NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 273

TOXICOLOGY AND CARCINOGENESIS STUDIES OF TRICHLOROETHYLENE

(CAS NO. 79-01-6)

IN FOUR STRAINS OF RATS

(ACI, AUGUST, MARSHALL, OSBORNE-MENDEL)

(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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(CAS NO. 79-01-6)

IN FOUR STRAINS OF RATS

(ACI, AUGUST, MARSHALL, OSBORNE-MENDEL)

(GAVAGE STUDIES)

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NOTE TO THE READER

This study was performed under the direction of the National Institute of Environmental Health Sciences as a function of the 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. Animal care and use were in accordance with the U.S. Public Health Service Policy on Humane Care and Use of Animals. All NTP toxicology and carcinogenesis studies are subjected to a data audit before being presented for public 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).

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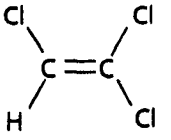

TRICHLOROETHYLENE
CAS No. 79-01-6

C_2HCl_3 Molecular weight 131.4

Synonyms: Acetylene trichloride; 1-chloro-2,2-dichloroethylene; 1,1-dichloro-2-chloroethylene; ethinyl trichloride; ethylene trichloride; 1,1,2-trichloroethylene; trichloroethene

Trade names of formulations: Algylen; Anamenth; Benzinol; Blacosolv; Blancosolv; Cecolene; Chlorilen; Chlorylea; Chlorylen; Chorylen; Circosolv; Crawhaspol; Densinfluat; Dow-Tri; Dukeron; Fleck-Flip; Flock Flip; Fluate; Gemalgene; Germalgene; Lanadin; Lethurin; Narcogen; Narkogen; Narkosoid; Nialk; Perma-A-Chlor; Perm-A-Clor; Petzinol; Philex; Threthylen; Threthylene; Trethylene; Tri; Triad; Trial; Triasol; Trichloran; Trichloren; Triclene; Tri-Clene; Trielene; Trielin; Triklone; Trilen; Trilene; Triline; Trimar; Triol; TRI-plus; TRI-plus M; Vestrol; Vitran; Westrosol

ABSTRACT

Trichloroethylene is an industrial solvent used primarily for vapor degreasing and cold cleaning. It was selected for study because of its industrial use and potential for human exposure. (An estimated 3.5 million workers are exposed to trichloroethylene.) In an earlier study (NCI TR 2), trichloroethylene (stabilized with epichlorohydrin and 1,2-epoxybutane) administered by gavage caused hepatocellular carcinomas in male and female B6C3F$_1$ mice. Trichloroethylene administration did not increase the incidence of tumors in male or female Osborne-Mendel rats. However, the survival of dosed rats was reduced, thereby compromising the sensitivity of the study to detect a carcinogenic effect.

The studies described in this report were conducted to compare the sensitivities of four strains of rats (ACI, August, Marshall, and Osborne-Mendel) to diisopropylamine-stabilized trichloroethylene. The results of the present studies demonstrate that long-term administration of trichloroethylene produces nephrotoxicity in four strains of rats and that the susceptibilities of these strains to the nephrotoxic effects of the chemical are similar. Because of chemically induced toxicity, reduced survival, and incomplete documentation of experimental data, the studies are considered inadequate for either comparing or assessing trichlorethylene-induced carcinogenesis in these strains of rats.

Toxicology and carcinogenesis studies of trichloroethylene (more than 99% pure, stabilized with 8 ppm diisopropylamine) were conducted by administering the chemical in corn oil by gavage at doses of 0, 500, or 1,000 mg/kg per day, 5 days per week, for 103 weeks to groups of 50 male and 50 female ACI, August, Marshall, and Osborne-Mendel rats. The doses were selected on the basis of results from 13-week gavage studies in which groups of 10 male and 10 female ACI, August, and Marshall rats received daily doses of trichloroethylene (male: 125-2,000 mg/kg; female: 63-1,000 mg/kg). Doses for Osborne-Mendel rats were selected to conform with doses used in an earlier carcinogenicity study in that strain (NCI TR 2).

In the 13-week studies, male ACI and August rats receiving 2,000 mg/kg trichloroethylene and male and female Marshall rats receiving 1,835 mg/kg had final mean body weights 12%-17% lower than those of the vehicle controls. All other dose groups had body weights comparable to those of the vehicle controls. Three male August rats dosed with 2,000 mg/kg died. Histopathologic evaluation of tissues revealed no lesions attributable to trichloroethylene administration in the 13-week studies. This absence of histopathologic findings did not accurately predict the nephrotoxic effects of long-term administration of trichloroethylene to rats.

Body Weight and Survival in the Two-Year Studies: In the 2-year studies, all dosed groups exhibited some reduction in mean body weights relative to the vehicle controls. Survival relative to vehicle controls was significantly reduced in 7/16 dosed groups (see following table). Also, the survival of high dose male Marshall rats was reduced by a large number of accidental deaths. Nephrotoxicity, reduced survival, and central nervous system toxicity (characterized by sedation, loss of consciousness, tremors, and convulsions) showed that the doses of trichloroethylene selected for the 2-year studies were too high.

SUMMARY OF SURVIVAL AND FINAL MEAN BODY WEIGHTS OF ACI, AUGUST, MARSHALL, AND OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDIES OF TRICHLOROETHYLENE

Group	Survival (a)	Final Mean Body Weight (percent of vehicle control)	Survival (a)	Final Mean Body Weight (percent of vehicle control)
	Male		Female	
ACI				
Untreated control	39/49	--	37/49	--
Vehicle control	38/50	--	35/50	--
500 mg/kg	(b) 19/50	89.0	20/50	91.7
1,000 mg/kg	(b) 11/50	87.5	(b) 19/50	93.0
August				
Untreated control	24/50	--	26/50	--
Vehicle control	21/50	--	23/50	--
500 mg/kg	13/50	93.5	26/50	94.5
1,000 mg/kg	16/49	87.7	25/50	92.4
Marshall				
Untreated control	32/50	--	31/50	--
Vehicle control	26/50	--	30/50	--
500 mg/kg	(b) 12/50	93.3	(b) 12/50	96.0
1,000 mg/kg	(c) 6/50	96.8	(b) 10/50	89.9
Osborne-Mendel				
Untreated control	18/50	--	19/50	--
Vehicle control	22/50	--	20/50	--
500 mg/kg	17/50	97.5	11/50	92.7
1,000 mg/kg	15/50	88.4	(b) 7/50	100.7

(a) Proportion of survivors after 2 years
(b) Survival was significantly ($P<0.05$) reduced relative to vehicle controls.
(c) Twenty-five animals were accidentally killed.

Renal Effects in the Two-Year Studies: Trichloroethylene caused tubular cell cytomegaly in 82%-100% of all dosed animals. In addition, trichloroethylene produced toxic nephropathy (which was distinguishable from age-related nephropathy) in 17%-80% of the dosed animals. Cytomegaly, karyomegaly, or toxic nephropathy was not found in untreated or vehicle control animals. Trichloroethylene administration was also associated with increased incidences of renal tubular cell adenomas and adenocarcinomas. The incidences of renal lesions are shown in the following table.

Other Pathologic Effects in the Two-Year Studies: An increased incidence of interstitial cell tumors of the testis was observed in high dose male Marshall rats (untreated control, 16/46; vehicle control, 17/46; low dose, 21/48; high dose, 32/48; P = 0.002). The incidences of pheochromocytomas of the adrenal gland were significantly reduced in male ACI, female August, female Marshall, and male and female Osborne-Mendel rats.

Genetic Toxicology: Trichloroethylene did not cause mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 with or without metabolic activation. In Chinese hamster ovary cells, trichloroethylene did not induce chromosomal aberrations; the results for sister chromatid exchanges were considered positive. Trichloroethylene was mutagenic to mouse L5178Y lymphoma cells in the presence of rat liver S9.

SUMMARY OF INCIDENCES OF RENAL LESIONS IN THE TWO-YEAR GAVAGE STUDIES OF TRICHLOROETHYLENE

	Male				Female			
Lesion	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg
ACI								
No. kidneys examined	49	50	49	49	49	48	47	43
Cytomegaly	0	0	40	48	0	0	43	42
Toxic nephropathy	0	0	18	18	0	0	21	19
Tubular cell adenoma	0	0	0	0	0	0	2	0
Tubular cell adenocarcinoma	0	0	1	0	0	0	(a) 1	1
August								
No. kidneys examined	50	50	50	49	50	49	48	50
Cytomegaly	0	0	46	46	0	0	46	50
Toxic nephropathy	0	0	10	31	0	0	8	29
Tubular cell adenoma	0	0	1	1	0	1	2	0
Tubular cell adenocarcinoma	0	0	1	0	0	0	2	0
Marshall								
No. kidneys examined	49	49	50	47	49	50	48	44
Cytomegaly	0	0	48	47	0	0	46	43
Toxic nephropathy	0	0	18	23	1	0	30	30
Tubular cell adenoma	2	0	1	0	1	1	1	0
Tubular cell adenocarcinoma	0	0	0	1	0	0	1	1
Osborne-Mendel								
No. kidneys examined	50	50	50	50	50	50	50	49
Cytomegaly	0	0	48	49	0	0	48	49
Toxic nephropathy	0	0	39	35	0	0	30	39
Tubular cell adenoma	0	0	6	1	1	0	0	1
Tubular cell adenocarcinoma	0	0	0	1	0	0	0	0

(a) Adenocarcinoma, NOS

Data Audit: Audits of the experimental data for these 2-year studies of trichloroethylene were conducted by the National Toxicology Program (Appendix Q). The results of the audits revealed evidence that the doses of trichloroethylene were too high. In addition, there was insufficient documentation of animal breeding, clinical observations, environmental conditions, and analytical chemistry data. Also, individual animal identification was not always verifiable.

Conclusions: Under the conditions of these 2-year gavage studies of trichloroethylene in male and female ACI, August, Marshall, and Osborne-Mendel rats, trichloroethylene administration caused renal tubular cell cytomegaly and toxic nephropathy in both sexes of the four strains. However, these are considered to be *inadequate studies of carcinogenic activity** because of chemically induced toxicity, reduced survival, and deficiencies in the conduct of the studies. Despite these limitations, tubular cell neoplasms of the kidney were observed in rats exposed to trichloroethylene and interstitial cell neoplasms of the testis were observed in Marshall rats exposed to trichloroethylene.

SUMMARY OF THE TWO-YEAR GAVAGE STUDIES OF TRICHLOROETHYLENE IN MALE AND FEMALE ACI, AUGUST, MARSHALL, AND OSBORNE-MENDEL RATS

Doses
0, 500, and 1,000 mg/kg trichloroethylene in corn oil, 5 d/wk

Level of evidence of carcinogenic activity
Inadequate study

As indicated by
Chemically induced toxicity, reduced survival, and deficiencies in study conduct

Other toxic effects
Renal tubular cytomegaly, toxic nephropathy

Neoplastic effects
Uncommon renal tubular cell neoplasms in exposed rats and testicular interstitial cell tumors in male Marshall rats

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*Explanation of Levels of Evidence of Carcinogenic Activity is on page 9.
Summaries of the Peer Review comments and the public discussions on this Technical Report appear on pages 13-14 and 16-17.

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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 NTP toxicology and carcinogenesis studies 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 study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans.

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence including: animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results ("Clear Evidence" and "Some Evidence"); one category for uncertain findings ("Equivocal Evidence"); one category for no observable effects ("No Evidence"); and one category for experiments that because of major flaws cannot be evaluated ("Inadequate Study"). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Reports series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following quintet is 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 Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related.
- **No Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.
- **Inadequate Study of Carcinogenic Activity** is demonstrated by studies that because of major qualitative or quantitative limitations cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. This should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- The adequacy of the experimental design and conduct;
- Occurrence of common versus uncommon neoplasia;
- Progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic lesions;
- Some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- Combining benign and malignant tumor incidences known or thought to represent stages of progression in the same organ or tissue;
- Latency in tumor induction;
- Multiplicity in site-specific neoplasia;
- Metastases;
- Supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- The presence or absence of dose relationships;
- The statistical significance of the observed tumor increase;
- The concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- Survival-adjusted analyses and false positive or false negative concerns;
- Structure-activity correlations; and
- In some cases, genetic toxicology.

These considerations together with the definitions as written should be used as composite guidelines for selecting one of the five categories. 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 induction by chemicals of more neoplasms than are generally found, or the earlier induction by chemicals of neoplasms that are commonly observed. 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.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Trichloroethylene in Four Strains of Rats is based on the 13-week studies that began in March or April 1977 and ended in June or July 1977 at Papanicolaou Research Institute and on the 2-year studies that began between December 1978 and November 1979 and ended between November 1980 and November 1981 at Papanicolaou Cancer Research Institute (Miami, Florida).

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PEER REVIEW PANEL (DECEMBER 1985)

The members of the Peer Review Panel who evaluated the draft Technical Report on trichloroethylene on December 9, 1985, 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 TRICHLOROETHYLENE (DECEMBER 1985)

On December 9, 1985, the draft Technical Report on the toxicology and carcinogenesis studies of trichloroethylene 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 at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. J. Mennear, NTP Chemical Manager, introduced the toxicology and carcinogenesis studies of trichloroethylene by reviewing the experimental designs, results, and proposed conclusions:

> These 2-year gavage studies of trichloroethylene in male and female ACI, August, Marshall, and Osborne-Mendel rats are considered to be inadequate studies of carcinogenicity because of insufficient survival in dosed animals and incomplete documentation of the conduct of the studies. However, under the conditions of these studies trichloroethylene administration was strongly associated with renal tubular cell cytomegaly and karyomegaly and toxic nephropathy in both sexes of the four strains. In addition, an increased incidence of renal tubular cell neoplasms in male Osborne-Mendel rats, and possibly in female ACI and female August rats, and an increased incidence of testicular interstitial cell tumors in male Marshall rats may have been associated with the administration of trichloroethylene.

Dr. Hooper, a principal reviewer, agreed with the proposed conclusions. He discussed deficiencies in study design, conduct, and recordkeeping. With regard to the large numbers of "accidental" or "gavage-related" deaths, he argued that gavage trauma is lethal when accompanied by the toxicity of trichloroethylene. Dr. Hooper proposed that inhalation studies in both rats and mice be designed to confirm or deny the assertion that trichloroethylene is a tissue- and species-specific carcinogen (mouse liver). He asked that reference be included to a 1983 Japanese inhalation study in which trichloroethylene was reported to produce pulmonary adenocarcinomas in female ICR mice.

As a second principal reviewer, Dr. Swenberg agreed with the conclusions but stated that these studies were inadequately designed, failing to utilize a previous study with Osborne-Mendel rats in dose selection. Beginning with the Abstract, it should be stated that the doses used exceeded the maximum tolerated dose in all four strains of rats. He detailed a number of suggested revisions. However, he said that the last sentence regarding kidney tumors should be deleted as the findings described have not been reproduced in several negative studies and are difficult to assess due to the severe renal toxicity.

As a third principal reviewer, Dr. Crowley also suggested that the last sentence should be deleted from the conclusions. He also asked for clarification concerning the relationship of gavage trauma with chemical toxicity in causation of "accidental" deaths. Dr. Mennear responded that the mortality originally termed "gavage-related deaths" was likely to be associated with toxicity of trichloroethylene.

Dr. E. McConnell, NIEHS, said that despite the deficiencies in these studies, the NTP considered the toxic renal lesions to be real and consistent with effects seen with other halogenated solvents.

In other discussion, Dr. Tannenbaum pointed out that the major metabolite of trichloroethylene in humans and rats is trichloroacetic acid, and this compound could be the cause of the nephrotoxicity, thus raising the question of whether there might be a threshold effect. Dr. Mirer cautioned against minimizing the importance of the renal toxicity in view of the fact that the doses used were in the same range as the occupationally permitted exposure levels in air. Dr. Perera spoke against deleting the last sentence of the conclusions, arguing that if the nontumor toxic effects should not be dismissed despite the deficiencies of the studies, then neither should the neoplastic effects. Dr. McConnell said that the toxic renal lesions were observed at very high incidence whereas the neoplastic changes were found at very low incidence. Dr. Swenberg stated that conclusions about carcinogenicity cannot be drawn from an inadequate study of carcinogenicity.

Dr. Scala said that the audit report findings suggest these studies are flawed and should not be published as an NTP Technical Report. The data on the kidney lesions could be reported separately. Dr. Jones said that the information should be made readily available. Dr. Purchase thought it difficult to recommend publication or not based on the present report. He suggested that the report be redrafted and brought back to the Panel.

Dr. Hooper moved that the report be deferred for extensive revision and then brought back to the Panel. Dr. Swenberg seconded the motion. Dr. Kociba requested that more information from the Audit Report be included in the redraft. Dr. Swenberg asked that information also be provided on the findings from an independent audit by the Halogenated Solvent Industry Alliance (HSIA). Dr. J. Huff, NIEHS, said that a revised Technical Report could be ready for consideration at the summer 1986 meeting. Dr. Hook summarized the motion to say that the Technical Report would be rewritten, adding a more extensive summary of the findings from audits conducted by both the NTP and HSIA and returned to the Panel for review. The Panel approved the motion by nine affirmative votes with two abstentions (Dr. Kociba and Dr. Purchase).

PEER REVIEW PANEL (AUGUST 1986)

The members of the Peer Review Panel who evaluated the draft Technical Report on trichloroethylene on August 19,1986, 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 TRICHLOROETHYLENE (AUGUST 1986)

On August 19, 1986, the draft Technical Report on the toxicology and carcinogenesis studies of trichloroethylene 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 at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. J. Mennear, NTP, introduced the studies by reviewing the experimental design, results, and proposed conclusions (inadequate studies of carcinogenic activity in the four strains of rats).

Dr. Hooper, a principal reviewer, stated that this version was improved considerably over the previous draft, especially in justifying dose selection, comparing renal toxicity in five rat strains (including F344), eliminating mention of gavage trauma as the major cause of decreased survival, and summarizing audit findings and deficiencies in the execution of the studies. Among many comments, Dr. Hooper suggested that significant carcinogenic effects should be included in the summary, even though the overall studies were judged inadequate for assessing carcinogenicity, and he cited specific increases in renal and testicular tumors. He asked for a clarifying discussion on what is meant by "accidental" deaths, since some of the excessive mortality could be due to anesthetic or toxic properties of the chemical. Dr. Hooper suggested that a more balanced discussion be given to the carcinogenic effects of chlorinated aliphatics, including findings from inhalation studies in which the carcinogenic responses appeared to be broader in terms of site.

As a second principal reviewer, Dr. Popp basically agreed with the conclusion that these were inadequate studies but felt that the report should more clearly and specifically state the basis for the studies' inadequacies. Dr. Popp indicated that statements in the text about significant increases in renal tumors could lead to a misunderstanding that these were positive studies. He thought that these statements could be better qualified.

As a third principal reviewer, Dr. Crowley questioned whether the report yet comes to grips with how serious the data problems are. For example, the results of the data audit indicate that analyses by dose group and evaluations of dose response may be potentially misleading. He said that if these were inadequate studies, the significant tumor findings should be downplayed or not presented at all. Dr. Crowley noted a possible exception, testicular tumors in Marshall rats, which did not involve a compromised organ and were statistically significant regardless of dose identification.

Most of the discussion was concerned with the weight that should be given to the renal and testicular tumors observed and whether statistical significances should be given within the context of inadequate studies. One viewpoint as supported by Dr. Purchase, Dr. Crowley, and Dr. Popp was that conclusions about carcinogenic activity from inadequate studies are unwarranted, as are statements about the statistical significance of low incidence rates in animals with uncertain identification. A second viewpoint, supported by Dr. Hooper, Dr. Mirer, and Dr. Perera, was that, although conclusions cannot be drawn from inadequate studies, more emphasis could be given to the tumor data if it is believed that there is a probable association between chemical administration and increased tumor incidence. Dr. J. Huff, NIEHS, stated that NTP staff agreed that these renal tumors were related to trichloroethylene administration, and he reported that combining data from male and female animals for both vehicle control and dosed groups shows only 2 renal tumors in vehicle controls versus 26 in dosed animals. Dr. S. Eustis, NIEHS, noted that there was an overemphasis regarding the purported misidentification of animals. Dr. J. Selkirk, NIEHS, said that the audit summary reinforced the idea

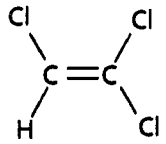
that animals were indeed identifiable and could be separated easily into dosed and vehicle control animals.

Dr. Hooper moved that the Technical Report on trichloroethylene be accepted with the conclusions as written, inadequate studies of carcinogenic activity in the four strains of rats, and with the addition of a statement to the summary that there were increased incidences of renal tubular cell tumors observed in dosed rats and an increased incidence of interstitial cell tumors of the testes in dosed Marshall rats. Dr. Mirer seconded the motion, and it was approved by six reviewers with three dissenting (Dr. Capen, Dr. Crowley, and Dr. Popp) and one abstaining (Dr. Purchase).

I. INTRODUCTION

Use
Chemical and Physical Properties of Trichloroethylene
Exposure and Production
Teratogenicity and Embryotoxicity
Genetic Toxicology
Carcinogenicity
Study Rationale

I. INTRODUCTION



TRICHLOROETHYLENE
CAS No. 79-01-6

C_2HCl_3 Molecular weight 131.4

Synonyms: Acetylene trichloride; 1-chloro-2,2-dichloroethylene; 1,1-dichloro-2-chloroethylene; ethinyl trichloride; ethylene trichloride; 1,1,2-trichloroethylene; trichloroethene

Trade names of formulations: Algylen; Anamenth; Benzinol; Blacosolv; Blancosolv; Cecolene; Chlorilen; Chlorylea; Chlorylen; Chorylen; Circosolv; Crawhaspol; Densinfluat; Dow-Tri; Dukeron; Fleck-Flip; Flock Flip; Fluate; Gemalgene; Germalgene; Lanadin; Lethurin; Narcogen; Narkogen; Narkosoid; Nialk; Perma-A-Chlor; Perm-A-Clor; Petzinol; Philex; Threthylen; Threthylene; Trethylene; Tri; Triad; Trial; Triasol; Trichloran; Trichloren; Triclene; Tri-Clene; Trielene; Trielin; Triklone; Trilen; Trilene; Triline; Trimar; Triol; TRI-plus; TRI-plus M; Vestrol; Vitran; Westrosol

Use

Trichloroethylene is an industrial solvent used primarily for vapor degreasing and cold cleaning of fabricated metal parts. Trichloroethylene has been used as a carrier solvent for the active ingredients of insecticides and fungicides; as a solvent for waxes, fats, resins, and oils; as a spot remover; as an anesthetic for medical, dental, and veterinary use; and as an extractant for spice oleoresins and for caffeine from coffee. Trichloroethylene may be found in printing inks, varnishes, adhesives, paints, lacquers, spot removers, rug cleaners, disinfectants, and cosmetic cleansing fluids. Trichloroethylene may be used as a chain terminator in polyvinyl chloride production and as an intermediate in the production of pentachloroethane (Kirk-Othmer, 1963, 1979; IARC, 1979; Defalque, 1961; Wetterhahn, 1972; USCFR, 1976; Valle-Riestra, 1974). Trichloroethylene is no longer used with food, drugs, or cosmetics (IARC, 1979; Food Chemical News, 1978). Before 1976, tolerances for trichloroethylene in decaffeinated ground coffee were set at 25 ppm (USCFR, 1976). Trichloroethylene is no longer used in the decaffeination of coffee.

Chemical and Physical Properties of Trichloroethylene

Selected physical and chemical properties of trichloroethylene are presented in Table 1. Seven reviews on trichloroethylene are available (Huff, 1971; Waters et al., 1976, 1977; Mercier, 1977; Lyman, 1978; IARC, 1979; v. Apeldoorn, 1984; WHO, 1985).

Exposure and Production

The general population is exposed to trichloroethylene at low concentrations (in the parts per billion range) in air, water, and food. Reduction of the use of the chemical in anesthesia, solvent extraction and fumigation of foodstuffs, and dry-cleaning of textiles has reduced exposure from these sources. Exposure during the production of trichloroethylene is relatively low because of the nature of the process. Industrial uses, such as metal degreasing, can involve high exposures. The respiratory route is the principal route of exposure with dermal exposure being an additional route. Oral intake is insignificant in industrial settings (WHO, 1985). In 1981, production of trichloroethylene was 117 million kg

TABLE 1. SELECTED CHEMICAL AND PHYSICAL PROPERTIES OF TRICHLOROETHYLENE

Description: Colorless liquid
Boiling point: 87° C
Density: 1.4642 g/ml at 20° C
Refractive index: n_D = 1.4773 at 20° C
Spectroscopy data: λ_{vap} <200 nm
Solubility: Water, 0.1% w/v at 20° C; miscible with acetone, ethanol, diethyl ether, chloroform, and oils
Volatility: Vapor pressure, 77 mm at 25° C
Vapor density: 4.54 (air = 1)
Stability: Nonflammable; when pure and containing a stabilizer, it is stable in presence of air, moisture, and light and in contact with metals up to 130° C. When heated with ozone, it decomposes rapidly into products such as hydrogen chloride, phosgene, carbon monoxide, and chlorine peroxide. At 700° C and above, the vapor decomposes to give a mixture of dichloroethylene, tetrachloroethylene, carbon tetrachloride, chloroform, and methyl chloride. Upon contact with certain metals, high temperatures, open flame, or ultraviolet light, it decomposes almost instantly to phosgene and/or hydrogen chloride, chlorine, and dichloroacetyl chloride. In the presence of alkali, trichloroethylene decomposes to dichloroacetylene.
Reactivity: The most important reaction of trichloroethylene is its oxidative breakdown by atmospheric oxygen, greatly accelerated by elevation of temperature and exposure to light, especially ultraviolet light; not hydrolyzed by water under normal conditions; reacts with alkali under pressure at 150° C to produce glycolic acid and with sulfuric acid to give monochloroacetic acid
Conversion factor: 1 ppm in air is equivalent to 5.37 mg/m^3

(USITC, 1982). An estimated 3.5 million workers are exposed to trichloroethylene (Page, 1979).

The recommended threshold limit value for industrial exposure to trichloroethylene is 50 ppm (ACGIH, 1985-86), and the Federal OSHA standard for trichloroethylene is 100 ppm. The California standard is set at 25 ppm.

Teratogenicity and Embryotoxicity

Trichloroethylene has been studied for teratogenic and embryo/fetotoxicologic potential in mice, rats, and rabbits. The results of these studies have not revealed consistent adverse effects in these species.

Mice: Swiss-Webster mice were exposed by inhalation to trichloroethylene at 300 ppm in air 7 hours per day on days 6-15 of gestation (Schwetz et al., 1975). The mice were observed daily throughout pregnancy, and maternal weights were recorded on days 6, 10, and 18 of gestation. No effects were observed on the average number of implantation sites per litter, litter size, incidence of fetal resorptions, fetal sex ratios, or fetal body measurements on day 18 of gestation. The incidences of gross and microscopic anomalies were not significantly greater among exposed than among control litters (Leong et al., 1975; Schwetz et al., 1975).

Rats: Exposure of Sprague Dawley and Charles River rats to trichloroethylene at 300 ppm produced no evidence of teratogenicity or maternal toxicity (Leong et al., 1975; Schwetz et al., 1975). Inhalation exposure of Sprague Dawley rats to trichloroethylene (500 ppm trichloroethylene, 7 hours per day, 5 days per week) during a 3-week pregestational period and on days 0-18 or days 6-18 of gestation caused no maternal or embryonal/fetal toxicity (Beliles et al., 1980). These authors concluded that neither the frequency nor character of the macro- or microscopic findings in the dosed groups indicated an adverse effect.

Female Long-Evans rats exposed to trichloroethylene at 1,800 ppm via inhalation 6 hours per day, 5 days per week, for 2 weeks before mating and/or on days 0-20 of gestation did not exhibit any signs of maternal toxicity (Dorfmueller et al., 1979). There was no indication of embryonic toxicity, and no significant compound-related effects were found in the number of corpora lutea, implantation sites per litter, fetal body weights, resorbed fetuses per litter, or sex ratios. No significant compound-related effects were observed in the analysis of total soft-tissue anomalies. However, prenatal exposure at 1,800 ppm trichloroethylene caused an elevation of incomplete ossification of the sternum, possibly indicative of delays in maturation but not considered to be a major malformation. The study

indicated no compound-related effects on general postnatal behavior, but there was a small depression of postnatal weight gains in offspring of the premating exposure group.

Rabbits: Female New Zealand white rabbits were exposed to trichloroethylene at 500 ppm in air 7 hours per day, 5 days per week, for 3 weeks pregestation and on days 0-21 or on days 7-21 of gestation (Beliles et al., 1980). The results revealed no evidence of maternal toxicity or embryotoxicity. The authors did report the occurrence of external hydrocephalus in a few fetuses in one of the study groups (four fetuses per two litters), but no definitive conclusion was made from these findings.

Genetic Toxicology

Trichloroethylene has been reported to be weakly mutagenic or nonmutagenic for *Salmonella typhmurium* strain TA100 (Baden et al., 1979; Bartsch et al., 1979; Simmon et al., 1977; Waskell, 1978). Cerna and Kypenova (1977) reported that trichloroethylene was mutagenic (without metabolic activation) in *S. typhimurium* strains TA1535 and TA1538 and in host-mediated assays with TA1950, TA1951, and TA1952. Greim et al. (1975) reported that microsomally activated reagent-grade trichloroethylene was slightly mutagenic for *Escherichia coli* K12, but Loprieno et al. (1979) found no mutagenic activity in a series of short-term tests using a distilled pure sample of trichloroethylene. Some of this variability may be due to differences in testing protocol, and some may be due to the presence of various stabilizers used in trichloroethylene. NTP studies demonstrated that epichlorohydrin, one chemical frequently used to stabilize trichloroethylene, is clearly mutagenic in Salmonella strains TA100 and TA1535, inducing base-substitution mutations (Canter et al., 1986). In contrast, diisopropylamine, which was the stabilizer in the trichloroethylene used in the NTP 13-week and 2-year rodent studies, is not mutagenic in Salmonella strains TA100, TA1535, TA1537, or TA98 when tested in a preincubation protocol with or without metabolic activation from Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 at doses up to 10,000 µg/plate (Mortelmans et al., 1986). Slacik-Erben et al. (1980) studied trichloroethylene (99.5% pure) in a dominant lethal test with male Han/BGA NMRI mice and found no mutagenic activity. The trichlorethylene used in that study was stabilized with 100 mg/liter triethanolamine, a nonmutagenic chemical (Mortelmans et al., 1986; Gulati et al., 1985; Yoon et al., 1985),

In studies conducted by the NTP (Appendix I), trichloroethylene, stabilized with diisopropylamine, did not cause mutations in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537, with or without metabolic activation by Aroclor 1254-induced male Sprague Dawley rat or male Syrian hamster liver S9 by a liquid-incubation procedure (Mortelmans et al., 1986). Trichloroethylene did not induce chromosomal aberrations in Chinese hamster ovary cells with or without metabolic activation; the results for sister chromatid exchanges were considered positive (Gulati et al., 1985). Trichloroethylene was mutagenic to mouse L5178Y lymphoma cells with but not without activation by Aroclor 1254-induced male F344 rat liver S9.

Carcinogenicity

Evidence for a carcinogenic effect of industrial-grade (greater than 99% pure) trichloroethylene was reported by the National Cancer Institute after the completion of studies in $B6C3F_1$ mice and Osborne-Mendel rats (NCI, 1976). Trichloroethylene was administered by gavage for 78 weeks; rats were then observed for an additional 32 weeks and mice for 12 weeks. In mice, time-weighted-average gavage doses of 1,170 and 2,340 mg/kg in males and 870 and 1,740 mg/kg in females were associated with significant increases in the incidences of hepatocellular carcinomas. Trichloroethylene administration was associated with increased incidences of alveolar/bronchiolar adenomas and carcinomas in male and female mice (male: vehicle control, 0/20; low dose, 5/50; high dose, 1/48; female: 1/20; 5/50; 7/47). These incidences were not statistically significant and were not considered to be evidence of carcinogenicity in mice. In Osborne-Mendel rats, time-weighted-average gavage doses of 550 and 1,100 mg/kg (both sexes) did not increase the incidences of primary tumors. However, as in several other carcinogenicity studies of chlorinated ethanes and

ethylenes (hexachloroethane, NCI, 1978a; 1,1,2,2-tetrachloroethane, NCI, 1978b; 1,1,2-trichloroethane, NCI, 1978c; tetrachloroethylene, NCI, 1977; pentachloroethane, NTP, 1983), the survival of the rats was compromised by the dose regimen.

The results of most of these carcinogenicity studies have been summarized (Weisburger, 1977) and reviewed (IARC, 1979). The International Agency for Research on Cancer (IARC) considered the trichloroethylene studies in Osborne-Mendel rats to be inadequate for evaluation and the studies in $B6C3F_1$ mice to provide limited evidence of carcinogenicity; that is, trichloroethylene was found to be carcinogenic in one species (IARC, 1979). IARC evaluated trichloroethylene as being "carcinogenic to mice after its oral administration, producing liver and lung neoplasms" (IARC, 1982).

The interpretation of the earlier trichloroethylene study (NCI, 1976) was complicated by the presence of certain additives, particularly epichlorohydrin (0.09%) in the study material. Epichlorohydrin had been previously shown to induce local sarcomas in mice following subcutaneous injection (Van Duuren et al., 1974) and was subsequently shown to cause nasal carcinomas in rats after inhalation exposure (Laskin et al., 1980). Further, epichlorohydrin is a mutagen for *S. typhimurium* strain TA100 (Simmon, 1977). Therefore, although the carcinogenicity of industrial-grade trichloroethylene (containing epichlorohydrin) in $B6C3F_1$ mice was firmly established, unequivocal statements regarding the carcinogenicity of pure trichloroethylene in mice could not be made.

Results of long-term inhalation studies with purified trichloroethylene (less than 0.25 ppm of each of five chlorinated hydrocarbon impurities as analyzed by gas chromatography/mass spectrophotometry, stabilized with 15 ppm triethanolamine) have been reported (Henschler et al., 1980). In these studies, male and female Wistar rats, NMRI mice, and Syrian hamsters were exposed to air containing up to 500 ppm trichloroethylene for 18 months (6 hours per day, 5 days per week). This regimen did not produce compound-related increases in primary tumors in these species. The investigators did report an increase in the incidence of malignant lymphomas in female mice (control, 9/29; low dose, 17/30; high dose, 18/28), but the relationship of this lesion to trichloroethylene exposure was considered questionable because of the high incidence of lymphomas in control mice.

In an inhalation experiment, Fukuda et al. (1983) exposed female ICR mice and SD rats to 50, 150, or 450 ppm trichloroethylene (containing 0.019% epichlorohydrin) 7 hours per day, 5 days per week for 104 weeks. These workers reported increased incidences of pulmonary adenocarcinomas in dosed mice (control, 1/49; 50 ppm, 3/50; 150 ppm, 8/50; 450 ppm, 7/46). No increase in liver tumors was reported. There were no increases in the incidences of tumors in female rats.

Henschler and coworkers compared the carcinogenicity of trichloroethylene stabilized with triethanolamine (0.0015%), epichlorohydrin (0.8%), 1,2-epoxybutane (0.8%), or epichlorohydrin plus 1,2-epoxybutane (0.25% and 0.25%) to that of industrial-grade trichloroethylene in groups of 50 male and 50 female ICR/HA-Swiss mice (Henschler et al., 1984). The study compounds were administered by gavage in corn oil 5 days per week. The original doses were 2.4 and 1.8 g/kg of trichloroethylene in males and females, respectively. Because of dose-related toxicity, administration was stopped after 34 weeks and then resumed during week 41 with doses that were one-half the original doses. The animals were not dosed during week 65, and dosing was terminated after week 68. Animals were observed until week 106. Amine-stabilized trichloroethylene did not cause an increased incidence of tumors in either sex. Trichloroethylene stabilized with epichlorohydrin, 1,2-epoxybutane, or both and industrial-grade trichloroethylene caused increases in the incidences of forestomach papillomas and squamous cell carcinomas. Although these results indicate that both epichlorohydrin- and 1,2-epoxybutane-stabilized trichloroethylene are carcinogenic in mice, no conclusion regarding amine-stabilized trichloroethylene can be reached because the shortened duration of administration (61 weeks) reduced the sensitivity of the studies for detecting carcinogenesis.

In a more recent study (NTP TR 243, in preparation), epichlorohydrin-free trichloroethylene, administered by gavage, was found to produce hepatocellular neoplasms in male and female $B6C3F_1$ mice and renal tubular cell adenomas and adenocarcinomas in male F344/N rats. The interpretation of the rat portion of the studies was confounded by the fact that both doses used (500 and 1,000 mg/kg per day) produced significant nontumor renal pathologic effects and significantly reduced the survival of male rats; therefore, the male rat study was judged to be inadequate to evaluate the presence or absence of a carcinogenic response to trichloroethylene. The most striking effect that trichloroethylene produced in rats was toxic nephrosis; it was found in 98% of the dosed males, in all of the dosed females, and in none of the controls. The lesion was first noticed in dosed rats that died early in the studies and was shown microscopically as frank enlargement of the nucleus and cytoplasm of scattered individual tubular cells that had brush borders and were located near the corticomedullary junction. The renal lesion was progressive, as shown by the fact that, as exposure time increased, the affected tubular cells were enlarged and the number of affected tubules and tubular cells was increased. Occasionally, some tubules were enlarged or dilated to the extent that they were difficult to identify as tubules. In animals that survived longer, there was a decrease in the number of enlarged cells, the corresponding tubules were dilated, and portions of the basement membrane had a stripped appearance. Periodic acid Schiff's stain was not useful in attempts to determine if the apparently stripped basement membrane was in fact naked or covered by a thin cytoplasmic membrane extending from the one or more remaining cytomegalic tubular cells. In the most advanced stage, the lesion extended to the subcapsular cortex, where enlarged tubular cells were readily found. Development of cytomegaly did not completely overshadow development of the normal aging rat nephropathy, which was also present.

Although Fukuda et al. (1983) reported increased incidences of pulmonary adenocarcinomas in mice that inhaled trichloroethylene for up to 104 weeks, most of the evidence for the carcinogenicity of trichloroethylene, like that of the chlorinated ethanes and ethylenes studied earlier (hexachloroethane, NCI, 1978a; 1,1,2,2-tetrachloroethane, NCI, 1978b; 1,1,2-trichloroethane, NCI, 1978c; tetrachloroethylene, NCI, 1977; pentachloroethane, NTP, 1983) comes from data obtained in gavage studies in mice. The interpretation of chemically induced carcinogenicity for these materials is based on increases in the incidences of hepatocellular neoplasms in male and female $B6C3F_1$ mice. Because this is a relatively common tumor in male mice of this strain (seen in approximately 32% of corn oil vehicle control males and 7% of vehicle control females), the significance of the lesion is frequently debated. Also, the reason for the apparent relative insensitivity of Osborne-Mendel and F344/N rats to the carcinogenic effects of members of this chemical class remains unknown. Possibly increased tumor incidences were not seen in rats because the animals did not survive long enough to develop the lesions.

Inter- or intraspecies differences in susceptibility to the effects of chemicals can be mediated through inherited pharmacokinetic mechanisms. Stott et al. (1982) reported that $B6C3F_1$ mice metabolize more trichloroethylene (per body weight) than do Osborne-Mendel rats. A similar difference in trichloroethylene metabolism between $B6C3F_1$ mice and Sprague Dawley rats has been reported (Parchman and Magee, 1982). Prout et al. (1985) compared the metabolism of trichloroethylene in $B6C3F_1$ and Swiss Webster mice and Osborne-Mendel and Wistar-derived rats. These investigators reported that in mice the metabolism of a single oral dose of trichloroethylene was linear over a dose range of 10-2,000 mg/kg. In rats, however, metabolism was independent of dose at 1,000 mg/kg and above. Consequently, at doses in excess of 1,000 mg/kg, mice are exposed to relatively higher concentrations of trichloroethylene metabolites. If a carcinogenic effect of trichloroethylene requires biotransformation of the parent molecule to a reactive metabolite, $B6C3F_1$ mice might be expected to be more susceptible than Osborne-Mendel or Sprague Dawley rats because the mice are exposed to higher concentrations of metabolites. Trichloroethylene epoxide has been suggested as an electrophilic metabolite of trichloroethylene (Van Duuren, 1975), but Miller and Guengerich (1982) have reported the results

of in vitro experiments which suggest that the epoxide may not be an intermediate in trichloroethylene metabolism.

Elcomb et al. (1985) administered 10 daily doses of 500, 1,000, or 1,500 mg/kg trichloroethylene by gavage to Osborne-Mendel and Wistar-derived rats and $B6C3F_1$ and Swiss Webster mice. The dose regimen increased liver weight and decreased hepatic DNA content in both species and increased hepatic DNA synthesis in mice but not in rats. Also, trichloroethylene increased hepatic peroxisomes in mice but not in rats. A relationship between peroxisome proliferation and hepatocarcinogenesis has been suggested (Reddy and Lalwani, 1983). If such a relationship exists, the insensitivity of rats to trichloroethylene-induced peroxisome proliferation might explain the species differences in hepatocellular responses to the chemical.

Study Rationale

To determine the effects of trichloroethylene in various strains of rats, the National Cancer Institute initiated a series of 2-year toxicology and carcinogenesis studies of trichloroethylene in several strains. The results obtained with F344/N rats and $B6C3F_1$ mice have been reported (NTP TR 243, in preparation), and the present report describes the results of studies in four additional strains of rats (ACI 9935, August 28807, Marshall 520, and Osborne-Mendel).

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF TRICHLOROETHYLENE

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

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 TRICHLOROETHYLENE

High purity "Hi-Tri" trichloroethylene was obtained in two lots from Missouri Solvents (Kansas City, Missouri).

Purity and identity analyses were conducted at Midwest Research Institute (Kansas City, Missouri) (Appendix J). The results of the elemental analyses for both lots were consistent with the theoretical values. Twelve impurities having an area totaling less than 0.04% of the area of the major peak were detected in lot no. TB05-206AA by one gas chromatography system. Eight impurities having an area less than 0.02% that of the major peak were detected in a second system. One impurity with an area of 0.02% that of the major peak was detected in lot no. TB08-039AA.

The infrared and nuclear magnetic resonance spectra of both lots were consistent with the literature spectra. "Hi-Tri" trichloroethylene contains 8 ppm of an amine stabilizer but no epichlorohydrin or 1,2-epoxybutane, as determined by gas chromatography/mass spectrometry.

Throughout the course of these studies, the trichloroethylene was stored at 4° C. Papanicolaou Cancer Research Institute periodically analyzed the study chemical versus a standard maintained at −20° C by gas chromatography with a 10% OV-101 glass column at 70° C. The chemical showed no decrease in purity over the course of the studies, even though a white flocculent material was noticed in the July 1979 reanalysis of lot no. TB05-206AA. A 5-gallon can of this material was returned to Midwest Research Institute for attempted purification. An analysis of the precipitate, which was present at a concentration of 25-30 ppm, is presented in Appendix K. Midwest Research Institute shipped the filtered trichloroethylene back to Papanicolaou Cancer Research Institute in October 1979.

A new lot (TB08-039AA) was received at Papanicolaou in December 1979 and was used immediately.

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

Weighed amounts of trichloroethylene were mixed with corn oil to give the desired concentrations of stock solutions (Table 2; Appendix L). Doses were administered at a constant volume. Three of the rat strains received 1.0 ml per dose. Osborne-Mendel rats received 5 ml/kg body weight for the first 7 weeks.

Trichloroethylene in corn oil (1% w/v) was found to be stable for 7 days at room temperature (Appendix L). Later, stock solutions of trichloroethylene in corn oil were found to be stable at 4° C for 8 weeks. Stock solutions were prepared once per week for the first 13 weeks of the 2-year studies and once per month for the remainder of the studies. Stock solutions were analyzed for trichloroethylene content by gas chromatography (Appendix M). Because 201/234 of the dose solutions analyzed were within ± 10% of the target concentrations, it is estimated that solutions were prepared within specifications 86% of the time (Table 3; Appendix N). Of the 33 dose mixtures varying from target concentrations by more than 10%, 24 were within ±15% of the target concentrations, 7 were within 20% of the target concentrations, and the remaining 2 were within 25% of the target concentrations.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxicity of trichloroethylene and to determine the doses to be used in the 2-year studies.

Male and female ACI, August, and Marshall rats were obtained from Papanicolaou Cancer Research Institute. August and ACI rats were assigned to cages according to a table of random numbers. Cages were then assigned to dosed and vehicle control groups according to another table of random numbers.

Rats were housed five per cage in polycarbonate cages. Purina Lab Chow® and water (via an

TABLE 2. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF TRICHLOROETHYLENE

Thirteen-Week Studies	Two-Year Studies
Preparation	
Trichloroethylene mixed with 100 ml corn oil to prepare stock solution for 1 wk	Trichloroethylene mixed with corn oil in mixing cylinder to prepare stock solution
Maximum Storage Time	
Generally 10 d	1 wk for the first 13 wk, then 1 mo
Storage Conditions	
2°-5° C	2°-5° C

TABLE 3. SUMMARY OF RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF TRICHLOROETHYLENE

Mean (percent of target concentration)	102.2
Standard deviation	6.61
Coefficient of variation (percent)	6.5
Range (percent of target concentration)	77.0-121.1
Number of samples	234

automatic watering system) were available ad libitum.

Groups of 10 male ACI and August rats were administered 0, 125, 250, 500, 1,000, or 2,000 mg/kg trichloroethylene in corn oil by gavage 5 days per week for 13 weeks. Groups of 10 female August and ACI rats were administered 0, 62.5, 125, 250, 500, or 1,000 mg/kg on the same schedule. Groups of 10 male Marshall rats were administered 0, 268, 308, 495, 932, or 1,834 mg/kg and groups of 10 female Marshall rats were administered 0, 134, 153, 248, 466, or 918 mg/kg on the same schedule. Further experimental details are summarized in Table 4.

Animals were checked twice daily; moribund animals were killed. Individual animal weights were recorded weekly. Clinical examinations were performed weekly.

At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Groups examined are listed in Table 4.

TWO-YEAR STUDIES

Study Design

Groups of 50 rats of each sex of four strains (ACI, August, Marshall, Osborne-Mendel) were administered 0, 500, or 1,000 mg/kg trichloroethylene in corn oil by gavage 5 days per week for 103 weeks. Groups of 50 rats of each sex and strain served as untreated controls.

Source and Specifications of Animals

The ACI 9935, August 28807, and Marshall 520 rats used in these studies were produced under strict barrier conditions at Papanicolaou Research Institute under a contract to the Carcinogenesis Program. The Osborne-Mendel rats were produced under similar conditions at CAMM Research Laboratory. Breeding stock for the foundation colonies at the production facilities originated at the National Institutes of Health Repository. The animals were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Animals were transferred to the study

TABLE 4. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF TRICHLOROETHYLENE

Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN	
Study Laboratory	
Papanicolaou Cancer Research Institute (Miami, FL)	Papanicolaou Cancer Research Institute (Miami, FL)
Size of Study Groups	
10 males and 10 females of each strain	50 males and 50 females of each strain
Doses	
ACI and August rats: male--0, 125, 250, 500, 1,000, or 2,000 mg/kg trichloroethylene in corn oil by gavage; ACI and August rats: female--0, 62.5, 125, 250, 500, or 1,000 mg/kg; Marshall rats: male--0, 268, 308, 495, 932, or 1,834 mg/kg; female--0, 134, 153, 248, 466, or 918 mg/kg; 1 ml dose volume	0, 500, or 1,000 mg/kg trichloroethylene in corn oil by gavage; groups of untreated controls also included; 1 ml dose vol (except Osborne-Mendel for the first 7 wk, dose vol--5 ml/kg)
Date of First Dose	
ACI: 3/28/77	ACI: 2/1/79; August: 10/15/79; Marshall: 12/11/78; Osborne-Mendel: 11/30/79
Date of Last Dose	
	ACI: 1/22/81; August: 10/2/81; Marshall: 11/28/80; Osborne-Mendel: 11/30/81
Duration of Dosing	
5 d/wk for 13 wk	5 d/wk for 103 wk
Type and Frequency of Observation	
Marshall rats observed 2 × d; weighed 1 × wk	Observed 2 × d; palpated weekly; weighed 1 × wk for 12-15 wk and then 1 × mo
Necropsy and Histologic Examination	
Necropsy performed on all animals; all vehicle control and high dose animals examined microscopically	Necropsy performed on all animals; histologic exam performed on all animals; tissues examined include: gross lesions and tissue masses, skin, mesenteric lymph nodes, mammary gland, salivary glands, thigh muscle, lungs and mainstem bronchi, heart, thyroid gland, parathyroids, esophagus, stomach, duodenum, ileum, colon, liver, vertebrae with bone marrow, thymus, larynx, trachea, pancreas, spleen, kidneys, adrenal glands, urinary bladder, brain, pituitary gland, spinal cord, eyes, seminal vesicles/prostate/testes or ovaries/uterus
ANIMALS AND ANIMAL MAINTENANCE	
Strain and Species	
ACI rats; August rats; Marshall rats	ACI 9935 rats; August 28807 rats; Marshall 520 rats; Osborne-Mendel rats
Animal Source	
Papanicolaou Cancer Research Institute	Papanicolaou Cancer Research Institute; except Osborne-Mendel: CAMM Research Lab Animals (Wayne, NJ)
Time Held Before Study	
	ACI: 3.5 wk; August: 2 wk; Marshall: 4 wk; Osborne-Mendel: 3 wk
Age When Placed on Study	
	ACI: 6.5 wk; August: 8 wk; Marshall: 7 wk; Osborne-Mendel: 8 wk
Age When Killed	
	ACI and August: 17-18 wk; Marshall: 110-111 wk

TABLE 4. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF TRICHLOROETHYLENE (Continued)

Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)	
Necropsy Dates ACI: 6/27/77; August: 7/19/77; Marshall: 6/13/77	ACI: 1/29/81-2/17/81; August: 10/12/81-10/15/81; Marshall: 12/8/80-12/16/80; Osborne-Mendel: 11/30/81-12/2/81
Method of Animal Distribution August and ACI: assigned to cages and then to dose groups according to tables of random numbers; Marshall: nonsystematized randomization	Two-step randomization
Feed Purina Lab Chow®; available ad libitum	Purina Lab Chow 5001 Pellets® (O.K. Feed Store, Miami, FL); available ad libitum
Bedding Wood chips	Sani-chip hardwood (Pinewood Products Co., O.K. Feed Store, Miami, FL)
Water Edstrom automatic watering system (Waterford, WI); available ad libitum	Edstrom automatic watering system (Waterford, WI); available ad libitum
Cages Polycarbonate; changed 2 × wk	Polycarbonate (Lab Products, Rochelle Park, NJ); changed 2 × wk
Cage Filters Filter covers (Monsanto Co., St. Louis, MO)	Cerex-spun nylon (Florida Filters, Miami, FL); changed 2 × mo
Animals per Cage 5	5
Animal Room Environment Temp--not recorded; hum--not recorded; fluorescent light 12 h/d; 18-20 room air changes/h	Av temp--23° C; humidity--52%-78%; fluorescent light 12 h/d; 10-15 room air changes/h

laboratory at 3-6 weeks of age and were quarantined for 2-4 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 6-8 weeks of age. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix O).

Animal Maintenance

Rats were housed five per cage in polycarbonate cages. Food and water were available ad libitum. Details of animal maintenance are summarized in Table 4.

Clinical Examinations and Pathology

All animals were observed twice daily, and clinical signs were recorded once per week. Body weights by cage were recorded once per week for the first 12-15 weeks of the studies and once per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals including those found dead, unless they were excessively autolyzed or cannibalized, missexed, or found missing. 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.

During necropsy, all organs and tissues were examined for grossly visible lesions. 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 evaluation was completed, the slides, paraffin blocks, and residual wet tissues were sent to the NCI/NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent quality assessment laboratory. The 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 assessment pathologist. The quality assessment report and slides were submitted to the Pathology Working Group (PWG) Chairperson, who reviewed all target tissues and those about which there was a disagreement between the laboratory and quality assessment pathologists.

Representative slides selected by the Chairperson were reviewed by the PWG, which includes the laboratory pathologist, without knowledge of previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the laboratory pathologist was asked to reconsider the original diagnosis. 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 analysis of pathology data, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Slides/tissues are generally not evaluated in a blind fashion (i.e., without knowledge of dose group) unless the lesions in question are subtle or unless there is an inconsistent diagnosis of lesions by the laboratory pathologist. Nonneoplastic lesions are not examined routinely by the quality assessment pathologist or PWG unless they are considered part of the toxic effect of the chemical.

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 to be missing or dead of other than natural causes; 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. 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. Continuity-corrected tests are used in the analysis of tumor incidence, and reported P values are one-sided.

Life Table Analysis--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 appoximates time to tumor onset. In this case, the life table test also provides a comparison of the time-specific tumor incidence.

Incidental Tumor Analysis--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 appendixes 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, 1985) are included for those tumors appearing to show compound-related effects.

III. RESULTS

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

Nonneoplastic Lesions of the Kidney

Neoplastic Lesions

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III. RESULTS

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted on male and female ACI, August, and Marshall rats. Data from previous studies of Osborne-Mendel rats (NCI, 1976) were used to set doses for the 2-year studies of the Osborne-Mendel strain. The results of the current 13-week studies are condensed, for comparative purposes, and presented in Tables 5 and 6. More detailed information is presented in Appendix P.

Doses used for ACI and August rats ranged from 125 to 2,000 mg/kg for males and 62.5 to 1,000 mg/kg for females. Doses for Marshall rats ranged from 268 to 1,834 mg/kg for males and 134 to 918 mg/kg for females.

With the exception of three male August rats that received 2,000 mg/kg, all animals survived to the end of the 13-week experimental period. In male rats, the highest dose administered reduced final mean body weights (relative to vehicle controls) in all three strains by more than 10%. These reductions ranged from 12% in Marshall rats to 17% in ACI rats. In females, final mean body weights relative to vehicle controls were somewhat depressed; however, none was depressed in excess of 8% (August). Body weight changes (percent) in female rats administered the highest dose (1,000 mg/kg in ACI and August; 918 mg/kg in Marshall) were comparable to those in males administered similar doses (1,000 mg/kg in ACI and August; 932 mg/kg in Marshall). No behavioral effects attributable to trichloroethylene administration were recorded. Similarly, the administration of the chemical for 13 weeks was not associated with histopathologic changes.

Dose Selection Rationale: Doses selected for the 2-year studies in ACI, August, Marshall, and Osborne-Mendel rats (both sexes) were 0, 500, and 1,000 mg/kg in corn oil by gavage, administered 5 days per week. The selection of these doses was based on survival (all rats dosed with 1,000 mg/kg trichloroethylene for 13 weeks survived for the entire study), body weight gains (in male rats, mean body weights of dosed animals at the end of the 13-week studies were from 91% to 96% those of vehicle controls; in females, final mean body weights of dosed animals were from 93% to 96% those of vehicle controls), and absence of histopathologic changes produced in ACI, August, and Marshall rats during the 13-week studies. Doses for the Osborne-Mendel rats (also 0, 500, and 1,000 mg/kg per day) were similar to the doses used in the earlier 2-year studies (NCI, 1976). The doses in those studies, expressed as time-weighted averages, were 550 and 1,100 mg/kg and significantly reduced survival in each sex. Both untreated control and corn oil vehicle control groups were used in the present studies.

TABLE 5. COMPARISON OF EFFECTS OF TRICHLOROETHYLENE ON SURVIVAL AND BODY WEIGHTS IN MALE ACI, AUGUST, AND MARSHALL RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES (a)

ACI			August			Marshall		
Dose (mg/kg)	Survival	Final Body Weight Relative to Veh. Cont. (percent)	Dose (mg/kg)	Survival	Final Body Weight Relative to Veh. Cont. (percent)	Dose (mg/kg)	Survival	Final Body Weight Relative to Veh. Cont. (percent)
0	10/10	--	0	10/10	--	0	10/10	--
125	10/10	99.6	125	10/10	101.2	268	10/10	103.2
250	10/10	94.2	250	10/10	96.7	308	10/10	104.9
500	10/10	97.7	500	10/10	95.9	495	10/10	100.8
1,000	10/10	90.7	1,000	10/10	95.9	932	10/10	93.9
2,000	10/10	82.6	2,000	7/10	84.6	1,834	10/10	87.9

(a) Trichloroethylene was mixed with corn oil and administered by gavage 5 d/wk for 13 weeks.

TABLE 6. COMPARISON OF EFFECTS OF TRICHLOROETHYLENE ON SURVIVAL AND BODY WEIGHTS IN FEMALE ACI, AUGUST, AND MARSHALL RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES (a)

ACI			August			Marshall		
Dose (mg/kg)	Survival	Final Body Weight Relative to Veh. Cont. (percent)	Dose (mg/kg)	Survival	Final Body Weight Relative to Veh. Cont. (percent)	Dose (mg/kg)	Survival	Final Body Weight Relative to Veh. Cont. (percent)
0	10/10	--	0	10/10	--	0	10/10	--
62.5	10/10	99.4	62.5	10/10	101.4	134	10/10	101.2
125	10/10	94.8	125	10/10	100.5	153	10/10	102.9
250	10/10	98.9	250	10/10	100.5	248	10/10	102.3
500	10/10	92.0	500	10/10	98.6	466	10/10	97.1
1,000	10/10	93.1	1,000	10/10	92.8	918	10/10	95.9

(a) Trichloroethylene was mixed with corn oil and administered by gavage 5 d/wk for 13 weeks.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Detailed data for each strain are presented in Tables 7 through 10 and in Figures 1 through 4. The final body weights (relative to vehicle controls) and percent of animals surviving to terminal kill are summarized in Table 11.

The final mean body weights of all dosed groups except for high dose female Osborne-Mendel rats were somewhat lower than those of the vehicle controls. Trichloroethylene at the 1,000 mg/kg dose reduced mean final body weight by 10% or more in ACI, August, and Osborne-Mendel males and Marshall females. Final mean body weights in other high dose groups ranged from 3% lower in Marshall males to 8% lower in August females. Final mean body weight depression at the 500 mg/kg dose exceeded 10% only in the ACI males. Final body weight decrements in other low dose groups ranged from 3% in Osborne-Mendel males to 8% in ACI females.

Clinical signs of central nervous system toxicity were observed in dosed animals. Male and female rats of all strains exhibited sporadic ataxia, lethargy, convulsions, and hindlimb paralysis after dosing. On several occasions, animals in all dosed groups lost consciousness. These effects were generally transient; however, later in the studies, some animals convulsed before dosing and during weighing periods.

Survival

Estimates of the probabilities of survival for each strain of male and female rats at the doses used in these studies and for untreated and vehicle controls are shown in Table 12 and in the Kaplan and Meier curves in Figures 5, 7, 9, and 11. Unadjusted survival curves are presented in Figures 6, 8, 10, and 12; in these curves, animals killed accidentally have not been censored.

Survival was significantly reduced in ACI males and high dose females, in high dose female Osborne-Mendel rats, and in female Marshall rats. Survival of male Marshall rats at both doses was reduced because of mortality that occurred during the administration of the chemical.

TABLE 7. MEAN BODY WEIGHTS AND SURVIVAL OF ACI RATS IN THE TWO-YEAR GAVAGE STUDIES OF TRICHLOROETHYLENE

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	500 mg/kg Av. Wt. (grams)	500 mg/kg Wt. (percent of veh. controls)	500 mg/kg No. of Survivors	1,000 mg/kg Av. Wt. (grams)	1,000 mg/kg Wt. (percent of veh. controls)	1,000 mg/kg No. of Survivors
MALE								
0	169	50	158	93	50	162	96	50
1	188	50	182	97	50	183	97	50
2	205	50	198	97	50	199	97	50
3	220	50	213	97	50	211	96	49
4	233	50	227	97	50	221	95	49
5	247	50	237	96	49	231	94	48
6	252	50	242	96	49	239	95	47
7	260	50	255	98	48	249	96	47
8	270	50	258	96	47	252	93	47
9	275	50	264	96	47	260	95	47
10	280	50	253	90	47	260	93	46
11	288	50	259	90	47	257	89	46
12	283	49	268	95	45	262	93	45
13	283	49	267	94	45	264	93	42
14	283	49	260	92	45	256	90	42
15	291	49	260	89	45	256	88	42
17	296	49	266	90	45	268	91	42
21	296	49	276	93	45	274	93	40
26	327	49	297	91	41	299	91	38
30	342	49	311	91	40	306	89	35
34	339	49	316	93	36	310	91	32
38	..	..	308	..	36	316	..	30
39	340	48	..	..	..	..	..	..
42	..	..	318	..	36	307	..	30
45	344	47	325	94	33	314	91	28
50	350	46	327	93	32	314	90	26
54	..	..	319	..	29	307	..	23
58	343	46	320	93	29	310	90	23
61	345	45	325	94	29	311	90	22
65	350	45	320	91	27	313	89	19
69	357	45	328	92	26	322	90	19
73	357	44	327	92	26	316	89	18
77	361	43	330	91	26	323	89	14
81	364	40	344	95	26	322	88	14
85	358	39	323	90	25	319	89	14
89	355	39	319	90	24	316	89	13
94	361	39	316	88	21	314	87	13
97	359	39	313	87	20	309	86	12
98	357	39	312	87	20	315	88	12
101	353	38	313	89	20	311	88	12
103	353	38	314	89	19	309	88	11
FEMALE								
0	129	50	127	98	50	126	98	50
1	139	50	139	100	50	137	99	50
2	148	50	141	95	50	144	97	50
3	153	50	150	98	50	151	99	50
4	157	50	157	100	50	156	99	50
5	169	50	164	97	50	162	96	49
6	173	50	166	96	50	165	95	49
7	171	50	173	101	50	171	100	49
8	182	50	172	95	50	172	95	49
9	172	50	174	101	50	175	102	48
10	181	50	161	89	50	172	95	47
11	180	50	175	97	49	177	98	47
12	187	50	178	95	49	181	97	46
13	189	50	180	95	48	181	96	46
14	184	49	182	99	48	178	97	46
15	184	49	182	99	48	178	97	46
17	185	49	181	98	47	186	101	43
21	188	49	186	99	45	186	99	43
26	206	48	198	96	45	201	98	41
30	218	48	200	92	45	205	94	39
34	216	48	201	93	44	207	96	39
38	..	..	202	..	44	204	..	39
39	212	48	..	..	..	..	..	..
42	..	..	205	..	44	205	..	38
45	213	47	211	99	44	208	98	36
50	217	47	212	98	41	213	98	36
54	..	..	203	..	40	205	..	33
58	224	45	209	93	40	214	96	31
61	226	45	213	94	40	217	96	31
65	225	45	210	93	35	214	95	27
69	230	44	213	93	33	220	96	27
73	232	44	214	92	31	211	91	25
77	238	44	222	93	29	223	94	24
81	240	44	211	88	29	221	92	24
85	237	43	217	92	28	221	93	22
89	239	43	219	92	23	224	94	21
94	246	42	219	89	21	227	92	21
97	244	39	221	91	21	226	93	21
98	243	39	218	90	21	229	94	20
101	242	36	222	92	20	227	94	20
103	242	35	222	92	20	225	93	19

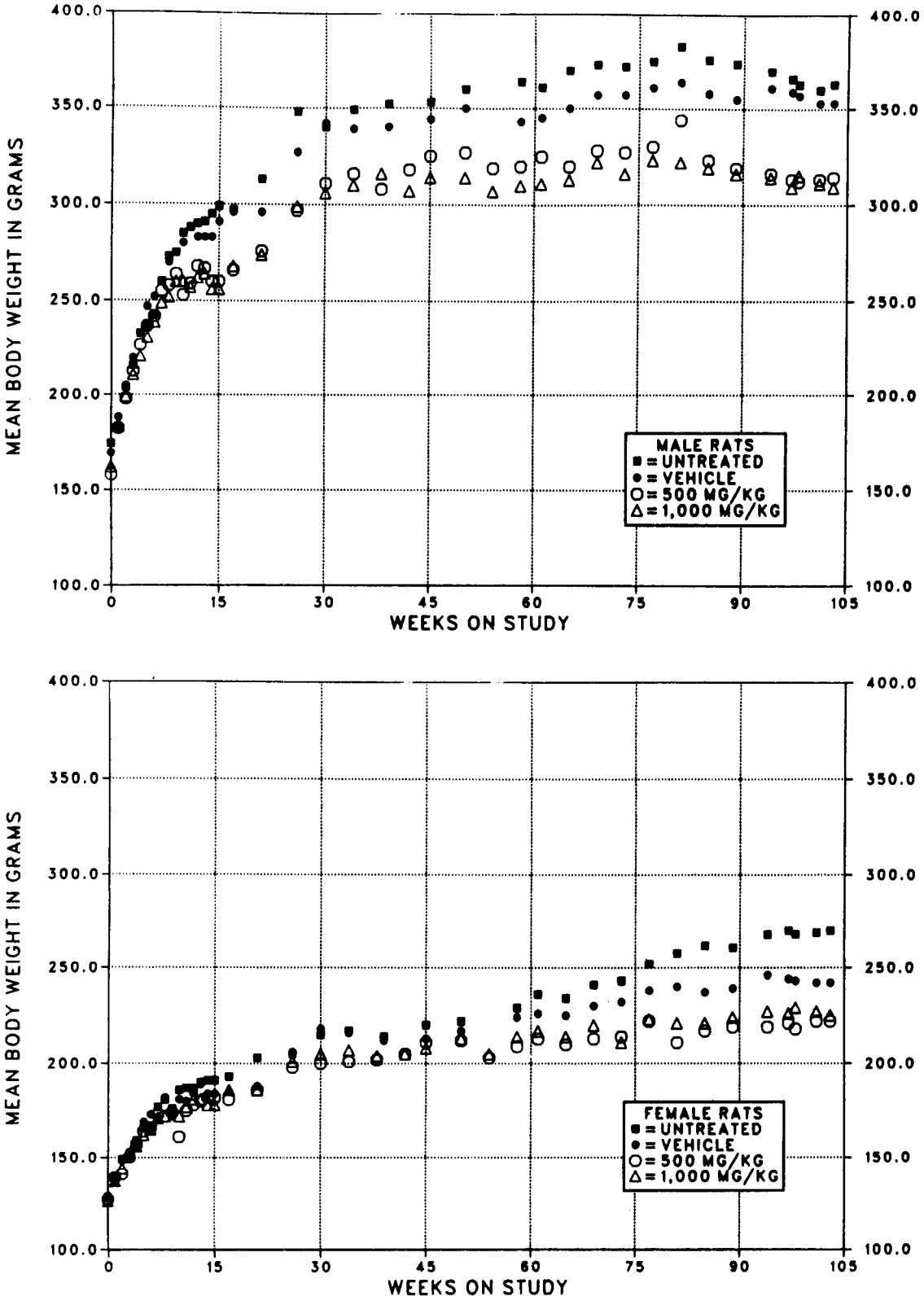


FIGURE 1. GROWTH CURVES FOR ACI RATS ADMINISTERED TRICHLOROETHYLENE IN CORN OIL BY GAVAGE FOR TWO YEARS

TABLE 8. MEAN BODY WEIGHTS AND SURVIVAL OF AUGUST RATS IN THE TWO-YEAR GAVAGE STUDIES OF TRICHLOROETHYLENE

Weeks on Study	Vehicle Control		500 mg/kg			1,000 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	162	50	167	103	50	163	101	50
1	193	50	186	96	50	183	95	50
2	227	50	223	98	50	216	95	50
3	241	50	209	87	50	232	96	50
4	256	50	238	93	50	242	95	50
5	234	50	248	106	50	250	107	50
6	245	49	257	105	50	262	107	49
7	266	49	270	102	49	273	103	48
8	271	49	279	103	49	277	102	46
10	292	49	287	98	48	288	99	46
12	297	49	295	99	48	289	97	46
13	303	49	300	99	48	296	98	46
16	319	49	320	100	45	308	97	45
20	322	49	318	99	44	320	99	45
25	345	49	336	97	42	330	96	43
30	354	49	351	99	40	329	93	40
33	366	49	359	98	38	345	94	37
38	381	49	370	97	36	351	92	37
41	391	49	372	95	36	356	91	37
45	396	49	370	93	36	357	90	36
49	399	49	..	..	..	..	..	..
50	..	..	375	..	36	362	..	34
54	407	47	382	94	35	364	89	34
57	407	47	..	..	..	..	..	..
58	..	..	382	..	35	371	..	33
62	413	46	380	92	35	366	89	30
65	418	46	380	91	33	363	87	30
69	..	..	389	..	29	371	..	26
70	416	42	..	..	..	..	..	..
73	421	40	385	91	28	374	89	23
76	417	38	382	92	27	359	86	23
79	412	36	399	97	25	368	89	23
83	409	36	377	92	24	365	89	22
87	408	33	364	89	23	362	89	20
91	405	31	372	92	19	362	89	19
96	399	29	363	91	17	356	89	18
100	391	25	364	93	16	336	86	16
104	382	21	357	93	13	335	88	16
FEMALE								
0	127	50	124	98	50	127	100	50
1	137	50	131	96	50	134	98	50
2	148	50	147	99	50	148	100	50
3	157	50	140	89	50	156	99	50
4	169	50	161	95	50	152	90	50
5	153	50	166	108	50	167	109	50
6	163	50	166	102	50	165	101	50
7	170	50	173	102	50	175	103	50
8	170	50	177	104	50	169	99	50
10	176	50	175	99	50	179	102	50
12	181	50	179	99	50	179	99	50
13	179	50	180	101	48	182	102	50
16	188	50	184	98	48	188	100	49
20	189	50	193	102	45	194	103	46
25	196	50	194	99	45	197	101	44
30	189	50	197	104	45	191	101	43
33	202	50	198	98	45	201	100	42
38	203	50	203	100	45	203	100	41
41	204	50	205	100	45	206	101	41
45	207	50	205	99	44	206	100	40
49	209	49	..	..	..	..	..	..
50	..	..	206	..	43	208	..	38
54	212	48	207	98	43	209	99	38
57	214	48	..	..	..	..	..	..
58	..	..	209	..	42	209	..	35
62	216	46	208	96	42	208	96	32
65	220	45	212	96	41	207	94	31
69	..	..	216	..	40	219	..	30
70	222	45	..	..	..	..	..	..
73	227	43	217	96	38	217	96	29
76	226	43	218	96	38	214	95	29
79	231	42	223	97	36	217	94	29
83	237	40	224	95	35	217	92	28
87	235	38	226	96	34	219	93	27
91	232	35	226	97	34	219	94	26
96	241	33	225	93	32	221	92	26
100	242	29	225	93	30	219	90	26
104	238	23	225	95	26	220	92	25

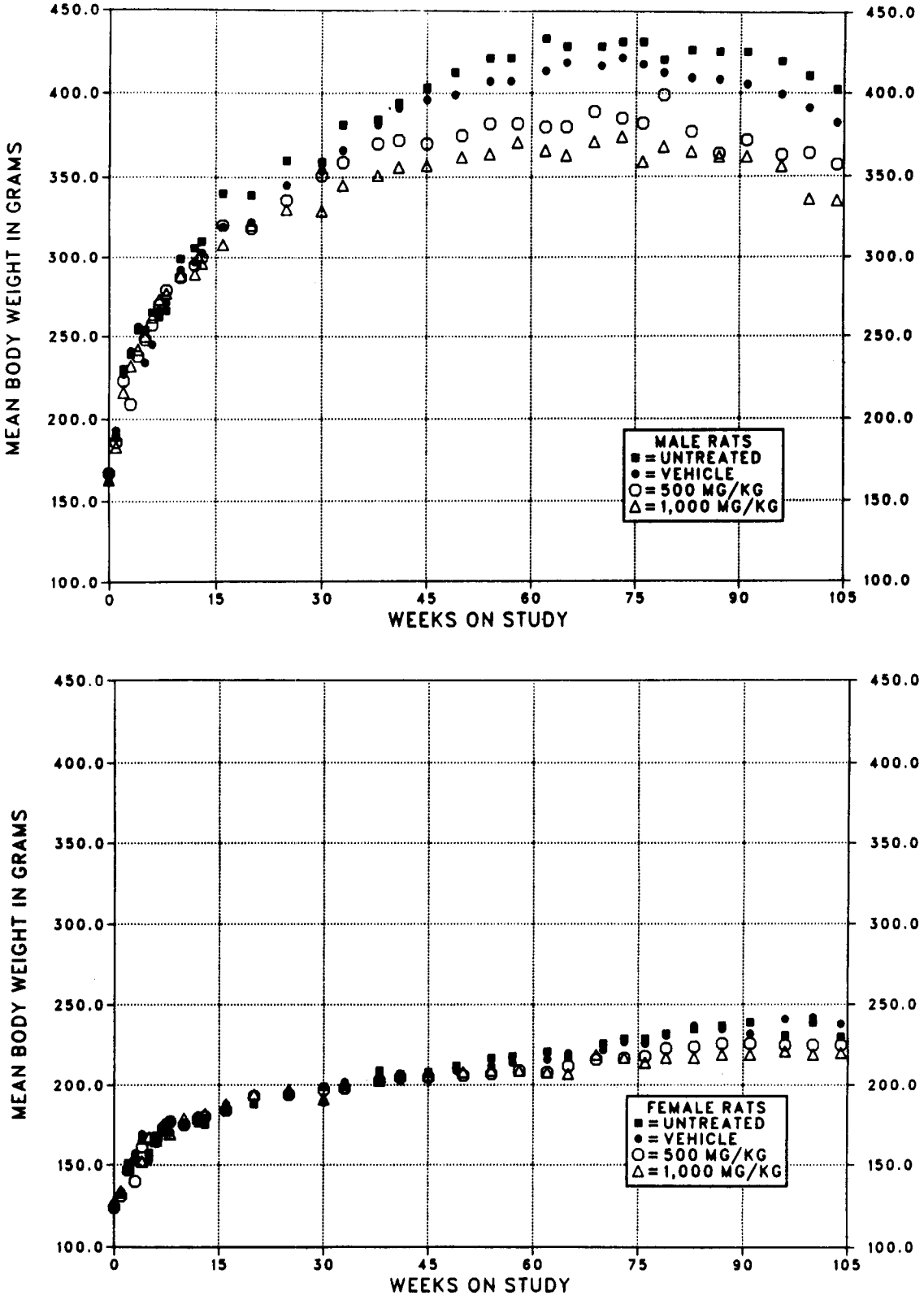


FIGURE 2. GROWTH CURVES FOR AUGUST RATS ADMINISTERED TRICHLOROETHYLENE IN CORN OIL BY GAVAGE FOR TWO YEARS

TABLE 9. MEAN BODY WEIGHTS AND SURVIVAL OF MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDIES OF TRICHLOROETHYLENE

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	500 mg/kg Av. Wt. (grams)	500 mg/kg Wt. (percent of veh. controls)	500 mg/kg No. of Survivors	1,000 mg/kg Av. Wt. (grams)	1,000 mg/kg Wt. (percent of veh. controls)	1,000 mg/kg No. of Survivors
MALE								
1	196	50	199	102	50	189	96	50
2	217	50	217	100	50	200	92	50
3	232	50	231	100	50	218	94	50
4	241	50	238	99	50	225	93	50
5	251	50	246	98	50	232	92	50
6	260	50	238	92	50	240	92	49
7	260	50	254	98	50	243	93	49
8	248	50	250	101	49	242	98	49
9	262	50	258	98	49	247	94	49
10	269	50	265	99	49	255	95	49
11	273	50	269	99	46	256	94	49
12	274	50	271	99	45	257	94	48
16	292	50	281	96	43	272	93	48
20	295	50	296	100	41	281	95	46
24	302	49	302	100	36	287	95	46
28	311	49	307	99	35	281	90	43
31	--	--	313	--	34	296	--	41
32	324	49	--	--	--	--	--	--
35	323	49	322	100	33	303	94	39
39	323	49	326	101	32	308	95	39
43	319	48	319	100	31	308	97	37
47	311	48	312	100	29	304	98	35
51	299	47	310	104	27	298	100	32
54	309	45	304	98	25	300	97	31
58	313	42	311	99	24	299	96	24
62	313	41	306	98	23	296	95	24
66	--	--	291	--	19	282	--	23
67	310	40	--	--	--	--	--	--
70	315	38	296	94	14	296	94	21
74	314	38	294	94	12	292	93	18
78	315	38	300	95	12	300	95	16
82	308	36	291	94	12	298	97	14
86	317	33	300	95	12	298	94	12
90	315	31	307	97	12	302	96	9
94	315	28	299	95	12	299	95	9
96	312	28	302	97	12	307	98	9
98	313	26	299	96	12	304	97	9
100	313	26	292	93	12	303	97	7
102	315	26	--	--	--	--	--	--
103	--	--	300	--	12	307	--	7
FEMALE								
1	144	50	140	97	50	143	99	50
2	155	50	149	96	50	152	98	50
3	161	50	155	96	50	157	98	50
4	166	50	161	97	50	161	97	50
5	171	50	161	94	50	161	94	50
6	169	50	167	99	50	165	98	50
7	174	50	169	97	50	170	98	50
8	168	50	172	102	50	172	102	50
9	178	50	174	98	50	171	96	48
10	182	50	179	98	50	178	98	48
11	179	50	181	101	50	177	99	48
12	187	50	180	96	50	178	95	48
16	196	50	190	97	49	189	96	48
20	205	50	200	98	48	199	97	48
24	217	50	202	93	48	200	92	48
28	216	50	208	96	48	199	92	48
31	--	--	213	--	48	206	--	42
32	229	50	--	--	--	--	--	--
35	233	50	225	97	47	219	94	40
39	237	50	230	97	47	222	94	40
43	241	50	229	95	47	223	93	39
47	234	50	227	97	47	218	93	39
51	235	49	232	99	46	222	94	39
54	241	49	228	95	45	222	92	38
58	245	49	236	96	44	224	91	33
62	244	49	232	95	43	222	91	31
66	--	--	240	--	40	224	--	30
67	243	49	--	--	--	--	--	--
70	255	47	238	93	37	228	89	27
74	253	47	238	94	35	228	90	23
78	257	44	244	95	27	231	90	21
82	263	44	239	91	24	224	85	19
86	259	43	240	93	23	228	88	18
90	258	40	240	93	21	236	91	13
94	257	37	237	92	20	231	90	13
96	252	36	236	94	18	231	92	13
98	248	35	236	95	17	227	92	11
100	247	31	237	96	14	222	90	10
102	247	30	--	--	--	--	--	--
103	--	--	235	--	13	227	--	10

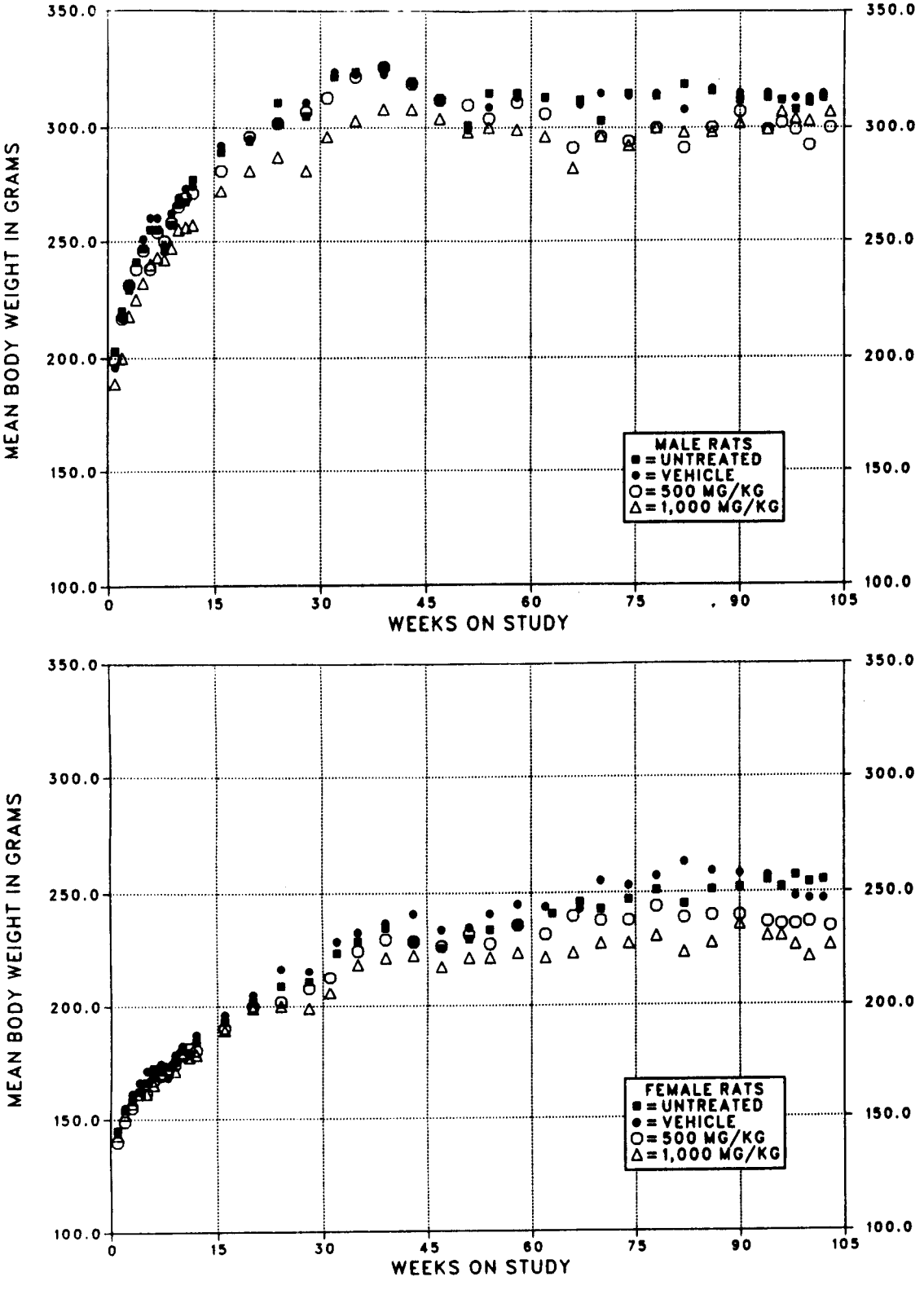


FIGURE 3. GROWTH CURVES FOR MARSHALL RATS ADMINISTERED TRICHLOROETHYLENE IN CORN OIL BY GAVAGE FOR TWO YEARS

TABLE 10. MEAN BODY WEIGHTS AND SURVIVAL OF OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDIES OF TRICHLOROETHYLENE

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	500 mg/kg Av. Wt. (grams)	500 mg/kg Wt. (percent of veh. controls)	500 mg/kg No. of Survivors	1,000 mg/kg Av. Wt. (grams)	1,000 mg/kg Wt. (percent of veh. controls)	1,000 mg/kg No. of Survivors
MALE								
0	197	50	197	100	50	199	101	50
1	252	50	246	98	50	247	98	50
2	285	50	272	95	50	269	94	50
3	307	50	280	91	50	289	94	50
4	329	50	315	96	50	312	95	49
5	338	50	338	100	50	337	100	49
6	352	50	347	99	50	345	98	49
7	364	50	360	99	50	353	97	49
8	372	50	370	99	50	348	94	49
9	375	50	376	100	50	359	96	49
10	390	50	387	99	49	365	94	49
11	394	50	393	100	49	373	95	49
12	403	50	385	96	48	376	93	48
13	402	50	397	99	48	387	96	48
17	415	50	412	99	48	391	94	48
20	437	50	432	99	48	400	92	48
23	446	50	441	99	48	416	93	47
26	450	50	440	98	48	420	93	46
29	470	50	456	97	47	433	92	45
33	476	49	467	98	45	435	91	45
37	478	49	472	99	45	442	92	43
41	489	49	472	97	45	445	91	42
46	493	49	482	98	44	444	90	39
50	502	49	481	96	44	446	89	37
53	511	49						
54			494		44	468		35
56	498	47						
57			499		44	466		33
61	520	47	502	97	44	467	90	33
64	532	47	507	95	43	470	88	32
67	533	46	503	94	42	461	86	31
69	530	44						
70			509		40	469		31
73	534	43	509	95	40	467	87	30
77	539	41	495	92	40	458	85	29
81	533	40	503	94	36	461	86	27
84	530	38						
85			504		32	458		24
90	532	35	503	95	28	452	85	23
93	519	31	491	95	26	440	85	21
97	517	28	490	95	25	438	85	19
100	499	24	478	96	18	410	82	17
104	476	22	464	97	17	421	88	14
FEMALE								
0	166	50	166	100	50	167	101	50
1	190	50	186	98	50	187	98	50
2	207	50	203	98	50	206	100	50
3	224	50	211	94	50	210	94	50
4	227	50	230	101	50	230	101	50
5	234	50	240	103	50	241	103	50
6	238	50	240	101	50	240	101	50
7	244	49	246	101	50	251	103	50
8	247	49	250	101	50	248	100	50
9	249	49	253	102	50	252	101	50
10	256	49	256	100	48	255	100	50
11	259	49	262	101	48	258	100	50
12	263	49	266	101	48	266	101	50
13	265	49	262	99	48	268	101	50
17	275	48	277	101	48	276	100	49
20	276	48	283	103	48	279	101	47
23	283	48	286	101	48	279	99	47
26	290	48	285	98	48	284	98	47
29	290	48	290	100	48	284	98	46
33	298	48	298	100	48	296	99	46
37	293	46	300	102	46	293	100	46
38	293	46						
41	297	45	296	100	45	286	96	46
46	296	45	295	100	44	288	97	46
50	301	44	298	99	44	292	97	45
53	303	43						
54			297		44	289		45
56	302	43						
57			296		44	297		45
61	310	43	304	98	42	300	97	43
64	307	41	301	98	41	299	97	43
67	307	41	305	99	41	300	98	42
69	308	40						
70			312		41	306		41
73	313	39	310	99	39	308	98	39
77	315	37	300	95	33	298	95	37
81	316	35	309	98	32	312	99	29
84	317	32						
85			305		31	313		28
90	322	31	302	94	23	306	95	22
93	319	30	296	93	21	297	93	21
97	317	26	301	95	17	306	97	18
100	319	22	302	95	15	307	96	15
104	303	18	281	93	10	305	101	7

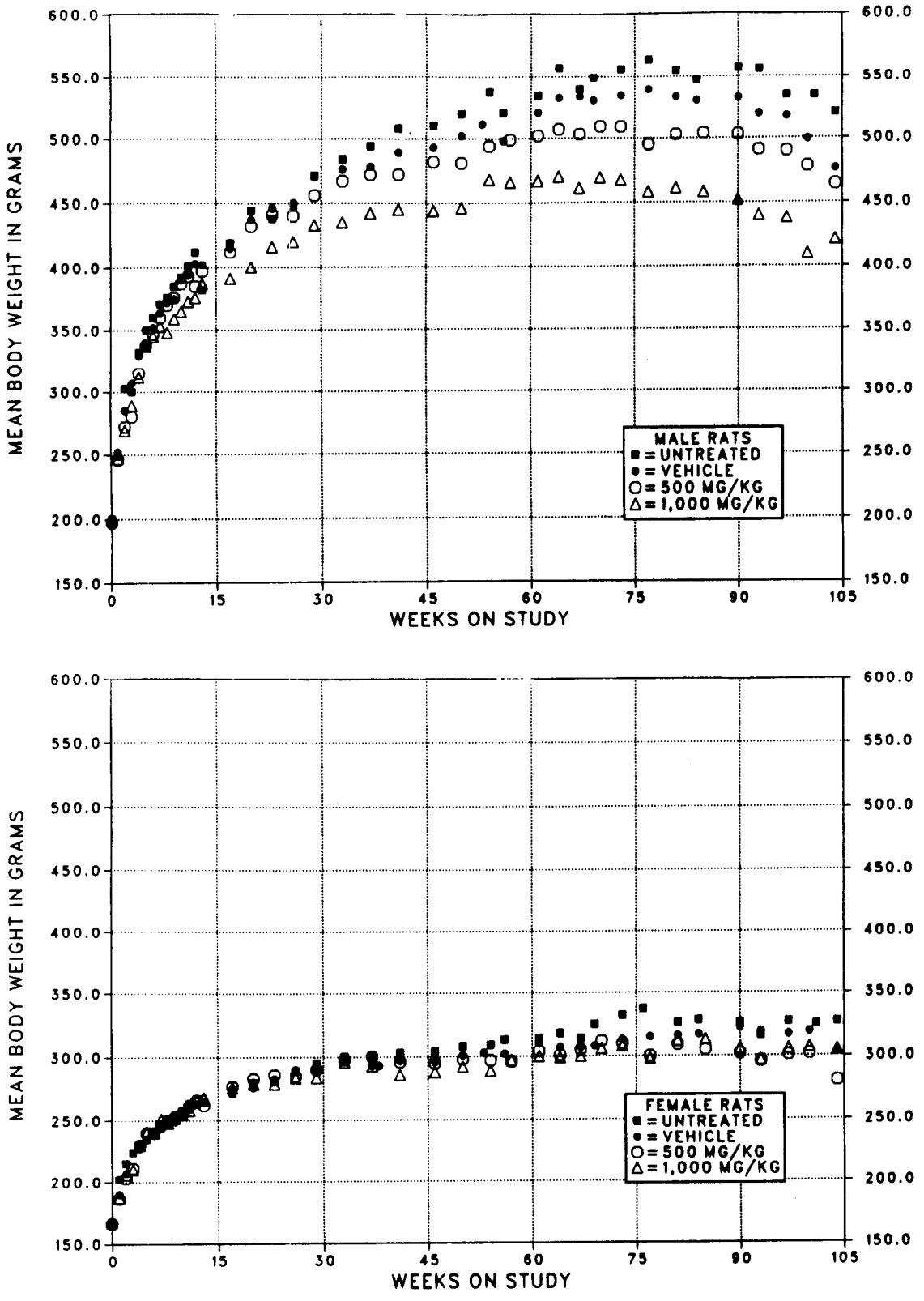


FIGURE 4. GROWTH CURVES FOR OSBORNE-MENDEL RATS ADMINISTERED TRICHLOROETHYLENE IN CORN OIL BY GAVAGE FOR TWO YEARS

TABLE 11. COMPARISON OF EFFECTS ON SURVIVAL AND FINAL BODY WEIGHTS IN ACI, AUGUST, MARSHALL, AND OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDIES OF TRICHLOROETHYLENE (a)

Group	Final Weight Relative to Vehicle Control (percent)	Survival (percent)	Final Weight Relative to Vehicle Control (percent)	Survival (percent)
	ACI (b)		August (c)	
MALE				
Untreated control	102.8	78	105.2	48
Vehicle control	--	76	--	42
500 mg/kg	89.0	(d) 38	93.5	26
1,000 mg/kg	87.5	(d) 22	87.7	32
FEMALE				
Untreated control	111.6	74	96.6	52
Vehicle control		70	--	46
500 mg/kg	91.7	40	94.5	52
1,000 mg/kg	93.0	(d) 38	92.4	50
	Marshall (e)		Osborne-Mendel (c)	
MALE				
Untreated control	99.4	64	109.2	42
Vehicle control	--	52	--	44
500 mg/kg	93.3	(d) 24	97.5	34
1,000 mg/kg	96.8	12	88.4	30
FEMALE				
Untreated control	103.2	62	107.9	38
Vehicle control	--	60	--	40
500 mg/kg	96.0	(d) 24	92.7	22
1,000 mg/kg	89.9	(d) 20	100.7	(d) 14

(a) Trichloroethylene was mixed in corn oil and administered by gavage 5 days per week.
(b) Final body weight recorded week 103
(c) Final body weight recorded week 104
(d) Survival was significantly ($P<0.05$) reduced relative to vehicle controls.
(e) Final body weight recorded week 100

TABLE 12. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF TRICHLOROETHYLENE (a)

	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg
MALE ACI RATS (b)				
Nonaccidental deaths before termination (c)	10	12	20	21
Accidentally killed	0	0	11	18
Animals missing	1	0	0	0
Killed at termination	36	37	19	11
Died during termination period	3	1	0	0
Survival P values (d)	--	0.001	0.019	0.002
FEMALE ACI RATS (b)				
Nonaccidental deaths before termination (c)	12	13	16	20
Accidentally killed	0	2	14	12
Animals missing	1	0	0	0
Killed at termination	36	33	20	17
Died during termination period	1	2	0	(e) 2
Survival P values (d)	--	0.021	0.202	0.034
MALE AUGUST RATS (f)				
Nonaccidental deaths before termination (c)	25	23	25	22
Accidentally killed	1	6	12	11
Animals missexed	0	0	0	1
Killed at termination	24	21	13	15
Died during termination period	0	0	0	1
Survival P values (d)	--	0.252	0.163	0.302
FEMALE AUGUST RATS (f)				
Nonaccidental deaths before termination (c)	24	26	18	12
Accidentally killed	0	1	6	13
Killed at termination	26	23	26	24
Died during termination period	0	0	0	1
Survival P values (d)	--	0.136	0.371	0.186
MALE MARSHALL RATS (g)				
Nonaccidental deaths before termination (c)	16	22	26	19
Accidentally killed	1	2	12	25
Animals missing	1	0	0	0
Killed at termination	32	26	12	6
Survival P values (d)	--	0.137	0.007	0.123
FEMALE MARSHALL RATS (g)				
Nonaccidental deaths before termination (c)	18	17	24	22
Accidentally killed	1	3	14	18
Killed at termination	31	30	12	10
Survival P values (d)	--	0.002	0.011	0.005
MALE OSBORNE-MENDEL RATS (h)				
Nonaccidental deaths before termination (c)	29	27	27	28
Accidentally killed	0	1	6	7
Killed at termination	18	22	17	14
Died during termination period	3	0	0	1
Survival P values (d)	--	0.173	0.657	0.195
FEMALE OSBORNE-MENDEL RATS (h)				
Nonaccidental deaths before termination (c)	31	22	33	37
Accidentally killed	0	8	6	6
Killed at termination	19	18	10	7
Died during termination period	0	2	1	0
Survival P values (d)	--	0.008	0.052	0.009

(a) Fifty animals initially in each study
(b) Terminal-kill period: weeks 104-106
(c) Includes animals killed in a moribund condition
(d) 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.
(e) Includes one accidentally killed animal; this animal is also included among those accidentally killed.
(f) Terminal-kill period: week 104
(g) Terminal-kill period: male--weeks 104-105; female--week 104
(h) Terminal-kill period: weeks 104-105

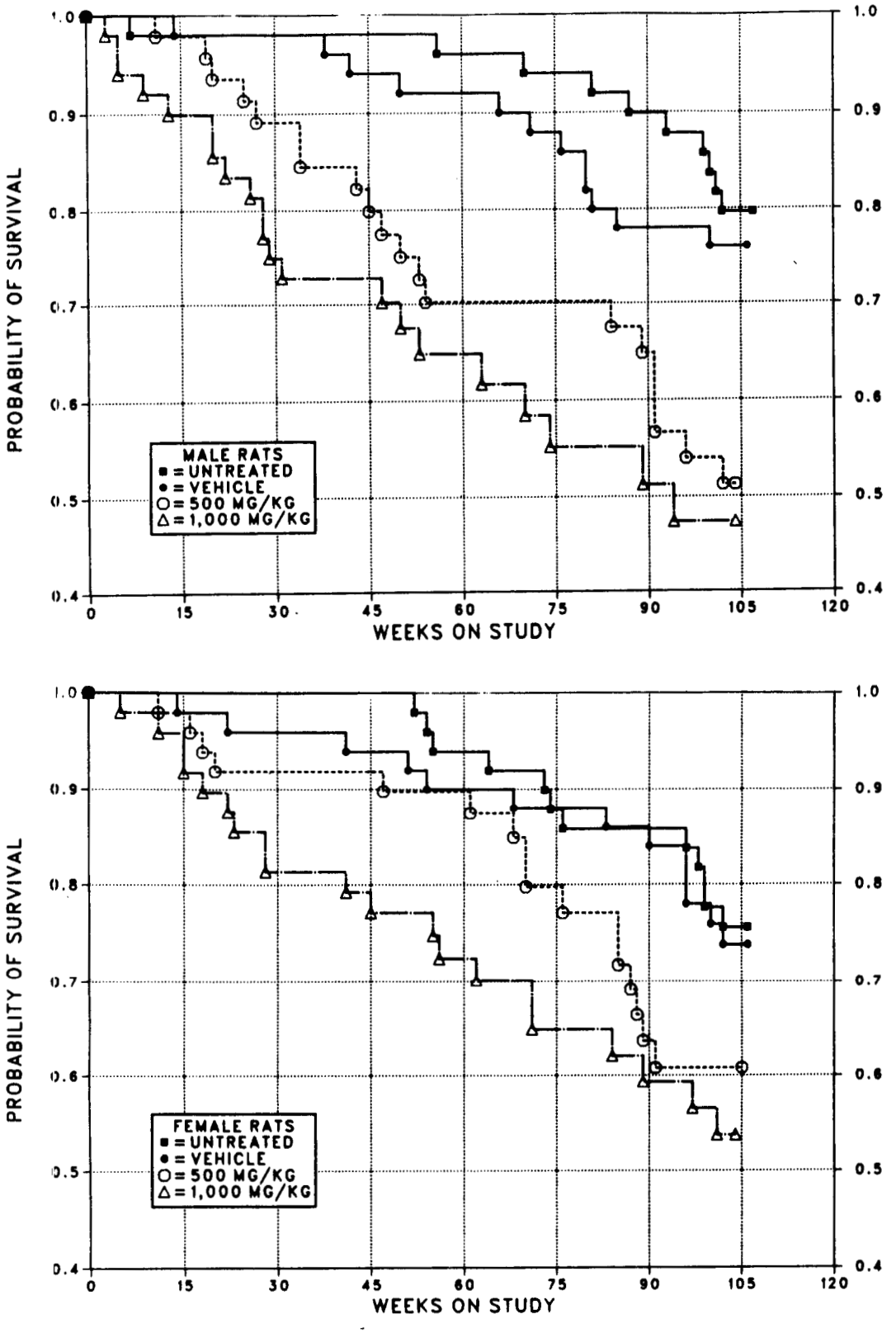
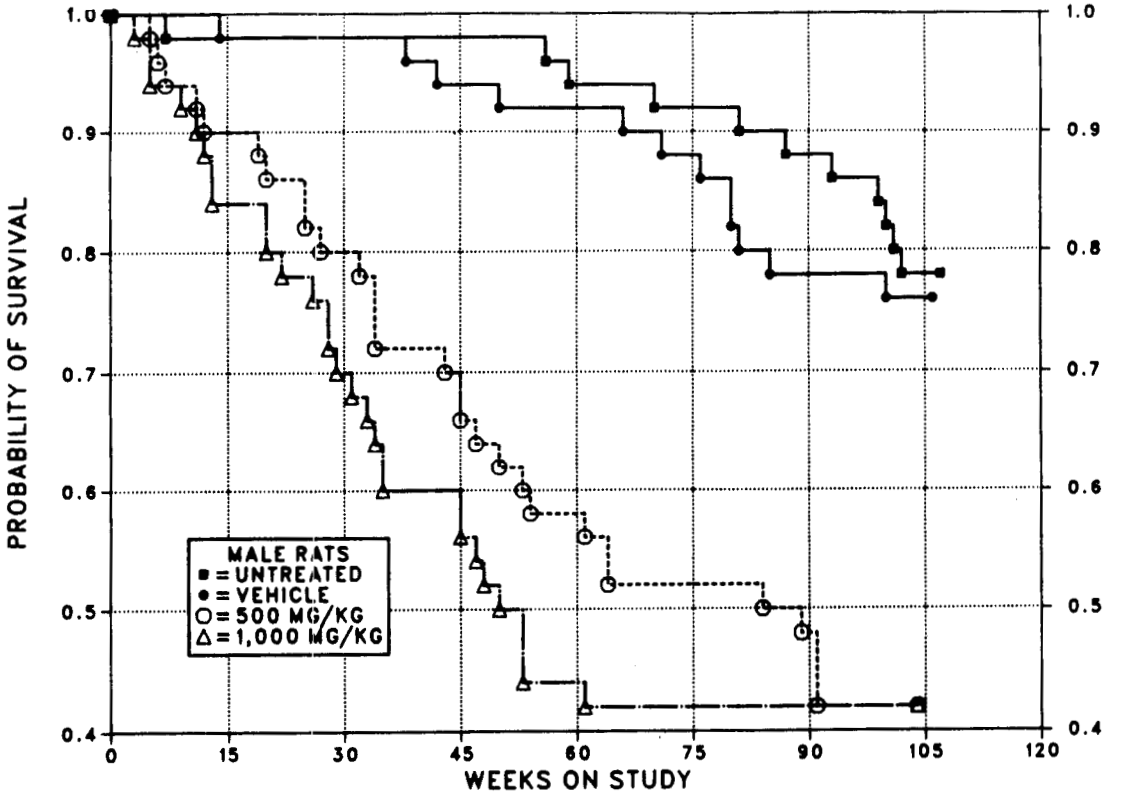


FIGURE 5. KAPLAN-MEIER SURVIVAL CURVES FOR ACI RATS ADMINISTERED TRICHLOROETHYLENE IN CORN OIL BY GAVAGE FOR TWO YEARS



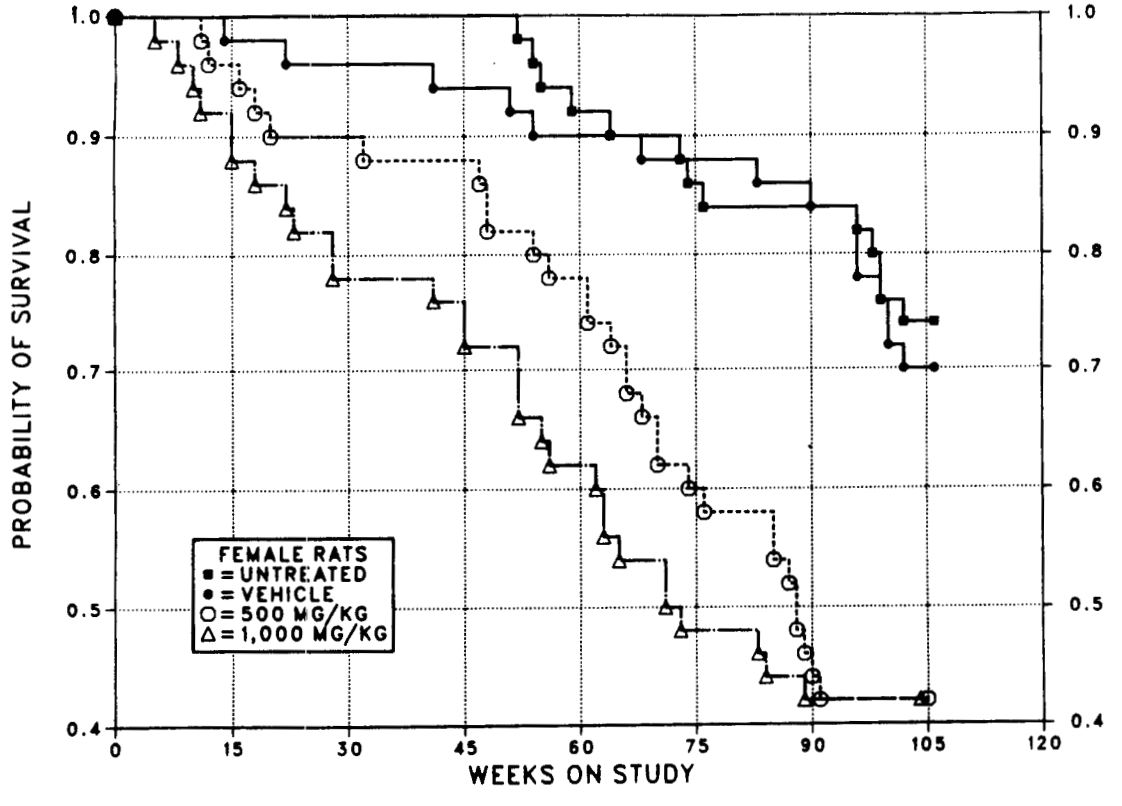


FIGURE 6. UNADJUSTED SURVIVAL CURVES FOR ACI RATS ADMINISTERED TRICHLOROETHYLENE IN CORN OIL BY GAVAGE FOR TWO YEARS

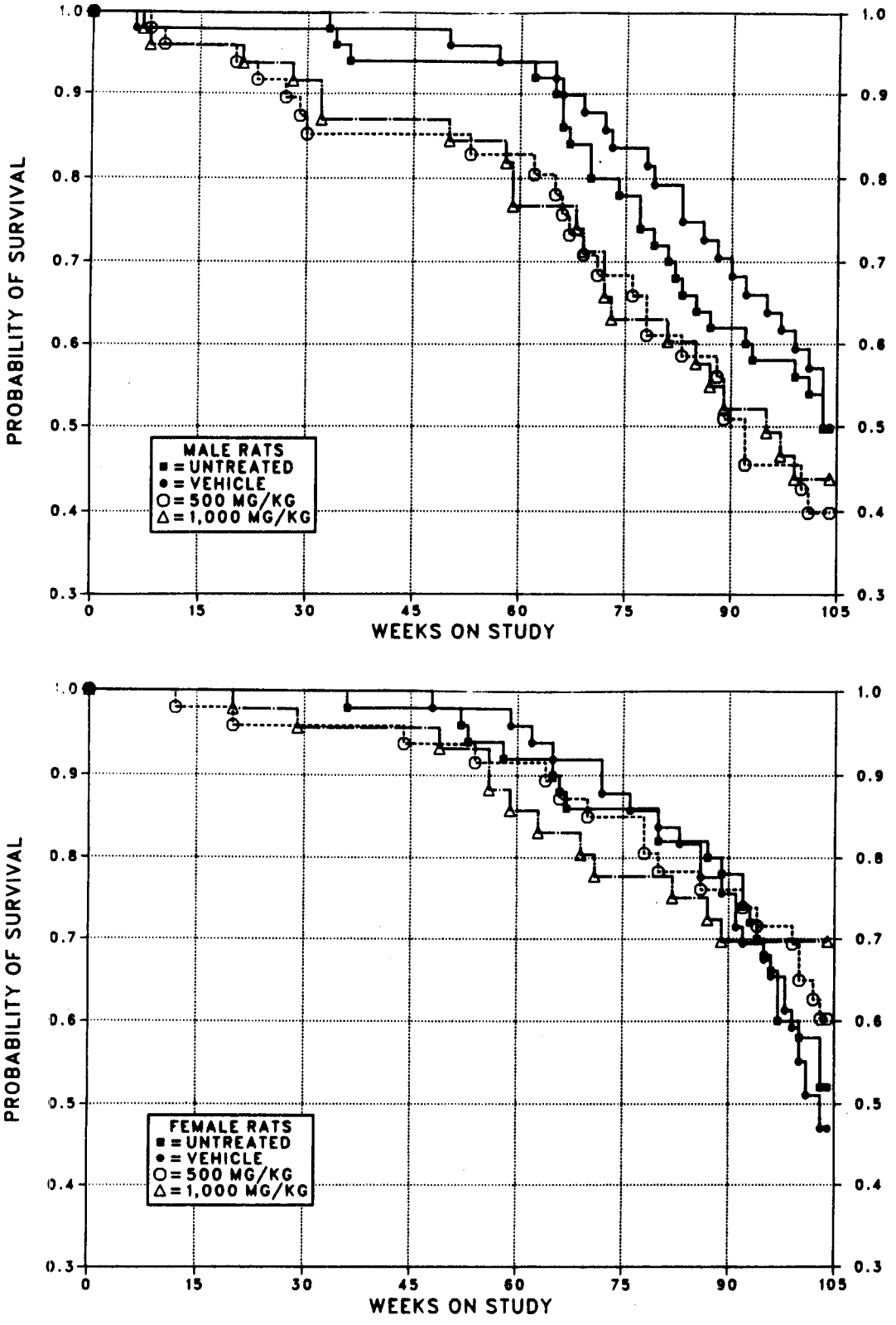
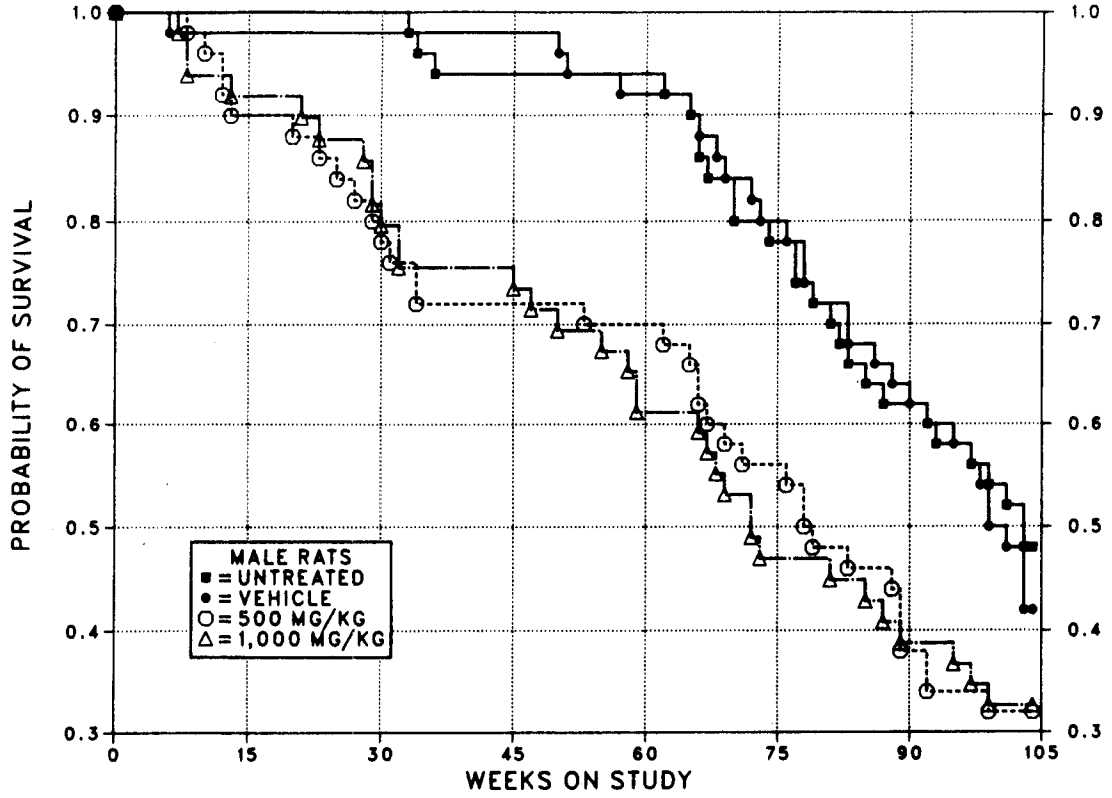


FIGURE 7. KAPLAN-MEIER SURVIVAL CURVES FOR AUGUST RATS ADMINISTERED TRICHLOROETHYLENE IN CORN OIL BY GAVAGE FOR TWO YEARS



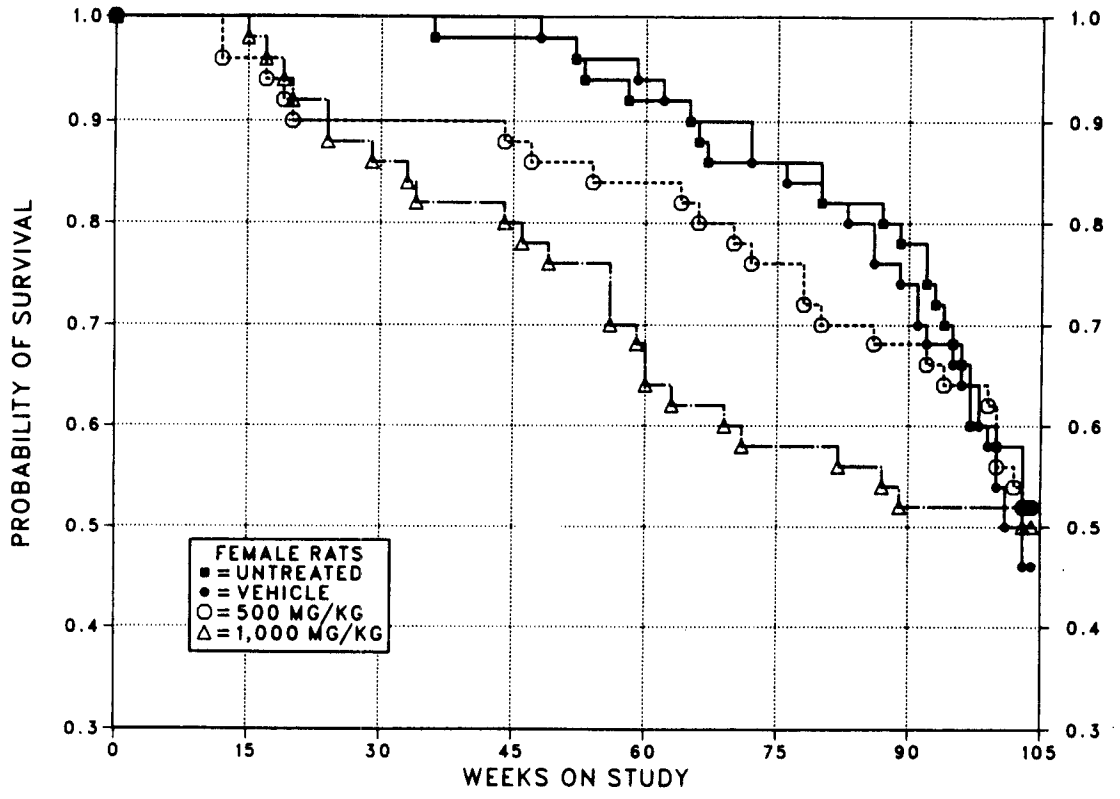


FIGURE 8. UNADJUSTED SURVIVAL CURVES FOR AUGUST RATS ADMINISTERED TRICHLOROETHYLENE IN CORN OIL BY GAVAGE FOR TWO YEARS

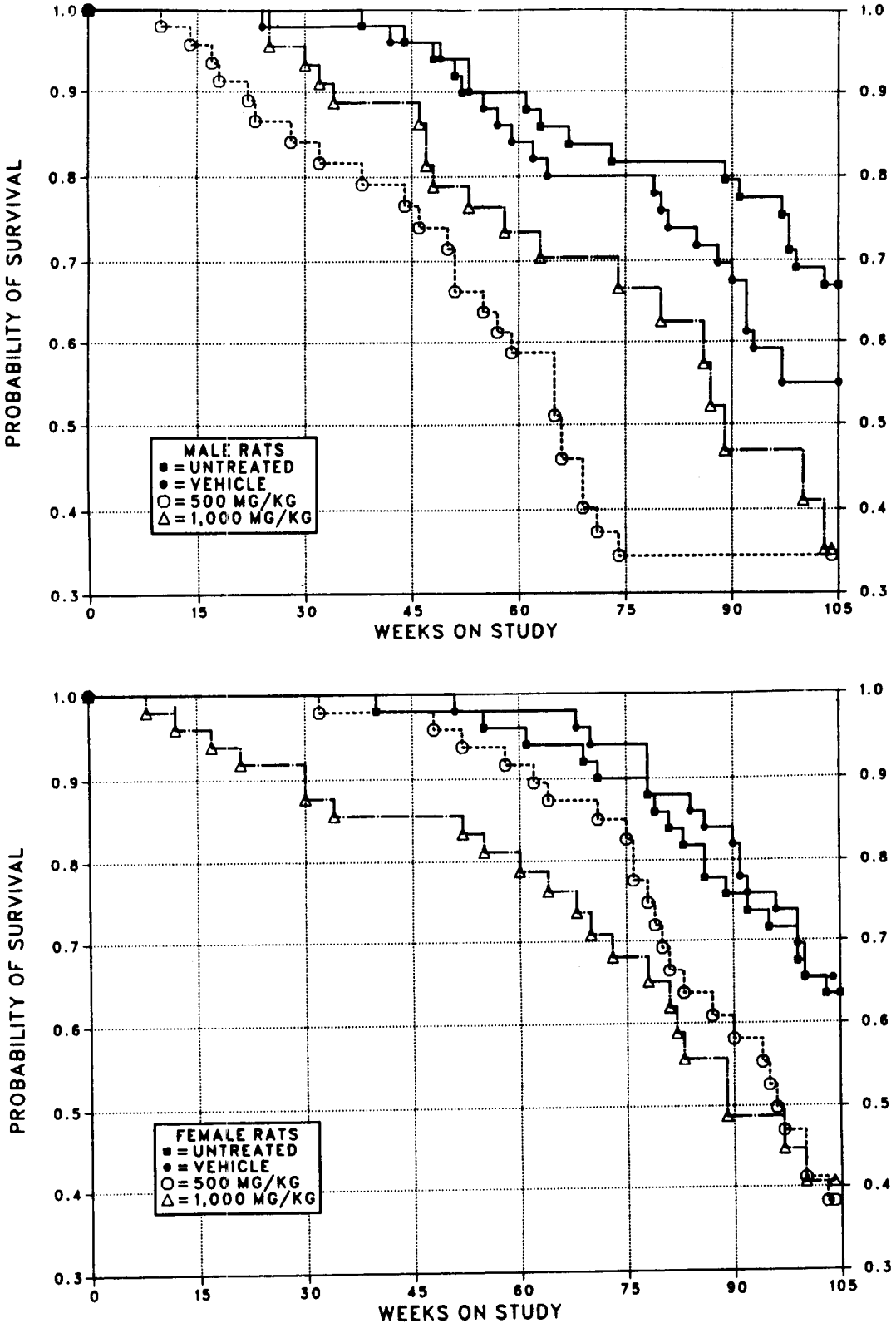
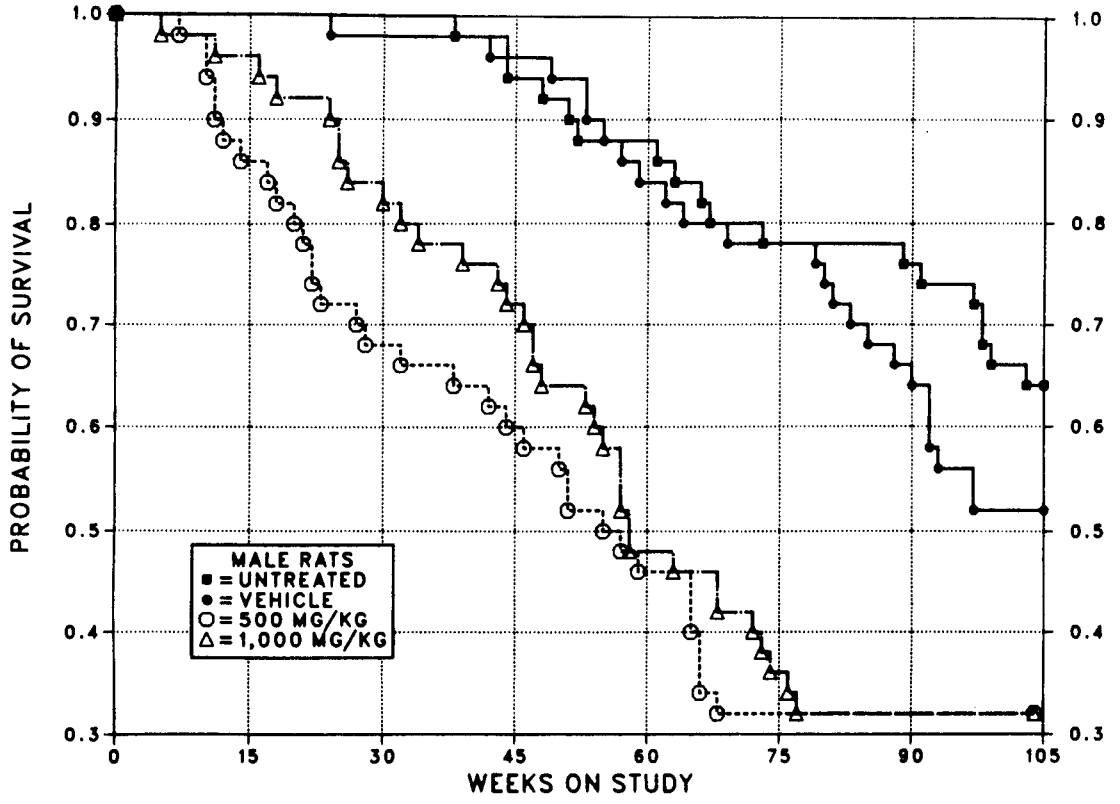


FIGURE 9. KAPLAN-MEIER SURVIVAL CURVES FOR MARSHALL RATS ADMINISTERED TRICHLOROETHYLENE IN CORN OIL BY GAVAGE FOR TWO YEARS



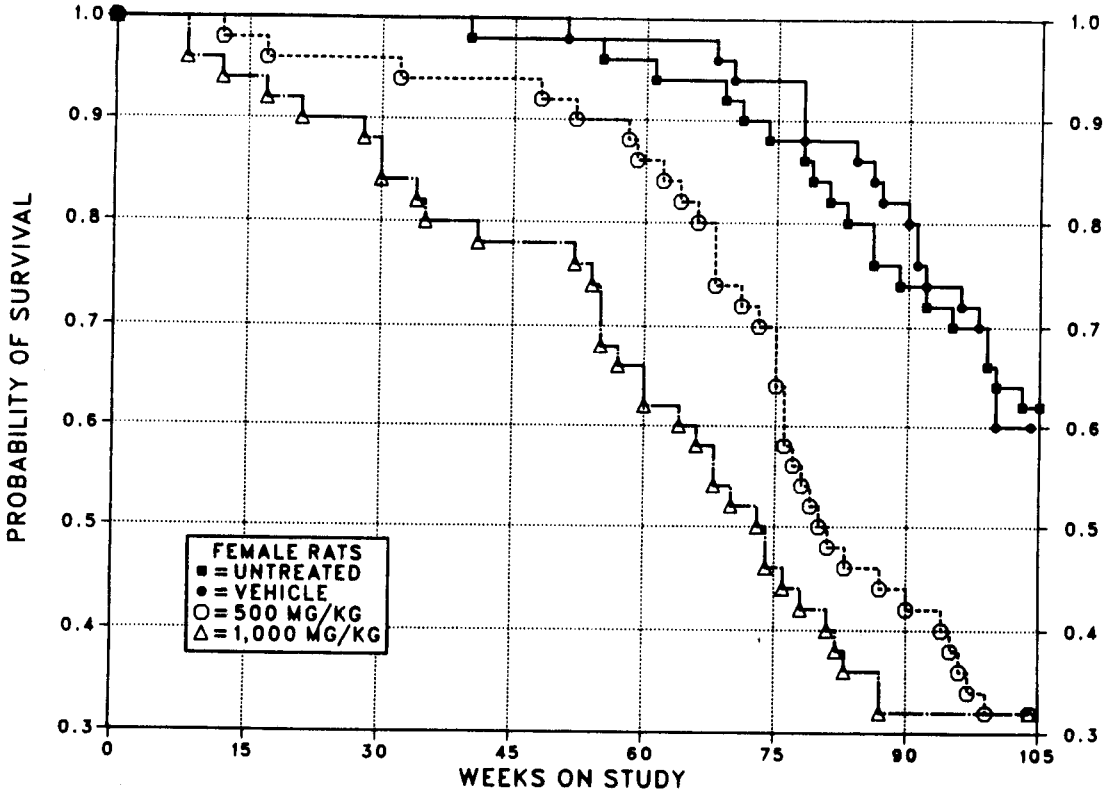


FIGURE 10. UNADJUSTED SURVIVAL CURVES FOR MARSHALL RATS ADMINISTERED TRICHLOROETHYLENE IN CORN OIL BY GAVAGE FOR TWO YEARS

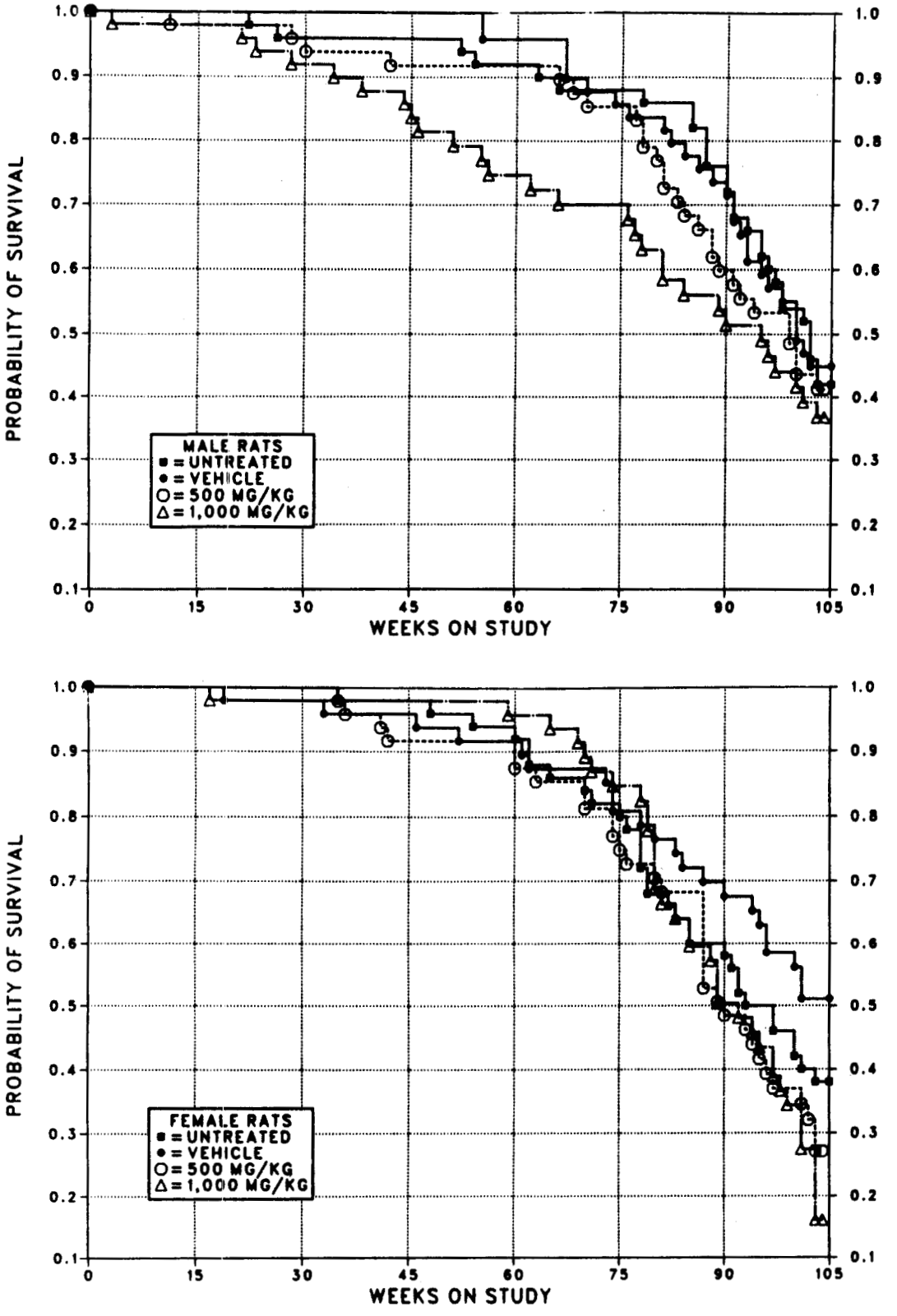


FIGURE 11. KAPLAN-MEIER SURVIVAL CURVES FOR OSBORNE-MENDEL RATS ADMINISTERED TRICHLOROETHYLENE IN CORN OIL BY GAVAGE FOR TWO YEARS

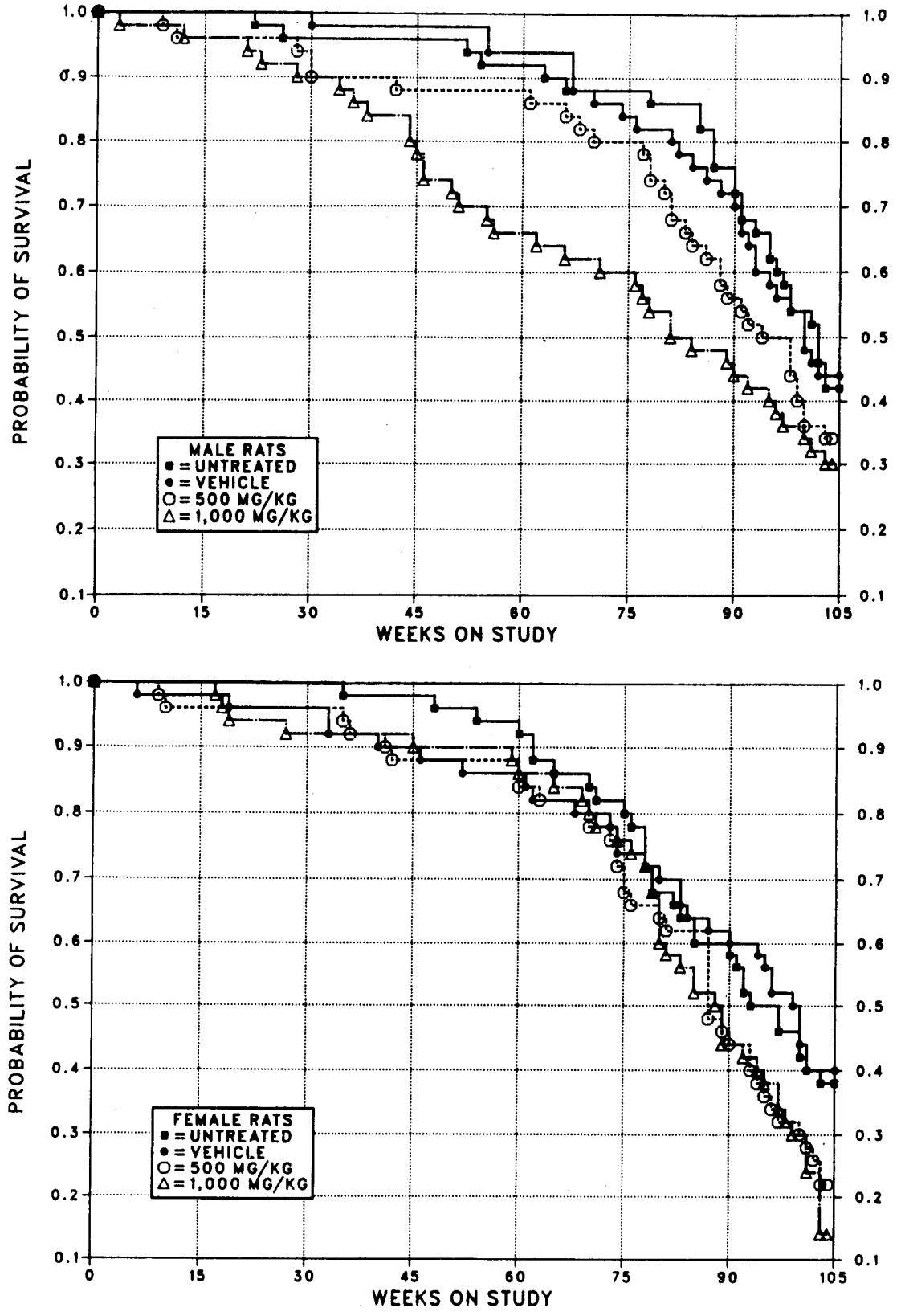


FIGURE 12. UNADJUSTED SURVIVAL CURVES FOR OSBORNE-MENDEL RATS ADMINISTERED TRICHLOROETHYLENE IN CORN OIL BY GAVAGE FOR TWO YEARS

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the kidney, testis, hematopoietic system, subcutaneous tissue, adrenal gland, pituitary gland, mammary gland, thyroid gland, and uterus.

Lesions in male rats are summarized in Appendixes A, C, E, and G. Lesions in female rats are summarized in Appendixes B, D, F, and H. Histopathologic findings on neoplasms are summarized in Tables A1, C1, E1, and G1 (male rats) and B1, D1, F1, and H1 (female rats). Tables A2, C2, E2, and G2 (male rats) and B2, D2, F2, and H2 (female rats) give the survival and tumor status for individual rats. Tables A3, C3, E3, and G3 (male rats) and B3, D3, F3, and H3 (female rats) contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in the vehicle control or in one of the dosed groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Tables A3, C3, E3, and G3 (male rats) and B3, D3, F3, and H3 (female rats) (footnotes). Findings on nonneoplastic lesions are summarized in Table A4, C4, E4, and G4 (male rats) and B4, D4, F4, and H4 (female rats). Statistical comparisons were made between vehicle control and dosed groups.

Nonneoplastic Lesions of the Kidney

Administration of trichloroethylene caused cytomegaly of renal tubular epithelial cells and toxic nephropathy in all four strains of rats (Tables 13 and 14). The inner cortex and outer stripe of the outer medulla were the primary areas affected. The epithelial cells of the pars recta (pars descendens) of the proximal tubule were enlarged and contained nuclei several times their normal size (karyomegaly). The enlarged nuclei were often hyperchromatic and irregular to oblong in shape. In kidneys with more extensive changes, tubular epithelial cells located in more superficial areas of the cortex were also affected. Other lesions observed in severely affected kidneys were diagnosed as toxic nephropathy to distinguish them from the common spontaneous nephropathy of aging rats. Toxic nephropathy occurred only in dosed rats and consisted of dilated tubules lined by elongated and flattened epithelial cells. The degree of flattening was often severe and was roughly proportional to the degree of dilation. The lumens of the affected tubules were empty or contained wisps of eosinophilic material.

Tubular cell hyperplasia occurred at low incidences in dosed male and female Osborne-Mendel rats and less frequently in untreated or vehicle control rats. One animal in each of the high dose male and female August and female Marshall and low dose male Marshall groups also had renal tubular cell hyperplasia. Tubular cell hyperplasia generally consisted of one or two tubules with stratified epithelium that partially or completely filled the tubular lumens. The affected tubular epithelial cells were large with abundant eosinophilic or basophilic cytoplasm and vesicular nuclei containing prominent nucleoli. Cells in mitosis were variable in number or absent. This lesion was distinctly different from the background tubular regeneration that is a component of spontaneous chronic progressive rat nephropathy. The latter lesion consists of cortical tubules lined by a single layer of cuboidal cells with small amounts of basophilic cytoplasm, vesicular nuclei, and variable mitoses.

No additional nonneoplastic lesions were observed which could be attributed to trichloroethylene administration.

TABLE 13. INCIDENCES OF RENAL CYTOMEGALY IN ACI, AUGUST, MARSHALL, AND OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDIES OF TRICHLOROETHYLENE (a)

Group	ACI	August	Marshall	Osborne-Mendel
MALE				
Vehicle control	0/50	0/50	0/49	0/50
500 mg/kg	40/49 (82%)	46/50 (92%)	48/50 (96%)	48/50 (96%)
1,000 mg/kg	48/49 (98%)	46/49 (94%)	47/47 (100%)	49/50 (98%)
FEMALE				
Vehicle control	0/48	0/49	0/50	0/50
500 mg/kg	43/47 (91%)	46/48 (96%)	46/48 (96%)	48/50 (96%)
1,000 mg/kg	42/43 (98%)	50/50 (100%)	43/44 (98%)	49/49 (100%)

(a) All incidences in dosed groups significantly greater ($P<0.01$) than those in the vehicle controls

TABLE 14. INCIDENCES OF TOXIC NEPHROPATHY IN ACI, AUGUST, MARSHALL, AND OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDIES OF TRICHLOROETHYLENE (a)

Group	ACI	August	Marshall	Osborne-Mendel
MALE				
Vehicle control	0/50	0/50	0/49	0/50
500 mg/kg	18/49 (37%)	10/50 (20%)	18/50 (36%)	39/50 (78%)
1,000 mg/kg	18/49 (37%)	31/49 (63%)	23/47 (49%)	35/50 (70%)
FEMALE				
Vehicle control	0/48	0/49	0/50	0/50
500 mg/kg	21/47 (45%)	8/48 (17%)	30/48 (63%)	30/50 (60%)
1,000 mg/kg	19/43 (44%)	29/50 (58%)	30/44 (68%)	39/49 (80%)

(a) All incidences in dosed groups significantly greater ($P<0.01$) than those in the vehicle controls

Neoplastic Lesions

Kidney: Neoplastic lesions of the kidney were characterized according to the following criteria. Tubular cell adenomas were discrete masses of epithelial cells with cytologic features similar to foci of tubular hyperplasia. The adenomas exhibited loss of tubular structure, although the tumor cells were arranged in irregular clusters incompletely separated by basement membranes. Tubular cell adenocarcinomas were larger than the adenomas, less discrete, and more heterogeneous in growth pattern. These tumor cells generally showed more pleomorphism than did the tumor cells of the tubular cell adenomas.

Proliferative renal cortical lesions were diagnosed in all strains of rats. The incidences of these lesions are summarized in Table 15, and the statistical analyses for the incidences in male Osborne-Mendel rats are shown in Table 16. Dosing with trichloroethylene significantly increased the incidence of renal tubular cell adenomas in male Osborne-Mendel rats at the low, but not the high, dose level.

TABLE 15. INCIDENCES OF RENAL CORTICAL PROLIFERATIVE LESIONS IN ACI, AUGUST, MARSHALL, AND OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDIES OF TRICHLOROETHYLENE

	Group	Tubular Cell Hyperplasia	Tubular Cell Adenoma	Tubular Cell Adenocarcinoma
MALE				
ACI	Untreated control	0/49	0/49	0/49
	Vehicle control	0/50	0/50	0/50
	500 mg/kg	0/49	0/49	1/49
	1,000 mg/kg	0/49	0/49	0/49
August	Untreated control	0/50	0/50	0/50
	Vehicle control	0/50	0/50	0/50
	500 mg/kg	0/50	1/50	1/50
	1,000 mg/kg	1/49	1/49	0/49
Marshall	Untreated control	0/49	2/49	0/49
	Vehicle control	0/49	0/49	0/49
	500 mg/kg	1/50	1/50	0/50
	1,000 mg/kg	0/47	0/47	1/47
Osborne-Mendel	Untreated control	0/50	0/50	0/50
	Vehicle control	0/50	0/50	0/50
	500 mg/kg	5/50	6/50	0/50
	1,000 mg/kg	3/50	1/50	1/50
FEMALE				
ACI	Untreated control	0/49	0/49	0/49
	Vehicle control	0/48	0/48	0/48
	500 mg/kg	0/47	2/47	(a) 1/47
	1,000 mg/kg	0/43	0/43	1/43
August	Untreated control	0/50	0/50	0/50
	Vehicle control	0/49	1/49	0/49
	500 mg/kg	0/48	2/48	2/48
	1,000 mg/kg	1/50	0/50	0/50
Marshall	Untreated control	1/49	1/49	0/49
	Vehicle control	1/50	1/50	0/50
	500 mg/kg	0/48	1/48	1/48
	1,000 mg/kg	1/44	0/44	1/44
Osborne-Mendel	Untreated control	0/50	1/50	0/50
	Vehicle control	1/50	0/50	0/50
	500 mg/kg	1/50	0/50	0/50
	1,000 mg/kg	3/49	1/49	0/49

(a) Adenocarcinoma, NOS

TABLE 16. ANALYSIS OF TUBULAR CELL RENAL LESIONS IN MALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (a)

	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg
Hyperplasia				
Overall Rates	0/50 (0%)	0/50 (0%)	5/50 (10%)	3/50 (6%)
Adenoma				
Overall Rates	0/50 (0%)	0/50 (0%)	6/50 (12%)	1/50 (2%)
Adjusted Rates	0.0%	0.0%	32.2%	6.7%
Terminal Rates	0/21 (0%)	0/22 (0%)	5/17 (29%)	1/15 (7%)
Life Table Test		P=0.246	P=0.007	P=0.424
Incidental Tumor Tests		P=0.243	P=0.007	P=0.424
Adenoma or Adenocarcinoma (b)				
Overall Rates	0/50 (0%)	0/50 (0%)	6/50 (12%)	2/50 (4%)
Adjusted Rates	0.0%	0.0%	32.2%	10.9%
Terminal Rates	0/21 (0%)	0/22 (0%)	5/17 (29%)	1/15 (7%)
Life Table Tests		P=0.125	P=0.007	P=0.158
Incidental Tumor Tests		P=0.122	P=0.007	P=0.158

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix G, Table G3.
(b) No historical data are available.

Testis: Interstitial cell tumors occurred with a positive trend in male ACI rats; the incidence in the high dose group was not significantly greater than that in the vehicle controls by the incidental tumor test (Table 17). The overall incidences in the dosed groups were lower than that in the vehicle controls, but if incidences are based on those animals surviving until the appearance of the first tumor (week 75), an increasing trend is evident (vehicle control, 36/43; low dose, 23/26; high dose, 17/17). In male Marshall rats, interstitial cell tumors and interstitial cell tumors or malignant interstitial cell tumors (combined) occurred with positive trends, and the incidences in the high dose group were significantly greater than those in the vehicle controls (Table 18).

TABLE 17. ANALYSIS OF TESTICULAR LESIONS IN MALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg
Interstitial Cell Hyperplasia				
Overall Rates	4/47 (9%)	5/49 (10%)	5/49 (10%)	3/49 (6%)
Interstitial Cell Tumor				
Overall Rates	38/47 (81%)	36/49 (73%)	23/49 (47%)	17/49 (35%)
Adjusted Rates	90.4%	94.7%	95.8%	100.0%
Terminal Rates	34/38 (89%)	36/38 (95%)	18/19 (95%)	11/11 (100%)
Incidental Tumor Tests		P=0.019	P=0.223	P=0.074

TABLE 18. ANALYSIS OF TESTICULAR LESIONS IN MALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg
Interstitial Cell Hyperplasia				
Overall Rates	2/46 (4%)	1/46 (2%)	6/48 (13%)	5/48 (10%)
Interstitial Cell Tumor				
Overall Rates	16/46 (35%)	17/46 (37%)	21/48 (44%)	31/48 (65%)
Adjusted Rates	46.9%	55.7%	95.1%	100.0%
Terminal Rates	14/32 (44%)	13/26 (50%)	11/12 (92%)	6/6 (100%)
Incidental Tumor Tests		P<0.001	P<0.001	P<0.001
Interstitial Cell Tumor, Malignant				
Overall Rates	0/46 (0%)	0/46 (0%)	0/48 (0%)	1/48 (2%)
Interstitial Cell Tumor or Interstitial Cell Tumor, Malignant				
Overall Rates	16/46 (35%)	17/46 (37%)	21/48 (44%)	32/48 (67%)
Adjusted Rates	46.9%	55.7%	95.1%	100.0%
Terminal Rates	14/32 (44%)	13/26 (50%)	11/12 (92%)	6/6 (100%)
Incidental Tumor Tests		P<0.001	P<0.001	P<0.001

Hematopoietic System: Leukemia occurred in female August rats with a statistically significant positive trend, but the incidences in the dosed groups were not significantly greater than that in the vehicle controls in the pairwise comparisons (Table 19).

Subcutaneous Tissue: Sarcomas occurred in male August rats with a significant positive trend, but the incidences in the dosed groups were not significantly greater than that in the vehicle controls in the pairwise comparisons (Table 20).

Adrenal Gland: Adrenal cortical adenomas occurred in female Osborne-Mendel rats with a significant positive trend by the life table test, and the incidence in the high dose group was significantly greater than that in the vehicle controls by the life table test (Table 21). The incidental tumor test, a more appropriate statistical test for this generally nonlethal neoplasm, revealed no statistically significant differences.

TABLE 19. ANALYSIS OF LEUKEMIA IN FEMALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg
Overall Rates	0/50 (0%)	1/50 (2%)	0/50 (0%)	5/50 (10%)
Adjusted Rates	0.0%	2.2%	0.0%	18.2%
Terminal Rates	0/26 (0%)	0/23 (0%)	0/26 (0%)	3/25 (12%)
Life Table Tests		P=0.027	P=0.523N	P=0.078
Incidental Tumor Tests		P=0.020	P=0.469N	P=0.059

TABLE 20. ANALYSIS OF SUBCUTANEOUS TISSUE SARCOMAS IN MALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg
Overall Rates	1/50 (2%)	0/50 (0%)	1/50 (2%)	(a) 3/49 (6%)
Adjusted Rates	3.8%	0.0%	2.9%	15.0%
Terminal Rates	0/24 (0%)	0/21 (0%)	0/13 (0%)	1/16 (6%)
Life Table Tests		P=0.033	P=0.440	P=0.064
Incidental Tumor Tests		P=0.032	P=0.519	P=0.050

(a) Includes one sarcoma, unclear primary or metastatic

TABLE 21. ANALYSIS OF ADRENAL GLAND LESIONS IN FEMALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg
Hyperplasia				
Overall Rates	1/49 (2%)	1/50 (2%)	4/50 (8%)	0/49 (0%)
Cortical Adenoma				
Overall Rates	13/49 (27%)	16/50 (32%)	13/50 (26%)	19/49 (39%)
Adjusted Rates	54.8%	55.6%	66.3%	92.7%
Terminal Rates	9/19 (47%)	9/20 (45%)	6/11 (55%)	6/7 (86%)
Life Table Tests		P=0.008	P=0.365	P=0.011
Incidental Tumor Tests		P=0.100	P=0.484N	P=0.127

Negative Trends and Lower Incidences

Adrenal Gland: Pheochromocytomas and pheochromocytomas or malignant pheochromocytomas (combined) occurred with significant negative trends in all strains and sexes except female ACI, male August, and male Marshall rats (Tables 22 to 25).

Several statistically significant negative trends and lower incidences of neoplasms were detected in various strains (Appendixes A-H).

Pituitary Gland: Adenomas occurred with significant negative trends in male and female August rats and in female Marshall rats.

Mammary Gland: Fibromas or fibroadenomas (combined) occurred in female August rats with a significant negative trend by life table analysis. The incidence of fibroadenomas in low dose female Marshall rats was significantly lower than that in the vehicle controls by the incidental tumor test.

Thyroid Gland: C-Cell adenomas occurred with significant negative trends in male August and male and female Osborne-Mendel rats.

Uterus: Endometrial stromal polyps occurred with a significant negative trend in female August rats, and the incidence of endometrial stromal polyps in low dose Osborne-Mendel females was significantly lower than that in the vehicle controls by the incidental tumor test.

TABLE 22. ANALYSIS OF ADRENAL GLAND LESIONS IN MALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg
Hyperplasia				
Overall Rates	0/48 (0%)	1/48 (2%)	0/44 (0%)	1/45 (2%)
Pheochromocytoma				
Overall Rates	4/48 (8%)	8/48 (17%)	0/44 (0%)	0/45 (0%)
Adjusted Rates	10.3%	21.1%	0.0%	0.0%
Terminal Rates	4/39 (10%)	8/38 (21%)	0/18 (0%)	0/11 (0%)
Life Table Tests		P=0.017N	P=0.047N	P=0.117N
Incidental Tumor Tests		P=0.017N	P=0.047N	P=0.117N

TABLE 23. ANALYSIS OF ADRENAL GLAND LESIONS IN AUGUST RATS IN THE TWO-YEAR GAVAGE STUDIES OF TRICHLOROETHYLENE

	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg
MALE				
Hyperplasia				
Overall Rates	4/49 (8%)	2/50 (4%)	3/49 (6%)	1/47 (2%)
Pheochromocytoma				
Overall Rates	16/49 (33%)	10/50 (20%)	5/49 (10%)	2/47 (4%)
Adjusted Rates	63.7%	41.0%	33.9%	12.5%
Terminal Rates	15/24 (63%)	7/21 (33%)	4/13 (31%)	2/16 (13%)
Life Table Tests		P=0.039N	P=0.455N	P=0.049N
Incidental Tumor Tests		P=0.053N	P=0.460N	P=0.073N
Pheochromocytoma, Malignant				
Overall Rates	0/49 (0%)	0/50 (0%)	1/49 (2%)	1/47 (2%)
Pheochromocytoma or Pheochromocytoma, Malignant				
Overall Rates	16/49 (33%)	10/50 (20%)	6/49 (12%)	3/47 (6%)
Adjusted Rates	63.7%	41.0%	41.3%	18.8%
Terminal Rates	15/24 (63%)	7/21 (33%)	5/13 (38%)	3/16 (19%)
Life Table Tests		P=0.090N	P=0.602N	P=0.104N
Incidental Tumor Tests		P=0.119N	P=0.610N	P=0.150N
FEMALE				
Hyperplasia				
Overall Rates	10/50 (20%)	5/48 (10%)	12/48 (25%)	0/50 (0%)
Pheochromocytoma				
Overall Rates	6/50 (12%)	9/48 (19%)	2/48 (4%)	0/50 (0%)
Adjusted Rates	20.5%	33.2%	7.7%	0.0%
Terminal Rates	4/26 (15%)	6/23 (26%)	2/26 (8%)	0/25 (0%)
Life Table Tests		P<0.001N	P=0.019N	P=0.003N
Incidental Tumor Tests		P=0.001N	P=0.034N	P=0.009N

TABLE 24. ANALYSIS OF ADRENAL GLAND LESIONS IN MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDIES OF TRICHLOROETHYLENE

	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg
MALE				
Hyperplasia				
Overall Rates	8/48 (17%)	6/48 (13%)	5/43 (12%)	3/43 (7%)
Pheochromocytoma or Pheochromocytoma, Malignant				
Overall Rates	23/48 (48%)	25/48 (52%)	12/43 (28%)	12/43 (28%)
Adjusted Rates	65.4%	75.1%	84.8%	90.9%
Terminal Rates	19/31 (61%)	18/26 (69%)	9/11 (82%)	5/6 (83%)
Life Table Tests		P=0.035	P=0.353	P=0.037
Incidental Tumor Tests		P=0.239	P=0.158	P=0.288
FEMALE				
Hyperplasia				
Overall Rates	16/47 (34%)	4/49 (8%)	5/47 (11%)	2/43 (5%)
Pheochromocytoma				
Overall Rates	30/47 (64%)	39/49 (80%)	15/47 (32%)	9/43 (21%)
Adjusted Rates	74.8%	92.7%	76.5%	67.0%
Terminal Rates	21/31 (68%)	26/29 (90%)	8/12 (67%)	6/10 (60%)
Life Table Tests		P=0.050N	P=0.263N	P=0.067N
Incidental Tumor Tests		P<0.001N	P=0.002N	P<0.001N
Pheochromocytoma, Malignant				
Overall Rates	4/47 (9%)	4/49 (8%)	0/47 (0%)	1/43 (2%)
Pheochromocytoma or Pheochromocytoma, Malignant				
Overall Rates	32/47 (68%)	40/49 (82%)	15/47 (32%)	9/43 (21%)
Adjusted Rates	79.8%	95.1%	76.5%	67.0%
Terminal Rates	23/31 (74%)	27/29 (93%)	8/12 (67%)	6/10 (60%)
Life Table Tests		P=0.036N	P=0.222N	P=0.050N
Incidental Tumor Tests		P<0.001N	P<0.001N	P<0.001N

TABLE 25. ANALYSIS OF ADRENAL GLAND LESIONS IN OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDIES OF TRICHLOROETHYLENE

	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg
MALE				
Hyperplasia				
Overall Rates	6/50 (12%)	4/50 (8%)	3/49 (6%)	5/50 (10%)
Pheochromocytoma				
Overall Rates	(a) 9/50 (18%)	(b) 13/50 (26%)	6/49 (12%)	3/50 (6%)
Adjusted Rates	34.8%	42.9%	31.6%	18.7%
Terminal Rates	6/21 (29%)	7/22 (32%)	5/17 (29%)	2/15 (13%)
Life Table Tests		P=0.028N	P=0.154N	P=0.052N
Incidental Tumor Tests		P=0.023N	P=0.128N	P=0.043N
FEMALE				
Hyperplasia				
Overall Rates	1/49 (2%)	1/50 (2%)	2/50 (4%)	2/49 (4%)
Pheochromocytoma				
Overall Rates	4/49 (8%)	8/50 (16%)	4/50 (8%)	1/49 (2%)
Adjusted Rates	16.1%	30.4%	18.8%	6.7%
Terminal Rates	2/19 (11%)	4/20 (20%)	1/11 (9%)	0/7 (0%)
Life Table Tests		P=0.080N	P=0.394N	P=0.118N
Incidental Tumor Tests		P=0.009N	P=0.178N	P=0.020N
Pheochromocytoma, Malignant				
Overall Rates	0/49 (0%)	1/50 (2%)	2/50 (4%)	0/49 (0%)
Pheochromocytoma or Pheochromocytoma, Malignant				
Overall Rates	4/49 (8%)	9/50 (18%)	6/50 (12%)	1/49 (2%)
Adjusted Rates	16.1%	33.1%	26.0%	6.7%
Terminal Rates	2/19 (11%)	4/20 (20%)	1/11 (9%)	0/7 (0%)
Life Table Tests		P=0.073N	P=0.564N	P=0.084N
Incidental Tumor Tests		P=0.004N	P=0.252N	P=0.009N

(a) One pheochromocytoma, malignant, was also observed.
(b) One pheochromocytoma, malignant, was also observed in an animal bearing a benign pheochromocytoma.

IV. DISCUSSION AND CONCLUSIONS

Thirteen-Week Studies
Two-Year Studies
Conclusions

IV. DISCUSSION AND CONCLUSIONS

The possibility of a strain difference in rat susceptibility to trichloroethylene prompted the National Cancer Institute to initiate a series of 2-year toxicology and carcinogenesis studies of trichloroethylene in five strains of rats. The results obtained with F344/N rats have been reported separately (NTP TR 243, in preparation), and the present report describes the results of studies in four additional strains (ACI, August, Marshall, and Osborne-Mendel). For comparative purposes, some data from the study in F344/N rats have been summarized in this discussion.

Thirteen-Week Studies

The results of the 13-week gavage studies of trichloroethylene in ACI, August, and Marshall rats were similar to those of previous 8- or 13-week studies in Osborne-Mendel or F344/N rats, respectively (NCI, 1976; NTP TR 243, in preparation). In males, trichloroethylene at the highest dose given, 2,000 mg/kg (1,834 mg/kg in Marshall males), consistently reduced final body weights by 12%-17%. Three of 10 male August rats died in the 2,000 mg/kg group. All male F344/N rats dosed with 2,000 mg/kg for 13 weeks survived (NTP TR 243, in preparation), and 5/5 Osborne-Mendel males dosed with 3,160 mg/kg per day, 5 days per week for 8 weeks, survived (NCI, 1976).

The highest dose studied in females for 13 weeks in the present studies (1,000 mg/kg in ACI and August; 918 mg/kg in Marshall) was not lethal but caused from 4% to 7% reductions in final body weights. In female F344/N rats, the 1,000 mg/kg dose produced a 3% decrease in final body weight (NTP TR 243, in preparation), and 3,160 mg/kg per day, 5 days per week for 8 weeks reduced final body weights of female Osborne-Mendel rats by 13% (NCI, 1976).

As in the earlier studies in rats, the chronic nephrotoxic effect of trichloroethylene observed in the 2-year studies was not predicted by the results of the short-term studies. In the studies in F344/N rats (NTP TR 243, in preparation), 13 weeks of dosing with trichloroethylene produced minimal to mild cytomegaly and karyomegaly of the tubular epithelial cells in the inner renal cortex in both sexes. These changes were so subtle that they were diagnosed only during a reevaluation of tissues which was prompted by the detection of more pronounced renal effects during the 2-year studies.

Two-Year Studies

The audits of the experimental data from the present studies revealed insufficient documentation of animal breeding, clinical observations, environmental conditions, and analytical chemistry data (Appendix Q). In addition, the production of central nervous system toxicity (characterized by sedation, loss of consciousness, tremors, and convulsive seizures) and reduced survival indicate that the doses selected for these studies were too high. For these reasons, these studies were considered inadequate to evaluate the presence or absence of carcinogenic potential of trichloroethylene in ACI, August, Marshall, and Osborne-Mendel rats. The studies do, however, demonstrate a clear nephrotoxic effect of trichloroethylene in rats.

Survival and body weights: All dosed groups except high dose female Osborne-Mendel rats exhibited some degree of final body weight depression. This depression was 10%-12% in five of the dose groups (all high dose males except Marshall, low dose ACI males, and high dose Marshall females). Final mean body weight decrements in other groups ranged from 3% in low dose Osborne-Mendel males to 8% in low dose ACI females. In the earlier studies in F344/N rats, trichloroethylene at 1,000 mg/kg reduced mean body weight gain of males by 13% and at 500 and 1,000 mg/kg reduced body weight gains of females by 12% and 18%, respectively.

Trichloroethylene administered at both doses significantly reduced the survival of ACI males and Marshall females. Trichloroethylene at 1,000 mg/kg also reduced the survival of female Osborne-Mendel and ACI rats. The low dose, but not the high dose, reduced the survival of male Marshall rats. In the earlier gavage studies of trichloroethylene in F344/N rats, both the 500 and 1,000 mg/kg doses significantly reduced the survival of males, whereas neither dose reduced the survival of females. It is not clear

whether the excessive mortality observed in many dosed groups was caused by gavage-related trauma, the anesthetic properties of the chemical, nephrotoxicity, or a combination of these factors.

The absence of a dose-response relationship in survival of male Marshall rats may be related to the high accidental death rate in the high dose group. Fifty percent of the animals in this group were accidentally killed, and animals that are considered to have died from accidental causes are not included in the Kaplan-Meier probability of survival calculation after the time of death. The incidences of accidental deaths also were high in other dosed groups. A total of 24% of all dosed animals died of accidental causes. This rate contrasts with an overall accidental death rate of 5% in vehicle control animals. All groups of dosed animals were affected, and the overall combined incidences were dose related (male: vehicle control, 9/200; low dose, 41/200; high dose, 61/200; female: 14/200; 40/200; 49/200). High accidental death rates were observed in other NTP studies in which trichloroethylene or tetrachloroethylene was administered by gavage. As suggested earler (NTP TR 243, in preparation), perhaps some effect of trichloroethylene and related chemicals predisposes repeatedly dosed animals to gavage accidents.

The survival of untreated and vehicle control Osborne-Mendel rats of each sex was poor relative to the other three strains and to historical survival of F344/N rats. However, survival of Osborne-Mendel control animals in the present study was similar to that of controls in the NCI studies (NCI, 1976) (male, 40/100, and female, 37/100, in the present study vs male, 26/100, and female, 51/100, in the earlier study).

Renal toxicity (nonproliferative changes): Earlier studies of trichloroethylene administered by gavage (NCI, 1976; NTP TR 243, in preparation) identified the kidney of Osborne-Mendel and F344/N rats and $B6C3F_1$ mice as a target organ for the production of nonneoplastic pathologic changes characterized as cytomegaly, karyomegaly, and toxic nephrosis of the tubular epithelial cells in the inner renal cortex. The identical lesion was reported in male and female F344/N rats exposed to tetrachloroethylene by inhalation (NTP, 1986). Neither Henschler et al. (1980) nor Fukuda et al. (1983) reported the presence of nonproliferative renal lesions in mice, rats, or hamsters exposed to trichloroethylene by inhalation. The results of the present studies show that the kidneys of ACI, August, and Marshall rats are affected similarly. The incidences of these lesions in five strains of rats are summarized in Table 26.

The nonneoplastic renal changes diagnosed in these studies were clearly attributable to the administration of trichloroethylene, since none of the untreated or vehicle control animals had the lesions. In the case of renal cytomegaly, the incidence of the change ranged from 82% to 100% in the dosed groups. Cytomegalic changes were diagnosed in dosed rats that died after as few as 26 weeks of exposure to trichloroethylene. The severity of the change appeared to be directly proportional to the duration of dosing.

Toxic nephropathy, which was clearly distinguishable from the spontaneous nephropathy of aging rats, was observed at increased incidences in dosed rats of each sex and strain but was noted only infrequently in animals that died before week 52. This lesion also appeared to increase in severity with longer exposure.

Renal toxicity (proliferative changes): Trichloroethylene produced a statistically significant increase in the incidence of renal tubular cell adenomas or adenocarcinomas (combined) in low dose male Osborne-Mendel rats. In addition, tubular cell hyperplasia was present in 5/50 low dose and 3/50 high dose Osborne-Mendel male rats. No proliferative tubular cell lesions were diagnosed in either control group. Although not statistically significant, proliferative lesions also were diagnosed in dosed male and female ACI and August rats, whereas no such lesions were detected in any of the control groups. Proliferative lesions of the renal tubular cells were diagnosed in dosed Marshall male and female rats, but these changes were also present in untreated and vehicle control rats.

TABLE 26. INCIDENCES OF RENAL CORTICAL LESIONS IN ACI, AUGUST, MARSHALL, OSBORNE-MENDEL, AND F334/N RATS IN THE TWO-YEAR GAVAGE STUDIES OF TRICHLOROETHYLENE

	Group	Toxic Nephropathy	Tubular Cell Hyperplasia	Tubular Cell Adenoma	Tubular Cell Adenocarcinoma
MALE					
ACI	Untreated control	0/49	0/49	0/49	0/49
	Vehicle control	0/50	0/50	0/50	0/50
	500 mg/kg	18/49	0/49	0/49	1/49
	1,000 mg/kg	18/49	0/49	0/49	0/49
August	Untreated control	0/50	0/50	0/50	0/50
	Vehicle control	0/50	0/50	0/50	0/50
	500 mg/kg	10/50	0/50	1/50	1/50
	1,000 mg/kg	31/49	1/49	1/49	0/49
Marshall	Untreated control	0/49	0/49	2/49	0/49
	Vehicle control	0/49	0/49	0/49	0/49
	500 mg/kg	18/50	1/50	1/50	0/50
	1,000 mg/kg	23/47	0/47	0/47	1/47
Osborne-Mendel	Untreated control	0/50	0/50	0/50	0/50
	Vehicle control	0/50	0/50	0/50	0/50
	500 mg/kg	39/50	5/50	6/50	0/50
	1,000 mg/kg	35/50	3/50	1/50	1/50
F344/N (a)	Untreated control	0/49	0/49	0/49	0/49
	Vehicle control	0/48	0/48	0/48	0/48
	500 mg/kg	48/49	0/49	2/49	0/49
	1,000 mg/kg	48/49	1/49	0/49	3/49
FEMALE					
ACI	Untreated control	0/49	0/49	0/49	0/49
	Vehicle control	0/48	0/48	0/48	0/48
	500 mg/kg	21/47	0/47	2/47	(b) 1/47
	1,000 mg/kg	19/43	0/43	0/43	1/43
August	Untreated control	0/50	0/50	0/50	0/50
	Vehicle control	0/49	0/49	1/49	0/49
	500 mg/kg	8/48	0/48	2/48	2/48
	1,000 mg/kg	29/50	1/50	0/50	0/50
Marshall	Untreated control	0/49	1/49	1/49	0/49
	Vehicle control	0/50	1/50	1/50	0/50
	500 mg/kg	30/48	0/48	1/48	1/48
	1,000 mg/kg	30/44	1/44	0/44	1/44
Osborne-Mendel	Untreated control	0/50	0/50	1/50	0/50
	Vehicle control	0/50	1/50	0/50	0/50
	500 mg/kg	30/50	1/50	0/50	0/50
	1,000 mg/kg	39/49	3/49	1/49	0/49
F344/N (a)	Untreated control	0/49	0/49	0/49	0/49
	Vehicle control	0/50	0/50	0/50	0/50
	500 mg/kg	48/49	0/49	0/49	0/49
	1,000 mg/kg	48/48	0/48	0/48	1/48

(a) Data for F344/N rats obtained from NTP Technical Report No. 243; toxic nephropathy was designated as cytomegaly in that report.
(b) Adenocarcinoma, NOS

Increased incidences of renal tubular cell adenomas or adenocarcinomas (combined) were found in five male F344/N rats dosed with trichloroethylene (NTP TR 243, in preparation), and a tubular cell adenocarcinoma was found in a low dose (time-weighted-average dose of 549 mg/kg of trichloroethylene) male Osborne-Mendel rat (NCI, 1976). The incidences of these lesions in the five strains of rats are shown in Table 26. Henschler et al. (1980) reported a total of four renal tumors (adenomas, cystadenomas, adenocarcinomas) in 60 male WIST rats exposed to trichloroethylene by inhalation at 100 or 500 ppm. No renal tumors were reported in male control rats.

Because the rats could not always be unequivocally assigned to a high or low dose group, tumor incidences in dosed groups of the same sex and strain were pooled and compared with incidences in the corresponding vehicle control groups. By this analysis, the incidence of renal tubular cell tumors in dosed male Osborne-Mendel rats was still elevated (tubular cell adenomas: vehicle control, 0/50; pooled dosed, 7/100; adenomas or adenocarcinomas (combined): vehicle control, 0/50; pooled dosed, 8/100). For all five rat strains studied, a total of 32 renal tubular cell neoplasms were observed in dosed animals, compared with 3 in all the vehicle control groups and 3 in all the untreated control groups.

Nonneoplastic kidney effects are common responses of F344 rats to the long-term administration of chlorinated ethanes and ethylenes. The NTP has also noted these effects in gavage studies of pentachloroethane (NTP, 1983) and trichloroethylene (NTP TR 243, in preparation) and in inhalation studies of tetrachloroethylene (NTP, 1986). Since these changes appear consistently in dosed rats but not in controls, they are considered to be due to trichloroethylene administration. This spectrum of kidney lesions appears to be similar to that described in male rats exposed to petroleum products (Mehlman et al., 1984). Unlike the petroleum-induced lesions, however, those produced by chlorinated ethanes and ethylenes appear in both male and female rats as well as in both sexes of mice (NTP TR 243, in preparation).

Testicular interstitial cell tumors: The incidences of testicular interstitial cell tumors were increased in dosed male ACI and Marshall rats. In ACI rats, these lesions showed a dose-related increase when based on animals surviving until the appearance of the first tumor. In Marshall rats, the incidence of interstitial cell tumors or malignant interstitial cell tumors (combined) in the high dose group was significantly increased and may be due to trichloroethylene. For ACI rats, the increased incidence at the high dose was significant only by life table analysis. This marginal effect was not considered to be chemically related.

Other tumors: Leukemia in female August rats and subcutaneous tissue sarcomas in male August rats occurred with positive trends, but the incidences in dosed groups were not significantly elevated relative to vehicle controls. In earlier studies in F344/N and Osborne-Mendel rats, the incidences of leukemia and subcutaneous neoplasms were not influenced by the administration of trichloroethylene.

Negative trends: Several negative trends in tumor incidences were observed in these studies. The majority of these findings were discounted either because there were nonsignificant differences in pairwise comparisons or because only the incidence in the low dose group was significantly reduced relative to the vehicle controls.

There were, however, more consistent negative trends in the incidences of adrenal gland pheochromocytomas in male ACI, female Marshall, and male and female August and Osborne-Mendel rats. We are unable to explain this effect. In the earlier study in F344/N rats, the incidence of pheochromocytomas appeared to be somewhat decreased in males (vehicle control, 4/45; low dose, 3/42; high dose, 1/44), but neither trend nor pairwise comparisons revealed statistically significant differences. No pheochromocytomas were diagnosed in any group of Osborne-Mendel rats dosed with trichloroethylene in an earlier study (NCI, 1976).

The results of these comparative studies of the toxicity of orally administered trichloroethylene

in four strains of rats show that there are few notable differences in the responsiveness of the strains to toxic doses of the chemical. Further, the responses of these four strains of rats were found to be similar to the response of F344/N rats.

The experimental and tabulated data for the NTP Technical Report on trichloroethylene were examined for accuracy, consistency, and compliance with Good Laboratory Practice requirements. As summarized in Appendix Q, the audits revealed problems with the conduct of the studies and with collection and documentation of the experimental data. Discrepancies were found that influenced the final interpretation of the results of these studies. The NTP also has reviewed a partial draft of an independent audit sponsored by the Halogenated Solvent Industry Alliance (HSIA) for which the findings were similar to those of the NTP audit. The findings of all audits were taken into consideration during the interpretation of the results of these studies and the preparation of this report.

Conclusions: Under the conditions of these 2-year gavage studies of trichloroethylene in male and female ACI, August, Marshall, and Osborne-Mendel rats, trichloroethylene administration caused renal tubular cell cytomegaly and toxic nephropathy in both sexes of the four strains. However, these are considered to be *inadequate studies of carcinogenic activity** because of chemically induced toxicity, reduced survival, and deficiencies in the conduct of the studies. Despite these limitations, tubular cell neoplasms of the kidney were observed in rats exposed to trichloroethylene and interstitial cell neoplasms of the testis were observed in Marshall rats exposed to trichloroethylene.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 9.
Summaries of the Peer Review comments and the public discussions on this Technical Report appear on pages 13-14 and 16-17.

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APPENDIX A

SUMMARY OF LESIONS IN MALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING	1			
ANIMALS NECROPSIED	49	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	49	50
INTEGUMENTARY SYSTEM				
*Skin	(49)	(50)	(49)	(50)
Squamous cell carcinoma		1 (2%)		
Basal cell carcinoma		1 (2%)		
RESPIRATORY SYSTEM				
*Tracheal lumen	(49)	(50)	(49)	(50)
Fibrosarcoma, metastatic		1 (2%)		
#Lung	(48)	(49)	(47)	(46)
Transitional cell carcinoma, metastatic			1 (2%)	
Alveolar/bronchiolar adenoma			2 (4%)	
Tubular cell adenoca, metastatic			1 (2%)	
Fibrosarcoma, metastatic		1 (2%)		
HEMATOPOIETIC SYSTEM				
*Multiple organs	(49)	(50)	(49)	(50)
Leukemia, NOS		1 (2%)		
Monocytic leukemia	2 (4%)	2 (4%)		
#Thymus	(3)	(7)	(12)	(24)
Malignant lymphoma, NOS			1 (8%)	
CIRCULATORY SYSTEM				
*Chin	(49)	(50)	(49)	(50)
Hemangiosarcoma	1 (2%)			
DIGESTIVE SYSTEM				
#Liver	(49)	(50)	(49)	(49)
Hepatocellular carcinoma		1 (2%)	1 (2%)	1 (2%)
#Pancreas	(46)	(50)	(47)	(44)
Acinar cell adenoma			1 (2%)	
URINARY SYSTEM				
#Kidney	(49)	(50)	(49)	(49)
Tubular cell adenocarcinoma			1 (2%)	
#Kidney/pelvis	(49)	(50)	(49)	(49)
Transitional cell papilloma	1 (2%)			
Transitional cell carcinoma	3 (6%)		1 (2%)	1 (2%)
#Urinary bladder	(44)	(44)	(47)	(42)
Squamous cell papilloma				1 (2%)
Transitional cell papilloma	1 (2%)		1 (2%)	
Transitional cell carcinoma		1 (2%)	1 (2%)	
ENDOCRINE SYSTEM				
#Pituitary	(48)	(39)	(33)	(29)
Adenoma, NOS	8 (17%)	6 (15%)	4 (12%)	3 (10%)
#Adrenal	(48)	(48)	(44)	(45)
Cortical adenoma	8 (17%)	6 (13%)	1 (2%)	
Pheochromocytoma	4 (8%)	8 (17%)		

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)				
#Thyroid	(48)	(46)	(40)	(39)
Follicular cell adenoma		1 (2%)		
C-cell adenoma	1 (2%)			
#Pancreatic islets	(46)	(50)	(47)	(44)
Islet cell adenoma		1 (2%)		
REPRODUCTIVE SYSTEM				
#Prostate	(48)	(49)	(45)	(43)
Carcinoma, NOS			1 (2%)	
Adenoma, NOS		3 (6%)		
Adenocarcinoma, NOS		1 (2%)		
#Testis	(47)	(49)	(49)	(49)
Interstitial cell tumor	38 (81%)	36 (73%)	23 (47%)	17 (35%)
NERVOUS SYSTEM				
#Brain/meninges	(49)	(50)	(47)	(47)
Granular cell tumor, NOS		1 (2%)		
SPECIAL SENSE ORGANS				
None				
MUSCULOSKELETAL SYSTEM				
None				
BODY CAVITIES				
*Thorax	(49)	(50)	(49)	(50)
Sarcoma, NOS	1 (2%)			
*Peritoneum	(49)	(50)	(49)	(50)
Mesothelioma, NOS	1 (2%)			
*Tunica vaginalis	(49)	(50)	(49)	(50)
Mesothelioma, NOS	1 (2%)			1 (2%)
ALL OTHER SYSTEMS				
Neck				
Neurilemoma, malignant		1		
Tail				
Fibrosarcoma		1		
ANIMAL DISPOSITION SUMMARY				
Animals initially in study	50	50	50	50
Natural death	9	8	18	18
Moribund sacrifice	4	5	2	3
Terminal sacrifice	36	37	19	11
Dosing accident			1	1
Accidentally killed, NOS			10	17
Animal missing	1			

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
TUMOR SUMMARY				
Total animals with primary tumors**	45	44	27	17
Total primary tumors	70	72	38	24
Total animals with benign tumors	42	39	24	17
Total benign tumors	61	61	32	21
Total animals with malignant tumors	7	9	6	2
Total malignant tumors	7	10	6	2
Total animals with secondary tumors##		1	2	
Total secondary tumors		2	2	
Total animals with tumors uncertain--benign or malignant	2	1		1
Total uncertain tumors	2	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

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: UNTREATED CONTROL

ANIMAL NUMBER	64 6	65 1	65 2	65 5	66 3	67 2	67 6	67 7	67 9	68 6	69 3	69 6	69 9	70 0	70 7	71 2	72 0	72 3	72 6	72 7	73 4	74 1	74 7	75 1	75 8
WEEKS ON STUDY	107	107	104	107	107	107	107	107	081	107	107	059	107	087	070	107	107	107	093	107	100	099	107	104	107
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	–	+	+
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	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	+	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	–	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	M	+	–	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	M	+	–	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	M*	+	+	+	+	+	+	+	+	+	+	+	+	+
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma				X																					
Transitional cell carcinoma														X											
Urinary bladder	+	+	+	+	+	–	+	+	+	–	+	M	+	–	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma																					X				
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	–	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS	X				X						X												X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	M	+	–	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma	X			X		X																			
Pheochromocytoma										X															
Thyroid	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	–	+	+	+	+	+	+	+	+	+
C-cell adenoma																									
Parathyroid	+	+	+	–	+	–	+	–	–	–	+	M	+	+	–	–	+	+	+	+	–	–	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	+	+	+	+	+	N	+	+	M	+	N	N	+	N	+	N	N	N	+	N	+	+
Testis	+	+	+	+	+	+	+	+	+	+	+	M	+	–	+	+	+	+	+	+	+	+	–	+	+
Interstitial cell tumor		X		X		X	X	X	X	X	X		X		X	X	X	X		X	X				X
Prostate	+	+	+	+	+	+	+	+	+	+	+	M	+	–	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
BODY CAVITIES																									
Pleura	N	N	N	N	N	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS																			X						
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	M	+	N	+	+	+	+	+	+	+	+	N	+	+
Mesothelioma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N
Monocytic leukemia									X																
Chin												M													
Hemangiosarcoma																							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 A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE ACI RATS: UNTREATED CONTROL (Continued)

ANIMAL NUMBER	760	761	764	772	775	777	781	782	786	792	793	801	802	804	807	811	812	813	818	820	823	824	825	834	840	TOTAL:
WEEKS ON STUDY	107	107	101	107	107	107	107	107	107	107	105	107	102	107	107	107	107	107	107	107	107	107	007	056	107	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	46
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	−	+	40
Thymus	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−		3
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	46
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Transitional cell papilloma																										1
Transitional cell carcinoma								X																	X	3
Urinary bladder	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	44
Transitional cell papilloma																										1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS			X									X	X		X											8
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cortical adenoma		X	X						X							X						X				8
Pheochromocytoma	X					X				X																4
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell adenoma										X																1
Parathyroid	+	+	−	−	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	−	−	−		33
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	+	+	+	+	+	N	+	+	N	N	+	+	N	+	+	+	N	+	+	N	N	N	*49
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
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	38
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	N	*49
Sarcoma, NOS																										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	N	*49
Mesothelioma, NOS																				X						1
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
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	*49
Monocytic leukemia			X																							2
Chin																										
Hemangiosarcoma																										1

• Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: VEHICLE CONTROL

ANIMAL NUMBER	644	649	654	660	662	664	665	667	669	671	673	680	684	687	692	697	701	702	705	711	713	716	721	728	730
WEEKS ON STUDY	105	105	105	080	080	105	105	105	071	105	105	105	081	100	105	076	042	105	014	105	105	105	105	106	050
INTEGUMENTARY SYSTEM																									
Skin	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	N	+	+
Squamous cell carcinoma																		X							
Basal cell carcinoma							X																		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Fibrosarcoma, metastatic																X									
Trachea	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Thymus	−	−	−	+	−	−	−	−	+	−	−	−	+	−	−	+	+	−	+	−	−	−	−	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma							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
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Transitional cell carcinoma																									X
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	−	−	+	+	+	−	+	+	+	+	+	−	−	−	+	−	+	+	+	+	+	+
Adenoma, NOS			X								X			X							X		X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																							X		
Pheochromocytoma								X		X								X			X				
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	−
Follicular cell adenoma																									
Parathyroid	+	−	−	−	+	−	+	+	+	+	+	+	−	+	+	−	−	−	−	+	+	−	+	+	−
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																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
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor	X	X	X			X		X		X	X	X			X			X		X		X	X	X	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS	X																								
Adenocarcinoma, NOS								X																	
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, 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
Leukemia, NOS					X																				
Monocytic leukemia				X																					
Neck, NOS																									
Neurilemoma, malignant													X												
Tail																									
Fibrosarcoma																X									
Tracheal lumen																									
Fibrosarcoma, metastatic																X									

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE ACI RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	7373	7443	7446	7448	7559	7665	7668	7669	7771	7779	7884	7888	7994	7995	7996	8000	8003	8005	8006	8009	8028	8030	8031	8032	8042	TOTAL:
WEEKS ON STUDY	105	105	105	106	105	105	104	105	085	105	105	105	105	105	105	105	105	105	105	106	038	105	106	066	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell carcinoma																										1
Basal cell carcinoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	46
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	45
Thymus	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	7
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										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	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	49
Large intestine	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	−	+	+	+	+	+	+	+	−	+	−	+	+	+	+	−	+	−	+	+	+	+	44
Transitional cell carcinoma																										1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	−	+	+	+	−	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	39
Adenoma, NOS																X										6
Adrenal	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	48
Cortical adenoma												X			X			X					X		X	6
Pheochromocytoma			X							X									X			X				8
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	48
Follicular cell adenoma													X													1
Parathyroid	+	−	+	+	+	+	−	+	−	−	+	+	−	+	+	+	+	−	−	+	−	+	+	+	+	30
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	+	+	+	+	+	N	N	+	N	N	N	+	+	N	N	N	N	N	N	N	+	N	+	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	36
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS		X				X																				3
Adenocarcinoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor, 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
Leukemia, NOS																										1
Monocytic leukemia							X																			2
Neck, NOS																										
Neurilemoma, malignant																										1
Tail																										
Fibrosarcoma																										1
Tracheal lumen																										
Fibrosarcoma, metastatic																										1

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: LOW DOSE

ANIMAL NUMBER	648	657	658	659	666	668	670	675	682	683	685	688	690	703	708	710	715	719	722	729	731	732	735	738	739
WEEKS ON STUDY	104	050	061	064	047	104	104	119	102	104	104	104	111	032	043	034	027	045	034	044	034	005	044	044	104
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	A	+	+	+	+	+	+
Transitional cell carcinoma, metastatic																									
Alveolar/bronchiolar adenoma	X		X																						
Tubular cell adenocarcinoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	+	+	A	+	−	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	−	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+
Lymph nodes	+	−	+	−	+	+	+	−	+	+	−	+	−	+	+	−	−	+	A	+	−	+	+	+	+
Thymus	−	−	−	−	+	−	−	+	+	−	−	−	−	+	−	+	−	A	A	−	+	+	−	−	−
Malignant lymphoma, NOS									X																
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	A	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+
Acinar cell adenoma																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	A	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	A	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	A	A	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Tubular cell adenocarcinoma																									
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Transitional cell carcinoma																									
Urinary bladder	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Transitional cell papilloma																									
Transitional cell carcinoma																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	−	+	+	+	+	−	−	−	+	−	+	A	+	−	−	+	+	+
Adenoma, NOS												X													X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	A	A	+	+	+	+	+	+
Cortical adenoma																									
Thyroid	+	+	+	+	+	−	+	+	+	+	+	+	−	−	−	−	+	+	A	+	−	+	+	+	+
Parathyroid	+	−	+	+	+	−	+	−	+	+	−	+	−	−	−	−	+	A	A	−	−	−	−	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	N	N	N	+	N	N	+	N	N	N	N	N	N	N	N	N	A	N	N	N	+	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Interstitial cell tumor	X					X	X		X	X	X	X								X			X	X	X
Prostate	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	A	+	+	−	+	+	+
Carcinoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	A	+	−	+	+	+	+

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE ACI RATS: LOW DOSE (Continued)

ANIMAL NUMBER	740	742	745	749	752	755	757	766	767	770	774	776	778	785	789	798	810	815	817	821	826	829	833	838	841	TOTAL: TISSUES
WEEKS ON STUDY	091	104	007	054	104	096	104	020	084	104	053	064	089	091	012	104	091	006	025	045	104	025	104	104	104	TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	47
Transitional cell carcinoma, metastatic											X															1
Alveolar/bronchiolar adenoma																										2
Tubular cell adenocarcinoma, metast																	X									1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	43
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph nodes	+	+	−	+	+	+	+	−	+	+	+	+	−	−	+	+	−	+	+	−	+	+	+	+	+	35
Thymus	−	−	+	−	−	−	−	+	+	−	−	−	−	−	−	−	−	−	+	+	−	−	−	−	−	12
Malignant lymphoma, NOS																										1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	48
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma	X																									1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	*49
Pancreas	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Acinar cell adenoma									X																	1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tubular cell adenocarcinoma																	X									1
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Transitional cell carcinoma											X															1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Transitional cell papilloma										X																1
Transitional cell carcinoma							X																			1
ENDOCRINE SYSTEM																										
[illegible]ary	+	+	−	+	+	+	+	−	+	+	−	−	+	+	−	+	−	−	−	+	+	−	+	+	+	33
Adenoma, NOS	X	X																								4
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	44
Cortical adenoma																								X		1
Thyroid	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	40
Parathyroid	+	+	−	−	+	−	+	−	+	+	−	+	−	−	−	−	−	−	+	−	−	−	−	−	−	19
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	N	N	N	N	N	N	+	N	N	N	N	N	+	+	N	N	N	N	N	N	N	N	*49
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor	X	X			X	X			X	X				X		X					X		X	X	X	23
Prostate	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Carcinoma, NOS										X																1
NERVOUS SYSTEM																										
Br[illegible]n	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: HIGH DOSE

ANIMAL NUMBER	6 4 3	6 4 5	6 4 7	6 5 0	6 5 3	6 5 6	6 6 1	6 7 4	6 7 8	6 8 1	6 8 9	6 9 1	6 9 4	6 9 5	6 9 8	7 0 4	7 0 6	7 0 9	7 1 4	7 1 7	7 1 8	7 2 4	7 2 5	7 3 3	7 3 6
WEEKS ON STUDY	1 0 4	0 2 6	0 2 2	0 2 8	0 3 4	0 7 7	0 8 9	1 0 4	0 7 4	0 3 1	0 6 3	0 0 3	1 0 4	0 9 4	0 3 5	0 4 7	0 1 3	0 3 5	0 3 3	0 5 3	1 0 2	0 7 5	0 6 5	1 0 4	0 1 3
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	−	A	+	+	+	+	+	+	+	+
Trachea	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	A	+	−	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	A	−	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Lymph nodes	+	−	−	−	+	−	+	+	−	−	+	+	+	−	+	+	A	+	−	+	+	+	+	+	−
Thymus	−	+	+	+	−	+	−	−	+	−	+	+	−	−	−	+	A	−	+	−	+	+	−	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	−	+	+	+	−	+	+	+	+	−	+	+	A	+	−	+	+	+	+	+	−
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Hepatocellular carcinoma														X											
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
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	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	−	+	+	−	+	+	−	+	+	+	A	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Transitional cell carcinoma																									
Urinary bladder	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	A	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	−	−	+	+	+	+	+	−	+	−	+	+	+	+	A	+	+	−	+	−	+	+	−
Adenoma, NOS	X																				X				
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	−	+	+	+	−	+	+	+
Thyroid	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	A	−	−	−	+	+	+	+	−
Parathyroid	−	+	−	+	+	−	+	+	−	−	−	−	+	−	−	+	A	−	−	−	−	+	−	−	−
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
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor	X					X	X	X					X	X							X	X		X	
Prostate	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	A	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE ACI RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	7 4 4	7 5 0	7 5 3	7 5 4	7 5 6	7 6 2	7 6 3	7 7 3	7 8 0	7 8 3	7 8 7	7 9 0	7 9 1	7 9 7	7 9 9	8 0 8	8 1 3	8 1 4	8 1 9	8 2 2	8 2 7	8 3 5	8 3 6	8 3 7	8 3 9	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	0 1 2	1 0 4	0 2 0	0 2 9	0 7 0	0 4 5	1 0 4	0 0 9	0 0 5	0 6 1	1 0 4	1 0 4	0 1 1	0 0 5	0 5 0	0 2 8	0 5 3	1 0 4	0 4 8	1 0 4	0 2 0	0 5 3	0 4 5	1 0 4	0 7 7	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	45
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	−	+	+	+	−	+	+	+	+	44
Lymph nodes	+	+	+	−	+	+	−	−	−	−	+	−	−	−	+	−	+	+	+	+	−	+	+	+	+	30
Thymus	+	−	−	−	+	−	−	+	+	+	−	+	−	+	−	−	−	−	+	−	+	+	+	−	+	24
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	−	−	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	40
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	−	+	+	+	+	44
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	−	+	+	+	+	46
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	46
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	−	+	+	43
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Transitional cell carcinoma																								X		1
Urinary bladder	+	+	+	+	+	+	+	−	−	+	+	+	+	−	+	+	+	+	+	+	−	+	−	+	+	42
Squamous cell papilloma																		X								1
ENDOCRINE SYSTEM																										
Pituitary	−	+	−	−	−	+	−	−	−	+	+	+	−	−	+	−	+	+	+	+	−	+	+	−	−	29
Adenoma, NOS												X														3
Adrenal	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	45
Thyroid	+	+	−	+	+	−	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	39
Parathyroid	−	+	−	+	+	−	+	+	−	−	−	−	+	−	−	−	−	+	−	+	−	+	−	+	−	18
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	N	N	N	N	N	N	N	N	+	+	N	N	N	N	N	N	N	+	N	N	N	+	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor		X					X				X	X						X		X				X	X	17
Prostate	+	+	−	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	−	+	−	+	+	43
NERVOUS SYSTEM																										
Brain	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	47
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS											X															1

* Animals necropsied

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg
Hematopoietic System: Leukemia				
Overall Rates (a)	2/49 (4%)	3/50 (6%)	0/49 (0%)	0/50 (0%)
Adjusted Rates (b)	4.6%	7.2%	0.0%	0.0%
Terminal Rates (c)	0/39 (0%)	1/38 (3%)	0/19 (0%)	0/11 (0%)
Life Table Tests (d)		P=0.139N	P=0.239N	P=0.384N
Incidental Tumor Tests (d)		P=0.093N	P=0.121N	P=0.423N
Cochran-Armitage Trend Test (d)		P=0.038N		
Fisher Exact Test			P=0.125N	P=0.121N
Pituitary: Adenoma				
Overall Rates (a)	8/48 (17%)	6/39 (15%)	4/33 (12%)	3/29 (10%)
Adjusted Rates (b)	19.9%	16.9%	19.5%	28.7%
Terminal Rates (c)	6/38 (16%)	5/34 (15%)	3/19 (16%)	2/9 (22%)
Life Table Tests (d)		P=0.257	P=0.522	P=0.315
Incidental Tumor Tests (d)		P=0.478	P=0.547N	P=0.607
Cochran-Armitage Trend Test (d)		P=0.329N		
Fisher Exact Test			P=0.480N	P=0.409N
Adrenal: Cortical Adenoma				
Overall Rates (a)	8/48 (17%)	6/48 (13%)	1/44 (2%)	0/45 (0%)
Adjusted Rates (b)	19.9%	15.8%	5.6%	0.0%
Terminal Rates (c)	7/39 (18%)	6/38 (16%)	1/18 (6%)	0/11 (0%)
Life Table Tests (d)		P=0.080N	P=0.260N	P=0.191N
Incidental Tumor Tests (d)		P=0.080N	P=0.260N	P=0.191N
Cochran-Armitage Trend Test (d)		P=0.006N		
Fisher Exact Test			P=0.070N	P=0.016N
Adrenal: Pheochromocytoma				
Overall Rates (a)	4/48 (8%)	8/48 (17%)	0/44 (0%)	0/45 (0%)
Adjusted Rates (b)	10.3%	21.1%	0.0%	0.0%
Terminal Rates (c)	4/39 (10%)	8/38 (21%)	0/18 (0%)	0/11 (0%)
Life Table Tests (d)		P=0.017N	P=0.047N	P=0.117N
Incidental Tumor Tests (d)		P=0.017N	P=0.047N	P=0.117N
Cochran-Armitage Trend Test (d)		P=0.001N		
Fisher Exact Test			P=0.004N	P=0.004N
Prostate: Adenoma				
Overall Rates (a)	0/48 (0%)	3/49 (6%)	0/45 (0%)	0/43 (0%)
Adjusted Rates (b)	0.0%	7.9%	0.0%	0.0%
Terminal Rates (c)	0/39(0%)	3/38 (8%)	0/19 (0%)	0/11 (0%)
Life Table Tests (d)		P=0.153N	P=0.266N	P=0.403N
Incidental Tumor Tests (d)		P=0.153N	P=0.266N	P=0.403N
Cochran-Armitage Trend Test (d)		P=0.046N		
Fisher Exact Test			P=0.137N	P=0.147N
Prostate: Adenoma, Adenocarcinoma, or Carcinoma				
Overall Rates (a)	0/48 (0%)	4/49 (8%)	1/45 (2%)	0/43 (0%)
Adjusted Rates (b)	0.0%	10.5%	5.3%	0.0%
Terminal Rates (c)	0/39 (0%)	4/38 (11%)	1/19 (5%)	0/11 (0%)
Life Table Tests (d)		P=0.176N	P=0.435N	P=0.311N
Incidental Tumor Tests (d)		P=0.176N	P=0.435N	P=0.311N
Cochran-Armitage Trend Test (d)		P=0.034N		
Fisher Exact Test			P=0.208N	P=0.076N
Testis: Interstitial Cell Tumor				
Overall Rates (a)	38/47 (81%)	36/49 (73%)	23/49 (47%)	17/49 (35%)
Adjusted Rates (b)	90.4%	94.7%	95.8%	100.0%
Terminal Rates (c)	34/38 (89%)	36/38 (95%)	18/19 (95%)	11/11 (100%)
Life Table Tests (d)		P<0.001	P=0.024	P<0.001
Incidental Tumor Tests (d)		P=0.019	P=0.223	P=0.074
Cochran-Armitage Trend Test (d)		P<0.001N		
Fisher Exact Test			P=0.006N	P<0.001N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (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 vehicle 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 rates. A negative trend or lower incidence in a dosed group is indicated by (N).

TABLE A4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING	1			
ANIMALS NECROPSIED	49	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	49	50
INTEGUMENTARY SYSTEM				
*Subcutaneous tissue	(49)	(50)	(49)	(50)
Inflammation, acute			1 (2%)	1 (2%)
Necrosis, NOS			1 (2%)	
RESPIRATORY SYSTEM				
*Nasal cavity	(49)	(50)	(49)	(50)
Inflammation, chronic				1 (2%)
Inflammation, chronic focal				1 (2%)
*Tracheal lumen	(49)	(50)	(49)	(50)
Hemorrhage	3 (6%)	1 (2%)	1 (2%)	5 (10%)
*Larynx	(49)	(50)	(49)	(50)
Inflammation, NOS			1 (2%)	
Inflammation, necrotizing				1 (2%)
#Trachea	(46)	(46)	(43)	(45)
Hemorrhage				2 (4%)
Inflammation, necrotizing			1 (2%)	
#Lung	(48)	(49)	(47)	(46)
Emphysema, alveolar				1 (2%)
Congestion, NOS		1 (2%)		3 (7%)
Edema, NOS	1 (2%)			2 (4%)
Hemorrhage	1 (2%)	4 (8%)	4 (9%)	14 (30%)
Inflammation, NOS		23 (47%)	6 (13%)	2 (4%)
Inflammation, focal		4 (8%)	1 (2%)	2 (4%)
Inflammation, acute focal			1 (2%)	
Inflammation, chronic focal		1 (2%)	3 (6%)	
Foreign material, NOS		13 (27%)	5 (11%)	3 (7%)
Pigmentation, NOS		1 (2%)		
#Lung/alveoli	(48)	(49)	(47)	(46)
Hemorrhage			1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM				
#Bone marrow	(47)	(50)	(45)	(45)
Hyperplasia, NOS	1 (2%)			
Hyperplasia, granulocytic		1 (2%)	1 (2%)	
#Spleen	(49)	(50)	(48)	(44)
Congestion, NOS				1 (2%)
Hemorrhage	1 (2%)		1 (2%)	
Hemosiderosis			1 (2%)	
Hyperplasia, lymphoid	1 (2%)			
Hematopoiesis			1 (2%)	
#Mediastinal lymph node	(40)	(45)	(35)	(30)
Hemorrhage			1 (3%)	
#Mesenteric lymph node	(40)	(45)	(35)	(30)
Hemorrhage		1 (2%)		2 (7%)
#Thymus	(3)	(7)	(12)	(24)
Multiple cysts				2 (8%)
Hemorrhage				3 (13%)
CIRCULATORY SYSTEM				
#Trachea	(46)	(46)	(43)	(45)
Embolus, septic		1 (2%)		

TABLE A4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM (Continued)				
#Lung	(48)	(49)	(47)	(46)
Thrombosis, NOS				1 (2%)
#Heart	(49)	(49)	(48)	(48)
Inflammation, focal	1 (2%)	1 (2%)	1 (2%)	
Inflammation, acute/chronic		1 (2%)		
Inflammation, chronic		6 (12%)		
Inflammation, chronic focal	2 (4%)	2 (4%)		
Fibrosis, focal			1 (2%)	
Necrosis, focal	2 (4%)			
Calcification, focal	1 (2%)			
*Aorta	(49)	(50)	(49)	(50)
Mineralization		1 (2%)		
Calcification, NOS				1 (2%)
Calcification, metastatic	1 (2%)			
*Pulmonary artery	(49)	(50)	(49)	(50)
Calcification, metastatic	1 (2%)			
DIGESTIVE SYSTEM				
#Liver	(49)	(50)	(49)	(49)
Hemorrhage		1 (2%)	1 (2%)	1 (2%)
Inflammation, acute focal	1 (2%)			
Inflammation, chronic focal	1 (2%)			
Necrosis, focal		1 (2%)	2 (4%)	
Metamorphosis, fatty	1 (2%)	2 (4%)		
Cytoplasmic vacuolization		1 (2%)		
Basophilic cyto change	1 (2%)	2 (4%)		1 (2%)
Clear cell change	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Cytologic alteration, NOS		1 (2%)		
Hepatocytomegaly	1 (2%)			
Angiectasis			1 (2%)	
#Liver/centrilobular	(49)	(50)	(49)	(49)
Necrosis, NOS	1 (2%)			
#Bile duct	(49)	(50)	(49)	(49)
Dilatation, NOS		1 (2%)		
Inflammation, chronic		1 (2%)		
Hyperplasia, NOS	1 (2%)			
#Pancreas	(46)	(50)	(47)	(44)
Hemorrhage			1 (2%)	
Inflammation, chronic				1 (2%)
Inflammation, granulomatous	1 (2%)			
Atrophy, focal				1 (2%)
Atrophy, granular	1 (2%)			
#Pancreatic duct	(46)	(50)	(47)	(44)
Degeneration, cystic	1 (2%)			
#Pancreatic acinus	(46)	(50)	(47)	(44)
Atrophy, NOS		1 (2%)		
Atrophy, focal	2 (4%)	1 (2%)		
Atrophy, granular		1 (2%)		
*Esophageal lumen	(49)	(50)	(49)	(50)
Hemorrhage	7 (14%)	1 (2%)	6 (12%)	3 (6%)
#Esophagus	(49)	(49)	(47)	(47)
Dilatation, NOS	1 (2%)			
Hemorrhage	1 (2%)			
Inflammation, necrotizing				1 (2%)
Abscess, chronic				1 (2%)
#Stomach	(49)	(49)	(48)	(46)
Calcification, metastatic	1 (2%)			
Hyperplasia, epithelial				2 (4%)
#Gastric mucosa	(49)	(49)	(48)	(46)
Hyperplasia, NOS		1 (2%)		

TABLE A4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)				
#Forestomach	(49)	(49)	(48)	(46)
Hyperplasia, epithelial	1 (2%)			
Hyperkeratosis	1 (2%)			
#Duodenum	(48)	(49)	(48)	(46)
Hemorrhage				1 (2%)
#Colon	(48)	(48)	(46)	(43)
Parasitism			1 (2%)	1 (2%)
URINARY SYSTEM				
#Kidney	(49)	(50)	(49)	(49)
Mineralization	39 (80%)	28 (56%)	14 (29%)	9 (18%)
Cast, NOS		1 (2%)		
Hydronephrosis	5 (10%)	4 (8%)	5 (10%)	5 (10%)
Hemorrhage			3 (6%)	
Inflammation, NOS				1 (2%)
Pyelonephritis, acute			1 (2%)	2 (4%)
Inflammation, acute	1 (2%)			
Pyelonephritis, acute/chronic		1 (2%)	1 (2%)	
Inflammation, chronic		1 (2%)		
Pyelonephritis, chronic	1 (2%)			
Nephropathy	48 (98%)	49 (98%)	40 (82%)	43 (88%)
Nephropathy, toxic			18 (37%)	18 (37%)
Necrosis, NOS		1 (2%)		
Necrosis, focal		1 (2%)		
Infarct, NOS				1 (2%)
Calcification, focal	2 (4%)	5 (10%)	7 (14%)	11 (22%)
Cytomegaly			40 (82%)	48 (98%)
Hyperplasia, epithelial	2 (4%)		1 (2%)	
Angiectasis	6 (12%)	1 (2%)		1 (2%)
#Kidney/cortex	(49)	(50)	(49)	(49)
Cyst, NOS				1 (2%)
#Kidney/tubule	(49)	(50)	(49)	(49)
Necrosis, NOS			1 (2%)	
#Kidney/pelvis	(49)	(50)	(49)	(49)
Dilatation, NOS	1 (2%)			
Hemorrhage	1 (2%)			
Inflammation, NOS				1 (2%)
Inflammation, focal				1 (2%)
Inflammation, suppurative				1 (2%)
Inflammation, acute	1 (2%)		1 (2%)	2 (4%)
Inflammation, chronic	1 (2%)			
Hyperplasia, epithelial	19 (39%)	15 (30%)	12 (24%)	6 (12%)
#Urinary bladder	(44)	(44)	(47)	(42)
Cast, NOS		1 (2%)		
Hemorrhage	2 (5%)	2 (5%)	3 (6%)	1 (2%)
Inflammation, suppurative	1 (2%)			
Inflammation, acute			2 (4%)	1 (2%)
Inflammation, acute diffuse	1 (2%)			
Inflammation, acute suppurative			1 (2%)	1 (2%)
Inflammation, acute/chronic			1 (2%)	
Inflammation, chronic	1 (2%)		1 (2%)	2 (5%)
Hyperplasia, epithelial	2 (5%)	1 (2%)	3 (6%)	1 (2%)
Hyperplasia, papillary	1 (2%)			

TABLE A4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM				
#Pituitary	(48)	(39)	(33)	(29)
Hamartoma		1 (3%)		
Pigmentation, NOS	2 (4%)	1 (3%)		
Hyperplasia, focal	1 (2%)	1 (3%)	1 (3%)	
#Adrenal	(48)	(48)	(44)	(45)
Accessory structure	1 (2%)			
Hemorrhage	1 (2%)			
Inflammation, acute focal	1 (2%)			
#Adrenal cortex	(48)	(48)	(44)	(45)
Hemorrhage			1 (2%)	
Degeneration, NOS		1 (2%)		
Metamorphosis, fatty	1 (2%)			
Lipoidosis	2 (4%)		2 (5%)	
Hyperplasia, focal		1 (2%)		1 (2%)
#Adrenal medulla	(48)	(48)	(44)	(45)
Hyperplasia, focal		1 (2%)		1 (2%)
#Thyroid	(48)	(46)	(40)	(39)
Hemorrhage			1 (3%)	
Inflammation, necrotizing			1 (3%)	
Hyperplasia, C-cell	1 (2%)			1 (3%)
REPRODUCTIVE SYSTEM				
*Mammary gland	(49)	(50)	(49)	(50)
Hyperplasia, epithelial				1 (2%)
Lactation	3 (6%)		1 (2%)	1 (2%)
#Prostate	(48)	(49)	(45)	(43)
Dilatation, NOS			1 (2%)	
Hemorrhage		2 (4%)	6 (13%)	3 (7%)
Inflammation, NOS			1 (2%)	2 (5%)
Inflammation, focal		2 (4%)		
Inflammation, suppurative	2 (4%)		3 (7%)	2 (5%)
Inflammation, acute			3 (7%)	1 (2%)
Inflammation, acute diffuse	1 (2%)			
Inflammation, acute suppurative	1 (2%)		1 (2%)	1 (2%)
Abscess, NOS				1 (2%)
Inflammation, acute/chronic			1 (2%)	1 (2%)
Inflammation, chronic	2 (4%)		1 (2%)	
Inflammation, chronic focal		2 (4%)		
Inflammation, chronic suppurative		1 (2%)		2 (5%)
Abscess, chronic				1 (2%)
Corpora amylacea		1 (2%)		
Foreign material, NOS		1 (2%)		
Pigmentation, NOS		1 (2%)		
Atrophy, NOS	1 (2%)			
Hyperplasia, epithelial		2 (4%)		
Hyperplasia, focal		1 (2%)		1 (2%)
*Seminal vesicle	(49)	(50)	(49)	(50)
Congenital hypoplasia			1 (2%)	
Dilatation, NOS				1 (2%)
Hemorrhage		2 (4%)	4 (8%)	1 (2%)
Inflammation, NOS				1 (2%)
Inflammation, acute			3 (6%)	1 (2%)
Inflammation, acute focal	1 (2%)			
Inflammation, acute suppurative	1 (2%)		1 (2%)	
Inflammation, acute/chronic				1 (2%)
Inflammation, chronic suppurative		1 (2%)		
Abscess, chronic				1 (2%)
Fibrosis	1 (2%)			
Hypoplasia, NOS	1 (2%)			1 (2%)
Atrophy, NOS	1 (2%)			

TABLE A4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)				
#Testis	(47)	(49)	(49)	(49)
Necrosis, focal			1 (2%)	
Infarct, acute			1 (2%)	
Calcification, focal			1 (2%)	
Atrophy, NOS	1 (2%)	8 (16%)	4 (8%)	4 (8%)
Atrophy, focal		1 (2%)	3 (6%)	
Atrophy, diffuse	1 (2%)	1 (2%)	3 (6%)	2 (4%)
Aspermatogenesis		1 (2%)	1 (2%)	2 (4%)
Hypospermatogenesis	1 (2%)			
Hyperplasia, interstitial cell	4 (9%)	5 (10%)	5 (10%)	3 (6%)
NERVOUS SYSTEM				
#Brain/meninges	(49)	(50)	(47)	(47)
Pigmentation, NOS				1 (2%)
#Brain	(49)	(50)	(47)	(47)
Corpora amylacea				1 (2%)
SPECIAL SENSE ORGANS				
None				
MUSCULOSKELETAL SYSTEM				
*Skeletal muscle	(49)	(50)	(49)	(50)
Abscess, NOS	1 (2%)			
*Muscle of neck	(49)	(50)	(49)	(50)
Inflammation, NOS				1 (2%)
Necrosis, focal				1 (2%)
BODY CAVITIES				
*Mediastinum	(49)	(50)	(49)	(50)
Inflammation, focal		1 (2%)		
*Pleura	(49)	(50)	(49)	(50)
Inflammation, focal	1 (2%)			
*Mesentery	(49)	(50)	(49)	(50)
Inflammation, granulomatous			1 (2%)	
ALL OTHER SYSTEMS				
*Multiple organs	(49)	(50)	(49)	(50)
Hemorrhage		1 (2%)		1 (2%)
Axilla				
Abscess, chronic		1		
SPECIAL MORPHOLOGY SUMMARY				
Animal missing/no necropsy	1			
Auto/necropsy/histo perf			1	1
Autolysis/no necropsy			1	

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX B

SUMMARY OF LESIONS IN FEMALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING	1			
ANIMALS NECROPSIED	49	50	50	46
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	49	50	45
INTEGUMENTARY SYSTEM				
*Subcutaneous tissue	(49)	(50)	(50)	(46)
Adenoma, NOS	1 (2%)			
Sarcoma, NOS		1 (2%)		1 (2%)
RESPIRATORY SYSTEM				
#Lung	(49)	(49)	(47)	(42)
Carcinoma, NOS, metastatic	1 (2%)			
Transitional cell carcinoma, metastatic			1 (2%)	
Alveolar/bronchiolar adenoma			1 (2%)	
Tubular cell adenocarcinoma, metastatic				1 (2%)
Endometrial stromal sarcoma, metastatic				1 (2%)
HEMATOPOIETIC SYSTEM				
*Multiple organs	(49)	(50)	(50)	(46)
Monocytic leukemia	2 (4%)			
#Lymph node	(43)	(47)	(36)	(28)
Carcinoma, NOS, metastatic	1 (2%)			
Sarcoma, NOS, metastatic				1 (4%)
#Liver	(49)	(49)	(46)	(39)
Leukemia, NOS				1 (3%)
#Thymus	(10)	(7)	(19)	(14)
Thymoma, malignant		1 (14%)		
Malignant lymphoma, lymphocytic type	1 (10%)	1 (14%)	2 (11%)	
CIRCULATORY SYSTEM				
#Uterus	(48)	(49)	(48)	(40)
Angiosarcoma	1 (2%)			
DIGESTIVE SYSTEM				
#Liver	(49)	(49)	(46)	(39)
Neoplastic nodule	1 (2%)	2 (4%)		
URINARY SYSTEM				
#Kidney	(49)	(48)	(47)	(43)
Adenocarcinoma, NOS			1 (2%)	
Tubular cell adenoma			2 (4%)	
Tubular cell adenocarcinoma				1 (2%)
Sarcoma, NOS	1 (2%)			
Nephroblastoma		1 (2%)		
#Kidney/pelvis	(49)	(48)	(47)	(43)
Transitional cell papilloma			2 (4%)	
Transitional cell carcinoma	1 (2%)	4 (8%)	3 (6%)	1 (2%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM				
#Pituitary	(47)	(42)	(36)	(32)
Carcinoma, NOS				1 (3%)
Adenoma, NOS	24 (51%)	18 (43%)	7 (19%)	7 (22%)
Adenocarcinoma, NOS		1 (2%)		
Chromophobe adenoma		1 (2%)		
Chromophobe carcinoma		1 (2%)		
#Adrenal	(49)	(48)	(44)	(40)
Cortical adenoma	1 (2%)	2 (4%)	1 (2%)	3 (8%)
Cortical carcinoma		1 (2%)		
Pheochromocytoma	1 (2%)	3 (6%)		2 (5%)
Pheochromocytoma, malignant			1 (2%)	
#Thyroid	(46)	(47)	(44)	(38)
Follicular cell adenoma				1 (3%)
REPRODUCTIVE SYSTEM				
*Mammary gland	(49)	(50)	(50)	(46)
Adenoma, NOS		1 (2%)		1 (2%)
Adenocarcinoma, NOS	1 (2%)	1 (2%)	1 (2%)	
Papillary adenoma	1 (2%)			
Fibroadenoma	1 (2%)	1 (2%)		
#Uterus	(48)	(49)	(48)	(40)
Carcinoma, NOS	1 (2%)			
Adenocarcinoma, NOS	1 (2%)			
Endometrial stromal polyp	1 (2%)	4 (8%)	3 (6%)	2 (5%)
Endometrial stromal sarcoma				1 (3%)
#Cervix uteri	(48)	(49)	(48)	(40)
Endometrial stromal sarcoma			1 (2%)	
#Uterus/endometrium	(48)	(49)	(48)	(40)
Carcinoma, NOS				1 (3%)
#Ovary	(48)	(46)	(46)	(38)
Luteoma	1 (2%)			
NERVOUS SYSTEM				
#Brain	(49)	(48)	(49)	(42)
Granular cell tumor, NOS		1 (2%)		1 (2%)
SPECIAL SENSE ORGANS				
*Zymbal gland	(49)	(50)	(50)	(46)
Adenosquamous carcinoma		1 (2%)		
MUSCULOSKELETAL SYSTEM				
*Skeletal muscle	(49)	(50)	(50)	(46)
Sarcoma, NOS				1 (2%)
BODY CAVITIES				
None				

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS				
*Multiple organs	(49)	(50)	(50)	(46)
Sarcoma, NOS			1 (2%)	
Periorbital region				
Sarcoma, NOS	1			
ANIMAL DISPOSITION SUMMARY				
Animals initially in study	50	50	50	50
Natural death	11	5	12	17
Moribund sacrifice	2	10	4	4
Terminal sacrifice	36	33	20	17
Dosing accident			2	3
Accidentally killed, NOS		2	12	9
Animal missing	1			
TUMOR SUMMARY				
Total animals with primary tumors**	34	33	21	18
Total primary tumors	42	46	26	25
Total animals with benign tumors	28	27	15	14
Total benign tumors	31	30	16	16
Total animals with malignant tumors	9	12	10	8
Total malignant tumors	10	13	10	8
Total animals with secondary tumors##	1		1	3
Total secondary tumors	2		1	3
Total animals with tumors uncertain--benign or malignant	1	3		1
Total uncertain tumors	1	3		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. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: UNTREATED CONTROL

ANIMAL NUMBER	00005	00006	00007	00008	01017	02202	02404	02505	02707	02808	02909	03033	03037	03039	04040	04202	84048	86383	86707	88808	87171	87275	87579	89393
WEEKS ON STUDY	10606	10404	10606	10606	10606	10606	05909	10606	10606	10606	09808	05505	10606	10606	06404	10806	10606	05202	10802	10202	10606	09909	09606	10606	07303
INTEGUMENTARY SYSTEM																								
Subcutaneous tissue	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																	X							
RESPIRATORY SYSTEM																								
Lungs and bronchi	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic																								
Trachea	+	+	+	+	+	+	M	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−
HEMATOPOIETIC SYSTEM																								
Bone marrow	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	M	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	−
Carcinoma, NOS, metastatic																								
Thymus	−	−	−	−	−	−	M	−	−	−	−	−	−	−	+	−	~	−	−	+	−	+	+	−	+
Malignant lymphoma, lymphocytic type																								
CIRCULATORY SYSTEM																								
Heart	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
Salivary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	−	+	+	+	+	−	−	+	+	+
Liver	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																								
Bile duct	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	M	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	−	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
Stomach	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	−	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																								
Kidney	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS											X													
Kidney/pelvis	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma																								
Urinary bladder	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
ENDOCRINE SYSTEM																								
Pituitary	+	+	+	+	+	+	M	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−
Adenoma, NOS		X	X		X	X				X			X	X		X			X				X	
Adrenal	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																								
Pheochromocytoma														X										
Thyroid	+	−	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Parathyroid	+	−	+	+	+	−	M	+	+	+	+	+	+	−	−	−	−	+	+	+	+	+	−	−
REPRODUCTIVE SYSTEM																								
Mammary gland	+	+	+	+	+	+	M	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																								
Papillary adenoma																								
Fibroadenoma	X																							
Uterus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																								
Adenocarcinoma, NOS																				X				
Endometrial stromal polyp																								
Angiosarcoma																								
Ovary	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Luteoma																						X		
NERVOUS SYSTEM																								
Brain	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																								
Multiple organs, NOS	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Monocytic leukemia													X									X		
Periorbital region							M																	
Sarcoma, NOS																								

+: 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 B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE ACI RATS: UNTREATED CONTROL (Continued)

ANIMAL NUMBER	90202	90206	91014	91515	91519	92026	93636	94040	94848	95050	95556	96869	97070	97575	97676	97717	97787	97979	98181	98484	99090	99191	99292	99494	99696	TOTAL:
WEEKS ON STUDY	054	106	099	106	106	106	074	106	106	076	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TISSUES / TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Adenoma, NOS																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS, metastatic																			X							1
Trachea	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph nodes	+	+	+	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Carcinoma, NOS, metastatic																			X							1
Thymus	−	−	−	−	−	−	+	−	−	+	−	−	−	−	+	−	+	−	+	−	−	−	−	−	−	10
Malignant lymphoma, lymphocytic type																	X									1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule																				X						1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, NOS																										1
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Transitional cell carcinoma																	X									1
Urinary bladder	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS		X	X	X	X		X		X		X	X		X		X	X	X					X		X	24
Adrenal	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma									X																	1
Pheochromocytoma																										1
Thyroid	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Parathyroid	−	−	+	−	+	+	+	+	+	−	+	−	+	+	−	−	−	+	+	+	−	−	+	+	+	31
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Adenocarcinoma, NOS																								X		1
Papillary adenoma																	X									1
Fibroadenoma																										1
Uterus	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS																			X							1
Adenocarcinoma, NOS																										1
Endometrial stromal polyp																								X		1
Angiosarcoma										X																1
Ovary	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Luteoma																										1
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	N	*49
Monocytic leukemia																										2
Periorbital region																										
Sarcoma, NOS	X																									1

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: VEHICLE CONTROL

ANIMAL NUMBER	000	020	021	032	045	444	445	449	500	586	588	589	600	606	669	670	678	682	683	685	689	690	692	697	904
WEEKS ON STUDY	100	090	106	106	106	014	106	106	106	096	099	106	106	106	106	106	106	106	051	106	106	106	106	106	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	+	−	−	−
Thymoma, malignant																						X			
Malignant lymphoma, lymphocytic type																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Nephroblastoma																									
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Transitional cell carcinoma													X							X		X			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	−	+
ENDOCRINE SYSTEM																									
Pituitary	+	−	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS			X	X			X	X						X	X	X	X						X	X	X
Adenocarcinoma, NOS																									
Chromophobe adenoma																									
Chromophobe carcinoma																			X						
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma			X													X									
Cortical carcinoma															X										
Pheochromocytoma																					X				
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	+	−	+	−	−	−	+	+	−	+	+	−	+	−	+	+	+	−	−	−	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS										X															
Adenocarcinoma, NOS																					X				
Fibroadenoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp									X				X							X					
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, NOS								X																	
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
Adenosquamous carcinoma																									

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE ACI RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	90 05	90 07	90 08	91 08	92 08	92 09	93 00	94 01	94 03	94 04	94 05	95 01	95 02	95 05	96 00	96 04	96 06	97 03	98 00	98 03	98 05	98 06	98 08	99 03	99 05	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	106	106	106	106	068	041	106	106	106	096	106	104	100	106	106	222	083	106	096	106	054	106	106	106	102	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS														X												1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	−	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	A	−	+	+	+	+	+	+	+	+	47
Thymus	−	−	−	−	−	−	+	−	−	−	−	+	−	+	−	A	−	−	+	−	−	−	−	−	−	7
Thymoma, malignant																										1
Malignant lymphoma, lymphocytic type							X																			1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	−	+	+	+	+	+	+	48
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	A	+	+	−	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule																										2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	49
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	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	A	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	−	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	−	+	+	+	+	+	+	47
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	−	+	+	+	+	+	+	−	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	48
Nephroblastoma																	X									1
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	48
Transitional cell carcinoma												X														4
Urinary bladder	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	A	+	+	−	+	+	+	+	+	+	43
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	A	+	+	−	−	+	+	+	+	−	42
Adenoma, NOS	X	X							X			X	X	X				X								18
Adenocarcinoma, NOS										X																1
Chromophobe adenoma																					X					1
Chromophobe carcinoma																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	−	+	+	+	+	+	+	48
Cortical adenoma																										2
Cortical carcinoma																										1
Pheochromocytoma				X													X									3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	−	+	+	+	−	47
Parathyroid	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	−	+	+	+	−	35
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	N	+	+	+	+	*50
Adenoma, NOS																										1
Adenocarcinoma, NOS																										1
Fibroadenoma																			X							1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	49
Endometrial stromal polyp										X																4
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	A	−	+	+	+	+	+	+	−	+	46
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	−	+	+	+	+	+	+	48
Granular cell tumor, NOS																										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	*50
Adenosquamous carcinoma					X																					1

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: LOW DOSE

ANIMAL NUMBER	00002	00004	00114	00115	00116	00119	00223	00226	00334	00335	00336	00341	00443	84433	84436	84437	85354	85557	85577	86262	86265	87373	87481	87771	89191
WEEKS ON STUDY	06 4	10 5	06 6	01 1	09 1	10 4	10 4	10 5	04 8	08 7	10 4	08 5	06 8	10 5	04 7	09 0	10 4	10 5	07 6	08 5	10 4	01 6	03 2	07 0	08 9
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Transitional cell carcinoma, metastatic													X												
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	−	+	+	−	−	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	−	+	+	+	+	+	+
Lymph nodes		−	+	+	+	+	+	+	+	+	+	+	A	−	+	+	−	+	+	−	+	+	−	−	− +
Thymus	−	−	−	+	−	−	−	−	+	−	−	A	−	−	+	−	+	−	+	+	−	+	−	+	+
Malignant lymphoma, lymphocytic type																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	−	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	−	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	−	+	+	+	+	+	+
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	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	−	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	−	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	−	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	−	+	+	+	+	−	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	−	+	+	+	+	+	+
Adenocarcinoma, NOS														X											
Tubular cell adenoma																X									
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	−	+	+	+	+	+	+
Transitional cell papilloma										X							X								
Transitional cell carcinoma		X											X												
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	−	−	+	−	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	−	−	+	−
Adenoma, NOS								X										X						X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	−	+	+	+	·	+	−
Cortical adenoma		X																							
Pheochromocytoma, malignant																				X					
Thyroid	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	−	−	−	+	+	+	+
Parathyroid	−	−	+	+	−	−	+	−	+	−	+	+	−	+	−	−	−	+	−	−	−	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+
Adenocarcinoma, NOS																									X
Uterus	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp							X																		
Endometrial stromal sarcoma																									
Ovary	−	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	−	+	+	+	+	+	+
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
Sarcoma, NOS																					X				

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE ACI RATS: LOW DOSE (Continued)

ANIMAL NUMBER	8 9 4	8 9 8	9 0 9	9 1 0	9 1 3	9 1 6	9 1 7	9 2 1	9 2 2	9 2 5	9 3 2	9 3 4	9 3 5	9 3 8	9 4 2	9 4 7	9 4 9	9 5 4	9 6 8	9 7 2	9 7 4	9 8 2	9 8 7	9 9 8	9 9 9	TOTAL:
WEEKS ON STUDY	0 6 6	0 1 2	1 0 5	1 0 4	0 7 4	1 0 4	1 0 5	0 6 1	1 0 4	0 1 8	1 0 4	0 8 8	0 9 9	0 2 0	0 5 6	1 0 4	1 0 4	1 0 5	0 7 0	0 4 8	0 5 4	0 8 8	1 0 4	0 6 1	1 0 4	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	47
Transitional cell carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma				X																						1
Trachea	+	+	+	+	+	+	+	+	+	+	+	−	+	A	−	+	+	+	−	+	−	+	+	+	+	41
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	−	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	−	+	+	+	46
Lymph nodes	−	+	+	+	−	+	+	+	+	−	+	−	+	A	+	+	+	+	+	+	+	−	+	+	+	36
Thymus	−	+	−	−	−	−	+	+	+	−	+	−	−	A	+	+	−	−	+	+	−	−	−	+	−	19
Malignant lymphoma, lymphocytic type											X					X										2
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	−	+	+	+	A	+	+	+	+	−	+	+	+	+	−	+	43
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	−	+	+	+	46
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	−	+	+	+	46
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	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	−	+	+	+	46
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	−	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	−	+	+	+	45
Small intestine	+	−	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	−	+	+	+	45
Large intestine	+	−	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	47
Adenocarcinoma, NOS																										1
Tubular cell adenoma																	X									2
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	47
Transitional cell papilloma																										2
Transitional cell carcinoma																									X	3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	−	+	+	+	+	+	+	−	45
ENDOCRINE SYSTEM																										
Pituitary	+	−	+	+	+	+	+	+	+	−	+	−	+	A	+	+	+	+	−	+	+	−	+	+	+	36
Adenoma, NOS											X					X		X							X	7
Adrenal	+	+	+	+	+	+	+	+	+	+	+	−	+	A	+	+	+	+	+	+	+	−	+	+	+	44
Cortical adenoma																										1
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	44
Parathyroid	−	+	+	−	−	+	+	+	−	−	+	−	+	A	+	−	+	+	−	−	−	−	+	+	+	25
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	N	+	+	+	N	N	+	+	+	+	+	N	+	+	+	N	*50
Adenocarcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	48
Endometrial stromal polyp									X									X								3
Endometrial stromal sarcoma												X														1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	46
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	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	N	*50
Sarcoma, NOS																										1

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: HIGH DOSE

ANIMAL NUMBER	001	003	009	010	011	012	013	018	030	031	038	044	851	852	853	861	864	876	881	884	886	887	888	895	896
WEEKS ON STUDY	073	104	062	104	084	028	104	045	056	052	104	015	089	071	101	104	104	104	104	063	104	111	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	N	+	A	N	+	+	+	+	N	+	+	+	+	+	+	+
Sarcoma, NOS																					X				
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma, metastatic					X																				
Endometrial stromal sarcoma, metastatic														X											
Trachea	+	+	+	+	−	+	+	+	+	−	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	−	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	−	−	−	−	+	−	+	−	+	A	−	−	+	−	+	+	+	+	+	−	−	+	+
Sarcoma, NOS, metastatic																					X				
Thymus	+	+	−	−	−	−	−	−	−	−	−	A	−	+	−	−	−	+	−	+	−	+	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	−	+	+	+	−	+	A	−	+	+	+	+	−	+	+	+	+	+	+	+
Liver	+	−	+	+	+	+	+	+	+	−	+	A	−	+	+	+	+	−	+	+	+	+	+	+	+
Leukemia, NOS																	X								
Bile duct	+	−	+	+	+	+	+	+	+	−	+	A	−	+	+	+	+	−	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	+	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	−	+	+	−	+	+	+	A	+	+	+	+	+	−	+	+	−	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma					X																				
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma				X																					
Urinary bladder	+	+	+	+	+	+	+	−	+	+	+	A	−	+	+	−	+	−	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	−	−	+	A	−	+	+	+	+	+	+	+	+	−	+	+	+
Carcinoma, NOS															X										
Adenoma, NOS							X									X	X	X							
Adrenal	+	+	+	+	+	+	+	+	+	+	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma											X										X				
Pheochromocytoma				X																					X
Thyroid	+	+	−	+	−	+	+	+	+	−	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma															X										
Parathyroid	+	+	−	+	−	+	+	+	−	−	+	A	−	+	+	+	+	+	−	−	+	−	−	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	A	N	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																X									
Uterus	+	+	+	+	+	+	+	−	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Endometrial stromal polyp							X												X						
Endometrial stromal sarcoma														X											
Ovary	+	+	+	+	+	+	+	−	+	+	+	A	+	−	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	−	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, NOS																			X						
MUSCULOSKELETAL SYSTEM																									
Muscle	N	N	+	N	N	+	N	+	+	+	N	A	N	N	N	N	N	N	N	N	N	+	N	N	N
Sarcoma, NOS						X																			

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE ACI RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	8 9 9	9 0 0	9 0 1	9 0 3	9 1 1	9 1 2	9 2 0	9 2 3	9 2 4	9 2 7	9 3 1	9 3 3	9 3 7	9 3 9	9 4 6	9 5 3	9 5 7	9 5 8	9 6 1	9 6 2	9 6 3	9 6 7	9 7 0	9 8 9	9 9 7	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	0 2 3	0 0 8	1 0 4	1 0 4	1 0 4	0 5 2	0 9 7	0 4 5	0 6 3	0 5 2	0 2 8	1 0 4	0 1 8	0 2 2	1 0 4	0 1 5	1 0 4	0 7 1	0 1 0	0 0 5	0 6 5	0 4 1	0 8 3	1 0 4	0 5 5	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	A	N	+	+	+	+	+	+	+	N	N	+	N	+	+	N	+	+	N	A	+	A	+	+	+	*46
Sarcoma, NOS																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	A	–	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	A	+	+	–	42
Tubular cell adenocarcinoma, metastatic																										1
Endometrial stromal sarcoma, metas																										1
Trachea	A	+	+	+	+	+	+	+	–	+	A	+	+	+	+	+	+	+	+	A	+	A	+	+	–	40
HEMATOPOIETIC SYSTEM																										
Bone marrow	A	–	–	+	+	+	+	–	+	+	A	+	–	+	+	+	+	+	–	A	+	A	+	+	+	40
Spleen	A	–	–	+	+	+	+	+	+	+	A	+	–	+	+	+	+	+	+	A	+	A	+	+	+	42
Lymph nodes	A	–	+	+	+	+	+	–	–	+	A	+	+	–	+	–	+	+	+	A	+	A	–	+	+	28
Sarcoma, NOS, metastatic																										1
Thymus	A	–	–	–	–	+	–	+	–	+	A	–	–	+	–	+	–	+	+	A	+	A	–	–	–	14
CIRCULATORY SYSTEM																										
Heart	A	–	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	A	+	+	–	42
DIGESTIVE SYSTEM																										
Salivary gland	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	A	–	+	–	39
Liver	A	–	+	+	+	+	+	+	+	+	A	+	–	+	+	+	+	+	+	A	+	A	+	+	+	39
Leukemia, NOS																										1
Bile duct	A	–	+	+	+	+	+	+	+	+	A	+	–	+	+	+	+	+	+	A	+	A	+	+	+	39
Gallbladder & common bile duct	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	A	N	N	N	*46
Pancreas	A	–	+	+	+	+	+	+	+	+	A	+	–	+	+	+	+	+	+	A	+	A	+	+	+	42
Esophagus	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	A	+	+	–	43
Stomach	A	–	+	+	+	+	+	+	+	+	A	+	–	+	+	+	+	+	+	A	+	A	+	+	+	42
Small intestine	A	–	+	+	+	+	+	+	+	+	A	+	–	+	+	+	+	+	+	A	+	A	–	+	+	41
Large intestine	A	–	+	+	+	+	+	+	+	+	A	+	–	+	+	+	+	+	+	A	+	A	–	+	+	38
URINARY SYSTEM																										
Kidney	A	–	+	+	+	+	+	+	+	+	A	+	–	+	+	+	+	+	+	A	+	A	+	+	+	43
Tubular cell adenocarcinoma																										1
Kidney/pelvis	A	–	+	+	+	+	+	+	+	+	A	+	–	+	+	+	+	+	+	A	+	A	+	+	+	43
Transitional cell carcinoma																										1
Urinary bladder	A	–	+	+	+	+	+	+	+	–	A	+	–	+	+	+	+	+	–	A	+	A	–	+	–	35
ENDOCRINE SYSTEM																										
Pituitary	A	–	+	+	+	+	+	+	–	+	A	+	–	–	+	–	+	+	–	A	–	A	–	+	–	32
Carcinoma, NOS																										1
Adenoma, NOS				X													X							X		7
Adrenal	A	–	+	+	+	+	+	+	+	+	A	+	–	+	+	+	+	+	–	A	+	A	+	+	–	40
Cortical adenoma												X														3
Pheochromocytoma																										2
Thyroid	A	+	+	+	+	+	+	+	–	+	A	+	+	+	+	+	+	+	+	A	+	A	–	+	–	38
Follicular cell adenoma																										1
Parathyroid	A	+	+	+	+	+	+	–	–	+	A	+	+	–	–	–	+	–	–	A	+	A	–	+	–	27
REPRODUCTIVE SYSTEM																										
Mammary gland	A	N	N	+	+	N	+	N	+	N	N	+	N	+	+	+	+	+	N	A	+	A	+	N	N	*46
Adenoma, NOS																										1
Uterus	A	–	+	+	+	+	+	+	+	+	A	+	–	+	+	+	+	+	+	A	+	A	–	+	–	40
Carcinoma, NOS			X																							1
Endometrial stromal polyp																										2
Endometrial stromal sarcoma																										1
Ovary	A	–	+	+	+	+	+	+	+	–	A	+	–	+	+	+	+	+	+	A	+	A	–	+	–	38
NERVOUS SYSTEM																										
Brain	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	A	+	+	–	42
Granular cell tumor, NOS																										1
MUSCULOSKELETAL SYSTEM																										
Muscle	A	N	N	N	N	+	N	+	+	+	N	N	N	+	N	+	N	N	+	A	+	A	N	N	N	*46
Sarcoma, NOS																										1

* Animals necropsied

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg
Kidney: Transitional Cell Carcinoma				
Overall Rates (a)	1/49 (2%)	4/48 (8%)	3/47 (6%)	1/43 (2%)
Adjusted Rates (b)	2.7%	11.8%	12.6%	5.3%
Terminal Rates (c)	1/37 (3%)	4/34 (12%)	2/20 (10%)	1/19 (5%)
Life Table Tests (d)		P=0.346N	P=0.549	P=0.388N
Incidental Tumor Tests (d)		P=0.264N	P=0.642N	P=0.388N
Cochran-Armitage Trend Test (d)		P=0.160N		
Fisher Exact Test			P=0.512N	P=0.217N
Kidney: Transitional Cell Papilloma or Carcinoma				
Overall Rates (a)	1/49 (2%)	4/48 (8%)	5/47 (11%)	1/43 (2%)
Adjusted Rates (b)	2.7%	11.8%	20.6%	5.3%
Terminal Rates (c)	1/37 (3%)	4/34 (12%)	3/20 (15%)	1/19 (5%)
Life Table Tests (d)		P=0.427N	P=0.216	P=0.388N
Incidental Tumor Tests (d)		P=0.299N	P=0.407	P=0.388N
Cochran-Armitage Trend Test (d)		P=0.193N		
Fisher Exact Test			P=0.486	P=0.217N
Kidney: Adenoma or Adenocarcinoma				
Overall Rates (a)	0/49 (0%)	0/48 (0%)	3/47 (6%)	1/43 (2%)
Adjusted Rates (b)	0.0%	0.0%	13.9%	4.3%
Terminal Rates (c)	0/37 (0%)	0/34 (0%)	2/20 (10%)	0/19 (0%)
Life Table Tests (d)		P=0.200	P=0.044	P=0.375
Incidental Tumor Tests (d)		P=0.310	P=0.104	P=0.581
Cochran-Armitage Trend Test (d)		P=0.343		
Fisher Exact Test			P=0.117	P=0.473
Pituitary: Adenoma				
Overall Rates (a)	24/47 (51%)	19/42 (45%)	7/36 (19%)	7/32 (22%)
Adjusted Rates (b)	59.8%	52.1%	33.7%	36.8%
Terminal Rates (c)	21/37 (57%)	16/33 (48%)	6/19 (32%)	7/19 (37%)
Life Table Tests (d)		P=0.095N	P=0.144N	P=0.149N
Incidental Tumor Tests (d)		P=0.068N	P=0.073N	P=0.109N
Cochran-Armitage Trend Test (d)		P=0.015N		
Fisher Exact Test			P=0.014N	P=0.032N
Pituitary: Adenoma, Adenocarcinoma, or Carcinoma				
Overall Rates (a)	24/47 (51%)	21/42 (50%)	7/36 (19%)	8/32 (25%)
Adjusted Rates (b)	59.8%	55.9%	33.7%	40.0%
Terminal Rates (c)	21/37(57%)	17/33 (52%)	6/19 (32%)	7/19 (37%)
Life Table Tests (d)		P=0.085N	P=0.076N	P=0.146N
Incidental Tumor Tests (d)		P=0.052N	P=0.029N	P=0.085N
Cochran-Armitage Trend Test (d)		P=0.011N		
Fisher Exact Test			P=0.005N	P=0.025N
Adrenal: Cortical Adenoma				
Overall Rates (a)	1/49 (2%)	2/48 (4%)	1/44 (2%)	3/40 (7%)
Adjusted Rates (b)	2.7%	5.7%	5.0%	15.8%
Terminal Rates (c)	1/37 (3%)	2/35 (6%)	1/20 (5%)	3/19 (16%)
Life Table Tests (d)		P=0.179	P=0.692N	P=0.235
Incidental Tumor Tests (d)		P=0.179	P=0.692N	P=0.235
Cochran-Armitage Trend Test (d)		P=0.329		
Fisher Exact Test			P=0.533N	P=0.413
Adrenal: Cortical Adenoma or Carcinoma				
Overall Rates (a)	1/49 (2%)	3/48 (6%)	1/44 (2%)	3/40 (7%)
Adjusted Rates (b)	2.7%	8.6%	5.0%	15.8%
Terminal Rates (c)	1/37 (3%)	3/35 (9%)	1/20 (5%)	3/19 (16%)
Life Table Tests (d)		P=0.314	P=0.519N	P=0.363
Incidental Tumor Tests (d)		P=0.314	P=0.519N	P=0.363
Cochran-Armitage Trend Test (d)		P=0.514		
Fisher Exact Test			P=0.342N	P=0.571

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg
Adrenal: Pheochromocytoma				
Overall Rates (a)	1/49 (2%)	3/48 (6%)	0/44 (0%)	2/40 (5%)
Adjusted Rates (b)	2.7%	7.9%	0.0%	10.5%
Terminal Rates (c)	1/37 (3%)	2/35 (6%)	0/20 (0%)	2/19 (11%)
Life Table Tests (d)		P=0.594	P=0.227N	P=0.599
Incidental Tumor Tests (d)		P=0.582N	P=0.139N	P=0.650
Cochran-Armitage Trend Test (d)		P=0.456N		
Fisher Exact Test			P=0.138N	P=0.587N
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant				
Overall Rates (a)	1/49 (2%)	3/48 (6%)	1/44 (2%)	2/40 (5%)
Adjusted Rates (b)	2.7%	7.9%	3.6%	10.5%
Terminal Rates (c)	1/37 (3%)	2/35 (6%)	0/20 (0%)	2/19 (11%)
Life Table Tests (d)		P=0.541	P=0.492N	P=0.599
Incidental Tumor Tests (d)		P=0.578N	P=0.267N	P=0.650
Cochran-Armitage Trend Test (d)		P=0.472N		
Fisher Exact Test			P=0.342N	P=0.587N
Mammary Gland: Adenoma, Papillary Adenoma, Fibroadenoma, or Adenocarcinoma				
Overall Rates (a)	3/49 (6%)	3/50 (6%)	1/50 (2%)	1/46 (2%)
Adjusted Rates (b)	8.1%	7.5%	4.2%	5.3%
Terminal Rates (c)	3/37 (8%)	1/35 (3%)	0/20 (0%)	1/19 (5%)
Life Table Tests (d)		P=0.428N	P=0.547N	P=0.555N
Incidental Tumor Tests (d)		P=0.466N	P=0.545N	P=0.658N
Cochran-Armitage Trend Test (d)		P=0.222N		
Fisher Exact Test			P=0.309N	P=0.341N
Uterus: Endometrial Stromal Polyp				
Overall Rates (a)	1/48 (2%)	4/49 (8%)	3/48 (6%)	2/40 (5%)
Adjusted Rates (b)	2.7%	10.7%	15.0%	10.5%
Terminal Rates (c)	1/37 (3%)	3/35 (9%)	3/20 (15%)	2/19 (11%)
Life Table Tests (d)		P=0.580N	P=0.505	P=0.641N
Incidental Tumor Tests (d)		P=0.546	P=0.434	P=0.668
Cochran-Armitage Trend Test (d)		P=0.348N		
Fisher Exact Test			P=0.512N	P=0.440N
Uterus: Endometrial Stromal Polyp or Sarcoma				
Overall Rates (a)	1/48 (2%)	4/49 (8%)	4/48 (8%)	3/40 (7%)
Adjusted Rates (b)	2.7%	10.7%	18.3%	13.8%
Terminal Rates (c)	1/37 (3%)	3/35 (9%)	3/20 (15%)	2/19 (11%)
Life Table Tests (d)		P=0.370	P=0.321	P=0.491
Incidental Tumor Tests (d)		P=0.428	P=0.369	P=0.594
Cochran-Armitage Trend Test (d)		P=0.535N		
Fisher Exact Test			P=0.631	P=0.613N

(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 vehicle 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 rates. A negative trend or lower incidence in a dosed group is indicated by (N).

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING	1			
ANIMALS NECROPSIED	49	50	50	46
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	49	50	45
INTEGUMENTARY SYSTEM				
*Subcutaneous tissue	(49)	(50)	(50)	(46)
Inflammation, acute suppurative		1 (2%)		
Inflammation, acute/chronic				1 (2%)
Inflammation, chronic	1 (2%)			
RESPIRATORY SYSTEM				
*Nasal cavity	(49)	(50)	(50)	(46)
Inflammation, suppurative	1 (2%)			1 (2%)
*Tracheal lumen	(49)	(50)	(50)	(46)
Hemorrhage		1 (2%)	2 (4%)	1 (2%)
#Trachea	(46)	(47)	(41)	(40)
Hemorrhage			1 (2%)	
#Peritracheal tissue	(46)	(47)	(41)	(40)
Inflammation, acute			1 (2%)	
#Lung/bronchus	(49)	(49)	(47)	(42)
Inflammation, acute focal	1 (2%)			
#Lung	(49)	(49)	(47)	(42)
Congestion, NOS	1 (2%)			2 (5%)
Edema, NOS	1 (2%)			
Hemorrhage	2 (4%)	6 (12%)	2 (4%)	1 (2%)
Inflammation, NOS		12 (24%)	7 (15%)	3 (7%)
Inflammation, focal		3 (6%)	8 (17%)	1 (2%)
Inflammation, multifocal		2 (4%)		
Pneumonia, lipid			1 (2%)	
Inflammation, acute				1 (2%)
Inflammation, acute focal			1 (2%)	
Abscess, NOS		1 (2%)		
Inflammation, chronic			1 (2%)	
Inflammation, chronic focal		1 (2%)	5 (11%)	1 (2%)
Inflammation, granulomatous			1 (2%)	2 (5%)
Inflammation granulomatous focal	1 (2%)	2 (4%)	2 (4%)	
Granuloma, foreign body			1 (2%)	
Parasitism	1 (2%)			
Foreign material, NOS		7 (14%)	3 (6%)	
Pigmentation, NOS		1 (2%)		2 (5%)
Hemosiderosis			1 (2%)	
Alveolar macrophages			1 (2%)	
#Lung/alveoli	(49)	(49)	(47)	(42)
Hemorrhage		1 (2%)		
HEMATOPOIETIC SYSTEM				
#Spleen	(48)	(49)	(46)	(42)
Hemosiderosis	3 (6%)	3 (6%)		1 (2%)
Depletion, lymphoid		1 (2%)		
Hematopoiesis	1 (2%)		2 (4%)	2 (5%)
#Splenic capsule	(48)	(49)	(46)	(42)
Hemorrhage	1 (2%)			
Fibrosis	1 (2%)			
#Lymph node	(43)	(47)	(36)	(28)
Necrosis, focal		1 (2%)		
Pigmentation, NOS				1 (4%)

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)				
#Mesenteric lymph node	(43)	(47)	(36)	(28)
Hemorrhage	1 (2%)			
Inflammation, NOS		1 (2%)		
#Liver	(49)	(49)	(46)	(39)
Hematopoiesis		1 (2%)	1 (2%)	1 (3%)
#Jejunum	(49)	(49)	(45)	(41)
Hyperplasia, lymphoid		1 (2%)		
#Thymus	(10)	(7)	(19)	(14)
Cyst, NOS	2 (20%)		5 (26%)	2 (14%)
Multiple cysts			4 (21%)	
Hemorrhage	1 (10%)			
CIRCULATORY SYSTEM				
#Heart	(49)	(48)	(49)	(42)
Mineralization	1 (2%)			
Inflammation, acute focal	1 (2%)			
Inflammation, chronic	1 (2%)		1 (2%)	
Inflammation, chronic focal			1 (2%)	
Fibrosis, focal	2 (4%)	1 (2%)		
Calcification, metastatic	1 (2%)			
DIGESTIVE SYSTEM				
#Liver	(49)	(49)	(46)	(39)
Traumatic abnormality				1 (3%)
Congestion, NOS		1 (2%)		
Hemorrhage	1 (2%)	1 (2%)		
Inflammation, focal			1 (2%)	
Necrosis, NOS			1 (2%)	
Necrosis, focal	3 (6%)			
Metamorphosis, fatty	1 (2%)	3 (6%)	4 (9%)	5 (13%)
Pigmentation, NOS			1 (2%)	
Hemosiderosis		1 (2%)		
Basophilic cyto change				1 (3%)
Clear cell change		1 (2%)	5 (11%)	3 (8%)
Cytologic alteration, NOS		1 (2%)		
Hepatocytomegaly		3 (6%)		6 (15%)
#Liver/centrilobular	(49)	(49)	(46)	(39)
Necrosis, NOS		1 (2%)		
#Bile duct	(49)	(49)	(46)	(39)
Inflammation, acute				1 (3%)
Inflammation, acute/chronic		1 (2%)		
Hyperplasia, NOS	2 (4%)			1 (3%)
Hyperplasia, focal	1 (2%)			
Hyperplasia, diffuse		1 (2%)		
#Pancreas	(48)	(48)	(46)	(42)
Cytoplasmic vacuolization		1 (2%)		
*Esophageal lumen	(49)	(50)	(50)	(46)
Hemorrhage	3 (6%)	2 (4%)	8 (16%)	8 (17%)
#Esophagus	(47)	(47)	(49)	(43)
Inflammation, acute		1 (2%)		
Inflammation, acute focal		1 (2%)		
Inflammation, granulomatous		1 (2%)		
Granuloma, foreign body			1 (2%)	
#Esophageal mucosa	(47)	(47)	(49)	(43)
Necrosis, NOS		1 (2%)		
#Stomach	(49)	(47)	(45)	(42)
Mineralization	1 (2%)			
Necrosis, focal	1 (2%)			
Calcification, metastatic		1 (2%)		
Hyperplasia, epithelial	1 (2%)			

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)				
#Forestomach	(49)	(47)	(45)	(42)
Hyperplasia, epithelial		3 (6%)	1 (2%)	
#Duodenum	(49)	(49)	(45)	(41)
Hemorrhage			1 (2%)	
#Ileum	(49)	(49)	(45)	(41)
Parasitism				1 (2%)
#Colon	(48)	(47)	(45)	(38)
Hemorrhage	1 (2%)			
Parasitism		1 (2%)	1 (2%)	
URINARY SYSTEM				
#Urinary bladder/cavity	(47)	(43)	(45)	(35)
Hemorrhage	1 (2%)	1 (2%)		
#Kidney	(49)	(48)	(47)	(43)
Mineralization	38 (78%)	38 (79%)	21 (45%)	16 (37%)
Hydronephrosis	3 (6%)	3 (6%)	4 (9%)	4 (9%)
Cyst, NOS			1 (2%)	
Hemorrhage	1 (2%)		1 (2%)	
Inflammation, acute/chronic			1 (2%)	
Pyelonephritis, acute/chronic	1 (2%)			
Inflammation, chronic			1 (2%)	
Nephropathy	46 (94%)	47 (98%)	42 (89%)	40 (93%)
Nephropathy, toxic			21 (45%)	19 (44%)
Nephrosis, hemoglobinuric		1 (2%)		
Infarct, acute			1 (2%)	
Calcification, NOS			1 (2%)	
Calcification, focal	5 (10%)	5 (10%)	14 (30%)	15 (35%)
Calcification, metastatic	1 (2%)			
Hemosiderosis		1 (2%)		
Cytomegaly			43 (91%)	42 (98%)
Hyperplasia, epithelial	2 (4%)		1 (2%)	1 (2%)
Angiectasis	6 (12%)	6 (13%)	1 (2%)	1 (2%)
#Renal papilla	(49)	(48)	(47)	(43)
Mineralization		1 (2%)		
#Kidney/tubule	(49)	(48)	(47)	(43)
Degeneration, NOS			1 (2%)	
#Kidney/pelvis	(49)	(48)	(47)	(43)
Hemorrhage		1 (2%)		
Hematoma, NOS			1 (2%)	
Inflammation, suppurative				1 (2%)
Inflammation, acute			1 (2%)	
Hyperplasia, epithelial	22 (45%)	22 (46%)	19 (40%)	11 (26%)
Angiectasis		1 (2%)		2 (5%)
#Urinary bladder	(47)	(43)	(45)	(35)
Hemorrhage		1 (2%)	1 (2%)	
Inflammation, NOS			1 (2%)	
Hyperplasia, epithelial			2 (4%)	
ENDOCRINE SYSTEM				
#Pituitary	(47)	(42)	(36)	(32)
Cyst, NOS	1 (2%)	1 (2%)	1 (3%)	1 (3%)
Pigmentation, NOS				1 (3%)
Hyperplasia, focal		2 (5%)		
Angiectasis		2 (5%)	1 (3%)	

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)				
#Adrenal	(49)	(48)	(44)	(40)
Necrosis, focal	1 (2%)	1 (2%)		
Lipoidosis				1 (3%)
Pigmentation, NOS	1 (2%)			
Angiectasis			1 (2%)	
#Adrenal cortex	(49)	(48)	(44)	(40)
Hemorrhage		1 (2%)		
Lipoidosis		1 (2%)		
Cytomegaly	1 (2%)	1 (2%)		1 (3%)
#Adrenal medulla	(49)	(48)	(44)	(40)
Hyperplasia, focal		3 (6%)	1 (2%)	
#Thyroid	(46)	(47)	(44)	(38)
Cyst, NOS				1 (3%)
Follicular cyst, NOS	1 (2%)			
Inflammation, chronic	1 (2%)			
Hyperplasia, C-cell		1 (2%)		
#Parathyroid	(31)	(35)	(25)	(27)
Hyperplasia, NOS		1 (3%)		
REPRODUCTIVE SYSTEM				
*Mammary gland	(49)	(50)	(50)	(46)
Lactation	1 (2%)	2 (4%)		
#Uterus	(48)	(49)	(48)	(40)
Hydrometra	1 (2%)		1 (2%)	2 (5%)
Hemorrhage			1 (2%)	
Hematometra	1 (2%)			
#Uterus/endometrium	(48)	(49)	(48)	(40)
Accessory structure				1 (3%)
Cyst, NOS		1 (2%)		
Hemorrhagic cyst		1 (2%)		
Hyperplasia, cystic	1 (2%)	6 (12%)		
Decidual alteration, NOS			1 (2%)	
#Ovary	(48)	(46)	(46)	(38)
Cyst, NOS		1 (2%)		
Follicular cyst, NOS	3 (6%)		2 (4%)	1 (3%)
NERVOUS SYSTEM				
#Brain/meninges	(49)	(48)	(49)	(42)
Pigmentation, NOS		1 (2%)		
*Central canal spinal cord	(49)	(50)	(50)	(46)
Retention fluid		1 (2%)		
#Brain	(49)	(48)	(49)	(42)
Hydrocephalus, internal	1 (2%)			
Hemorrhage	1 (2%)	1 (2%)		
Inflammation, acute focal	1 (2%)			
Inflammation, chronic		1 (2%)		
Malacia			1 (2%)	
*Spinal cord	(49)	(50)	(50)	(46)
Hemorrhage	1 (2%)			
SPECIAL SENSE ORGANS				
*Eye/cornea	(49)	(50)	(50)	(46)
Inflammation, acute suppurative	1 (2%)			

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE ACI RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM				
*Skeletal muscle	(49)	(50)	(50)	(46)
Abscess, chronic				1 (2%)
*Muscle of neck	(49)	(50)	(50)	(46)
Inflammation, chronic			1 (2%)	
BODY CAVITIES				
*Mediastinum	(49)	(50)	(50)	(46)
Inflammation, NOS		1 (2%)		
Abscess, chronic				1 (2%)
*Peritoneum	(49)	(50)	(50)	(46)
Inflammation, NOS				1 (2%)
*Pleura	(49)	(50)	(50)	(46)
Inflammation, acute focal				1 (2%)
ALL OTHER SYSTEMS				
Site unknown				
Inflammation, granulomatous		1		
SPECIAL MORPHOLOGY SUMMARY				
No lesion reported			2	1
Animal missing/no necropsy	1			
Auto/necropsy/histo perf			2	
Auto/necropsy/no histo		1		1
Autolysis/no necropsy				4

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX C

SUMMARY OF LESIONS IN MALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	49
INTEGUMENTARY SYSTEM				
*Skin	(50)	(50)	(50)	(49)
Squamous cell carcinoma	1 (2%)		1 (2%)	
Basal cell carcinoma	1 (2%)			
*Subcutaneous tissue	(50)	(50)	(50)	(49)
Sarcoma, NOS	1 (2%)		1 (2%)	2 (4%)
Sarcoma, NOS, unclear primary or metasta				1 (2%)
Fibroma	1 (2%)			1 (2%)
RESPIRATORY SYSTEM				
#Lung	(50)	(50)	(50)	(49)
Squamous cell carcinoma			1 (2%)	
Alveolar/bronchiolar adenoma	1 (2%)			
Sarcoma, NOS, metastatic		1 (2%)		
HEMATOPOIETIC SYSTEM				
*Multiple organs	(50)	(50)	(50)	(49)
Malignant lymphoma, NOS			1 (2%)	2 (4%)
Malignant lymphoma, histiocytic type	1 (2%)			
Leukemia, NOS	2 (4%)			
Monocytic leukemia		1 (2%)		
CIRCULATORY SYSTEM				
*Skeletal muscle	(50)	(50)	(50)	(49)
Hemangioma			1 (2%)	
#Heart	(50)	(50)	(50)	(49)
Carcinoma, NOS	1 (2%)			
Carcinoma, NOS, metastatic	1 (2%)			
DIGESTIVE SYSTEM				
#Salivary gland	(47)	(50)	(49)	(46)
Sarcoma, NOS, unclear primary or metast				1 (2%)
#Liver	(50)	(50)	(50)	(48)
Bile duct adenoma	1 (2%)			
Neoplastic nodule			1 (2%)	1 (2%)
#Stomach	(50)	(50)	(50)	(49)
Papilloma, NOS				1 (2%)
#Forestomach	(50)	(50)	(50)	(49)
Squamous cell papilloma		1 (2%)		
URINARY SYSTEM				
#Kidney	(50)	(50)	(50)	(49)
Squamous cell carcinoma			1 (2%)	
Tubular cell adenoma			1 (2%)	1 (2%)
Tubular cell adenocarcinoma			1 (2%)	
#Urinary bladder	(50)	(50)	(47)	(44)
Transitional cell papilloma	1 (2%)	1 (2%)		
Transitional cell carcinoma		1 (2%)		

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM				
#Pituitary	(46)	(44)	(41)	(41)
Carcinoma, NOS		3 (7%)		
Adenoma, NOS	15 (33%)	23 (52%)	6 (15%)	4 (10%)
Chromophobe adenoma	1 (2%)		1 (2%)	
#Adrenal	(49)	(50)	(49)	(47)
Cortical adenoma	6 (12%)	5 (10%)	3 (6%)	5 (11%)
Pheochromocytoma	15 (31%)	10 (20%)	5 (10%)	2 (4%)
Pheochromocytoma, malignant			1 (2%)	1 (2%)
#Adrenal medulla	(49)	(50)	(49)	(47)
Pheochromocytoma	1 (2%)			
Neurilemoma		1 (2%)		
#Thyroid	(49)	(46)	(44)	(45)
C-cell adenoma	3 (6%)	7 (15%)		
C-cell carcinoma		1 (2%)		
#Parathyroid	(40)	(26)	(32)	(24)
Adenoma, NOS			1 (3%)	
#Pancreatic islets	(49)	(50)	(49)	(48)
Islet cell adenoma	5 (10%)	5 (10%)		1 (2%)
REPRODUCTIVE SYSTEM				
*Mammary gland	(50)	(50)	(50)	(49)
Adenoma, NOS				1 (2%)
Fibroma			1 (2%)	
Fibroadenoma	1 (2%)	1 (2%)		
*Preputial gland	(50)	(50)	(50)	(49)
Carcinoma, NOS		1 (2%)		1 (2%)
Adenoma, NOS	1 (2%)			
#Testis	(50)	(50)	(50)	(49)
Interstitial cell tumor	36 (72%)	34 (68%)	30 (60%)	26 (53%)
NERVOUS SYSTEM				
#Brain	(50)	(50)	(50)	(49)
Granular cell tumor, NOS	1 (2%)	1 (2%)		1 (2%)
Granular cell tumor, malignant			1 (2%)	
Astrocytoma		1 (2%)		
Oligodendroglioma	1 (2%)			
*Spinal cord	(50)	(50)	(50)	(49)
Astrocytoma	1 (2%)			
SPECIAL SENSE ORGANS				
None				
MUSCULOSKELETAL SYSTEM				
None				

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
BODY CAVITIES				
*Mediastinum	(50)	(50)	(50)	(49)
Sarcoma, NOS, unclear primary or metast		1(2%)		
ALL OTHER SYSTEMS				
None				
ANIMAL DISPOSITION SUMMARY				
Animals initially in study	50	50	50	50
Natural death	16	10	17	17
Moribund sacrifice	9	13	8	6
Terminal sacrifice	24	21	13	15
Dosing accident	1	2	3	7
Accidentally killed, NOS		4	9	4
Animal missexed				1
TUMOR SUMMARY				
Total animals with primary tumors**	43	45	32	27
Total primary tumors	98	98	58	52
Total animals with benign tumors	40	43	32	27
Total benign tumors	88	88	49	42
Total animals with malignant tumors	8	8	7	5
Total malignant tumors	9	8	8	6
Total animals with secondary tumors##	1	1		
Total secondary tumors	1	1		
Total animals with tumors uncertain--benign or malignant	1	1	1	2
Total uncertain tumors	1	1	1	2
Total animals with tumors uncertain--primary or metastatic		1		1
Total uncertain tumors		1		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 C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: UNTREATED CONTROL

ANIMAL NUMBER	151	152	157	159	162	168	169	179	180	186	190	197	199	202	208	219	223	224	226	228	229	232	233	239	246
WEEKS ON STUDY	085	077	087	104	082	104	101	103	104	034	104	104	070	104	062	079	104	104	097	081	104	104	104	104	070
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma					X																				
Basal cell carcinoma	X																								
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Fibroma								X																	
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																							X		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Thymus	−	−	−	−	−	−	−	−	−	+	−	−	−	−	+	+	−	−	−	−	−	−	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS					X																				
Carcinoma, NOS, metastatic																									
DIGESTIVE SYSTEM																									
Salivary gland	+	+	−	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct adenoma																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Adenoma, NOS				X							X			X				X	X			X		X	
Chromophobe adenoma															X										
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma				X							X							X							
Pheochromocytoma						X			X					X			X					X		X	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma												X													
Parathyroid	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Islet cell adenoma							X				X											X			
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	N	+	+	+	+	+	N
Fibroadenoma				X																					
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor	X	X	X	X	X	X		X	X		X	X		X			X	X	X	X	X	X	X	X	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Adenoma, NOS			X																						
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, NOS																									
Oligodendroglioma																									
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma																									
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, histiocytic type																									
Leukemia, NOS																				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 C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE AUGUST RATS: UNTREATED CONTROL (Continued)

ANIMAL NUMBER	261	268	270	273	274	276	277	281	283	285	287	295	299	300	301	302	305	306	310	311	313	328	331	338	340	TOTAL:
WEEKS ON STUDY	036	104	104	099	033	066	104	104	104	104	104	067	104	103	104	093	104	065	077	092	104	074	066	104	083	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+		*50
Squamous cell carcinoma																										1
Basal cell carcinoma																										1
Subcutaneous tissue	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+		*50
Sarcoma, NOS														X												1
Fibroma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Alveolar/bronchiolar adenoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+		49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Spleen	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Thymus	+	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–		6
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Carcinoma, NOS																										1
Carcinoma, NOS, metastatic																					X					1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Bile duct adenoma															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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Small intestine	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Transitional cell papilloma																				X						1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+		46
Adenoma, NOS				X			X	X					X			X				X	X			X		15
Chromophobe adenoma																										1
Adrenal	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Cortical adenoma							X			X						X										6
Pheochromocytoma								X	X	X	X				X	X	X				X			X		16
Thyroid	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
C-cell adenoma								X							X											3
Parathyroid	+	–	+	–	+	+	+	+	+	–	+	–	+	+	+	+	+	+	–	+	+	+	–	–	+	40
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Islet cell adenoma							X				X															5
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	N	+	+	*50
Fibroadenoma																										1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Interstitial cell tumor		X	X	X		X		X	X	X	X		X	X	X		X			X	X	X		X	X	36
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
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
Adenoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Granular cell tumor, NOS														X												1
Oligodendroglioma																		X								1
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+		*50
Astrocytoma												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
Malignant lymphoma, histiocytic type						X																				1
Leukemia, NOS																										2

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: VEHICLE CONTROL

ANIMAL NUMBER	142	144	148	150	158	166	167	170	175	176	177	178	181	185	192	201	205	207	210	212	213	214	215	217	218
WEEKS ON STUDY	097	073	104	079	103	104	104	104	051	083	072	104	104	104	104	104	104	006	090	104	088	092	078	069	104
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS, metastatic																								X	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	
Thymus	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma							X																		
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma																									
Transitional cell carcinoma														X											
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+
Carcinoma, NOS																									
Adenoma, NOS	X		X	X	X	X	X				X	X	X		X	X	X			X		X			
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma							X						X												
Pheochromocytoma	X				X			X						X	X	X				X					
Neurilemoma																	X								
Thyroid	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma					X		X	X						X									X		X
C-cell carcinoma																									
Parathyroid	+	−	−	−	+	+	−	+	−	+	−	−	+	−	+	+	+	−	+	+	+	−	−	−	−
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma														X	X	X									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	N	N	+	+	+	N	+	+	+	+	+	+	+	+	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
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, NOS					X																				
Astrocytoma																						X			
BODY CAVITIES																									
Mediastinum	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
Sarcoma, NOS, unclear primary or metastatic																								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
Monocytic leukemia																					X				

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE AUGUST RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	222	225	234	237	243	244	247	248	249	254	260	278	279	288	289	292	296	304	308	318	333	334	335	336	337	TOTAL:
WEEKS ON STUDY	050	099	068	065	098	083	104	095	057	078	076	066	101	103	086	099	104	104	104	104	103	104	104	106	104	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS, metastatic																										1
Trachea	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Thymus	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Small intestine	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional cell papilloma																							X			1
Transitional cell carcinoma																										1
ENDOCRINE SYSTEM																										
Pituitary	+	+	−	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Carcinoma, NOS																	X		X						X	3
Adenoma, NOS	X				X			X					X	X	X			X		X			X			23
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma						X							X										X			5
Pheochromocytoma														X				X		X						10
Neurilemoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	46
C-cell adenoma					X																					7
C-cell carcinoma																						X				1
Parathyroid	−	+	−	−	+	+	+	+	−	−	+	−	+	+	+	−	+	−	+	+	+	−	−	+	−	26
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																X							X			5
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	+	+	N	+	N	+	N	N	+	+	N	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma														X												1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor		X			X		X			X	X			X		X	X	X	X	X	X	X		X	X	34
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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
Granular cell tumor, NOS																										1
Astrocytoma																										1
BODY CAVITIES																										
Mediastinum	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
Sarcoma, NOS, unclear prim or metastat																										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
Monocytic leukemia																										1

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: LOW DOSE

ANIMAL NUMBER	141	143	146	147	149	154	160	165	171	172	173	174	182	183	184	187	189	195	200	203	204	209	216	220	236
WEEKS ON STUDY	104	089	076	088	053	104	025	010	100	071	034	092	012	047	067	020	044	044	034	083	043	092	078	040	066
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																								X	
Subcutaneous tissue	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Trachea	+	+	−	+	+	+	−	−	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	−
Thymus	−	−	+	+	−	−	−	+	−	−	+	−	+	−	−	+	−	−	+	−	−	−	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Tubular cell adenoma												X													
Tubular cell adenocarcinoma																		X							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	−	+	+	A	+	+	−	−	+	+	+	+	+	−	−	−	+	+	+	+	+	+	+	+	−
Adenoma, NOS																				X				X	
Chromophobe adenoma										X															
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma		X				X								X				X							
Pheochromocytoma, malignant																					X				
Thyroid	+	+	−	+	+	+	−	−	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+
Parathyroid	+	+	−	+	+	+	−	−	+	+	+	−	−	+	+	−	+	+	−	+	+	−	−	+	+
Adenoma, NOS																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	N	N	+	N	N	+	+	N	+	N	+	N	N	+	+	N	+	+	+	N	+	+
Fibroma																						X			
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor	X	X	X			X			X			X		X	X		X	X		X	X		X	X	X
Prostate	+	+	+	A	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, malignant																									
MUSCULOSKELETAL SYSTEM																									
Muscle	N	+	N	+	N	N	+	+	N	N	N	N	+	N	N	+	N	N	N	N	N	N	N	N	N
Hemangioma		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																

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE AUGUST RATS: LOW DOSE (Continued)

ANIMAL NUMBER	241	252	257	258	262	266	267	271	272	275	282	284	290	291	297	298	309	312	317	320	322	324	325	326	330	TOTAL:
WEEKS ON STUDY	027	089	089	031	104	065	062	104	013	079	102	104	030	104	069	088	104	012	066	029	099	104	101	023	078	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell carcinoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS						X																				1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma		X																								1
Trachea	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+		42
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+		49
Spleen	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Lymph nodes	+	+	+	−	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+		43
Thymus	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−		9
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Neoplastic nodule																										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		*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+			48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+			48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Squamous cell carcinoma		X																								1
Tubular cell adenoma																										1
Tubular cell adenocarcinoma																										1
Urinary bladder	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+		47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		41
Adenoma, NOS																X						X	X		X	6
Chromophobe adenoma																										1
Adrenal	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma												X									X	X				3
Pheochromocytoma																	X									5
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	44
Parathyroid	+	+	+	+	−	−	−	+	−	+	+	+	+	+	−	+	+	−	−	+	−	+	+	−	+	32
Adenoma, NOS								X																		1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	N	N	+	N	N	+	N	N	N	+	N	+	N	+	+	N	N	N	N	+	+	N	N	*50
Fibroma																										1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor		X	X		X	X		X		X	X	X				X	X		X		X	X	X		X	30
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor, malignant					X																					1
MUSCULOSKELETAL SYSTEM																										
Muscle	+	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	+	N	+	N	N	N	+	N	*50
Hemangioma																										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																										1

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: HIGH DOSE

ANIMAL NUMBER	145	153	155	156	161	163	164	188	191	193	194	196	198	206	211	221	227	230	231	235	238	240	242	245	251
WEEKS ON STUDY	021	067	104	104	087	008	032	104	072	104	066	058	029	097	029	095	006	055	030	032	013	104	044	073	068
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Sarcoma, NOS, unclear primary or metastatic								X																	
Fibroma														X											
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	−	−	+	+	+	+	−	+	+	+	+	S	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	−	−	+	−	+	−	+	+	+	+	+	S	−	−	+	−	+	+	+	+
Thymus	+	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	S	−	+	−	+	−	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+
Sarcoma, NOS, unclear primary or metastatic								X																	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	S	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	S	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	S	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	S	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	S	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+
Papilloma, NOS																									X
Small intestine	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	S	+	+	−	+	+	+	−	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	−	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Urinary bladder	+	+	+	+	−	+	−	+	−	+	+	+	+	+	+	+	S	+	+	+	+	+	+	−	+
ENDOCRINE SYSTEM																									
Pituitary	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+
Adenoma, NOS								X																	
Adrenal	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	−
Cortical adenoma								X																	
Pheochromocytoma			X																						
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	−	−	+	+	+	+	−	+	+	+	+	S	+	+	+	+	+	+	+	+
Parathyroid	−	+	+	+	+	−	−	+	+	+	−	−	+	+	+	+	S	+	+	−	+	−	+	−	−
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	S	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	+	+	N	N	+	+	N	N	N	N	+	N	N	S	N	N	N	+	+	N	+	+
Adenoma, NOS																						X			
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+
Interstitial cell tumor		X	X	X	X			X		X	X			X		X						X	X	X	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	S	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+
Granular cell tumor, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	S	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS					X																				

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE AUGUST RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	253	255	256	259	263	264	265	269	280	286	293	294	303	307	314	315	316	319	321	323	327	329	332	339	341	TOTAL:
WEEKS ON STUDY	104	104	023	007	059	104	104	089	099	047	047	069	028	085	104	008	044	045	050	081	059	044	072	044	044	TISSUES / TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue																										*49
Sarcoma, NOS																										2
Sarcoma, NOS, unclear prim or metasta																										1
Fibroma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	−	−	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	42
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	−	+	−	+	+	+	+	−	−	−	−	+	+	−	+	−	+	−	+	+	−	+	+	33
Thymus	−	−	+	+	−	−	−	−	−	−	−	−	−	−	−	+	−	−	+	−	−	−	−	−	−	8
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	46
Sarcoma, NOS, unclear prim or metasta																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Neoplastic nodule														X												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	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma, NOS																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	44
Large intestine	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	−	+	+	+	+	−	+	+	44
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tubular cell adenoma																									X	1
Urinary bladder	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
ENDOCRINE SYSTEM																										
Pituitary	+	+	−	−	−	+	+	−	+	+	+	−	+	+	+	−	−	+	+	+	+	+	+	+	+	41
Adenoma, NOS	X					X																			X	4
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Cortical adenoma							X		X	X															X	5
Pheochromocytoma										X																2
Pheochromocytoma, malignant																	X									1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	45
Parathyroid	+	+	−	−	+	−	−	+	+	+	−	−	−	−	−	−	+	−	−	−	+	−	−	+	−	24
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma						X																				1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	+	+	N	+	N	N	N	+	N	+	N	N	N	N	N	+	N	N	+	+	N	*49
Adenoma, NOS																										1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor	X	X				X	X	X	X	X				X	X		X			X		X		X	X	26
Prostate	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	46
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	*49
Carcinoma, NOS	X																									1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granular cell tumor, 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	*49
Malignant lymphoma, NOS																	X									2

* Animals necropsied

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg
Subcutaneous Tissue: Sarcoma or Sarcoma, Unclear Primary or Metastatic				
Overall Rates (a)	1/50 (2%)	0/50 (0%)	1/50 (2%)	3/49 (6%)
Adjusted Rates (b)	3.8%	0.0%	2.9%	15.0%
Terminal Rates (c)	0/24 (0%)	0/21 (0%)	0/13 (0%)	1/16 (6%)
Life Table Tests (d)		P=0.033	P=0.440	P=0.064
Incidental Tumor Tests (d)		P=0.032	P=0.519	P=0.050
Cochran-Armitage Trend Test (d)		P=0.058		
Fisher Exact Test			P=0.500	P=0.117
Pituitary: Adenoma				
Overall Rates (a)	16/46 (35%)	23/44 (52%)	7/41 (17%)	4/41 (10%)
Adjusted Rates (b)	55.5%	70.3%	34.9%	26.7%
Terminal Rates (c)	11/23 (48%)	12/21 (57%)	2/11 (18%)	4/15 (27%)
Life Table Tests (d)		P=0.001N	P=0.069N	P=0.002N
Incidental Tumor Tests (d)		P<0.001N	P=0.010N	P<0.001N
Cochran-Armitage Trend Test (d)		P<0.001N		
Fisher Exact Test			P=0.001N	P<0.001N
Pituitary: Carcinoma				
Overall Rates (a)	0/46 (0%)	3/44 (7%)	0/41 (0%)	0/41 (0%)
Adjusted Rates (b)	0.0%	14.3%	0.0%	0.0%
Terminal Rates (c)	0/23 (0%)	3/21 (14%)	0/11 (0%)	0/15 (0%)
Life Table Tests (d)		P=0.074N	P=0.252N	P=0.183N
Incidental Tumor Tests (d)		P=0.074N	P=0.252N	P=0.183N
Cochran-Armitage Trend Test (d)		P=0.042N		
Fisher Exact Test			P=0.134N	P=0.134N
Pituitary: Adenoma or Carcinoma				
Overall Rates (a)	16/46 (35%)	26/44 (59%)	7/41 (17%)	4/41 (10%)
Adjusted Rates (b)	55.5%	80.2%	34.9%	26.7%
Terminal Rates (c)	11/23 (48%)	15/21 (71%)	2/11 (18%)	4/15 (27%)
Life Table Tests (d)		P<0.001N	P=0.027N	P<0.001N
Incidental Tumor Tests (d)		P<0.001N	P=0.002N	P<0.001N
Cochran-Armitage Trend Test (d)		P<0.001N		
Fisher Exact Test			P<0.001N	P<0.001N
Adrenal: Cortical Adenoma				
Overall Rates (a)	6/49 (14%)	5/50 (10%)	3/49 (6%)	5/47 (11%)
Adjusted Rates (b)	23.5%	20.0%	20.4%	29.4%
Terminal Rates (c)	5/24 (21%)	3/21 (14%)	2/13 (15%)	4/16 (25%)
Life Table Tests (d)		P=0.356	P=0.627N	P=0.414
Incidental Tumor Tests (d)		P=0.271	P=0.633N	P=0.333
Cochran-Armitage Trend Test (d)		P=0.533		
Fisher Exact Test			P=0.369N	P=0.590
Adrenal: Pheochromocytoma				
Overall Rates (a)	16/49 (33%)	10/50 (20%)	5/49 (10%)	2/47 (4%)
Adjusted Rates (b)	63.7%	41.0%	33.9%	12.5%
Terminal Rates (c)	15/24 (63%)	7/21 (33%)	4/13 (31%)	2/16 (13%)
Life Table Tests (d)		P=0.039N	P=0.455N	P=0.049N
Incidental Tumor Tests (d)		P=0.053N	P=0.460N	P=0.073N
Cochran-Armitage Trend Test (d)		P=0.012N		
Fisher Exact Test			P=0.140N	P=0.018N
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant				
Overall Rates (a)	16/49 (33%)	10/50 (20%)	6/49 (12%)	3/47 (6%)
Adjusted Rates (b)	63.7%	41.0%	41.3%	18.8%
Terminal Rates (c)	15/24 (63%)	7/21 (33%)	5/13 (38%)	3/16 (19%)
Life Table Tests (d)		P=0.090N	P=0.602N	P=0.104N
Incidental Tumor Tests (d)		P=0.119N	P=0.610N	P=0.150N
Cochran-Armitage Trend Test (d)		P=0.033N		
Fisher Exact Test			P=0.220N	P=0.046N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg
Thyroid: C-Cell Adenoma				
Overall Rates (a)	3/49 (6%)	7/46 (15%)	0/44 (0%)	0/45 (0%)
Adjusted Rates (b)	13.0%	27.1%	0.0%	0.0%
Terminal Rates (c)	3/23 (13%)	4/21 (19%)	0/13 (0%)	0/16 (0%)
Life Table Tests (d)		P=0.005N	P=0.041N	P=0.030N
Incidental Tumor Tests (d)		P=0.005N	P=0.035N	P=0.030N
Cochran-Armitage Trend Test (d)		P=0.001N		
Fisher Exact Test			P=0.007N	P=0.007N
Thyroid: C-Cell Adenoma or Carcinoma				
Overall Rates (a)	3/49 (6%)	8/46 (17%)	0/44 (0%)	0/45 (0%)
Adjusted Rates (b)	13.0%	31.4%	0.0%	0.0%
Terminal Rates (c)	3/23 (13%)	5/21 (24%)	0/13 (0%)	0/16 (0%)
Life Table Tests (d)		P=0.003N	P=0.027N	P=0.018N
Incidental Tumor Tests (d)		P=0.003N	P=0.023N	P=0.018N
Cochran-Armitage Trend Test (d)		P<0.001N		
Fisher Exact Test			P=0.003N	P=0.003N
Pancreatic Islets: Islet Cell Adenoma				
Overall Rates (a)	5/49 (10%)	5/50 (10%)	0/49 (0%)	1/48 (2%)
Adjusted Rates (b)	19.8%	22.0%	0.0%	6.3%
Terminal Rates (c)	4/24 (17%)	4/21 (19%)	0/13 (0%)	1/16 (6%)
Life Table Tests (d)		P=0.079N	P=0.088N	P=0.181N
Incidental Tumor Tests (d)		P=0.094N	P=0.098N	P=0.210N
Cochran-Armitage Trend Test (d)		P=0.040N		
Fisher Exact Test			P=0.030N	P=0.112N
Testis: Interstitial Cell Tumor				
Overall Rates (a)	36/50 (72%)	34/50 (68%)	30/50 (60%)	26/49 (53%)
Adjusted Rates (b)	97.2%	97.1%	96.7%	100.0%
Terminal Rates (c)	23/24 (96%)	20/21 (95%)	12/13 (92%)	16/16 (100%)
Life Table Tests (d)		P=0.279	P=0.049	P=0.385
Incidental Tumor Tests (d)		P=0.129	P=0.055	P=0.179
Cochran-Armitage Trend Test (d)		P=0.078N		
Fisher Exact Test			P=0.267N	P=0.094N

(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 vehicle 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 rates. A negative trend or lower incidence in a dosed group is indicated by (N).

TABLE C4. SUMMARY OF THE INCIDENCE NONNEOPLASTIC LESIONS OF MALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	49
INTEGUMENTARY SYSTEM				
*Subcutaneous tissue	(50)	(50)	(50)	(49)
Hemorrhage	1 (2%)			
Abscess, chronic			1 (2%)	1 (2%)
RESPIRATORY SYSTEM				
*Tracheal lumen	(50)	(50)	(50)	(49)
Hemorrhage		1 (2%)	1 (2%)	
#Trachea	(49)	(48)	(42)	(42)
Inflammation, acute	1 (2%)			
Foreign material, NOS	2 (4%)	1 (2%)	2 (5%)	3 (7%)
#Tracheal submucosa	(49)	(48)	(42)	(42)
Hemorrhage				1 (2%)
#Lung	(50)	(50)	(50)	(49)
Aspiration, foreign body			1 (2%)	
Emphysema, alveolar				2 (4%)
Congestion, NOS			3 (6%)	8 (16%)
Edema, NOS			1 (2%)	4 (8%)
Hemorrhage	2 (4%)	4 (8%)	13 (26%)	12 (24%)
Inflammation, NOS	2 (4%)	1 (2%)	2 (4%)	
Inflammation, focal	4 (8%)	7 (14%)	1 (2%)	2 (4%)
Inflammation, multifocal	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Inflammation, interstitial	1 (2%)			
Pneumonia, aspiration		1 (2%)		
Bronchopneumonia, acute	3 (6%)		1 (2%)	1 (2%)
Inflammation, acute	4 (8%)	1 (2%)	2 (4%)	5 (10%)
Inflammation, acute/chronic			1 (2%)	
Inflammation, chronic	1 (2%)	3 (6%)		1 (2%)
Pneumonia, interstitial chronic				1 (2%)
Inflammation, chronic focal	1 (2%)	4 (8%)	4 (8%)	2 (4%)
Inflammation, granulomatous	5 (10%)	4 (8%)	2 (4%)	3 (6%)
Inflammation, granulomatous focal	6 (12%)	19 (38%)	16 (32%)	12 (24%)
Foreign material, NOS	2 (4%)	3 (6%)	10 (20%)	8 (16%)
Alveolar macrophages				1 (2%)
#Lung/alveoli	(50)	(50)	(50)	(49)
Hemorrhage	1 (2%)		1 (2%)	
HEMATOPOIETIC SYSTEM				
#Bone marrow	(50)	(50)	(49)	(49)
Hyperplasia, granulocytic				1 (2%)
#Spleen	(49)	(50)	(48)	(49)
Congestion, NOS			2 (4%)	2 (4%)
Hemorrhage			1 (2%)	
Hyperplasia, lymphoid		1 (2%)		
Hematopoiesis	6 (12%)	5 (10%)	2 (4%)	8 (16%)
#Lymph node	(48)	(45)	(43)	(33)
Congestion, NOS			2 (5%)	
#Pancreatic lymph node	(48)	(45)	(43)	(33)
Hemorrhage			1 (2%)	
#Mesenteric lymph node	(48)	(45)	(43)	(33)
Congestion, NOS				2 (6%)
Hemorrhage	1 (2%)		2 (5%)	2 (6%)
#Liver	(50)	(50)	(50)	(48)
Hematopoiesis	1 (2%)			

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)				
#Thymus	(6)	(1)	(9)	(8)
Hemorrhage			2 (22%)	1 (13%)
Karyorrhexis			1 (11%)	
CIRCULATORY SYSTEM				
#Heart	(50)	(50)	(50)	(49)
Mineralization				1 (2%)
Hemorrhage				1 (2%)
Inflammation, focal	1 (2%)			
Inflammation, chronic	1 (2%)	1 (2%)		
Inflammation, chronic focal	1 (2%)	1 (2%)		
Fibrosis, focal	1 (2%)			
Degeneration, NOS		1 (2%)		
#Myocardium	(50)	(50)	(50)	(49)
Degeneration, NOS	1 (2%)			
#Endocardium	(50)	(50)	(50)	(49)
Hyperplasia, focal	1 (2%)			
*Pulmonary artery	(50)	(50)	(50)	(49)
Calcification, focal		1 (2%)	1 (2%)	1 (2%)
DIGESTIVE SYSTEM				
#Salivary gland	(47)	(50)	(49)	(46)
Inflammation, chronic focal				1 (2%)
Atrophy, focal		2 (4%)	1 (2%)	
#Liver	(50)	(50)	(50)	(48)
Congestion, NOS	1 (2%)			1 (2%)
Congestion, passive				1 (2%)
Congestion, acute passive				1 (2%)
Hemorrhage	1 (2%)			
Inflammation, NOS		1 (2%)		
Inflammation, focal				2 (4%)
Inflammation, acute	1 (2%)			
Inflammation, chronic				1 (2%)
Inflammation, granulomatous focal				1 (2%)
Fibrosis, focal				1 (2%)
Necrosis, focal	3 (6%)	4 (8%)	2 (4%)	5 (10%)
Necrosis, diffuse		1 (2%)		1 (2%)
Necrosis, hemorrhagic	1 (2%)			
Necrosis, central	3 (6%)	2 (4%)	2 (4%)	1 (2%)
Necrosis, peripheral		1 (2%)		
Metamorphosis, fatty	9 (18%)	4 (8%)	1 (2%)	2 (4%)
Lipoidosis		2 (4%)		
Cytoplasmic change, NOS		4 (8%)		
Basophilic cyto change				1 (2%)
Focal cellular change	2 (4%)	2 (4%)	1 (2%)	
Eosinophilic cyto change				1 (2%)
Clear cell change	6 (12%)			
Cytologic alteration, NOS	1 (2%)		1 (2%)	
Hepatocytomegaly	2 (4%)			
#Liver/centrilobular	(50)	(50)	(50)	(48)
Necrosis, NOS		1 (2%)		
Necrosis, hemorrhagic	1 (2%)			
Metamorphosis, fatty			1 (2%)	
#Liver/hepatocytes	(50)	(50)	(50)	(48)
Necrosis, NOS	1 (2%)			

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)				
#Bile duct	(50)	(50)	(50)	(48)
Inflammation, chronic	1 (2%)	4 (8%)	1 (2%)	
Inflammation, chronic focal	1 (2%)			
Fibrosis		1 (2%)		
Sclerosis			1 (2%)	
Hyperplasia, NOS	5 (10%)	6 (12%)	1 (2%)	
Hyperplasia, focal		1 (2%)		
#Pancreas	(49)	(50)	(49)	(48)
Hemorrhage	1 (2%)	1 (2%)	1 (2%)	
Inflammation, focal				1 (2%)
Inflammation, acute focal		1 (2%)		
Atrophy, NOS	1 (2%)			
Atrophy, focal	2 (4%)	1 (2%)	2 (4%)	4 (8%)
#Pancreatic acinus	(49)	(50)	(49)	(48)
Atrophy, NOS	20 (41%)	2 (4%)	2 (4%)	
Atrophy, focal	12 (24%)	29 (58%)	17 (35%)	13 (27%)
Atrophy, diffuse	1 (2%)	3 (6%)	2 (4%)	
*Esophageal lumen	(50)	(50)	(50)	(49)
Hemorrhage	1 (2%)	2 (4%)	2 (4%)	2 (4%)
#Esophagus	(50)	(48)	(48)	(47)
Dilatation, NOS		2 (4%)		
Inflammation, interstitial	1 (2%)			
Inflammation, acute		1 (2%)		
Inflammation, granulomatous		1 (2%)		
#Stomach	(50)	(50)	(50)	(49)
Edema, NOS				1 (2%)
Inflammation, acute/chronic			1 (2%)	
#Gastric mucosa	(50)	(50)	(50)	(49)
Erosion		1 (2%)		
Hyperkeratosis				1 (2%)
#Gastric submucosa	(50)	(50)	(50)	(49)
Inflammation, focal		1 (2%)		
Inflammation, chronic	1 (2%)	1 (2%)		
Inflammation, granulomatous	2 (4%)			
#Forestomach	(50)	(50)	(50)	(49)
Ulcer, NOS		1 (2%)		
Inflammation, acute/chronic		1 (2%)		
Degeneration, NOS		1 (2%)		
Hyperplasia, epithelial	5 (10%)	1 (2%)		
Hyperkeratosis	2 (4%)			1 (2%)
#Colon	(49)	(50)	(50)	(44)
Hemorrhage			1 (2%)	
Parasitism	2 (4%)	1 (2%)		1 (2%)
*Rectum	(50)	(50)	(50)	(49)
Ulcer, acute			1 (2%)	
URINARY SYSTEM				
#Kidney	(50)	(50)	(50)	(49)
Mineralization	1 (2%)			
Cast, NOS		1 (2%)	2 (4%)	
Hydronephrosis	1 (2%)	1 (2%)		
Cyst, NOS	2 (4%)	3 (6%)		1 (2%)
Inflammation, chronic focal	2 (4%)	1 (2%)		
Nephropathy	43 (86%)	47 (94%)	32 (64%)	36 (73%)
Nephropathy, toxic			10 (20%)	31 (63%)
Infarct, healed			1 (2%)	
Pigmentation, NOS	1 (2%)			
Cytomegaly			46 (92%)	46 (94%)
Hyperplasia, tubular cell				1 (2%)

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM (Continued)				
#Kidney/tubule	(50)	(50)	(50)	(49)
Dilatation, NOS		1 (2%)		1 (2%)
Degeneration, NOS	1 (2%)	1 (2%)		1 (2%)
Atypia, NOS			1 (2%)	1 (2%)
#Kidney/pelvis	(50)	(50)	(50)	(49)
Hyperplasia, epithelial	3 (6%)	1 (2%)		
#Urinary bladder	(50)	(50)	(47)	(44)
Hemorrhage			1 (2%)	1 (2%)
#Urinary bladder/mucosa	(50)	(50)	(47)	(44)
Hyperplasia, papillary	1 (2%)			
ENDOCRINE SYSTEM				
#Pituitary	(46)	(44)	(41)	(41)
Cyst, NOS	3 (7%)	1 (2%)		
Hemorrhage				1 (2%)
Hyperplasia, NOS	1 (2%)			
Hyperplasia, focal	2 (4%)	2 (5%)	4 (10%)	1 (2%)
Angiectasis	2 (4%)		1 (2%)	
#Adrenal	(49)	(50)	(49)	(47)
Congestion, NOS	1 (2%)			
Inflammation, focal			1 (2%)	
Inflammation, chronic focal			1 (2%)	
Necrosis, cortical				1 (2%)
Lipoidosis		1 (2%)		
#Adrenal cortex	(49)	(50)	(49)	(47)
Lipoidosis	2 (4%)	1 (2%)		
Focal cellular change		1 (2%)		
Hyperplasia, NOS		1 (2%)		
Hyperplasia, focal		4 (8%)		
#Adrenal medulla	(49)	(50)	(49)	(47)
Cytomegaly	1 (2%)			
Hyperplasia, NOS	1 (2%)	1 (2%)	1 (2%)	
Hyperplasia, focal	3 (6%)	1 (2%)	2 (4%)	1 (2%)
#Thyroid	(49)	(46)	(44)	(45)
Follicular cyst, NOS			1 (2%)	
Inflammation, granulomatous focal				1 (2%)
Hyperplasia, C-cell	1 (2%)	3 (7%)		
#Pancreatic islets	(49)	(50)	(49)	(48)
Hyperplasia, NOS		1 (2%)		
Hyperplasia, focal			1 (2%)	
REPRODUCTIVE SYSTEM				
*Mammary gland	(50)	(50)	(50)	(49)
Pigmentation, NOS				1 (2%)
Hyperplasia, NOS	1 (2%)		1 (2%)	
Lactation	2 (4%)	3 (6%)	1 (2%)	1 (2%)
#Prostate	(50)	(50)	(48)	(46)
Edema, NOS				1 (2%)
Hemorrhage			1 (2%)	1 (2%)
Inflammation, NOS			1 (2%)	
Inflammation, focal		2 (4%)		
Inflammation, acute	1 (2%)			1 (2%)
Inflammation, acute focal			1 (2%)	
Inflammation, acute/chronic		1 (2%)		
Inflammation, chronic			1 (2%)	1 (2%)
Inflammation, chronic focal	1 (2%)	2 (4%)	1 (2%)	
Fibrosis, focal				1 (2%)
Hyperplasia, epithelial		1 (2%)		

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)				
#Prostatic duct	(50)	(50)	(48)	(46)
Polyp, NOS	1 (2%)			
*Seminal vesicle	(50)	(50)	(50)	(49)
Hemorrhage			1 (2%)	
Inflammation, NOS			1 (2%)	
#Testis	(50)	(50)	(50)	(49)
Edema, interstitial	1 (2%)			
Hemorrhage			1 (2%)	1 (2%)
Fibrosis, diffuse		1 (2%)		
Degeneration, NOS			1 (2%)	2 (4%)
Syncytial alteration				1 (2%)
Atrophy, NOS	5 (10%)	11 (22%)	5 (10%)	5 (10%)
Atrophy, diffuse	1 (2%)	1 (2%)		
Hyperplasia, interstitial cell	7 (14%)	9 (18%)	6 (12%)	10 (20%)
#Testis/tubule	(50)	(50)	(50)	(49)
Degeneration, NOS	1 (2%)			
Atrophy, focal	1 (2%)			1 (2%)
NERVOUS SYSTEM				
#Brain/meninges	(50)	(50)	(50)	(49)
Fibrosis	1 (2%)			
#Brain	(50)	(50)	(50)	(49)
Hydrocephalus, internal	1 (2%)	2 (4%)		
Cyst, NOS		1 (2%)		
Hemorrhage	1 (2%)			2 (4%)
SPECIAL SENSE ORGANS				
*Harderian gland	(50)	(50)	(50)	(49)
Inflammation, focal				1 (2%)
Inflammation, chronic			1 (2%)	
Inflammation, chronic focal			2 (4%)	
*Middle ear	(50)	(50)	(50)	(49)
Inflammation, acute suppurative			1 (2%)	
MUSCULOSKELETAL SYSTEM				
*Muscle of neck	(50)	(50)	(50)	(49)
Inflammation, granulomatous			1 (2%)	
BODY CAVITIES				
*Mediastinum	(50)	(50)	(50)	(49)
Inflammation, acute suppurative			1 (2%)	
ALL OTHER SYSTEMS				
*Multiple organs	(50)	(50)	(50)	(49)
Hemorrhage		1 (2%)		
Inflammation, hemorrhagic				1 (2%)
Adipose tissue				
Inflammation, NOS			1	

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
SPECIAL MORPHOLOGY SUMMARY				
Animal missexed/no necropsy				1
Auto/necropsy/histo perf			1	

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microsopically.
# Number of animals examined microscopically at this site

APPENDIX D

SUMMARY OF LESIONS IN FEMALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*Skin	(50)	(50)	(50)	(50)
Squamous cell carcinoma	1 (2%)			
Malignant melanoma			1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)	1 (2%)		
RESPIRATORY SYSTEM				
#Lung	(50)	(50)	(50)	(50)
Undifferentiated carcinoma, metastatic		1 (2%)		
Squamous cell carcinoma, metastatic	1 (2%)			
Alveolar/bronchiolar adenoma			1 (2%)	
Sarcoma, NOS, metastatic	1 (2%)			
HEMATOPOIETIC SYSTEM				
*Multiple organs	(50)	(50)	(50)	(50)
Malignant lymphoma, NOS			2 (4%)	
Leukemia, NOS		1 (2%)		1 (2%)
Monocytic leukemia				2 (4%)
#Liver	(50)	(48)	(48)	(50)
Leukemia, NOS				2 (4%)
CIRCULATORY SYSTEM				
None				
DIGESTIVE SYSTEM				
#Liver	(50)	(48)	(48)	(50)
Neoplastic nodule		2 (4%)		
URINARY SYSTEM				
#Kidney	(50)	(49)	(48)	(50)
Tubular cell adenoma		1 (2%)	2 (4%)	
Tubular cell adenocarcinoma			2 (4%)	
Sarcoma, NOS, metastatic	1 (2%)			
ENDOCRINE SYSTEM				
#Pituitary	(49)	(49)	(47)	(43)
Adenoma, NOS	42 (86%)	32 (65%)	26 (55%)	18 (42%)
Chromophobe adenoma		3 (6%)		
Meningioma				1 (2%)
#Adrenal	(50)	(48)	(48)	(50)
Cortical adenoma	4 (8%)	6 (13%)	6 (13%)	5 (10%)
Cortical carcinoma		1 (2%)		
Pheochromocytoma	6 (12%)	9 (19%)	2 (4%)	
#Thyroid	(50)	(49)	(49)	(50)
Follicular cell adenoma	1 (2%)		2 (4%)	
C-cell adenoma			3 (6%)	1 (2%)
C-cell carcinoma			1 (2%)	

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)				
#Pancreatic islets	(50)	(49)	(48)	(48)
Islet cell adenoma	1 (2%)		1 (2%)	1 (2%)
Islet cell carcinoma			1 (2%)	
REPRODUCTIVE SYSTEM				
*Mammary gland	(50)	(50)	(50)	(50)
Undifferentiated carcinoma		1 (2%)		
Adenoma, NOS	3 (6%)	4 (8%)	4 (8%)	
Adenocarcinoma, NOS		1 (2%)		1 (2%)
Fibroma	1 (2%)	2 (4%)		
Fibroadenoma	13 (26%)	10 (20%)	8 (16%)	4 (8%)
*Clitoral gland	(50)	(50)	(50)	(50)
Carcinoma, NOS				1 (2%)
#Uterus	(50)	(49)	(48)	(49)
Sarcoma, NOS	2 (4%)	1 (2%)		
Leiomyosarcoma			1 (2%)	
Endometrial stromal polyp	1 (2%)	3 (6%)		
Carcinosarcoma	1 (2%)			
#Ovary	(49)	(47)	(47)	(46)
Luteoma			1 (2%)	
NERVOUS SYSTEM				
*Peripheral nerve	(50)	(50)	(50)	(50)
Neurofibrosarcoma			1 (2%)	
#Brain	(50)	(49)	(50)	(50)
Granular cell tumor, NOS	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Granular cell tumor, malignant	1 (2%)		2 (4%)	
Ependymoma				1 (2%)
Astrocytoma			1 (2%)	
SPECIAL SENSE ORGANS				
None				
MUSCULOSKELETAL SYSTEM				
None				
BODY CAVITIES				
None				
ALL OTHER SYSTEMS				
*Multiple organs	(50)	(50)	(50)	(50)
Adenoma, NOS	1 (2%)			
Thigh				
Sarcoma, NOS	1			

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY				
Animals initially in study	50	50	50	50
Natural death	4	4	5	6
Moribund sacrifice	20	22	13	7
Terminal sacrifice	26	23	26	24
Dosing accident		1	3	6
Accidentally killed, nda			1	
Accidentally killed, NOS			2	7
TUMOR SUMMARY				
Total animals with primary tumors**	45	43	35	29
Total primary tumors	81	79	69	39
Total animals with benign tumors	44	40	32	24
Total benign tumors	73	70	56	29
Total animals with malignant tumors	5	6	11	9
Total malignant tumors	7	6	12	9
Total animals with secondary tumors##	2	1		
Total secondary tumors	3	1		
Total animals with tumors uncertain--benign or malignant	1	3	1	1
Total uncertain tumors	1	3	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

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: UNTREATED CONTROL

ANIMAL NUMBER	342	346	351	353	354	355	357	360	370	375	379	388	392	396	414	417	419	422	424	426	431	433	435	439	440
WEEKS ON STUDY	104	052	094	092	036	080	096	087	100	104	104	097	104	104	104	104	104	104	104	104	104	104	104	089	080
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic																									
Sarcoma, NOS, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS, metastatic																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	
ENDOCRINE SYSTEM																									
Pituitary	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS	X		X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma			X												X										
Pheochromocytoma			X						X						X										
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																			X						
Parathyroid	+	+	+	−	−	+	−	+	−	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	−
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS												X													
Fibroma				X																					
Fibroadenoma						X			X				X										X		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS														X											
Endometrial stromal polyp																					X				
Carcinosarcoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, NOS														X											
Granular cell tumor, malignant	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
Adenoma, NOS								X																	
Thigh, NOS																									
Sarcoma, NOS																									

+: 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 D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE AUGUST RATS: UNTREATED CONTROL (Continued)

ANIMAL NUMBER	44404	44406	45303	45909	46306	46505	47101	47303	47505	47808	47909	49404	49907	50101	50505	50606	50704	50804	51004	51304	52203	52707	53202	53304	54202	TOTAL:
WEEKS ON STUDY	10404	05303	05808	09202	10303	10303	10404	10404	10404	06605	10404	09707	09707	09905	10404	10404	10404	06807	10404	10404	10303	10404	09903	10404	06606	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell carcinoma												X														1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS												X														1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic												X														1
Sarcoma, NOS, metastatic			X																							1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymus	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	0
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS, metastatic			X																							1
Urinary bladder	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		42
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma								X											X							4
Pheochromocytoma	X						X												X							6
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																										1
Parathyroid	+	−	−	−	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																					X					1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS				X										X												3
Fibroma																										1
Fibroadenoma					X	X			X		X	X	X		X				X				X			13
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS												X														2
Endometrial stromal polyp																										1
Carcinosarcoma															X											1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor, NOS																										1
Granular cell tumor, malignant																										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
Adenoma, NOS																										1
Thigh, NOS																										
Sarcoma, NOS			X																							1

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: VEHICLE CONTROL

ANIMAL NUMBER	345	347	358	359	362	364	367	368	371	372	393	394	395	397	401	407	410	423	430	432	434	442	447	452	454
WEEKS ON STUDY	065	104	100	104	104	072	086	104	104	098	104	072	104	100	062	083	104	104	091	048	104	104	104	104	098
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Undifferentiated carcinoma, metastatic																				X					
Trachea	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	−	+	−	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
Thymus	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule				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
Pancreas	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	−	+	+	+	+	−	−	−	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																	X								
Urinary bladder	+	+	−	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS		X	X				X	X	X	X	X			X		X	X	X	X			X	X	X	X
Chromophobe adenoma						X						X								X					
Adrenal	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																						X			X
Cortical carcinoma																									
Pheochromocytoma								X	X		X						X								X
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	−	+	+	−
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+
Undifferentiated carcinoma																				X					
Adenoma, NOS				X								X													
Adenocarcinoma, NOS																									
Fibroma																									
Fibroadenoma													X	X											
Uterus	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Endometrial stromal polyp																	X	X							
Ovary	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, 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
Leukemia, NOS	X																								

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE AUGUST RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	45 56	45 58	46 62	46 64	46 68	47 72	48 84	48 85	48 86	48 87	49 96	49 99	50 09	51 11	51 12	51 15	51 17	51 18	51 19	52 21	52 24	52 26	52 29	53 31	53 33	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	07 6	09 9	10 4	10 4	05 2	10 4	10 4	10 3	10 1	10 4	10 4	08 0	10 1	10 3	08 6	08 9	10 4	10 4	09 1	10 4	05 9	09 5	09 2	09 6	10 4	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS	X																									1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Undiff. carcinoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Thymus	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	0
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Neoplastic nodule																							X			2
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	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tubular cell adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS		X	X	X		X		X	X	X	X	X		X			X		X	X		X	X		X	32
Chromophobe adenoma																										3
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cortical adenoma						X														X				X	X	6
Cortical carcinoma																		X								1
Pheochromocytoma				X										X				X					X			9
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid	−	−	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	42
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Undifferentiated carcinoma																										1
Adenoma, NOS									X														X			4
Adenocarcinoma, NOS												X														1
Fibroma																			X					X		2
Fibroadenoma						X		X	X	X				X	X					X		X				10
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, NOS													X													1
Endometrial stromal polyp			X																							3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granular cell tumor, 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
Leukemia, NOS																										1

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: LOW DOSE

ANIMAL NUMBER	34 8	36 6	37 3	37 4	37 6	38 2	38 4	38 5	38 6	38 7	38 9	39 0	40 4	40 5	40 8	40 9	41 3	41 6	42 1	42 7	42 8	43 7	43 8	44 1	44 5
WEEKS ON STUDY	072	044	104	070	104	104	104	104	104	104	054	017	104	104	104	086	102	104	104	012	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant melanoma																	X								
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																	X								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Lymph nodes	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	–	+	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	+	–	–	–	–	–
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Small intestine	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Tubular cell adenoma																									
Tubular cell adenocarcinoma																	X							X	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS			X			X	X	X		X			X	X		X	X	X	X				X	X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Cortical adenoma										X													X	X	
Pheochromocytoma													X												
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Follicular cell adenoma			X																						X
C-cell adenoma										X			X												
C-cell carcinoma								X																	
Parathyroid	–	–	–	+	–	+	–	–	–	+	–	–	+	+	–	+	+	–	+	+	–	+	–	–	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Islet cell adenoma						X																			
Islet cell carcinoma																						X			
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS										X												X	X		
Fibroadenoma						X			X							X	X				X				
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Leiomyosarcoma																X									
Ovary	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Luteoma																									
NERVOUS SYSTEM																									
Nerves	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
Neurofibrosarcoma																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, NOS															X										
Granular cell tumor, malignant									X										X						
Astrocytoma																									
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																									

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE AUGUST RATS: LOW DOSE (Continued)

ANIMAL NUMBER	44 48	44 49	45 51	45 55	45 57	46 60	46 61	47 70	47 74	47 76	48 82	48 83	48 89	49 00	49 91	49 93	50 03	51 14	52 20	52 23	52 25	53 30	53 36	53 38	54 41	TOTAL:
WEEKS ON STUDY	09 2	10 4	10 4	07 8	10 4	04 7	10 4	02 0	10 4	06 4	08 0	10 0	09 4	07 8	06 6	10 4	09 9	10 4	01 2	10 0	01 9	10 4	10 4	10 3	10 0	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Malignant melanoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Trachea	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	48
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	4
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	48
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	48
Tubular cell adenoma	X				X																					2
Tubular cell adenocarcinoma																										2
Urinary bladder	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS		X	X	X	X		X				X	X	X	X		X							X	X		26
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	48
Cortical adenoma			X																			X	X			6
Pheochromocytoma							X																			2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma																										2
C-cell adenoma																						X				3
C-cell carcinoma																										1
Parathyroid	+	–	–	–	–	–	+	–	+	–	+	+	+	–	–	–	+	+	–	–	–	+	+	+	+	23
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	48
Islet cell adenoma																										1
Islet cell carcinoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	*50
Adenoma, NOS												X														4
Fibroadenoma	X	X																						X		8
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	48
Leiomyosarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	47
Luteoma																									X	1
NERVOUS SYSTEM																										
Nerves	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
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor, NOS																										1
Granular cell tumor, malignant																										2
Astrocytoma													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
Malignant lymphoma, NOS																		X		X						2

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: HIGH DOSE

ANIMAL NUMBER	343	344	349	350	352	356	361	363	369	377	378	380	381	383	391	398	399	400	402	403	406	411	412	415	418
WEEKS ON STUDY	060	104	104	115	117	087	104	024	104	069	056	034	063	020	104	044	044	104	104	104	103	046	089	059	024
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	−	+	+	+	+	+	+	+	+
Thymus	−	−	−	+	−	−	−	+	−	−	−	+	−	−	−	−	+	−	−	−	−	−	−	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, NOS																									
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	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	−	+
Large intestine	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	−	+	+	−	−	+	−	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	−	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+
Adenoma, NOS		X	X			X												X	X	X	X				
Meningioma																					X				
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma							X		X							X									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																									
Parathyroid	−	+	+	−	−	+	−	−	+	−	−	−	−	−	+	+	+	+	+	+	+	−	+	+	−
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma			X																						
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	N	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Fibroadenoma			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																			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	−	+	−	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, NOS																									
Ependymoma				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
Leukemia, NOS																									
Monocytic leukemia																							X		

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE AUGUST RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	42 20	42 25	42 29	43 36	44 43	45 50	46 66	46 67	46 69	47 77	48 80	48 81	48 88	49 92	49 95	49 98	50 00	50 02	50 04	51 16	52 28	53 35	53 37	53 39	54 40	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	04 99	10 04	07 71	01 99	10 04	10 04	10 44	10 04	10 04	10 04	03 33	10 04	10 44	06 80	02 99	05 56	10 04	10 04	08 82	10 04	10 44	05 56	10 04	10 04	10 44	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	−	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	44
Thymus	+	−	−	+	−	−	−	−	−	−	+	−	−	−	+	+	−	−	−	−	−	−	−	−	−	10
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia, NOS					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	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	46
Large intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	44
ENDOCRINE SYSTEM																										
Pituitary	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	43
Adenoma, NOS		X					X	X				X	X				X	X		X	X		X		X	18
Meningioma																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma							X					X														5
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell adenoma										X																1
Parathyroid	+	−	−	−	+	+	+	+	+	+	+	+	+	+	−	−	−	+	−	−	+	−	+	−	+	28
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	*50
Adenocarcinoma, NOS																							X			1
Fibroadenoma		X											X			X										4
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																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor, NOS												X														1
Ependymoma																										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, NOS																	X									1
Monocytic leukemia																			X							2

* Animals necropsied

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg
Hematopoietic System: Leukemia				
Overall Rates (a)	0/50 (0%)	1/50 (2%)	0/50 (0%)	5/50 (10%)
Adjusted Rates (b)	0.0%	2.2%	0.0%	18.2%
Terminal Rates (c)	0/26 (0%)	0/23 (0%)	0/26 (0%)	3/25 (12%)
Life Table Tests (d)		P=0.027	P=0.523N	P=0.078
Incidental Tumor Tests (d)		P=0.020	P=0.469N	P=0.059
Cochran-Armitage Trend Test (d)		P=0.037		
Fisher Exact Test			P=0.500N	P=0.102
Kidney: Tubular Cell Adenoma or Adenocarcinoma				
Overall Rates (a)	0/50 (0%)	1/49 (2%)	4/48 (8%)	0/50 (0%)
Adjusted Rates (b)	0.0%	4.3%	13.6%	0.0%
Terminal Rates (c)	0/26 (0%)	1/23 (4%)	2/26 (8%)	0/25 (0%)
Life Table Tests (d)		P=0.390N	P=0.210	P=0.483N
Incidental Tumor Tests (d)		P=0.570N	P=0.123	P=0.483N
Cochran-Armitage Trend Test (d)		P=0.384N		
Fisher Exact Test			P=0.174	P=0.495N
Pituitary Gland: Chromophobe Adenoma				
Overall Rates (a)	0/49 (0%)	3/49 (6%)	0/47 (0%)	0/43 (0%)
Adjusted Rates (b)	0.0%	6.4%	0.0%	0.0%
Terminal Rates (c)	0/26 (0%)	0/23 (0%)	0/26 (0%)	0/25 (0%)
Life Table Tests (d)		P=0.062N	P=0.150N	P=0.197N
Incidental Tumor Tests (d)		P=0.015N	P=0.058N	P=0.053N
Cochran-Armitage Trend Test (d)		P=0.044N		
Fisher Exact Test			P=0.129N	P=0.147N
Pituitary Gland: Adenoma				
Overall Rates (a)	42/49 (86%)	35/49 (71%)	26/47 (55%)	18/43 (42%)
Adjusted Rates (b)	97.7%	84.9%	76.0%	66.6%
Terminal Rates (c)	25/26 (96%)	17/23 (74%)	18/26 (69%)	16/25 (64%)
Life Table Tests (d)		P=0.001N	P=0.053N	P=0.003N
Incidental Tumor Tests (d)		P=0.033N	P=0.173N	P=0.055N
Cochran-Armitage Trend Test (d)		P=0.003N		
Fisher Exact Test			P=0.077N	P=0.004N
Adrenal Gland: Cortical Adenoma				
Overall Rates (a)	4/50 (8%)	6/48 (13%)	6/48 (13%)	5/50 (10%)
Adjusted Rates (b)	14.0%	22.4%	23.1%	20.0%
Terminal Rates (c)	3/26 (12%)	4/23 (17%)	6/26 (23%)	5/25 (20%)
Life Table Tests (d)		P=0.401N	P=0.550N	P=0.480N
Incidental Tumor Tests (d)		P=0.520N	P=0.604N	P=0.599
Cochran-Armitage Trend Test (d)		P=0.409N		
Fisher Exact Test			P=0.621	P=0.471N
Adrenal Gland: Cortical Adenoma or Carcinoma				
Overall Rates (a)	4/50 (8%)	7/48 (15%)	6/48 (13%)	5/50 (10%)
Adjusted Rates (b)	14.0%	26.5%	23.1%	20.0%
Terminal Rates (c)	3/26 (12%)	5/23 (22%)	6/26 (23%)	5/25 (20%)
Life Table Tests (d)		P=0.281N	P=0.420N	P=0.353N
Incidental Tumor Tests (d)		P=0.384N	P=0.472N	P=0.534N
Cochran-Armitage Trend Test (d)		P=0.296N		
Fisher Exact Test			P=0.500N	P=0.351N
Adrenal Gland: Pheochromocytoma				
Overall Rates (a)	6/50 (12%)	9/48 (19%)	2/48 (4%)	0/50 (0%)
Adjusted Rates (b)	20.5%	33.2%	7.7%	0.0%
Terminal Rates (c)	4/26 (15%)	6/23 (26%)	2/26 (8%)	0/25 (0%)
Life Table Tests (d)		P<0.001N	P=0.019N	P=0.003N
Incidental Tumor Tests (d)		P=0.001N	P=0.034N	P=0.009N
Cochran-Armitage Trend Test (d)		P<0.001N		
Fisher Exact Test			P=0.025N	P=0.001N

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg
Thyroid: C-Cell Adenoma				
Overall Rates (a)	0/50 (0%)	0/49 (0%)	3/49 (6%)	1/50 (2%)
Adjusted Rates (b)	0.0%	0.0%	12.0%	4.0%
Terminal Rates (c)	0/26 (0%)	0/23 (0%)	3/25 (12%)	1/25 (4%)
Life Table Tests (d)		P=0.403	P=0.134	P=0.517
Incidental Tumor Tests (d)		P=0.403	P=0.134	P=0.517
Cochran-Armitage Trend Test (d)		P=0.385		
Fisher Exact Test			P=0.121	P=0.505
Thyroid: C-Cell Adenoma or Carcinoma				
Overall Rates (a)	0/50 (0%)	0/49 (0%)	4/49 (8%)	1/50 (2%)
Adjusted Rates (b)	0.0%	0.0%	16.0%	4.0%
Terminal Rates (c)	0/26 (0%)	0/23 (0%)	4/25 (16%)	1/25 (4%)
Life Table Tests (d)		P=0.418	P=0.071	P=0.517
Incidental Tumor Tests (d)		P=0.418	P=0.071	P=0.517
Cochran-Armitage Trend Test (d)		P=0.398		
Fisher Exact Test			P=0.059	P=0.505
Mammary Gland: Adenoma				
Overall Rates (a)	3/50 (6%)	4/50 (8%)	4/50 (8%)	0/50 (0%)
Adjusted Rates (b)	8.2%	12.5%	14.4%	0.0%
Terminal Rates (c)	0/26 (0%)	1/23 (4%)	3/26 (12%)	0/25 (0%)
Life Table Tests (d)		P=0.069N	P=0.612N	P=0.090N
Incidental Tumor Tests (d)		P=0.135N	P=0.562	P=0.132N
Cochran-Armitage Trend Test (d)		P=0.060N		
Fisher Exact Test			P=0.643	P=0.059N
Mammary Gland: Adenoma, Adenocarcinoma, or Carcinoma				
Overall Rates (a)	3/50 (6%)	6/50 (12%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	8.2%	16.3%	14.4%	4.0%
Terminal Rates (c)	0/26 (0%)	1/23 (4%)	3/26 (12%)	1/25 (4%)
Life Table Tests (d)		P=0.058N	P=0.367N	P=0.097N
Incidental Tumor Test (d)		P=0.079N	P=0.429N	P=0.075N
Cochran-Armitage Trend Test (d)		P=0.042N		
Fisher Exact Test			P=0.370N	P=0.056N
Mammary Gland: Fibroadenoma				
Overall Rates (a)	13/50 (26%)	10/50 (20%)	8/50 (16%)	4/50 (8%)
Adjusted Rates (b)	38.2%	33.1%	25.9%	14.3%
Terminal Rates (c)	6/26 (23%)	4/23 (17%)	4/26 (15%)	3/25 (12%)
Life Table Tests (d)		P=0.072N	P=0.353N	P=0.090N
Incidental Tumor Test (d)		P=0.356N	P=0.563	P=0.385N
Cochran-Armitage Trend Test (d)		P=0.060		
Fisher Exact Test			P=0.398N	P=0.074N
Mammary Gland: Fibroma or Fibroadenoma				
Overall Rates (a)	14/50 (28%)	12/50 (24%)	8/50 (16%)	4/50 (8%)
Adjusted Rates (b)	39.8%	36.9%	25.9%	14.3%
Terminal Rates (c)	6/26 (23%)	4/23 (17%)	4/26 (15%)	3/25 (12%)
Life Table Tests (d)		P=0.031N	P=0.210N	P=0.045N
Incidental Tumor Tests (d)		P=0.240N	P=0.512N	P=0.304N
Cochran-Armitage Trend Test (d)		P=0.020N		
Fisher Exact Test			P=0.227N	P=0.027N
Mammary Gland: All Tumors (e)				
Overall Rates (a)	17/50 (34%)	17/50 (34%)	12/50 (24%)	5/50 (10%)
Adjusted Rates (b)	44.9%	45.7%	38.1%	18.2%
Terminal Rates (c)	6/26 (23%)	5/23 (22%)	7/26 (27%)	4/25 (16%)
Life Table Tests (d)		P=0.008N	P=0.188N	P=0.013N
Incidental Tumor Tests (d)		P=0.061N	P=0.440N	P=0.058N
Cochran-Armitage Trend Test (d)		P=0.003N		
Fisher Exact Test			P=0.189N	P=0.004N

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg
Uterus: Endometrial Stromal Polyp				
Overall Rates (a)	1/50 (2%)	3/49 (6%)	0/48 (0%)	0/49 (0%)
Adjusted Rates (b)	3.8%	13.0%	0.0%	0.0%
Terminal Rates (c)	1/26 (4%)	3/23 (13%)	0/26 (0%)	0/25 (0%)
Life Table Tests (d)		P=0.030N	P=0.098N	P=0.105N
Incidental Tumor Tests (d)		P=0.030N	P=0.098N	P=0.105N
Cochran-Armitage Trend Test (d)		P=0.038N		
Fisher Exact Test			P=0.125N	P=0.121N
Brain: Granular Cell Tumor				
Overall Rates (a)	2/50 (4%)	1/49 (2%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	7.7%	4.5%	11.5%	4.0%
Terminal Rates (c)	2/26 (8%)	1/22 (5%)	3/26 (12%)	1/25 (4%)
Life Table Tests (d)		P=0.567N	P=0.365	P=0.734N
Incidental Tumor Tests (d)		P=0.567N	P=0.365	P=0.734N
Cochran-Armitage Trend Test (d)		P=0.603N		
Fisher Exact Test			P=0.316	P=0.747N

(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 vehicle 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 rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) Includes undifferentiated carcinoma, adenoma, adenocarcinoma, fibroma, and fibroadenoma

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*Skin	(50)	(50)	(50)	(50)
Ulcer, NOS	1 (2%)	1 (2%)		
Inflammation, chronic	1 (2%)	2 (4%)		
Ulcer, chronic		1 (2%)		
Inflammation, chronic diffuse		1 (2%)		
Inflammation, granulomatous focal	1 (2%)			
*Subcutaneous tissue	(50)	(50)	(50)	(50)
Hemorrhage				1 (2%)
Inflammation, necrotizing			1 (2%)	
Abscess, NOS			1 (2%)	
Inflammation, granulomatous				1 (2%)
Foreign material, NOS				2 (4%)
RESPIRATORY SYSTEM				
*Nasal cavity	(50)	(50)	(50)	(50)
Inflammation, acute suppurative			1 (2%)	
*Tracheal lumen	(50)	(50)	(50)	(50)
Hemorrhage			1 (2%)	4 (8%)
*Larynx	(50)	(50)	(50)	(50)
Inflammation, chronic		1 (2%)		
Foreign material, NOS		1 (2%)		
#Trachea	(50)	(48)	(47)	(47)
Inflammation, chronic		1 (2%)		
Foreign material, NOS			1 (2%)	4 (9%)
#Lung	(50)	(50)	(50)	(50)
Bronchiectasis		1 (2%)		1 (2%)
Atelectasis				1 (2%)
Congestion, NOS			2 (4%)	2 (4%)
Edema, NOS				1 (2%)
Hemorrhage	1 (2%)	2 (4%)	4 (8%)	3 (6%)
Inflammation, NOS			2 (4%)	1 (2%)
Inflammation, focal	1 (2%)	2 (4%)	3 (6%)	2 (4%)
Inflammation, multifocal		1 (2%)	4 (8%)	
Pneumonia, aspiration		1 (2%)		
Bronchopneumonia, acute		1 (2%)	2 (4%)	
Inflammation, acute	1 (2%)			1 (2%)
Inflammation, acute focal		1 (2%)		
Inflammation, chronic		1 (2%)		1 (2%)
Inflammation, chronic focal		3 (6%)	3 (6%)	3 (6%)
Inflammation, granulomatous	2 (4%)	1 (2%)	2 (4%)	3 (6%)
Inflammation, granulomatous focal	11 (22%)	12 (24%)	18 (36%)	17 (34%)
Foreign material, NOS	4 (8%)	4 (8%)	4 (8%)	10 (20%)
Hemosiderosis			1 (2%)	

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM				
#Bone marrow	(50)	(47)	(49)	(50)
Hyperplasia, granulocytic				1 (2%)
#Spleen	(50)	(49)	(48)	(49)
Congestion, NOS		1 (2%)	1 (2%)	2 (4%)
Hemosiderosis	3 (6%)	1 (2%)	2 (4%)	2 (4%)
Hyperplasia, lymphoid		1 (2%)		
Hematopoiesis	14 (28%)	16 (33%)	15 (31%)	8 (16%)
#Lymph node	(47)	(43)	(49)	(44)
Congestion, NOS	1 (2%)			
Abscess, NOS			1 (2%)	
#Mesenteric lymph node	(47)	(43)	(49)	(44)
Congestion, NOS	1 (2%)		1 (2%)	
Hemorrhage		1 (2%)		2 (5%)
#Liver	(50)	(48)	(48)	(50)
Hematopoiesis			1 (2%)	
#Thymus			(4)	(10)
Hemorrhage			1 (25%)	1 (10%)
CIRCULATORY SYSTEM				
*Multiple organs	(50)	(50)	(50)	(50)
Periarteritis			1 (2%)	
#Heart	(50)	(50)	(50)	(50)
Thrombosis, NOS				1 (2%)
Inflammation, chronic focal				1 (2%)
Inflammation, chronic diffuse				1 (2%)
*Pulmonary artery	(50)	(50)	(50)	(50)
Calcification, focal		1 (2%)		
*Sup. panc-duod. artery	(50)	(50)	(50)	(50)
Thrombosis, NOS			1 (2%)	
Degeneration, hyaline	1 (2%)			
#Pancreas	(50)	(49)	(48)	(48)
Periarteritis		1 (2%)		
DIGESTIVE SYSTEM				
#Salivary gland	(50)	(48)	(47)	(47)
Inflammation, chronic	1 (2%)			
Inflammation, granulomatous focal				1 (2%)
#Liver	(50)	(48)	(48)	(50)
Congestion, NOS				1 (2%)
Congestion, chronic passive		1 (2%)		
Hemorrhage	2 (4%)			
Inflammation, focal			1 (2%)	1 (2%)
Inflammation, acute focal	1 (2%)			1 (2%)
Inflammation, acute/chronic			1 (2%)	
Inflammation, chronic			1 (2%)	
Inflammation, chronic focal		2 (4%)		
Necrosis, NOS				1 (2%)
Necrosis, focal		3 (6%)	2 (4%)	2 (4%)
Necrosis, central	1 (2%)		1 (2%)	1 (2%)
Metamorphosis, fatty	1 (2%)	3 (6%)		
Lipoidosis	2 (4%)		2 (4%)	
Pigmentation, NOS			1 (2%)	
Mitotic alteration				1 (2%)
Focal cellular change	1 (2%)			1 (2%)
Clear cell change				1 (2%)
Hepatocytomegaly	2 (4%)	5 (10%)	3 (6%)	1 (2%)
Angiectasis			1 (2%)	
Regeneration, NOS			1 (2%)	1 (2%)
#Liver/midlobular	(50)	(48)	(48)	(50)
Lipoidosis			1 (2%)	

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)				
#Bile duct	(50)	(48)	(48)	(50)
Dilatation, NOS	1 (2%)			
Inflammation, chronic		1 (2%)		2 (4%)
Fibrosis	1 (2%)			
Sclerosis	1 (2%)			
Hyperplasia, NOS	1 (2%)		1 (2%)	5 (10%)
Hyperplasia, focal			1 (2%)	1 (2%)
#Pancreas	(50)	(49)	(48)	(48)
Inflammation, acute/chronic			2 (4%)	
Inflammation, chronic	1 (2%)			1 (2%)
Fibrosis, multifocal			1 (2%)	
Atrophy, focal	4 (8%)	2 (4%)	4 (8%)	4 (8%)
#Pancreatic duct	(50)	(49)	(48)	(48)
Inflammation, acute	1 (2%)			
#Pancreatic acinus	(50)	(49)	(48)	(48)
Atrophy, NOS		4 (8%)	2 (4%)	
Atrophy, focal	21 (42%)	27 (55%)	24 (50%)	25 (52%)
Atrophy, diffuse	7 (14%)	2 (4%)	2 (4%)	
*Esophageal lumen	(50)	(50)	(50)	(50)
Hemorrhage		2 (4%)		4 (8%)
#Esophagus	(50)	(49)	(49)	(49)
Penetrating wound		1 (2%)		
Inflammation, NOS				1 (2%)
Foreign material, NOS				1 (2%)
Hyperkeratosis			1 (2%)	
#Periesophageal tissue	(50)	(49)	(49)	(49)
Inflammation, NOS				1 (2%)
Inflammation, acute				1 (2%)
#Stomach	(50)	(48)	(48)	(48)
Edema, NOS	1 (2%)			
Inflammation, NOS		1 (2%)		
#Gastric submucosa	(50)	(48)	(48)	(48)
Inflammation, granulomatous	1 (2%)			
#Forestomach	(50)	(48)	(48)	(48)
Hyperplasia, epithelial		1 (2%)	1 (2%)	
Hyperkeratosis		1 (2%)		
#Colon	(50)	(43)	(48)	(47)
Hemorrhage		1 (2%)		
Parasitism	3 (6%)	2 (5%)	1 (2%)	1 (2%)
URINARY SYSTEM				
#Kidney	(50)	(49)	(48)	(50)
Calculus, gross observation only	1 (2%)			
Mineralization	5 (10%)	3 (6%)	3 (6%)	
Cast, NOS	1 (2%)			
Hydronephrosis	4 (8%)	1 (2%)	3 (6%)	
Cyst, NOS	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Inflammation, acute focal				1 (2%)
Inflammation, chronic	1 (2%)			
Inflammation, granulomatous			1 (2%)	
Fibrosis, diffuse	1 (2%)			
Nephropathy	47 (94%)	37 (76%)	42 (88%)	42 (84%)
Nephropathy, toxic			8 (17%)	29 (58%)
Calcification, focal		1 (2%)		2 (4%)
Cytomegaly			46 (96%)	50 (100%)
Hyperplasia, tubular cell				1 (2%)
#Kidney/tubule	(50)	(49)	(48)	(50)
Dilatation, NOS		1 (2%)		
Degeneration, NOS			1 (2%)	
Atypia, NOS			1 (2%)	

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM (Continued)				
#Kidney/pelvis	(50)	(49)	(48)	(50)
Dilatation, NOS				1 (2%)
Hemorrhage	3 (6%)		2 (4%)	
Hyperplasia, epithelial	10 (20%)	1 (2%)	4 (8%)	3 (6%)
#Urinary bladder	(48)	(46)	(47)	(44)
Inflammation, NOS	1 (2%)			
Inflammation, acute diffuse				1 (2%)
Hyperplasia, epithelial	1 (2%)	1 (2%)		1 (2%)
Angiectasis			1 (2%)	
ENDOCRINE SYSTEM				
#Pituitary	(49)	(49)	(47)	(43)
Cyst, NOS	1 (2%)		1 (2%)	1 (2%)
Congestion, NOS	1 (2%)			
Hyperplasia, NOS	1 (2%)			
Hyperplasia, focal		1 (2%)	4 (9%)	3 (7%)
Angiectasis			2 (4%)	
#Adrenal	(50)	(48)	(48)	(50)
Cyst, NOS		1 (2%)		
Congestion, NOS			2 (4%)	
Hemorrhage			1 (2%)	
Necrosis, cortical	1 (2%)			
Lipoidosis		2 (4%)		
Angiectasis	1 (2%)	1 (2%)	2 (4%)	1 (2%)
#Adrenal/capsule	(50)	(48)	(48)	(50)
Inflammation, chronic			1 (2%)	
#Adrenal cortex	(50)	(48)	(48)	(50)
Congestion, NOS			1 (2%)	
Hemorrhage			1 (2%)	
Inflammation, focal			1 (2%)	
Lipoidosis	3 (6%)	1 (2%)		1 (2%)
Focal cellular change		1 (2%)	1 (2%)	
Cytomegaly		1 (2%)	1 (2%)	
Hyperplasia, NOS	1 (2%)	1 (2%)		
Hyperplasia, focal		4 (8%)	1 (2%)	1 (2%)
#Adrenal medulla	(50)	(48)	(48)	(50)
Focal cellular change	1 (2%)	1 (2%)		
Hyperplasia, NOS	2 (4%)			
Hyperplasia, focal	8 (16%)	5 (10%)	12 (25%)	
#Thyroid	(50)	(49)	(49)	(50)
Inflammation, chronic focal	1 (2%)			
Hyperplasia, C-cell	1 (2%)	2 (4%)	2 (4%)	1 (2%)
REPRODUCTIVE SYSTEM				
*Mammary gland	(50)	(50)	(50)	(50)
Cyst, NOS				1 (2%)
Degeneration, cystic			1 (2%)	
Hyperplasia, NOS	1 (2%)			
Hyperplasia, focal				1 (2%)
Hyperplasia, cystic				1 (2%)
Lactation	30 (60%)	21 (42%)	20 (40%)	7 (14%)
*Vaginal mucosa	(50)	(50)	(50)	(50)
Degeneration, NOS	3 (6%)	3 (6%)		

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE AUGUST RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)				
#Uterus	(50)	(49)	(48)	(49)
Dilatation, NOS				4 (8%)
Hydrometra	1 (2%)	1 (2%)	4 (8%)	2 (4%)
Hemorrhage			1 (2%)	
Inflammation, NOS			1 (2%)	
Inflammation, acute	1 (2%)			
Inflammation, acute/chronic				1 (2%)
Metaplasia, squamous		1 (2%)		
#Uterus/endometrium	(50)	(49)	(48)	(49)
Cyst, NOS		1 (2%)		
Inflammation, acute				1 (2%)
Degeneration, NOS				1 (2%)
Hyperplasia, NOS		1 (2%)		
Hyperplasia, cystic	1 (2%)			
#Ovary	(49)	(47)	(47)	(46)
Cyst, NOS	2 (4%)		3 (6%)	
Follicular cyst, NOS	1 (2%)		2 (4%)	3 (7%)
NERVOUS SYSTEM				
#Brain	(50)	(49)	(50)	(50)
Hydrocephalus, internal				1 (2%)
Hemorrhage		1 (2%)	3 (6%)	1 (2%)
SPECIAL SENSE ORGANS				
*Middle ear	(50)	(50)	(50)	(50)
Inflammation, acute suppurative			1 (2%)	
MUSCULOSKELETAL SYSTEM				
None				
BODY CAVITIES				
*Mediastinum	(50)	(50)	(50)	(50)
Abscess, NOS			1 (2%)	
*Pleura	(50)	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)		
*Pericardium	(50)	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)		
ALL OTHER SYSTEMS				
None				
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 E

SUMMARY OF LESIONS IN MALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

TABLE E1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING	1			
ANIMALS NECROPSIED	49	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50	50
INTEGUMENTARY SYSTEM				
*Skin	(49)	(50)	(50)	(50)
Trichoepithelioma	2 (4%)		1 (2%)	1 (2%)
*Subcutaneous tissue	(49)	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)			
Teratoma, benign			1 (2%)	
RESPIRATORY SYSTEM				
#Lung	(47)	(49)	(50)	(47)
Neoplasm, NOS, unclear primary or metas			1 (2%)	
Alveolar/bronchiolar adenoma	1 (2%)			
Tubular cell adenocarcinoma, metastatic				1 (2%)
Pheochromocytoma, metastatic	1 (2%)	3 (6%)	1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM				
*Multiple organs	(49)	(50)	(50)	(50)
Malignant lymphoma, histiocytic type				1 (2%)
CIRCULATORY SYSTEM				
#Spleen	(46)	(48)	(43)	(46)
Hemangiosarcoma			1 (2%)	
#Heart	(47)	(49)	(50)	(48)
Tubular cell adenocarcinoma, metastatic				1 (2%)
Pheochromocytoma, metastatic		1 (2%)		
DIGESTIVE SYSTEM				
#Liver	(47)	(49)	(50)	(47)
Carcinoma, NOS, metastatic		1 (2%)		
#Cecum	(41)	(45)	(43)	(43)
Adenocarcinoma in adenomatous polyp	1 (2%)			
URINARY SYSTEM				
#Kidney	(49)	(49)	(50)	(47)
Tubular cell adenoma	2 (4%)		1 (2%)	
Tubular cell adenocarcinoma				1 (2%)
Interstitial cell tumor, invasive				1 (2%)
#Urinary bladder	(41)	(45)	(41)	(44)
Transitional cell carcinoma	1 (2%)			
ENDOCRINE SYSTEM				
#Pituitary	(36)	(21)	(25)	(28)
Chromophobe adenoma	1 (3%)	2 (10%)		
#Adrenal	(48)	(48)	(43)	(43)
Cortical adenoma		2 (4%)		
Pheochromocytoma	19 (40%)	21 (44%)	12 (28%)	11 (26%)
Pheochromocytoma, malignant	4 (8%)	5 (10%)	1 (2%)	2 (5%)
#Thyroid	(41)	(41)	(41)	(40)
C-cell adenoma	8 (20%)	4 (10%)	5 (12%)	2 (5%)
C-cell carcinoma	4 (10%)	1 (2%)		1 (3%)

TABLE E1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)				
#Parathyroid	(15)	(16)	(21)	(18)
Adenoma, NOS		2 (13%)		1 (6%)
#Pancreatic islets	(42)	(49)	(46)	(46)
Islet cell adenoma	1 (2%)	1 (2%)		
REPRODUCTIVE SYSTEM				
#Testis	(46)	(46)	(48)	(48)
Interstitial cell tumor	16 (35%)	17 (37%)	21 (44%)	31 (65%)
Interstitial cell tumor, malignant				1 (2%)
NERVOUS SYSTEM				
#Brain	(45)	(48)	(50)	(47)
Glioma, NOS				1 (2%)
Astrocytoma				1 (2%)
*Spinal cord	(49)	(50)	(50)	(50)
Meningioma		1 (2%)		
SPECIAL SENSE ORGANS				
None				
MUSCULOSKELETAL SYSTEM				
*Skull	(49)	(50)	(50)	(50)
Mixed mesenchymal tumor, benign		1 (2%)		
*Vertebra	(49)	(50)	(50)	(50)
Meningioma, invasive		1 (2%)		
BODY CAVITIES				
*Mediastinum	(49)	(50)	(50)	(50)
Carcinoma, NOS		1 (2%)		
*Peritoneum	(49)	(50)	(50)	(50)
Sarcoma, NOS		1 (2%)		
Mesothelioma, NOS		2 (4%)	1 (2%)	1 (2%)
Mesothelioma, malignant				2 (4%)
*Peritoneal mesothelium	(49)	(50)	(50)	(50)
Mesothelioma, NOS	1 (2%)			
*Tunica vaginalis	(49)	(50)	(50)	(50)
Mesothelioma, NOS	1 (2%)		1 (2%)	
ALL OTHER SYSTEMS				
None				
ANIMAL DISPOSITION SUMMARY				
Animals initially in study	50	50	50	50
Natural death	13	14	20	16
Moribund sacrifice	3	8	6	3
Terminal sacrifice	32	26	12	6
Dosing accident		1		
Accidentally killed, NOS	1	1	12	25
Animal missing	1			

TABLE E1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
TUMOR SUMMARY				
Total animals with primary tumors**	38	37	23	32
Total primary tumors	63	61	46	57
Total animals with benign tumors	35	35	22	32
Total benign tumors	50	50	41	46
Total animals with malignant tumors	11	9	2	7
Total malignant tumors	11	9	2	10
Total animals with secondary tumors##	1	5	1	3
Total secondary tumors	1	6	1	4
Total animals with tumors uncertain--benign or malignant	2	2	2	1
Total uncertain tumors	2	2	2	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 E2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: UNTREATED CONTROL

ANIMAL NUMBER	69 96	69 98	69 99	70 01	70 05	71 11	71 18	72 20	73 33	73 36	74 41	74 42	74 46	75 50	75 52	76 64	77 72	77 74	77 76	77 78	78 86	78 89	79 92	79 96	80 02
WEEKS ON STUDY	105	105	044	105	105	105	105	052	105	105	105	089	105	105	105	067	105	048	105	098	091	105	105	051	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+
Trichoepithelioma																									
Subcutaneous tissue	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+
Sarcoma, NOS														X											
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X																		
Pheochromocytoma, metastatic																					X				
Trachea	+	+	−	+	+	+	+	−	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	−	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph nodes	+	+	−	−	+	+	+	−	+	+	−	+	+	−	+	+	−	−	+	+	+	−	+	−	
Thymus	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	
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	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	
Esophagus	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Small intestine	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	
Large intestine	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	−	+	+	−	+	
Adenocarcinoma in adenomatous polyp																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Urinary bladder	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	−	
Transitional cell carcinoma																									
ENDOCRINE SYSTEM																									
Pituitary	−	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	−	−	+	−	+	+	+	+	−
Chromophobe adenoma							X																		
Adrenal	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma		X			X		X			X		X	X	X	X		X						X		X
Pheochromocytoma, malignant																					X				
Thyroid	+	+	−	+	+	+	+	−	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	−	+
C-cell adenoma	X				X								X						X						X
C-cell carcinoma		X		X		X																			
Parathyroid	+	−	−	+	+	−	+	−	−	−	+	−	−	+	−	−	−	−	−	−	−	+	+	−	+
Pancreatic islets	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+
Islet cell adenoma										X															
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	N	N	N	N	N	N	N	N	N	+	+	N	N	+	N	+	N	N	+	N	N	N
Testis	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor				X									X				X			X		X			
Prostate	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+
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											X														
Tunica vaginalis	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									

+: 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 E2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MARSHALL RATS: UNTREATED CONTROL (Continued)

ANIMAL NUMBER	81 18	82 20	82 21	82 22	82 26	83 30	83 33	83 34	83 37	83 38	84 40	84 44	84 45	84 48	85 51	85 57	85 58	86 61	86 64	86 67	87 72	88 86	88 89	89 91	89 92	TOTAL:
WEEKS ON STUDY	105	105	103	098	066	073	105	105	105	061	105	044	038	105	105	099	105	105	105	063	097	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	M	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	*49
Trichoepithelioma						X															X					2
Subcutaneous tissue	+	+	+	+	M	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	*49
Sarcoma, NOS																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Alveolar/bronchiolar adenoma																										1
Pheochromocytoma, metastatic																										1
Trachea	+	+	+	+	M	+	+	+	+	A	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	41
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	M	+	+	+	+	A	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Spleen	+	−	+	−	M	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph nodes	+	+	+	+	M	+	−	+	+	+	+	−	−	+	+	+	+	+	+	+	−	+	+	+	+	36
Thymus	−	−	−	−	M	−	−	−	−	A	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	0
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
DIGESTIVE SYSTEM																										
Salivary gland	−	+	−	+	M	+	+	+	−	A	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Liver	+	+	+	+	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Bile duct	+	+	+	+	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Gallbladder & common bile duct	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Pancreas	+	+	+	−	M	+	+	+	+	A	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Esophagus	+	+	+	+	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	45
Stomach	+	+	+	−	M	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	47
Small intestine	+	+	+	−	M	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Large intestine	+	+	+	−	M	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	41
Adenocarcinoma in adenomatous polyp																							X			1
URINARY SYSTEM																										
Kidney	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tubular cell adenoma																	X		X							2
Urinary bladder	+	+	+	−	M	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	−	+	+	+	+	41
Transitional cell carcinoma	X																									1
ENDOCRINE SYSTEM																										
Pituitary	+	+	−	+	M	−	+	+	+	A	+	+	+	+	−	+	+	+	−	+	+	+	−	+	+	36
Chromophobe adenoma																										1
Adrenal	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma		X	X					X			X			X		X		X							X	19
Pheochromocytoma, malignant																	X					X		X		4
Thyroid	+	+	+	+	M	+	+	+	+	A	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	41
C-cell adenoma								X														X	X			8
C-cell carcinoma																		X								4
Parathyroid	+	−	−	+	M	−	+	−	−	A	+	−	−	−	−	+	−	−	−	−	−	−	−	+	−	15
Pancreatic islets	+	+	+	−	M	+	+	+	+	A	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	+	N	M	+	N	N	+	N	N	N	N	+	N	+	+	+	N	N	+	N	N	+	+	*49
Testis	+	+	+	+	M	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Interstitial cell tumor	X	X					X	X	X		X				X	X						X		X	X	16
Prostate	+	+	+	+	M	+	+	+	+	A	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	44
NERVOUS SYSTEM																										
Brain	+	+	+	+	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
BODY CAVITIES																										
Peritoneum	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Mesothelioma, NOS																										1
Tunica vaginalis	+	+	+	+	M	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Mesothelioma, NOS						X																				1

* Animals necropsied

TABLE E2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: VEHICLE CONTROL

ANIMAL NUMBER	69 3	69 4	69 5	69 7	70 7	70 8	71 2	71 3	71 7	72 4	72 6	73 5	73 7	74 3	74 5	75 3	75 5	75 8	76 1	76 5	76 7	76 8	77 0	77 1	77 7
WEEKS ON STUDY	105	088	105	105	105	057	105	105	104	024	105	105	105	093	105	062	097	104	105	105	105	105	104	092	079
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	−	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Lymph nodes	+	−	−	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+
Thymus	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	+	−	−	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma, metastatic																									
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+
Liver	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, 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	N
Pancreas	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+
Stomach	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	−	−	−	+	+	−	−	+	−	−	−	+	+	+	−	−	−	−	−	−	+	−	−
Chromophobe adenoma		X													X										
Adrenal	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																			X						
Pheochromocytoma	X	X	X	X				X			X	X						X	X	X	X		X	X	X
Pheochromocytoma, malignant									X																
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
C-cell adenoma																		X	X		X				
C-cell carcinoma																									
Parathyroid	−	−	−	+	+	+	+	−	−	−	−	−	−	−	+	+	−	+	−	+	+	−	−	−	−
Adenoma, NOS					X		X																		
Pancreatic islets	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	N	N	+	N	N	N	N	N	+	N	+	+	N	N	N	+	+	+	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor			X	X					X			X	X	X						X	X	X	X		X
Prostate	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
Spinal cord	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meningioma																	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
Mixed mesenchymal tumor, benign																									
Meningioma, invasive																	X								
BODY CAVITIES																									
Mediastinum	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																									
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
Sarcoma, NOS														X											
Mesothelioma, NOS																									X

TABLE E2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MARSHALL RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	790	791	793	798	804	807	817	819	839	841	850	859	860	865	866	869	873	874	877	880	881	883	884	887	888	TOTAL:
WEEKS ON STUDY	080	083	105	105	059	105	105	042	104	105	081	092	069	105	085	053	053	055	097	064	090	105	105	049	092	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma, metastatic				X											X				X							3
Trachea	−	+	+	−	+	+	−	−	+	+	+	−	+	+	+	+	+	+	−	−	−	+	+	+	−	38
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph nodes	+	−	−	+	+	−	−	+	+	+	−	−	+	+	−	+	−	−	−	+	−	+	+	+	−	33
Thymus	+	−	−	−	−	−	−	−	+	−	+	−	−	−	+	−	−	−	−	−	+	−	−	−	−	7
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma, metastatic																			X							1
DIGESTIVE SYSTEM																										
Salivary gland	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	−	+	+	+	−	43
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS, metastatic																									X	1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Small intestine	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	−	+	+	−	+	44
Large intestine	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	−	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	−	+	45
ENDOCRINE SYSTEM																										
Pituitary	−	+	−	−	+	+	−	+	−	+	−	−	+	+	+	+	+	+	−	−	−	−	−	+	−	21
Chromophobe adenoma																										2
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	48
Cortical adenoma											X															2
Pheochromocytoma	X			X			X		X					X									X	X		21
Pheochromocytoma, malignant				X								X			X											5
Thyroid	−	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	−	−	−	+	+	−	−	41
C-cell adenoma																		X								4
C-cell carcinoma										X																1
Parathyroid	−	+	+	+	−	−	−	−	−	−	−	+	+	−	−	+	−	−	−	−	−	+	−	−	−	16
Adenoma, NOS																										2
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma									X																	1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	+	N	+	+	N	+	+	+	N	N	N	N	N	N	N	N	N	N	+	*50
Testis	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	−	+	+	+	+	+	46
Interstitial cell tumor						X	X		X	X		X			X											17
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	48
Spinal cord	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Meningioma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	+	N	N	N	N	N	N	N	+	N	N	+	+	+	N	+	N	N	N	N	N	*50
Mixed mesenchymal tumor, benign								X																		1
Meningioma, invasive																										1
BODY CAVITIES																										
Mediastinum	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
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
Sarcoma, NOS																										1
Mesothelioma, NOS																			X							2

* Animals necropsied

TABLE E2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: LOW DOSE

ANIMAL NUMBER	70	70	70	70	71	71	71	72	72	72	73	73	73	74	74	74	74	75	75	75	76	76	78	78	78
WEEKS ON STUDY	066	104	111	104	069	104	065	104	110	110	223	104	069	050	114	117	032	020	065	057	111	104	104	066	022
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	N	+	+	+	N	+	+	N	N	+	N	+	+	N	+	+	+	+
Trichoepithelioma																						X			
Subcutaneous tissue	+	+	+	+	+	+	+	N	+	+	+	N	+	+	N	N	+	N	+	+	N	+	+	+	+
Teratoma, benign													X												
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplasm, NOS, unclear primary or metastatic																			X						
Pheochromocytoma, metastatic																									
Trachea	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	−	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	−	+	+	+	+	+	−	−	+	+	+	−	−	−	+	+	+	+	−	+	−	+	+
Spleen	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph nodes	−	−	+	+	−	−	+	+	−	−	−	+	−	−	−	−	−	+	+	+	−	+	−	+	−
Thymus	−	−	+	−	+	−	+	−	+	+	+	−	−	−	−	+	+	−	−	−	−	−	−	+	+
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	−	+	+	+	+	−	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																				X					
Urinary bladder	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	−	−	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	−	+	+	+	+	+	−	−	−	+	+	−	−	−	+	−	−	−	−	+	+	+	−
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+
Pheochromocytoma				X		X	X	X				X											X		
Pheochromocytoma, malignant																									
Thyroid	−	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
C-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
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor	X	X		X			X	X				X	X	X						X		X	X	X	
Prostate	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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				X																					
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																							X		

TABLE E2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MARSHALL RATS: LOW DOSE (*Continued*)

ANIMAL NUMBER	78801	79404	79901	80004	80016	80406	80905	81104	81202	81604	82308	82406	82505	83101	83505	84303	84407	85202	85303	85506	86303	87101	87504	87905	89002	TOTAL:
WEEKS ON STUDY	05101	02101	10404	05101	04606	10404	05505	10404	04202	10404	06808	06606	03808	07404	05909	04404	02707	01202	00707	02808	07101	01808	10404	06505	02202	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	N	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	N	+	+	N	+	+	+	*50
Trichoepithelioma																										1
Subcutaneous tissue	+	N	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	N	+	+	N	+	+	+	*50
Teratoma, benign																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplasm, NOS, unclear prim or meta																										1
Pheochromocytoma, metastatic																							X			1
Trachea	+	+	+	–	~	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	–	+	41
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	–	–	+	–	–	+	+	+	36
Spleen	+	–	–	+	+	+	–	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	43
Hemangiosarcoma								X																		1
Lymph nodes	–	–	+	–	+	+	+	–	+	–	+	+	+	–	+	+	–	–	+	+	–	–	+	+	+	25
Thymus	–	–	–	+	–	+	–	–	–	+	–	~	–	–	–	–	–	+	+	–	–	+	+	–	+	18
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	–	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	42
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	N	*50
Pancreas	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	46
Esophagus	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	–	+	+	+	+	–	+	–	+	+	43
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma																										1
Urinary bladder	–	+	+	–	+	+	+	+	+	+	+	+	+	–	+	–	–	+	+	+	+	+	+	+	+	41
ENDOCRINE SYSTEM																										
Pituitary	–	–	–	+	–	+	+	+	+	+	–	+	+	+	+	–	–	–	–	–	–	–	+	+	–	25
Adrenal	–	+	+	+	–	+	+	+	–	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	43
Pheochromocytoma			X			X				X	X											X		X		12
Pheochromocytoma, malignant																								X		1
Thyroid	+	+	+	–	+	+	–	+	+	+	+	+	–	+	+	+	+	+	–	+	–	–	+	+	+	41
C-cell adenoma			X					X															X			5
Parathyroid	+	–	+	–	+	+	–	–	–	–	+	–	–	–	+	+	–	–	–	+	–	–	+	+	+	21
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	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	48
Interstitial cell tumor			X			X		X		X	X	X										X		X	X	21
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	–	+	+	+	+	+	+	44
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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																										1
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS																										1

* Animals necropsied

TABLE E2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: HIGH DOSE

ANIMAL NUMBER	70 00	70 09	71 10	71 19	72 23	72 25	72 27	72 28	73 31	73 34	73 38	74 47	75 51	75 59	76 62	76 66	76 69	77 73	77 75	77 79	78 81	78 83	78 84	78 85	79 95
WEEKS ON STUDY	05 58	05 57	06 68	06 25	06 76	08 80	10 04	02 25	00 05	08 89	05 53	02 24	01 11	04 48	06 68	04 43	07 77	08 87	10 04	06 63	03 30	08 83	05 55	07 72	02 66
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Trichoepithelioma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	−	+	+	+	+
Tubular cell adenocarcinoma, metastatic																		X							
Pheochromocytoma, metastatic																									
Trachea	−	+	+	+	+	+	+	+	−	+	+	+	−	A	+	+	+	+	+	+	−	+	+	+	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	−	−	A	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	−	+	+	−	+
Lymph nodes	+	+	−	−	−	A	+	+	−	+	+	−	+	A	−	+	+	+	+	+	−	−	+	+	−
Thymus	−	+	−	−	−	A	−	−	+	+	+	−	+	A	−	+	+	−	−	−	−	+	−	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	−	+	+	+	+
Tubular cell adenocarcinoma, metastatic																		X							
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	−	+	+	−	+	+	+	−
Liver	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
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	+	+	+	+	+	A	+	−	+	+	+	+	+	A	+	+	+	+	+	+	−	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	−	+	+	+	−
Stomach	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	−	+	+	+	+
Small intestine	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	−	+	+	+	+
Large intestine	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	−	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	−	+	+	+	+
Tubular cell adenocarcinoma																		X							
Interstitial cell tumor, invasive																									
Urinary bladder	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	−	+	−	−	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	A	−	−	−	+	−	−	−	A	+	+	+	−	−	+	−	+	+	+	−
Adrenal	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	−	+	+	+	+
Pheochromocytoma		X			X														X						
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	+	−	−	+	+	+	A	+	+	+	+	+	+	−	+	+	+	−
C-cell adenoma																			X						
C-cell carcinoma																									
Parathyroid	+	−	−	−	+	A	+	−	−	−	−	−	−	A	−	−	−	+	−	−	−	−	−	−	−
Adenoma, NOS																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	+	+	+	N	N	+	N	N	N	N	+	N	+	N	+	N	N	N	N	+	N
Testis	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor	X	X	X		X		X			X					X		X	X	X	X		X	X	X	
Interstitial cell tumor, malignant																									
Prostate	+	+	+	+	−	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Br[illegible]	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	−	+	+	+	+
([illegible]na, NOS																		X							
A[illegible]ocytoma																									
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										X															
Mesothelioma, malignant																				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, histiocytic type																									

TABLE E2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MARSHALL RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	79 7	80 3	80 5	80 8	81 0	81 3	81 4	81 5	82 7	82 8	82 9	83 2	83 6	84 2	84 6	84 9	85 4	85 5	86 2	86 8	87 0	87 6	87 8	88 2	88 5	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	05 7	04 7	03 2	04 4	05 4	10 0	05 7	10 4	10 4	07 4	01 8	01 6	10 3	04 6	08 8	05 8	07 3	10 4	03 9	04 7	08 2	09 8	08 3	03 4	10 4	
INTEGUMENTARY SYSTEM																										
Skin	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Trichoepithelioma																	X									1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Tubular cell adenocarcinoma, metastatic																										1
Pheochromocytoma, metastatic													X													1
Trachea	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	41
HEMATOPOI ETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph nodes	+	–	–	–	–	+	+	–	+	+	+	–	+	+	–	+	+	+	–	–	+	–	–	–	+	27
Thymus	–	+	+	–	+	–	+	–	+	–	–	+	–	+	–	+	–	–	+	+	+	–	–	–	–	21
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tubular cell adenocarcinoma, metastatic																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	–	–	+	+	+	+	+	41
Liver	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Bile duct	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Small intestine	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	44
Large intestine	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	–	43
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Tubular cell adenocarcinoma																										1
Interstitial cell tumor, invasive						X																				1
Urinary bladder	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
ENDOCRINE SYSTEM																										
Pituitary	+	+	–	+	–	+	+	+	+	+	–	–	–	+	–	+	+	–	–	–	+	+	–	+	+	28
Adrenal	+	–	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Pheochromocytoma						X		X	X						X			X			X		X		X	11
Pheochromocytoma, malignant													X		X											2
Thyroid	+	+	+	+	+	+	+	–	+	+	+	–	+	–	–	+	+	+	+	–	+	+	+	+	+	40
C-cell adenoma																		X								2
C-cell carcinoma						X																				1
Parathyroid	+	+	+	–	+	+	+	–	–	–	+	–	+	–	–	+	–	+	+	–	+	+	–	–	+	18
Adenoma, NOS																									X	1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	N	N	N	+	N	N	+	+	N	N	+	N	+	N	N	+	N	N	N	+	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Interstitial cell tumor	X		X		X		X	X	X	X			X		X		X	X	X		X	X	X	X	X	31
Interstitial cell tumor, malignant						X																				1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	47
Glioma, NOS																										1
Astrocytoma																								X		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																										1
Mesothelioma, malignant						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
Malignant lymphoma, histiocytic type													X													1

* Animals necropsied

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg
Adrenal: Pheochromocytoma				
Overall Rates (a)	19/48 (40%)	21/48 (44%)	12/43 (28%)	11/43 (26%)
Adjusted Rates (b)	55.6%	69.1%	84.8%	89.4%
Terminal Rates (c)	16/31 (52%)	17/26 (65%)	9/11 (82%)	5/6 (83%)
Life Table Tests (d)		P=0.014	P=0.147	P=0.021
Incidental Tumor Tests (d)		P=0.095	P=0.119	P=0.127
Cochran-Armitage Trend Test (d)		P=0.040N		
Fisher Exact Test			P=0.088N	P=0.055N
Adrenal: Pheochromocytoma, Malignant				
Overall Rates (a)	4/48 (8%)	5/48 (10%)	1/43 (2%)	2/43 (5%)
Adjusted Rates (b)	12.1%	16.2%	9.1%	21.4%
Terminal Rates (c)	3/31 (10%)	2/26 (8%)	1/11 (9%)	0/6 (0%)
Life Table Tests (d)		P=0.517	P=0.420N	P=0.524
Incidental Tumor Tests (d)		P=0.440N	P=0.695	P=0.500N
Cochran-Armitage Trend Test (d)		P=0.165N		
Fisher Exact Test			P=0.129N	P=0.266N
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant				
Overall Rates (a)	23/48 (48%)	25/48 (52%)	12/43 (28%)	12/43 (28%)
Adjusted Rates (b)	65.4%	75.1%	84.8%	90.9%
Terminal Rates (c)	19/31 (61%)	18/26 (69%)	9/11 (82%)	5/6 (83%)
Life Table Tests (d)		P=0.035	P=0.353	P=0.037
Incidental Tumor Tests (d)		P=0.239	P=0.158	P=0.288
Cochran-Armitage Trend Test (d)		P=0.010N		
Fisher Exact Test			P=0.016N	P=0.016N
Thyroid: C-Cell Adenoma				
Overall Rates (a)	8/41 (20%)	4/41 (10%)	5/41 (12%)	2/40 (5%)
Adjusted Rates (b)	25.0%	14.0%	41.7%	40.0%
Terminal Rates (c)	8/32 (25%)	3/25 (12%)	5/12 (42%)	2/5 (40%)
Life Table Tests (d)		P=0.129	P=0.113	P=0.385
Incidental Tumor Tests (d)		P=0.172	P=0.153	P=0.513
Cochran-Armitage Trend Test (d)		P=0.292N		
Fisher Exact Test			P=0.500	P=0.350N
Thyroid: C-Cell Adenoma or Carcinoma				
Overall Rates (a)	12/41 (29%)	5/41 (12%)	5/41 (12%)	3/40 (7%)
Adjusted Rates (b)	37.5%	17.9%	41.7%	47.5%
Terminal Rates (c)	12/32 (38%)	4/25 (16%)	5/12 (42%)	2/5 (40%)
Life Table Tests (d)		P=0.078	P=0.178	P=0.206
Incidental Tumor Tests (d)		P=0.170	P=0.228	P=0.424
Cochran-Armitage Trend Test (d)		P=0.308N		
Fisher Exact Test			P=0.631N	P=0.370N
Testis: Interstitial Cell Tumor				
Overall Rates (a)	16/46 (35%)	17/46 (37%)	21/48 (44%)	31/48 (65%)
Adjusted Rates (b)	46.9%	55.7%	95.1%	100.0%
Terminal Rates (c)	14/32 (44%)	13/26 (50%)	11/12 (92%)	6/6 (100%)
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=0.005		
Fisher Exact Test			P=0.323	P=0.007
Testis: Interstitial Cell Tumor or Interstitial Cell Tumor, Malignant				
Overall Rates (a)	16/46 (35%)	17/46 (37%)	21/48 (44%)	32/48 (67%)
Adjusted Rates (b)	46.9%	55.7%	95.1%	100.0%
Terminal Rates (c)	14/32 (44%)	13/26 (50%)	11/12 (92%)	6/6 (100%)
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=0.003		
Fisher Exact Test			P=0.323	P=0.004

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg
All Sites: Mesothelioma				
Overall Rates (a)	2/49 (4%)	2/50 (4%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	5.5%	6.0%	16.7%	24.5%
Terminal Rates (c)	1/32 (3%)	0/26 (0%)	2/12 (17%)	0/6 (0%)
Life Table Tests (d)		P=0.063	P=0.356	P=0.127
Incidental Tumor Tests (d)		P=0.244	P=0.090	P=0.496
Cochran-Armitage Trend Test (d)		P=0.406		
Fisher Exact Test			P=0.691N	P=0.500

(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 vehiclecontrols. 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 rates. A negative trend or lower incidence in a dosed group is indicated by (N).

TABLE E4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING	1			
ANIMALS NECROPSIED	49	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50	50
INTEGUMENTARY SYSTEM				
*Skin	(49)	(50)	(50)	(50)
Epidermal inclusion cyst		1 (2%)		
Hemorrhage		1 (2%)		
Abscess, chronic	1 (2%)			
*Subcutaneous tissue	(49)	(50)	(50)	(50)
Granuloma, NOS		1 (2%)		
RESPIRATORY SYSTEM				
*Nasal cavity	(49)	(50)	(50)	(50)
Vegetable foreign body			1 (2%)	
Impaction, NOS				1 (2%)
Hemorrhage			1 (2%)	
Inflammation, NOS		2 (4%)		
Inflammation, suppurative		1 (2%)	4 (8%)	2 (4%)
Inflammation, acute			1 (2%)	
Inflammation, acute suppurative				1 (2%)
#Trachea	(41)	(38)	(41)	(41)
Wound, NOS				1 (2%)
Lacerated wound		1 (3%)		2 (5%)
Penetrating wound				1 (2%)
Foreign material, NOS		1 (3%)	1 (2%)	2 (5%)
#Peritracheal tissue	(41)	(38)	(41)	(41)
Abscess, chronic		1 (3%)		
#Lung	(47)	(49)	(50)	(47)
Emphysema, alveolar		1 (2%)	1 (2%)	
Collapse		1 (2%)	1 (2%)	
Congestion, NOS	11 (23%)	8 (16%)	21 (42%)	19 (40%)
Edema, NOS		1 (2%)	3 (6%)	5 (11%)
Hemorrhage	4 (9%)	6 (12%)	12 (24%)	15 (32%)
Bronchopneumonia, NOS	1 (2%)			
Bronchopneumonia, focal		1 (2%)		
Inflammation, focal	19 (40%)	29 (59%)	14 (28%)	6 (13%)
Pneumonia, lipid		1 (2%)		
Pneumonia, aspiration			1 (2%)	1 (2%)
Bronchopneumonia, acute		1 (2%)		
Inflammation, chronic focal	1 (2%)	6 (12%)	14 (28%)	10 (21%)
Inflammation, granulomatous focal	3 (6%)	1 (2%)		4 (9%)
Granuloma, pyogenic		1 (2%)		1 (2%)
Fibrosis, focal				1 (2%)
Foreign material, NOS			4 (8%)	11 (23%)
Hemosiderosis		1 (2%)		
Alveolar macrophages			1 (2%)	
Hyperplasia, adenomatous		1 (2%)		
HEMATOPOIETIC SYSTEM				
*Harderian gland	(49)	(50)	(50)	(50)
Mastocytosis				1 (2%)
*Blood	(49)	(50)	(50)	(50)
Leukocytosis, NOS	1 (2%)			
Hypochromasia	1 (2%)			
#Bone marrow	(46)	(49)	(36)	(45)
Hyperplasia, granulocytic	1 (2%)	1 (2%)		1 (2%)

TABLE E4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)				
#Spleen	(46)	(48)	(43)	(46)
Hamartoma		1 (2%)		
Congestion, NOS			2 (5%)	
Hemosiderosis	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Atrophy, NOS		1 (2%)		
Hematopoiesis	4 (9%)	1 (2%)		2 (4%)
Erythropoiesis				1 (2%)
Myelopoiesis		1 (2%)		
#Lymph node	(36)	(33)	(25)	(27)
Plasmacytosis	1 (3%)			
#Mandibular lymph node	(36)	(33)	(25)	(27)
Hemorrhage	1 (3%)	1 (3%)		
#Mesenteric lymph node	(36)	(33)	(25)	(27)
Hemorrhage	7 (19%)	4 (12%)		
Inflammation, chronic focal				1 (4%)
Fibrosis, focal	1 (3%)			
#Liver	(47)	(49)	(50)	(47)
Hematopoiesis		1 (2%)		
#Peyers patch	(43)	(44)	(48)	(44)
Hyperplasia, lymphoid	1 (2%)			
#Thymus		(7)	(18)	(21)
Hemorrhage			2 (11%)	6 (29%)
Involution, NOS			1 (6%)	
CIRCULATORY SYSTEM				
#Lung	(47)	(49)	(50)	(47)
Perivasculitis			1 (2%)	2 (4%)
#Heart	(47)	(49)	(50)	(48)
Thrombosis, NOS				1 (2%)
Thrombus, organized			1 (2%)	
Inflammation, focal		1 (2%)	1 (2%)	
Inflammation, interstitial	1 (2%)	1 (2%)		
Inflammation, chronic	1 (2%)			
Fibrosis, focal	3 (6%)	2 (4%)	6 (12%)	
Endocardiosis		1 (2%)		
#Endocardium	(47)	(49)	(50)	(48)
Endocarditis, verrucous	1 (2%)			
#Cardiac valve	(47)	(49)	(50)	(48)
Thrombus, organized				1 (2%)
Fibrosis	1 (2%)			
*Artery	(49)	(50)	(50)	(50)
Mineralization		1 (2%)		
Periarteritis		1 (2%)		
*Pulmonary artery	(49)	(50)	(50)	(50)
Calcification, focal	1 (2%)	4 (8%)		
DIGESTIVE SYSTEM				
#Salivary gland	(40)	(43)	(42)	(41)
Inflammation, chronic			1 (2%)	
#Liver	(47)	(49)	(50)	(47)
Cyst, NOS	1 (2%)			
Multilocular cyst	1 (2%)			
Congestion, NOS	1 (2%)	2 (4%)	1 (2%)	3 (6%)
Congestion, chronic passive	1 (2%)			
Hemorrhage			3 (6%)	1 (2%)
Inflammation, NOS	22 (47%)	31 (63%)	6 (12%)	
Inflammation, focal			2 (4%)	1 (2%)
Inflammation, acute/chronic		1 (2%)		

TABLE E4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM				
#Liver (Continued)	(47)	(49)	(50)	(47)
Degeneration, NOS			1 (2%)	
Necrosis, focal	1 (2%)		5 (10%)	
Necrosis, hemorrhagic	1 (2%)			
Necrosis, central	2 (4%)			
Metamorphosis, fatty	7 (15%)	3 (6%)	7 (14%)	
Nuclear enlargement			1 (2%)	
Basophilic cyto change	1 (2%)			
Clear cell change	5 (11%)	4 (8%)	3 (6%)	2 (4%)
Cell size alteration	1 (2%)			
Depletion, glycogen		1 (2%)		
#Liver/periportal	(47)	(49)	(50)	(47)
Atrophy, NOS	1 (2%)			
#Pancreas	(42)	(49)	(46)	(46)
Inflammation, chronic focal	1 (2%)			1 (2%)
Necrosis, hemorrhagic	1 (2%)			
Atrophy, NOS	1 (2%)			
Atrophy, focal	1 (2%)			
*Pharynx	(49)	(50)	(50)	(50)
Granuloma, foreign body		1 (2%)		
#Esophagus	(45)	(47)	(44)	(47)
Lacerated wound		1 (2%)	1 (2%)	2 (4%)
Penetrating wound				1 (2%)
Inflammation, granulomatous focal			1 (2%)	
Perforation, inflammatory				1 (2%)
#Gastric mucosa	(47)	(47)	(48)	(47)
Calcification, metastatic		1 (2%)		
#Small intestine	(43)	(44)	(48)	(44)
Impaction, NOS			1 (2%)	
#Colon	(41)	(45)	(43)	(43)
Parasitism	3 (7%)	3 (7%)	2 (5%)	6 (14%)
*Rectum	(49)	(50)	(50)	(50)
Parasitism		1 (2%)		
URINARY SYSTEM				
#Kidney	(49)	(49)	(50)	(47)
Congenital hydronephrosis	10 (20%)	7 (14%)	5 (10%)	1 (2%)
Hydronephrosis	1 (2%)	1 (2%)	3 (6%)	1 (2%)
Cyst, NOS	1 (2%)			1 (2%)
Congestion, NOS	1 (2%)		1 (2%)	
Hemorrhage	2 (4%)			
Pyelonephritis, NOS		1 (2%)	1 (2%)	
Glomerulonephritis, focal		1 (2%)		
Pyelonephritis, focal	1 (2%)			
Glomerulonephritis, acute		1 (2%)		
Glomerulonephritis, subacute	1 (2%)			
Glomerulonephritis, chronic		1 (2%)		
Inflammation, granulomatous focal			1 (2%)	
Nephropathy	45 (92%)	49 (100%)	47 (94%)	46 (98%)
Nephropathy, toxic			18 (36%)	23 (49%)
Nephrosis, NOS	1 (2%)			
Necrosis, medullary			1 (2%)	
Calcification, focal	21 (43%)	14 (29%)	8 (16%)	5 (11%)
Pigmentation, NOS				1 (2%)
Cytomegaly			48 (96%)	47 (100%)
Hyperplasia, tubular cell			1 (2%)	
#Renal papilla	(49)	(49)	(50)	(47)
Inflammation, acute			1 (2%)	

TABLE E4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
BODY CAVITIES				
*Thorax	(49)	(50)	(50)	(50)
Inflammation, necrotizing		1 (2%)		
*Peritoneal cavity	(49)	(50)	(50)	(50)
Hemoperitoneum			1 (2%)	
*Pleural cavity	(49)	(50)	(50)	(50)
Hemorrhage				1 (2%)
ALL OTHER SYSTEMS				
*Multiple organs	(49)	(50)	(50)	(50)
Hemorrhage			1 (2%)	
SPECIAL MORPHOLOGY SUMMARY				
No lesion reported				1
Animal missing/no necropsy	1			
Auto/necropsy/histo perf	1			2

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

TABLE E4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM (Continued)				
#Kidney/pelvis	(49)	(49)	(50)	(47)
Inflammation, NOS	1 (2%)			
Inflammation, suppurative	1 (2%)			
Inflammation, acute	1 (2%)	2 (4%)	1 (2%)	
Hyperplasia, epithelial	2 (4%)			
#Urinary bladder	(41)	(45)	(41)	(44)
Calculus, unknown gross or micro		1 (2%)		
Hemorrhage	1 (2%)		2 (5%)	
Inflammation, NOS	1 (2%)			
Inflammation, hemorrhagic		1 (2%)		
Inflammation, acute			1 (2%)	
Inflammation, acute focal		1 (2%)		
Inflammation, acute hemorrhagic				1 (2%)
#Urinary bladder/mucosa	(41)	(45)	(41)	(44)
Hyperplasia, papillary		1 (2%)		
*Urethra	(49)	(50)	(50)	(50)
Inflammation, acute			1 (2%)	
ENDOCRINE SYSTEM				
#Pituitary	(36)	(21)	(25)	(28)
Cyst, NOS			1 (4%)	1 (4%)
Hyperplasia, chromophobe cell	3 (8%)			
#Adrenal	(48)	(48)	(43)	(43)
Hemorrhage		1 (2%)		
Hyperplasia, focal		1 (2%)		
Angiectasis		2 (4%)		
#Adrenal cortex	(48)	(48)	(43)	(43)
Hemorrhage	1 (2%)	2 (4%)		1 (2%)
Degeneration, lipoid	2 (4%)	1 (2%)		1 (2%)
Hyperplasia, focal	2 (4%)	1 (2%)	1 (2%)	
Angiectasis			1 (2%)	
#Adrenal medulla	(48)	(48)	(43)	(43)
Hyperplasia, NOS		1 (2%)		
Hyperplasia, focal	8 (17%)	5 (10%)	5 (12%)	3 (7%)
#Thyroid	(41)	(41)	(41)	(40)
Cyst, NOS		1 (2%)		
Follicular cyst, NOS			2 (5%)	
Hyperplasia, C-cell	6 (15%)	10 (24%)	4 (10%)	1 (3%)
REPRODUCTIVE SYSTEM				
*Mammary gland	(49)	(50)	(50)	(50)
Hyperplasia, cystic	1 (2%)			
#Prostate	(44)	(47)	(44)	(47)
Retention of content				1 (2%)
Hemorrhage			1 (2%)	
Inflammation, NOS	4 (9%)	5 (11%)	2 (5%)	3 (6%)
Inflammation, focal	30 (68%)	29 (62%)	14 (32%)	16 (34%)
Inflammation, multifocal				1 (2%)
Inflammation, suppurative	1 (2%)		3 (7%)	
Inflammation, hemorrhagic		1 (2%)		
Inflammation, acute	1 (2%)		2 (5%)	
Inflammation, acute suppurative		2 (4%)		1 (2%)
Inflammation, acute hemorrhagic				1 (2%)
Inflammation, acute	1 (2%)		2 (5%)	
Inflammation, acute suppurative		2 (4%)		1 (2%)
Inflammation, acute hemorrhagic				1 (2%)
Inflammation, acute/chronic	2 (5%)	2 (4%)		2 (4%)
Inflammation, chronic				1 (2%)
Inflammation, chronic focal			1 (2%)	

TABLE E4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM				
#Prostate (Continued)	(44)	(47)	(44)	(47)
Abscess, chronic				1 (2%)
Inflammation, granulomatous focal		1 (2%)		
Granuloma, pyogenic				1 (2%)
Corpora amylacea	37 (84%)	38 (81%)	19 (43%)	29 (62%)
Hyperplasia, NOS		1 (2%)	1 (2%)	
Hyperplasia, papillary			1 (2%)	
*Seminal vesicle	(49)	(50)	(50)	(50)
Congenital hypoplasia	1 (2%)		2 (4%)	
Retention of content				1 (2%)
Hemorrhage			2 (4%)	
Inflammation, NOS		1 (2%)		
Inflammation, focal	1 (2%)	1 (2%)		
Inflammation, suppurative	1 (2%)	1 (2%)	2 (4%)	
Inflammation, hemorrhagic		1 (2%)		
Inflammation, acute			1 (2%)	1 (2%)
Inflammation, acute suppurative		2 (4%)		
Inflammation, acute hemorrhagic				1 (2%)
Abscess, NOS			1 (2%)	
Inflammation, acute/chronic		2 (4%)		
Inflammation chronic suppurative	1 (2%)			
Atrophy, NOS				2 (4%)
#Testis	(46)	(46)	(48)	(48)
Agenesis		2 (4%)		
Hemorrhage		1 (2%)		
Lipogranuloma			1 (2%)	
Calcification, focal		1 (2%)		
Syncytial alteration		1 (2%)		
Atrophy, NOS			1 (2%)	
Atrophy, focal	3 (7%)	1 (2%)	1 (2%)	
Aspermatogenesis	1 (2%)	2 (4%)		1 (2%)
Hypospermatogenesis			1 (2%)	
Hyperplasia, interstitial cell	2 (4%)	1 (2%)	6 (13%)	5 (10%)
Dysplasia, NOS	1 (2%)			
#Rete testis	(46)	(46)	(48)	(48)
Hyperplasia, NOS				1 (2%)
*Epididymis	(49)	(50)	(50)	(50)
Inflammation, focal	1 (2%)			
Inflammation, interstitial			1 (2%)	
NERVOUS SYSTEM				
*Spinal cord	(49)	(50)	(50)	(50)
Hemorrhage		1 (2%)		
SPECIAL SENSE ORGANS				
*Harderian gland	(49)	(50)	(50)	(50)
Inflammation, focal				1 (2%)
Inflammation, acute focal			1 (2%)	
Inflammation, chronic			3 (6%)	1 (2%)
Inflammation, chronic focal		2 (4%)	7 (14%)	8 (16%)
*Middle ear	(49)	(50)	(50)	(50)
Inflammation, suppurative			2 (4%)	
MUSCULOSKELETAL SYSTEM				
*Muscle hip/thigh	(49)	(50)	(50)	(50)
Degeneration, NOS			1 (2%)	
Atrophy, serous		1 (2%)		

APPENDIX F

SUMMARY OF LESIONS IN FEMALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

TABLE F1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MARSHALL RATS IN THE *TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE*

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	48
INTEGUMENTARY SYSTEM				
*Skin	(50)	(50)	(50)	(48)
Squamous cell carcinoma			1 (2%)	
Basal cell tumor		1 (2%)		
Basal cell carcinoma		1 (2%)		
Trichoepithelioma		1 (2%)		
RESPIRATORY SYSTEM				
#Lung	(50)	(49)	(49)	(46)
Neoplasm, NOS, metastatic			1 (2%)	
Squamous cell carcinoma, metastatic			1 (2%)	
Pheochromocytoma, metastatic	3 (6%)	3 (6%)		1 (2%)
Sarcoma, NOS, metastatic			1 (2%)	
HEMATOPOIETIC SYSTEM				
*Multiple organs	(50)	(50)	(50)	(48)
Malignant lymphoma, NOS	1 (2%)			
Malignant lymphoma, undiffer type			1 (2%)	
Malignant lymphoma, lymphocytic type		1 (2%)		
Malignant lymphoma, histiocytic type	1 (2%)			
Lymphocytic leukemia		1 (2%)		
CIRCULATORY SYSTEM				
*Axilla	(50)	(50)	(50)	(48)
Hemangiosarcoma		1 (2%)		
#Lung	(50)	(49)	(49)	(46)
Hemangiosarcoma, metastatic		1 (2%)		
DIGESTIVE SYSTEM				
*Buccal mucosa	(50)	(50)	(50)	(48)
Undifferentiated carcinoma			1 (2%)	
#Stomach	(49)	(49)	(46)	(43)
Squamous cell papilloma				1 (2%)
URINARY SYSTEM				
#Kidney	(49)	(50)	(48)	(44)
Tubular cell adenoma	1 (2%)	1 (2%)	1 (2%)	
Tubular cell adenocarcinoma			1 (2%)	1 (2%)
#Kidney/pelvis	(49)	(50)	(48)	(44)
Transitional cell papilloma			2 (4%)	1 (2%)
Transitional cell carcinoma	1 (2%)	1 (2%)		2 (5%)
#Urinary bladder	(45)	(46)	(40)	(40)
Transitional cell papilloma			1 (3%)	

TABLE F1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM				
#Pituitary	(42)	(45)	(38)	(42)
Carcinoma, NOS	1 (2%)			
Chromophobe adenoma	22 (52%)	18 (40%)	8 (21%)	6 (14%)
Chromophobe carcinoma	1 (2%)	1 (2%)		
Acidophil adenoma		1 (2%)		
Acidophil carcinoma	1 (2%)			
#Adrenal	(47)	(49)	(47)	(43)
Cortical adenoma	4 (9%)	5 (10%)	2 (4%)	3 (7%)
Pheochromocytoma	30 (64%)	39 (80%)	15 (32%)	9 (21%)
Pheochromocytoma, malignant	4 (9%)	4 (8%)		1 (2%)
#Thyroid	(48)	(43)	(46)	(43)
Adenoma, NOS	1 (2%)			
C-cell adenoma	12 (25%)	10 (23%)	5 (11%)	4 (9%)
C-cell carcinoma	1 (2%)		2 (4%)	1 (2%)
#Pancreatic islets	(48)	(49)	(46)	(42)
Islet cell adenoma	2 (4%)			
REPRODUCTIVE SYSTEM				
*Mammary gland	(50)	(50)	(50)	(48)
Adenocarcinoma, NOS	1 (2%)	3 (6%)		
Fibroadenoma	7 (14%)	11 (22%)	2 (4%)	4 (8%)
*Vagina	(50)	(50)	(50)	(48)
Papilloma, NOS				1 (2%)
#Uterus	(47)	(50)	(45)	(44)
Endometrial stromal polyp	6 (13%)	3 (6%)	5 (11%)	2 (5%)
#Uterus/endometrium	(47)	(50)	(45)	(44)
Carcinoma, NOS				2 (5%)
#Ovary	(47)	(48)	(45)	(44)
Granulosa cell carcinoma		1 (2%)		
NERVOUS SYSTEM				
#Brain	(50)	(50)	(50)	(48)
Chromophobe carcinoma, invasive		1 (2%)		
Acidophil carcinoma, invasive	1 (2%)			
SPECIAL SENSE ORGANS				
None				
MUSCULOSKELETAL SYSTEM				
*Mandible	(50)	(50)	(50)	(48)
Sarcoma, NOS			1 (2%)	
BODY CAVITIES				
*Thorax	(50)	(50)	(50)	(48)
Fibrosarcoma			1 (2%)	
*Mediastinum	(50)	(50)	(50)	(48)
Nonchromaffin paraganglioma			1 (2%)	
ALL OTHER SYSTEMS				
None				

TABLE F1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY				
Animals initially in study	50	50	50	50
Natural death	10	7	14	19
Moribund sacrifice	8	10	10	3
Terminal sacrifice	31	30	12	10
Accidentally killed, NOS	1	3	14	18
TUMOR SUMMARY				
Total animals with primary tumors**	46	47	31	22
Total primary tumors	97	104	50	38
Total animals with benign tumors	45	46	28	19
Total benign tumors	85	90	42	31
Total animals with malignant tumors	10	11	8	7
Total malignant tumors	12	14	8	7
Total animals with secondary tumors##	4	5	3	1
Total secondary tumors	4	5	3	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 F2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: UNTREATED CONTROL

ANIMAL NUMBER	0001	0004	0008	0110	0114	0119	0220	0222	0226	0332	0335	0337	0338	0445	0550	0555	0557	0560	0563	0566	0572	0576	0577	0588	8993
WEEKS ON STUDY	0899	0794	1055	1055	1003	0778	0992	1055	0999	1055	0883	1055	0740	1055	0555	0881	1055	1055	0779	1055	1055	0995	0771	1055	0886
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma, metastatic																									
Trachea	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	−	−	+	+	−	−	+	+	+	+	−	+	−	−	−	+	+	+	+	+	+	−	+	+	+
Thymus	+	−	−	−	−	−	+	−	−	−	−	−	+	−	−	+	−	−	−	−	−	−	+	−	+
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	−	−	+	+	+	+	+	−	−	+	+	+	−	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma																									
Urinary bladder	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−
ENDOCRINE SYSTEM																									
Pituitary	+	−	+	+	−	+	+	+	+	−	+	+	+	−	+	+	−	+	+	+	+	−	+	+	+
Carcinoma, NOS																			X						
Chromophobe adenoma				X			X	X	X		X	X						X		X			X		X
Chromophobe carcinoma																									
Acidophil carcinoma																									
Adrenal	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Cortical adenoma	X																			X	X				
Pheochromocytoma	X			X	X		X		X	X		X		X		X			X	X	X			X	X
Pheochromocytoma, malignant								X																	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+
Adenoma, NOS																									X
C-cell adenoma			X									X								X		X		X	
C-cell carcinoma								X																	
Parathyroid	+	−	−	+	+	+	−	−	+	−	−	−	−	−	−	+	−	+	+	+	−	−	−	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	N	N	+	+	+
Adenocarcinoma, NOS																									
Fibroadenoma															X			X	X						
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp	X			X															X	X					
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acidophil carcinoma, invasive																									
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																									
Malignant lymphoma, histiocytic type																									

+: 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 F2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MARSHALL RATS: UNTREATED CONTROL (Continued)

ANIMAL NUMBER	897	903	907	908	911	912	914	916	917	923	924	926	927	942	953	959	968	969	970	981	984	991	993	995	997	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	105	105	105	086	081	105	105	069	105	105	105	105	105	105	105	105	100	105	105	099	105	105	105	105	105	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma, metastatic											X					X		X								3
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	−	+	+	+	−	−	−	−	−	+	+	−	+	+	+	+	−	+	−	−	+	31
Thymus	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	6
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
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	N	*50
Pancreas	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
URINARY SYSTEM																										
Kidney	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tubular cell adenoma																X										1
Kidney/pelvis	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Transitional cell carcinoma	X																									1
Urinary bladder	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
ENDOCRINE SYSTEM																										
Pituitary	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Carcinoma, NOS																										1
Chromophobe adenoma	X	X			X	X		X	X	X	X			X				X					X	X			22
Chromophobe carcinoma																				X						1
Acidophil carcinoma																	X									1
Adrenal	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Cortical adenoma																		X								4
Pheochromocytoma	X		X						X		X	X	X	X	X		X	X	X	X	X	X	X		X	30
Pheochromocytoma, malignant											X					X		X								4
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS																										1
C-cell adenoma						X	X		X			X	X	X										X		12
C-cell carcinoma																										1
Parathyroid	+	+	+	+	+	−	+	+	+	+	−	+	−	−	+	−	+	−	+	−	+	−	+	+	−	27
Pancreatic islets	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma		X											X													2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	N	+	N	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	*50
Adenocarcinoma, NOS																	X									1
Fibroadenoma	X	X									X												X			7
Uterus	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	47
Endometrial stromal polyp	X																X									6
Ovary	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acidophil carcinoma, invasive																	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
Malignant lymphoma, NOS								X																		1
Malignant lymphoma, histiocytic type				X																						1

* Animals necropsied

TABLE F2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: VEHICLE CONTROL

ANIMAL NUMBER	0002	0003	0005	0012	0016	0017	0023	0025	0028	0039	0042	0043	0044	0053	0059	0069	0071	0078	0080	0082	0090	0092	8995	8998	9000
WEEKS ON STUDY	1044	0788	0788	1100	0991	1044	1044	0551	1044	0884	1044	1044	1044	0887	0778	0688	0999	1044	1044	1100	0999	1044	1044	1044	1044
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+
Basal cell tumor																									
Basal cell carcinoma																									
Trichoepithelioma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma, metastatic	X																					X			
Hemangiosarcoma, metastatic																									
Trachea	+	+	+	−	+	+	+	−	−	+	+	+	+	+	+	−	+	+	+	+	−	+	−	−	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	−	−	+	+	+	−	−	−	−	−	−	+	+	−	−	+	+	+	−	+	+	−	+	+
Thymus	−	+	+	−	−	−	−	+	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−
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	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma																									
Urinary bladder	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−
Chromophobe adenoma		X		X						X		X			X				X		X	X	X		
Chromophobe carcinoma																	X								
Acidophil adenoma																									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma											X												X		
Pheochromocytoma	X	X		X	X	X	X		X		X	X	X		X	X	X	X	X	X		X	X	X	X
Pheochromocytoma, malignant	X						X															X			
Thyroid	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	−	−	+	+	+	+
C-cell adenoma							X				X		X						X					X	
Parathyroid	+	+	+	−	−	−	+	−	−	−	+	+	+	−	+	−	+	−	+	−	−	−	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+
Adenocarcinoma, NOS																			X			X			
Fibroadenoma	X	X	X		X													X			X		X	X
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp						X																			
Ovary	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell carcinoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chromophobe carcinoma, invasive																	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, lymphocytic type								X																	
Lymphocytic leukemia																									X
Axilla, NOS																									
Hemangiosarcoma																									

TABLE F2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MARSHALL RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	902	906	920	928	930	935	936	939	944	946	949	955	960	964	966	971	972	974	975	976	977	983	989	996	999	TOTAL:
WEEKS ON STUDY	104	091	104	086	104	104	104	100	104	098	070	104	104	104	092	104	104	104	104	104	104	090	104	096	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	*50
Basal cell tumor																									X	1
Basal cell carcinoma																X										1
Trichoepithelioma																X										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma, metastatic																X										3
Hemangiosarcoma, metastatic								X																		1
Trachea	+	+	+	+	+	+	+	−	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	39
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	−	+	−	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	−	−	+	−	31
Thymus	−	+	−	−	−	−	−	−	−	−	+	−	+	−	−	−	−	−	−	−	−	−	−	−	−	7
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	46
Large intestine	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	−		45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma																						X				1
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional cell carcinoma			X																							1
Urinary bladder	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Chromophobe adenoma	X	X				X							X			X	X		X			X			X	18
Chromophobe carcinoma																										1
Acidophil adenoma												X														1
Adrenal	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma		X	X			X																				5
Pheochromocytoma			X	X	X	X	X	X	X	X		X	X		X			X	X	X	X	X	X	X	X	39
Pheochromocytoma, malignant																X										4
Thyroid	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
C-cell adenoma					X				X						X				X							10
Parathyroid	−	+	+	−	+	+	−	+	−	−	−	−	−	+	+	−	−	−	−	−	+	−	+	−	−	22
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	+	N	+	+	+	+	+	N	+	+	N	+	+	N	+	+	N	+	+	+	+	N	*50
Adenocarcinoma, NOS	X																									3
Fibroadenoma				X		X																		X		11
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp				X						X																3
Ovary	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Granulosa cell carcinoma								X																		1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chromophobe carcinoma, invasive																										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, lymphocytic type																										1
Lymphocytic leukemia																										1
Axilla, NOS																										
Hemangiosarcoma								X																		1

* Animals necropsied

TABLE F2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: LOW DOSE

ANIMAL NUMBER	001	011	029	030	031	041	046	051	056	065	068	070	073	074	075	079	081	083	085	087	091	894	896	901	909
WEEKS ON STUDY	099	052	064	104	095	076	075	100	104	058	094	076	079	075	068	087	032	090	068	059	104	073	100	096	075
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplasm, NOS, metastatic																									
Squamous cell carcinoma, metastatic																									
Sarcoma, NOS, metastatic																X									
Trachea	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Undifferentiated carcinoma																									
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	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	−	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	−	+	+	+	−	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
URINARY SYSTEM																									
Kidney	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Tubular cell adenocarcinoma																							X		
Kidney/pelvis	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma													X												
Urinary bladder	+	−	+	+	+	−	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	−	+	−
Transitional cell papilloma													X												
ENDOCRINE SYSTEM																									
Pituitary	−	+	+	+	−	+	+	+	+	−	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+
Chromophobe adenoma						X		X														X			X
Adrenal	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma				X					X									X			X		X	X	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
C-cell adenoma									X																
C-cell carcinoma					X								X												
Parathyroid	+	−	+	+	−	−	−	−	+	+	+	+	−	+	−	+	+	−	−	−	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+
Fibroadenoma																									
Uterus	+	−	+	+	+	−	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Endometrial stromal polyp														X											
Ovary	+	−	+	+	+	−	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	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																									
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	N
Fibrosarcoma																									
Mediastinum	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
Nonchromaffin paraganglioma	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, undiffer type																								X	

TABLE F2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MARSHALL RATS: LOW DOSE (Continued)

ANIMAL NUMBER	91 13	91 15	91 18	92 21	92 22	92 29	93 31	93 32	93 33	94 43	94 45	94 47	95 50	95 51	95 52	95 54	95 57	96 63	96 85	97 78	97 79	98 82	98 86	98 87	98 88	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	08 1	06 8	06 6	04 8	10 4	10 4	10 4	09 7	08 2	07 6	10 4	07 7	07 1	01 2	10 4	10 4	10 4	08 3	10 3	01 7	10 4	07 8	10 4	10 3	08 0	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell carcinoma																								X		1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplasm, NOS, metastatic																			X							1
Squamous cell carcinoma, metastatic																								X		1
Sarcoma, NOS, metastatic																										1
Trachea	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	−	+	45
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	47
Lymph nodes	+	−	+	−	+	−	+	+	+	−	+	+	+	+	−	−	−	+	−	+	−	+	+	+	−	29
Thymus	+	+	−	−	−	−	−	−	−	+	−	−	+	+	−	−	+	−	−	+	−	+	−	−	+	16
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
Undifferentiated carcinoma	X																									1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	48
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	46
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	45
Large intestine	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	43
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	48
Tubular cell adenoma																					X					1
Tubular cell adenocarcinoma																										1
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	48
Transitional cell papilloma										X																2
Urinary bladder	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	−	+	+	+	40
Transitional cell papilloma																										1
ENDOCRINE SYSTEM																										
Pituitary	−	+	+	−	+	+	+	+	+	+	+	+	−	−	+	−	+	+	−	−	+	+	+	+	+	38
Chromophobe adenoma								X							X		X								X	8
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	47
Cortical adenoma								X			X															2
Pheochromocytoma	X	X					X				X				X		X							X	X	X	15
Thyroid	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	−	+	+	46
C-cell adenoma					X						X						X				X					5
C-cell carcinoma																										2
Parathyroid	+	+	+	−	+	−	−	+	+	−	+	−	+	−	+	−	+	+	−	−	−	−	−	+	−	27
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	N	+	N	+	+	N	+	+	+	+	N	N	+	+	N	+	+	+	+	+	+	+	*50
Fibroadenoma																					X		X			2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	45
Endometrial stromal polyp			X		X								X										X			5
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	45
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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
Sarcoma, NOS																										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	N	*50
Fibrosarcoma																						X				1
Mediastinum	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
Nonchromaffin paraganglioma																										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, undiffer type																										1

* Animals necropsied

TABLE F2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: HIGH DOSE

ANIMAL NUMBER	0006	0007	0009	0113	0115	0118	0021	0024	0027	0033	0034	0036	0040	0047	0048	0049	0052	0054	0058	0061	0062	0064	0067	0084	0086
WEEKS ON STUDY	1044	0688	0644	0733	0744	0730	0889	0877	0770	0774	0554	1044	0441	0555	0666	1046	0996	0824	1044	0778	0881	1044	0122	0899	0334
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma, metastatic																									
Trachea	+	+	−	+	+	A	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Spleen	+	+	+	+	+	A	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	−	−	+	+	−	A	−	+	−	−	+	−	−	−	−	+	−	−	+	+	+	+	+	+	+
Thymus	−	+	−	−	−	A	−	+	+	−	+	−	+	+	+	−	+	−	−	+	+	+	+	+	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	A	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	−	+	+	+	+	A	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	+	+	+	+	+	A	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	A	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	A	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma																						X			
Kidney/pelvis	+	+	+	+	+	A	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma																									
Transitional cell carcinoma			X																						
Urinary bladder	+	+	+	+	+	A	+	+	+	+	+	+	−	−	+	+	+	+	+	+	−	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	−	+	+	+	−	A	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Chromophobe adenoma																		X							
Adrenal	+	+	+	+	+	A	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−
Cortical adenoma							X								X										
Pheochromocytoma																X		X	X			X			
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
C-cell adenoma																		X	X						
C-cell carcinoma												X													
Parathyroid	−	−	+	−	−	A	−	−	+	−	−	+	−	+	+	+	+	+	+	−	−	+	−	+	−
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	N	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																				X	X				
Vagina	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papilloma, NOS																									
Uterus	+	+	+	+	+	A	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Endometrial stromal polyp																									
Ovary	+	+	+	+	+	A	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE F2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MARSHALL RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	089	099	004	005	010	019	025	034	037	038	040	041	048	056	058	061	062	067	073	080	085	090	092	094	098	TOTAL:
WEEKS ON STUDY	017	076	060	089	055	055	104	044	083	008	052	087	014	088	044	028	035	021	097	068	100	044	030	057	060	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	A	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	46
Pheochromocytoma, metastatic																						X				1
Trachea	A	+	+	+	+	+	−	+	−	+	−	+	−	+	−	+	+	+	+	+	+	+	A	+	−	38
HEMATOPOIETIC SYSTEM																										
Bone marrow	A	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	A	+	+	44
Spleen	A	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	A	+	+	43
Lymph nodes	A	−	+	−	+	+	+	−	−	−	+	+	+	−	+	−	−	−	+	−	−	−	A	+	+	23
Thymus	A	+	+	−	+	−	−	−	−	+	−	+	−	+	−	+	−	+	−	−	−	−	A	−	−	21
CIRCULATORY SYSTEM																										
Heart	A	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	46
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	A	−	+	44
Liver	A	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	46
Bile duct	A	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	46
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	A	N	N	*48
Pancreas	A	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	A	+	+	42
Esophagus	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	A	+	+	46
Stomach	A	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	43
Squamous cell papilloma																					X					1
Small intestine	A	−	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	A	+	+	42
Large intestine	A	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	A	+	+	41
URINARY SYSTEM																										
Kidney	A	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	A	+	+	44
Tubular cell adenocarcinoma																										1
Kidney/pelvis	A	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	A	+	+	44
Transitional cell papilloma																								X		1
Transitional cell carcinoma								X																		2
Urinary bladder	A	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	−	A	+	+	40
ENDOCRINE SYSTEM																										
Pituitary	A	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	A	+	+	42
Chromophobe adenoma				X			X								X					X	X					6
Adrenal	A	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	A	+	+	43
Cortical adenoma							X																			3
Pheochromocytoma								X	X				X						X			X				9
Pheochromocytoma, malignant																						X				1
Thyroid	A	+	+	+	+	+	+	+	−	+	−	+	+	−	+	+	+	+	+	+	+	+	A	+	+	43
C-cell adenoma															X									X		4
C-cell carcinoma																										1
Parathyroid	A	+	−	−	−	+	+	+	−	−	−	−	−	−	+	+	−	−	+	+	+	+	A	+	−	22
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	+	N	+	+	N	+	+	N	+	+	N	+	+	+	+	N	+	+	+	N	A	+	N	*48
Fibroadenoma																			X		X					4
Vagina	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	*48
Papilloma, NOS																						X				1
Uterus	A	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	44
Carcinoma, NOS																X								X		2
Endometrial stromal polyp							X															X				2
Ovary	A	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	44
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	48

* Animals necropsied

TABLE F3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg
Kidney: Transitional Cell Papilloma or Carcinoma				
Overall Rates (a)	1/49 (2%)	1/50 (2%)	2/48 (4%)	3/44 (7%)
Adjusted Rates (b)	3.2%	3.3%	6.7%	15.5%
Terminal Rates (c)	1/31 (3%)	1/30 (3%)	0/12 (0%)	1/10 (10%)
Life Table Tests (d)		P=0.060	P=0.302	P=0.095
Incidental Tumor Tests (d)		P=0.205	P=0.515	P=0.278
Cochran-Armitage Trend Test (d)		P=0.184		
Fisher Exact Test			P=0.485	P=0.262
Pituitary: Chromophobe Adenoma				
Overall Rates (a)	22/42 (52%)	18/45 (40%)	8/38 (21%)	6/42 (14%)
Adjusted Rates (b)	64.4%	51.7%	36.3%	39.2%
Terminal Rates (c)	15/26 (58%)	11/26 (42%)	2/11 (18%)	2/9 (22%)
Life Table Tests (d)		P=0.412N	P=0.482N	P=0.506N
Incidental Tumor Tests (d)		P=0.036N	P=0.097N	P=0.079N
Cochran-Armitage Trend Test (d)		P=0.004N		
Fisher Exact Test			P=0.052N	P=0.007N
Pituitary: Chromophobe Adenoma or Carcinoma				
Overall Rates (a)	23/42 (55%)	19/45 (42%)	8/38 (21%)	6/42 (14%)
Adjusted Rates (b)	65.5%	53.1%	36.3%	39.2%
Terminal Rates (c)	15/26 (58%)	11/26 (42%)	2/11 (18%)	2/9 (22%)
Life Table Tests (d)		P=0.357N	P=0.427N	P=0.458N
Incidental Tumor Tests (d)		P=0.023N	P=0.062N	P=0.057N
Cochran-Armitage Trend Test (d)		P=0.002N		
Fisher Exact Test			P=0.034N	P=0.004N
Pituitary: Adenoma				
Overall Rates (a)	22/42 (52%)	19/45 (42%)	8/38 (21%)	6/42 (14%)
Adjusted Rates (b)	64.4%	54.9%	36.3%	39.2%
Terminal Rates (c)	15/26 (58%)	12/26 (46%)	2/11 (18%)	2/9 (22%)
Life Table Tests (d)		P=0.354N	P=0.429N	P=0.453N
Incidental Tumor Tests (d)		P=0.026N	P=0.075N	P=0.062N
Cochran-Armitage Trend Test (d)		P=0.002N		
Fisher Exact Test			P=0.034N	P=0.004N
Pituitary: Adenoma or Carcinoma				
Overall Rates (a)	25/42 (60%)	20/45 (44%)	8/38 (21%)	6/42 (14%)
Adjusted Rates (b)	67.3%	56.2%	36.3%	39.2%
Terminal Rates (c)	15/26 (58%)	12/26 (46%)	2/11 (18%)	2/9 (22%)
Life Table Tests (d)		P=0.304N	P=0.376N	P=0.408N
Incidental Tumor Tests (d)		P=0.016N	P=0.047N	P=0.044N
Cochran-Armitage Trend Test (d)		P=0.001N		
Fisher Exact Test			P=0.021N	P=0.002N
Adrenal: Cortical Adenoma				
Overall Rates (a)	4/47 (9%)	5/49 (10%)	2/47 (4%)	3/43 (7%)
Adjusted Rates (b)	12.1%	15.9%	13.4%	18.8%
Terminal Rates (c)	3/31 (10%)	4/29 (14%)	1/12 (8%)	1/10 (10%)
Life Table Tests (d)		P=0.346	P=0.620N	P=0.394
Incidental Tumor Tests (d)		P=0.551	P=0.514N	P=0.649N
Cochran-Armitage Trend Test (d)		P=0.333N		
Fisher Exact Test			P=0.235N	P=0.433N
Adrenal: Pheochromocytoma				
Overall Rates (a)	30/47 (64%)	39/49 (80%)	15/47 (32%)	9/43 (21%)
Adjusted Rates (b)	74.8%	92.7%	76.5%	67.0%
Terminal Rates (c)	21/31 (68%)	26/29 (90%)	8/12 (67%)	6/10 (60%)
Life Table Tests (d)		P=0.050N	P=0.263N	P=0.067N
Incidental Tumor Tests (d)		P<0.001N	P=0.002N	P<0.001N
Cochran-Armitage Trend Test (d)		P<0.001N		
Fisher Exact Test			P<0.001N	P<0.001N

TABLE F3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg
Adrenal: Pheochromocytoma, Malignant				
Overall Rates (a)	4/47 (9%)	4/49 (8%)	0/47 (0%)	1/43 (2%)
Adjusted Rates (b)	12.9%	13.8%	0.0%	10.0%
Terminal Rates (c)	4/31 (13%)	4/29 (14%)	0/12 (0%)	1/10 (10%)
Life Table Tests (d)		P=0.354N	P=0.222N	P=0.593N
Incidental Tumor Tests (d)		P=0.354N	P=0.222N	P=0.593N
Cochran-Armitage Trend Test (d)		P=0.100N		
Fisher Exact Test			P=0.064N	P=0.224N
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant				
Overall Rates (a)	32/47 (68%)	40/49 (82%)	15/47 (32%)	9/43 (21%)
Adjusted Rates (b)	79.8%	95.1%	76.5%	67.0%
Terminal Rates (c)	23/31 (74%)	27/29 (93%)	8/12 (67%)	6/10 (60%)
Life Table Tests (d)		P=0.036N	P=0.222N	P=0.050N
Incidental Tumor Tests (d)		P<0.001N	P<0.001N	P<0.001N
Cochran-Armitage Trend Test (d)		P<0.001N		
Fisher Exact Test			P<0.001N	P<0.001N
Thyroid: C-Cell Adenoma				
Overall Rates (a)	12/48 (25%)	10/43 (23%)	5/46 (11%)	4/43 (9%)
Adjusted Rates (b)	37.3%	31.8%	45.5%	26.2%
Terminal Rates (c)	11/31 (35%)	9/30 (30%)	5/11 (45%)	2/10 (20%)
Life Table Tests (d)		P=0.432	P=0.394	P=0.561
Incidental Tumor Tests (d)		P=0.552N	P=0.423	P=0.473N
Cochran-Armitage Trend Test (d)		P=0.046N		
Fisher Exact Test			P=0.101N	P=0.071N
Thyroid: C-Cell Adenoma or Carcinoma				
Overall Rates (a)	13/48 (27%)	10/43 (23%)	7/46 (15%)	5/43 (12%)
Adjusted Rates (b)	40.4%	31.8%	50.1%	35.5%
Terminal Rates (c)	12/31 (39%)	9/30 (30%)	5/11 (45%)	3/10 (30%)
Life Table Tests (d)		P=0.219	P=0.150	P=0.364
Incidental Tumor Tests (d)		P=0.403	P=0.249	P=0.593
Cochran-Armitage Trend Test (d)		P=0.096N		
Fisher Exact Test			P=0.244N	P=0.128N
Mammary Gland: Adenocarcinoma				
Overall Rates (a)	1/50 (2%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	3.0%	10.0%	0.0%	0.0%
Terminal Rates (c)	0/31 (0%)	3/30 (10%)	0/12 (0%)	0/10 (0%)
Life Table Tests (d)		P=0.157N	P=0.320N	P=0.366N
Incidental Tumor Tests (d)		P=0.157N	P=0.320N	P=0.366N
Cochran-Armitage Trend Test (d)		P=0.037N		
Fisher Exact Test			P=0.121N	P=0.121N
Mammary Gland: Fibroadenoma				
Overall Rates (a)	7/50 (14%)	11/50 (22%)	2/50 (4%)	4/48 (8%)
Adjusted Rates (b)	19.8%	28.2%	16.7%	24.2%
Terminal Rates (c)	5/31 (16%)	5/30 (17%)	2/12 (17%)	0/10 (0%)
Life Table Tests (d)		P=0.418N	P=0.159N	P=0.601N
Incidental Tumor Tests (d)		P=0.087N	P=0.024N	P=0.120N
Cochran-Armitage Trend Test (d)		P=0.023N		
Fisher Exact Test			P=0.007N	P=0.054N
Mammary Gland: Fibroadenoma or Adenocarcinoma				
Overall Rates (a)	8/50 (16%)	14/50 (28%)	2/50 (4%)	4/48 (8%)
Adjusted Rates (b)	22.2%	36.8%	16.7%	24.2%
Terminal Rates (c)	5/31 (16%)	8/30 (27%)	2/12 (17%)	0/10 (0%)
Life Table Tests (d)		P=0.228N	P=0.076N	P=0.429N
Incidental Tumor Tests (d)		P=0.032N	P=0.009N	P=0.062N
Cochran-Armitage Trend Test (d)		P=0.003N		
Fisher Exact Test			P=0.001N	P=0.011N

TABLE F3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg
Uterus: Endometrial Stromal Polyp				
Overall Rates (a)	6/47 (13%)	3/50 (6%)	5/45 (11%)	2/44 (5%)
Adjusted Rates (b)	17.0%	8.2%	23.2%	20.0%
Terminal Rates (c)	3/30 (10%)	1/30 (3%)	2/12 (17%)	2/10 (20%)
Life Table Tests (d)		P=0.244	P=0.107	P=0.409
Incidental Tumor Tests (d)		P=0.533	P=0.386	P=0.505
Cochran-Armitage Trend Test (d)		P=0.489N		
Fisher Exact Test			P=0.300	P=0.561

(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 vehicle 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 rates. A regular trend or lower incidence in a dosed group is indicated by (N).

TABLE F4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	48
INTEGUMENTARY SYSTEM				
*Subcutaneous tissue	(50)	(50)	(50)	(48)
Inflammation, necrotizing				1 (2%)
Foreign material, NOS			1 (2%)	1 (2%)
RESPIRATORY SYSTEM				
*Nasal cavity	(50)	(50)	(50)	(48)
Inflammation, NOS			1 (2%)	
Inflammation, suppurative		2 (4%)	6 (12%)	1 (2%)
Inflammation, acute/chronic				1 (2%)
Inflammation chronic suppurative			1 (2%)	
*Larynx	(50)	(50)	(50)	(48)
Granuloma, foreign body			1 (2%)	
#Trachea	(47)	(39)	(45)	(38)
Wound, NOS			1 (2%)	
Lacerated wound				1 (3%)
Penetrating wound				1 (3%)
Inflammation, acute focal	1 (2%)			
Foreign material, NOS	1 (2%)		2 (4%)	3 (8%)
#Peritracheal tissue	(47)	(39)	(45)	(38)
Abscess, chronic			1 (2%)	
#Lung	(50)	(49)	(49)	(46)
Emphysema, alveolar				2 (4%)
Collapse	2 (4%)		3 (6%)	1 (2%)
Congestion, NOS	5 (10%)	6 (12%)	10 (20%)	12 (26%)
Congestion, chronic passive	1 (2%)			
Edema, NOS	1 (2%)	1 (2%)	3 (6%)	2 (4%)
Hemorrhage	5 (10%)	6 (12%)	9 (18%)	10 (22%)
Bronchopneumonia, NOS		2 (4%)	1 (2%)	
Bronchopneumonia, focal			2 (4%)	
Inflammation, focal	1 (2%)	19 (39%)	10 (20%)	2 (4%)
Inflammation, interstitial		1 (2%)		
Inflammation, necrotizing			1 (2%)	
Bronchopneumonia, acute	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Inflammation, acute focal		1 (2%)		
Abscess, NOS			1 (2%)	
Inflammation, chronic focal		6 (12%)	11 (22%)	7 (15%)
Inflammation, granulomatous focal	3 (6%)	6 (12%)	1 (2%)	11 (24%)
Foreign material, NOS	1 (2%)	1 (2%)	5 (10%)	9 (20%)
Hemosiderosis		1 (2%)		
Russell body	1 (2%)			
Alveolar macrophages		1 (2%)	1 (2%)	1 (2%)
Hyperplasia, alveolar epithelium	1 (2%)			1 (2%)
HEMATOPOIETIC SYSTEM				
#Bone marrow	(50)	(50)	(48)	(44)
Hyperplasia, granulocytic			2 (4%)	
#Spleen	(49)	(49)	(47)	(43)
Congestion, NOS		1 (2%)	1 (2%)	
Hemosiderosis	4 (8%)	2 (4%)	2 (4%)	
Hematopoiesis	6 (12%)	12 (24%)	5 (11%)	3 (7%)
Erythropoiesis	1 (2%)			
#Mandibular lymph node	(31)	(31)	(29)	(23)
Hemorrhage			1 (3%)	1 (4%)

TABLE F4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)				
#Mesenteric lymph node	(31)	(31)	(29)	(23)
Hemorrhage	2 (6%)		2 (7%)	
Inflammation, chronic focal	1 (3%)			
#Liver	(50)	(49)	(48)	(46)
Hematopoiesis			1 (2%)	
#Thymus	(6)	(7)	(16)	(21)
Multiple cysts		1 (14%)		
Hemorrhage			1 (6%)	
Involution, NOS		1 (14%)		
CIRCULATORY SYSTEM				
*Multiple organs	(50)	(50)	(50)	(48)
Arteriolosclerosis			1 (2%)	
#Lung	(50)	(49)	(49)	(46)
Thrombosis, NOS		1 (2%)		
Perivasculitis	1 (2%)		1 (2%)	
#Heart	(50)	(49)	(50)	(46)
Thrombus, mural		1 (2%)		
Thrombus, fibrin			1 (2%)	
Inflammation, focal	1 (2%)			
Fibrosis	2 (4%)			
Fibrosis, focal	2 (4%)		1 (2%)	1 (2%)
Periarteritis		1 (2%)		
Calcification, focal	1 (2%)	1 (2%)		
*Aorta	(50)	(50)	(50)	(48)
Polyangiitis				1 (2%)
Calcification, metastatic				1 (2%)
*Pulmonary artery	(50)	(50)	(50)	(48)
Calcification, focal	5 (10%)	1 (2%)		
#Pancreas	(48)	(49)	(46)	(42)
Periarteritis			1 (2%)	
*Mesentery	(50)	(50)	(50)	(48)
Periarteritis			1 (2%)	
DIGESTIVE SYSTEM				
#Salivary gland	(47)	(46)	(47)	(44)
Inflammation, NOS				1 (2%)
Inflammation, acute			1 (2%)	
Inflammation, chronic				1 (2%)
Atrophy, focal		1 (2%)		
#Liver	(50)	(49)	(48)	(46)
Congestion, NOS	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Congestion, passive	1 (2%)	1 (2%)		1 (2%)
Congestion, acute passive			1 (2%)	
Inflammation, focal	1 (2%)	1 (2%)	1 (2%)	
Necrosis, NOS	1 (2%)	1 (2%)		1 (2%)
Necrosis, focal	2 (4%)		2 (4%)	1 (2%)
Necrosis, central	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Metamorphosis, fatty	1 (2%)	1 (2%)	3 (6%)	1 (2%)
Mitotic alteration		1 (2%)		
Basophilic cyto change	1 (2%)			
Eosinophilic cyto change	1 (2%)			
Clear cell change	2 (4%)	7 (14%)		2 (4%)
Atrophy, NOS	1 (2%)			
Depletion, glycogen	1 (2%)			

TABLE F4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)				
#Esophagus	(49)	(50)	(50)	(46)
Lacerated wound		3 (6%)	3 (6%)	6 (13%)
Diverticulum				1 (2%)
Impaction, NOS	2 (4%)			
Inflammation, granulomatous		1 (2%)		
#Stomach	(49)	(49)	(46)	(43)
Calcification, metastatic				1 (2%)
#Gastric mucosa	(49)	(49)	(46)	(43)
Inflammation, focal			1 (2%)	
Hyperkeratosis			1 (2%)	
#Colon	(44)	(45)	(43)	(41)
Hemorrhage				1 (2%)
Parasitism	3 (7%)	3 (7%)	2 (5%)	4 (10%)
*Rectum	(50)	(50)	(50)	(48)
Parasitism				1 (2%)
URINARY SYSTEM				
#Kidney	(49)	(50)	(48)	(44)
Congenital hydronephrosis	23 (47%)	21 (42%)	17 (35%)	12 (27%)
Calculus, unknown gross or micro			1 (2%)	1 (2%)
Hydronephrosis				5 (11%)
Hemorrhage		1 (2%)		
Pyelonephritis, NOS				1 (2%)
Pyelonephritis, acute			1 (2%)	
Pyelonephritis, healed	1 (2%)			
Nephropathy	49 (100%)	50 (100%)	47 (98%)	39 (89%)
Nephropathy, toxic			30 (63%)	30 (68%)
Degeneration, hyaline	1 (2%)			
Calcification, focal	19 (39%)	11 (22%)	12 (25%)	13 (30%)
Cytomegaly			46 (96%)	43 (98%)
Hyperplasia, tubular cell	1 (2%)	1 (2%)		1 (2%)
Angiectasis				1 (2%)
#Renal papilla	(49)	(50)	(48)	(44)
Necrosis, focal			1 (2%)	
#Kidney/pelvis	(49)	(50)	(48)	(44)
Calculus, unknown gross or micro	6 (12%)			
Dilatation, NOS			1 (2%)	
Hemorrhage		1 (2%)		
Hematoma, NOS		1 (2%)		
Calcium deposit	1 (2%)			
Hyperplasia, epithelial	2 (4%)		2 (4%)	1 (2%)
Metaplasia, squamous	1 (2%)			
#Urinary bladder	(45)	(46)	(40)	(40)
Calculus, unknown gross or micro				1 (3%)
Hemorrhage				1 (3%)
Hyperplasia, epithelial				1 (3%)
Metaplasia, squamous	1 (2%)			1 (3%)
ENDOCRINE SYSTEM				
#Pituitary	(42)	(45)	(38)	(42)
Cyst, NOS	1 (2%)		1 (3%)	
Multiple cysts		1 (2%)		
Hemorrhage		2 (4%)		1 (2%)
Hyperplasia, focal	1 (2%)			
Hyperplasia, chromophobe cell	2 (5%)	2 (4%)	4 (11%)	2 (5%)

TABLE F4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)				
#Adrenal	(47)	(49)	(47)	(43)
Cyst, NOS		1 (2%)		
Hemorrhage		1 (2%)	1 (2%)	1 (2%)
Hematoma, NOS	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Degeneration, lipoid		1 (2%)	1 (2%)	1 (2%)
Hyperplasia, focal	1 (2%)			
Angiectasis	2 (4%)	5 (10%)	9 (19%)	6 (14%)
#Adrenal cortex	(47)	(49)	(47)	(43)
Hemorrhage	6 (13%)	3 (6%)	7 (15%)	5 (12%)
Hematoma, NOS				1 (2%)
Degeneration, lipoid	4 (9%)	3 (6%)	4 (9%)	3 (7%)
Necrosis, focal			1 (2%)	
Metamorphosis, fatty				1 (2%)
Lipoidosis			1 (2%)	
Atrophy, NOS				1 (2%)
Atrophy, diffuse		1 (2%)		
Hyperplasia, focal	9 (19%)	5 (10%)	4 (9%)	3 (7%)
Hyperplasia, diffuse		1 (2%)		
Angiectasis	4 (9%)	1 (2%)	5 (11%)	2 (5%)
#Adrenal medulla	(47)	(49)	(47)	(43)
Hyperplasia, focal	16 (34%)	4 (8%)	5 (11%)	2 (5%)
#Thyroid	(48)	(43)	(46)	(43)
Follicular cyst, NOS			1 (2%)	
Hyperplasia, C-cell	11 (23%)	6 (14%)	5 (11%)	6 (14%)
Angiectasis	1 (2%)			
#Parathyroid	(27)	(22)	(27)	(22)
Hyperplasia, NOS				1 (5%)
REPRODUCTIVE SYSTEM				
*Mammary gland	(50)	(50)	(50)	(48)
Galactocele		1 (2%)	1 (2%)	
Hyperplasia, cystic		1 (2%)		
Lactation	4 (8%)		1 (2%)	
#Uterus	(47)	(50)	(45)	(44)
Hydrometra	1 (2%)			3 (7%)
Hematometra		1 (2%)	1 (2%)	
Pyometra		1 (2%)		
Hemosiderosis	2 (4%)	1 (2%)	1 (2%)	
#Cervix uteri	(47)	(50)	(45)	(44)
Cyst, NOS	1 (2%)	2 (4%)		
Multiple cysts	1 (2%)			
Inflammation, focal			1 (2%)	
#Uterus/endometrium	(47)	(50)	(45)	(44)
Multilocular cyst				1 (2%)
Inflammation, NOS				1 (2%)
Hemosiderosis				3 (7%)
#Ovary	(47)	(48)	(45)	(44)
Cyst, NOS	4 (9%)	4 (8%)	2 (4%)	2 (5%)
Luteinized follic cyst			1 (2%)	
Multiple cysts		1 (2%)		
Parovarian cyst			1 (2%)	
Hemosiderosis		1 (2%)		

TABLE F4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MARSHALL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM				
#Brain	(50)	(50)	(50)	(48)
Hemorrhage	2 (4%)	1 (2%)	1 (2%)	
Calcification, focal				1 (2%)
SPECIAL SENSE ORGANS				
*Eye	(50)	(50)	(50)	(48)
Retinopathy				1 (2%)
Cataract				1 (2%)
*Harderian gland	(50)	(50)	(50)	(48)
Inflammation, acute/chronic				2 (4%)
Inflammation, chronic			2 (4%)	
Inflammation, chronic focal	1 (2%)		2 (4%)	4 (8%)
Atrophy, focal	1 (2%)			
MUSCULOSKELETAL SYSTEM				
None				
BODY CAVITIES				
*Pleural cavity	(50)	(50)	(50)	(48)
Hydrothorax		1 (2%)		
*Pericardium	(50)	(50)	(50)	(48)
Inflammation, chronic				1 (2%)
ALL OTHER SYSTEMS				
Lumbar region				
Fracture, NOS	1			
Lower leg				
Abscess, chronic			1	
SPECIAL MORPHOLOGY SUMMARY				
Auto/necropsy/histo perf				1
Autolysis/no necropsy				2

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX G

SUMMARY OF LESIONS IN MALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

TABLE G1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*Skin	(50)	(50)	(50)	(50)
Squamous cell carcinoma	1 (2%)			
Keratoacanthoma			1 (2%)	
Fibroma			1 (2%)	2 (4%)
*Subcutaneous tissue	(50)	(50)	(50)	(50)
Sarcoma, NOS	2 (4%)		2 (4%)	
Fibroma	3 (6%)	4 (8%)	3 (6%)	
RESPIRATORY SYSTEM				
*Nasal cavity	(50)	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)			
#Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma		1 (2%)		1 (2%)
Alveolar/bronchiolar carcinoma		1 (2%)		
Sarcoma, NOS, metastatic			1 (2%)	
HEMATOPOIETIC SYSTEM				
*Multiple organs	(50)	(50)	(50)	(50)
Leukemia, NOS				1 (2%)
Monocytic leukemia	1 (2%)	1 (2%)		1 (2%)
*Thorax	(50)	(50)	(50)	(50)
Plasma cell myeloma				1 (2%)
#Pancreas	(50)	(49)	(50)	(50)
Malignant lymphoma, NOS	1 (2%)			
#Ileum	(48)	(49)	(50)	(48)
Malignant lymphoma, NOS		1 (2%)		
CIRCULATORY SYSTEM				
None				
DIGESTIVE SYSTEM				
#Salivary gland	(47)	(48)	(49)	(47)
Adenoma, NOS		1 (2%)		
#Liver	(50)	(50)	(50)	(49)
Bile duct adenoma		1 (2%)	1 (2%)	1 (2%)
Neoplastic nodule	1 (2%)	1 (2%)		1 (2%)
Hepatocellular carcinoma				1 (2%)
#Pancreas	(50)	(49)	(50)	(50)
Acinar cell adenoma				1 (2%)
#Stomach	(50)	(50)	(50)	(50)
Squamous cell carcinoma	2 (4%)		1 (2%)	1 (2%)
#Forestomach	(50)	(50)	(50)	(50)
Papillomatosis	1 (2%)			
Squamous cell carcinoma	3 (6%)	3 (6%)	2 (4%)	
#Duodenum	(48)	(49)	(50)	(48)
Adenocarcinoma, NOS	1 (2%)			
#Jejunum	(48)	(49)	(50)	(48)
Carcinoma, NOS			1 (2%)	

TABLE G1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM				
#Kidney	(50)	(50)	(50)	(50)
Tubular cell adenoma			6 (12%)	1 (2%)
Tubular cell adenocarcinoma				1 (2%)
Liposarcoma		1 (2%)		
Nephroblastoma				1 (2%)
ENDOCRINE SYSTEM				
#Pituitary	(46)	(42)	(45)	(38)
Carcinoma, NOS	1 (2%)			
Adenoma, NOS	16 (35%)	11 (26%)	7 (16%)	10 (26%)
#Adrenal	(50)	(50)	(49)	(50)
Cortical adenoma	11 (22%)	9 (18%)	11 (22%)	11 (22%)
Cortical carcinoma		1 (2%)		
Pheochromocytoma	9 (18%)	13 (26%)	6 (12%)	3 (6%)
Pheochromocytoma, malignant	1 (2%)	1 (2%)		
#Thyroid	(48)	(49)	(48)	(48)
Follicular cell adenoma				1 (2%)
C-cell adenoma	4 (8%)	8 (16%)	4 (8%)	1 (2%)
C-cell carcinoma		1 (2%)		
#Thyroid follicle	(48)	(49)	(48)	(48)
Cystadenoma, NOS			1 (2%)	
#Parathyroid	(33)	(38)	(30)	(33)
Adenoma, NOS	2 (6%)			
#Pancreatic islets	(50)	(49)	(50)	(50)
Islet cell adenoma	1 (2%)	3 (6%)	2 (4%)	
Islet cell carcinoma		1 (2%)		
REPRODUCTIVE SYSTEM				
*Mammary gland	(50)	(50)	(50)	(50)
Cystadenoma, NOS				1 (2%)
Fibroma	1 (2%)			
Fibroadenoma	1 (2%)			
#Prostate	(49)	(49)	(50)	(50)
Adenoma, NOS		1 (2%)		1 (2%)
#Testis	(50)	(49)	(50)	(50)
Interstitial cell tumor	1 (2%)			1 (2%)
NERVOUS SYSTEM				
*Nerve tract	(50)	(50)	(50)	(50)
Neurilemoma			1 (2%)	
#Brain	(49)	(49)	(50)	(50)
Granular cell tumor, NOS		1 (2%)		
#Cerebellum	(49)	(49)	(50)	(50)
Medulloblastoma				1 (2%)
SPECIAL SENSE ORGANS				
None				
MUSCULOSKELETAL SYSTEM				
*Skeletal muscle	(50)	(50)	(50)	(50)
Sarcoma, NOS			1 (2%)	

TABLE G1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLORETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
BODY CAVITIES				
*Tunica vaginalis	(50)	(50)	(50)	(50)
Mesothelioma, NOS	1 (2%)			
ALL OTHER SYSTEMS				
*Multiple organs	(50)	(50)	(50)	(50)
Squamous cell carcinoma		1 (2%)		
Sarcoma, NOS, metastatic	1 (2%)			
Forearm				
Mesenchymoma, malignant			1	
ANIMAL DISPOSITION SUMMARY				
Animals initially in study	50	50	50	50
Natural death	22	19	18	22
Moribund sacrifice	10	8	9	7
Terminal sacrifice	18	22	17	14
Dosing accident			6	2
Accidentally killed, NOS		1		5
TUMOR SUMMARY				
Total animals with primary tumors**	39	37	35	29
Total primary tumors	66	66	52	44
Total animals with benign tumors	34	35	29	22
Total benign tumors	50	52	44	35
Total animals with malignant tumors	13	11	8	8
Total malignant tumors	14	12	8	8
Total animals with secondary tumors##	1		1	
Total secondary tumors	1		1	
Total animals with tumors uncertain-- benign or malignant	2	2		1
Total uncertain tumors	2	2		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 G2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: UNTREATED CONTROL

ANIMAL NUMBER	003	008	009	010	011	017	018	020	021	042	045	049	051	054	058	067	073	078	079	081	082	083	090	094	105
WEEKS ON STUDY	105	105	054	105	090	102	091	105	063	093	090	105	085	098	026	105	103	105	105	052	095	085	087	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS									X																
Fibroma																					X				
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal 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
Carcinoma, NOS																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillomatosis																									
Squamous cell carcinoma					X						X		X										X		
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Large intestine	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS				X	X						X	X		X			X								X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma	X	X														X			X						
Pheochromocytoma					X			X																	X
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
C-cell adenoma																									
Parathyroid	+	+	−	+	−	−	−	+	+	+	−	+	+	+	+	+	−	+	−	+	+	+	+	+	−
Adenoma, NOS	X																					X			
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma								X																	
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	N	N	+	+	+	+	+	N	+	+	N	+	N	+	+	+	+	N	N	+	+	N	N
Fibroma																									
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor																							X		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, 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
Sarcoma, NOS, metastatic									X																
Monocytic leukemia																									

+: 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 G2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE OSBORNE-MENDEL RATS: UNTREATED CONTROL (Continued)

ANIMAL NUMBER	107	111	116	118	121	124	133	135	139	142	147	152	156	157	163	165	169	176	177	183	185	187	195	197	198	TOTAL:
WEEKS ON STUDY	104	105	022	087	096	097	104	105	105	105	078	104	091	103	101	098	087	105	066	105	102	095	105	102	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell carcinoma																X										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS															X											2
Fibroma															X	X										3
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal 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	*50
Carcinoma, NOS													X													1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	3
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
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
Malignant lymphoma, NOS														X												1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papillomatosis				X																						1
Squamous cell carcinoma						X																				5
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma, NOS		X																								1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Carcinoma, NOS																			X							1
Adenoma, NOS							X	X	X				X	X				X		X	X				X	16
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma	X			X			X			X	X		X			X										11
Pheochromocytoma		X		X				X				X						X						X		9
Pheochromocytoma, malignant									X																	1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell adenoma		X						X				X						X								4
Parathyroid	+	+	−	−	+	+	−	−	+	+	−	−	+	+	−	+	+	+	−	−	+	+	+	+	+	33
Adenoma, NOS																										2
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	+	N	+	N	+	+	N	+	+	N	+	+	N	+	+	+	+	+	+	+	+	N	*50
Fibroma																						X				1
Fibroadenoma																					X					1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, 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
Sarcoma, NOS, metastatic																										1
Monocytic leukemia														X												1

* Animals necropsied

TABLE G2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: VEHICLE CONTROL

ANIMAL NUMBER	007	014	015	019	024	027	030	040	043	052	053	055	056	057	059	061	062	064	070	071	072	078	080	084	086
WEEKS ON STUDY	105	100	088	105	105	105	030	067	105	105	102	105	096	105	093	105	093	105	070	067	082	105	105	100	095
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X																				
Alveolar/bronchiolar carcinoma																								X	
Trachea	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	–	–	–	–	–	–	+	A	–	–	–	–	–	–	–	–	–	–	–	–	A	–	–	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct adenoma																	X								
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma	X		X		X																				
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liposarcoma														X											
Urinary bladder	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	–	A	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+
Adenoma, NOS	X			X					X															X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma	X	X	X									X												X	
Cortical carcinoma																									
Pheochromocytoma						X			X				X	X	X			X				X			
Pheochromocytoma, malignant																		X							
Thyroid	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma										X		X			X	X									
C-cell carcinoma																									
Parathyroid	+	+	+	+	+	–	+	A	+	+	+	+	+	+	+	+	+	–	–	+	+	–	–	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma										X	X														
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	+	N	+	N	+	+	+	+	+	N	+	N	N	N	+	+	N	+	N	N	+	+
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																		X							
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, 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
Squamous cell carcinoma																								X	
Monocytic leukemia																			X						

TABLE G2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE OSBORNE-MENDEL RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	091	096	097	100	103	114	115	119	120	125	126	127	136	137	140	148	153	158	160	162	166	170	188	191	200	TOTAL:
WEEKS ON STUDY	105	086	105	105	105	091	055	067	098	076	092	100	105	105	074	105	081	105	105	091	101	090	105	084	055	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	*50
Fibroma		X									X									X		X				4
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	48
Thymus	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	3
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	48
Adenoma, NOS																							X			1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct adenoma																										1
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										3
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	49
Malignant lymphoma, NOS																					X					1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liposarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	−	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	42
Adenoma, NOS			X			X							X			X			X				X	X		11
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma				X		X							X	X												9
Cortical carcinoma																				X						1
Pheochromocytoma	X	X	X						X	X					X											13
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell adenoma				X									X					X	X							8
C-cell carcinoma									X																	1
Parathyroid	+	+	−	+	+	+	−	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	−	+	−	38
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	49
Islet cell adenoma									X																	3
Islet cell carcinoma																							X			1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	N	+	+	N	+	+	N	N	+	N	+	N	+	+	+	+	N	N	N	N	+	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	49
Adenoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	49
Granular cell tumor, 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
Squamous cell carcinoma																										1
Monocytic leukemia																										1

* Animals necropsied

TABLE G2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: LOW DOSE

ANIMAL NUMBER	001	006	012	013	016	023	028	032	034	035	041	044	050	060	065	068	069	077	087	099	099	104	106	122	128
WEEKS ON STUDY	104	094	088	104	104	111	084	091	104	104	104	104	104	100	070	104	078	083	030	081	068	098	028	100	009
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma		X																							
Fibroma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Fibroma	X																X								
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	+	−	+	−	+	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct adenoma																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																			X						
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma					X							X	X												
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−
Adenoma, NOS										X	X	X		X		X									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Cortical adenoma			X		X			X						X		X		X						X	
Pheochromocytoma					X		X		X		X					X									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−
C-cell adenoma										X			X												
Cystadenoma, NOS				X																					
Parathyroid	+	+	+	+	+	+	+	+	+	−	−	+	−	−	−	−	−	+	−	−	−	+	−	+	−
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma					X																				
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	+	+	N	+	+	+	+	N	+	+	N	+	+	+	N	N	+	+	+	N	+	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Muscle	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														
ALL OTHER SYSTEMS																									
Nerve tract																									
Neurilemoma																								X	
Forearm, NOS																									
Mesenchymoma, malignant					X																				

TABLE G2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE OSBORNE-MENDEL RATS: LOW DOSE (Continued)

ANIMAL NUMBER	130	131	132	138	141	143	149	150	151	159	164	167	168	172	173	174	175	179	180	182	186	189	192	196	199	TOTAL:
WEEKS ON STUDY	104	104	030	104	092	099	086	104	104	103	042	061	104	080	104	088	078	081	098	089	099	099	077	068	104	098	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Keratoacanthoma																										1
Fibroma								X																		1
Subcutaneous tissue	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																		X		X						2
Fibroma									X																	3
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS, metastatic																		X								1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	−	−	+	−	−	−	−	−	−	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	8
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct adenoma				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
Squamous cell carcinoma			X													X										3
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS	X																									1
Large intestine	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma		X		X															X							6
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma, NOS							X								X											7
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma	X									X				X								X				11
Pheochromocytoma																								X		6
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell adenoma									X													X				4
Cystadenoma, NOS																										1
Parathyroid	+	+	+	−	+	+	+	−	+	+	−	+	−	−	+	−	+	+	+	+	−	+	−	+	+	30
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma		X																								2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	N	+	N	+	N	+	+	+	N	N	+	+	N	+	+	+	+	+	+	+	+	N	+	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
Muscle	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
Sarcoma, NOS																										1
ALL OTHER SYSTEMS																										
Nerve tract																										
Neurilemoma																										1
Forearm, NOS																										
Mesenchymoma, malignant																										1

* Animals necropsied

TABLE G2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: HIGH DOSE

ANIMAL NUMBER	0002	0004	0005	0022	0025	0026	0029	0031	0033	0036	0037	0038	0039	0046	0047	0048	0063	0066	0074	0075	0085	0088	0089	0092	0093
WEEKS ON STUDY	071	056	076	066	044	090	104	092	023	104	012	011	084	044	078	104	044	044	046	044	095	044	034	028	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	–	+	+
Thymus	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	+	–	–	+	+	+	–	
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct adenoma																									
Neoplastic nodule																									
Hepatocellular carcinoma							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															
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Tubular cell adenocarcinoma								X																	
Nephroblastoma																		X							
Urinary bladder	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	–	–	+
Adenoma, NOS						X								X		X				X					X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma						X				X							X								X
Pheochromocytoma																X									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
Follicular cell adenoma																									
C-cell adenoma																									
Parathyroid	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	–	+	–	+	+	–
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	+	N	+	N	+	N	N	N	+	+	N	+	+	N	+	N	N	N	N	N	N	+
Cystadenoma, NOS																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS					X																				
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Medulloblastoma													X												
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	N
Plasma cell myeloma																							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
Leukemia, NOS																									
Monocytic leukemia																									

TABLE G2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE OSBORNE-MENDEL RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	095	101	102	108	109	110	112	113	117	123	129	134	144	145	146	154	155	161	171	178	181	184	190	193	194	TOTAL:
WEEKS ON STUDY	104	081	104	103	062	055	104	050	089	036	077	100	104	097	046	003	096	038	081	104	104	051	021	045	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma														X							X					2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X																						1
Trachea	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	–	+	+	44
Thymus	+	–	–	–	–	+	–	–	–	+	–	–	–	–	+	+	–	+	–	–	–	+	+	–	–	13
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	47
Liver	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bile duct adenoma	X																									1
Neoplastic nodule																									X	1
Hepatocellular carcinoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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																										1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																							X			1
Small intestine	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma	X																									1
Tubular cell adenocarcinoma																										1
Nephroblastoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	–	–	+	–	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	–	+	38
Adenoma, NOS		X					X					X		X											X	10
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma							X			X	X		X	X						X					X	11
Pheochromocytoma				X																					X	3
Thyroid	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma																						X				1
C-cell adenoma	X																									1
Parathyroid	+	–	+	+	–	–	+	–	–	–	+	–	+	–	+	+	+	–	+	+	–	–	+	+	+	33
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	N	+	N	+	N	N	N	N	+	+	N	+	N	N	+	N	+	+	N	N	N	N	N	*50
Cystadenoma, NOS																	X									1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor														X												1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Medulloblastoma																										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	N	*50
Plasma cell myeloma																										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, NOS																			X							1
Monocytic leukemia		X																								1

* Animals necropsied

TABLE G3. ANALYSIS OF PRIMARY TUMORS IN MALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg
Subcutaneous Tissue: Fibroma				
Overall Rates (a)	3/50 (6%)	4/50 (8%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	9.8%	13.6%	14.0%	0.0%
Terminal Rates (c)	0/21 (0%)	1/22 (5%)	2/17 (12%)	0/15 (0%)
Life Table Tests (d)		P=0.112N	P=0.612N	P=0.129N
Incidental Tumor Tests (d)		P=0.095N	P=0.547N	P=0.130N
Cochran-Armitage Trend Test (d)		P=0.049N		
Fisher Exact Test			P=0.500N	P=0.059N
Integumentary System: Fibroma				
Overall Rates (a)	3/50 (6%)	4/50 (8%)	4/50 (8%)	2/50 (4%)
Adjusted Rates (b)	9.8%	13.6%	19.8%	11.6%
Terminal Rates (c)	0/21 (0%)	1/22 (5%)	3/17 (18%)	1/15 (7%)
Life Table Tests (d)		P=0.468N	P=0.519	P=0.528N
Incidental Tumor Tests (d)		P=0.451N	P=0.582	P=0.548N
Cochran-Armitage Trend Test (d)		P=0.274N		
Fisher Exact Test			P=0.643	P=0.339N
Integumentary System: Fibroma or Sarcoma				
Overall Rates (a)	4/50 (8%)	4/50 (8%)	6/50 (12%)	2/50 (4%)
Adjusted Rates (b)	15.0%	13.6%	24.7%	11.6%
Terminal Rates (c)	2/21 (10%)	1/22 (5%)	3/17 (18%)	1/15 (7%)
Life Table Tests (d)		P=0.509N	P=0.255	P=0.528N
Incidental Tumor Tests (d)		P=0.489N	P=0.340	P=0.548N
Cochran-Armitage Trend Test (d)		P=0.290N		
Fisher Exact Test			P=0.370	P=0.339N
Stomach: Squamous Cell Carcinoma				
Overall Rates (a)	(e) 5/50 (10%)	3/50 (6%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	18.4%	11.5%	7.3%	2.1%
Terminal Rates (c)	2/22 (9%)	2/22 (9%)	0/17 (0%)	0/15 (0%)
Life Table Tests (d)		P=0.342N	P=0.583	P=0.421N
Incidental Tumor Tests (d)		P=0.053N	P=0.431N	P=0.230N
Cochran-Armitage Trend Test (d)		P=0.238N		
Fisher Exact Test			P=0.661	P=0.309N
Kidney: Tubular Cell Adenoma				
Overall Rates (a)	0/50 (0%)	0/50 (0%)	6/50 (12%)	1/50 (2%)
Adjusted Rates (b)	0.0%	0.0%	32.2%	6.7%
Terminal Rates (c)	0/21 (0%)	0/22 (0%)	5/17 (29%)	1/15 (7%)
Life Table Tests (d)		P=0.246	P=0.007	P=0.424
Incidental Tumor Tests (d)		P=0.243	P=0.007	P=0.424
Cochran-Armitage Trend Test (d)		P=0.406		
Fisher Exact Test			P=0.013	P=0.500
Kidney: Tubular Cell Adenoma or Adenocarcinoma				
Overall Rates (a)	0/50 (0%)	0/50 (0%)	6/50 (12%)	2/50 (4%)
Adjusted Rates (b)	0.0%	0.0%	32.2%	10.9%
Terminal Rates (c)	0/21 (0%)	0/22 (0%)	5/17 (29%)	1/15 (7%)
Life Table Tests (d)		P=0.125	P=0.007	P=0.158
Incidental Tumor Tests (d)		P=0.122	P=0.007	P=0.158
Cochran-Armitage Trend Test (d)		P=0.252		
Fisher Exact Test			P=0.013	P=0.247
Pituitary: Adenoma				
Overall Rates (a)	(f) 16/46 (35%)	11/42 (26%)	7/45 (16%)	10/38 (26%)
Adjusted Rates (b)	55.4%	42.0%	35.0%	50.6%
Terminal Rates (c)	9/21 (43%)	8/22 (36%)	5/17 (29%)	6/15 (40%)
Life Table Tests (d)		P=0.277	P=0.419N	P=0.294
Incidental Tumor Tests (d)		P=0.287	P=0.334N	P=0.300
Cochran-Armitage Trend Test (d)		P=0.542N		
Fisher Exact Test			P=0.169N	P=0.595

TABLE G3. ANALYSIS OF PRIMARY TUMORS IN MALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg
Adrenal: Cortical Adenoma				
Overall Rates (a)	11/50 (22%)	9/50 (18%)	11/49 (22%)	11/50 (22%)
Adjusted Rates (b)	40.3%	32.4%	41.1%	54.4%
Terminal Rates (c)	7/21 (33%)	5/22 (23%)	3/17 (18%)	7/15 (47%)
Life Table Tests (d)		P=0.094	P=0.215	P=0.115
Incidental Tumor Tests (d)		P=0.109	P=0.327	P=0.160
Cochran-Armitage Trend Test (d)		P=0.356		
Fisher Exact Test			P=0.382	P=0.402
Adrenal: Cortical Adenoma or Carcinoma				
Overall Rates (a)	11/50 (22%)	10/50 (20%)	11/49 (22%)	11/50 (22%)
Adjusted Rates (b)	40.3%	34.4%	41.1%	54.4%
Terminal Rates (c)	7/21 (33%)	5/22 (23%)	3/17 (18%)	7/15 (47%)
Life Table Tests (d)		P=0.137	P=0.286	P=0.165
Incidental Tumor Tests (d)		P=0.161	P=0.435	P=0.221
Cochran-Armitage Trend Test (d)		P=0.452		
Fisher Exact Test			P=0.479	P=0.500
Adrenal: Pheochromocytoma				
Overall Rates (a)	(g) 9/50 (18%)	(h) 13/50 (26%)	6/49 (12%)	3/50 (6%)
Adjusted Rates (b)	34.8%	42.9%	31.6%	18.7%
Terminal Rates (c)	6/21 (29%)	7/22 (32%)	5/17 (29%)	2/15 (13%)
Life Table Tests (d)		P=0.028N	P=0.154N	P=0.052N
Incidental Tumor Tests (d)		P=0.023N	P=0.128N	P=0.043N
Cochran-Armitage Trend Test (d)		P=0.004N		
Fisher Exact Test			P=0.068N	P=0.006N
Thyroid: C-Cell Adenoma				
Overall Rates (a)	4/48 (8%)	8/49 (16%)	4/48 (8%)	1/48 (2%)
Adjusted Rates (b)	19.0%	33.9%	21.4%	6.7%
Terminal Rates (c)	4/21 (19%)	7/22 (32%)	3/17 (18%)	1/15 (7%)
Life Table Tests (d)		P=0.038N	P=0.312N	P=0.055N
Incidental Tumor Tests (d)		P=0.038N	P=0.299N	P=0.057N
Cochran-Armitage Trend Test (d)		P=0.011N		
Fisher Exact Test			P=0.188N	P=0.017N
Thyroid: C-Cell Adenoma or Carcinoma				
Overall Rates (a)	4/48 (8%)	9/49 (18%)	4/48 (8%)	1/48 (2%)
Adjusted Rates (b)	19.0%	36.3%	21.4%	6.7%
Terminal Rates (c)	4/21 (19%)	7/22 (32%)	3/17 (18%)	1/15 (7%)
Life Table Tests (d)		P=0.022N	P=0.224N	P=0.038N
Incidental Tumor Tests (d)		P=0.022N	P=0.211N	P=0.039N
Cochran-Armitage Trend Test (d)		P=0.005N		
Fisher Exact Test			P=0.124N	P=0.008N
Pancreatic Islets: Islet Cell Adenoma				
Overall Rates (a)	1/50 (2%)	3/49 (6%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	4.8%	12.0%	11.8%	0.0%
Terminal Rates (c)	1/21 (5%)	1/22 (5%)	2/17 (12%)	0/15 (0%)
Life Table Tests (d)		P=0.152N	P=0.602N	P=0.203N
Incidental Tumor Tests (d)		P=0.155N	P=0.590N	P=0.213N
Cochran-Armitage Trend Test (d)		P=0.079N		
Fisher Exact Test			P=0.490N	P=0.117N
Pancreatic Islets: Islet Cell Adenoma or Carcinoma				
Overall Rates (a)	1/50 (2%)	4/49 (8%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	4.8%	16.1%	11.8%	0.0%
Terminal Rates (c)	1/21 (5%)	2/22 (9%)	2/17 (12%)	0/15 (0%)
Life Table Tests (d)		P=0.082N	P=0.448N	P=0.127N
Incidental Tumor Tests (d)		P=0.083N	P=0.435N	P=0.133N
Cochran-Armitage Trend Test (d)		P=0.035N		
Fisher Exact Test			P=0.329N	P=0.056N

(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 vehicle 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 rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) One instance of papillomatosis was also observed.
(f) One carcinoma, NOS, was also observed.
(g) One malignant pheochromocytoma was also observed.
(h) One animal also had a malignant pheochromocytoma.

TABLE G4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*Skin	(50)	(50)	(50)	(50)
Cyst, NOS		1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)	(50)
Hemorrhage		1 (2%)	1 (2%)	
Inflammation, NOS				1 (2%)
Inflammation, acute		1 (2%)		
Abscess, NOS			1 (2%)	
Inflammation, granulomatous			1 (2%)	
RESPIRATORY SYSTEM				
*Tracheal lumen	(50)	(50)	(50)	(50)
Hemorrhage			1 (2%)	1 (2%)
*Bronchial lumen	(50)	(50)	(50)	(50)
Hemorrhage				1 (2%)
*Larynx	(50)	(50)	(50)	(50)
Inflammation, acute necrotizing			1 (2%)	
#Lung	(50)	(50)	(50)	(50)
Vegetable foreign body				2 (4%)
Emphysema, alveolar				1 (2%)
Atelectasis			1 (2%)	
Congestion, NOS	4 (8%)	1 (2%)	3 (6%)	11 (22%)
Edema, NOS	2 (4%)	1 (2%)	1 (2%)	3 (6%)
Hemorrhage	8 (16%)	5 (10%)	6 (12%)	2 (4%)
Inflammation, NOS		1 (2%)		
Inflammation, focal		2 (4%)		2 (4%)
Bronchopneumonia, acute		1 (2%)		
Inflammation, acute			1 (2%)	3 (6%)
Inflammation, acute necrotizing			1 (2%)	
Inflammation, chronic	1 (2%)	1 (2%)	1 (2%)	
Inflammation, chronic focal	2 (4%)		1 (2%)	
Inflammation, granulomatous				1 (2%)
Inflammation, granulomatous focal		1 (2%)	5 (10%)	6 (12%)
Foreign material, NOS			1 (2%)	2 (4%)
Hyperplasia, epithelial		1 (2%)		
#Lung/alveoli	(50)	(50)	(50)	(50)
Hemorrhage				1 (2%)
HEMATOPOIETIC SYSTEM				
#Bone marrow	(50)	(49)	(50)	(50)
Hyperplasia, NOS	2 (4%)			
#Spleen	(50)	(49)	(50)	(50)
Hemorrhage	1 (2%)		1 (2%)	
Hyperplasia, reticulum cell				1 (2%)
Hyperplasia, lymphoid		1 (2%)		1 (2%)
Hematopoiesis	4 (8%)	3 (6%)	4 (8%)	4 (8%)
#Lymph node	(49)	(48)	(49)	(44)
Hemorrhage			3 (6%)	
Inflammation, NOS		1 (2%)		
Inflammation, chronic			1 (2%)	
Necrosis, focal			1 (2%)	
Angiectasis			1 (2%)	

TABLE G4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)				
#Pancreatic lymph node	(49)	(48)	(49)	(44)
Edema, NOS	1 (2%)			
Hemorrhage				1 (2%)
Inflammation, NOS		1 (2%)		
Inflammation, chronic		1 (2%)		
Hyperplasia, NOS			1 (2%)	
Angiectasis	1 (2%)	1 (2%)		
Hyperplasia, lymphoid		1 (2%)		
#Mesenteric lymph node	(49)	(48)	(49)	(44)
Hemorrhage	1 (2%)	2 (4%)		2 (5%)
#Liver	(50)	(50)	(50)	(49)
Hematopoiesis	1 (2%)			
#Colon	(48)	(47)	(49)	(48)
Hyperplasia, lymphoid	2 (4%)			
#Thymus	(3)	(3)	(8)	(13)
Hemorrhage	1 (33%)	2 (67%)	2 (25%)	2 (15%)
Inflammation, chronic				1 (8%)
Hyperplasia, lymphoid				1 (8%)
CIRCULATORY SYSTEM				
#Lung	(50)	(50)	(50)	(50)
Perivasculitis			1 (2%)	
#Heart	(50)	(50)	(50)	(50)
Thrombosis, NOS		2 (4%)		
Inflammation, focal		3 (6%)		
Inflammation, interstitial			1 (2%)	1 (2%)
Inflammation, active chronic		1 (2%)		
Inflammation, chronic focal	1 (2%)	2 (4%)		
Fibrosis		1 (2%)		
Fibrosis, focal		1 (2%)		1 (2%)
Endocardiosis	1 (2%)			
Calcification, focal	1 (2%)			
#Auricular appendage	(50)	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)			1 (2%)
#Endocardium	(50)	(50)	(50)	(50)
Inflammation with fibrosis		1 (2%)		
*Coronary artery	(50)	(50)	(50)	(50)
Calcification, NOS		1 (2%)		
*Pulmonary artery	(50)	(50)	(50)	(50)
Calcification, focal		1 (2%)	2 (4%)	
#Pancreas	(50)	(49)	(50)	(50)
Periarteritis	1 (2%)			
*Esophageal lumen	(50)	(50)	(50)	(50)
Thrombosis, NOS			1 (2%)	
#Testis	(50)	(49)	(50)	(50)
Periarteritis	1 (2%)	1 (2%)		
DIGESTIVE SYSTEM				
#Salivary gland	(47)	(48)	(49)	(47)
Inflammation, chronic	1 (2%)		1 (2%)	1 (2%)
Inflammation, chronic focal	1 (2%)	1 (2%)	1 (2%)	
Degeneration, NOS				2 (4%)
Metamorphosis, fatty	1 (2%)			
Cytoplasmic vacuolization		1 (2%)	1 (2%)	
Atrophy, focal		1 (2%)		
Atrophy, diffuse	1 (2%)			

TABLE G4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)				
#Liver	(50)	(50)	(50)	(49)
Congestion, NOS	2 (4%)	1 (2%)		1 (2%)
Hemorrhage		1 (2%)		1 (2%)
Inflammation, focal			2 (4%)	
Inflammation, chronic			1 (2%)	
Fibrosis, multifocal	1 (2%)			
Necrosis, focal	1 (2%)	2 (4%)	5 (10%)	2 (4%)
Necrosis, central	2 (4%)			1 (2%)
Metamorphosis, fatty		1 (2%)	1 (2%)	
Lipoidosis	1 (2%)	1 (2%)		
Cytoplasmic change, NOS	12 (24%)	13 (26%)	16 (32%)	13 (27%)
Basophilic cyto change			1 (2%)	1 (2%)
Focal cellular change	1 (2%)	1 (2%)		1 (2%)
Clear cell change			1 (2%)	
Cytologic alteration, NOS			1 (2%)	1 (2%)
Angiectasis		1 (2%)		
#Liver/centrilobular	(50)	(50)	(50)	(49)
Necrosis, NOS		1 (2%)		
Metamorphosis, fatty	1 (2%)			
#Bile duct	(50)	(50)	(50)	(49)
Dilatation, NOS	1 (2%)		2 (4%)	
Inflammation, chronic	1 (2%)	2 (4%)	1 (2%)	
Fibrosis, focal			1 (2%)	
Hyperplasia, NOS	1 (2%)	6 (12%)	3 (6%)	
Hyperplasia, cystic			1 (2%)	
#Pancreas	(50)	(49)	(50)	(50)
Dilatation/ducts				1 (2%)
Inflammation, fibrinous		1 (2%)		
Inflammation, chronic		1 (2%)	1 (2%)	
Inflammation, granulomatous	1 (2%)	1 (2%)		
#Pancreatic acinus	(50)	(49)	(50)	(50)
Atrophy, NOS	1 (2%)		1 (2%)	
Atrophy, focal	6 (12%)	6 (12%)	3 (6%)	
*Esophageal lumen	(50)	(50)	(50)	(50)
Hemorrhage	1 (2%)		1 (2%)	
#Stomach	(50)	(50)	(50)	(50)
Mineralization			1 (2%)	
Cyst, NOS				1 (2%)
Inflammation, NOS			1 (2%)	
Inflammation, chronic	1 (2%)			
Inflammation, chronic focal		1 (2%)	1 (2%)	
#Gastric mucosa	(50)	(50)	(50)	(50)
Inflammation, NOS			1 (2%)	
Erosion	1 (2%)			
Hyperkeratosis				1 (2%)
#Forestomach	(50)	(50)	(50)	(50)
Edema, NOS		1 (2%)		
Ulcer, NOS	1 (2%)			
Inflammation, chronic	1 (2%)			
Hyperplasia, epithelial		2 (4%)		
Hyperkeratosis	1 (2%)	1 (2%)		
#Colon	(48)	(47)	(49)	(48)
Parasitism	8 (17%)	11 (23%)	11 (22%)	10 (21%)
#Cecum	(48)	(47)	(49)	(48)
Parasitism	1 (2%)			
*Rectum	(50)	(50)	(50)	(50)
Parasitism				1 (2%)

TABLE G4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM				
#Kidney	(50)	(50)	(50)	(50)
Mineralization	1 (2%)	1 (2%)	1 (2%)	
Cast, NOS	2 (4%)		1 (2%)	
Hydronephrosis		1 (2%)		1 (2%)
Cyst, NOS			1 (2%)	
Congestion, NOS	1 (2%)			
Hemorrhage	1 (2%)			
Inflammation, acute	1 (2%)			1 (2%)
Nephropathy	50 (100%)	50 (100%)	44 (88%)	47 (94%)
Nephropathy, toxic			39 (78%)	35 (70%)
Calcification, focal				1 (2%)
Cytomegaly			48 (96%)	49 (98%)
Hyperplasia, tubular cell			5 (10%)	3 (6%)
Hyperplasia, cystic	1 (2%)			
#Kidney/medulla	(50)	(50)	(50)	(50)
Hyperplasia, epithelial	1 (2%)	2 (4%)		
#Kidney/tubule	(50)	(50)	(50)	(50)
Dilatation, NOS			1 (2%)	
#Kidney/pelvis	(50)	(50)	(50)	(50)
Hemorrhage			1 (2%)	
Hyperplasia, epithelial	1 (2%)		2 (4%)	
#Urinary bladder	(50)	(46)	(50)	(49)
Calculus, gross observation only				1 (2%)
Cast, NOS				1 (2%)
Hemorrhage		2 (4%)		
Inflammation, NOS				1 (2%)
Inflammation, acute/chronic		1 (2%)		
Hyperplasia, epithelial			1 (2%)	
ENDOCRINE SYSTEM				
#Pituitary	(46)	(42)	(45)	(38)
Cyst, NOS	2 (4%)	2 (5%)	1 (2%)	
Abscess, NOS	1 (2%)			
Hyperplasia, focal	3 (7%)	2 (5%)	1 (2%)	
#Adrenal	(50)	(50)	(49)	(50)
Cyst, NOS	2 (4%)			
Hemorrhage		1 (2%)		1 (2%)
Inflammation, chronic focal			1 (2%)	
Necrosis, NOS		1 (2%)		
Necrosis, focal			1 (2%)	
Metamorphosis, fatty	1 (2%)			
Lipoidosis	6 (12%)	12 (24%)	8 (16%)	5 (10%)
Cytoplasmic vacuolization	1 (2%)			
Focal cellular change		1 (2%)		
Hyperplasia, NOS		1 (2%)		
Angiectasis	1 (2%)	2 (4%)	4 (8%)	2 (4%)
#Adrenal cortex	(50)	(50)	(49)	(50)
Hemorrhage				1 (2%)
Metamorphosis, fatty	1 (2%)			
Lipoidosis	1 (2%)		3 (6%)	1 (2%)
Focal cellular change	1 (2%)			1 (2%)
Cytologic alteration, NOS			1 (2%)	
Hyperplasia, NOS		1 (2%)		
Hyperplasia, focal			1 (2%)	
#Adrenal medulla	(50)	(50)	(49)	(50)
Hyperplasia, NOS	2 (4%)	1 (2%)		1 (2%)
Hyperplasia, focal	4 (8%)	3 (6%)	3 (6%)	4 (8%)

TABLE G4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE OSBORNE-MENDEL RATS IN THE TWO-YEAR STUDY OF TRICHOLOETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)				
#Thyroid	(48)	(49)	(48)	(48)
Cyst, NOS			2 (4%)	4 (8%)
Follicular cyst, NOS				1 (2%)
Hyperplasia, C-cell	1 (2%)	5 (10%)	5 (10%)	3 (6%)
Hyperplasia, follicular cell	2 (4%)			
#Parathyroid	(33)	(38)	(30)	(33)
Hyperplasia, NOS		1 (3%)	1 (3%)	
#Pancreatic islets	(50)	(49)	(50)	(50)
Hyperplasia, focal	1 (2%)			
REPRODUCTIVE SYSTEM				
*Preputial gland	(50)	(50)	(50)	(50)
Abscess, NOS	1 (2%)			
#Prostate	(49)	(49)	(50)	(50)
Cyst, NOS		1 (2%)		
Hemorrhage				2 (4%)
Inflammation, focal				1 (2%)
Inflammation, acute	1 (2%)			
Inflammation, acute focal	2 (4%)	1 (2%)		
Inflammation, acute suppurative				1 (2%)
Inflammation, acute necrotizing		1 (2%)		
Inflammation, acute/chronic	1 (2%)	1 (2%)		
Inflammation, chronic		1 (2%)		1 (2%)
Inflammation, chronic focal		1 (2%)	1 (2%)	
Inflammation, granulomatous		1 (2%)		
Hyperplasia, NOS		1 (2%)		
*Seminal vesicle	(50)	(50)	(50)	(50)
Inflammation, acute focal				1 (2%)
*Coagulating gland	(50)	(50)	(50)	(50)
Hyperplasia, focal				1 (2%)
#Testis	(50)	(49)	(50)	(50)
Atrophy, NOS	1 (2%)	7 (14%)	1 (2%)	2 (4%)
Atrophy, focal			1 (2%)	
Atrophy, diffuse		1 (2%)		
Hyperplasia, interstitial cell	1 (2%)			
NERVOUS SYSTEM				
#Brain	(49)	(49)	(50)	(50)
Cyst, NOS				1 (2%)
Congestion, NOS		1 (2%)		
Hemorrhage	1 (2%)	2 (4%)		2 (4%)
*Spinal cord	(50)	(50)	(50)	(50)
Hemorrhage				1 (2%)
Calcification, focal				1 (2%)
*Pineal body	(50)	(50)	(50)	(50)
Degeneration, NOS			1 (2%)	
SPECIAL SENSE ORGANS				
*Eye/lacrimal gland	(50)	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	1 (2%)	
Inflammation, chronic focal			1 (2%)	
Atrophy, NOS			1 (2%)	
MUSCULOSKELETAL SYSTEM				
*Pharyngeal muscle	(50)	(50)	(50)	(50)
Inflammation, acute necrotizing			1 (2%)	

TABLE G4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
BODY CAVITIES				
*Thorax	(50)	(50)	(50)	(50)
Abscess, chronic				1 (2%)
*Mediastinum	(50)	(50)	(50)	(50)
Hemorrhage				1 (2%)
Abscess, NOS		1 (2%)		
Inflammation, active chronic		1 (2%)		
*Abdominal cavity	(50)	(50)	(50)	(50)
Necrosis, fat	1 (2%)			
*Epicardium	(50)	(50)	(50)	(50)
Inflammation, chronic				1 (2%)
ALL OTHER SYSTEMS				
*Multiple organs	(50)	(50)	(50)	(50)
Hemorrhage				1 (2%)
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 H

SUMMARY OF LESIONS IN FEMALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

TABLE H1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*Subcutaneous tissue	(50)	(50)	(50)	(50)
Fibroma			2 (4%)	1 (2%)
RESPIRATORY SYSTEM				
#Lung	(50)	(50)	(50)	(50)
Carcinoma, NOS, metastatic			1 (2%)	
Squamous cell carcinoma, metastatic			1 (2%)	
Alveolar/bronchiolar adenoma				1 (2%)
Alveolar/bronchiolar carcinoma			1 (2%)	
Osteosarcoma, metastatic				1 (2%)
HEMATOPOIETIC SYSTEM				
*Multiple organs	(50)	(50)	(50)	(50)
Malignant lymphoma, NOS	1 (2%)	1 (2%)		2 (4%)
Malignant lymphoma, lymphocytic type			1 (2%)	
Monocytic leukemia	2 (4%)		2 (4%)	
*Mediastinum	(50)	(50)	(50)	(50)
Malignant lymphoma, undiffer type		1 (2%)		
#Liver	(50)	(50)	(50)	(49)
Leukemia, NOS			1 (2%)	
CIRCULATORY SYSTEM				
#Liver	(50)	(50)	(50)	(49)
Angioma			1 (2%)	
DIGESTIVE SYSTEM				
#Liver	(50)	(50)	(50)	(49)
Carcinoma, NOS, metastatic			1 (2%)	
Bile duct carcinoma			1 (2%)	
Neoplastic nodule	1 (2%)			2 (4%)
#Pancreas	(50)	(50)	(48)	(49)
Squamous cell carcinoma, metastatic			1 (2%)	
Adenocarcinoma, NOS, metastatic			1 (2%)	
#Stomach	(50)	(48)	(50)	(49)
Squamous cell carcinoma				1 (2%)
#Forestomach	(50)	(48)	(50)	(49)
Papillomatosis	1 (2%)			
#Duodenum	(50)	(48)	(49)	(49)
Adenocarcinoma, NOS		1 (2%)		
URINARY SYSTEM				
#Kidney	(50)	(50)	(50)	(49)
Tubular cell adenoma	1 (2%)			1 (2%)
Nephroblastoma			1 (2%)	
#Urinary bladder	(48)	(48)	(49)	(50)
Adenocarcinoma, NOS, metastatic				1 (2%)

TABLE H1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM				
#Pituitary	(47)	(46)	(47)	(46)
Carcinoma, NOS		1 (2%)		
Adenoma, NOS	13 (28%)	13 (28%)	9 (19%)	8 (17%)
Papillary adenoma		1 (2%)		
Chromophobe adenoma	1 (2%)			
#Adrenal	(49)	(50)	(50)	(49)
Cortical adenoma	13 (27%)	16 (32%)	13 (26%)	19 (39%)
Pheochromocytoma	3 (6%)	8 (16%)	4 (8%)	1 (2%)
Pheochromocytoma, malignant		1 (2%)	1 (2%)	
#Adrenal medulla	(49)	(50)	(50)	(49)
Pheochromocytoma	1 (2%)			
Pheochromocytoma, malignant			1 (2%)	
#Thyroid	(49)	(49)	(49)	(49)
Follicular cell adenoma	1 (2%)	1 (2%)		
C-cell adenoma	5 (10%)	15 (31%)	5 (10%)	1 (2%)
#Parathyroid	(37)	(32)	(32)	(32)
Adenoma, NOS				1 (3%)
#Pancreatic islets	(50)	(50)	(48)	(49)
Islet cell adenoma		3 (6%)	1 (2%)	
REPRODUCTIVE SYSTEM				
*Mammary gland	(50)	(50)	(50)	(50)
Adenoma, NOS		1 (2%)	1 (2%)	1 (2%)
Adenocarcinoma, NOS		1 (2%)	1 (2%)	1 (2%)
Fibroma		1 (2%)	1 (2%)	1 (2%)
Mixed tumor, benign			1 (2%)	
Fibroadenoma	17 (34%)	14 (28%)	7 (14%)	11 (22%)
*Vagina	(50)	(50)	(50)	(50)
Squamous cell carcinoma				1 (2%)
#Uterus	(50)	(49)	(49)	(50)
Carcinoma, NOS	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Carcinoma, NOS, metastatic			1 (2%)	
Papillomatosis			1 (2%)	
Squamous cell papilloma		1 (2%)		
Squamous cell carcinoma			1 (2%)	
Adenoma, NOS	1 (2%)			
Adenocarcinoma, NOS		1 (2%)	5 (10%)	2 (4%)
Multiple polyposis			1 (2%)	
Sarcoma, NOS	1 (2%)			
Endometrial stromal polyp	4 (8%)	6 (12%)	1 (2%)	6 (12%)
Carcinosarcoma				1 (2%)
#Uterus/endometrium	(50)	(49)	(49)	(50)
Carcinoma, NOS				1 (2%)
Adenocarcinoma, NOS		1 (2%)		
#Ovary	(49)	(48)	(49)	(49)
Carcinoma, NOS			1 (2%)	
Papillary adenoma			1 (2%)	
Granulosa cell tumor			1 (2%)	
Granulosa cell carcinoma				1 (2%)
NERVOUS SYSTEM				
*Nerve tract	(50)	(50)	(50)	(50)
Neurilemoma	1 (2%)			
SPECIAL SENSE ORGANS				
None				

TABLE H1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM				
*Maxilla	(50)	(50)	(50)	(50)
Osteosarcoma				1 (2%)
*Skeletal muscle	(50)	(50)	(50)	(50)
Rhabdomyosarcoma				1 (2%)
BODY CAVITIES				
*Abdominal cavity	(50)	(50)	(50)	(50)
Bile duct carcinoma, metastatic			1 (2%)	
ALL OTHER SYSTEMS				
*Multiple organs	(50)	(50)	(50)	(50)
Carcinoma, NOS			2 (4%)	
Undifferentiated carcinoma			1 (2%)	
Carcinosarcoma, metastatic				1 (2%)
Mesothelioma, malignant	1 (2%)			
Lower leg				
Sarcoma, NOS				1
Site unknown				
Carcinoma, NOS		1		
ANIMAL DISPOSITION SUMMARY				
Animals initially in study	50	50	50	50
Natural death	14	7	16	16
Moribund sacrifice	17	17	18	21
Terminal sacrifice	19	18	10	7
Dosing accident		6	4	5
Accidentally killed, NOS		2	2	1
TUMOR SUMMARY				
Total animals with primary tumors**	44	40	36	37
Total primary tumors	69	90	72	68
Total animals with benign tumors	40	39	29	32
Total benign tumors	62	80	49	52
Total animals with malignant tumors	6	8	19	12
Total malignant tumors	6	10	22	14
Total animals with secondary tumors##			5	3
Total secondary tumors			7	3
Total animals with tumors uncertain--benign or malignant	1		1	2
Total uncertain tumors	1		1	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 H2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: UNTREATED CONTROL

ANIMAL NUMBER	20 01	20 04	20 07	21 16	21 19	22 22	22 24	22 28	23 37	23 38	23 39	24 40	24 42	24 44	25 57	25 58	26 60	26 61	26 62	26 67	27 75	27 77	27 78	28 81	28 82
WEEKS ON STUDY	105	085	105	062	101	093	105	105	100	078	092	105	078	100	100	097	082	105	105	035	071	105	105	083	079
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Lymph nodes	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Thymus	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	A	–	–	–	–	
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillomatosis																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma												X													
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS			X		X									X				X	X			X			
Chromophobe adenoma																									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma							X	X	X		X						X						X		
Pheochromocytoma																								X	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
C-cell adenoma																X			X				X		
Parathyroid	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	–	–	+	
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+
Fibroadenoma		X		X		X							X	X								X			X
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS																									
Sarcoma, NOS																									
Endometrial stromal polyp	X																								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Nerve tract																									
Neurilemoma															X										
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, malignant																									
Malignant lymphoma, NOS																									
Monocytic leukemia		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 H2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE OSBORNE-MENDEL RATS: UNTREATED CONTROL (Continued)

ANIMAL NUMBER	285	291	300	310	312	314	315	317	323	324	331	335	337	348	350	353	355	356	358	359	360	374	376	385	387	388	TOTAL:
WEEKS ON STUDY	079	097	105	105	105	076	075	091	105	105	078	062	070	103	105	105	085	092	048	090	054	105	065	105	060		TISSUES TUMORS
RESPIRATORY SYSTEM																											
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	47
Thymus	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−		3
CIRCULATORY SYSTEM																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																											
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−			46
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			*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Papillomatosis																			X								1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Tubular cell adenoma																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+			48
ENDOCRINE SYSTEM																											
Pituitary	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−			47
Adenoma, NOS				X					X	X					X	X						X		X			13
Chromophobe adenoma																					X						1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+			49
Cortical adenoma			X		X					X				X	X					X		X					13
Pheochromocytoma					X										X					X							4
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+			49
Follicular cell adenoma				X																							1
C-cell adenoma															X							X					5
Parathyroid	+	−	+	−	+	+	−	+	+	+	+	+	−	+	+	+	+	+	−	−	−	−	+	+	−		37
REPRODUCTIVE SYSTEM																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	*50
Fibroadenoma	X		X	X					X		X	X		X	X		X			X							17
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS			X																								1
Adenoma, NOS													X														1
Sarcoma, NOS																			X								1
Endometrial stromal polyp					X		X														X						4
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	49
NERVOUS SYSTEM																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																											
Nerve tract																											
Neurilemoma																											1
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	N	*50
Mesothelioma, malignant																		N									1
Malignant lymphoma, NOS		X																									1
Monocytic leukemia								X																			2

* Animals necropsied

TABLE H2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: VEHICLE CONTROL

ANIMAL NUMBER	203	209	210	218	221	230	235	243	246	247	251	252	255	269	270	286	287	289	290	292	293	296	301	311	313
WEEKS ON STUDY	074	096	105	099	105	033	105	105	105	083	105	068	062	095	040	105	096	105	105	074	101	046	073	105	105
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Lymph nodes	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	−	−	−	−	+	−	−	−	−	−	−	−	+	+	−	−	−	−	−	−	−	−	−	−
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Adenocarcinoma, NOS									X																
Large intestine	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																					X				
Adenoma, NOS	X		X	X	X		X				X						X		X						
Papillary adenoma		X																							
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma	X				X		X	X	X				X		X		X		X				X		
Pheochromocytoma		X									X				X										
Pheochromocytoma, malignant				X																					
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma	X																								
C-cell adenoma			X		X			X	X		X		X			X				X	X			X
Parathyroid	−	+	+	+	+	−	+	−	−	+	+	+	−	−	+	+	+	+	−	+	+	+	+	−	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																		X							X
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+
Adenoma, NOS																									
Adenocarcinoma, NOS													X												
Fibroma																									
Fibroadenoma						X	X										X		X		X			X	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Squamous cell papilloma																									
Adenocarcinoma, NOS																					X				
Endometrial stromal polyp												X					X								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BODY CAVITIES																									
Mediastinum	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, undifferentiated type																									
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											
Site unknown																									
Carcinoma, NOS																					X				

TABLE H2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE OSBORNE-MENDEL RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	318	321	322	328	333	334	336	338	339	351	352	362	369	372	375	378	379	381	382	390	391	396	397	399	400	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	100	033	080	006	100	105	087	078	019	090	105	104	101	104	052	061	105	083	105	105	100	094	105	105	084	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	–	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	46
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	4
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma, NOS																										1
Large intestine	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	46
Carcinoma, NOS																										1
Adenoma, NOS						X					X						X			X				X		13
Papillary adenoma																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma						X		X			X					X					X	X				16
Pheochromocytoma	X						X				X													X	X	8
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma																										1
C-cell adenoma	X													X			X		X	X						15
Parathyroid	+	–	+	–	+	+	+	+	–	+	+	+	+	+	–	–	–	+	–	–	+	–	+	+	+	32
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma													X													3
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	*50
Adenoma, NOS																						X				1
Adenocarcinoma, NOS																										1
Fibroma										X																1
Fibroadenoma							X	X				X		X	X	X			X			X				14
Uterus	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS						X																				1
Squamous cell papilloma										X																1
Adenocarcinoma, NOS																								X		2
Endometrial stromal polyp											X					X	X								X	6
Ovary	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BODY CAVITIES																										
Mediastinum	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, undiffer type									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
Malignant lymphoma, NOS																										1
Site unknown																										
Carcinoma, NOS																										1

* Animals necropsied

TABLE H2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: LOW DOSE

ANIMAL NUMBER	21 11	21 12	21 13	21 17	22 29	23 32	23 33	23 34	23 36	24 41	24 48	25 50	25 59	26 85	26 66	26 68	27 73	27 76	27 79	28 83	28 88	29 94	29 97	29 98	29 99
WEEKS ON STUDY	07 70	09 93	10 44	10 44	10 03	09 96	10 00	01 10	10 44	08 81	10 44	04 41	03 55	08 89	09 93	07 75	07 73	08 80	08 87	06 60	08 87	00 09	10 44	04 42	06 60
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+
Fibroma							X																		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic														X											
Squamous cell carcinoma, metastatic																									
Alveolar/bronchiolar carcinoma									X																
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	−	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	−	−	−	−	−	−	+	−	−	−	+	+	−	−	−	−	−	−	+	−	+	−	+	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic																									
Bile duct carcinoma																					X				
Angioma																									
Leukemia, NOS																							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	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic																									
Adenocarcinoma, NOS, metastatic																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nephroblastoma													X												
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	−
Adenoma, NOS			X	X			X								X										
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma					X				X																
Pheochromocytoma		X																			X				
Pheochromocytoma, malignant						X																			
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma									X						X										
Parathyroid	+	−	−	+	+	−	−	+	+	+	−	+	−	−	+	−	−	+	+	+	+	+	+	−	+
Pancreatic islets	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS											X														
Adenocarcinoma, NOS																							X		
Fibroma		X																							
Mixed tumor, benign																									
Fibroadenoma					X																		X		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS									X																
Carcinoma, NOS, metastatic														X											
Papillomatosis															X										
Squamous cell carcinoma																									
Adenocarcinoma, NOS											X														
Multiple polyposis																									
Endometrial stromal polyp																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS														X											
Papillary adenoma				X																					
Granulosa cell tumor																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Bile duct carcinoma, metastatic																					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
Carcinoma, NOS																									
Undifferentiated carcinoma										X															
Malignant lymphoma, lymphocytic type																				X					
Monocytic leukemia												X													

TABLE H2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE OSBORNE-MENDEL RATS: LOW DOSE (Continued)

ANIMAL NUMBER	302	304	306	308	309	316	319	320	329	332	344	345	347	349	354	355	357	364	365	367	368	383	384	392	393	TOTAL:
WEEKS ON STUDY	104	076	075	104	095	104	103	070	036	087	104	087	087	087	104	094	074	104	097	090	074	102	101	063	087	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma								X																		2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, metastatic																										1
Squamous cell carcinoma, metastatic																							X			1
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph nodes	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Thymus	−	−	−	−	−	−	−	−	+	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	8
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, metastatic																									X	1
Bile duct carcinoma																										1
Angioma																									X	1
Leukemia, NOS																										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	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell carcinoma, metastatic																							X			1
Adenocarcinoma, NOS, metastatic				X																						1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nephroblastoma																										1
Urinary bladder	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS				X			X				X				X								X			9
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma	X		X	X	X	X				X	X	X	X	X				X								13
Pheochromocytoma											X	X														4
Pheochromocytoma, malignant																									X	2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	49
C-cell adenoma	X						X																X			5
Parathyroid	+	−	+	+	+	+	+	+	−	−	+	+	−	+	+	+	+	+	+	−	+	−	+	−	−	32
Pancreatic islets	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma																									X	1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS																										1
Adenocarcinoma, NOS																										1
Fibroma																										1
Mixed tumor, benign																					X					1
Fibroadenoma	X						X						X								X	X				7
Uterus	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS																		X								2
Carcinoma, NOS, metastatic																										1
Papillomatosis																										1
Squamous cell carcinoma																							X			1
Adenocarcinoma, NOS				X		X				X										X						5
Multiple polyposis										X																1
Endometrial stromal polyp																				X						1
Ovary	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS																										1
Papillary adenoma																										1
Granulosa cell tumor																		X								1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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
Bile duct carcinoma, metastatic																										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
Carcinoma, NOS																X									X	2
Undifferentiated carcinoma																										1
Malignant lymphoma, lymphocytic type																										1
Monocytic leukemia												X														2

* Animals necropsied

TABLE H2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE: HIGH DOSE

ANIMAL NUMBER	202	205	206	208	214	215	220	223	225	226	227	231	245	249	253	254	256	263	264	271	272	274	280	284	295
WEEKS ON STUDY	089	078	103	019	017	101	018	104	027	060	103	079	098	069	074	104	104	104	071	101	089	080	089	085	097
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Osteosarcoma, metastatic						X																			
Trachea	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	–	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	–	–	–	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																		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
Pancreas	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma															X										
Small intestine	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic													X												
ENDOCRINE SYSTEM																									
Pituitary	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
Adenoma, NOS	X										X		X			X			X						
Adrenal	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma						X		X								X	X	X			X	X	X		
Pheochromocytoma																									
Thyroid	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																									
Parathyroid	+	+	–	–	–	–	–	–	+	–	+	+	+	–	+	+	+	–	–	–	+	+	+	+	–
Adenoma, NOS																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+
Adenoma, NOS																	X								
Adenocarcinoma, NOS			X																						
Fibroma																									
Fibroadenoma						X																	X		X
Vagina	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																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS		X																							
Adenocarcinoma, NOS													X												
Endometrial stromal polyp												X									X				
Carcinosarcoma																									
Ovary	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell carcinoma						X																			
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	+	+	N	+	N	N	N	N	N	N	N	+	+	N	N	N	N	N	N	N	N	N
Osteosarcoma						X																			
Muscle	N	N	N	+	+	N	+	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N
Rhabdomyosarcoma																									
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
Carcinosarcoma, metastatic																									
Malignant lymphoma, NOS												X								X					
Lower leg, NOS																									
Sarcoma, NOS																						X			

TABLE H2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE OSBORNE-MENDEL RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	30 03	30 05	30 07	32 25	32 26	32 27	33 30	34 40	34 41	34 42	34 43	34 46	36 61	36 63	36 66	37 70	37 71	37 73	37 77	38 80	38 86	38 89	39 94	39 95	39 98	TOTAL:
WEEKS ON STUDY	08 80	10 83	08 88	08 83	10 44	05 59	09 99	08 80	09 92	08 80	09 97	10 03	09 94	07 00	06 65	07 99	10 04	10 04	07 66	10 03	04 55	10 11	09 95	08 81	08 85	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma								X																		1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma									X																	1
Osteosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	46
Thymus	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	3
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule												X														2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tubular cell adenoma																						X				1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic																										1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma, NOS			X		X							X														8
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma		X	X		X	X		X		X		X	X				X			X	X					19
Pheochromocytoma																						X				1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell adenoma																						X				1
Parathyroid	+	+	+	+	+	−	+	+	+	+	+	+	−	−	−	+	+	+	−	+	−	+	+	+	+	32
Adenoma, NOS							X																			1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	*50
Adenoma, NOS																										1
Adenocarcinoma, NOS																										1
Fibroma																									X	1
Fibroadenoma	X				X			X	X			X					X			X				X		11
Vagina	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							X																			1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS							X																			2
Adenocarcinoma, NOS																		X								2
Endometrial stromal polyp		X						X					X											X		6
Carcinosarcoma													X													1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granulosa cell carcinoma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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
Muscle	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
Rhabdomyosarcoma						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
Carcinosarcoma, metastatic													X													1
Malignant lymphoma, NOS																										2
Lower leg, NOS																										
Sarcoma, NOS																										1

* Animals necropsied

TABLE H3. ANALYSIS OF PRIMARY TUMORS IN FEMALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE

	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg
Hematopoietic System: Leukemia				
Overall Rates (a)	2/50 (4%)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	6.5%	0.0%	13.9%	0.0%
Terminal Rates (c)	0/19 (0%)	0/20 (0%)	1/11 (9%)	0/7 (0%)
Life Table Tests (d)		P=0.528	P=0.089	(e)
Incidental Tumor Tests (d)		P=0.596	P=0.109	(e)
Cochran-Armitage Trend Test (d)		P=0.640		
Fisher Exact Test			P=0.121	(e)
Pituitary: Adenoma				
Overall Rates (a)	14/47 (30%)	(f) 14/46 (30%)	9/47 (19%)	8/46 (17%)
Adjusted Rates (b)	62.4%	56.5%	57.9%	50.6%
Terminal Rates (c)	11/19 (58%)	10/20 (50%)	5/11 (45%)	2/7 (29%)
Life Table Tests (d)		P=0.387	P=0.519	P=0.458
Incidental Tumor Tests (d)		P=0.353N	P=0.466N	P=0.364N
Cochran-Armitage Trend Test (d)		P=0.084N		
Fisher Exact Test			P=0.154N	P=0.111N
Pituitary: Adenoma or Carcinoma				
Overall Rates (a)	14/47 (30%)	15/46 (33%)	9/47 (19%)	8/46 (17%)
Adjusted Rates (b)	62.4%	58.5%	57.9%	50.6%
Terminal Rates (c)	11/19 (58%)	10/20 (50%)	5/11 (45%)	2/7 (29%)
Life Table Tests (d)		P=0.475	P=0.599	P=0.541
Incidental Tumor Tests (d)		P=0.250N	P=0.355N	P=0.258N
Cochran-Armitage Trend Test (d)		P=0.054N		
Fisher Exact Test			P=0.106N	P=0.074N
Adrenal: Cortical Adenoma				
Overall Rates (a)	13/49 (27%)	16/50 (32%)	13/50 (26%)	19/49 (39%)
Adjusted Rates (b)	54.8%	55.6%	66.3%	92.7%
Terminal Rates (c)	9/19 (47%)	9/20 (45%)	6/11 (55%)	6/7 (86%)
Life Table Tests (d)		P=0.008	P=0.365	P=0.011
Incidental Tumor Tests (d)		P=0.100	P=0.484N	P=0.127
Cochran-Armitage Trend Test (d)		P=0.272		
Fisher Exact Test			P=0.330N	P=0.310
Adrenal: Pheochromocytoma				
Overall Rates (a)	4/49 (8%)	8/50 (16%)	4/50 (8%)	1/49 (2%)
Adjusted Rates (b)	16.1%	30.4%	18.8%	6.7%
Terminal Rates (c)	2/19 (11%)	4/20 (20%)	1/11 (9%)	0/7 (0%)
Life Table Tests (d)		P=0.080N	P=0.394N	P=0.118N
Incidental Tumor Tests (d)		P=0.009N	P=0.178N	P=0.020N
Cochran-Armitage Trend Test (d)		P=0.011N		
Fisher Exact Test			P=0.178N	P=0.017N
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant				
Overall Rates (a)	4/49 (8%)	9/50 (18%)	6/50 (12%)	1/49 (2%)
Adjusted Rates (b)	16.1%	33.1%	26.0%	6.7%
Terminal Rates (c)	2/19 (11%)	4/20 (20%)	1/11 (9%)	0/7 (0%)
Life Table Tests (d)		P=0.073N	P=0.564N	P=0.084N
Incidental Tumor Tests (d)		P=0.004N	P=0.252N	P=0.009N
Cochran-Armitage Trend Test (d)		P=0.008N		
Fisher Exact Test			P=0.288N	P=0.009N
Thyroid: C-Cell Adenoma				
Overall Rates (a)	5/49 (10%)	15/49 (31%)	5/49 (10%)	1/49 (2%)
Adjusted Rates (b)	24.2%	60.7%	32.7%	6.7%
Terminal Rates (c)	4/19 (21%)	11/20 (55%)	2/11 (18%)	0/7 (0%)
Life Table Tests (d)		P=0.006N	P=0.127N	P=0.013N
Incidental Tumor Tests (d)		P<0.001N	P=0.053N	P=0.003N
Cochran-Armitage Trend Test (d)		P<0.001N		
Fisher Exact Test			P=0.011N	P<0.001N

TABLE H3. ANALYSIS OF PRIMARY TUMORS IN FEMALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	Untreated Control	Vehicle Control	500 mg/kg	1,000 mg/kg
Pancreatic Islets: Islet Cell Adenoma				
Overall Rates (a)	0/50 (0%)	3/50 (6%)	1/48 (2%)	0/49 (0%)
Adjusted Rates (b)	0.0%	14.1%	3.2%	0.0%
Terminal Rates (c)	0/19 (0%)	2/20 (10%)	0/11 (0%)	0/7 (0%)
Life Table Tests (d)		P=0.153N	P=0.456N	P=0.294N
Incidental Tumor Tests (d)		P=0.078N	P=0.365N	P=0.221N
Cochran-Armitage Trend Test (d)		P=0.063N		
Fisher Exact Test			P=0.324N	P=0.125N
Mammary Gland: Fibroadenoma				
Overall Rates (a)	17/50 (34%)	14/50 (28%)	7/50 (14%)	11/50 (22%)
Adjusted Rates (b)	50.0%	45.1%	39.4%	56.3%
Terminal Rates (c)	5/19 (26%)	6/20 (30%)	2/11 (18%)	2/7 (29%)
Life Table Tests (d)		P=0.335	P=0.291N	P=0.350
Incidental Tumor Tests (d)		P=0.289N	P=0.104N	P=0.330N
Cochran-Armitage Trend Test (d)		P=0.271N		
Fisher Exact Test			P=0.070N	P=0.322N
Mammary Gland: Fibroma or Fibroadenoma				
Overall Rates (a)	17/50 (34%)	15/50 (30%)	8/50 (16%)	12/50 (24%)
Adjusted Rates (b)	50.0%	46.9%	42.2%	57.7%
Terminal Rates (c)	5/19 (26%)	6/20 (30%)	2/11 (18%)	2/7 (29%)
Life Table Tests (d)		P=0.320	P=0.324N	P=0.338
Incidental Tumor Tests (d)		P=0.240N	P=0.096N	P=0.262N
Cochran-Armitage Trend Test (d)		P=0.277N		
Fisher Exact Test			P=0.077N	P=0.326N
Mammary Gland: All Tumors (g)				
Overall Rates (a)	17/50 (34%)	16/50 (32%)	9/50 (18%)	14/50 (28%)
Adjusted Rates (b)	50.0%	48.2%	48.6%	69.5%
Terminal Rates (c)	5/19 (26%)	6/20 (30%)	3/11 (27%)	3/7 (43%)
Life Table Tests (d)		P=0.202	P=0.352N	P=0.229
Incidental Tumor Tests (d)		P=372N	P=0.106N	P=0.367N
Cochran-Armitage Trend Test (d)		P=0.366N		
Fisher Exact Test			P=0.083N	P=0.414N
Uterus: Adenocarcinoma				
Overall Rates (a)	(h) 0/50 (0%)	2/49 (4%)	5/49 (10%)	2/50 (4%)
Adjusted Rates (b)	0.0%	9.3%	32.7%	19.3%
Terminal Rates (c)	0/19 (0%)	1/20 (5%)	3/11 (27%)	1/7 (14%)
Life Table Tests (d)		P=0.234	P=0.080	P=0.422
Incidental Tumor Tests (d)		P=0.426	P=0.151	P=0.580
Cochran-Armitage Trend Test (d)		P=0.573N		
Fisher Exact Test			P=0.218	P=0.684N
Uterus: Endometrial Stromal Polyp				
Overall Rates (a)	4/50 (8%)	6/49 (12%)	1/49 (2%)	6/50 (12%)
Adjusted Rates (b)	14.5%	19.8%	4.3%	24.9%
Terminal Rates (c)	2/19 (11%)	2/20 (10%)	0/11 (0%)	0/7 (0%)
Life Table Tests (d)		P=0.365	P=0.122N	P=0.386
Incidental Tumor Tests (d)		P=0.379N	P=0.039N	P=0.414N
Cochran-Armitage Trend Test (d)		P=0.558N		
Fisher Exact Test			P=0.056N	P=0.606N
Multiple Organs: Carcinoma				
Overall Rates (a)	0/50 (0%)	(i) 1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	0.0%	3.8%	10.9%	0.0%
Terminal Rates (c)	0/19 (0%)	0/20 (0%)	0/11 (0%)	0/7 (0%)
Life Table Tests (d)		P=0.482N	P=0.227	P=0.602N
Incidental Tumor Tests (d)		P=0.203N	P=0.434	P=0.433N
Cochran-Armitage Trend Test (d)		P=0.378N		
Fisher Exact Test			P=0.309	P=0.500N

TABLE H3. ANALYSIS OF PRIMARY TUMORS IN FEMALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (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 vehicle 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 rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the 1,000 mg/kg and vehicle control groups.
(f) Incidence includes one papillary adenoma.
(g) Includes adenoma, adenocarcinoma, fibroma, and fibroadenoma. A mixed tumor, benign, was observed in a low dose animal that also had a fibroadenoma.
(h) One adenoma, NOS, was present.
(i) Carcinoma, NOS; site unknown.

TABLE H4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE OSBORNE-MENDEL RATS IN THE GAVAGE STUDY OF TRICHLOROETHYLENE

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*Subcutaneous tissue	(50)	(50)	(50)	(50)
Abscess, chronic		2 (4%)		1 (2%)
RESPIRATORY SYSTEM				
*Nasal cavity	(50)	(50)	(50)	(50)
Ulcer, NOS		1 (2%)		
*Tracheal lumen	(50)	(50)	(50)	(50)
Vegetable foreign body	1 (2%)			
#Trachea	(49)	(50)	(47)	(47)
Inflammation, NOS			1 (2%)	
Inflammation, chronic			1 (2%)	1 (2%)
Inflammation, chronic focal				1 (2%)
Hyperplasia, epithelial			1 (2%)	
#Lung	(50)	(50)	(50)	(50)
Vegetable foreign body		3 (6%)	3 (6%)	
Emphysema, alveolar		1 (2%)	1 (2%)	2 (4%)
Collapse		1 (2%)		
Congestion, NOS	1 (2%)	2 (4%)	4 (8%)	5 (10%)
Edema, NOS	1 (2%)	1 (2%)	3 (6%)	3 (6%)
Hemorrhage	2 (4%)	3 (6%)	6 (12%)	3 (6%)
Inflammation, NOS	1 (2%)			1 (2%)
Bronchopneumonia, focal		1 (2%)		
Inflammation, focal	3 (6%)	5 (10%)	1 (2%)	1 (2%)
Inflammation, necrotizing		1 (2%)		
Bronchopneumonia, acute			1 (2%)	
Inflammation, acute/chronic			1 (2%)	
Inflammation, chronic		2 (4%)		2 (4%)
Inflammation, chronic focal	1 (2%)	1 (2%)	1 (2%)	
Inflammation, granulomatous	1 (2%)	4 (8%)	2 (4%)	2 (4%)
Inflammation, granulomatous focal	3 (6%)	1 (2%)	4 (8%)	8 (16%)
Inflammation necro granulomatous		1 (2%)		
Infection, bacterial	1 (2%)			
Proteinosis, alveolar		1 (2%)		
Calcification, metastatic		1 (2%)		
Foreign material, NOS			1 (2%)	1 (2%)
#Lung/alveoli	(50)	(50)	(50)	(50)
Histiocytosis		1 (2%)		
HEMATOPOIETIC SYSTEM				
#Bone marrow	(50)	(50)	(50)	(49)
Hyperplasia, granulocytic				1 (2%)
#Spleen	(49)	(49)	(48)	(49)
Congestion, NOS			1 (2%)	
Hemorrhage	1 (2%)			
Abscess, NOS		1 (2%)		
Inflammation, granulomatous focal		1 (2%)		
Necrosis, focal			2 (4%)	
Hemosiderosis	2 (4%)		1 (2%)	1 (2%)
Depletion, lymphoid			1 (2%)	
Hyperplasia, lymphoid			1 (2%)	
Hematopoiesis	11 (22%)	8 (16%)	14 (29%)	11 (22%)

TABLE H4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)				
#Lymph node	(47)	(46)	(45)	(46)
Congestion, NOS	1 (2%)			
Hemorrhage	1 (2%)			
Degeneration, cystic	1 (2%)			
#Mandibular lymph node	(47)	(46)	(45)	(46)
Hemorrhage			1 (2%)	
Plasmacytosis		1 (2%)		
#Mesenteric lymph node	(47)	(46)	(45)	(46)
Inflammation, chronic			1 (2%)	
Hyperplasia, reticulum cell			1 (2%)	
#Liver	(50)	(50)	(50)	(49)
Hematopoiesis	1 (2%)	2 (4%)	1 (2%)	
#Thymus	(3)	(4)	(8)	(3)
Congestion, NOS			1 (13%)	
Hemorrhage			2 (25%)	1 (33%)
CIRCULATORY SYSTEM				
#Lung	(50)	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)			
#Heart	(50)	(49)	(50)	(49)
Hemorrhage			1 (2%)	
Inflammation, chronic		1 (2%)		
Inflammation, chronic focal		4 (8%)	1 (2%)	
Endocardiosis			1 (2%)	
Necrosis, focal		1 (2%)		
*Coronary artery	(50)	(50)	(50)	(50)
Calcification, metastatic	1 (2%)			
*Pulmonary artery	(50)	(50)	(50)	(50)
Mineralization		1 (2%)		
Calcification, focal	1 (2%)	1 (2%)		
Calcification, metastatic	1 (2%)			
#Liver	(50)	(50)	(50)	(49)
Perivasculitis			1 (2%)	
#Pancreas	(50)	(50)	(48)	(49)
Periarteritis	1 (2%)			
DIGESTIVE SYSTEM				
#Salivary gland	(46)	(50)	(50)	(47)
Atrophy, NOS		1 (2%)		
Atrophy, focal				1 (2%)
#Liver	(50)	(50)	(50)	(49)
Congestion, NOS			1 (2%)	
Hemorrhage				1 (2%)
Inflammation, focal				2 (4%)
Inflammation, active chronic				1 (2%)
Inflammation, chronic focal	1 (2%)			
Peliosis hepatis	1 (2%)			
Necrosis, focal	1 (2%)		5 (10%)	
Necrosis, diffuse		1 (2%)		
Necrosis, central			1 (2%)	
Metamorphosis, fatty	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Lipoidosis				2 (4%)
Pigmentation, NOS	1 (2%)			
Cytoplasmic change, NOS	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Basophilic cyto change	1 (2%)			
Focal cellular change	1 (2%)			1 (2%)
Clear cell change		1 (2%)		2 (4%)
Cytologic alteration, NOS		1 (2%)		
Hepatocytomegaly				1 (2%)

TABLE H4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)				
#Liver/centrilobular	(50)	(50)	(50)	(49)
Necrosis, NOS				1 (2%)
#Bile duct	(50)	(50)	(50)	(49)
Dilatation, NOS				1 (2%)
Inflammation, chronic	1 (2%)		2 (4%)	1 (2%)
Hyperplasia, NOS	5 (10%)	3 (6%)	2 (4%)	1 (2%)
Hyperplasia, focal		1 (2%)	1 (2%)	
Hyperplasia, diffuse			1 (2%)	
#Pancreas	(50)	(50)	(48)	(49)
Hemorrhage		1 (2%)		
Inflammation, acute/chronic			1 (2%)	
Inflammation, chronic			2 (4%)	1 (2%)
Inflammation, chronic focal				1 (2%)
Atrophy, focal		1 (2%)		
#Pancreatic acinus	(50)	(50)	(48)	(49)
Atrophy, NOS	1 (2%)			
Atrophy, focal	3 (6%)	2 (4%)	3 (6%)	3 (6%)
*Esophageal lumen	(50)	(50)	(50)	(50)
Hemorrhage	2 (4%)	4 (8%)		1 (2%)
#Esophagus	(50)	(48)	(50)	(50)
Hyperkeratosis	1 (2%)			
#Thoracic esophagus	(50)	(48)	(50)	(50)
Granulation tissue				1 (2%)
#Stomach	(50)	(48)	(50)	(49)
Inflammation, suppurative				1 (2%)
Calcification, metastatic		1 (2%)		
#Gastric mucosa	(50)	(48)	(50)	(49)
Inflammation, NOS	1 (2%)			
Hyperplasia, epithelial	1 (2%)			
Hyperkeratosis	1 (2%)			
#Forestomach	(50)	(48)	(50)	(49)
Inflammation, NOS	1 (2%)			
Hyperplasia, epithelial	1 (2%)	1 (2%)		
Hyperkeratosis	1 (2%)			
#Jejunum	(50)	(48)	(49)	(49)
Hemorrhage		1 (2%)		
#Colon	(50)	(48)	(47)	(50)
Parasitism	7 (14%)	5 (10%)	7 (15%)	7 (14%)
URINARY SYSTEM				
#Kidney	(50)	(50)	(50)	(49)
Mineralization	8 (16%)	3 (6%)	3 (6%)	
Cast, NOS	4 (8%)	7 (14%)	2 (4%)	1 (2%)
Hydronephrosis	2 (4%)		1 (2%)	4 (8%)
Cyst, NOS	2 (4%)	1 (2%)		
Hemorrhage		1 (2%)		
Inflammation, acute focal	1 (2%)			
Inflammation, acute/chronic		1 (2%)		
Inflammation, chronic				1 (2%)
Inflammation, chronic focal	1 (2%)			
Inflammation, granulomatous focal		1 (2%)		
Fibrosis				1 (2%)
Nephropathy	43 (86%)	43 (86%)	41 (82%)	47 (96%)
Nephropathy, toxic			30 (60%)	39 (80%)
Necrosis, focal	1 (2%)			
Calcification, focal	1 (2%)	4 (8%)	2 (4%)	2 (4%)
Calcification, metastatic		1 (2%)		
Cytomegaly			48 (96%)	49 (100%)
Hyperplasia, tubular cell		1 (2%)	1 (2%)	3 (6%)
#Kidney/cortex	(50)	(50)	(50)	(49)
Degeneration, NOS	1 (2%)			

TABLE H4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM (Continued)				
#Kidney/medulla	(50)	(50)	(50)	(49)
Hyperplasia, NOS	1 (2%)			
Hyperplasia, epithelial	6 (12%)	5 (10%)	2 (4%)	
#Kidney/tubule	(50)	(50)	(50)	(49)
Dilatation, NOS			1 (2%)	
#Kidney/pelvis	(50)	(50)	(50)	(49)
Hemorrhage	2 (4%)			
Inflammation, acute	1 (2%)	1 (2%)		
Hyperplasia, epithelial	2 (4%)	4 (8%)	5 (10%)	6 (12%)
#Urinary bladder	(48)	(48)	(49)	(50)
Hemorrhage		1 (2%)		
Inflammation, acute		1 (2%)		
Inflammation, acute/chronic	1 (2%)	1 (2%)		
Inflammation, chronic	1 (2%)			
Hyperplasia, epithelial	1 (2%)	1 (2%)		
ENDOCRINE SYSTEM				
#Pituitary	(47)	(46)	(47)	(46)
Cyst, NOS		1 (2%)	2 (4%)	1 (2%)
Congestion, NOS		1 (2%)		
Hemorrhage			1 (2%)	
Hyperplasia, focal	1 (2%)	2 (4%)	1 (2%)	2 (4%)
#Adrenal	(49)	(50)	(50)	(49)
Congestion, NOS				1 (2%)
Hemorrhage	1 (2%)	1 (2%)	2 (4%)	
Degeneration, NOS				2 (4%)
Degeneration, cystic		1 (2%)		
Necrosis, focal			1 (2%)	1 (2%)
Metamorphosis, fatty			1 (2%)	
Lipoidosis	2 (4%)	2 (4%)		
Angiectasis	3 (6%)	6 (12%)	9 (18%)	12 (24%)
#Adrenal cortex	(49)	(50)	(50)	(49)
Degeneration, NOS				1 (2%)
Lipoidosis			3 (6%)	1 (2%)
Focal cellular change	1 (2%)		1 (2%)	
Atrophy, NOS	1 (2%)			
Hyperplasia, NOS			1 (2%)	
Hyperplasia, focal	1 (2%)	1 (2%)	3 (6%)	
Angiectasis	1 (2%)			
#Adrenal medulla	(49)	(50)	(50)	(49)
Hyperplasia, NOS				1 (2%)
Hyperplasia, focal	1 (2%)	1 (2%)	2 (4%)	1 (2%)
#Thyroid	(49)	(49)	(49)	(49)
Cyst, NOS		2 (4%)	3 (6%)	6 (12%)
Inflammation, chronic		1 (2%)		
Hyperplasia, C-cell	4 (8%)	1 (2%)	2 (4%)	1 (2%)
REPRODUCTIVE SYSTEM				
*Mammary gland	(50)	(50)	(50)	(50)
Cyst, NOS	1 (2%)			1 (2%)
Hemorrhage	1 (2%)			
Degeneration, NOS		1 (2%)		
Hyperplasia, NOS	1 (2%)			
Lactation	11 (22%)	4 (8%)	4 (8%)	7 (14%)
*Vagina	(50)	(50)	(50)	(50)
Hyperplasia, epithelial			1 (2%)	1 (2%)
*Vaginal mucosa	(50)	(50)	(50)	(50)
Hyperplasia, cystic	1 (2%)			

TABLE H4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)				
#Uterus	(50)	(49)	(49)	(50)
Dilatation, NOS	4 (8%)	7 (14%)	2 (4%)	6 (12%)
Hydrometra	6 (12%)	2 (4%)	8 (16%)	6 (12%)
Epidermal inclusion cyst		1 (2%)		
Hemorrhage	3 (6%)		1 (2%)	
Hematometra	1 (2%)	1 (2%)	4 (8%)	
Inflammation, NOS	1 (2%)	2 (4%)	1 (2%)	
Ulcer, NOS			4 (8%)	1 (2%)
Pyometra		1 (2%)	3 (6%)	1 (2%)
Inflammation, acute	3 (6%)		1 (2%)	2 (4%)
Inflammation, acute focal	1 (2%)			
Inflammation, acute necrotizing			1 (2%)	
Inflammation, acute/chronic	1 (2%)		2 (4%)	3 (6%)
Inflammation, chronic			1 (2%)	1 (2%)
Necrosis, hemorrhagic				1 (2%)
Pigmentation, NOS			1 (2%)	
Hyperplasia, epithelial	1 (2%)	1 (2%)		1 (2%)
Hyperkeratosis		2 (4%)	1 (2%)	1 (2%)
Metaplasia, NOS		1 (2%)	1 (2%)	
Metaplasia, squamous	1 (2%)	3 (6%)	7 (14%)	4 (8%)
#Uterus/endometrium	(50)	(49)	(49)	(50)
Cyst, NOS			1 (2%)	
Ulcer, NOS		1 (2%)		
Inflammation, acute			1 (2%)	1 (2%)
Hyperplasia, NOS		1 (2%)	2 (4%)	3 (6%)
Hyperplasia, cystic	12 (24%)	8 (16%)	9 (18%)	4 (8%)
Metaplasia, NOS	3 (6%)	1 (2%)	1 (2%)	
Metaplasia, squamous	1 (2%)	2 (4%)	1 (2%)	2 (4%)
#Ovary	(49)	(48)	(49)	(49)
Cyst, NOS	3 (6%)	4 (8%)	1 (2%)	5 (10%)
Follicular cyst, NOS	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Inflammation, suppurative		1 (2%)		
Inflammation, acute	1 (2%)	1 (2%)		
NERVOUS SYSTEM				
#Brain	(50)	(50)	(50)	(49)
Cyst, NOS		1 (2%)		
Hemorrhage		1 (2%)	2 (4%)	
Abscess, NOS			1 (2%)	
Inflammation, chronic focal			1 (2%)	
*Spinal cord	(50)	(50)	(50)	(50)
Hemorrhage			1 (2%)	
SPECIAL SENSE ORGANS				
*Harderian gland	(50)	(50)	(50)	(50)
Inflammation, chronic		1 (2%)		1 (2%)
Inflammation, chronic focal				1 (2%)
MUSCULOSKELETAL SYSTEM				
None				

TABLE H4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE OSBORNE-MENDEL RATS IN THE TWO-YEAR GAVAGE STUDY OF TRICHLOROETHYLENE (Continued)

	CONTROL (UNTR)	CONTROL (VEH)	LOW DOSE	HIGH DOSE
BODY CAVITIES				
*Peritoneum	(50)	(50)	(50)	(50)
Inflammation, acute focal		1 (2%)		
*Pleura	(50)	(50)	(50)	(50)
Inflammation, acute			1 (2%)	
*Pericardium	(50)	(50)	(50)	(50)
Inflammation, chronic		1 (2%)		
Inflammation, chronic focal		1 (2%)		
ALL OTHER SYSTEMS				
*Multiple organs	(50)	(50)	(50)	(50)
Hemorrhage		1 (2%)		
SPECIAL MORPHOLOGY SUMMARY				
Auto/necropsy/histo perf	1			

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX I

GENETIC TOXICOLOGY OF TRICHLOROETHYLENE

TABLE I1. MUTAGENICITY OF TRICHLOROETHYLENE IN *SALMONELLA TYPHIMURIUM*

Strain	Dose (µg/plate)	Revertants/plate (a,b) −S9	+S9 (rat)	+S9 (hamster)
TA100	0	148 ± 4.6	136 ± 9.3	139 ± 5.0
	10	151 ± 2.0	131 ± 5.5	136 ± 10.8
	33	137 ± 5.2	114 ± 11.9	152 ± 6.1
	100	143 ± 6.1	115 ± 10.9	143 ± 11.3
	333	128 ± 4.2	135 ± 6.6	130 ± 0.9
	1,000	(c) 123 ± 2.9	(c) 134 ± 13.7	(c) 141 ± 5.2
TA1535	0	29 ± 2.0	11 ± 0.6	14 ± 1.3
	10	28 ± 0.6	16 ± 1.5	14 ± 1.2
	33	27 ± 1.0	11 ± 2.2	14 ± 1.0
	100	22 ± 2.9	11 ± 0.3	12 ± 1.7
	333	24 ± 0.9	17 ± 3.5	15 ± 3.2
	1,000	(c) 11 ± 4.3	(c) 8 ± 3.5	(c) 10 ± 0.9
TA98	0	19 ± 2.1	24 ± 3.8	28 ± 1.2
	10	21 ± 2.0	21 ± 1.2	28 ± 1.3
	33	16 ± 2.3	29 ± 0.3	38 ± 2.3
	100	18 ± 1.5	26 ± 4.5	28 ± 3.5
	333	19 ± 4.0	25 ± 2.6	24 ± 0.0
	1,000	(c) 17 ± 3.0	(c) 25 ± 3.8	(c) 25 ± 2.2
TA1537	0	7 ± 1.5	6 ± 1.0	4 ± 0.9
	10	7 ± 2.0	8 ± 1.2	8 ± 0.3
	33	7 ± 0.7	7 ± 2.7	9 ± 0.9
	100	6 ± 0.6	6 ± 1.5	7 ± 1.5
	333	9 ± 0.7	6 ± 1.9	7 ± 2.7
	1,000	(c) 5 ± 0.6	(c) 6 ± 1.8	(c) 6 ± 0.3

(a) The S9 fractions were prepared from the liver of Aroclor 1254-induced male Sprague-Dawley rats and male Syrian hamsters. Cells and study compound or dimethyl sulfoxide 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 were 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
(c) Slight toxicity

TABLE I2. MUTAGENICITY OF TRICHLOROETHYLENE IN L5178Y MOUSE LYMPHOMA CELLS IN THE ABSENCE OF S9 (a)

Compound	Concentration	Total Mutant Clones	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutation Frequency (mutants/10^6 clonable cells)
DMSO	1%	68	114.8	110	20
		74	94.0	98	26
		94	105.5	99	30
		68	111.7	91	20
Ethylmethane sulfonate					
	250 µg/kg	1,188	67.8	33.8	584
Trichloroethylene (nl/ml)					
	25.0	69	103.2	95.0	22
		84	98.7	85.6	28
		56	94.8	89.2	20
	50.0	49	95.0	92.5	17
		74	91.8	66.1	27
		83	110.5	73.3	25
	100.0	46	99.8	62.5	15
		53	97.3	80.9	18
		107	124.3	66.3	29
	200.0	63	90.3	55.7	23
		72	104.7	45.2	23
		58	79.8	17.4	24

(a) Experiments were performed twice, and all doses were tested in duplicate or triplicate. 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 I3. MUTAGENICITY OF TRICHLOROETHYLENE IN L5178Y MOUSE LYMPHOMA CELLS IN THE PRESENCE OF S9 (a)

Compound	Concentration	Total Mutant Clones	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutation Frequency (mutants/10^6 clonable cells)
DMSO	1%	227	107.2	102	71
		178	93.0	114	64
		233	113.0	102	69
		261	105.8	98	82
3-Methylcholanthrene					
	2.5 µg/ml	802	83.2	35.2	321
		813	90.5	44.6	299
		775	79.5	21.5	325
Trichloroethylene (nl/ml)					
	25.0	331	98.7	65.6	112
		265	96.0	73.7	92
		308	104.7	73.9	98
	50.0	342	105.8	55.8	108
		311	108.3	60.6	96
		284	108.0	59.9	88
	100.0	403	89.5	48.0	150
		382	99.8	39.2	128
		257	81.7	38.7	105
	200.0	498	95.0	17.2	175
		448	94.3	19.9	158
		441	99.8	15.9	147

(a) Experiments were performed twice, and all doses were tested in duplicate. 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. S9 was prepared from the liver of Aroclor 1254-induced male F344 rats.

TABLE I4. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY TRICHLOROETHYLENE (a)

	−S9 (b)		+S9 (c)	
	Dose (µg/ml)	SCEs/Cell (d)	Dose (µg/ml)	SCEs/Cell (d)
DMSO (10 µl)		7.6	DMSO (10 µl)	8.4
Trichloroethylene				
	499	7.7	401	10.1
	596	8.2	499	10.1
	700	9.1	596	9.5
Mitomycin C			Cyclophosphamide	
	0.005	20.4	1.5	20.0

(a) SCE = sister chromatid exchange
(b) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then 10 µM bromodeoxyuridine (BrdU) was added, and incubation was continued for 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.
(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 liver of Aroclor 1254-induced male Sprague-Dawley rats.
(d) Cells were then collected by mitotic shake-off, treated for 3 minutes with KCl (75 mM), washed twice with fixative, and dropped onto slides and air-dried. Staining was by a modified technique (after Perry and Wolff, 1974; Goto et al., 1978).

TABLE I5. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY TRICHLOROETHYLENE (a)

	−S9 (b)		+S9 (c)	
	Dose (µg/ml)	Abs/100 Cells (percent cells with abs)	Dose (µg/ml)	Abs/100 Cells (percent cells with abs)
DMSO (10 µl)		7 (7)	DMSO (10 µl)	2 (2)
Trichloroethylene				
	745	2 (2)	499	6 (5)
	801	4 (4)	700	7 (5)
			745	8 (6)
	14,900	4 (3)	14,900	2 (2)
Mitomycin C			Cyclophosphamide	
	0.500	24 (18)	50	94 (35)

(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.
(c) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, 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 and fixed as above. S9 was from the liver of Aroclor 1254-induced male Sprague-Dawley rats.

APPENDIX J

CHEMICAL CHARACTERIZATION

OF TRICHLOROETHYLENE

I. Identity and Purity Determinations of Lot No. TB05-206AA Performed by the Analytical Chemistry Laboratory

A. Physical properties

	Determined	Literature Values
1. Boiling point:	86.0° ± 0.8(δ)° C at 737 mm (visual, micro boiling point); 84.5°-87° C (Dupont 900 DTA)	86.7° C at 760 mm (Gallant, 1966)
2. Index of refraction:	n_D^{20}: 1.4766 ± 0.0002(δ)	n_D^{20}: 1.4776 (Bachman et al., 1950)
3. Density:	d_{23}^{22}: 1.46315 ± 0.00002(δ) g/ml	d^{23}: 1.458 (read from graph) (Gallant, 1966)

B. Spectral data

1. Infrared

Instrument:	Beckman IR-12	
Cell:	0.015-mm liquid cell, sodium chloride windows	
Results:	See Figure J-1	Consistent with literature spectrum (Sadtler Standard Spectra)

2. Ultraviolet/visible

Instrument:	Cary 118	
Concentration:	1 mg/ml	0.0002%
Solvent:	Methanol	Methanol
Results:	No absorbance between 800 and 350 nm. No maximum between 208 and 350 nm, but a gradual increase in absorbance toward the solvent cutoff at 208 nm.	No maximum observed in the near ultraviolet range (Lacher et al., 1950)

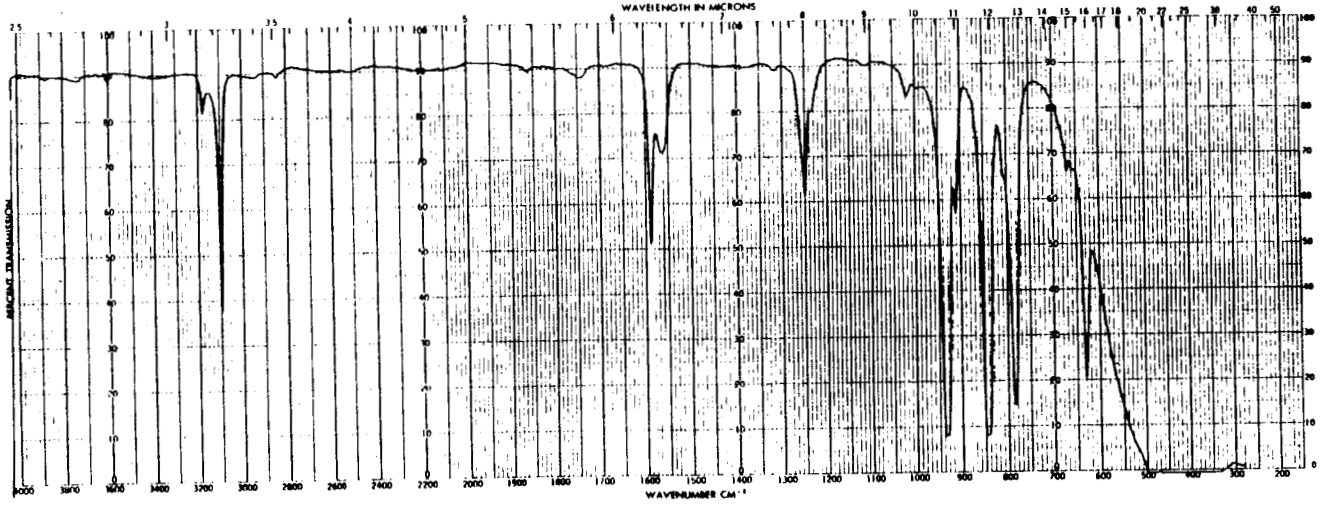

FIGURE J-1. INFRARED ABSORPTION SPECTRUM OF TRICHLOROETHYLENE (LOT NO. TB05-20(

3. Nuclear magnetic resonance	Determined	Literature Values
Instrument:	Varian HA-100	
Solvent:	Neat, with added tetramethylsilane	
Assignments:	See Figure J-2	Consistent with literature spectrum (Sadtler Standard Spectra)
Chemical shift (δ):	s, 6.34 ppm	
Integration ratios:	1.00	

C. **Water analysis (Karl Fischer):** 0.0097% ± 0.0020(δ)%

D. **Elemental analysis**

Element	C	H	Cl
Theory	18.28	0.77	80.95
Determined	18.31	0.78	80.69
	18.45	0.80	80.85

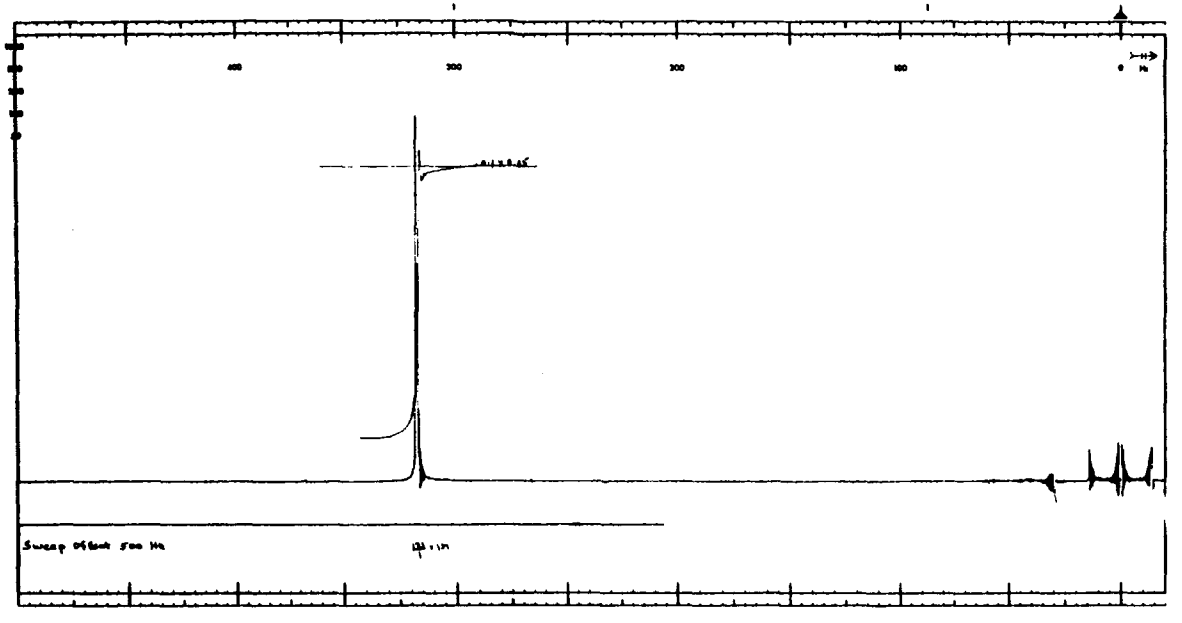

FIGURE J-2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF TRICHLOROETHYLENE (LOT NO. TB05-206AA)

E. Gas chromatography

Instrument: Tracor MT 220
Detector: Flame ionization
Inlet temperature: 200° C
Detector temperature: 255° C

System 1

Column: 10% Carbowax 20M-TPA on 80/100 Chromosorb W(AW), 1.8 m × 4 mm ID, glass
Oven temperature program: 50° C, 5 min; 50°-200° C at 10° C/min

Results: Major peak and 12 impurities. The total area of the impurities is less than 0.04% of the major peak.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	0.3	0.10	trace, < 0.001
2	1.2	0.40	trace, < 0.001
3	1.4	0.47	0.002
4	2.0	0.67	0.001
5	2.1	0.70	trace, < 0.001
6	2.4	0.80	0.001
7	3.0	1.00	100
8	7.4	2.47	0.001
9	7.9	2.63	0.02
10	9.8	3.27	trace, < 0.001
11	10.3	3.43	0.003
12	11.8	3.93	trace, < 0.001
13	12.4	4.13	0.003

System 2

Column: 20% SP2100/0.1% Carbowax 1500 on 80/100 Supelcoport, 1.8 m × 4 mm ID, glass
Oven temperature program: 50° C, 5 min; 50°-170° C at 10° C/min

Results: Major peak and eight impurities. All impurities have areas less than 0.01% of the major peak. The total area of the impurities is less than 0.02% of the major peak.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	2.6	0.50	0.0005
2	3.8	0.73	0.004
3	5.2	1.00	100
4	7.4	1.42	0.002
5	7.7	1.48	0.002
6	8.8	1.69	0.004
7	9.4	1.81	0.0005
8	10.2	1.96	0.0005
9	13.9	2.67	0.002

II. Identity and Purity of Lot No. TB08-039AA

A. Spectral data	Determined	Literature Values
1. Infrared		
Instrument:	Beckman IR-12	
Cell:	Thin film between silver chloride plates	
Results:	See Figure J-3	Spectrum consistent with literature spectrum (Sadtler Standard Spectra)
2. Ultraviolet/visible		
Instrument:	Cary 118	
Solvent:	Methanol	Methanol
Results:	No absorbance between 800 and 350 nm at a concentration of 1% (v/v). No absorbance maximum between 350 and 215 nm but a gradual increase in absorbance toward 215 nm at a concentration of 0.0004% (v/v).	No maximum observed in the near ultraviolet range. (Lacher et al., 1950)
3. Nuclear magnetic resonance		
Instrument:	Varian HA-100	
Solvent:	Neat, with added tetramethylsilane	
Assignments:	See Figure J-4	Spectrum consistent with literature spectrum (Sadtler Standard Spectra)
Chemical shift (δ):	s, 6.43 ppm	

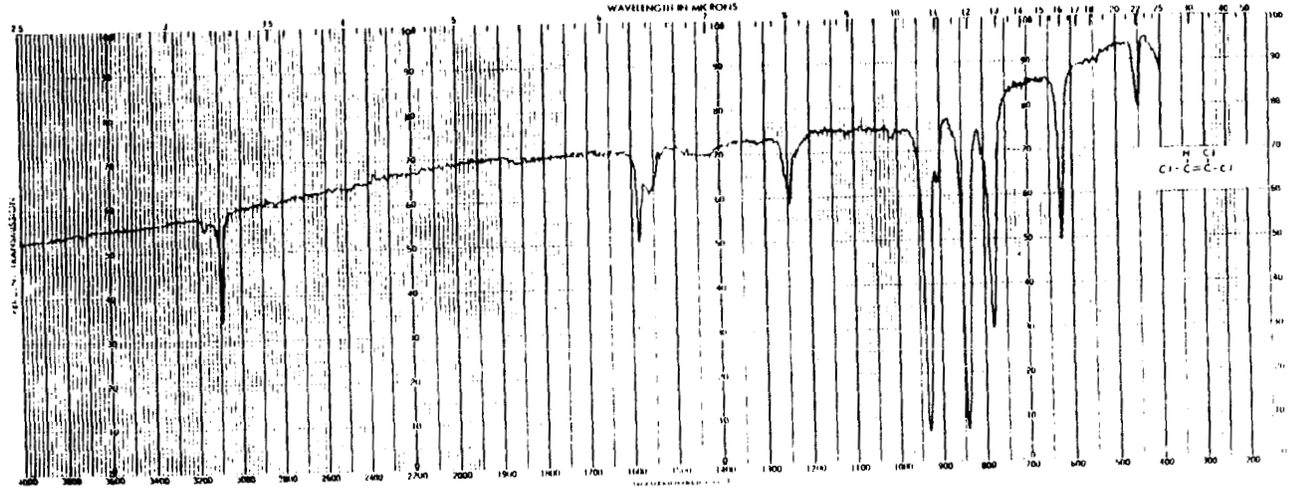

FIGURE J-3. INFRARED ABSORPTION SPECTRUM OF TRICHLOROETHYLENE (LOT NO. TB08-039AA)

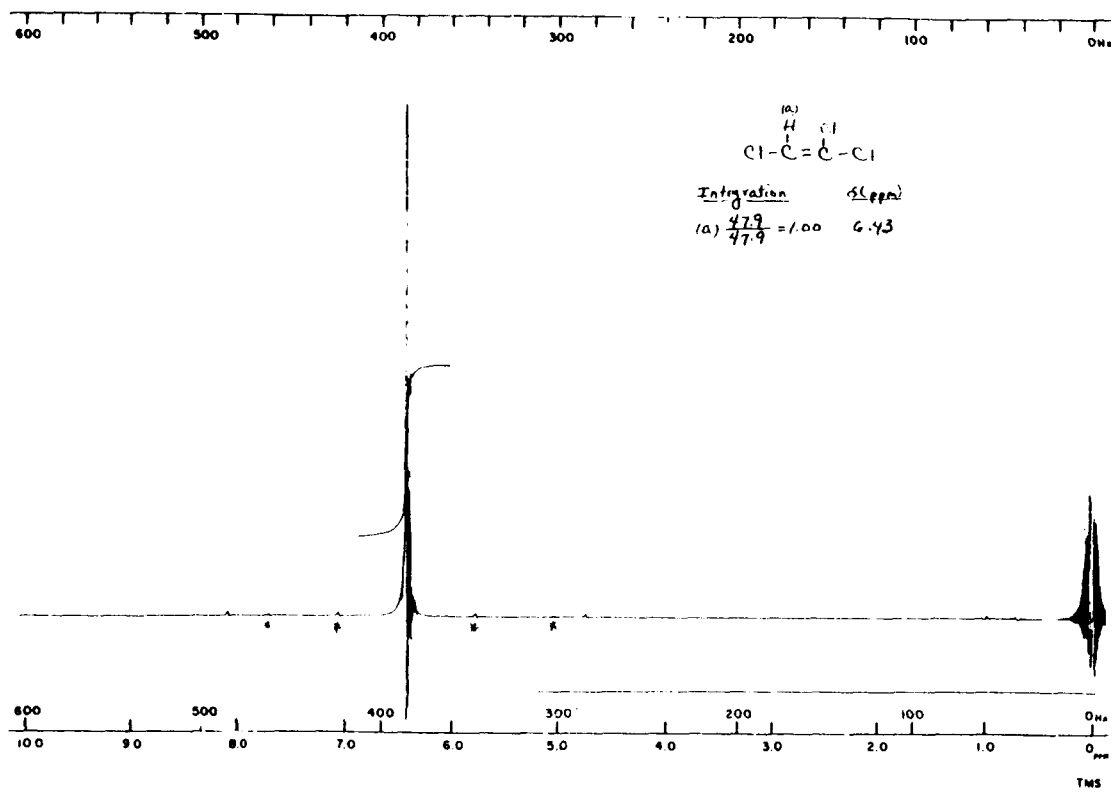

FIGURE J-4. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF TRICHLOROETHYLENE (LOT NO. TB08-039AA)

B. Elemental analysis

Element	C	H	Cl
Theory	18.28	0.77	80.95
Determined	18.29	0.80	80.78
	18.15	0.81	80.95

C. Water analysis (Karl Fischer): <0.003%

D. Gas chromatography

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

System 1

Column: 10% Carbowax 20M-TPA on 80/100 Chromosorb W (AW), 1.8 m × 4 mm ID, glass
Oven temperature program: 50° C, for 5 min; 50°-200° C at 10° C/min
Sample injected: Neat liquid (3.5 µl) and solutions of 1.0% and 0.5% (v/v) trichloroethylene in *o*-dichlorobenzene to quantitate the major peak and check for detector overload

Results: Major peak and one impurity after the major peak with an area 0.02% of the major peak.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	3.9	1.00	100
2	11.2	2.87	0.02

System 2

Detector temperature: 240° C
Column: 20% SP2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass
Oven temperature program: 50° C, for 5 min; 50°-170° C at 10° C/min
Samples injected: Neat liquid (3 µl) and solutions of 1.0% and 0.5% trichloroethylene in *o*-dichlorobenzene to quantitate the major peak and check for detector overload.

Results: Major peak and one impurity after the major peak with an area of 0.02% of the major peak.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	6.3	1.00	100
2	8.3	1.32	0.02

III. Quantitation of Impurity Present in Lot No. TB05-206AA

Analysis by gas chromatography

A. System

Instrument: Varian 3700
Detector: Flame ionization
Inlet temperature: 200° C
Detector temperature: 250° C
Carrier gas: Nitrogen, 70 ml/min
Column: 80/100 Carbopack C/0.1% SP1000; 1.8 m × 4 mm ID, glass
Oven temperature program: 50° C, isothermal

B. Results: Trichloroethylene, when injected as a neat liquid on the above system, had a retention time of 16.0 minutes and contained a peak with a retention time of 7.2 minutes with a shoulder at 7.6 minutes. The shoulder was enhanced by addition of an epichlorohydrin standard to the sample (0.001%, v/v, relative to trichloroethylene).

C. Conclusions: Calculation of the amount of epichlorohydrin present in the unspiked sample by the standard addition method showed that, if epichlorohydrin was present in this lot of trichloroethylene, it was at a level less than or equal to 0.001% (v/v).

IV. Identification of the Impurity in Lot No. TB05-206AA

Analysis by gas chromatography/mass spectrometry

A. System

Instrument: Varian 311-A Mass Spectrometer interfaced via a single-stage glass jet separator to a Varian 2700 Gas Chromatograph. Data handled by an Incos 2300 Data System
Column: 80/100 Carbopack C/0.1% SP1000; 1.8 m × 2 mm ID, glass
Column oven temperature: Ambient
Heated zone temperatures
Inlet: 170° C
Transfer line: 300° C
Helium separator: 275° C
Carrier: Helium, 30 ml/min
Scan range: 5-350 amu
Scan times (sec): up: 2.50 top: 0.00
down: 0.00 bottom: 0.50
Accelerator voltage: 3000
Electron multiplier voltage: −2000
Resolution: 801
Sample injected: 5 µl of neat trichloroethylene

B. Results: The impurity corresponding to the peak reported in III.B. (with a retention time of 7.2 minutes) eluted in 9.65 minutes on this system. The spectrum obtained from this peak and a literature spectrum of *n*-pentane are given below.

Spectrum of Impurity		Literature Spectrum of *n*-Pentane	
m/e	Relative Abundance (percent of m/e 43)	m/e	Relative Abundance (percent of m/e 43)
43	100	43	100
41	62	42	59
42	61	41	41
39	26	27	34
27	25	29	25
29	17	39	14
57	11	57	13
72	7	72	9

C. Conclusions: The impurity with the retention time of 7.2 minutes, reported in III.B., was identified on the basis of its mass spectrum as *n*-pentane.

V. Chemical Stability at the Study Laboratory

A. Storage conditions: The chemical was stored at −20° C.

B. Bulk analysis

Instrument: Varian 3700 with CDS 111 Data System
Detector: Flame ionization
Temperature
Detector: 200° C
Injector: 130° C
Oven: 70° C, isothermal
Carrier gas: Nitrogen, 60 ml/min
Column: 10% OV-101 on 100/120 Supelcoport
Sample injected: Neat liquid (1 µl)

C. Results

Date of Analysis	Lot No.	Purity (percent) Bulk	Purity (percent) Reference
04/12/79	TB05206AA	--	99.96
07/31/79		99.15	
12/17/79		99.96	99.99
04/23/80		99.96	99.96
08/19/80		99.15	100.00
11/20/80	TB08039AA	--	99.95
12/03/80		99.95	99.94
03/13/81		99.95	99.95
03/17/81		99.96	99.95
06/22/81		99.95	99.94
12/21/81		99.97	99.98

D. Conclusion: No notable degradation was observed.

APPENDIX K

IDENTIFICATION OF FOREIGN MATERIAL FOUND IN TRICHLOROETHYLENE, LOT NO. TB05-206AA

APPENDIX K. IDENTIFICATION OF FOREIGN MATERIAL

I. Analysis

A. Undissolved solids: The original sample of this lot of trichloroethylene was received in a 55-gallon drum and then transferred to 5-gallon drums. In July 1979, two drums were returned to Midwest Research Institute for analysis of flocculent material. The contents of two of these drums was filtered through ashless filter paper. The material was air dried and then weighed. Ten gallons (85 kg) of trichloroethylene was found to contain 260 mg of undissolved solid material. This represents undissolved solids at a level of 3 ppm. The empty drums were then cut open and visually inspected. None of the solids had remained in the drums. The drums were found to be uncoated on the inside and patches of light corrosion were found, probably due to the action of hydrochloric acid.

B. Dissolved solids: The amount of dissolved solids was determined by evaporating 100-ml aliquots of filtered trichloroethylene to dryness and weighing the residue. The trichloroethylene was found to contain dissolved solids at a level of 25.6 ± 1.7(δ) ppm.

C. Melting point determination: A Büchi Model 510® melting point apparatus was used to determine the melting characteristics of the foreign material. No melting was observed. At 110° C, the sample began to darken and continued to darken until complete decomposition was evident at 290° C.

D. Elemental analysis (a)

Element	Percent Found in Foreign Material
C	41.29
H	4.21
N	<0.05
Cl	0.95

(a) Analysis performed by Galbraith Laboratories, Inc., 2323 Sycamore Drive, Knoxville, Tennesee 37921

E. Spark-source mass spectrometry (a)

Uranium	<1.2	Iodine	2.9	Calcium	>1.0%
Thorium	<2.4	Tellurium		Potassium	>0.5%
Bismuth	2.5	Tin	3.1	Chlorine	≈1,800
Lead	31	Indium	Internal standard	Sulfur	≈1,600
Thallium	<3.0			Phosphorus	≈4,000
Mercury	NR	Yttrium	6.2	Silicon	>0.5%
Rhenium	Internal standard	Strontium	39	Aluminum	600
		Bromine	17	Magnesium	>1.0%
Tungsten	<1.2	Arsenic	<1.2	Sodium	>1.0%
Hafnium	<2.8	Zinc	380	Fluorine	300
Erbium	<1.8	Copper	990	Oxygen	NR
Samarium	<1.2	Nickel	1.4	Nitrogen	NR
Neodymium	<1.8	Cobalt	1.3	Carbon	NR
Cerium	2.0	Iron	≈3,100	Boron	10
Lanthanum	1.6	Manganese	360	Lithium	8.6
Barium	3.4	Chromium	38		
Cesium		Titanium	58		

(a) Analysis performed by Camp Dresser and McKee, Inc., 11455 W. 48th Avenue, Wheat Ridge, Colorado 80033. Data are expressed in parts per million (by weight) of foreign material unless otherwise noted. All elements for which values are not entered are < 1.0 ppm.
NR = not reported

F. Free acid titration: Titration of aliquots of trichloroethylene with 0.01 N sodium hydroxide indicated the presence of 6.14 ± 0.25(δ) ppm free acid (as hydrochloric acid).

G. Infrared spectroscopy

Instrument: Beckman IR-12
Cell: Thin film on silver chloride plates
Sample preparation: Toluene suspension of precipitated material

Results: The absorbances at 2,530, 1,795, 1,440, and 700 cm^{-1} are characteristic of calcium carbonate. The other absorbances at 2,930, 2,860, 967, and 912 cm^{-1} are compatible with an unsaturated hydrocarbon (Figure K-1).

H. Direct inlet mass spectrometry: The 70 eV mass spectrum (Table K1) was obtained from the foreign material. The spectrum indicates that the material was a mixture. Alkane and alkene fragmentation series were clearly evident. However, it was felt that the spectrum obtained may not be representative of the compound because of the nonvolatile and thermally unstable nature of the material (see Section I.C.). Spectra obtained from low density polyethylene, silicon rubber, and Teflon® did not correspond to the spectrum of the foreign material.

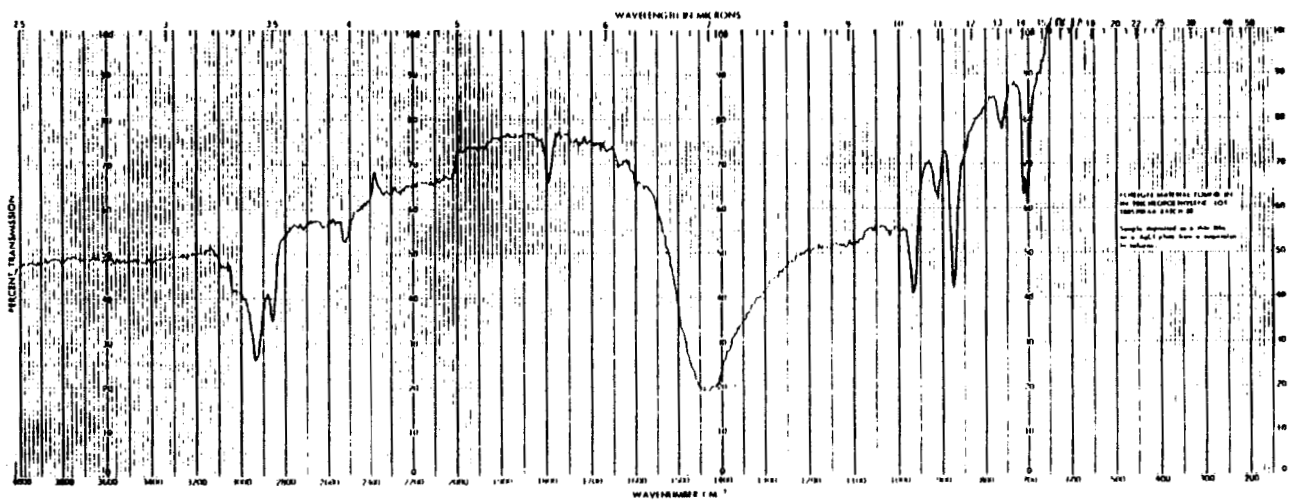

FIGURE K-1. INFRARED ABSORPTION SPECTRUM OF PRECIPITATE FOUND IN TRICHLOROETHYLENE (LOT NO. TB05-206AA)

TABLE K1. ANALYSIS BY DIRECT INLET MASS SPECTROMETRY OF FOREIGN MATERIAL FOUND IN TRICHLOROETHYLENE

m/e	Relative Abundance (percent of m/e 69)	m/e	Relative Abundance (percent of m/e 69)
69	100	137	18
55	94	121	18
98	92	99	18
83	75	59	17
57	60	54	17
97	60	87	17
81	56	125	17
129	55	108	16
73	52	151	15
95	51	80	15
43	50	93	15
41	49	42	14
67	48	79	14
44	41	124	14
71	38	39	14
60	36	239	13
85	36	94	13
84	35	107	13
311	35	138	13
96	35	152	12
135	34	171	12
70	32	53	12
111	32	126	11
109	30	101	11
56	30	29	11
112	26	143	11
313	26	72	11
236	24	61	10
123	22	89	10
339	21	91	10
110	21	113	10
116	21	149	10
237	20	157	10
185	19	165	10
		115	10

II. Summary of Analytical Data

The precipitated material was present in trichloroethylene at a level of 3 ppm. Nonvolatile and nonfilterable residue was present at a level of 25.6 ± 1.7(δ) ppm. The results of elemental analysis indicated that the precipitate contained 41.29% carbon, 4.21% hydrogen, 0.95% chlorine, and no detectable nitrogen. Spark-source mass spectrometry indicated the presence of calcium, magnesium, and sodium at levels greater than 1% and potassium at levels greater than 0.5%. The dried precipitate was a fibrous-type material that decomposed on heating. Decomposition began at 110° C and was completed at 290° C. The infrared spectroscopy (see Figure K-1) indicated that the material was a mixture of calcium carbonate and probably an unsaturated hydrocarbon. Mass spectroscopy also indicated that the material was a mixture probably containing alkane and alkene materials.

APPENDIX L

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

APPENDIX L. PREPARATION AND CHARACTERIZATION

I. Stability of Trichloroethylene in Corn Oil at Room Temperature

A. Sample preparation: A 1% (w/v) solution of trichloroethylene in corn oil was prepared for each day of the study as follows: 10 ml of corn oil was transferred into a 50-ml Hypo-vial, the vial was sealed, and then approximately 95 mg of trichloroethylene (measured exactly for each sample) was added via a 100-µl syringe. The samples were shaken and stored at room temperature from 1 to 7 days.

B. Extraction and analysis: Each sample was extracted with 20 ml of methanol, which was injected into the sample vial via a 10-ml syringe. Samples for analysis were withdrawn directly from the top methanol layer in the vial and analyzed by gas chromatography with the following system.

Instrument: Tracor MT 220
Column: Chromosorb 102, 60/80 mesh, 1.8 m × 2 mm ID, glass
Detection: Flame ionization
Oven temperature: 160° C, isothermal
Detector temperature: 260° C
Inlet temperature: 200° C
Retention time of compound: 4.15 min

C. Results

End of Day	Average Percent Trichloroethylene in Chemical/Vehicle Mixture (a)
1	1.00 ± 0.05
2	0.96 ± 0.05
3	0.99 ± 0.05
4	0.98 ± 0.05
5	1.00 ± 0.05
6	0.98 ± 0.05
7	0.99 ± 0.05

(a) Corrected for an average spiked recovery yield of 61.7% ± 0.9%.
Target concentration of chemical/vehicle mixture, 1.00%.

D. Conclusion: Trichloroethylene mixed with corn oil is stable for 7 days at room temperature.

II. Stability of Trichloroethylene in Corn Oil at 4° C

A. Sample preparation and analysis: Sample preparation and analysis procedures were the same as for the room temperature study.

B. Results

Number of Weeks After Mixing	Target Concentration (a) 59.5	235.5
1	60.4	240
2	59.2	236.9
3	56.9	236.9
4	58.4	236.9
5	56.9	235.3
6	57.3	235.3
7	55.4	227.6
8	55.8	239.6

(a) Milligrams trichloroethylene/milliliter sample

C. Conclusions: Trichloroethylene mixed with corn oil is stable for 4 weeks at 4° C.

APPENDIX M

METHODS OF ANALYSIS OF DOSE MIXTURES

I. Study Laboratory

A. System

Instrument: Varian 3700 with CDS III Integrator
Detector: Flame ionization
Detector temperature: 200° C
Injector temperature: 130° C
Oven temperature: 70° C (isothermal)
Carrier: Nitrogen, 30 ml/min
Column: 10% OV-101 on 100/120 Supelcoport; 10 foot × 1/8 inch stainless steel until 4/28/80, then 15 foot × 1/4 inch glass column

B. Procedure: Initially, the concentration of trichloroethylene in dose mixtures was calculated from the percent recovery after the trichloroethylene/corn oil mixture was extracted into methanol. The recovery for this method was usually about 65% and was replaced on March 16, 1979, with a more reliable procedure, the internal-standard method.

A 2-ml aliquot of a trichloroethylene/corn oil mixture was diluted to 25 ml with an internal-standard solution containing 1.5 mg octane/ml chloroform. A 3-µl aliquot of this mixture was injected into the gas chromatograph. If the sample was too concentrated (i.e., if the peak went offscale), the solution was rediluted as stated above with 2- to 25-ml portions of internal-standard solution.

II. Analysis Performed at Midwest Research Institute

A. Extraction and analysis: The samples were allowed to equilibrate to room temperature; aliquots (approximately 5 g) of the chemical/vehicle mixture were transferred into 50-ml septum vials and accurately weighed. Methanol (5 ml) was added to each aliquot. Blanks and standards were prepared by weighing corn oil (5 g) into septum vials and spiking each sample with methanol or trichloroethylene in methanol (5 ml). Two standard solutions of trichloroethylene were prepared, and the standards were diluted further with methanol and added to the corn oil samples to give standards bracketing the concentration range of the sample. The samples were extracted immediately after spiking as follows.

Methanol (10-20 ml) containing *n*-butyl alcohol (6 or 11.34 mg/ml) or *n*-hexyl alcohol (1.8 or 2.5 mg/ml) as an internal standard was added to each sample. The septum vials were sealed and the compound extracted into the methanol by mechanical mixing on a vortex mixer for 30 seconds followed by 30 seconds in an ultrasonic vibratory bath. The vials were centrifuged for 3 minutes to separate the corn oil/methanol layers and sampled directly from the top methanol layer for analysis by gas chromatography.

Instrumental parameters

Instrument: Tracor MT-220 with Hewlett-Packard 3380A integrator or Varian 3700 with autosampler and Varian CDS III-C integrator
Column: GP 20% SP2100/0.1% Carbowax 1500, on 100/120 mesh Supelcoport, 1.8 m × 4 mm ID, glass, silanized
Detection: Flame ionization

	Tracor MT-220	Varian 3700
Temperatures		
Inlet:	230° C	200° C
Oven:	65° C, isothermal	80° C, isothermal
Detector:	230° C	250° C
Carrier gas:	Nitrogen, 70 ml/min	Nitrogen, 30 ml/min
Volume of solution injected:	5 µl	3 µl
Retention time of trichloroethylene:	3.7-4.1 min	2.3-5.5 min
Retention time of internal standard:	2.8-3.1 min	4.2 min (*n*-butyl alcohol) 6.5-10.6 min (hexyl alcohol)

B. Quality control procedures: Analyses were performed in triplicate for the study chemical/vehicle sample and in duplicate for the blank corn oil sample. Spiked samples were prepared from two separately weighed standard solutions. The chemical/vehicle samples, the blank corn oil samples, and the spiked samples were all extracted and prepared for analysis in the same manner. Blank samples showed no interference from the corn oil at the retention time of the major component. A calibration curve was established with the spiked sample extracts.

III. Analysis Performed by Raltech Scientific Services, Inc.

A. Standard preparation: Trichloroethylene (6.25 g) was weighed into a 25-ml volumetric flask and diluted to volume with methanol. This stock solution was 250 mg/ml. Dilutions of the stock standard were made to obtain working standards of 5, 25, 50, and 125 mg/ml. Dilutions were made in methanol. *n*-Butanol (5 g) was weighed into a 500-ml volumetric flask and diluted to volume with methanol to obtain a 10 mg/ml internal standard solution.

B. Sample preparation and analysis: Sample aliquots (5 g) were transferred into 50-ml septum vials along with 5 ml of methanol and 20 ml of the methanol internal standard. The septum vials were sealed with Teflon®-faced septa, mixed on a Vortex mixer for 1 minute, and placed in an ultrasonic bath for 30 seconds. The vials were centrifuged for 5 minutes, and the upper methanol layer was sampled directly by syringe for gas chromatographic analysis.

C. Instrumental operating parameters

Instrument: Hewlett-Packard 5730 A Gas Chromatograph
Detector: Flame ionization
Column: 1.8 m × 4 mm ID glass on-column injection
Column packing: 20% SP2100/0.1% Carbowax 1500 by weight on 100/120 Supelcoport
Carrier gas: Nitrogen, 50 ml/min
Temperatures
Column: 70° C
Detector: 250° C
Injector: 200° C
Injection volume: 5 µl

Data were generated and analyzed on a Hewlett-Packard 3350 laboratory automation system.

D. Quality assurance: The sample was analyzed in triplicate. Duplicate blanks were prepared by adding 5 ml of methanol and 20 ml of methanol internal standard to 5 g of blank corn oil and extracting. Aliquots (5 ml) of the working trichloroethylene standards, ranging from 5 to 50 mg/ml, were added to 5 g of blank corn oil along with 20 ml of methanol internal standard. These extracted standards were equivalent to 5-250 mg/g of trichloroethylene in corn oil.

APPENDIX N

RESULTS OF ANALYSIS OF DOSE MIXTURES

TABLE N1. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF TRICHLOROETHYLENE

Date Mixed	Concentration (mg/ml) Target (T)	Determined (D) (a)	Percent D/T	Date Mixed	Concentration (mg/ml) Target (T)	Determined (D) (a)	Percent D/T
11/16/78	333.5	322.1	96.6	09/26/79	619.8	597.4	96.4
12/08/78	164.3	164.4	100.1	10/12/79	615.9	581.7	94.4
12/14/78	72.5	66.6	91.9	10/15/79	325.3	319.1	98.1
	170.0	175.4	103.2	10/17/79	164.8	157.1	95.3
	334.5	273.2	81.7		730.0	664.0	91.0
12/21/78	189.5	145.9	77.0	10/19/79	365.4	351.0	96.1
12/28/78	200.0	210.6	105.3	11/21/79	499.5	479.6	96.0
01/04/79	218.4	214.7	98.3	12/10/79	546.0	506.8	92.8
01/11/79	78.5	77.2	98.3	12/14/79	553.3	512.6	92.6
	356.6	354.8	99.5	12/17/79	628.8	582.6	92.7
	225.4	214.7	95.3	12/20/79	566.1	522.8	92.4
01/18/79	232.0	238.2	102.7	01/02/80	600.8	602.4	100.3
01/25/79	240.2	214.7	89.4	01/09/80	663.6	625.7	94.3
01/31/79	243.0	236.6	97.4		577.2	566.7	98.2
	161.8	150.8	93.2	01/16/80	628.4	592.6	94.3
02/07/79	357.5	364.1	101.8	01/24/80	696.2	666.7	95.8
	74.9	69.0	92.1	02/06/80	70.6	79.4	112.5
	242.2	251.2	103.7		70.6	70.3	(b) 99.6
	182.8	175.4	96.0		74.4	84.8	114.0
02/14/79	246.9	255.1	103.3		74.4	76.8	(b) 103.2
	198.5	191.8	96.6	02/07/80	339.4	364.8	107.5
02/21/79	510.0	537.1	105.3		182.5	184.6	101.2
	423.0	434.5	102.7		218.7	240.1	109.8
02/28/79	512.3	519.2	101.3		218.7	203.1	(b) 92.9
	441.2	441.6	100.1		122.3	140.3	114.7
	699.8	727.7	104.0		122.3	119.5	(b) 97.7
	514.9	525.1	102.0	02/14/80	306.9	335.3	109.3
03/07/79	462.9	460.9	99.6		160.5	172.9	107.7
	156.0	168.4	107.9		204.5	225.4	110.2
03/14/79	477.0	513.7	107.7		204.5	187.4	(b) 91.6
03/21/79	497.6	499.2	100.3		101.6	113.7	111.9
03/28/79	492.9	517.8	105.1		101.6	98.5	(b) 96.9
04/04/79	728.4	765.1	105.0	02/22/80	308.3	337.7	109.5
	156.9	165.8	105.7		183.7	206.4	112.4
	68.0	69.8	102.6		183.7	173.2	(b) 94.3
	544.2	570.6	104.9		159.9	178.6	111.7
	519.8	545.9	105.0		159.9	149.8	(b) 93.7
04/11/79	519.0	511.7	98.6		91.7	105.3	114.8
04/18/79	512.9	542.7	105.8		91.7	94.5	(b) 103.1
04/25/79	524.5	543.0	103.5	02/27/80	116.1	135.5	116.7
05/01/79	729.8	736.9	101.0		116.1	119.4	(b) 102.8
	161.9	175.8	108.6		592.6	619.2	104.5
	561.6	601.4	107.1		153.2	175.7	114.7
	524.5	562.0	107.1		153.2	145.8	(b) 95.2
05/30/79	751.6	756.1	100.6	02/28/80	130.6	138.5	106.0
	573.0	602.1	105.1		130.5	118.7	(b) 91.0
	535.2	547.1	102.2		198.3	205.8	103.8
	156.5	164.5	105.1	03/05/80	330.4	358.9	108.6
06/27/79	161.2	166.6	103.3		75.8	88.0	116.1
	730.2	731.0	100.1		75.8	74.3	(b) 98.0
	561.2	584.5	104.2		69.4	78.6	113.3
	548.2	567.8	103.6		69.4	69.5	(b) 100.1
07/19/79	591.0	567.0	95.9		218.7	258.2	118.1
07/25/79	755.0	778.1	103.1		218.7	204.7	(b) 93.6
	164.4	164.6	100.1	03/12/80	214.3	222.7	103.9
07/31/79	597.4	573.6	96.0	03/19/80	319.5	344.6	107.9
08/15/79	606.5	578.6	95.4		319.5	342.2	107.1
08/21/79	85.4	84.7	99.2		158.8	175.1	110.3
	716.2	680.5	95.0		158.8	148.4	(b) 93.5
08/27/79	612.5	557.5	91.0	03/26/80	224.0	248.1	110.8
09/13/79	615.8	572.1	92.9		224.0	211.1	(b) 94.2
09/19/79	732.8	662.0	90.3		282.1	314.2	111.4
	164.8	161.5	98.0		282.1	261.4	(b) 107.9

TABLE N1. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF TRICHLOROETHYLENE (Continued)

Date Mixed	Concentration (mg/ml) Target (T)	Determined (D) (a)	Percent D/T	Date Mixed	Concentration (mg/ml) Target (T)	Determined (D) (a)	Percent D/T
03/27/80	391.6	421.0	107.5	10/08/80	149.3	176.9	118.5
	275.5	305.4	110.9		149.3	154.5	(b) 103.5
	275.5	254.4	(b) 92.3		118.6	138.7	116.9
04/02/80	174.2	168.4	96.7		118.6	126.5	(b) 106.7
	69.7	72.2	103.6	10/17/80	240.8	266.0	110.5
	66.0	68.9	104.4		240.8	238.1	(b) 98.9
04/08/80	121.9	137.0	112.4		147.7	162.9	110.3
04/09/80	162.6	170.9	105.1		147.7	146.7	(b) 99.3
	106.4	111.0	104.3	10/23/80	159.3	165.2	103.7
04/16/80	198.4	199.7	100.7		109.6	110.0	100.4
	96.8	101.1	104.4	10/29/80	191.0	193.5	101.3
04/22/80	215.7	220.1	102.0		103.5	107.0	103.4
	141.8	146.0	103.0	11/05/80	304.0	303.5	99.8
	148.1	140.8	95.1		226.6	227.4	100.4
04/23/80	118.9	120.3	101.2	11/13/80	240.4	235.5	98.0
04/30/80	225.4	230.3	102.2		149.1	156.0	104.6
	65.1	68.0	104.5	11/18/80	313.9	316.3	100.8
	73.8	79.6	107.9		226.7	232.1	102.4
	327.3	330.2	100.9	11/25/80	370.6	363.6	98.1
05/07/80	313.4	324.0	103.4		209.4	215.8	103.1
	213.7	221.8	103.8	12/10/80	247.2	250.9	101.5
	416.4	429.5	103.1		148.4	155.0	104.4
	278.7	279.9	100.4	12/17/80	157.0	164.3	104.6
05/13/80	216.5	220.7	101.9		110.6	115.6	104.5
	329.1	323.2	98.2	12/23/80	189.9	218.4	115.0
05/22/80	292.2	286.1	97.9		189.9	215.3	(b) 113.4
	228.4	233.8	102.4		104.1	113.8	109.3
06/04/80	106.2	113.1	106.5	01/07/81	465.9	454.5	97.6
	163.8	164.8	100.6		297.5	297.6	100.0
06/11/80	99.1	96.4	97.3	01/20/81	363.2	354.8	97.7
	179.5	173.9	96.9		207.0	200.9	97.1
06/18/80	149.7	153.6	102.6	02/17/81	194.3	205.3	105.7
	121.7	128.0	105.2		107.8	119.9	111.2
06/25/80	228.0	238.4	104.6		107.8	120.7	(b) 112.0
	145.1	151.4	104.3		107.8	114.8	(b) 106.5
07/02/80	315.8	323.0	102.3		370.7	370.7	100.0
	210.7	220.0	104.4		218.7	232.7	106.4
07/09/80	350.9	355.7	101.4	02/18/81	253.6	266.5	105.1
	203.3	213.4	105.0		150.6	161.1	107.0
07/16/80	298.0	279.5	93.8	02/24/81	108.0	122.7	113.6
	223.8	211.6	94.5		108.0	113.6	(b) 105.2
07/23/80	435.4	403.1	92.6	02/25/81	108.0	116.8	108.1
	295.8	275.4	93.1	03/17/81	373.6	360.5	96.5
07/30/80	185.8	198.8	107.0		217.8	214.3	98.4
	102.5	105.6	103.0		461.3	449.1	97.4
08/13/80	149.8	168.2	112.3		299.5	295.9	98.8
	149.8	162.1	(b) 108.2	04/28/81	192.4	189.2	98.3
	120.5	137.8	114.4		192.4	177.9	(b,c) 92.5
	120.3	132.3	(b) 110.0		111.1	117.0	105.4
08/20/80	236.2	245.9	104.1		111.1	110.0	(b,c) 99.0
	149.8	159.3	106.3		254.8	246.7	96.8
08/27/80	171.9	163.2	94.9		254.8	244.8	(b,c) 96.1
	356.5	371.5	104.2		155.1	160.6	103.5
09/03/80	206.4	216.9	105.1		155.1	154.6	(b,c) 99.7
09/10/80	301.9	293.0	97.1	05/26/81	458.3	475.6	103.8
	235.8	253.2	107.4		297.9	312.2	104.8
09/17/80	444.7	453.3	101.9		364.9	383.1	105.0
	286.0	300.5	105.1		217.5	224.4	103.2
09/24/80	319.0	335.6	105.2	06/23/81	182.3	172.3	94.5
	220.9	232.0	105.0		113.6	99.4	(d) 87.5
10/01/80	187.7	227.3	121.1		113.6	103.3	(b,d) 90.9
	187.7	193.6	(b) 103.1		252.1	229.9	91.2
	102.9	122.1	118.7		154.1	147.8	95.9
	102.9	102.7	(b) 99.8		361.7	339.2	93.8

TABLE N1. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF TRICHLOROETHYLENE (Continued)

Date Mixed	Concentration (mg/ml) Target (T)	Determined (D) (a)	Percent D/T	Date Mixed	Concentration (mg/ml) Target (T)	Determined (D) (a)	Percent D/T
06/23/81	219.4	217.0	98.9		251.3	254.1	101.1
	154.1	142.8	92.7		251.3	246.2	(b,c) 98.0
07/01/81	110.0	111.7	101.5		151.3	148.9	98.4
07/21/81	361.9	345.9	95.6		151.3	144.6	(b,c) 95.6
	218.8	203.8	93.1	09/15/81	336.4	318.2	94.6
	458.0	446.2	97.4		219.2	205.0	93.5
	312.4	295.8	94.7		440.4	415.6	94.4
08/18/81	181.4	172.9	95.3		297.1	284.9	95.9
	181.4	173.2	(b,c) 95.5	10/13/81	245.2	237.6	96.9
	112.6	113.6	100.9		150.6	148.5	98.6
	112.6	112.9	(b,c) 100.3				

Mean (percent of target)	102.2
Standard deviation	6.61
Coefficient of variation (percent)	6.5
Range (percent of target)	77.0-121.1
Number of samples	234

(a) Results of duplicate analysis
(b) Repeat analysis; not included in mean
(c) Different sample preparation method used
(d) Not used in the studies

TABLE N2. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF TRICHLOROETHYLENE

Date Mixed	Target Concentration (mg/ml)	Determined Concentration Study Laboratory (a)	Determined Concentration Referee Laboratory (b)
03/19/80	158.8	175.1	160.4
03/17/81	217.8	214.3	221.1
06/23/81	154.1	147.8	150.0
09/15/81	336.4	318.2	329.0

(a) Results of duplicate analysis
(b) Results of triplicate analysis

APPENDIX O

SENTINEL ANIMAL PROGRAM

APPENDIX O. 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 study 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 rats of each strain and 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 control animals 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
PVM (pneumonia virus of mice)	RCV (rat coronavirus)
Sendai (August, 18 mo; Marshall, 24 mo)	Sendai
KRV (Kilham rat virus)	M. Ad. (mouse adenovirus) (Marshall, 24 mo)
H-1 (Toolan's H-1 virus)	MHV (mouse hepatitis virus) (Marshall, 24 mo)
Reo 3 (reovirus type 3) (Marshall, 24 mo)	
Poly (polyoma virus) (Marshall, 24 mo)	
Ectro (infectious ectromelia) (Marshall, 24 mo)	

II. Results

Results are presented in Table O1.

TABLE O1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS IN THE TWO-YEAR GAVAGE STUDIES OF TRICHLOROETHYLENE (a)

Interval (months)	No. of Animals	Positive Serologic Reaction for
ACI		
18	10/10	PVM
	1/10	KRV
	10/10	Sendai
	8/10	RCV
August		
6	7/10	PVM
	9/10	RCV
18	7/10	PVM
Marshall		
18	9/9	PVM
	9/9	Sendai
	9/9	RCV
24	9/9	PVM
	8/9	Sendai
	3/9	RCV
Osborne-Mendel		
12	--	None positive

(a) Blood samples were taken from sentinel animals at 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 (Bethesda, MD) for determination of antibody titers.

APPENDIX P

SURVIVAL AND MEAN BODY WEIGHTS OF ACI, AUGUST, AND MARSHALL RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF TRICHLOROETHYLENE

TABLE P1. SURVIVAL AND MEAN BODY WEIGHTS OF ACI RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF TRICHLOROETHYLENE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial	Final	Change	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	46	258	+212	--
125	10/10	67	257	+190	99.6
250	10/10	57	243	+186	94.2
500	10/10	55	252	+197	97.7
1,000	10/10	52	234	+182	90.7
2,000	10/10	52	213	+161	82.6
FEMALE					
0	10/10	45	174	+129	--
62.5	10/10	63	173	+110	99.4
125	10/10	51	165	+114	94.8
250	10/10	51	172	+121	98.9
500	10/10	45	160	+115	92.0
1,000	10/10	37	162	+125	93.1

(a) Number surviving/number in group

TABLE P2. SURVIVAL AND MEAN BODY WEIGHTS OF AUGUST RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF TRICHLOROETHYLENE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial	Final	Change	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	79	338	+259	--
125	10/10	88	342	+254	101.2
250	10/10	94	327	+233	96.7
500	10/10	91	324	+233	95.9
1,000	10/10	94	324	+230	95.9
2,000	7/10	81	286	+205	84.6
FEMALE					
0	10/10	78	207	+129	--
62.5	10/10	80	210	+130	101.4
125	10/10	82	208	+126	100.5
250	10/10	78	208	+130	100.5
500	10/10	76	204	+128	98.6
1,000	10/10	73	192	+119	92.8

(a) Number surviving/number in group

TABLE P3. SURVIVAL AND MEAN BODY WEIGHTS OF MARSHALL RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF TRICHLOROETHYLENE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial	Final	Change	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	112	247	+135	--
268	10/10	140	255	+115	103.2
308	10/10	134	259	+125	104.9
495	10/10	118	249	+131	100.8
932	10/10	111	232	+121	93.9
1,834	10/10	128	217	+89	87.9
FEMALE					
0	10/10	95	171	+76	--
134	10/10	114	173	+59	101.2
153	10/10	109	176	+67	102.9
248	10/10	108	175	+67	102.3
466	10/10	96	166	+70	97.1
918	10/10	94	164	+70	95.9

(a) Number surviving/number in group

APPENDIX Q

AUDIT SUMMARY

APPENDIX Q. AUDIT SUMMARY

The experimental data, documents, and pathology materials for the NTP Technical Report on the 2-year toxicology and carcinogenesis studies of trichloroethylene administered by gavage in corn oil to ACI, August, Marshall, and Osborne-Mendel rats were examined for completeness, consistency, and accuracy. These studies, initiated by the National Cancer Institute under a prime contract to Tracor Jitco, Inc., were conducted at the Papanicolaou Cancer Research Institute, Miami, Florida, between December 1978 and November 1981. The experiments were started before the NTP required compliance with Good Laboratory Practice (GLP) regulations of the Food and Drug Administration (implemented by the NTP October 1, 1981). The following three contractors conducted the audits:

(1) Immuquest Laboratories, Inc., Rockville, Maryland: Toxicology and pathology data for studies in *ACI and August rats* (October through November 1983) and chemistry data for all studies (November 1983). Personnel conducting the audits were Pamela Errico, M.A.; Caroline Reese; Karen Witkin, Ph.D.; and Ronald Schueler, D.V.M.

(2) Argus Research Laboratories, Inc., Horsham, Pennsylvania: Toxicology and pathology data for studies in *Marshall rats* (March 1984). Personnel conducting the audit were Jane Goeke, Ph.D., and F. Garner, D.V.M.

(3) Clement Associates, Inc., Washington, DC: Pathology data for studies conducted in *Osborne-Mendel rats* (March 1984). The audit was conducted by Miriam Anver, D.V.M., Ph.D. The toxicology portion of the studies in Osborne-Mendel rats was not audited.

The audit reports are on file at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. The audits included a review of:

(1) Inlife toxicology data for 5%-10% of the study animals.
(2) All records concerning dosing, clinical signs, and mortality of study animals.
(3) All Individual Animal Data Records to examine for correspondence between necropsy observations and histologic findings.
(4) Wet tissues from a random 10% sample of the study animals to verify animal identification and to examine for untrimmed masses.
(5) All slides and blocks of tissue from both sexes of all strains in the high dose and vehicle control groups to examine for proper match and inventory.
(6) All available analytical chemistry and dose mixture data.

The audit of the inlife phase of these studies, which were conducted before implementation of GLP requirements, identified a number of omissions in study documentation. These included: (1) absence of complete study protocol, (2) absence of animal breeding and husbandry records, and (3) absence of environmental condition records. The clinical observation records showed inconsistent recording of palpable masses and other clinical signs, missing or incorrectly recorded body weights, and occasional discrepancies between mortality and clinical records which, taken collectively, leave open the possibility that some animals may have been misidentified during the studies. The records also documented clinical observation of toxicity associated with administration of doses. In addition, there were incidents recorded where malfunctions in automated watering systems resulted in flooding of animal cages.

The contract governing the conduct of these studies did not require the retention of animal carcasses containing individual animal identifying markers; however, examination of the residual, formalin-fixed tissues (wet tissues) revealed that ears but not feet for most animals had been preserved. Ears contained the first two digits of the three- and four-digit identification numbers used. Review of the wet tissues for 240 rats showed that 237 of them had an ear punch that matched the bag label. The slide/block audit showed good match up, but sections taken from a number of blocks appeared to

be incomplete (i.e., the blocks did not always have corresponding full-face sections). Instances of gross observations without corresponding microscopic diagnoses and untrimmed potential lesions in wet tissues which were detected by the audit were reviewed by NTP staff and were either resolved satisfactorily or believed to have no impact on interpretation of the study results.

Original records documenting the chemical analyses performed by the study laboratory were not available to fully validate the chemistry portion of the studies. Those records that were available indicated that samples taken from seven chemical/vehicle preparations were shipped to Midwest Research Institute (MRI) for analysis. The analyses performed by MRI were well documented and showed good agreement with those reported by the study laboratory. The bulk chemical purity was documented by the MRI records. Audit of the study laboratory's chemical use log indicated that dose preparation calculations were valid and that sufficient chemical was available for the conduct of the studies. Comparison of the chemical use log with the dose preparation log showed that the amount of chemical used matched the amount checked out.

These studies were not required to be conducted under GLP standards. Nevertheless, retrospective audit of the available documents and materials shows that recordkeeping was less than adequate to fully document all of the procedures followed and the original data generated. The Tracor Jitco Statement of Work, applicable under the terms of the contract governing this study, is presumed to have been followed in lieu of a formal study protocol and system for documenting procedures actually followed. The most significant audit findings from review of the existing study records and data involved inconsistent recording of inlife records of clinical observations and palpable masses and the absence of complete carcass identification information in wet tissues. Thus, the possibility that some animals may have been mixed up during the conduct of the studies cannot be excluded. Because of the characteristic kidney lesions produced by trichloroethylene, it is unlikely that dosed and vehicle control animals were confused. It is recognized, however, that total confidence cannot be placed in the differentiation of all high dose from low dose animals. Incidents of misdosing (animals dosed twice in 1 day or given incorrect doses) were reported. Tissue accountability for the kidney was generally adequate. Despite incomplete chemistry records, the original data that are available indicate that animals were dosed with trichloroethylene and that dose mixtures were prepared properly.

The NIEHS/NTP concludes that the incomplete documentation for these studies reveals certain gaps and inconsistencies that have been considered in the interpretations given in the Technical Report.

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NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS PUBLISHED AS OF JANUARY 1988

TR No.	CHEMICAL
201	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Dermal)
206	Dibromochloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane (Inhalation)
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butylbenzyl Phthalate
214	Caprolactam
215	Bisphenol A
216	11-Aminoundecanoic Acid
217	Di(2-ethylhexyl)phthalate
219	2,6-Dichloro-*p*-phenylenediamine
220	C.I. Acid Red 14
221	Locust Bean Gum
222	C.I. Disperse Yellow 3
223	Eugenol
224	Tara Gum
225	D & C Red No. 9
226	C.I. Solvent Yellow 14
227	Gum Arabic
228	Vinylidene Chloride
229	Guar Gum
230	Agar
231	Stannous Chloride
232	Pentachloroethane
233	2-Biphenylamine Hydrochloride
234	Allyl Isothiocyanate
235	Zearalenone
236	D-Mannitol
237	1,1,1,2-Tetrachloroethane
238	Ziram
239	Bis(2-chloro-1-methylethyl)ether
240	Propyl Gallate
242	Diallyl Phthalate (Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
247	L-Ascorbic Acid
248	4,4'-Methylenedianiline Dihydrochloride
249	Amosite Asbestos
250	Benzyl Acetate
251	Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
267	Propylene Oxide
269	Telone II®
271	HC Blue No. 1
272	Propylene
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
281	H.C. Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No. 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethy)phosphonium Sulfate and Tetrakis(hydroxymethy)phosphonium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	*o*-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane
307	Ephedrine Sulfate
308	Chlorinated Paraffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	*n*-Butyl Chloride
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
323	Dimethyl Methylphosphonate
324	Boric Acid
325	Pentachloronitrobenzene
326	Ethylene Oxide
327	Xylenes (Mixed)
328	Methyl Carbamate

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