46.0%	74.5%
Terminal Rates (c)	2/26 (8%)	15/37 (41%)	22/32 (69%)
Life Table Tests (d)	P<0.001	P=0.003	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test		P<0.001	P<0.001
Forestomach: Squamous Cell Carcinoma			
Overall Rates (a)	0/49 (0%)	5/49 (10%)	7/49 (14%)
Adjusted Rates (b)	0.0%	11.6%	19.6%
Terminal Rates (c)	0/26 (0%)	2/37 (5%)	5/32 (16%)
Life Table Tests (d)	P=0.014	P=0.061	P=0.019
Incidental Tumor Tests (d)	P=0.013	P=0.031	P=0.016
Cochran-Armitage Trend Test (d)	P=0.008		
Fisher Exact Test		P=0.028	P=0.006
Forestomach: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	3/49 (6%)	24/49 (49%)	36/49 (73%)
Adjusted Rates (b)	10.3%	54.1%	85.5%
Terminal Rates (c)	2/26 (8%)	17/37 (46%)	26/32 (81%)
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test		P<0.001	P<0.001
Harderian Gland: Papillary Adenoma			
Overall Rates (a)	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	0.0%	5.1%	8.7%
Terminal Rates (c)	0/26 (0%)	1/37 (3%)	2/32 (6%)
Life Table Tests (d)	P=0.102	P<0.001	P=0.160
Incidental Tumor Tests (d)	P=0.099	P<0.001	P=0.148
Cochran-Armitage Trend Test (d)	P=0.082		
Fisher Exact Test		P<0.001	P=0.121
Harderian Gland: Adenoma or Papillary Adenoma			
Overall Rates (a)	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	3.4%	5.1%	8.7%
Terminal Rates (c)	0/26 (0%)	1/37 (3%)	2/32 (6%)
Life Table Tests (d)	P=0.274	P=0.620	P=0.378
Incidental Tumor Tests (d)	P=0.253	P=0.446	P=0.343
Cochran-Armitage Trend Test (d)	P=0.222		
Fisher Exact Test		P=0.500	P=0.309

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE (Continued)

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence. A negative trend or lower incidence is indicated by (N).

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLPROPENE

	Vehicle Control	100 mg/kg	200 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	3/50 (6%)	2/48 (4%)	3/43 (7%)
Adjusted Rates (b)	8.1%	4.7%	10.3%
Terminal Rates (c)	3/37 (8%)	2/43 (5%)	2/27 (7%)
Life Table Tests (d)	P=0.455	P=0.431N	P=0.514
Incidental Tumor Tests (d)	P=0.433	P=0.431N	P=0.498
Cochran-Armitage Trend Test (d)	P=0.518		
Fisher Exact Test		P=0.520N	P=0.587
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	10/50 (20%)	8/48 (17%)	6/44 (14%)
Adjusted Rates (b)	23.3%	17.6%	16.7%
Terminal Rates (c)	5/37 (14%)	6/43 (14%)	1/27 (4%)
Life Table Tests (d)	P=0.360N	P=0.318N	P=0.430N
Incidental Tumor Tests (d)	P=0.176N	P=0.605N	P=0.216N
Cochran-Armitage Trend Test (d)	P=0.247N		
Fisher Exact Test		P=0.435N	P=0.295N
Hematopoietic System: Lymphoma or Leukemia			
Overall Rates (a)	12/50 (24%)	8/48 (17%)	8/44 (18%)
Adjusted Rates (b)	26.9%	17.6%	23.1%
Terminal Rates (c)	5/37 (14%)	6/43 (14%)	3/27 (11%)
Life Table Tests (d)	P=0.406N	P=0.179N	P=0.495N
Incidental Tumor Tests (d)	P=0.219N	P=0.557N	P=0.281N
Cochran-Armitage Trend Test (d)	P=0.274N		
Fisher Exact Test		P=0.258N	P=0.333N
Circulatory System: Hemangioma			
Overall Rates (a)	4/50 (8%)	0/48 (0%)	0/44 (0%)
Adjusted Rates (b)	9.8%	0.0%	0.0%
Terminal Rates (c)	2/37 (5%)	0/43 (0%)	0/27 (0%)
Life Table Tests (d)	P=0.022N	P=0.055N	P=0.115N
Incidental Tumor Tests (d)	P=0.036N	P=0.164N	P=0.107N
Cochran-Armitage Trend Test (d)	P=0.019N		
Fisher Exact Test		P=0.064N	P=0.076N
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	5/50 (10%)	0/48 (0%)	0/44 (0%)
Adjusted Rates (b)	12.0%	0.0%	0.0%
Terminal Rates (c)	2/37 (5%)	0/43 (0%)	0/27 (0%)
Life Table Tests (d)	P=0.010N	P=0.029N	P=0.072N
Incidental Tumor Tests (d)	P=0.019N	P=0.141N	P=0.060N
Cochran-Armitage Trend Test (d)	P=0.008N		
Fisher Exact Test		P=0.031N	P=0.039N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	2/50 (4%)	3/48 (6%)	0/44 (0%)
Adjusted Rates (b)	5.4%	7.0%	0.0%
Terminal Rates (c)	2/37 (5%)	3/43 (7%)	0/27 (0%)
Life Table Tests (d)	P=0.270N	P=0.569	P=0.310N
Incidental Tumor Tests (d)	P=0.270N	P=0.569	P=0.310N
Cochran-Armitage Trend Test (d)	P=0.235N		
Fisher Exact Test		P=0.480	P=0.280N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	3/48 (6%)	0/44 (0%)
Adjusted Rates (b)	10.8%	7.0%	0.0%
Terminal Rates (c)	4/37 (11%)	3/43 (7%)	0/27 (0%)
Life Table Tests (d)	P=0.075N	P=0.418N	P=0.109N
Incidental Tumor Tests (d)	P=0.075N	P=0.418N	P=0.109N
Cochran-Armitage Trend Test (d)	P=0.063N		
Fisher Exact Test		P=0.523N	P=0.076N

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 3-CHLORO-2-METHYLEPROPENE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Forestomach: Squamous Cell Papilloma			
Overall Rates (a)	0/50 (0%)	15/48 (31%)	29/44 (66%)
Adjusted Rates (b)	0.0%	32.5%	80.2%
Terminal Rates (c)	0/37 (0%)	12/43 (28%)	20/27 (74%)
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test		P<0.001	P<0.001
Forestomach: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	0/50 (0%)	16/48 (33%)	31/44 (70%)
Adjusted Rates (b)	0.0%	34.7%	81.5%
Terminal Rates (c)	0/37 (0%)	13/43 (30%)	20/27 (74%)
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test		P<0.001	P<0.001
Pituitary: Chromophobe Adenoma			
Overall Rates (a)	9/46 (20%)	11/47 (23%)	5/39 (13%)
Adjusted Rates (b)	24.5%	24.9%	19.2%
Terminal Rates (c)	8/35 (23%)	9/42 (21%)	5/26 (19%)
Life Table Tests (d)	P=0.355N	P=0.555	P=0.390N
Incidental Tumor Tests (d)	P=0.339N	P=0.548	P=0.373N
Cochran-Armitage Trend Test (d)	P=0.273N		
Fisher Exact Test		P=0.422	P=0.296N
Mammary Gland: Adenocarcinoma			
Overall Rates (a)	1/50 (2%)	4/48 (8%)	1/44 (2%)
Adjusted Rates (b)	2.2%	9.1%	3.7%
Terminal Rates (c)	0/37 (0%)	3/43 (7%)	1/27 (4%)
Life Table Tests (d)	P=0.486	P=0.213	P=0.690
Incidental Tumor Tests (d)	P=0.540	P=0.139	P=0.727N
Cochran-Armitage Trend Test (d)	P=0.550		
Fisher Exact Test		P=0.168	P=0.720

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence. A negative trend or lower incidence is indicated by (N).

APPENDIX F

HISTORICAL INCIDENCES OF TUMORS IN F344/N RATS AND B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE

TABLE F1. HISTORICAL INCIDENCE OF STOMACH TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Number of Animals Examined	Number of Tumors in Vehicle Controls	Site	Diagnosis
Historical Incidence at Litton Bionetics, Inc.				
Diallylphthalate	50	0	--	--
Tris(2-ethylhexyl)phosphate	48	0	--	--
2,4-Toluene diisocyanate	49	0	--	--
TOTAL	147	0	--	--
Overall Historical Incidence				
	1,062	1	Stomach, NOS	Squamous cell papilloma
		1	Stomach, NOS	Squamous cell carcinoma
		2	Forestomach	Squamous cell papilloma
		1	Cardiac stomach	Squamous cell papilloma
TOTAL		(b) 5 (0.5%)		

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) No more than one tumor was observed in any vehicle control group.

TABLE F2. HISTORICAL INCIDENCE OF STOMACH TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Number of Animals Examined	Number of Tumors in Vehicle Controls	Site	Diagnosis
Historical Incidence at Litton Bionetics, Inc.				
Diallylphthalate	50	0	--	--
Tris(2-ethylhexyl)phosphate	50	0	--	--
2,4-Toluene diisocyanate	50	1	Stomach, NOS	Squamous cell papilloma
TOTAL	150	1 (0.6%)		
Overall Historical Incidence				
1,073	2	Stomach, NOS	Squamous cell papilloma	
	1	Stomach, NOS	Squamous cell carcinoma	
	1	Gastric mucosa	Squamous cell papilloma	
	1	Forestomach	Squamous cell papilloma	
Total	(b) 5 (0.5%)			

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) No more than one tumor was observed in any vehicle control group.

TABLE F3. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Keratoacanthoma in Vehicle Controls
Historical Incidence at Litton Bionetics, Inc.	
Diallylphthalate	5/50
Tris(2-ethylhexyl)phosphate	1/50
2,4-Toluene diisocyanate	1/50
TOTAL	7/150 (4.7%)
SD (b)	4.62%
Range (c)	
High	5/50
Low	1/50
Overall Historical Incidence	
TOTAL	(d) 26/1,094 (2.4%)
SD (b)	2.36%
Range (c)	
High	5/50
Low	0/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Two of these tumors were observed in the subcutaneous tissue; the remaining were seen in the skin. The range is the same for both skin and integumentary system.

TABLE F4. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Fibroma	Fibrosarcoma	Fibroma or Fibrosarcoma
Historical Incidence at Litton Bionetics, Inc.			
Diallylphthalate	1/50	0/50	1/50
Tris(2-ethylhexyl)phosphate	1/50	0/50	1/50
2,4-Toluene diisocyanate	0/50	2/50	2/50
TOTAL	2/150 (1.3%)	2/150 (1.3%)	4/150 (2.7%)
SD (b)	1.15%	2.31%	1.15%
Range (c)			
High	1/50	2/50	2/50
Low	0/50	0/50	1/50
Overall Historical Incidence			
TOTAL	13/1,095 (1.2%)	7/1,095 (0.6%)	20/1,095 (1.8%)
SD (b)	1.33%	1.30%	1.50%
Range (c)			
High	2/50	2/50	2/50
Low	0/50	0/50	0/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F5. HISTORICAL INCIDENCE OF ADRENAL GLAND TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Pheochromocytoma	Malignant Pheochromocytoma	All Pheochromocytomas
Historical Incidence at Litton Bionetics, Inc.			
Diallylphthalate	13/50	0/50	13/50
Tris(2-ethylhexyl)phosphate	2/50	0/50	2/50
2,4-Toluene diisocyanate	12/50	0/50	12/50
Total	27/150 (18.0%)	0/150 (0.0%)	27/150 (18.0%)
SD (b)	12.17%	0%	12.17%
Range (c)			
High	13/50	0/50	13/50
Low	2/50	0/50	2/50
Overall Historical Incidence			
Total	193/1,135 (17.0%)	10/1,135 (0.9%)	202/1,135 (17.8%)
SD (b)	10.20%	1.51%	10.13%
Range (c)			
High	19/49	3/48	19/49
Low	1/50	0/52	1/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F6. HISTORICAL INCIDENCE OF RENAL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Number of Animals Examined	Number of Tumors in Vehicle Controls	Diagnosis
Historical Incidence at Litton Bionetics, Inc.			
Diallylphthalate	50	0	--
Tris(2-ethylhexyl)phosphate	50	0	--
2,4-Toluene diisocyanate	50	1	Adenocarcinoma, NOS
TOTAL	150	1 (0.6%)	
Overall Historical Incidence			
	1,091	2	Adenocarcinoma, NOS
		2	Tubular cell adenocarcinoma
		1	Transitional cell papilloma
TOTAL		(b) 4 (0.4%)	Tubular cell
		1 (0.1%)	Transitional cell

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) No more than one tumor was observed in any vehicle control group.

TABLE F7. HISTORICAL INCIDENCE OF URINARY BLADDER TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Number of Animals Examined	Number of Tumors in Vehicle Controls
Historical Incidence at Litton Bionetics, Inc.		
	150	0
Overall Historical Incidence		
	1,040	0

(a) Data as of March 16, 1983, for studies of at least 104 weeks

TABLE F8. HISTORICAL INCIDENCE OF TESTICULAR TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Interstitial Cell Tumors in Vehicle Controls
Historical Incidence at Litton Bionetics, Inc.	
Diallylphthalate	48/50
Tris(2-ethylhexyl)phosphate	42/50
2,4-Toluene diisocyanate	48/50
TOTAL	138/150 (92.0%)
SD (b)	6.93%
Range (c)	
High	48/50
Low	42/50
Overall Historical Incidence	
TOTAL	(d) 985/1,090 (90.4%)
SD (b)	5.75%
Range (c)	
High	48/50
Low	37/49

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes one interstitial cell tumor, malignant

TABLE F9. HISTORICAL INCIDENCE OF STOMACH TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Number of Animals Examined	Number of Tumors in Vehicle Controls	Site	Diagnosis
Historical Incidence at Litton Bionetics, Inc.				
Diallylphthalate	49	0		
2,4-Toluene diisocyanate	48	1	Forestomach	Papilloma, NOS
Tris(2-ethylhexyl)phosphate	50	1	Stomach	Squamous cell papilloma
TOTAL	147	2 (1.4%)		
Overall Historical Incidence				
	1,005	1	Stomach, NOS	Papilloma, NOS
		2	Stomach, NOS	Squamous cell papilloma
		2	Stomach, NOS	Squamous cell carcinoma
		1	Forestomach	Papilloma, NOS
		1	Forestomach	Squamous cell carcinoma
TOTAL		(b) 7 (0.7%)		

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) No more than two tumors were observed in any control group.

TABLE F10. HISTORICAL INCIDENCE OF STOMACH TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Number of Animals Examined	Number of Tumors in Vehicle Controls	Site	Diagnosis
Historical Incidence at Litton Bionetics, Inc.				
Diallylphthalate	48	0	--	--
2,4-Toluene diisocyanate	49	0	--	
Tris(2-ethylhexyl)phosphate	48	0	--	--
TOTAL	145	0	--	--
Overall Historical Incidence				
	1,027	2	Stomach,NOS	Squamous cell papilloma
		1	Stomach, NOS	Adenocarcinoma, NOS
		1	Gastric mucosa	Squamous cell papilloma
		1	Gastric mucosa	Adenoma, NOS
		1	Gastric mucosa	Adenomatous polyp, NOS
		1	Forestomach	Squamous cell papilloma
Total squamous cell tumors:		(b) 4 (0.4%)		

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) No more than two tumors of any description were observed in any control group.

TABLE F11. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Litton Bionetics, Inc.			
Diallylphthalate	0/50	7/50	7/50
2,4-Toluene diisocyanate	5/49	6/49	11/49
Tris(2-ethylhexyl)phosphate	7/50	9/50	15/50
TOTAL	12/149 (8.1%)	22/149 (14.8%)	33/149 (22.1%)
SD (b)	7.24%	2.95%	8.00%
Range (c)			
High	7/50	9/50	15/50
Low	0/50	6/49	7/50
Overall Historical Incidence			
TOTAL	133/1,084 (12.3%)	(d) 222/1,084 (20.5%)	340/1,084 (31.4%)
SD (b)	6.70%	7.90%	10.30%
Range (c)			
High	13/50	18/50	25/50
Low	0/50	4/50	5/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) One hepatoblastoma also was observed.

TABLE F12. HISTORICAL INCIDENCE OF CIRCULATORY SYSTEM TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Hemangioma	Hemangiosarcoma	Hemangioma or Hemangiosarcoma
Historical Incidence at Litton Bionetics, Inc.			
Diallylphthalate	1/50	2/50	3/50
2,4-Toluene diisocyanate	0/50	0/50	0/50
Tris(2-ethylhexyl)phosphate	0/49	3/49	3/49
TOTAL	1/149 (0.7%)	5/149 (3.4%)	6/149 (4.0%)
SD (b)	1.15%	3.11%	3.50%
Range (c)			
High	1/50	3/49	3/49
Low	0/50	0/50	0/50
Overall Historical Incidence			
TOTAL	9/1,137 (0.8%)	30/1,137 (2.6%)	39/1,137 (3.4%)
SD (b)	1.34%	2.43%	2.91%
Range (c)			
High	2/50	3/49	4/50
Low	0/97	0/50	0/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

APPENDIX G

CHEMICAL CHARACTERIZATION OF

3-CHLORO-2-METHYLPROPENE

APPENDIX G. CHEMICAL CHARACTERIZATION

I. Identity and Purity Determinations of 3-Chloro-2-methylpropene Performed by the Analytical Chemistry Laboratory

A. Lot no. 110967

1. Physical properties	Determined	Literature Values
a. Boiling point:	68.2 ± 0.6 (δ)° C at 729 torr (visual, micro boiling point) 69.8°-71.8° C (Dupont 900 DTA)	71°-72° C (Merck Index, 1976)
b. Refractive index:	n_D^{20}: 1.4277 ± 0.0004 (δ)	n_D^{20}: 1.4274 (Merck Index, 1976)
c. Density:	$d_{22}^{24.5}$: 0.9245 ± 0.0003 (δ) g/ml	d_4^{20}: 0.9165 g/ml d_{20}^{20}: 0.926-0.930 g/ml for commercial grade (Merck Index, 1976)
d. Appearance:	Clear, colorless liquid	
2. Spectral data		
a. Infrared		
Instrument:	Beckman IR-12	
Cell:	0.054 mm liquid cell with sodium chloride windows	
Results:	See Figure 5	Consistent with literature spectrum (Sadtler Standard Spectra)
b. Ultraviolet/visible		
Instrument:	Cary 118	
Concentration:	1%	
Solvent:	Methanol	
Results:	No absorbance between 350 and 800 nm; no maximum between 212 and 350 nm but a gradual increase in absorbance toward the solvent cutoff at 212 nm	No literature reference found

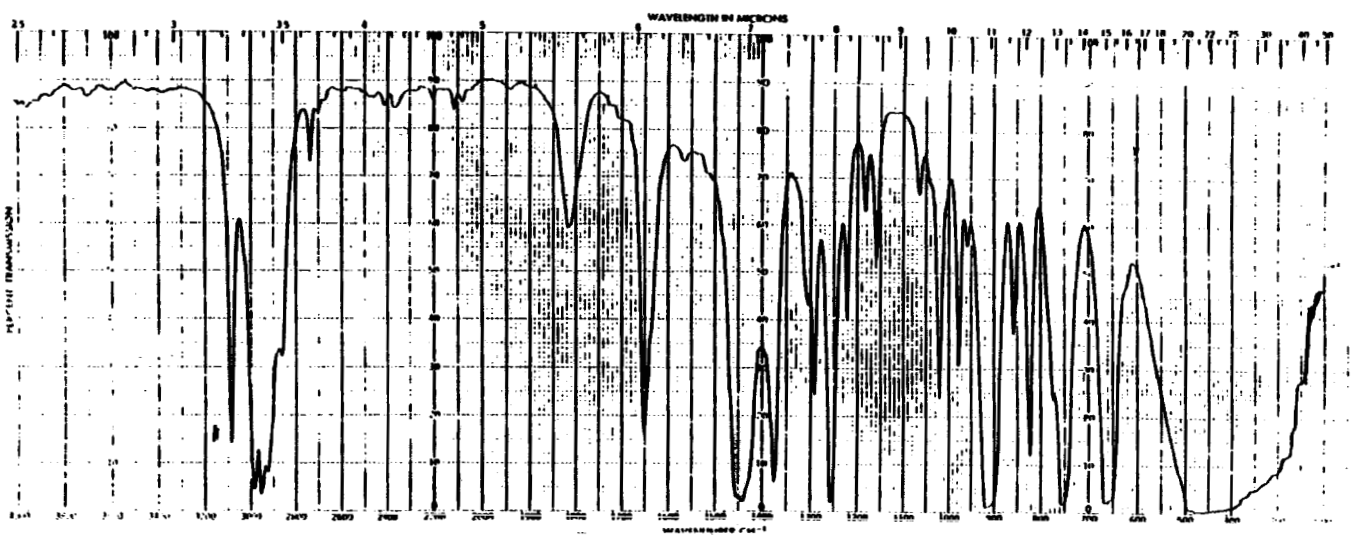

FIGURE 5. INFRARED ABSORPTION SPECTRUM OF 3-CHLORO-2-METHYLPROPENE (LOT NO. 110967)

c. **Nuclear magnetic resonance**

	Determined	Literature Values
Instrument:	Varian HA-100	
Solvent:	Neat, tetramethylsilane added	
Assignments:	See Figure 6	Consistent with literature spectrum (Sadtler Standard Spectra); impurity peaks e, f, and g are larger in literature spectrum; peaks h and i are approximately the same size in sample and in literature spectra

Chemical shift (δ):

a	m, 1.77 ppm
b	d, 3.88 ppm
c	m, 4.81 ppm
d	m, 4.95 ppm
e	1.02 ppm
f	2.10 ppm
g	3.41 ppm
h	1.68 ppm
i	5.66 ppm

Peaks h and i are consistent in chemical shift with peaks for dimethylvinyl chloride; concentration of dimethylvinyl chloride based on integration of peak h: 5%

Coupling constant:

J_{ac}	= 1.6 Hz
J_{ad}	= 1.0 Hz
J_{bd}	= 1.0 Hz

Integration ratios:

a	2.98
b	2.00
c	1.02
d	1.00
e	0.05
f	0.02
g	0.08
h	0.28
i	0.05

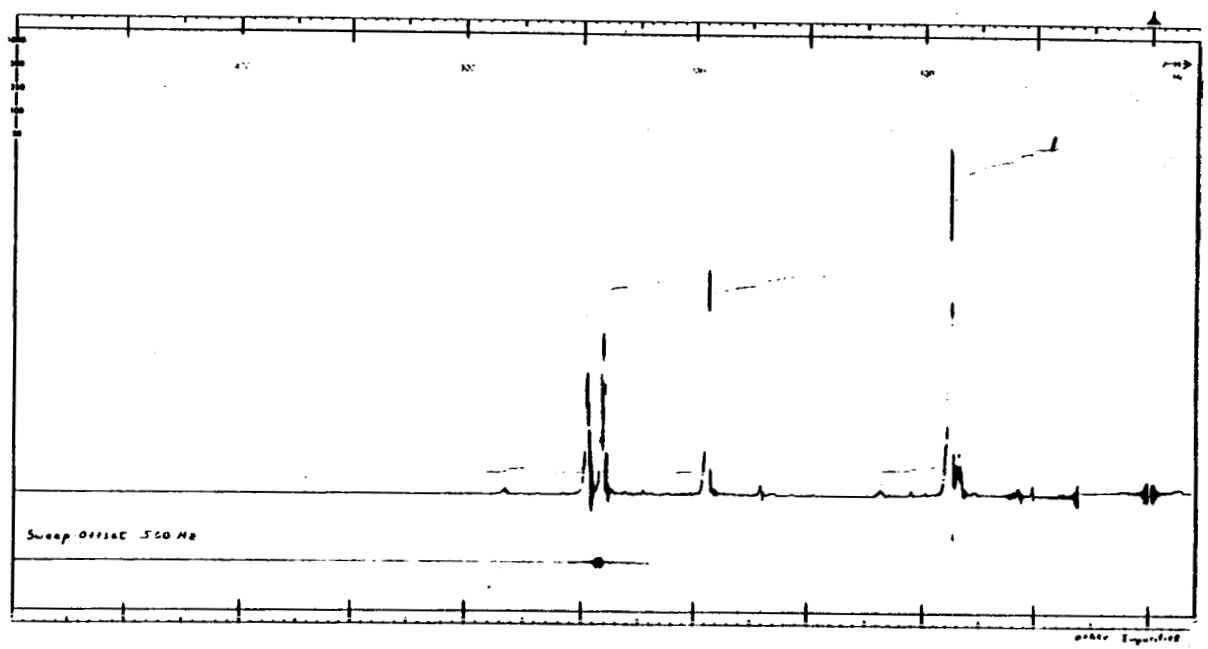

FIGURE 6. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF 3-CHLORO-2-METHYLPROPENE (LOT NO. 110967)

3. **Water analysis (Karl Fischer):** 0.029% ± 0.002 (δ)%

4. **Titration for acidic components:** 34 ± 5 (δ) ppm (assumed to be HCl)

5. **Elemental analysis**

Element	C	H	Cl
Theory	53.05	7.79	39.16
Determined	52.86	7.71	39.07
	52.96	7.83	39.10

6. **Chromatographic analysis:** Gas chromatography

Instrument: Tracor MT 220
Detector: Flame ionization
Inlet temperature: 200° C
Detector temperature: 270° C
Carrier gas: Nitrogen, 70 ml/min

a. **System 1**

Column: 20% SP 2100/0.1% Carbowax 1500 on 100/200 mesh Supelcoport, 1.8 m × 4 mm ID, glass
Oven temperature program: 50° C, 5 min; 50°-170° C at 10° C/min
Sample injected: 6µl neat liquid, diluted to 1% and 0.5% in *o*-dichlorobenzene to quantitate the major peak and check for overloading

Results: Major peak and 31 impurities. One impurity had an area 3% that of the major peak area; the combined area of the other 30 impurities was less than 0.3% that of the major peak area.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	0.3	0.1	<0.001
2	0.6	0.2	<0.001
3	0.8	0.3	<0.001
4	1.1	0.4	<0.01
5	1.3	0.5	0.07
6	2.7	1.0	100
7	3.8	1.4	<0.02 (shoulder)
8	4.1	1.5	0.01
9	5.4	2.0	<0.01
10	5.7	2.1	<0.01
11	6.6	2.4	<0.01
12	7.4	2.8	<0.001
13	9.0	3.3	<0.01
14	9.6	3.6	<0.001
15	10.1	3.8	<0.01
16	11.0	4.1	<0.01
17	11.4	4.2	<0.001
18	11.8	4.4	<0.001
19	12.3	4.6	<0.001
20	12.9	4.8	<0.01
21	13.3	4.9	<0.01
22	13.8	5.1	<0.001
23	14.1	5.2	3
24	14.9	5.5	<0.001
25	15.4	5.7	<0.01
26	16.5	6.1	<0.001
27	16.7	6.2	<0.001
28	18.5	6.9	<0.01
29	19.0	7.0	<0.01
30	20.4	7.6	<0.01
31	21.5	8.0	<0.01
32	24.4	9.1	0.07

b. System 2

Column: 10% Carbowax 20M-TPA on 80/100 mesh Chromosorb W AW, 1.8 m × 4 mm ID, glass
Oven temperature program: 50° C, 5 min; 50°-200° C at 10° C/min
Sample injected: 6 µl neat liquid, diluted to 1% in *o*-dichlorobenzene to quantitate the major peak

Results: Major peak and 26 impurities. One impurity had an area 6% that of the major peak area, and another 3% that of the major peak area; the combined area of the other 24 impurities was less than 0.3% that of the major peak area.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	0.4	0.2	<0.01
2	0.6	0.4	0.09
3	0.9	0.6	6
4	1.6	1.0	100
5	3.5	2.1	<0.01
6	7.7	4.7	0.01
7	8.2	5.1	<0.01
8	8.4	5.2	<0.01
9	8.6	5.2	<0.01
10	9.2	5.6	<0.01
11	9.7	6.1	<0.01
12	10.0	6.2	<0.01
13	10.6	6.5	<0.01
14	10.8	6.6	<0.01
15	11.2	6.9	<0.01
16	11.6	7.1	<0.01
17	12.0	7.3	<0.01
18	12.5	7.6	3
19	13.3	8.1	<0.01
20	13.4	8.2	<0.01
21	13.7	8.4	<0.01
22	14.3	8.7	<0.01
23	14.5	8.9	<0.01
24	14.9	9.1	<0.01
25	15.4	9.4	<0.01
26	16.7	10.2	<0.01
27	18.7	11.4	0.1

Note: Under these conditions, dimethylvinyl chloride, an isomer of 3-chloro-2-methylpropene, had a retention time of 1.1 minute. Peak no. 3 could be dimethylvinyl chloride, but this was not confirmed by addition of dimethylvinyl chloride to the sample.

7. **Conclusions:** The results of the elemental analysis agree with the theoretical values. Gas chromatography with one system indicated 31 impurities, one with an area 3% that of the major peak; the combined areas of the other 30 impurities totaled less than 0.3% that of the major peak. A second system indicated 26 impurities; the two largest impurities had areas 6% and 3% that of the major peak. Titration for acidic components indicated 34 $\pm$ 5 ppm acidity (assumed to be HCl). The infrared spectrum was consistent with the structure. The nuclear magnetic resonance spectrum was basically consistent with the structure but indicated five peaks attributed to impurities. The chemical shifts of two of these were consistent with the shifts observed for dimethylvinyl chloride. By this assignment, the integration ratios indicated a concentration of 5% dimethylvinyl chloride. The retention time of the 6% impurity observed in one gas chromatographic system was consistent with that of dimethylvinyl choride, but this assignment was not confirmed by addition of dimethylvinyl chloride to the samples used for gas chromatography or nuclear magnetic resonance spectroscopy.

B. Lot no. P091781

1. **Appearance:** Clear, colorless liquid

2. **Spectral data**

	Determined	Literature Values
a. Infrared		
Instrument:	Perkin Elmer	
Cell:	Thin film between silver chloride plates	
Results:	See Figure 7	Consistent with structure and literature spectrum (Sadtler Standard Spectra)
b. Ultraviolet/visible		
Instrument:	Cary 219	
Solvent:	Methanol	
Results:	No absorbance maximum between 800 nm and 217 nm was observed, but a gradual increase in absorbance toward the solvent cutoff at 217 nm was observed for a 1% (v/v) solution	No literature reference found; spectrum consistent with structure
c. Nuclear magnetic resonance		
Instrument:	Varian EM-360A	
Solvent:	Neat; tetramethylsilane internal standard added	
Assignments:	See Figure 8	Consistent with structure and literature spectrum (Sadtler Standard Spectra)
Chemical shift (δ):	a m, 1.82 ppm b s, 3.94 ppm c m, 4.86 ppm d m, 5.00 ppm e 1.60 ppm f 1.72 ppm g 5.72 ppm	

(e, f, and g above are assumed to be impurities)

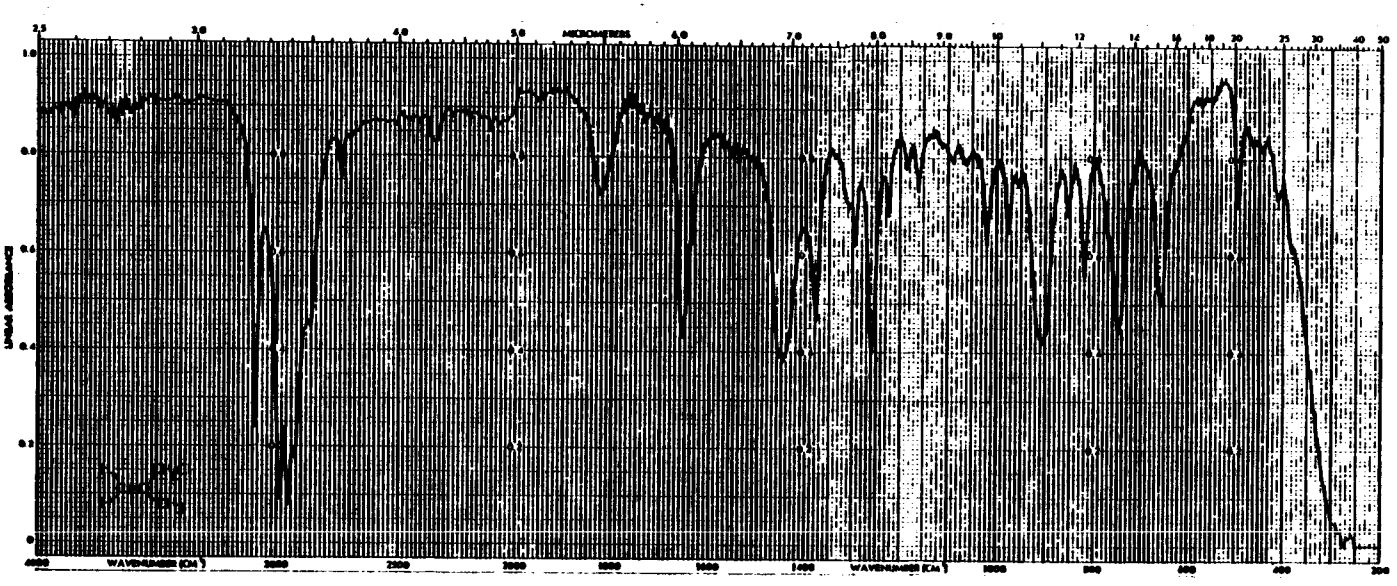

FIGURE 7. INFRARED ABSORPTION SPECTRUM OF 3-CHLORO-2-METHYLPROPENE (LOT NO. P091781)

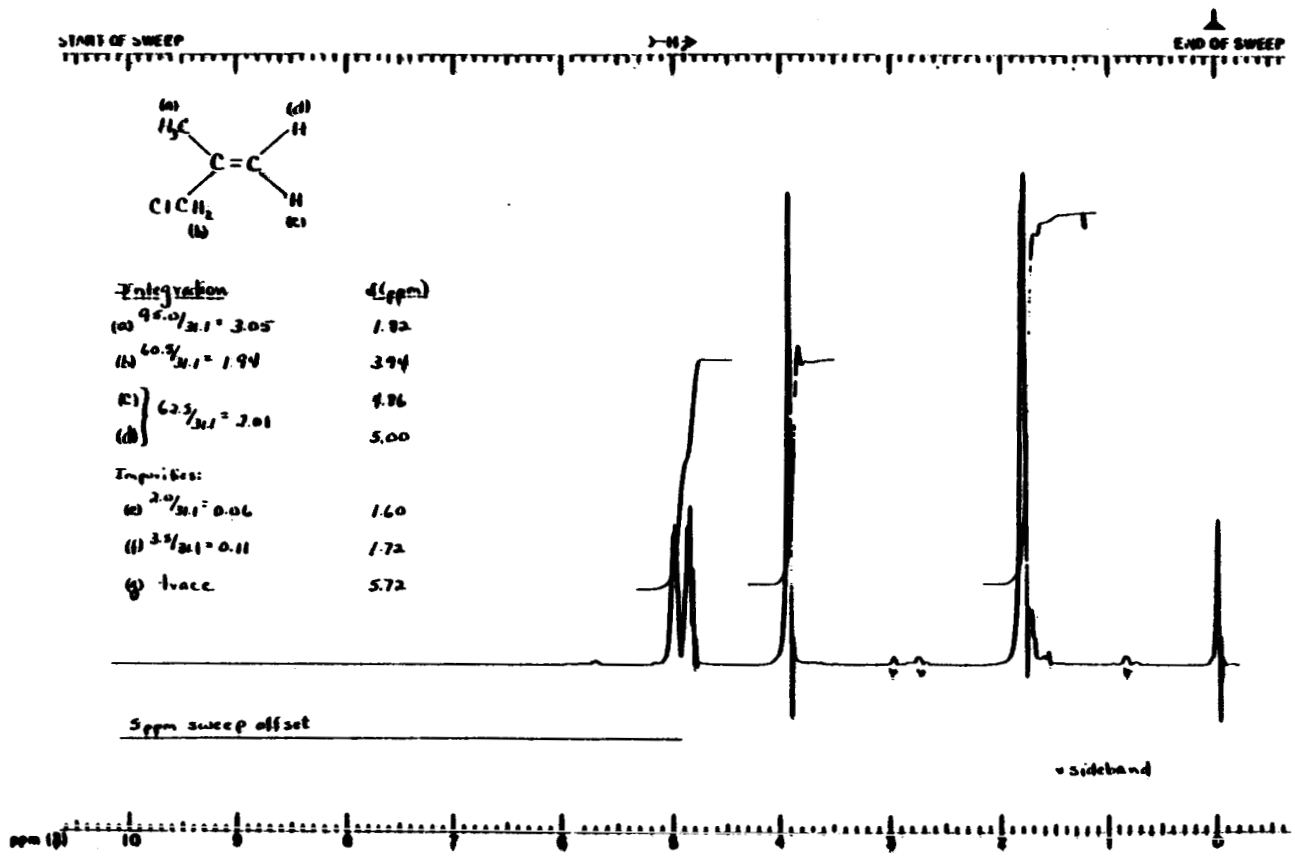

FIGURE 8. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF 3-CHLORO-2-METHYLPROPENE (LOT NO. P091781)

Integration ratios:

a	3.05
b	1.94
c, d	2.01
e	0.06
f	0.11
g	trace

3. **Water analysis (Karl Fischer):** < 0.01%

4. **Titration of acidic components**

   a. **Method:** Aliquots (5 ml) of the sample were diluted with 25 ml methanol and titrated with 0.1N sodium hydroxide. The titration was monitored visually to the phenolphthalein endpoint.

   b. **Results:** 159 ± 1 (s) ppm (calculated as hydrochloric acid).

5. **Elemental analysis**

Element	C	H	Cl
Theory	53.05	7.79	39.16
Determined	53.49	7.78	38.69
	53.64	7.72	38.55

6. **Chromatographic analysis:** Gas chromatography

   Instrument: Varian 3700
   Detector: Flame ionization
   Inlet temperature: 200° C
   Detector temperature: 250° C
   Carrier gas: Nitrogen, 70 ml/min

   a. **System 1**

      Column: 10% Carbowax 20M-TPA on 80/100 Chromosorb W (AW)
      Oven temperature program: 50° C for 5 min then 50°-200° C at 10° C/min
      Samples injected: Neat liquid (4 µl) and 1% (v/v) and 0.5% (v/v) solutions of 3-chloro-2-methylpropene in *o*-dichlorobenzene to quantitate impurities and check linearity of detector response

      Results: Major peak and 10 impurities with individual areas greater than 0.01% that of the major peak area. Three impurities eluting before the major peak and seven eluting after the major peak had a combined area 6.65% that of the major peak area. Peak no. 3 was identified by spiking as dimethylvinyl chloride. Quantitation against standards indicated a concentration of 3.6% ± 0.5% (v/v) dimethylvinyl chloride in the sample.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	0.5	0.26	0.03
2	0.6	0.32	(a) 0.48
3	1.1	0.58	(a) 5.1
major 4	1.9	1.00	100
5	2.8	1.47	0.01
6	5.1	2.68	0.40
7	9.0	4.74	0.05
8	9.7	5.11	0.02
9	14.2	7.47	0.20
10	14.6	7.68	0.28
11	15.7	8.26	0.12

(a) Measurements taken from chromatograms of 1% solution

b. System 2

Column: 20% SP 2100/0.1% Carbowax 1500 on 100/120 Supelcoport
Oven temperature program: 50° C for 5 min then 50°-170° C at 10° C/min
Samples injected (a): Neat liquid (4 µl) and 1% (v/v) and 0.5% (v/v) solutions of 3-chloro-2-methylpropene in *o*-dichlorobenzene to quantitate impurities and check linearity of detector response

Results: Major peak and four impurities with individual areas greater than 0.01% that of the major peak area. One impurity eluting before the major peak and four eluting after the major peak had a combined area 1.11% that of the major peak area.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	1.6	0.6	0.43
major 2	2.8	1.0	100
3	4.2	1.5	0.01
4	6.6-6.9	2.4-2.5	0.41
5	16.1	5.7	0.26

7. **Conclusions:** The sample was identified as 3-chloro-2-methylpropene by spectroscopy. Less than 0.01% water was found in the sample. Gas chromatography with one system indicated impurities totaling 6.65% that of the major peak, and with a second system, impurities totaling 1.11% that of the major peak. The largest peak in the first system (5.1%) was identified by spiking as dimethylvinyl chloride and quantitated against standards at 3.6% ± 0.5% (v/v) in the sample. This impurity was not observed in the second system and is believed to have coeluted with the major peak, accounting for the lower relative total area of impurities in that system.

II. Chemical Stability Study of Lot No. 110967 Performed by the Analytical Chemistry Laboratory

A. Sample storage: Samples of 3-chloro-2-methylpropene were stored for 2 weeks at −20°, 5°, 25°, and 60° C.

B. Analytical method: Gas chromatography

Instrument: Bendix 2500
Detector: Flame ionization
Column: 20% SP 2100/0.1% Carbowax 1500 on 100/120 mesh Supelcoport, 4 mm × 1.8 m, glass
Carrier gas: Nitrogen, 40 ml/min
Retention time: 2.7 min
Temperatures
Inlet: 100° C
Detector: 285° C
Oven: 30° C, isothermal

C. Results: One impurity was detected in all samples at the detection sensitivity used for this study. The retention time was 1.4 minute, and the peak area was constant at 0.41% ± 0.002% relative to the major component.

Storage Temperature (degrees centigrade)	Area of Major Peak Relative to −20° Sample (percent)
−20	100 ± 4
5	102 ± 4
25	102 ± 4
60	100 ± 4

D. Conclusion: 3-Chloro-2-methylpropene is stable as the bulk chemical when stored for 2 weeks at temperatures of up to 60° C.

III. Chemical Stability Study of Lot No. 1 10967 Performed by the Study Laboratory

A. Storage conditions: 4° C

B. Analytical methods for purity and identity

1. **Purity:** Gas-liquid chromatography

   Instrument: Hewlett Packard 5880 with 7672A Liquid Sampler
   Column: 1.8 m × 2 mm ID, silanized glass, 20% SP 2100/0.1% Carbowax 1500 on 100/120 mesh Supelcoport
   Detector: Flame ionization
   Detector temperature: 270° C
   Inlet temperature: 200° C
   Oven temperature program: 50° C for 5 min, 50°-200° at 10° C/min, 200° for 5 min
   Carrier gas: Nitrogen, 40 ml/min
   Sample size: 3 µl neat liquid, followed by 1% and 0.5% 3-chloro-2-methylpropene in o-dichlorobenzene to quantitate major peak and check for detector overloading

2. **Identity:** Infrared spectroscopy

   Instrument: Perkin Elmer Model 283B, 398, or 457
   Cell: Neat liquid

C. Results

1. **Gas chromatography**

		Percent Impurities	
Date	Lot No.	Bulk	Reference
05/10/78	110967	99.8	--
10/06/78		97.8	--
07/09/79		95.6	94.6
12/18/79		92.6	--
05/07/80		94.6	95.2
08/08/80		93.5	93.9
04/07/81		94.7	93.9
08/12/81		96.4	95.8
09/24/81	P091781	98.9	--
01/19/82		99.1	99.1
05/20/82		99.3	99.3
09/08/82		99.4	99.3

2. **Infrared:** All bulk and reference spectra were essentially identical.

D. Conclusion: No notable degradation occurred during the studies.

APPENDIX H

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

APPENDIX H. PREPARATION AND CHARACTERIZATION

Studies Conducted at the Analytical Chemistry Laboratory

I. **Sample preparation and storage:** Solutions of 3-chloro-2-methylpropene in corn oil (2.25% w/v; 22.5 mg/ml) were prepared in duplicate for storage of 0, 5, 6, or 7 days, respectively. A typical sample was prepared as follows: 2 ml of corn oil was transferred into an 8.5-ml septum vial, and the vial was sealed (Microsep F-138 gas chromatography septa with Teflon® film facing from Canton BioMedical Products, Inc.; aluminum crimp seals from Wheaton Scientific Co., Inc.) and weighed. Approximately 45 mg of 3-chloro-2-methylpropene then was injected via microliter syringe, and the vial was reweighed. The sample was agitated on a vortex mixer for 30 seconds and then stored at room temperature (25° C) in the dark for the appropriate time period.

II. **Sample extraction and analysis:** At the end of each storage time period, the appropriate samples were extracted with 2 ml of absolute methanol that was injected into the vials with a 2-ml syringe. The two-phase mixtures were thoroughly agitated on the vortex mixer for 1 minute and placed in an ultrasonic vibratory bath for 1 minute. Aliquots for analysis were removed directly from the upper (methanol) layer of each sample by microliter syringe and analyzed by the gas chromatographic system described below.

Instrument: Bendix 2500
Column: 1.8 m × 2 mm ID, silanized glass, 20% SP 2100/0.1% Carbowax 1500 on 100/120 mesh Supelcoport
Detection: Flame ionization
Temperatures
Inlet: 100° C
Oven: 30° C, isothermal
Detector: 285° C
Carrier gas: Nitrogen, 40 ml/min
Retention time: 2.7 min

III. **Results**

Storage Time (days)	Average Percent Chemical Found in Chemical/Vehicle Mixture (a)
1	(b) 2.27 ± 0.20
5	1.97 ± 0.17
6	2.04 ± 0.18
7	1.97 ± 0.17

(a) Corrected for a spike recovery of 70.8% ± 4.3%
(b) The original concentration of 3-chloro-2-methylpropene in corn oil at time of sample preparation was 2.27% with a variation among samples of 0.02%.

IV. **Conclusion:** 3-Chloro-2-methylpropene mixed with corn oil at the 2.25% concentration is stable, within the error limits of this study, when stored in the dark at room temperature (25° C) for 7 days, with an average loss of 0.27% after 5, 6, and 7 days of storage.

APPENDIX I

METHODS OF ANALYSIS OF DOSE MIXTURES

APPENDIX I. METHODS OF ANALYSIS

Analysis Performed at Analytical Chemistry Laboratory

I. **Preparation of standard spiked corn oil:** Two standard solutions of 3-chloro-2-methylpropene were prepared independently in methanol. The solutions were diluted with methanol to make four additional standards. Aliquots (20 ml) of the six standard solutions were pipetted into individual 35-ml septum vials containing 2 g of undosed corn oil to make spiked corn oil standards bracketing the specified dose range of the referee sample. One 35-ml septum vial containing 2 g of undosed corn oil was treated with 20 ml of methanol for use as a blank. After the vials with Teflon®-lined septa were sealed, the spiked corn oils and the corn oil blank were used in the analysis procedure described below.

II. **Preparation of referee sample:** Three portions (approximately 2 g each) of the referee sample were transferred to individual tared 35-ml septum vials and weighed to the nearest 0.001 g. Methanol (20 ml) was pipetted into each vial; the vials then were sealed, and the samples were analyzed immediately by the procedure below.

III. **Analysis procedure:** Vials containing the samples, standards, and the blank were agitated for 10 seconds on a vortex mixer and then shaken at maximum stroke for 20 minutes on a wrist-action shaker. After the extraction mixtures were centrifuged for 3 minutes, a 5-ml aliquot of the methanol layer from each vial was diluted to 10 ml with methanol. The solutions were mixed; then the 3-chloro-2-methylpropene content was determined by the gas chromatographic systems described below.

Instrument: Varian 3700 Gas chromatograph with Autosampler and Varian CDS 111-C integrator
Detection: Flame ionization
Detector temperature: 250° C
Inlet temperature: 200° C
Carrier gas: Nitrogen, 30 ml/min
Volume of solution injected: 3-5 µl

A. System 1

Column: 1% SP 1000 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass, silanized
Oven temperature program: 60° or 70° C, isothermal
Internal standard: None or anisole
Retention times
3-chloro-2-methylpropene at 60° C: 6.2 min
Internal standard at 60° C: 4.2 min

Results: The total amount of 3-chloro-2-methylpropene in the referee corn oil samples was computed from the linear regression equation obtained from the standard data by relating the peak area of each spiked corn oil sample to the amount of chemical in the respective spiked corn oil sample.

B. System 2

Column: 1% SP 2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass, silanized
Oven temperature program: 38° C, isothermal
Internal standard: 1,2-dichloroethylene
Retention times
3-chloro-2-methylpropene: 4.0 min
Internal standard: 2.3 min

IV. **Quality Assurance Measures:** The referee corn oil sample was analyzed in triplicate, and the undosed corn oil sample was analyzed once. Individually spiked portions of undosed corn oil (six concentrations bracketing the specified dose range of the referee sample) were prepared from two independently weighed standards and were used for obtaining standard data. Triplicate injections of each standard and sample were made into the gas chromatograph in a randomized order.

APPENDIX J

RESULTS OF ANALYSIS OF DOSE MIXTURES

TABLE J1. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE

Date Mixed	Concentration (a) of 3-Chloro-2-methylpropene in Corn Oil (mg/ml)		Determined as a Percent of Target
	Target	Determined	
04/14/80	5	5.48	109.64
	10	9.70	97.0
	20	18.20	91.0
	30	27.00	90.0
	40	36.00	90.0

(a) Results of duplicate analysis

TABLE J2. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE

Date Mixed	Concentration (a) of 3-Chloro-2-methylpropene in Corn Oil for Target Concentration (mg/ml)			
	10	15	20	30
08/12/80	10.2	--	20.7	--
08/19/80	--	15.3	--	30.3
10/07/80	--	15.8	--	30.9
12/02/80	10.9	16.4	22.1	31.5
01/29/81	--	15.3	18.3	29.7
03/24/81	10.1	16.3	20.1	
05/19/81	(b) 12.5	15.9	21.2	(b) 34.9
05/22/81	(c) 10.4	--	(c) 21.2	(c) 31.5
07/14/81	11.0	15.6	21.1	(b) 33.4
07/17/81	--	--	--	(b,c) 34.8
07/20/81	--	--	--	(c) 30.0
07/21/81	(d)	(d)	(d)	(d)
07/23/81	(e) 9.8	(e) 14.5	(b,e) 2.8	(e) 29.9
07/24/81	--	--	(f) 23.2	--
07/28/81	10.2	14.9	19.9	30.3
08/04/81	10.4	15.1	--	--
08/11/81	--	--	20.0	--
08/18/81	--	--	--	29.8
09/18/81	11.7	16.4	20.8	32.7
09/11/81	11.2	--	--	--
11/03/81	11.0	15.9	21.0	31.3
12/29/81	10.0	14.9	21.9	30.6
02/23/82	(b) 11.4	16.1	(b) 24.2	31.5
02/26/82	(g) 11.2	--	(g) 23.0	--
03/03/82	(c) 11.0	--	(c) 22.0	--
04/20/82	9.8	14.0	(f) 22.3	29.6
06/15/82	10.9	15.9	20.7	31.3
Mean (mg/ml)	10.7	15.5	20.0	31.2
Standard deviation	0.77	0.70	4.80	1.50
Coefficient of variation (percent)	7.2	4.5	24.0	4.8
Range (mg/ml)	9.8-12.5	14.0-16.4	2.8-24.2	29.6-34.9
Number of samples	15	16	16	15

(a) Results of duplicate analysis
(b) Out of specifications. Not used in the study.
(c) Remix. Not included in the mean.
(d) Probable analytical error. Not included in the mean.
(e) Remixes of 7/21/81. Included in the mean.
(f) Out of specifications. Not remixed.
(g) Remixes used for 2 days. Not included in the mean.

TABLE J3. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (a)	
		Study Laboratory	Referee Laboratory
10/07/80	15	15.8	14.7
03/24/81	20	20.1	21.1
12/29/81	30	30.6	29.9
04/20/82	10	9.8	10.2

(a) Results of triplicate analysis

APPENDIX K

SENTINEL ANIMAL PROGRAM

APPENDIX K. SENTINEL ANIMAL PROGRAM

I. Methods

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via viral serology on sera from extra (sentinel) animals in the test rooms. These animals are untreated, and these animals and the study animals are both subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Fifteen $B6C3F_1$ mice and 15 F344/N rats of each sex are selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group are killed at 6, 12, and 18 months on study. Data from animals surviving 24 months are collected from 5/50 randomly selected vehicle controls of each sex and species. The blood from each animal is collected and clotted, and the serum is separated. The serum is cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral antibody titers. The following tests are performed:

	Hemagglutination Inhibition	Complement Fixation	ELISA
Mice	PVM (pneumonia virus of mice) Reo 3 (reovirus type 3) GDVII (Theiler's encephalomyelitis virus) Poly (polyoma virus) MVM (minute virus of mice) Ectro (infectious ectromelia) Sendai	M.Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus) Sendai (24 mo)	MHV (mouse hepatitis virus)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai	RCV (rat coronavirus) Sendai (24 mo)	

II. Results

Results are presented in Table K1.

TABLE K1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF 3-CHLORO-2-METHYLPROPENE (a)

	Interval (months)	No. of Animals	Positive Serologic Reaction for
RATS			
	6	1/10	RCV
		3/10	Sendai
	12	3/10	RCV
		10/10	Sendai
	18	1/9	RCV
		9/9	Sendai
	24	9/9	RCV
MICE			
	6	--	None positive
	12	--	None positive
	18	1/10	PVM
		9/10	Sendai
	24	8/8	Sendai
		9/10	MHV
		1/10	PVM

(a) Blood samples were taken from sentinel animals at approximately 6, 12, and 18 months after the start of dosing and from the vehicle control animals just before they were killed; samples were sent to Microbiological Associates, Inc. (Bethesda, MD) for the Animal Disease Screening Program.

APPENDIX L

GENETIC TOXICOLOGY OF

3-CHLORO-2-METHYLPROPENE

TABLE L1. MUTAGENICITY OF 3-CHLORO-2-METHYLPROPENE IN *SALMONELLA TYPHIMURIUM*

Strain	Dose (µg/plate)	Revertants/plate (a,b) −S9	+S9 (rat)	+S9 (hamster)
TA100	0	135 ± 20.7	144 ± 3.5	130 ± 3.6
	100	142 ± 8.7	210 ± 6.8	197 ± 11.1
	333	133 ± 11.4	197 ± 5.7	189 ± 3.2
	1,000	124 ± 11.7	202 ± 10.0	185 ± 2.7
	3,333	Toxic	268 ± 10.0	233 ± 21.1
	10,000	Toxic	Toxic	Toxic
TA1535	0	6 ± 1.0	10 ± 1.2	10 ± 0.9
	100	7 ± 0.6	9 ± 0.3	12 ± 1.2
	333	3 ± 0.3	12 ± 1.0	12 ± 0.9
	1,000	Toxic	Toxic	13 ± 0.9
	3,333	Toxic	Toxic	16 ± 1.8
	10,000	Toxic	Toxic	1 ± 0.3
TA1537	0	4 ± 1.2	7 ± 0.7	7 ± 1.8
	100	7 ± 0.9	4 ± 0.6	5 ± 0.3
	333	4 ± 0.3	10 ± 2.3	5 ± 2.2
	1,000	Toxic	18 ± 0.9	8 ± 1.2
	3,333	Toxic	21 ± 1.0	8 ± 1.7
	10,000	Toxic	1 ± 0.7	2 ± 0.3
TA98	0	19 ± 1.8	23 ± 1.8	23 ± 1.9
	100	21 ± 2.1	27 ± 2.1	26 ± 1.7
	333	19 ± 0.9	22 ± 1.3	22 ± 1.0
	1,000	8 ± 0.7	34 ± 4.4	25 ± 2.7
	3,333	Toxic	31 ± 2.7	23 ± 0.9
	10,000	Toxic	6 ± 0.6	Toxic

(a) The S9 fractions were prepared from the livers of Aroclor 1254-induced male Sprague-Dawley rats and male Syrian hamsters. Cells and study compound or solvent (water) were incubated for 20 minutes at 37° C in the presence of either S9 or buffer. After the addition of soft agar, the contents of each tube was poured onto minimal medium, and the plates were incubated at 37° C for 48 hours (Haworth et al., 1983). The experiment was performed twice, each in triplicate; because the results were similar, data from only one experiment are shown.
(b) Mean ± standard error

TABLE L2. MUTAGENICITY OF 3-CHLORO-2-METHYLPROPENE IN L5178Y/TK$^{+/-}$ MOUSE LYMPHOMA CELLS IN THE ABSENCE OF S9

Compound (a) (Dose)	Total Mutant Clones	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutation Frequency (mutants/10^6 clonable cells)
Absolute ethanol (1%)				
	80	76.8	114.0	35
	92	95.2	112.0	32
	136	67.0	72.0	68
	134	87.7	88.0	51
Ethyl methanesulfonate (250 µg/ml)				
	871	67.8	44.5	428
	1,000	86.8	55.6	384
	789	63.0	45.8	417
3-Chloro-2-methylpropene (nl/ml)				
20	0	16.0	15.5	0
	5	17.5	26.2	10
	54	94.8	159.4	19
30	111	97.3	120.5	38
	163	130.3	103.6	42
	113	102.3	104.7	37
40	168	78.8	73.7	71
	160	109.7	107.3	49
	159	77.5	67.3	68
50	239	94.8	55.0	84
	218	97.5	60.3	75
	194	90.3	43.2	72
80	545	54.2	10.3	335
	369	67.7	15.8	182
	467	60.5	9.3	257

(a) Experiments were performed twice, and all doses were tested in triplicate except the solvent control that was tested in quadruplicate. Because the results were similar, data from only one experiment are shown. The protocol was basically that of Clive et al. (1979). Cells (6×10^5/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium to determine the percentage of viable cells.

TABLE L3. INDUCTION OF SISTER-CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY 3-CHLORO-2-METHYLPROPENE (a)

−S9 (b)		+S9 (c)	
Dose (µg/ml)	SCE/Cell (d)	Dose (µg/ml)	SCE/Cell (d)
Negative control	8.1	Negative control	7.9
DMSO	9.2	DMSO	8.6
3-Chloro-2-methylpropene		3-Chloro-2-methylpropene	
5	11.0	5	9.3
16	12.0	16	10.0
50	12.2	50	11.3
160	21.8	160	15.6
Mitomycin C		Cyclophosphamide	
0.001	26.3	0.300	14.0
0.010	61.9	2	33.9

(a) SCE = sister-chromatid exchange
(b) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent at 37° C; 2 hours after initiation of treatment, 10 µM BrdU was added, and incubation was continued for an additional 22-24 hours. Cells were washed, fresh medium containing BrdU (10 µM) and colcemid (0.1 µg/ml) was added, and incubation was continued for 2-3 hours (Galloway et al., 1985).
(c) In the presence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then cells were washed, and medium containing 10 µM BrdU was added. Cells were incubated for a further 26 hours, with colcemid (0.1 µg/ml) present for the final 2-3 hours. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats (Galloway et al., 1985).
(d) Cells were collected by mitotic shake-off, treated for 3 minutes with potassium chloride (75 mM), washed twice with fixative, and dropped onto slides and air-dried (Galloway et al., 1985).

TABLE L4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY 3-CHLORO-2-METHYLPROPENE (a)

−S9 (b)		+S9 (c)	
Dose (µg/ml)	Abs/100 Cells (percent cells w/abs)	Dose (µg/ml)	Abs/100 Cells (percent cells w/abs)
Negative control	1 (1)	Negative control	0 (0)
DMSO	0 (0)	DMSO	0 (0)
3-Chloro-2-methylpropene		3-Chloro-2-methylpropene	
120	7 (7)	5	0 (0)
160	8 (8)	16	0 (0)
200	13 (12)	50	1 (1)
		160	4 (4)
Mitomycin C		Cyclophosphamide	
0.125	26 (23)	15	55 (40)
0.250	42 (28)	50	144 (68)

(a) Abs = aberrations
(b) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid (0.1 µg/ml) was added. After a further 2-3 hours of incubation, cells were harvested by mitotic shake-off, fixed, and stained in 6% Giemsa (Galloway et al., 1985).
(c) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, fresh medium was added, and incubation was continued for 8-10 hours. Colcemid (0.1 µg/ml) was added for the last 2-3 hours of incubation; then cells were harvested by mitotic shake-off, fixed, and stained in 6% Giemsa. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats (Galloway et al., 1985).

APPENDIX M

INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Pelleted Diet: June 1980 to July 1982

(Manufactured by Zeigler Bros., Inc., Gardners, PA)

TABLE M1. INGREDIENTS OF NIH 07 RAT AND MOUSE RATION (a)

Ingredients (b)	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Brewer's dried yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

(a) NIH, 1978; NCI, 1976
(b) Ingredients should be ground to pass through a U.S. Standard Screen No. 16 before being mixed.

TABLE M2. VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION (a)

	Amount	Source
Vitamins		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D_3	4,600,000 IU	D-activated animal sterol
d-α-Tocopheryl acetate	20,000 IU	
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	*d*-Calcium pantothenate
Folic acid	2.2 g	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
B_{12}	4,000 µg	
Biotin	140.0 mg	*d*-Biotin
K_3	2.8 g	Menadione activity
Choline	560.0 g	Choline chloride
Minerals		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

(a) Per ton (2,000 lb) of finished product

TABLE M3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION (a)

Nutrient	Mean	Range	Number of Samples
Crude protein (percent by weight)	24.04 ± 0.75	22.7-25.1	24
Crude fat (percent by weight)	4.84 ± 0.80	4.1-5.7	24
Crude fiber (percent by weight)	3.40 ± 0.29	2.9-4.3	24
Ash (percent by weight)	6.56 ± 0.50	5.7-7.43	24
Essential Amino Acids (percent of total diet)			
Arginine	1.260	1.21-1.31	2
Cystine	0.395	0.39-0.40	2
Glycine	1.175	1.15-1.20	2
Histidine	0.553	0.530-0.576	2
Isoleucine	0.908	0.881-0.934	2
Leucine	1.905	1.85-1.96	2
Lysine	1.250	1.20-1.30	2
Methionine	0.310	0.306-0.314	2
Phenylalanine	0.967	0.960-0.974	2
Threonine	0.834	0.827-0.840	2
Tryptophan	0.175	0.171-0.178	2
Tyrosine	0.587	0.566-0.607	2
Valine	1.085	1.05-1.12	2
Essential Fatty Acids (percent of total diet)			
Linoleic	2.37		1
Linolenic	0.308		1
Arachidonic	0.008		1
Vitamins			
Vitamin A (IU/kg)	11,146 ± 2,291	7,200-17,000	24
Vitamin D (IU/kg)	6,300		1
α-Tocopherol (ppm)	37.6	31.1-44.0	2
Thiamine (ppm)	17.6 ± 3.3	7.4-27.0	(b) 23
Riboflavin (ppm)	6.9	6.1-7.4	2
Niacin (ppm)	75	65-85	2
Pantothenic acid (ppm)	30.2	29.8-30.5	2
Pyridoxine (ppm)	7.2	5.6-8.8	2
Folic acid (ppm)	2.1	1.8-2.4	2
Biotin (ppm)	0.24	0.21-0.27	2
Vitamin B_{12} (ppb)	12.8	10.6-15.0	2
Choline (ppm)	3,315	3,200-3,430	2
Minerals			
Calcium (percent)	1.29 ± 0.21	0.81-1.69	24
Phosphorus (percent)	1.00 ± 0.07	0.88-1.10	24
Potassium (percent)	0.809	0.772-0.846	2
Chloride (percent)	0.557	0.479-0.635	2
Sodium (percent)	0.304	0.258-0.349	2
Magnesium (percent)	0.172	0.166-0.177	2
Sulfur (percent)	0.278	0.270-0.285	2
Iron (ppm)	418	409-426	2
Manganese (ppm)	90.8	86.0-95.5	2
Zinc (ppm)	55.1	54.2-56.0	2
Copper (ppm)	12.68	9.65-15.70	2
Iodine (ppm)	2.58	1.52-3.64	2
Chromium (ppm)	1.86	1.79-1.93	2
Cobalt (ppm)	0.57	0.49-0.65	2

(a) One or two batches of feed analyzed for nutrients reported in this table were manufactured in January and/or April 1983.
(b) One batch (7/22/81) not analyzed for thiamine

TABLE M4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminant	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.42 ± 0.21	<0.05-1.06	24
Cadmium (ppm)	0.09 ± 0.02	<0.05-0.10	24
Lead (ppm)	0.99 ± 0.72	0.42-3.37	24
Mercury (ppm) (a)	< 0.05		
Selenium (ppm)	0.31 ± 0.08	0.14-0.52	24
Aflatoxins (ppb) (a,b)	<10	<5.0-<10.0	24
Nitrate nitrogen (ppm) (c)	8.15 ± 3.65	<2.1-17.0	24
Nitrite nitrogen (ppm) (c)	2.23 ± 1.59	<0.4-6.9	24
BHA (ppm) (d,e)	4.55 ± 3.59	<0.5-13.0	24
BHT (ppm) (d)	2.55 ± 1.40	0.8-5.9	24
Aerobic plate count (CFU/g) (h)	40,592 ± 32,056	4,900-120,000	24
Coliform (MPN/g) (f)	30.3 ± 53.2	<3-240	23
Coliform (MPN/g) (g)	74.8 ± 224.5	<3-1,100	24
E. Coli (MPN/g) (h)	<3		24
Total nitrosamines (ppb) (i,j)	7.20 ± 7.04	0.8-24.5	21
Total nitrosamines (ppb) (i,k)	29.40 ± 64.76	0.8-273.2	24
N-Nitrosodimethylamine (ppb) (i,j)	5.67 ± 6.49	0.8-20.0	21
N-Nitrosodimethylamine (ppb) (i,k)	27.67 ± 64.38	0.8-272	24
N-Nitrosopyrrolidine (ppb)	1.35 ± 0.92	0-3.5	24
Pesticides (ppm)			
α-BHC (a,l)	<0.01		24
β-BHC (a)	<0.02		24
γ-BHC-Lindane (a)	<0.01		24
δ-BHC (a)	<0.01		24
Heptachlor (a)	<0.01		24
Aldrin (a)	<0.01		24
Heptachlor epoxide (a)	<0.01		24
DDE (a)	<0.01		24
DDD (a)	<0.01		24
DDT (a)	<0.01		24
HCB (a)	<0.01		24
Mirex (a)	<0.01		24
Methoxychlor (a,m)	<0.05	0.09 (8/26/81)	24
Dieldrin (a)	<0.01		24
Endrin (a)	<0.01		24
Telodrin (a)	<0.01		24
Chlordane (a)	<0.05		24
Toxaphene (a)	<0.1		24
Estimated PCB's (a)	<0.2		24
Ronnel (a)	<0.01		24
Ethion (a)	<0.02		24
Trithion (a)	<0.05		24
Diazinon (a,m)	<0.1	0.2 (4/27/81)	24
Methyl parathion (a)	<0.02		24
Ethyl parathion (a)	<0.02		24
Malathion (n)	0.09 ± 0.06	<0.05-0.27	24
Endosulfan I (a)	<0.01		24
Endosulfan II (a)	<0.01		24
Endosulfan sulfate (a)	<0.03		24

TABLE M4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION (Continued)

(a) All values were less than the detection limit, given in the table as the mean.
(b) Detection limit reduced from 10 ppb to 5 ppb after 7/81
(c) Source of contamination: Alfalfa, grains, and fish meal
(d) Source of contamination: Soy oil and fish meal
(e) Two batches contained less than 0.5 ppm.
(f) Excludes one very high value of 1,100 obtained in batch produced on 12/16/80
(g) Includes the high value listed in footnote f
(h) All values were less than 3 MPN/g. MPN = most probable number.
(i) All values were corrected for percent recovery.
(j) Mean, standard deviation, and range exclude three very high values in the range of 115-273.2 ppb in batches produced on 1/26/81, 2/23/81, and 4/27/81.
(k) Mean, standard deviation, and range include the very high values given in footnote j.
(l) BHC = hexachlorocyclohexane or benzene hexachloride
(m) One observation was above the detection limit. The value and the date it was obtained are listed under the range.
(n) Eleven batches contained more than 0.05 ppm.

APPENDIX N

DATA AUDIT SUMMARY

APPENDIX N. DATA AUDIT SUMMARY

The data from the 2-year toxicology and carcinogenesis studies of 3-chloro-2-methylpropene in F344/N rats and B6C3F$_1$ mice were audited for accuracy, completeness, and procedures consistent with Good Laboratory Practice regulations by personnel from ImmuQuest Laboratory, Inc., from August 20 to September 7, 1984, at the NTP Repository, Rockville, Maryland. The studies were begun at Litton Bionetics, Inc., Kensington, Maryland, before the NTP required full compliance with Good Laboratory Practice procedures in October 1981. The members of the audit team were: P. Errico, C. Reese, K. Witkin, L. Brennecke, and D. Haynes. The full audit report is on file at the National Toxicology Program, NIEHS.

The records were reviewed for body weights, clinical observations, correlation between gross and microscopic observations, animal identification, and wet tissue examinations from a randomly selected 10% of the animals in each group. All the chemistry, environmental, and mortality records were examined. Slide and block matches were performed on all high dose and vehicle control animals.

The inlife data included the study protocol, animal shipment receipts, method of randomization of animals, method of animal identification, condition of the animals during and at the end of the quarantine period, dosing records (animal weights, volume administered, date of mix used, dose volume calculation), clinical observations, mortality, and environmental conditions. Sera collection and viral data were recorded at regular intervals during the 2-year period. The data were found to have been appropriately and completely recorded.

The pathology records from a randomly selected 10% of the rats and mice were reviewed. Most of the animals were identifiable by the method indicated (toe clips, ear punch/tab). One rat and three mice were unidentifiable because of missing ear tag or missing ears. Some tissues/organs were missing from the wet tissue bags. A number of tissues for which gross observations had been notated were apparently not examined microscopically. Most of these grossly described masses were recorded for the nontarget organs. However, grossly observed masses in the forestomach not examined microscopically were found in one high dose male rat, one low dose male mouse, two high dose male mice, one low dose female mouse, and three high dose female mice. No errors were noted in slide/block match, data entry, or disposition code for the tissues that were trimmed and examined microscopically. The untrimmed masses in the forestomach were examined histologically, and the final Technical Report reflects the revised diagnoses. No additional gross lesions were observed in the forestomachs of vehicle control rats and mice.

In conclusion, no discrepancies that might have affected the final interpretations of the 2-year studies of 3-chloro-2-methylpropene were noted. The data examined in the audit are considered adequate to meet the objectives of the study.

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