NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 391

TOXICOLOGY AND CARCINOGENESIS STUDIES OF TRIS(2-CHLOROETHYL) PHOSPHATE

(CAS NO. 115-96-8)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): 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. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were 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 Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

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.

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NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

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NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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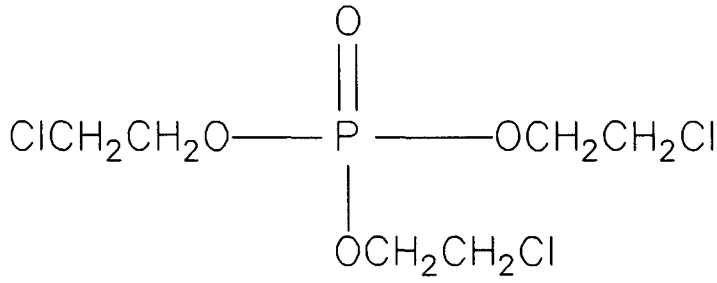
ABSTRACT



TRIS(2-CHLOROETHYL) PHOSPHATE

CAS No. 115-96-8
$C_6H_{12}Cl_3PO_4$
Molecular Weight: 285.5

Synonyms: 2-Chloroethanol phosphate (3:1), Tris(β-chloroethyl) phosphate
Trade Names: Fyrol CEF, Disflamoll TCA, NIAX flame retardant

Tris(2-chloroethyl) phosphate (TRCP), a flame-retardant plasticizer used in plastics, polymeric foams, and synthetic fibers, was studied as part of the National Toxicology Program's class study of trisalkyl phosphate flame retardants. Toxicology and carcinogenesis studies were conducted by administering TRCP (approximately 98% pure) in corn oil by gavage to groups of F344/N rats and B6C3F$_1$ mice of each sex for 16 days, 16 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium* and Chinese hamster ovary (CHO) cells.

16-Day Studies: There were no chemical-related deaths, differences in final mean body weight, or histopathological lesions in rats receiving 22 to 350 mg/kg TRCP or in mice receiving 44 to 700 mg/kg TRCP for 12 doses over 16 days. Serum cholinesterase activity in female rats receiving 175 or 350 mg/kg TRCP was reduced slightly (80% of control levels), but enzyme activity in dosed male rats and in mice was similar to that in controls.

16-Week Studies: Rats received 22 to 350 mg/kg TRCP for 16 weeks (female) or 18 weeks (male). Several male and female rats in the 175 or 350 mg/kg dose groups died from chemical toxicity. Final mean body weights of female rats receiving 350 mg/kg were 20% greater than those of controls; final mean body weights of the remaining groups of dosed female rats and dosed male rats were similar. Chemical-related neuronal necrosis occurred in the hippocampus and thalamus of female rats and, to a lesser extent, of male rats. Serum cholinesterase activity was reduced in females receiving 175 or 350 mg/kg TRCP.

There were no chemical-related deaths, differences in final mean body weight, or differences in cholinesterase activity in mice receiving 44 to 700 mg/kg TRCP for 16 weeks. Tubule epithelial cells with enlarged nuclei (cytomegaly and karyomegaly) were observed in the kidneys of high-dose (700 mg/kg) male and female mice.

2-Year Studies: The 2-year studies in rats were conducted by administering 0, 44, or 88 mg/kg TRCP to groups of 60 males and females, 5 days per week for up to 104 weeks; 9 or 10 rats of each dose group were evaluated at 66 weeks. The survival of high-dose male and female rats was reduced relative to that of controls. Final mean body weights of surviving rats were similar to those of controls. The principal chemical-related effects occurred in the kidney and brain of dosed rats. Focal hyperplasia of the renal tubule epithelium and renal tubule adenomas were markedly increased in male rats receiving 88 mg/kg TRCP and, to a lesser extent, in female rats (renal tubule hyperplasia, male rats: 0/50; 2/50; 24/50; female rats: 0/50; 3/50; 16/50; renal tubule adenoma, male rats: 1/50; 5/50; 24/50; female rats: 0/50; 2/50; 5/50). Renal tubule carcinomas occurred in one control and one high-dose male rat. Degenerative lesions consisting of gliosis, mineralization, hemorrhage, and/or hemosiderin accumulation occurred in the cerebrum and brain stem of more than 50% of female rats receiving 44 or 88 mg/kg TRCP; similar lesions were seen in only a few dosed males. Slightly increased incidences of thyroid gland follicular cell neoplasms (male rats: 1/50; 2/48; 5/50; female rats: 0/50; 3/50; 4/50) and mononuclear cell leukemia (male rats: 5/50; 14/50; 13/50; female rats: 14/50; 16/50; 20/50) occurred in dosed males and females, but it is uncertain whether these were related to chemical administration.

The 2-year studies in mice were conducted by administering 0, 175, or 350 mg/kg TRCP to groups of 60 males and females, 5 days per week for up to 104 weeks; 8 to 10 mice of each sex per dose group were evaluated at 66 weeks. There were no significant differences in survival between dosed and control groups of either sex, and final mean body weights of mice were similar among all groups. The principal chemical-related effects occurred in the kidney, in which nuclear enlargement (karyomegaly) of tubule epithelial cells was present in approximately 80% of high-dose mice. In the original diagnosis, renal tubule adenomas were seen in one control male, one high-dose male, and one low-dose female. A carcinoma was also seen in one high-dose male. In a subsequent examination of step sections of all the mouse kidneys, adenomas were found in one low-dose male and two high-dose males. The incidences of renal tubule neoplasms in the original and step sections combined were 1/50, 1/50, and 4/50 for males. Female mice receiving TRCP demonstrated a marginally increased incidence of neoplasms (primarily adenomas) of the harderian gland (3/50; 8/50; 7/50); in addition, three harderian gland neoplasms occurred in high-dose female mice evaluated after 66 weeks.

Genetic Toxicology: TRCP was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, TA1537, or TA98 with or without exogenous metabolic activation (S9), and it tested negative for the induction of chromosomal aberrations in Chinese hamster ovary (CHO) cells. TRCP produced an equivocal response in the presence of S9 for the induction of sister chromatid exchanges (SCE) in CHO cells.

Conclusions: Under the conditions of these 2-year gavage studies, there was *clear evidence of carcinogenic activity** for male and female F344/N rats receiving tris(2-chloroethyl) phosphate as shown by increased incidences of renal tubule adenomas. Thyroid follicular cell neoplasms and mononuclear cell leukemia in male and female rats may have been related to chemical administration. There was *equivocal evidence of carcinogenic activity* for male $B6C3F_1$ mice as shown by a marginally increased incidence of renal tubule cell neoplasms. There was *equivocal evidence of carcinogenic activity* for female $B6C3F_1$ mice as shown by a marginally increased incidence of harderian gland adenomas.

Renal tubule cell hyperplasia in male and female rats and gliosis, hemorrhage, pigmentation (hemosiderin accumulation), and mineralization in the brains of female rats were associated with the administration of tris(2-chloroethyl) phosphate. Karyomegaly of renal tubule epithelial cells in male and female mice was also chemical related.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 8. A summary of peer review comments and the public discussion on this Technical Report appears on page 10.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Tris(2-Chloroethyl) Phosphate

Variable	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 44, or 88 mg/kg 5 days per week	0, 44, or 88 mg/kg 5 days per week	0, 175, or 350 mg/kg 5 days per week	0, 175, or 350 mg/kg 5 days per week
Body weights	Dosed similar to controls	Dosed similar to controls	Dosed similar to controls	Dosed similar to controls
2-Year survival rates	36/50, 33/50, 25/50	32/50, 33/50, 17/50	25/50, 25/50, 25/50	31/50, 37/50, 35/50
Nonneoplastic effects	Renal tubule hyperplasia	Renal tubule hyperplasia; gliosis, hemorrhage, hemosiderosis, and mineralization in the cerebrum and brain stem	Karyomegaly of renal tubule epithelial cells	Karyomegaly of renal tubule epithelial cells
Neoplastic effects				
Chemical-related effects	Renal tubule adenomas (1/50; 5/50; 24/50); renal tubule carcinoma (1/50; 0/50; 1/50)	Renal tubule adenomas (0/50; 2/50; 5/50)	None attributed to TRCP	None attributed to TRCP
Equivocal effects	Thyroid follicular cell neoplasms; (1/50; 2/48; 5/50) mononuclear cell leukemia (5/50; 14/50; 13/50)	Thyroid follicular cell neoplasms; (0/50; 3/50; 4/50) mononuclear cell leukemia (14/50; 16/50; 20/50)	Renal tubule neoplasms (adenoma: 1/50; 1/50; 3/50; carcinoma: 0/50; 0/50; 1/50)	Harderian gland (adenoma or carcinoma: 3/50; 8/50; 7/50)
Level of evidence of carcinogenic activity	Clear evidence	Clear evidence	Equivocal evidence	Equivocal evidence
Genetic toxicology				
Salmonella typhimurium				
Gene mutation:	Negative with and without S9			
Sister chromatid exchanges				
Chinese hamster ovary cells *in vitro*:	Negative without S9; equivocal with S9			
Chromosomal aberrations				
Chinese hamster overy cells *in vitro*:	Negative with and without S9			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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. 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. 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 cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report 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 five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to 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. Such consideration 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:

- 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 to neoplastic 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);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- 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.

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on tris(2-chloroethyl) phosphate on April 25, 1990, 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:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF PEER REVIEW COMMENTS

On April 25, 1990, the draft Technical Report on the toxicology and carcinogenesis studies of tris(2-chloroethyl) phosphate received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Committee and associated Panel of Experts. The review meeting was held at the National Institute of Health Sciences, Research Triangle Park, NC.

Dr. H. B. Matthews, NIEHS, began the discussion by reviewing the experimental design, results, and proposed conclusions (*clear evidence of carcinogenic activity* for male and female rats, *no evidence of carcinogenic activity* for male mice, and *equivocal evidence of carcinogenic activity* for female mice).

Dr. Matthews reported on step sectioning of the kidneys in mice, which revealed in males an additional control mouse with hyperplasia, an adenoma in one mouse in the low-dose group, and two additional hyperplasias and two adenomas in the high-dose group. Because of the additional kidney tumors found in dosed male mice, Dr. Matthews said that consideration should be given to changing the conclusion to *equivocal evidence.*

Dr. Garman, a principal reviewer, was in general agreement with the conclusions. However, he was not convinced that the increased incidence of harderian gland lesions in female mice was related to chemical treatment. And, with the additional information from the step sections of the kidneys in mice, he thought the level of evidence for male mice might be raised.

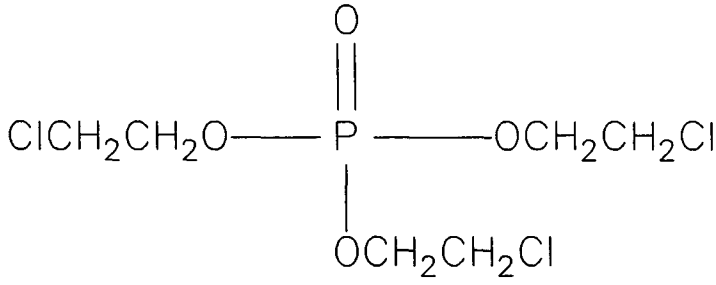
Dr. Gold, the second principal reviewer, agreed with the conclusions in male rats and male and female mice. She thought that the evaluation in male rats should be based on combined renal tubule carcinomas and adenomas, rather than on the adenomas alone. In female rats, she thought the low incidence of benign kidney tumors was supportive of only *some evidence of carcinogenic activity.* Dr. Gold questioned whether the incidence of a rarely observed tumor, granular cell tumors of the brain, in male and female rats might support equivocal evidence. Dr. S. Eustis, NIEHS, commented that these tumors are of meningeal origin in the rat and the meninges are rarely a site of carcinogenic activity even with a potent carcinogen, and thus, these tumors were not considered chemically related. Dr. Silbergeld was unconvinced that there was not a relationship, particularly since the site and mode of neurotoxic action apparently had not been characterized for this chemical. Dr. Matthews stated that there had been neurotoxicity studies done including some brain chemistry as well as evaluation of delayed behavioral effects after a single dose.

Dr. McKnight, the third principal reviewer, agreed with the overall conclusions for rats and mice. However, for mice, she thought that, based on survival rates and weight gain in the 2-year studies, it was not clear that the maximum tolerated dose was achieved. Dr. Matthews said that the significantly increased incidences of renal tubule karyomegaly at low and high doses in both sexes indicated that adequate doses had been used. For female rats, Dr. McKnight noted that the significant positive trend for thyroid follicular cell neoplasms and the significantly greater incidence in high dose versus control supported including them under *clear evidence.* Dr. Eustis responded that the small numbers of tumors and the absence of increases in preneoplastic lesions (hyperplasias) spoke against raising the level of evidence. For male rats, Dr. McKnight argued that mononuclear cell leukemias should be included under *clear evidence* based on a significant positive trend test and positive pairwise comparisons for both high- and low-dose groups with controls. Dr. McKnight thought too much emphasis was put on the highly variable historical control range as contrasted to the concurrent control values for leukemias in discounting their significance in the TRCP studies. Dr. J. Hasman, NIEHS, agreed that the primary emphasis should be on concurrent controls, but felt that it was also important to consider that the leukemia rate in high-dose male rats was essentially identical to the average control response for the three previous studies in the same laboratory.

Dr. Garman moved that the conclusions be accepted as written for male and female rats, *clear evidence of carcinogenic activity.* Dr. Longnecker seconded the motion, which was accepted by seven "yes" votes (Drs. Carlson, Davis, Hayden, Longnecker, McKnight, Silbergeld, Zeise) to four "no" votes

(Drs. Ashby, Garman, Gold, Goodman). Dr. Garman moved that the conclusions for male mice be changed from *no evidence of carcinogenic activity* to *equivocal evidence of carcinogenic activity* based on the additional renal tubule neoplasms revealed in the resectioning examination. Dr. Ashby seconded the motion, which was accepted unanimously with 11 votes. Dr. Garman moved that the conclusions be accepted as written for female mice, *equivocal evidence of carcinogenic activity.* Dr. Ashby seconded the motion, which was accepted unanimously with 11 votes.

INTRODUCTION



TRIS(2-CHLOROETHYL) PHOSPHATE

CAS No. 115-96-8
$C_6H_{12}Cl_3PO_4$
Molecular Weight: 285.5

Synonyms: 2-Chloroethanol phosphate (3:1), Tris(β-chloroethyl) phosphate
Trade Names: Fyrol CEF, Disflamoll TCA, NIAX flame retardant

CHEMICAL AND PHYSICAL PROPERTIES

Tris(2-chloroethyl) phosphate (TRCP) is a clear, transparent liquid with a slight odor, a boiling point of 330° C, and a freezing point of -55° C. It is soluble in alcohols, esters, ketones, benzenoid hydrocarbons, and chlorinated hydrocarbons, but less soluble in aliphatic solvents. It is soluble in water up to 7,000 ppm. Phosphoric acid esters slowly hydrolyze in aqueous solutions at pH 7 and 25° C (Lefaux, 1968; Mabey and Mill, 1978; Clayton and Clayton, 1981; Dean, 1987).

PRODUCTION AND USE

TRCP is a flame-retardant plasticizer produced by reacting phosphorus oxychloride with ethylene oxide in the presence of aluminum chloride. No reliable production data are available. It is used in polyurethane and polyisocyanurate foams, carpet backings, flame-laminated polyurethane foams, flame-retardant paints and lacquers, epoxy resins, phenolic resins, amino resins, poly (vinyl acetate) coatings and adhesives, urethane coatings, cast acrylic sheeting, polyester resins, and wood-resin composites such as particle board (*Kirk-Othmer*, 1980).

HUMAN EXPOSURE AND HEALTH EFFECTS

Human exposure to TRCP is expected to occur primarily in the workplace and as a result of trace exposure in the environment. From the National Occupational Exposure Survey conducted in 1981-1983, the NIOSH estimated that 4,979 workers were potentially exposed in the United States. However, no reports were found to indicate that TRCP has been associated with human toxicity, and occupational standards have not been established by OSHA. TRCP may be released into the environment via effluents from the manufacture of the wide variety of products in which it is added as a plasticizer or flame retardant. This compound has been detected in a number of environmental samples. It is expected to be mobile in soil and susceptible to significant leaching. Sufficient data are not available

to predict the significance of biodegradation in soil or water.

The potential for consumer exposure to TRCP is unknown. In samples of fruit and fruit juices taken from ten cities in 1979, one contained 0.002 ppm TRCP (Gartrell *et al.*, 1985a,b). In a survey of foods from different U.S. cities from 1980 to 1982, TRCP was found in 1 of 13 samples of toddler foods at a concentration of 0.0385 ppm and in 1 of 27 samples of meat, fish, and poultry at a concentration of 0.0067 ppm (Gartrell *et al.*, 1986).

METABOLISM

There are no published reports regarding the metabolism and disposition of TRCP. However, recent work by the NTP has shown that TRCP is rapidly absorbed from the gastronintestinal tract with peak concentrations in plasma 5 minutes following gavage administration of 175 mg/kg. During the first 30 minutes following dosing, plasma concentrations of TRCP were twofold higher in female rats than in males, but neither blood concentrations nor tissue levels differed significantly at later time points. TRCP was distributed to all major tissues with no apparent accumulation at any site. The major route of excretion, greater than 90%, was in the urine with approximately 6% of the dose in feces and a trace exhaled as CO_2 or as volatiles. In animals given ^{14}C-labeled TRCP, the elimination of compound-derived radioactivity was more rapid in mice, which excreted greater than 70% of an oral dose of 175 mg/kg in the urine within 8 hours versus 40% for male and female rats. TRCP was excreted relatively rapidly in the form of at least five metabolites. The major metabolite was bis(2-chloroethyl)carboxymethylphosphate; two additional metabolites were bis(2-chloroethyl) phosphate and the glucuronide conjugate of bis(2-chloroethyl)carboxymethylphosphate (Matthews, H.B., unpublished data).

TOXICITY

Toxicity in Animals

Only a few studies of the toxic effects of TRCP in animals have been reported. When administered orally to rats, TRCP was moderately toxic with an LD_{50} of 1,410 mg/kg (Smyth *et al.*, 1951). Other studies found LD_{50} values of 501 mg/kg in male rats and 794, 501, and 430 mg/kg in female rats, depending on the lot tested (Ulsamer *et al.*, 1980). TRCP produced prolonged epileptiform convulsions when given by intraperitoneal injection to rats, but no brain lesions were reported, and brain acetylcholinesterase was weakly inhibited. It does not appear to be readily absorbed through the skin and is not a dermal irritant (Clayton and Clayton, 1981). Although several chlorinated alkyl phosphates have been shown to produce delayed neurotoxicity in hens, TRCP (Fyrol CEF, 10 mL/kg) failed to show behavioral or histopathological evidence of delayed neurotoxicity (Sprague *et al.*, 1981). In another study, TRCP was not toxic to insects or fish, it did not synergise insecticide activity, and it was only a weak inhibitor of acetylcholinesterase (Eldefrawi *et al.*, 1977).

Carcinogenicity

No epidemiological studies were found which indicate whether TRCP is carcinogenic to humans. In long-term skin paint studies in Swiss mice, TRCP showed no significant carcinogenic, initiating, or promoting potential (Sala *et al.*, 1982). Other members of this class of compounds, however, have demonstrated carcinogenicity in 2-year rodent studies. Tris(2,3-dibromopropyl) phosphate produced neoplasms of the kidney in male and female rats and in male mice, of the forestomach and lung in mice of both sexes, and of the liver in female mice (NCI, 1978a). Trimethylphosphate produced neoplasms of the subcutaneous tissue in male rats and of the uterus in female mice (NCI, 1978b). Tris(2-ethylhexyl) phosphate produced neoplasms of the adrenal gland in male rats and of the liver in female mice (NTP, 1984).

Genetic Toxicity

There are only limited genetic toxicology data for TRCP. The chemical was not mutagenic in bacteria (Simmon and Kuahanen, 1978; Nakamura *et al.*, 1979; Haworth *et al.*, 1983) and did not induce chromosomal aberrations in Chinese hamster ovary (CHO) cells with or without exogenous metabolic activation (S9) (Galloway *et al.*, 1987). Results of a CHO cell sister chromatid exchange (SCE) test were regarded as equivocal due to a positive response seen in one trial with S9 but which was not observed in a repeat trial under the same conditions (Galloway *et al.*, 1987). The structural analogue, tris(2-bromoethyl) phosphate, was reported

to be mutagenic in *Salmonella typhimurium* strains TA100 and TA1535 with and without S9 (Nakamura *et al.*, 1979); and the phosphite derivative, tris (2-chloroethyl) phosphite, was weakly positive for the induction of gene mutations in *S. typhimurium* strain TA100 without S9 (Haworth *et al.*, 1983).

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF TRIS(2-CHLOROETHYL) PHOSPHATE

Tris(2-chloroethyl) phosphate (TRCP), manufactured by Stauffer Chemical Company (Westport, CT), was obtained in one lot (lot no. 0101F-1-3) from the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory and confirmed by the study laboratory (Microbiological Associates, Inc., Bethesda, MD). Appendix H presents details of these analyses.

The study chemical, a clear liquid, was identified as TRCP by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The subject lot was approximately 98% pure, as determined by elemental analysis, Karl Fischer water analysis, titration of acidic components, thin-layer chromatography, and gas chromatography.

Stability studies performed with gas chromatography indicated that TRCP was stable as a bulk chemical for at least 2 weeks in sealed containers at temperatures up to 25° C. During the 2-year studies, the stability of the bulk chemical was monitored by infrared spectroscopy, gas chromatography, and titration for acid components; no degradation of the study material was seen throughout the studies.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

Formulations were prepared by mixing appropriate amounts of TRCP and corn oil (Giant Foods, Inc., Washington, DC) (Appendix H, Table H1). Gas chromatographic analysis of corn oil solutions of TRCP showed no decrease in concentration after storage for 21 days in the dark at room temperature (20° to 24° C) or under simulated dosing conditions (open to air and light for 3 hours). During the studies, the dose formulations were stored at 0° ± 5° C for 2 weeks.

The study laboratory conducted periodic analyses of the dose formulations of TRCP by gas chromatography (Appendix H, Tables H2 and H3). During the 2-year studies, the dose formulations were analyzed at approximately 8-week intervals by gas chromatography. These analyses indicated that the formulations were within ± 10% of the target concentrations throughout the 2-year studies. Results of periodic referee analyses performed by the analytical chemistry laboratory indicated generally good agreement with the results from the study laboratory (Appendix H, Table H4).

16-DAY STUDIES

Short-term, repeated-dose studies of TRCP were conducted in rodents to evaluate whether the substance was associated with any cumulative toxic effects or altered serum cholinesterase activity. Male and female F344/N rats and B6C3F$_1$ mice obtained from Harlan Industries (Indianapolis, IN) were observed for 20 to 21 days before the studies began. The rats were 7 weeks old when placed on study, and the mice were 9 weeks old. Routine viral serology was performed on the sera of representative animals during quarantine and at the termination of the studies. Animals were assigned to weight groups, then to cages using a random number table; group numbers were assigned with another random number table.

Groups of 5 rats of each sex received 0, 22, 44, 88, 175, or 350 mg/kg TRCP in corn oil by gavage 5 days per week for 12 doses over 16 days. Groups of 5 mice of each sex were administered 0, 44, 88, 175, 350, or 700 mg/kg TRCP in corn oil by gavage on the same schedule.

Animals were housed 5 per cage, with water and feed available *ad libitum*. The rats and mice were

observed twice daily; they were weighed at the beginning of the studies, at the end of the first and second weeks, and at necropsy. Details of study design and animal maintenance are summarized in Table 1. At scheduled terminal sacrifice, blood was collected by aortic puncture from all surviving animals, and serum was prepared and assayed for cholinesterase activity according to the method of Ellman *et al.* (1961). All animals, including those that died during the test as well as those that survived until the scheduled kill, received a complete necropsy. Organs that were weighed and tissues that were examined histopathologically are listed in Table 1.

16-Week Studies

Sixteen-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to TRCP and to determine the concentrations to be used in the 2-year studies.

Male and female F344/N rats (4 to 5 weeks old) and male and female B6C3F$_1$ mice (5 to 6 weeks old) were obtained from Charles River Breeding Laboratories (Kingston, NY), observed for 21 days, distributed to weight classes, and assigned to cages using a random number table. Cages were assigned to dosed and control groups by another table of random numbers. Rats were 8 to 9 weeks old when placed on study, and mice were 9 to 10 weeks old. Routine viral serology was performed on the sera of representative animals during quarantine and at the termination of the studies.

Groups of 10 rats of each sex were administered 0, 22, 44, 88, 175, or 350 mg/kg TRCP in corn oil by gavage 5 days per week for 16 weeks (females) to 18 weeks (males). Groups of 10 mice of each sex received 0, 44, 88, 175, 350, or 700 mg/kg TRCP in corn oil by gavage 5 days per week for 16 weeks.

Animals were housed 5 per cage, with feed and water available *ad libitum*. They were observed twice daily for morbidity and mortality. Individual animal weights were recorded at the start and termination of the studies; group mean weights and differential weight gain relative to controls were determined weekly. Table 1 summarizes further experimental details.

At scheduled terminal sacrifice, blood was collected by aortic puncture from all surviving animals, and serum was prepared and assayed for cholinesterase activity according to the method of Ellman *et al.* (1961).

At the end of the observation period, survivors were killed, and a complete, detailed necropsy was performed on all animals. Organs that were weighed and the tissues that were examined histopathologically are listed in Table 1.

2-Year Studies

Study Design

Groups of 60 rats of each sex received 0, 44, or 88 mg/kg TRCP in corn oil by gavage 5 days a week for up to 103 weeks. Groups of 60 mice of each sex were administered 0, 175, or 350 mg/kg TRCP on the same schedule. Ten animals per sex per group from each species were predesignated for interim evaluation (necropsy, hematology, and clinical chemistry) at 66 weeks.

Source and Specifications of Animals

The male and female F344/N rats and B6C3F$_1$ mice used in these studies were obtained from the National Cancer Institute's Frederick Cancer Research Facility (Frederick, MD). Rats were 5 to 7 weeks old and mice were 5 to 6 weeks old upon arrival at the study laboratory. After all animals were quarantined for 20 days, a complete necropsy was performed on 5 animals of each sex and species to assess their health status. Serologic analyses were performed on those animals sacrificed during quarantine and on sentinel animals at 6, 12, and 18 months to test for *Mycoplasma pulmonis* (by ELISA), pneumonia virus of mice (PVM), Kilham rat virus (KRV), Toolan's H-1 virus (H-1), Sendai, and rat coronavirus sialodacryoadenitis virus (RCV-SDA). The rodents were placed on study at 8 to 10 weeks (rats) or 8 to 9 weeks (mice) of age. Details of animal health monitoring are presented in Appendix J.

Animal Maintenance

Animals were housed 5 per cage. Feed and water were available *ad libitum*; analyses of feed are given in Appendix I. Cages were rotated every other

week. Further details of animal maintenance are given in Table 1.

Clinical Examinations and Pathology

All animals were observed two times per day for morbidity and mortality. Clinical signs, along with individual size and location of palpable tissue masses and other lesions, were recorded at least monthly. Body weights were recorded once per week for the first 13 weeks of the studies and once per month thereafter.

During the 2-year studies, animals scheduled for the 15-month interim sacrifice were bled (with and without anticoagulant) to analyze hematology and clinical chemistry responses to the administration of TRCP. The following hematology measures were evaluated: red blood cell count, mean corpuscular volume, hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell count, white blood cell differential, and reticulocyte count. Clinical chemistry measures included: alanine transaminase, aspartate transaminase, blood urea nitrogen, sorbitol dehydrogenase, alkaline phosphatase, serum cholinesterase, creatinine, and cholesterol.

Animals found moribund, those sacrificed at 15 months, and those surviving to the end of the studies were killed. A necropsy was performed on all animals including those found dead.

During necropsy, all organs and tissues were examined for grossly visible lesions; histopathologic examinations were performed on all masses and grossly detectable lesions in all dose groups. All tissues and organs from all dose groups were fixed in 10% neutral buffered formalin, processed by standard procedures, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Complete histopathological examinations were performed on all groups of male and female rats, and on all control and high-dose mice. Selected tissues were examined in low-dose mice. All animals found dead or killed before terminal sacrifice were also subjected to a complete histopathological examination. Table 1 lists those tissues and organs that were examined microscopically.

After pathology evaluations were completed by the laboratory pathologist and the pathology data entered into the Toxicology Data Management System (TDMS), the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit for accuracy of labeling and animal identification and for thoroughness of tissue trimming. 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 sections of brain, kidney, liver, spleen, and thyroid gland (rats) or all sections of harderian gland, kidney, and liver (mice), and all tissues from a randomly selected 10% of the animals were re-evaluated microscopically by a quality assessment pathologist.

The quality assessment report and slides were submitted to the Pathology Working Group (PWG) chairperson, who reviewed microscopically all tissues about which there was a disagreement in diagnosis between the laboratory and quality assessment pathologists. Representative examples of potential chemical-related nonneoplastic lesions, most renal neoplasms, and examples of disagreements in diagnosis between the laboratory and quality assessment pathologists were selected by the PWG chairperson for review by the full PWG. The PWG included the quality assessment pathologist as well as other pathologists experienced in rodent toxicology, who examined the tissues without knowledge of dose group or previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the final diagnosis was changed to reflect the opinion of the PWG. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell *et al.* (1986).

Statistical Methods

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958)

and is presented graphically. Animals were censored from the survival analyses at the time they were found to be missing or dead from other than natural causes; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test for dose-related trends. When significant survival differences were detected, additional analyses using these procedures were carried out to determine the point in time at which significant differences in the survival curves were first detected. All reported P values for the survival analysis are two-sided.

Calculation of Incidence

The incidence of neoplastic or nonneoplastic lesions is given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators include only those animals for which the site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) before tissue sampling for histopathology, 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

The majority of tumors in this study were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was a logistic regression analysis, which assumed that the diagnosed tumors were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, tumor prevalence was modeled as a logistic function of chemical exposure and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if it did not significantly enhance the fit of the model. The dosed and control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). When tumors are incidental, this comparison of the time-specific tumor prevalences also provides a comparison of time-specific tumor incidence (McKnight and Crowley, 1984).

In addition to logistic regression, alternate methods of statistical analysis were used, and the results of these tests are summarized in the appendixes. These include the life table test (Cox, 1972; Tarone, 1975), appropriate for rapidly lethal tumors, and the Fisher exact test and the Cochran-Armitage test (Armitage, 1971; Gart *et al.*, 1979), procedures based on the overall proportion of tumor-bearing animals.

Tests of significance include pairwise comparisons of each dosed group with controls and a test for an overall dose-response trend. Continuity-corrected tests were used in the analysis of tumor incidence, and reported P values are one-sided. These procedures also were used to evaluate selected nonneoplastic lesions. For further discussion of these statistical methods, see Haseman (1984).

Analysis of Continuous Variables

For all end points, dosed groups were compared with the control group using the nonparametric multiple comparison test of Dunn (1964) or Shirley (1977). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose response trends and to determine whether Dunn's or Shirley's test was more appropriate for pairwise comparisons.

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, tumor incidence in control animals from the NTP historical control data base (Haseman *et al.*, 1984, 1985) are included for those tumors appearing to show compound-related effects.

QUALITY ASSURANCE METHODS

The prechronic and chronic studies were conducted in compliance with FDA Good Laboratory Practice

Regulations (21 CFR Part 58). In addition, as study records were submitted to the NTP Archives, they were audited retrospectively by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and preliminary draft of the NTP Technical Report were conducted. Audit procedures are presented in the reports, which are on file at the NIEHS. The audit findings were reviewed and assessed by NTP staff so that all had been resolved or were otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICOLOGY

The genetic toxicity of TRCP was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium* and to induce sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells. The methods and materials employed in these studies are given in Appendix F.

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Tris(2-Chloroethyl) Phosphate

16-Day Studies	16-Week Studies	2-Year Studies
Study Laboratory		
Microbiological Associates (Bethesda, MD)	Microbiological Associates	Microbiological Associates
Strain and Species		
Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$
Animal Source		
Harlan Industries, Inc. (Indianapolis, IN)	Charles River Breeding Laboratories (Kingston, NY)	Frederick Cancer Research Facility (Frederick, MD)
Time Held Before Study		
Rats: 20 days Mice: 21 days	Rats: 21 days Mice: 21 days	Rats: 20 days Mice: 20 days
Age When Placed on Study		
Rats: 7 weeks Mice: 9 weeks	Rats: 8-9 weeks Mice: 9-10 weeks	Rats: 8-10 weeks Mice: 8-9 weeks
Date of First Dose		
Rats: 11 May 1981 Mice: 12 May 1981	Rats: 19 August 1981 Mice: 19 August 1981	Rats: 7 September 1982 Mice: 13 September 1982
Duration of Dosing		
16 days (5 days/week)	Rats: 16 weeks (5 days/week) for females, 18 weeks (5 days/week) for males Mice: 16 weeks (5 days/week)	103 weeks (5 days/week)
Date of Last Dose		
Rats: 26 May 1981 Mice: 27 May 1981	Rats: 6-17 December 1981 Mice: 29 November-6 December 1981	Rats: 24 August 1984 Mice: 31 August 1984
Necropsy Dates		
Rats: 27-28 May 1981 Mice: 28-29 May 1981	Rats: 7-18 December 1981 Mice 30 November-7 December 1981	Rats: 4-6 September 1984 Mice: 10-12 September 1984
Age When Killed		
Rats: 9 weeks Mice: 11 weeks	Rats: 24-27 weeks Mice: 25-28 weeks	Rats: 112-114 weeks Mice: 112-113 weeks
Size of Study Groups		
5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Method of Animal Distribution		
Animals distributed to weight classes and then randomized to cages and test and control groups using a random number table	Same as 16-day studies	Same as 16-day studies

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Tris(2-Chloroethyl) Phosphate (continued)

16-Day Studies	16-Week Studies	2-Year Studies
Animals per Cage 5	5	5
Method of Animal Identification Ear punch and ear clip	Ear punch and ear clip	Ear tag
Diet NIH-07 Rat and Mouse Ration, pellets (Zeigler Bros., Inc., Gardners, PA); available *ad libitum*	NIH-07 Rat and Mouse Ration, powder (rats) or pellets (mice), Zeigler Bros, Inc., Gardners, PA); available *ad libitum*	Same as 16-day studies
Maximum Storage Time for Feed 120 days postmilling	Same as 16-day studies	Same as 16-day studies
Water Tap water by Edstrom automatic watering system (Lab Products, Rochelle Park, NJ and Hazleton Systems, Inc., Aberdeen, MD); available *ad libitum*	Same as 16-day studies	Same as 16-day studies
Cages Polycarbonate (Lab Products, Inc., Rochelle Park, NJ and Hazleton Systems, Inc., Aberdeen, MD)	Same as 16-day studies	Same as 16-day studies
Bedding Shurfire hardwood chips (P.J. Murphy Forest Products Corp., Rochelle Park, NJ); changed twice weekly	Same as 16-day studies	Same as 16-day studies
Cage Filters Spun-bonded polyester (Snow Filtration, Inc., Cincinnati, OH); changed biweekly	Same as 16-day studies	Same as 16-day studies
Animal Room Environment Temperature: 70°-80° F Humidity: 26%-76% Fluorescent light: 12 hours/day Room air changes: 12-15/hour	Temperature: 70°-81° F Humidity: 10%-78% Fluorescent light: 12 hours/day Room air changes: 12-15/hour	Temperature: 60°-86° F Humidity: 15%-84% Fluorescent light: 12 hours/day Room air changes: 12-15/hour
Doses Rats: 0, 22, 44, 88, 175, or 350 mg/kg TRCP in corn oil, 5 ml/kg Mice: 0, 44, 88, 175, 350, or 700 mg/kg TRCP in corn oil, 10 ml/kg	Same as 16-day studies	Rats: 0, 44, or 88 mg/kg TRCP in corn oil, 5 ml/kg Mice: 0, 175, or 350 mg/kg TRCP in corn oil, 10 ml/kg

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Tris(2-Chloroethyl) Phosphate (continued)

16-Day Studies	16-Week Studies	2-Year Studies
Vehicle Corn oil (Giant Foods, Inc., Washington, DC)	Same as 16-day studies	Same as 16-day studies
Gavage Method Stainless steel gavage needle with ball tip: 3-inch, 18 gauge Cornwall syringe for rats or 1-inch, 20 gauge Cornwall syringe for mice (Popper & Sons, Inc.)	Same as 16-day studies	Same as 16-day studies
Type and Frequency of Observation Observed daily; body weight initially, weekly, and at termination; clinical observation daily through day 7, weekly thereafter	Observed daily; body weight initially, weekly, and at termination; clinical examination weekly	Observed twice daily; body weight initially, weekly through week 13, monthly after week 13, and at 3-4 week intervals for the last 3 months; clinical observation monthly
Special Studies Serum cholinesterase activity: Serum collected from surviving rats and mice at termination by aortic puncture. Activity determined on day of collection.	Serum cholinesterase activity: Determined at termination in surviving rats and mice; procedure same as in 16-day studies.	
Necropsy, Histopathology, and Clinical Pathology		
Necropsy Necropsy performed on all animals. Organ weights obtained from those surviving until necropsy (brain, heart, liver, lung, right kidney, and thymus).	**Necropsy** Necropsy performed on all animals. Organ weights, same as the 16-day studies.	**Necropsy** Necropsy performed on all animals. At 66-week interim sacrifice, organ weights were recorded for brain, kidney, and liver.
Histopathology Complete histopathology on all control and 350 mg/kg (rats) or 700 mg/kg (mice) males and females, including the following organs: adrenals, bone (including marrow), bone marrow (sternum), brain, clitoral gland, epididymis, esophagus, gallbladder (mice only), harderian gland, heart, kidney, large intestines (cecum, colon, rectum), liver, lung with bronchi, lymph nodes (mandibular, mesenteric), mammary glands, nasal cavity and turbinates, ovaries, pancreas, parathyroid, pituitary, preputial gland, prostate, salivary gland, seminal vesicles, skin, small intestines (duodenum, ileum, jejunum), spleen, stomach, testes, thymus, thyroid, trachea, urinary bladder, uterus, tissue masses, and gross lesions.	**Histopathology** Complete histopathology performed on all control animals as well as on the two highest dose groups of rats (175 mg/kg, 350 mg/kg) and all high-dose mice (700 mg/kg). Tissues and organs examined were the same as in the 16-day studies. In addition, the following organs were examined in mid-dose groups: brain in female rats receiving 88 mg/kg; kidneys in mice receiving 44, 88, 175, or 350 mg/kg.	**Histopathology** At 66-week interim sacrifice and 104-week terminal sacrifice, complete histopathology conducted on all groups of male and female rats and on all control and high-dose mice (350 mg/kg). Tissues and organs examined were the same as in the 16-day studies. In addition, the following organs were examined in low-dose mice: harderian gland, kidney, liver, lung, and stomach (175 mg/kg). **Clinical Pathology** Clinical pathology studies were conducted at 66 weeks. ***Hematology:*** hematocrit, hemoglobin, erythrocytes, leukocytes with differential, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, and reticulocyte count ***Clinical chemistry:*** blood urea nitrogen, serum glucose, creatinine, alkaline phosphatase, serum cholinesterase, cholesterol, sorbitol dehydrogenase, alanine aminotransferase, and aspartate aminotransferase

RESULTS

RATS

16-Day Studies

Groups of five F344/N rats of each sex received 0, 22, 44, 88, 175, or 350 mg/kg tris(2-chloroethyl) phosphate (TRCP) in corn oil by gavage 5 days per week for 12 doses over 16 days. All rats lived to the end of the studies, and no clinical signs of toxicity were observed. There were no significant differences in body weight gain between dosed and control rats (Table 2).

Brain, heart, right kidney, liver, lung, and thymus weights were obtained at necropsy for all rats. Group mean organ weights and organ-weight-to-body-weight ratios for male and female rats are shown in Appendix E, Tables E1 and E2. Mean absolute and relative kidney weights for males receiving 175 or 350 mg/kg were significantly greater than those of controls, as were absolute and relative liver weights for high-dose females. Significant decreases in organ weight parameters included decreased absolute and relative lung weights in females receiving 88 to 350 mg/kg ($P \leq 0.01$). Other marginal changes in organ weights were not considered related to chemical administration.

Cholinesterase activity was determined on fresh sera collected at necropsy (Appendix G, Table G1). Cholinesterase activity was not reduced in dosed male rats; however, the enzyme activity determined for female rats administered 175 or 350 mg/kg TRCP was approximately 80% that of controls (175 mg/kg females, $P \leq 0.01$; 350 mg/kg females, $P \leq 0.05$).

TABLE 2
Survival and Mean Body Weights of Rats in the 16-Day Gavage Studies of Tris(2-Chloroethyl) Phosphate

Dose (mg/kg)	Survival[a]	Mean Body Weights (g)			Final Weight Relative to Controls (%)
		Initial[b]	Final	Change[c]	
Male					
0	5/5	146 ± 5	203 ± 4	56 ± 3	
22	5/5	149 ± 2	203 ± 3	54 ± 2	100
44	5/5	150 ± 5	198 ± 7	48 ± 4	97
88	5/5	144 ± 8	199 ± 3	55 ± 6	98
175	5/5	147 ± 4	209 ± 4	62 ± 4	103
350	5/5	149 ± 2	202 ± 6	54 ± 4	100
Female					
0	5/5	116 ± 2	140 ± 3	24 ± 2	
22	5/5	114 ± 2	140 ± 4	26 ± 3	100
44	5/5	112 ± 2	139 ± 4	27 ± 3	99
88	5/5	112 ± 3	140 ± 4	28 ± 2	100
175	5/5	111 ± 3	139 ± 4	28 ± 3	99
350	5/5	112 ± 3	144 ± 7	32 ± 4	103

[a] Number surviving/number initially in group
[b] Initial group mean body weight given as mean ± standard error. Weights and calculations are based on animals surviving to the end of the study, except where noted. Differences from the control group are not significant by Dunn's or Shirley's test.
[c] Mean body weight change of the survivors given as mean ± standard error

No gross or histopathologic lesions attributable to TRCP were observed at any dose level. However, degenerative and inflammatory lesions characteristic of sialodacryoadenitis virus (SDA) infection were observed in the salivary glands and lung of most dosed and control rats. Elevated antibody titers to rat coronavirus confirmed the presence of this infectious disease.

16-Week Studies

Groups of ten rats of each sex received 0, 22, 44, 88, 175, or 350 mg/kg TRCP in corn oil by gavage 5 days per week for 16 weeks (female) or 18 weeks (male). During week 4 of the studies, the two most concentrated dosing solutions were incorrectly prepared, and for the first 3 days of that week, the rats in the two highest dose groups received double the target levels (the 175 mg/kg group received 350 mg/kg and the 350 mg/kg group received 700 mg/kg). As a result of the overdosing, two females in each of these groups died, and others exhibited signs of toxicity, including ataxia, excessive salivation, gasping, and convulsions. The overdosed males showed no signs of toxicity, and none died. The rats in these two groups were not dosed on the fourth day of week 4 to allow them to recover; dosing was resumed according to protocol on the following day.

During the 16-week studies, there were additional deaths of rats in the two highest dose groups (one male receiving 175 mg/kg, five high-dose males, and three high-dose females) that were not associated with the overdosing (Table 3).

TABLE 3
Survival and Mean Body Weights of Rats in the 16-Week Gavage Studies of Tris(2-Chloroethyl) Phosphate

Dose (mg/kg)	Survival[a]	Mean Body Weights (g)			Final Weight Relative to Controls (%)
		Initial[b]	Final	Change[c]	
Male					
0	10/10	144 ± 3	360 ± 4	217 ± 4	
22	9/10[d]	140 ± 3	366 ± 7	226 ± 6	102
44	10/10	140 ± 4	352 ± 5	213 ± 4	98
88	10/10	137 ± 4	348 ± 7	211 ± 3	97
175	9/10[e]	141 ± 7	358 ± 11	217 ± 6	99
350	4/10[f]	144 ± 7	352 ± 11	209 ± 5	98
Female					
0	10/10	109 ± 1	191 ± 2	82 ± 1	
22	8/10[g]	110 ± 1	187 ± 3	77 ± 2	98
44	10/10	108 ± 1	189 ± 2	82 ± 2	99
88	10/10	107 ± 1	185 ± 2	78 ± 2	97
175	8/10[h]	104 ± 1*	199 ± 7	94 ± 7	104
350	5/10[i]	109 ± 1	230 ± 17	122 ± 17	120

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
[a] Number surviving/number initially in group
[b] Initial group mean body weight given as mean ± standard error. Weights and calculations are based on animals surviving to the end of the study, except where noted.
[c] Mean body weight change of the survivors given as mean ± standard error
[d] Week of death: 14
[e] Week of death: 12
[f] Week of death: 5,10,12,12,13,13
[g] Week of death: 14,16
[h] Week of death: 4,5
[i] Week of death: 4,5,13,16,16

Female rats receiving 175 or 350 mg/kg experienced occasional periods of hyperactivity after dosing. Periodic convulsions were noted in high-dose females during week 12. Four additional deaths occurred as a result of gavage trauma (one 22 mg/kg male, two 22 mg/kg females, and one 350 mg/kg male).

Final mean body weights were generally similar among dosed and control male rats, although the final mean body weight of surviving high-dose females was about 20% greater than the control value. The final absolute and relative (organ-weight-to-body-weight and organ-weight-to-brain-weight ratios) weights of liver and kidney were significantly increased in high-dose males ($P \leq 0.01$) and in females receiving 44 to 350 mg/kg TRCP ($P \leq 0.01$). These differences were considered related to the administration of TRCP (Tables E3 and E4).

Cholinesterase activity data, determined on fresh sera collected at necropsy, are given in Appendix G, Table G2. Female rats receiving 175 or 350 mg/kg TRCP had levels that were 75% or 59% of the control value, respectively ($P \leq 0.01$). Cholinesterase activity was not reduced in male rats.

Necropsy examination showed no gross lesions attributable to chemical administration. However, necrosis of neurons of the hippocampus was observed histologically in the brains of 10/10 females and 2/10 males receiving 350 mg/kg TRCP and in 8/10 females receiving 175 mg/kg. The affected neurons were predominantly in the dorsomedial portion of the pyramidal row of the hippocampus (Figure 1). In the more severe lesions, mineral deposits were present in the affected areas of the brain. In the high-dose female rats, neuronal necrosis was also observed in the thalamus.

Dose Selection Rationale for the 2-Year Studies

Doses of 44 and 88 mg/kg TRCP were selected for the chronic study because of the chemically related deaths of rats receiving 350 mg/kg and the brain lesions in rats receiving 175 or 350 mg/kg. The overdosing of rats that occurred for 3 days during week 3 of the prechronic study was not thought to have compromised dose selection for the chronic studies.

2-Year Studies

Body Weights and Clinical Signs

Group mean body weights and mean body weights relative to control values are presented by week on study in Tables 4 and 5. Growth curves, plotting mean body weights against week on test, are shown in Figure 2. Body weights of rats receiving TRCP were not significantly different from those of controls. There were no clinical signs in rats attributable to the administration of TRCP.

Survival

Estimates of the probability of survival of male and female rats administered TRCP in corn oil at the doses used in these studies and for vehicle controls are shown in the Kaplan-Meier curves in Figure 3. The numbers of rats dying early or surviving to the end of the studies are given in Table 6. Survival to study termination was reduced in the high-dose males and females. Although female rats dying early or sacrificed while moribund frequently had brain lesions, male rats did not.

66-Week Interim Evaluation

Ten male and ten female rats in each dose group were predesignated for interim sacrifice and evaluation at 66 weeks. One female receiving 88 mg/kg died on day 261, and one vehicle control male died on day 408; the remaining lived until interim sacrifice on days 458 and 459. There were no chemical-related alterations in hematologic parameters; however, the mean values for serum alkaline phosphatase and alanine transferase were significantly decreased in females receiving 88 mg/kg.

At necropsy, the mean absolute and relative liver and kidney weights of male rats receiving 88 mg/kg TRCP were significantly increased relative to those of controls ($P \leq 0.01$). These increases were considered to be chemical related (Tables E5 and E6).

An adenoma of the renal tubule was observed in one high-dose male and degenerative lesions of the brain were seen in three high-dose females. The brain lesions, located in the cerebrum and thalamus, were focal. They were characterized by necrosis of the neuropil with accumulation of inflammatory

TABLE 4
Mean Body Weights and Survival of Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate

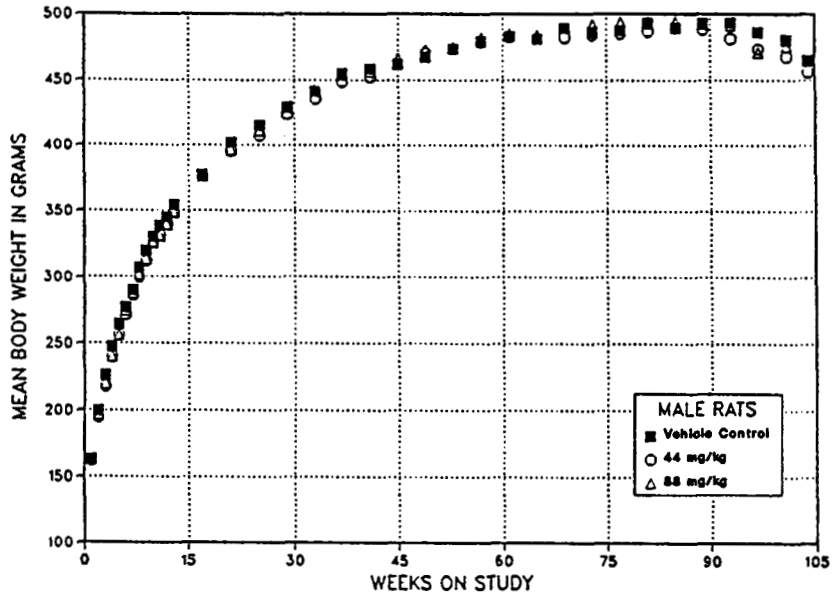
Weeks on Study	Vehicle Control		44 mg/kg			88 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	163	60[a]	162	99	60[a]	163	100	60[a]
2	199	60	195	98	60	197	99	60
3	226	60	218	97	60	220	97	60
4	248	60	240	97	60	240	97	60
5	264	60	256	97	60	256	97	60
6	277	60	271	98	60	275	99	60
7	290	60	286	99	60	288	99	60
8	307	60	300	98	60	302	98	60
9	319	60	312	98	60	313	98	60
10	330	60	326	99	60	326	99	60
11	338	60	331	98	60	331	98	60
12	345	60	339	98	60	339	98	60
13	355	60	349	98	60	348	98	60
17	378	60	376	100	60	376	100	60
21	402	60	396	98	60	396	99	60
25	415	60	408	98	60	411	99	60
29	429	60	424	99	60	429	100	60
33	441	60	436	99	60	442	100	60
37	455	60	449	99	60	454	100	60
41	458	60	452	99	60	457	100	60
45	462	60	462	100	60	466	101	60
49	468	60	471	101	60	473	101	60
53	474	59	473	100	60	476	100	60
57	479	59	479	100	60	482	101	60
61	483	55	483	100	60	485	100	60
65	481	55	481	100	59	484	101	60
69[b]	489	44	482	99	48	492	100	47
77	488	42	485	100	47	494	101	46
81	493	40	487	99	46	495	100	44
85	490	40	489	100	43	494	101	42
89	493	37	489	99	42	492	100	42
93	494	36	482	98	38	492	100	38
97	486	36	474	97	35	471	97	34
101	480	36	467	97	34	476	99	26
104	465	36	456	98	33	466	100	25
Terminal sacrifice		36			33			25
Mean for weeks								
1-13	282		276	98		277	98	
14-52	434		430	99		434	100	
53-104	484		479	99		485	100	

[a] Includes interim sacrifice animals
[b] Interim sacrifice occurred

TABLE 5
Mean Body Weights and Survival of Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate

Weeks on Study	Vehicle Control Av. Wt. (g)	Vehicle Control No. of Survivors	44 mg/kg Av. Wt. (g)	44 mg/kg Wt. (% of controls)	44 mg/kg No. of Survivors	88 mg/kg Av. Wt. (g)	88 mg/kg Wt. (% of controls)	88 mg/kg No. of Survivors
1	122	60[a,b]	122	100	60[a]	121	100	60[a]
2	140	60	138	99	60	139	99	60
3	149	60	146	98	60	147	99	60
4	159	60	157	99	60	155	98	60
5	166	60	164	99	60	161	97	60
6	170	60	167	98	60	167	98	60
7	176	60	172	98	60	170	97	60
8	180	60	178	99	60	175	97	60
9	185	60	183	99	60	180	97	60
10	189	60	186	98	60	184	97	60
11	189	60	188	99	60	185	98	60
12	191	60	186	97	60	185	97	60
13	193	60	191	99	59	190	98	60
17	205	60	202	98	59	199	97	60
21	213	60	207	97	59	206	97	60
25	215	59	208	97	56	208	96	59
29	226	59	218	96	56	215	95	59
33	233	59	228	98	56	226	97	59
37	241	59	233	97	56	231	96	59
41	245	59	236	96	56	234	96	58
45	249	59	239	96	55	238	96	57
49	258	58	250	97	55	247	96	57
53	266	57	256	96	55	256	96	57
57	274	57	262	96	55	258	94	56
61	279	56[b]	270	97	55	266	95	56
65	289	55	279	97	55	277	96	55
69[c]	295	45	288	98	45	282	96	44
73	301	44	297	99	45	291	97	43
77	312	44	306	98	45	296	95	40
81	314	44	310	99	44	302	96	37
85	315	43	308	98	43	300	95	34
89	314	42	309	98	41	299	95	27
93	322	39	311	97	40	303	94	26
97	320	39[b]	312	98	38	294	92	25
101	323	35	319	99	36	301	93	22
104	321	33	322	100	33	295	92	17
Terminal sacrifice		32		33				17
Mean for weeks								
1-13	170		168	99		166	98	
14-52	232		225	97		223	96	
53-104	303		296	98		287	95	

[a] Includes interim sacrifice animals
[b] The number of animals weighed for this week is less than the number of survivors.
[c] Interim sacrifice occurred



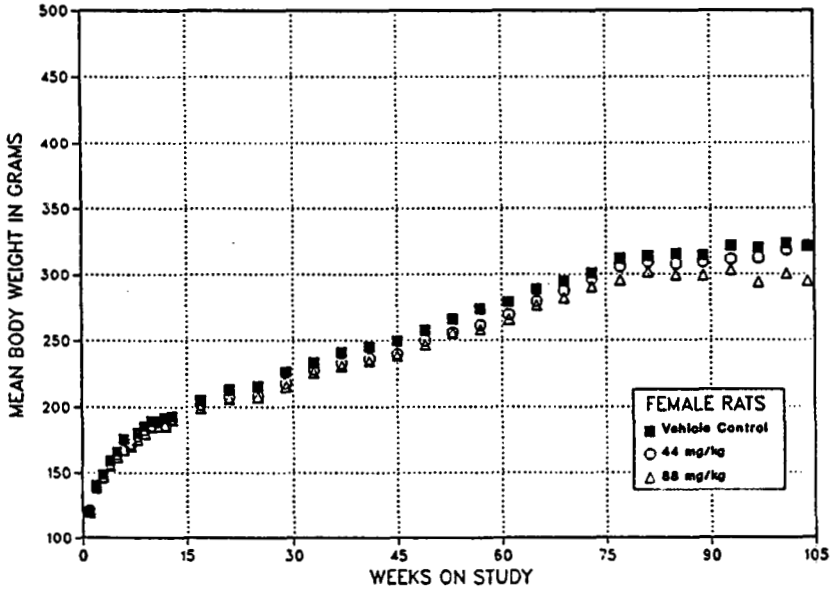


Figure 2
Growth Curves for Male and Female Rats Administered Tris(2-Chloroethyl) Phosphate by Gavage for 2 Years

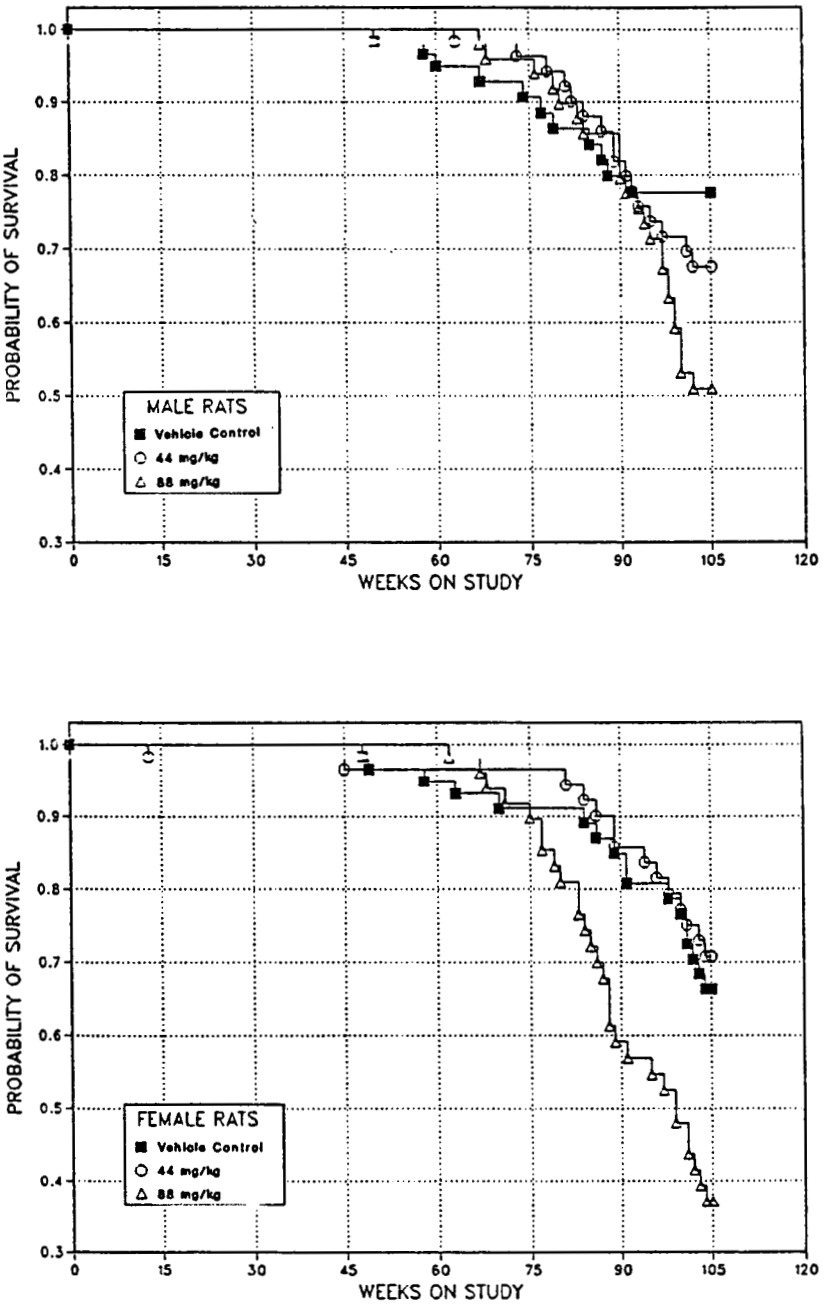


Figure 3
Kaplan-Meier Survival Curves for Male and Female Rats Administered Tris(2-Chloroethyl) Phosphate by Gavage for 2 Years

TABLE 6
Survival of Rats in the 2-Year Gavage Studies of Tris(2-Chloroethyl) Phosphate

	Vehicle Control	44 mg/kg	88 mg/kg
Male			
Animals initially in study	60	60	60
Natural deaths	6	9	10
Moribund kills	5	7	14
Gavage deaths	4	1	0
Accidents	0	0	1[a]
Interim sacrifices	9	10	10
Animals surviving to study termination	36	33	25
Percent survival at end of study[b]	78	68	51
Mean survival days[c]	631	647	639
Survival P values[d]	0.033	0.558	0.043
Female			
Animals initially in study	60	60	60
Natural deaths	9	4	7
Moribund kills	8	10	22
Gavage deaths	0	3	4
Accidents	1	0	1
Interim sacrifices	10	10	9
Animals surviving to study termination	32[e]	33	17
Percent survival at end of study	66	71	37
Mean survival days	635	622	593
Survival P values	0.005	0.731N	0.008

[a] One rat was not designated for 66-week interim sacrifice, but was inadvertently killed along with the predesignated animals.
[b] Kaplan-Meier determinations (survival rates adjusted for gavage deaths, accidents, and interim sacrifices)
[c] Mean of all deaths (uncensored, censored, terminal sacrifice)
[d] The first entry is the result of the trend test (Tarone, 1975). Subsequent entries are the results of pairwise tests (Cox, 1972). Negative trends are indicated by N.
[e] One of these animals was found dead on the day of terminal sacrifice.

cells, reactive gliosis, and endothelial hypertrophy and hyperplasia. Other observed lesions were considered incidental and unrelated to the administration of TRCP.

Pathology and Statistical Analysis of Results

Summaries of the incidence of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one dose group, and historical control incidence for the neoplasms mentioned in this section are presented in Appendix A for male rats and in Appendix B for female rats. The principal neoplastic and nonneoplastic effects associated with the administration of TRCP occurred in the kidney and brain of male and female rats. Other statistically significant or biologically noteworthy changes in the incidence of neoplastic or nonneoplastic lesions occurred in the thyroid gland, hematopoietic system, uterus, clitoral gland, and lung.

Kidney: Focal hyperplasia of the renal tubule epithelium and adenomas of the renal tubule were markedly increased in incidence, relative to controls, in male rats receiving 88 mg/kg TRCP; the incidence of renal tubule adenomas was also slightly increased in the 44 mg/kg group (Table 7). Carcinomas of the renal tubule occurred in one control and one high-dose male. Although the incidence of focal hyperplasia was markedly increased in female rats as well, adenomas occurred in fewer dosed females than males. Renal tubule neoplasms are rare in F344/N rats, particularly females, and have occurred in 12/2,142 (0.6%, range 0%-2%) male and 2/2,144 (0.1%, range: 0%-2%) female corn oil gavage historical controls. Thus, the increased incidence in dosed rats of each sex was considered biologically significant.

Hyperplasia of the renal tubule epithelium occurred in the convoluted tubules of the cortex. The lesions were focal or multifocal and were characterized by stratification of the epithelial cells with partial to complete obliteration of the tubule lumens (Figure 4a). The adenomas also occurred in the cortex and consisted of cells morphologically similar to those in the foci of hyperplasia. They were discrete solid masses of epithelial cells, generally five or more tubular cross sections in diameter (Figure 4b). The cells were often enlarged with abundant eosinophilic or amphophilic cytoplasm and prominent nuclei. . The carcinomas were large masses exhibiting greater cellular atypia and/or pleomorphism (Figure 4c).

Brain: Degenerative lesions associated with the administration of TRCP occurred in over 40% of female rats receiving 88 mg/kg (Table 8). Similar lesions occurred in a few male rats, but these lesions were not clearly chemical related. The degenerative lesions were located in the cerebral cortex and brain stem, involved both the gray matter and white matter, and were focal in distribution. The lesions were in the thalamus, hypothalamus, basal ganglia (especially the caudate nucleus and putamen), frontal cortex, and parietal cortex. Other affected structures included the cingulate cortex, olfactory cortex, superior colliculus, hippocampus, geniculate body, globus pallidus, ventral pallidum, and amygdaloid nuclear region. The lesions varied in severity from minimal to marked and often involved extensive areas. In some animals, the lesions were bilateral and symmetrical; in others, they were bilateral and asymmetrical or unilateral. The active lesions were characterized by degeneration and necrosis with hemorrhage, while resolving lesions exhibited loss of neurons and neuropil, proliferation of glial cells, capillary hyperplasia, hypertrophy of the tunica media of small vessels, and hemosiderin-laden macrophages (Figures 5a, 5b, and 5c). Deposits of mineral occurred in some of these foci.

Granular cell tumors occurred in the meninges of three high-dose male rats and two low-dose female rats. Granular cell tumors are uncommon in F344/N rats, occurring in 3/2,142 (0.1%, range 0%-4%) male and 6/2,145 (0.3%, range 0%-2%) female corn oil gavage historical controls. They are benign tumors believed to be derived from the meninges. Because of the low numbers and lack of a dose response in females, they were not considered to be related to the administration of TRCP.

Thyroid Gland: The incidence of follicular cell neoplasms of the thyroid gland was slightly increased in rats receiving TRCP (male rats: 1/50, 2/48, 5/50; female rats: 0/50, 3/50, 4/50) (Table 9). The neoplasms were not considered fatal, and many were observed in animals surviving to the end of the study. Logistic regression was thus considered the

TABLE 7
Kidney Lesions in Rats in the 2-Year Gavage Studies of Tris(2-Chloroethyl) Phosphate

	Vehicle Control	44 mg/kg	88 mg/kg
Male			
Renal Tubule: Hyperplasia			
Overall rates[a]	0/50 (0%)	2/50 (4%)	24/50 (48%)
Renal Tubule: Adenoma[b]			
Overall rates	1/50 (2%)	5/50 (10%)	24/50 (48%)
Terminal rates[c]	1/36 (3%)	5/33 (15%)	15/25 (60%)
First incidence (days)	729 (T)	729 (T)	575
Logistic regression tests[d]	P<0.001	P=0.083	P<0.001
Renal Tubule: Carcinoma			
Overall rates	1/50 (2%)	0/50 (0%)	1/50 (2%)
Renal Tubule: Adenoma or Carcinoma[e]			
Overall rates	2/50 (4%)	5/50 (10%)	25/50 (50%)
Terminal rates	2/36 (6%)	5/33 (15%)	16/25 (64%)
First incidence (days)	729 (T)	729 (T)	575
Logistic regression tests	P<0.001	P=0.181	P<0.001
Female			
Renal Tubule: Hyperplasia			
Overall rates	0/50 (0%)	3/50 (6%)	16/50 (32%)
Renal Tubule: Adenoma[f]			
Overall rates	0/50 (0%)	2/50 (4%)	5/50 (10%)
Terminal rates	0/32 (0%)	2/33 (6%)	5/17 (29%)
First incidence (days)		729 (T)	729 (T)
Logistic regression tests	P=0.001	P=0.245	P=0.003

(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals examined at site
[b] 2-year historical incidence for vehicle control groups in NTP corn oil gavage studies (mean ± standard deviation): 5/2,142 (0.2% ± 0.6%); range 0%-2%
[c] Observed 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 the pairwise comparisons between the controls and that dosed group.
[e] 2-year historical incidence of renal tubule adenoma or adenocarcinoma for vehicle control groups in NTP corn oil gavage studies (mean ± standard deviation): 12/2,142 (0.6% ± 0.9%); range 0%-2%
[f] 2-year historical incidence for vehicle control groups in NTP corn oil gavage studies (mean ± standard deviation): 1/2,144 (0.1% ± 0.3%); range 0%-2%

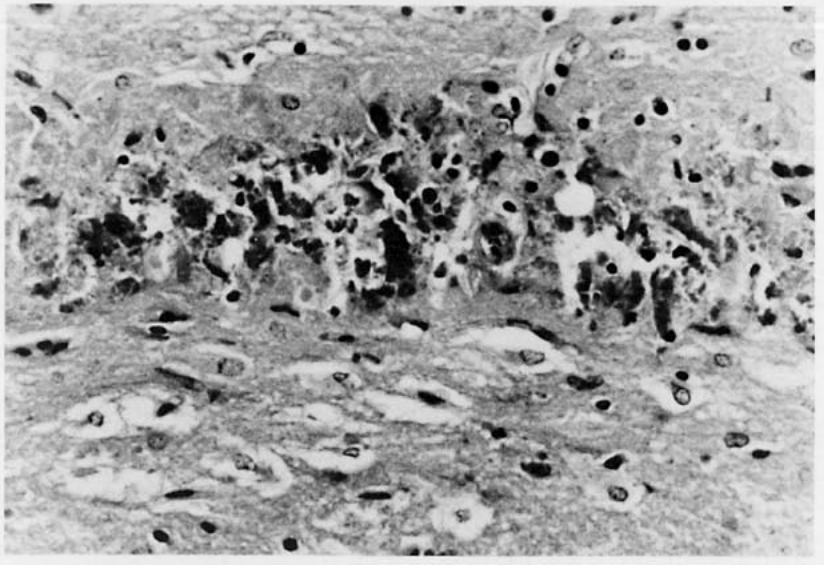


FIGURE 1. Necrosis of neurons in the pyramidal cell layer of the hippocampus in the brain of a female rat given 350 mg/kg tris(2-chloroethyl) phosphate for 16 weeks. (H&E, x300)

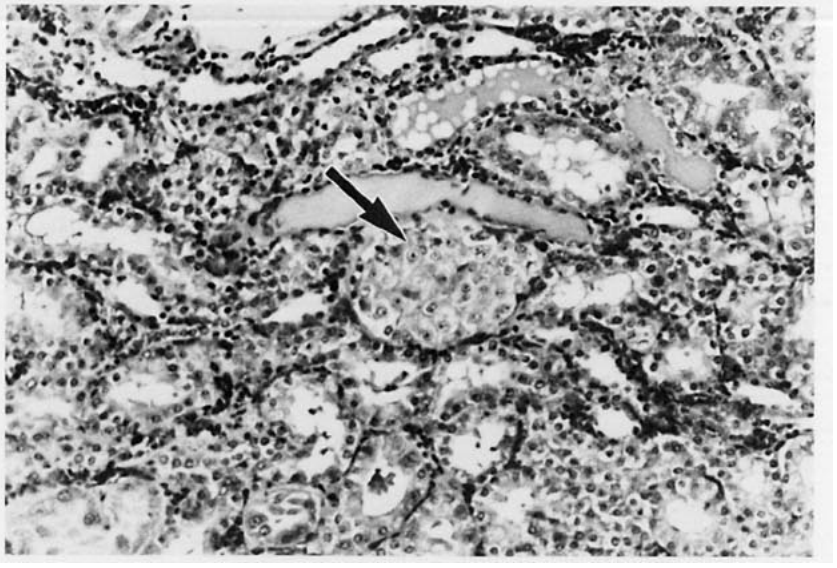


FIGURE 4a. Focal renal tubule hyperplasia (arrow) in the kidney of a male rat given 88 mg/kg tris(2-chloroethyl) phosphate for 2 years. (H&E, x150)

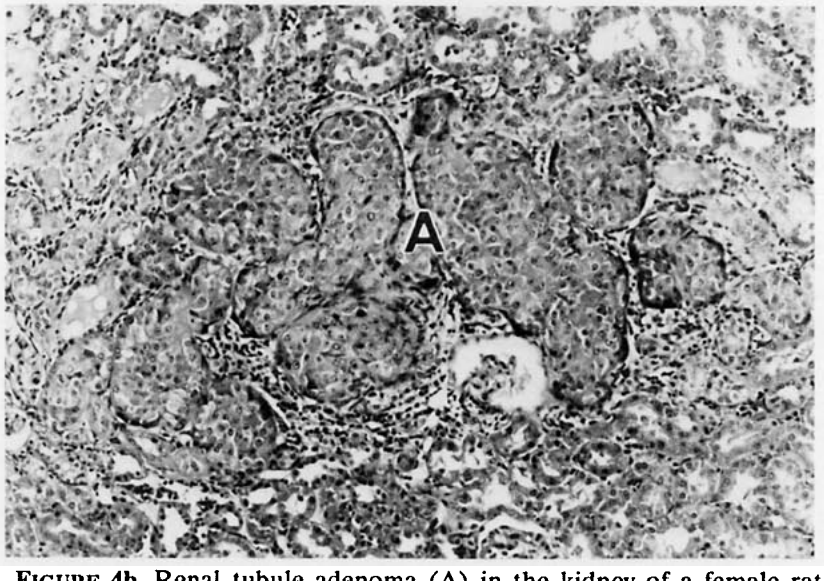


FIGURE 4b. Renal tubule adenoma (A) in the kidney of a female rat given 44 mg/kg tris(2-chloroethyl) phosphate for 2 years. (H&E, x100)

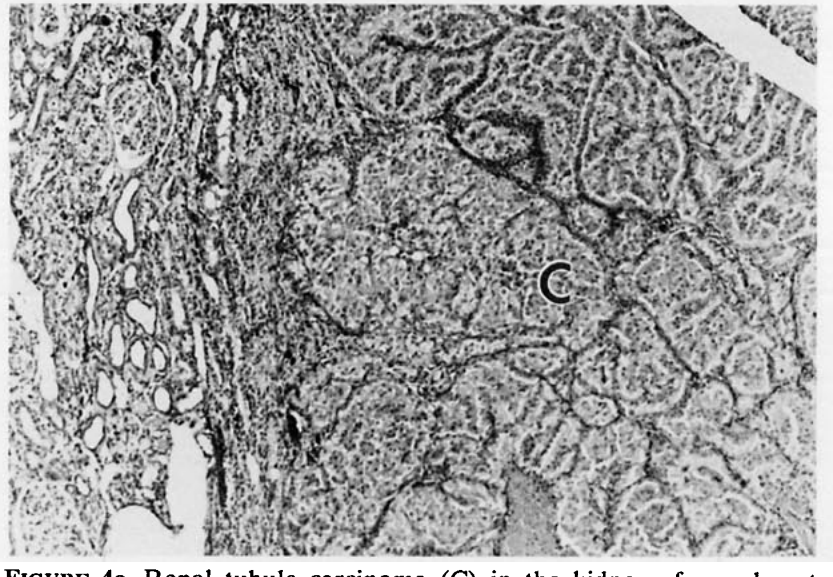


FIGURE 4c. Renal tubule carcinoma (C) in the kidney of a male rat given 88 mg/kg tris(2-chloroethyl) phosphate. (H&E, x60)

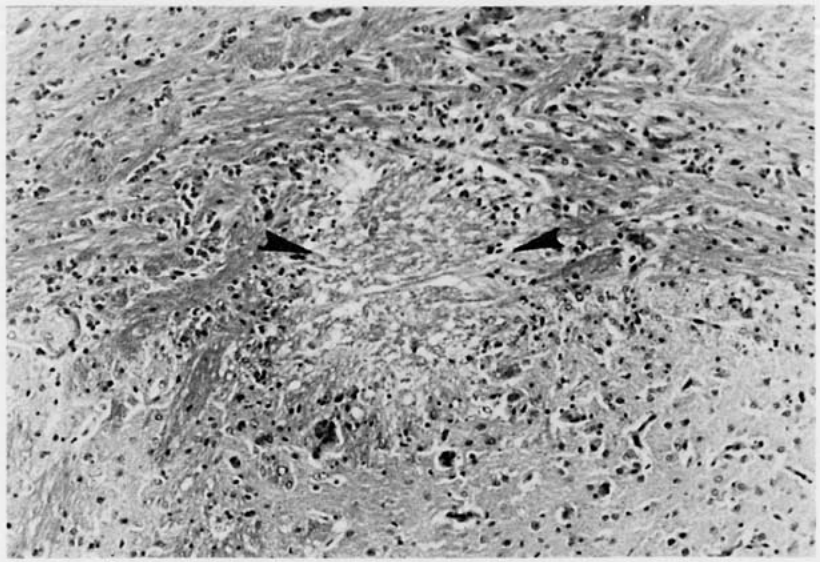


FIGURE 5a. Acute focal necrosis in the external capsule of the basal ganglia in the brain of a female rat given 88 mg/kg tris(2-chloroethyl) phosphate for 2 years. Note the pale area lacking visible cell nuclei between the arrows. (H&E, x100)

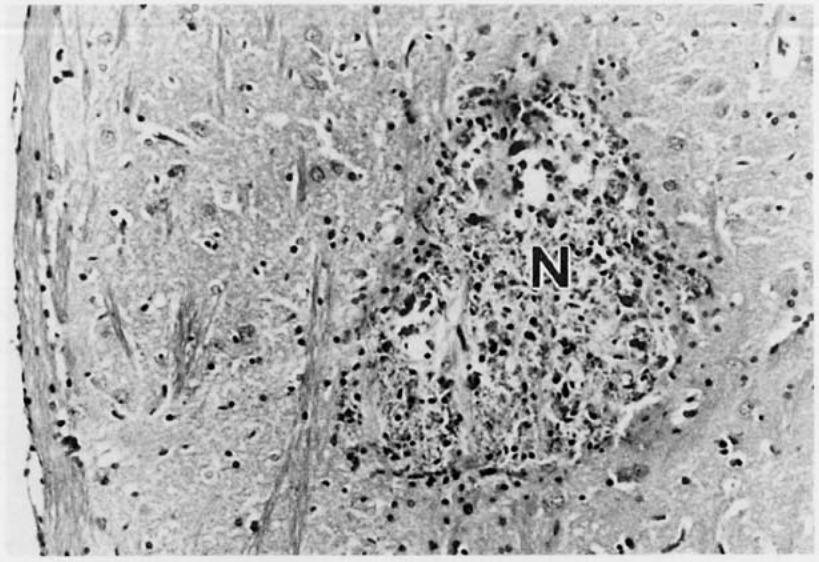


FIGURE 5b. Focal necrosis in the thalamus in the brain of a female rat given 88 mg/kg tris(2-chloroethyl) phosphate for 2 years. The lesion in this animal is of longer duration than that in Figure 5a. There is an infiltrate of phagocytic cells in the area of necrosis. (H&E, x150)

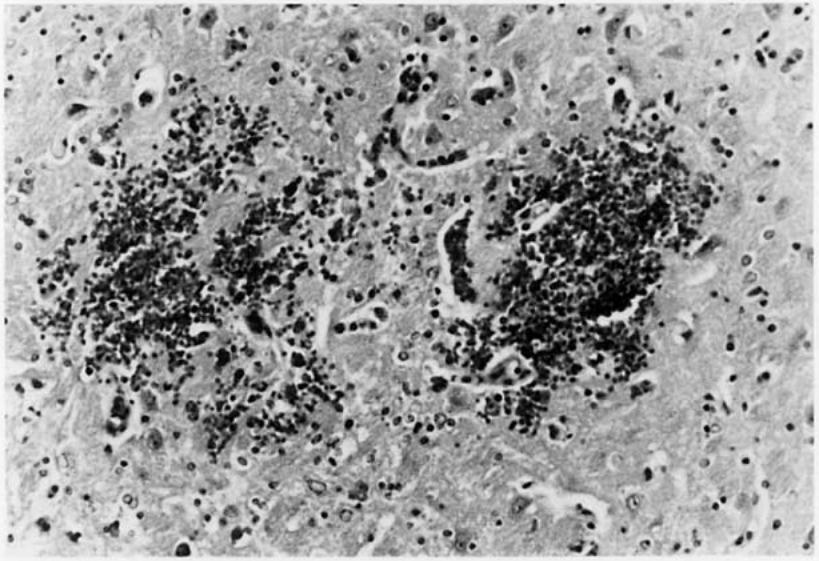


FIGURE 5c. Hemorrhage in the thalamus in the brain of a female rat given 88 mg/kg tris(2-chloroethyl) phosphate for 2 years. (H&E, x150)

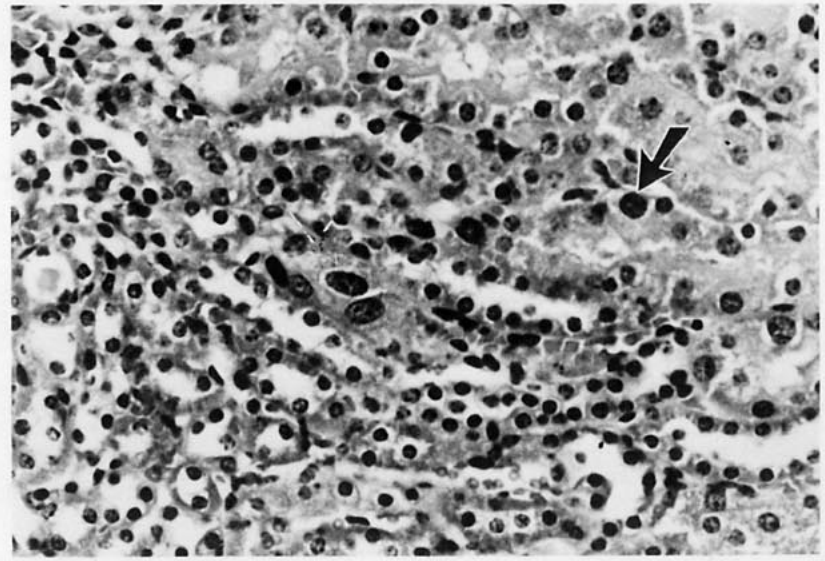


FIGURE 8. Karyomegaly (arrows) of individual cells in the kidney of a female mouse given tris(2-chloroethyl) phosphate for 2 years. (H&E, x300)

TABLE 8
Selected Brain Lesions in Rats in the 2-Year Gavage Studies of Tris(2-Chloroethyl) Phosphate

	Vehicle Control	44 mg/kg	88 mg/kg
Male (number examined)	50	49	50
Nonneoplastic lesions			
Brain stem, hemorrhage			1 (2%)
Brain stem, pigmentation, hemosiderin	1 (2%)		
Cerebrum, gliosis, focal			1 (2%)
Cerebrum, hemorrhage		1 (2%)	1 (2%)
Cerebrum, pigmentation, hemosiderin			1 (2%)
Pons, hemorrhage			3 (6%)
Neoplastic lesions			
Granular cell tumor benign			3 (6%)
Female (number examined)	50	50	50
Nonneoplastic lesions			
Brain stem, gliosis	1 (2%)		15 (30%)**
Brain stem, hemorrhage	1 (2%)		12 (24%)**
Brain stem, mineralization			7 (14%)**
Brain stem, necrosis			1 (2%)
Brain stem, pigmentation, hemosiderin	1 (2%)		17 (34%)**
Cerebrum, gliosis			19 (38%)**
Cerebrum, hemorrhage	1 (2%)		17 (34%)**
Cerebrum, mineralization			15 (30%)**
Cerebrum, pigmentation, hemosiderin			22 (44%)**
Pons, hemorrhage		1 (2%)	
Neoplastic lesions			
Cerebellum, meninges, granular cell tumor benign		2 (4%)	

** Significantly different ($P \leq 0.01$) from the control group by logistic regression tests

TABLE 9
Thyroid Gland Lesions in Rats in the 2-Year Gavage Studies of Tris(2-Chloroethyl) Phosphate

	Vehicle Control	44 mg/kg	88 mg/kg
Male			
Follicular Cell: Hyperplasia			
Overall rates[a]	0/50 (0%)	0/48 (0%)	0/50 (0%)
Follicular Cell: Adenoma[b]			
Overall rates	1/50 (2%)	2/48 (4%)	3/50 (6%)
Terminal rates[c]	1/36 (3%)	1/32 (3%)	2/25 (8%)
First Incidence (days)	729 (T)	574	674
Logistic regression tests[d]	P=0.224	P=0.487	P=0.279
Follicular Cell: Carcinoma			
Overall rates	0/50 (0%)	0/48 (0%)	2/50 (4%)
Terminal rates	0/36 (0%)	0/32 (0%)	1/25 (4%)
First Incidence (days)			696
Logistic regression tests	P=0.090	---	P=0.224
Follicular Cell: Adenoma or Carcinoma[e]			
Overall rates	1/50 (2%)	2/48 (4%)	5/50 (10%)
Terminal rates	1/36 (3%)	1/32 (3%)	3/25 (12%)
First Incidence (days)	729 (T)	574	674
Logistic regression tests	P=0.060	P=0.487	P=0.087
Female			
Follicular Cell: Hyperplasia			
Overall rates	1/50 (2%)	0/50 (0%)	1/50 (2%)
Follicular Cell: Adenoma			
Overall rates	0/50 (0%)	1/50 (2%)	1/50 (2%)
Follicular Cell: Carcinoma			
Overall rates	0/50 (0%)	2/50 (4%)	3/50 (6%)
Terminal rates	0/32 (0%)	2/33 (6%)	2/17 (12%)
First incidence (days)		729 (T)	718
Logistic regression tests	P=0.023	P=0.245	P=0.044
Follicular Cell: Adenoma or Carcinoma[f]			
Overall rates	0/50 (0%)	3/50 (6%)	4/50 (8%)
Terminal rates	0/32 (0%)	2/33 (6%)	3/17 (18%)
First incidence (days)		697	718
Logistic regression tests	P=0.011	P=0.120	P=0.014

(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals examined at site
[b] 2-year historical incidence for vehicle control groups in NTP corn oil gavage studies (mean ± standard deviation): 21/2,106 (1.0% ± 1.7%); range 0%-8%
[c] Observed 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 the pairwise comparisons between the controls and that dosed group.
[e] 2-year historical incidence for vehicle control groups in NTP corn oil gavage studies (mean ± standard deviation): 51/2,106 (2.4% ± 2.3%); range 0%-10%
[f] 2-year historical incidence for vehicle control groups in NTP corn oil gavage studies (mean ± standard deviation): 34/2,107 (1.6% ± 1.6%); range 0%-6%

most appropriate statistical analysis. There was a significant trend for follicular cell neoplasms in females, and the incidence in high-dose females was significantly greater than in controls. Furthermore, the combined incidence of follicular cell neoplasms in high-dose rats exceeded the upper rates for NTP historical controls (males 51/2,106, 2.4%, range 0%-10%; females 34/2,107, 1.6%, range 0%-6%). Although the incidence of follicular cell neoplasms in dosed male and female rats was only marginally increased and there was no supporting evidence of hyperplasia, these neoplasms may have been related to the administration of TRCP.

Hematopoietic System: The incidence of mononuclear cell leukemia was increased in both male and female rats receiving TRCP (male rats: 5/50, 14/50, 13/50; female rats: 14/50, 16/50, 20/50) (Table 10). Since mononuclear cell leukemia is a fatal neoplasm, the life table test was considered the most appropriate analysis. There were significant positive trends in both sexes, and the incidence in males receiving 44 or 88 mg/kg and females receiving 88 mg/kg was significantly greater than in their respective controls. Leukemia has occurred in 371/2,149 (17.3%, range 2%-44%) male and 422/2,150 (19.6%, range 4%-42%) female corn oil gavage historical controls. Thus, the incidence in dosed males and females in the TRCP studies was within the range of historical controls.

Uterus: Uterine stromal sarcomas occurred in three female rats receiving 88 mg/kg TRCP, but in no control or low-dose females. Although the trend test was significant (P=0.032), the incidence in the high-dose group was not significantly greater than in concurrent controls and not substantially different from the mean rate in corn oil gavage historical controls (44/2,132, 2.1%, range 0%-8%). Thus, the stromal sarcomas were not considered related to chemical administration.

Lung and Clitoral Gland: There was an increased incidence of nonneoplastic lesions in the lungs and clitoral glands of female rats; these lesions were not believed to be directly related to administration of TRCP. Focal hemorrhage in the lung was observed in 0/50 control, 3/50 low-dose, and 7/50 high-dose female rats. These were considered agonal lesions

TABLE 10
Mononuclear Cell Leukemia in Rats in the 2-Year Gavage Studies of Tris(2-Chloroethyl) Phosphate

	Vehicle Control	44 mg/kg	88 mg/kg
Male			
Mononuclear Cell Leukemia[a]			
Overall rates[b]	5/50 (10%)	14/50 (28%)	13/50 (26%)
Terminal rates[c]	3/36 (8%)	12/33 (36%)	6/25 (24%)
First incidence (days)	539	620	584
Life table tests[d]	P=0.010	P=0.017	P=0.018
Logistic regression tests[d]	P=0.033	P=0.025	P=0.035
Female			
Mononuclear Cell Leukemia[e]			
Overall rates	14/50 (28%)	16/50 (32%)	20/50 (40%)
Terminal rates	10/32 (31%)	8/33 (24%)	7/17 (41%)
First incidence (days)	335	561	469
Life table tests	P=0.006	P=0.441	P=0.006
Logistic regression tests	P=0.076	P=0.399	P=0.093

[a] 2-year historical incidence for vehicle control groups in NTP corn oil gavage studies (mean ± standard deviation): 321/2,149 (14.9% ± 10.8%); range 0%-44%
[b] Number of tumor-bearing animals/number of animals examined at site
[c] Observed 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 the pairwise comparisons between the controls and that dosed group.
[e] 2-year historical incidence for vehicle control groups in NTP corn oil gavage studies (mean ± standard deviation): 329/2,150 (15.3% ± 10.6%); range 0%-33%

associated with cardiovascular collapse in animals dying of toxicity or neoplasia. Ectasia of the ducts of the clitoral gland was observed in 1/34 control, 4/35 low-dose, and 7/32 high-dose females; this slight increase was attributed to normal biological variation.

MICE

16-Day Studies

Groups of five B6C3F$_1$ mice of each sex received 0, 44, 88, 175, 350, or 700 mg/kg TRCP in corn oil by gavage 5 days per week for 12 doses over 16 days. Gavage trauma accounted for the deaths of three mice before the end of the studies; there were no chemical-related deaths (Table 11). Mice given 350 or 700 mg/kg TRCP exhibited ataxia and convulsive movements during the first 3 days of dosing. Group mean body weights of male and female mice were similar to control values at the end of the studies (Table 11).

Weights of brain, heart, lung, liver, right kidney, and thymus were obtained at necropsy for all mice surviving until scheduled sacrifice. Group mean organ weights and organ-weight-to-body-weight ratios are given in Appendix E, Tables E7 and E8. There were no chemical-related changes in absolute or relative organ weights.

Cholinesterase activity was determined on fresh sera collected at necropsy, and although there was considerable variation in the values obtained, none was considered chemical related (Appendix G, Table G3). Gross or microscopic lesions attributable to the administration of TRCP were not observed.

16-Week Studies

Groups of ten B6C3F$_1$ mice of each sex were given 0, 44, 88, 175, 350, or 700 mg/kg TRCP in corn oil by gavage 5 days per week for 16 weeks. During week 4 of the studies, the two most concentrated dosing solutions were incorrectly prepared, and for the first 3 days of week 4, the mice in the two highest dose groups received double the target levels (the 350 mg/kg group received 700 mg/kg and the 700 mg/kg group received 1,400 mg/kg). There were no chemical-related deaths, although gavage trauma caused the deaths of three male and two female mice before the end of the studies (Table 12). Weight gain and group mean body weights at the end of the studies were similar among dosed and control mice. Cholinesterase activity determined on fresh sera collected at necropsy was similar among dosed and control mice (Appendix G, Table G4).

The mean absolute and/or relative liver weights were significantly increased in females receiving 175 to 700 mg/kg and in males receiving 700 mg/kg (Appendix E, Tables E9 and E10). These increases were considered to be chemical related. The absolute and relative testis weights of high-dose males were decreased relative to those of control males ($P \leq 0.01$). Male mice receiving 175 to 700 mg/kg had significantly reduced relative kidney weights ($P \leq 0.01$), but the mean absolute kidney weight was significantly reduced in high-dose males only.

Although necropsy examination showed no gross lesions attributable to chemical administration, epithelial cells with enlarged nuclei (cytomegaly and karyomegaly) were observed in the renal tubules in all male and female mice receiving 700 mg/kg TRCP. These lesions were observed primarily in the proximal convoluted tubules of the inner cortex and outer stripe of the outer medulla and, to a lesser extent, in the straight portion of the loops of Henle in the outer medulla.

Dose Selection Rationale for the 2-Year Studies

Doses selected for the chronic studies in mice were 175 and 350 mg/kg TRCP because of the renal lesions and significantly reduced mean absolute and relative kidney weights in mice receiving 700 mg/kg.

2-Year Studies

Body Weights and Clinical Signs

Group mean body weights and mean body weights relative to control values are presented by week on study in Tables 13 and 14. Growth curves, plotting mean body weights against week on test, are shown in Figure 6. Body weights of mice receiving TRCP were not significantly different from those of controls, and there were no clinical signs of toxicity in mice.

Survival

Estimates of the probability of survival of male and female mice administered TRCP in corn oil at the

Table 11
Survival and Mean Body Weights of Mice in the 16-Day Gavage Studies of Tris(2-Chloroethyl) Phosphate

Dose (mg/kg)	Survival[a]	Mean Body Weights (g)			Final Weight Relative to Controls (%)
		Initial[b]	Final	Change[c]	
Male					
0	5/5	24.7 ± 0.6	23.9 ± 0.6	–0.8 ± 0.3	
44	5/5	25.4 ± 0.6	24.6 ± 0.5	–0.7 ± 0.4	103
88	5/5	24.8 ± 0.7	24.9 ± 0.9	0.1 ± 0.4	104
175	4/5[d]	25.2 ± 0.4	25.2 ± 0.9	0.2 ± 0.6	106
350	4/5[e]	24.7 ± 0.2	24.5 ± 0.3	–0.2 ± 0.2	102
700	5/5	24.5 ± 0.6	25.1 ± 0.4	0.6 ± 0.2*	105
Female					
0	5/5	17.9 ± 0.3	21.3 ± 0.5	3.4 ± 0.4	
44	5/5	20.8 ± 0.4**	21.3 ± 0.3	0.6 ± 0.2**	100
88	5/5	21.4 ± 0.3**	22.0 ± 0.5	0.6 ± 0.4**	103
175	5/5	20.0 ± 0.5*	21.6 ± 0.7	1.6 ± 0.4*	102
350	5/5	21.0 ± 0.3**	22.1 ± 0.4	1.1 ± 0.4*	104
700	4/5[f]	20.6 ± 0.2*	20.9 ± 0.4	0.3 ± 0.6**	98

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Number surviving/number initially in group
[b] Initial group mean body weight given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.
[c] Mean body weight change of the survivors given as mean ± standard error
[d] Day of death: 15
[e] Day of death: 11
[f] Day of death: 14

TABLE 12
Survival and Mean Body Weights of Mice in the 16-Week Gavage Studies of Tris(2-Chloroethyl) Phosphate

Dose (mg/kg)	Survival[a]	Mean Body Weights (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	24.1 ± 0.3	34.3 ± 0.7	10.2 ± 0.8	
44	10/10	24.7 ± 0.2	34.6 ± 0.7	9.9 ± 0.7	101
88	10/10	24.4 ± 0.3	35.5 ± 0.8	11.2 ± 0.7	104
175	9/10[d]	25.2 ± 0.4	37.5 ± 1.1	12.3 ± 1.2	109
350	9/10[e]	24.9 ± 0.4	36.7 ± 1.0	11.8 ± 0.8	107
700	9/10[f]	24.6 ± 0.2	32.1 ± 1.0	7.5 ± 0.9	94
Female					
0	10/10	19.3 ± 0.2	25.8 ± 0.2	6.5 ± 0.1	
44	10/10	19.4 ± 0.4	26.8 ± 0.6	7.4 ± 0.3	104
88	10/10	19.3 ± 0.3	27.2 ± 0.7	8.0 ± 0.5	106
175	9/10[g]	19.3 ± 0.3	26.5 ± 0.5	7.2 ± 0.4	103
350	9/10[h]	19.3 ± 0.4	26.6 ± 0.5	7.3 ± 0.3	103
700	10/10	18.9 ± 0.3	25.6 ± 0.6	6.8 ± 0.4	99

[a] Number surviving/number initially in group
[b] Initial group mean body weight given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study. Differences from the control group are not significant by Dunn's or Shirley's test.
[c] Mean body weight change of the survivors given as mean ± standard error
[d] Week of death: 15
[e] Week of death: 11
[f] Week of death: 14
[g] Week of death: 2
[h] Week of death: 1

TABLE 13
Mean Body Weights and Survival of Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate

Weeks on Study	Vehicle Control Av. Wt. (g)	Vehicle Control No. of Survivors	175 mg/kg Av. Wt. (g)	175 mg/kg Wt. (% of controls)	175 mg/kg No. of Survivors	350 mg/kg Av. Wt. (g)	350 mg/kg Wt. (% of controls)	350 mg/kg No. of Survivors
1	25.0	60[a]	25.8	103	60[a]	26.0	104	60[a]
2	28.0	60	28.2	101	59	27.6	99	60
3	29.5	60	29.9	101	59	30.2	102	60
4	30.6	59	31.0	101	59	30.8	101	60
5	31.6	59	31.6	100	59[b]	—[c]	—[c]	—[c]
6	32.1	59	32.7	102	59	32.3	101	60
7	32.5	59	33.1	102	59	32.7	101	60
9	34.4	59	34.7	101	59	34.7	101	60
10	36.0	59	35.9	100	59	35.3	98	59
11	35.5	59	34.6	98	59	35.3	99	59
12	36.9	59	36.9	100	59	36.4	99	59
13	37.6	59	37.3	99	59	37.0	98	59
17	39.9	59	39.9	100	59	39.1	98	58
21	41.7	59	41.7	100	59[b]	41.6	99	55
25	43.5	59	43.6	100	59	42.8	100	55
29	46.2	59	46.7	101	59	46.0	100	55
33	48.0	59	48.2	100	59	46.1	96	55
37	49.9	58	50.1	100	59	48.1	96	55
41	50.4	58	50.8	101	59	49.8	99	55
45	49.9	55	50.2	101	57	50.2	101	54
49	50.3	55	50.7	101	57	50.8	101	54
53	51.3	55	51.0	99	57	51.0	99	54
57	51.7	55	51.4	99	56	50.7	98	54
61	51.6	55	51.6	100	56	51.0	99	54
65	52.3	54	50.9	97	56	51.2	98	54
69[d]	51.5	45	51.6	100	46	50.2	98	45
73	51.5	44	52.0	101	45	51.6	100	45
77	51.5	44	51.1	99	44	51.1	99	44
81	50.8	44	50.8	100	44	49.4	97	44
85	51.1	44	50.7	99	43	49.0	96	42
89	50.3	44	49.1	98	43	49.7	99	40
93	49.2	39	48.5	99	38	49.0	100	37
97	47.7	32	48.9	103	30	49.0	103	32
101	46.9	27	47.9	102	27	47.4	101	29
104	44.1	25	45.5	103	25	44.8	102	25
Terminal sacrifice		25			25			25
Mean for weeks								
1-13	32.5		32.6	100		32.6	100	
17-65	48.2		48.2	100		47.6	99	
69-104	49.5		49.6	100		49.1	99	

[a] Includes interim sacrifice animals
[b] The number of animals weighed for this week is less than the number of animals surviving.
[c] No weights recorded.
[d] Interim sacrifice occurred

TABLE 14
Mean Body Weights and Survival of Female Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate

Weeks on Study	Vehicle Control Av. Wt. (g)	Vehicle Control No. of Survivors	175 mg/kg Av. Wt. (g)	175 mg/kg Wt. (% of controls)	175 mg/kg No. of Survivors	350 mg/kg Av. Wt. (g)	350 mg/kg Wt. (% of controls)	350 mg/kg No. of Survivors
1	19.9	60[a]	19.7	99	60[a]	19.6	99	60[a]
2	21.2	60	21.9	103	60	21.6	102	60
3	22.7	60	22.9	101	60	23.0	101	60
4	23.3	60	23.9	103	60	24.0	103	60[b]
5	23.7	60	24.1	102	60	23.9	101	60
6	24.2	60	24.5	101	60	24.6	102	60
7	24.5	60	25.0	102	60	24.8	101	60
9	25.3	60	26.2	104	60	25.7	102	60
10	26.0	60	26.1	100	60	26.3	101	60
11	25.8	60	25.7	100	60	26.1	101	59
12	26.6	60	26.4	99	60	26.5	100	59
13	26.5	60[b]	27.0	102	60	26.9	102	59
17	27.8	60	28.4	102	60	28.1	101	59
21	29.3	60	29.6	101	60	29.9	102	59
25	31.6	60	31.0	98	60	31.3	99	59
29	32.1	60	33.3	104	60	34.0	106	59
33	33.9	60	34.0	100	60	34.5	102	59
37	34.6	59	35.9	104	60	36.3	105	59
41	36.6	59	36.8	101	60	36.9	101	59
45	37.4	55	40.0	107	60	39.6	106	59
49	39.3	55	41.1	105	59	41.3	105	59
53	40.5	53	42.7	105	59	43.2	107	59
57	39.9	53	41.9	105	59	43.0	108	59
61	40.0	52	42.7	107	59	42.9	107	59
65	40.1	52	43.3	108	59	42.3	106	59
69[c]	41.0	42	43.3	106	49	43.8	107	49
73	42.6	42	45.1	106	49	45.7	107	47
77	42.4	42	45.4	107	49	46.2	109	46
81	42.3	39	45.4	107	49	45.5	108	45
85	43.9	39	46.2	105	49	46.0	105	44
89	45.2	38	46.8	104	48	46.7	103	44
93	44.9	36	46.9	105	45	46.5	104	43
97	44.4	34	47.6	107	39	45.8	101	41
101	44.6	33	47.1	106	37	45.5	102	37
104	44.1	31	45.8	104	37	43.8	99	35
Terminal sacrifice		31			37			35
Mean for weeks								
1-14	24.3		24.5	101		24.4	100	
17-65	35.6		37.0	104		37.2	104	
69-104	43.5		46.0	106		45.6	105	

[a] Includes interim sacrifice animals
[b] The number of animals weighed for this week is less than the number of animals surviving.
[c] Interim sacrifice occurred.

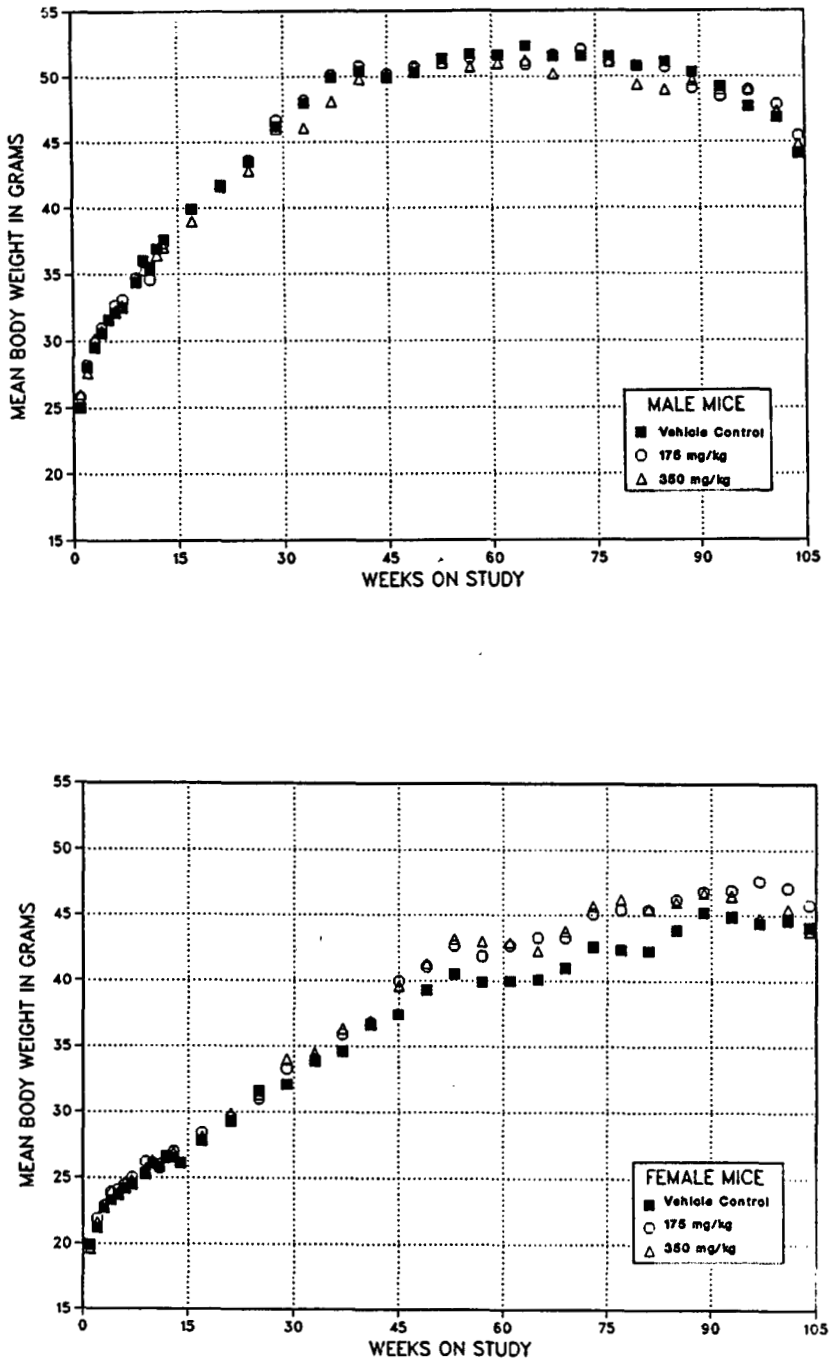


Figure 6
Growth Curves for Male and Female Mice Administered Tris(2-Chloroethyl) Phosphate by Gavage for 2 Years

doses used in these studies and for vehicle controls are shown in the Kaplan-Meier curves in Figure 7. The numbers of mice dying early or surviving to the end of the studies are given in Table 15. There were no significant differences in survival between dosed and control groups of either sex.

66-Week Interim Evaluations

Ten male and ten female mice in each dose group were predesignated for interim evaluation at 66 weeks. Of the predesignated mice, two control and two high-dose males died before week 66 (controls, weeks 43 and 64; 350 mg/kg group, weeks 17 and 18). One control female died in week 43.

There were no alterations in hematology or clinical chemistry that were judged to be related to administration of TRCP. Adenomas of the harderian gland were seen in two high-dose females and a carcinoma was observed in a third; none occurred in control or low-dose female mice. Other lesions observed showed no potentially chemical-related trends or effects and were considered incidental.

Pathology and Statistical Analysis of Results

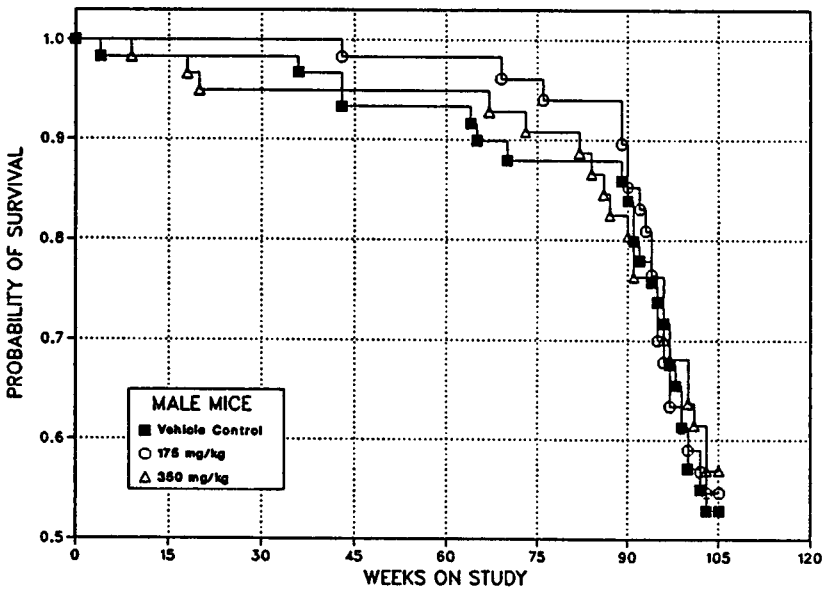
Summaries of the incidence of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one dose group, and historical control incidence for the neoplasms mentioned in this section are presented in Appendix C for male mice and in Appendix D for female mice. The principal nonneoplastic effects associated with the administration of TRCP occurred in the kidney of mice and are described below. Other statistically significant or biologically noteworthy changes in the incidence of neoplastic or nonneoplastic lesions occurred in the liver and mammary gland of mice.

Kidney: Single sections of the left and right kidneys were initially examined microscopically at the laboratory conducting the study. Karyomegaly (nuclear enlargement) was observed in the kidneys of approximately 80% of mice receiving 350 mg/kg TRCP and less frequently in mice receiving 175 mg/kg (Table 16). The affected cells were in the proximal convoluted tubules of the inner cortex and outer stripe of the outer medulla and, to a lesser extent, in the pars recta of the loops of Henle in the outer medulla. The lesion was minimal in most mice and consisted of only a few widely scattered tubule epithelial cells with enlarged hyperchromatic single nuclei (Figure 8). Adenomas of the renal tubule were observed in one control male, one high-dose male, and one low-dose female, and a carcinoma was seen in a second high-dose male. Further, focal hyperplasia was seen in a high-dose male mouse.

Because of the rare spontaneous occurrence of renal tubule neoplasms in male B6C3F$_1$ mice (historical vehicle controls: 8/2,183, 0.4%), the remaining portions of left and right kidney were embedded in paraffin and sectioned to produce approximately 4 to 6 additional H&E-stained sections per mouse for microscopic examination. The results of this evaluation and the composite results of these step sections and original section combined are also shown in Table 16. In the step sections of kidneys, focal hyperplasia was identified in two 350 mg/kg males at the 66-week interim sacrifice. Focal hyperplasia was also identified in one control and two 350 mg/kg males, one 175 mg/kg female, and two 350 mg/kg female mice. Renal tubule adenomas were seen in one 175 mg/kg male and two 350 mg/kg male mice. Thus, the incidence of renal tubule neoplasms in original and step sections combined was 1/50, 1/50, and 4/50.

Liver: The incidence of eosinophilic foci in the liver was increased in high-dose males (Table 17), although the incidence of basophilic or clear cell foci were not. Eosinophilic, basophilic, and clear cell foci comprise a morphological continuum with hepatocellular adenoma and are believed to be precursors of hepatocellular neoplasms. They are distinguished from adenomas primarily on the basis of size, degree of compression of surrounding parenchyma, and degree of distortion or loss of normal lobular architecture. There was a significant positive trend for hepatocellular adenoma in mice (P=0.045), but the incidence of adenoma and adenoma or carcinoma combined in the dosed groups was not significantly greater than that in controls. Thus, it is uncertain if the increase in eosinophilic foci in male mice is related to the administration of TRCP.

Harderian Gland: Female mice receiving TRCP demonstrated a marginally increased incidence of neoplasms (primarily adenomas) of the harderian gland, which is in the orbit posterior to the eye



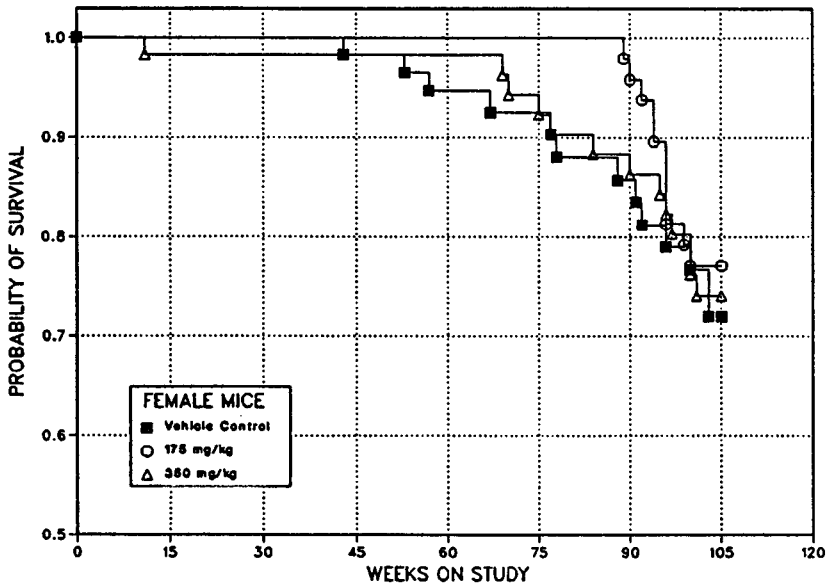


Figure 7
Kaplan-Meier Survival Curves for Male and Female Mice Administered Tris(2-Chloroethyl) Phosphate by Gavage for 2 Years

TABLE 15
Survival of Mice in the 2-Year Gavage Studies of Tris(2-Chloroethyl) Phosphate

	Vehicle Control	175 mg/kg	350 mg/kg
Male			
Animals initially in study	60	60	60
Natural deaths	14	13	9
Moribund kills	10	8	12
Gavage deaths	3	4	5
Missing	0	0	1
Interim sacrifices	8	10	8
Animals surviving to study termination	25	25	25
Percent survival at end of study[a]	53	55	57
Mean survival days[b]	619	621	604
Survival P values[c]	0.745N	0.883N	0.792N
Female			
Animals initially in study	60	60	60
Natural deaths	6	6	8
Moribund kills	7	5	5
Gavage deaths	6	2	2
Accidents	1	0	0
Interim sacrifices	9	10	10
Animals surviving to study termination	31	37	35
Percent survival at end of study	72	77	74
Mean survival days	612	663	649
Survival P values	0.826N	0.551N	0.915N

[a] Kaplan-Meier determinations (survival rates adjusted for gavage deaths, accidents, and interim sacrifices)
[b] Mean of all deaths (uncensored, censored, terminal sacrifice)
[c] The first entry is the result of the trend test (Tarone, 1975). Subsequent entries are the results of pairwise tests (Cox, 1972). Negative trends are indicated by N.

TABLE 16
Selected Renal Tubule Cell Lesions in Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate

	Vehicle Control	175 mg/kg	350 mg/kg
Original Sections			
Male			
Karyomegaly	2/50	16/50**	39/50**
Hyperplasia[a]	0/50	0/50	1/50
Adenoma	1/50	0/50	1/50
Adenocarcinoma	0/50	0/50	1/50
Female			
Karyomegaly	0/50	5/49*	44/50**
Adenoma	0/50	1/49	0/50
Step Sections			
Male			
Hyperplasia[a]	1/50	0/50	2/50
Adenoma	0/50	1/50	2/50
Female			
Hyperplasia	0/50	1/49	2/50
Adenoma	0/50	0/49	0/50
Original and Step Sections Combined			
Male			
Hyperplasia[a]	1/50	0/50	3/50
Adenoma	1/50	1/50	3/50
Adenocarcinoma	0/50	0/50	1/50
Female			
Hyperplasia	0/50	1/49	2/50
Adenoma	0/50	1/49	0/50

* Significantly different ($P \leq 0.05$) from the control group by logistic regression tests
** $P \leq 0.01$
[a] Hyperplasia was also present in two 350 mg/kg males at the 66-week interim sacrifice. One 350 mg/kg male had both hyperplasia and adenoma.

TABLE 17
Selected Liver Lesions in Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate

	Vehicle Control	175 mg/kg	350 mg/kg
Basophilic Focus			
Overall rates[a]	1/50 (2%)	2/50 (4%)	1/50 (2%)
Clear Cell Focus			
Overall rates	4/50 (8%)	1/50 (2%)	5/50 (10%)
Eosinophilic Focus			
Overall rates	0/50 (0%)	3/50 (6%)	8/50 (16%)
Hepatocellular Adenoma			
Overall rates	20/50 (40%)	18/50 (36%)	28/50 (56%)
Terminal rates[b]	12/25 (48%)	10/25 (40%)	18/25 (18%)
First incidence (days)	636	623	571
Logistic regression tests[c]	P=0.045	P=0.450N	P=0.055
Hepatocellular Carcinoma			
Overall rates	10/50 (20%)	10/50 (20%)	10/50 (20%)
Terminal rates	2/25 (8%)	4/25 (16%)	4/25 (16%)
First incidence (days)	620	532	469
Logistic regression tests	P=0.548	P=0.598	P=0.598
Hepatocellular Adenoma or Carcinoma[d]			
Overall rates	26/50 (52%)	27/50 (54%)	33/50 (66%)
Terminal rates	13/25 (52%)	13/25 (52%)	18/25 (72%)
First incidence (days)	620	532	469
Logistic regression tests	P=0.073	P=0.488	P=0.087

[a] Number of tumor-bearing animals/number of animals examined at site
[b] Observed incidence at terminal kill
[c] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to the pairwise comparisons between the controls and that dosed group.
[d] 2-year historical incidence for vehicle control groups in NTP corn oil gavage studies (mean ± standard deviation): 8/2,183 (0.4% ± 0.7%); range 0%-2%

(adenoma or carcinoma: 3/50, 8/50, 7/50) (Table 18). The incidence of focal hyperplasia of the harderian gland was also slightly increased in the low-dose group. Although the incidence of neoplasms in the dosed groups was not significantly greater than in controls, the marginal increase is notable because of the findings at the 66-week interim evaluation. If the incidence rates for the interim sacrifice groups and 2-year animals are combined, there is a significant trend, and the incidence in the high-dose group is significantly greater than that in controls (adenoma or carcinoma: 3/59, 8/60, 10/60).

Mammary Gland: Adenocarcinomas of the mammary gland occurred in three high-dose female mice with a marginally significant positive trend (logistic regression, P=0.042). However, a fibroadenoma occurred in a single control female mouse, and the trend test for fibroadenoma or adenocarcinoma combined was not significant. Moreover, the incidence of adenocarcinomas in this study falls well within the range of mammary gland neoplasms in NTP female historical vehicle controls (36/2,193, 1.6%, range 0%-10%). Thus, the mammary gland adenocarcinomas are not considered to be related to chemical administration.

Miscellaneous: Vascular neoplasms (hemangioma or hemangiosarcoma combined, all sites) occurred in control and low-dose male mice but not in the high-dose group (controls, 6/50; 175 mg/kg, 6/50; 350 mg/kg, 0/50). Similarly, malignant lymphomas occurred with a significant negative trend in female mice; the incidence in the high-dose group was significantly less than that in controls (controls, 10/50; 175 mg/kg, 7/50; 350 mg/kg, 3/50). The decreased incidence of these neoplasms was not considered related to chemical administration.

GENETIC TOXICOLOGY

Data for all three measures of genetic toxicity are presented in Appendix F. TRCP was not mutagenic when tested up to toxic levels in *Salmonella typhimurium* strains TA100, TA1535, TA1537, and TA98 in a preincubation protocol with or without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Haworth *et al.* 1983). In cytogenetic tests with Chinese hamster ovary (CHO) cells, TRCP did not induce a significant increase in chromosomal aberrations in either the presence or the absence of S9 (Galloway *et al.*, 1987). Results of the CHO cell sister chromatid exchange (SCE) test were equivocal (Galloway *et al.*, 1987). No increase in SCE was observed without S9; in the presence of S9, one trial showed a significant response at the two highest doses tested, but the second trial, conducted up to the same maximum concentration, was negative.

TABLE 18
Selected Lesions of the Harderian Gland in Female Mice from the 66-Week Interim Evaluation and 104-Week Terminal Evaluation during the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate

	Vehicle Control	175 mg/kg	350 mg/kg
Focal Hyperplasia			
66-Week[a]			
Overall rates[b]	0/9 (0%)	0/10 (0%)	0/10 (0%)
2-Year			
Overall rates	1/49 (2%)	4/49 (8%)	2/49 (4%)
Combined			
Overall rates	1/58 (2%)	4/59 (7%)	2/59 (3%)
Adenoma			
66-Week			
Overall rates	0/9 (0%)	0/10 (0%)	2/10 (20%)
2-Year			
Overall rates	3/50 (6%)	7/50 (14%)	7/50 (14%)
Adjusted rates[c]	9.7%	18.1%	19.2%
Terminal rates[d]	3/31 (10%)	6/37 (16%)	6/35 (17%)
First incidence (days)	729 (T)	658	676
Logistic regression tests[e]	P=0.184	P=0.232	P=0.214
Combined			
Overall rates	3/59 (5%)	7/60 (12%)	9/60 (15%)
Logistic regression tests	P=0.070	P=0.230	P=0.085
Adenoma or Carcinoma			
66-Week			
Overall rates	0/9 (0%)	0/10 (0%)	3/10 (30%)
2-Year			
Overall rates	3/50 (6%)	8/50 (16%)	7/50 (14%)
Adjusted rates	9.7%	20.8%	19.2%
Terminal rates	3/31 (10%)	7/37 (19%)	6/35 (17%)
First incidence (days)	729 (T)	658	676
Logistic regression tests	P=0.193	P=0.157	P=0.214
Combined			
Overall rates	3/59 (5%)	8/60 (13%)	10/60 (17%)
Logistic regression tests	P=0.044	P=0.156	P=0.049

(T)Terminal sacrifice
[a] Statistical calculations were not performed on 66-week data.
[b] Number of tumor-bearing animals/number of animals examined at site
[c] Kaplan-Meier estimated lifetime tumor incidence after adjustment for intercurrent mortality.
[d] Observed incidence at terminal kill
[e] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to the pairwise comparisons between the controls and that dosed group.

DISCUSSION AND CONCLUSIONS

Tris(2-chloroethyl) phosphate (TRCP) was studied as a part of a class study of trisalkyl phosphate flame retardants. Others in this class studied by the NTP are tris(2,3-dibromopropyl) phosphate (TBP) and tris(2-ethylhexyl) phosphate (TEHP). TBP was a carcinogen for both sexes of rats and mice, causing kidney tumors in rats, tumors of the kidney, lung, and stomach in male mice, and tumors of the liver, lung, and stomach in female mice (NCI, 1978a). For TEHP, the NTP found equivocal evidence of carcinogenicity in male rats based on an increase in adrenal pheochromocytomas and some evidence of carcinogenicity for female mice based on an increase in hepatocellular carcinomas (NTP, 1984). The potential toxicity and carcinogenicity of TRCP were evaluated by administering the chemical by gavage to F344/N rats and $B6C3F_1$ mice in 16-day, 16-week or 18-week, and 2-year studies. In the 16-day studies no mortality occurred in groups of rats given TRCP in doses ranging from 22 to 350 mg/kg or in groups of mice given doses from 44 to 700 mg/kg. No lesions in organs or tissues attributable to toxic effects of the chemical were observed. In the 16-week studies, several male and female rats receiving 175 or 350 mg/kg died. Whether the deaths of these rats were directly related to the lesions observed in the brains of these rats or to functional derangements is uncertain. No mice died as a result of receiving 44 to 700 mg/kg TRCP for 16 weeks.

Mild inhibition of serum cholinesterase activity was seen in female rats administered 175 or 350 mg/kg TRCP in both prechronic studies, but not in male rats or in mice. The sex/species specificity for this and other toxic effects is possibly related to differences in rates of metabolism. The clinical signs of ataxia, excessive salivation, gasping, and convulsions that were observed in the female rats following the accidental overdose may have been the result of cholinesterase inhibition. Alternatively, some of the clinical signs may be attributed to the neuronal necrosis in the hippocampus and thalamus or to other functional derangements in the brain.

Organophosphorus compounds react at the esteratic subsite of acetylcholinesterase, resulting in phosphorylation of the enzyme. The affinity of a compound for acetylcholinesterase and the stability of the phosphorylated enzyme are determined by the groups attached to the phosphate molecule. Based on the results reported here for TRCP and those in the literature regarding tris(2,3-dibromopropyl) phosphate (Ulsamer *et al.*, 1980; Sprague *et al*, 1981), the anticholinesterase activity of this family of trisalkyl phosphates—TRCP, TEHP, and TBP—would seem to be minimal.

One of the major effects of TRCP in these studies was the neurotoxicity observed in rats. In the 16-week studies, neuronal necrosis in the hippocampus and thalamus were observed more frequently and in lower dose groups in females than in males. Similarly, in the 2-year studies, more than 40% of the high-dose females were affected while only a few males showed similar lesions. Neurotoxicity was not observed in mice in either the prechronic or the 2-year studies. These sex and species differences may be related to differing rates of metabolism and elimination. Serum levels of TRCP have been shown to be significantly higher in female rats during the first 30 minutes after a single gavage administration than in males receiving a similar dose. Moreover, mice excreted greater than 70% of an oral dose of 175 mg/kg in an 8-hour period compared to approximately 40% for rats (Matthews *et al.*, 1990).

In the 16-week studies, neuronal necrosis was seen primarily in the CA1 region of the pyramidal neurons of the hippocampus and in the thalamus. Transient occlusion of the cerebral blood vessels had a similar effect on CA1 pyramidal neurons in rats (Pulsinelli and Brierley, 1979; Johansen *et al.*, 1984), suggesting that cerebral ischemia is one possible mechanism for the effect in TRCP-dosed rats. Alternatively, the loss of pyramidal cells from the hippocampus may have been related to the convulsions caused by TRCP. Lesions in Ammon's horn and other regions of the hippocampus have been found in epileptic patients (Ben-Ari *et al.*, 1981). Seizures induced by a compound used as a model for epilepsy, kainic acid, have also been

associated with hippocampal neuronal damage (Ben-Ari, 1985).

Although the hippocampus was the most prominent location for brain lesions in the 16-week studies, lesions in rats in the 2-year studies were located primarily in the brain stem and cerebral cortex. The gliosis and mineralization that were observed represent repair of the neuropil following necrosis. The hemorrhage and accumulation of hemosiderin suggest that TRCP may have a direct effect on small blood vessels, perhaps causing small infarcts which subsequently heal by proliferation of glial cells. This notion is supported by a report of an hemorrhagic effect in rats given intraperitoneal injections of TRCP, 125 mg/kg, for 37 days (Clayton and Clayton, 1981). The different pattern of lesions in the 2-year studies also suggests that the hippocampal lesions in the 16-week studies may have been indirectly caused by TRCP (e.g., as a result of ischemia).

Several other organophosphorus compounds are known to produce degenerative changes in the peripheral nervous system and spinal cord (Abou-Donia *et al.*, 1980), and some highly toxic organophosphates such as soman cause damage to the central nervous system including the hippocampus (McLeod *et al.*, 1984). This report appears to be the first one of brain lesions induced by TRCP or by any organophosphate flame retardant.

Administration of TRCP to rats for up to two years was associated with a marked increase in the incidence of adenomas of the renal tubule. These adenomas occurred in nearly 50% of high-dose males and in 10% of low-dose males. Although the numerical increase was not as pronounced in female rats, renal tubule adenomas occur less frequently in female than in male historical control rats; thus, the 10% incidence in the 88 mg/kg female group is clearly related to chemical administration. This effect is supported by the marked increase in the incidence of renal tubule cell hyperplasia in both sexes. The renal tubule proliferative lesions were small, usually microscopic. Malignant tumors were found in a control male and in a high-dose male. Thus, the renal response in rats appears to be restricted to hyperplasia and benign tumors.

Adenoma and carcinoma of the renal tubule constitute a morphological continuum, and there are no cytologic features that clearly and unambiguously distinguish the more benign neoplasms from those with the ability to metastasize. Although cellular anaplasia and atypia are present in some neoplasms and are indicators of malignancy, some well-differentiated renal tubule neoplasms without atypia metastasize. In man and rodents, size of the neoplasm often correlates best with metastatic capability and thus with biological behavior (Bennington and Beckwith, 1975; Hard, 1986). Furthermore, small neoplasms similar to those diagnosed as adenomas in the NTP studies of TRCP have been shown to precede the development of large renal tubule carcinomas in models of renal carcinogenesis employing potent carcinogens (Hard, 1986). Therefore, we believe that the renal adenoma represents an early stage in the development of carcinoma. For these reasons, the marked increase in the incidence of renal tubule neoplasms in rats administered TRCP is considered to represent clear evidence of carcinogenic activity.

Thyroid follicular cell neoplasms occurred with a significant positive trend in female rats, and the incidence of follicular cell adenoma or carcinoma combined was significantly greater in high-dose females than in controls. The incidence of follicular cell neoplasms was also increased in high-dose males, but this increase was not statistically significant. The combined incidence of follicular cell neoplasms in high-dose male and female rats equals or exceeds the upper rates for NTP historical controls (males 51/2,106, 2.4%, range 0%-10%; females 34/2,107, 1.6%, range 0%-6%). However, the low incidence of follicular cell hyperplasia did not support a chemical effect on the thyroid gland; no hyperplasia was seen in males, and only one dosed and one control female had follicular cell hyperplasia. The lack of hyperplasia in rats argues against considering the follicular cell neoplasms as related to TRCP since most thyroid carcinogens also induce hyperplasia. There was no increase in follicular cell neoplasms in dosed mice; the follicular cell adenomas in a single treated male and in one treated female mouse were considered incidental lesions. Therefore, it is uncertain if the thyroid follicular cell neoplasms in rats are related to the administration of TRCP.

There was a marginal increase in the incidence of mononuclear cell leukemia in dosed male and female rats. Mononuclear cell leukemia is also called large granular lymphocyte leukemia and

believed to arise in the spleen. In males, the increase was not clearly dose related and was due, in part, to a lower than expected rate in the control group. In female rats, the increase was marginal and restricted to the high-dose group. The incidence rates for all leukemias in NTP historical controls are quite variable (males, 2% to 44%; females, 4% to 42%). Thus, for both males and females the highest rate is within the historical control range. These marginal increases in leukemia in male and female rats were not considered to be clearly related to administration of TRCP.

$B6C3F_1$ mice were less sensitive to the effects of TRCP, and doses in the 2-year studies were about four times greater than those administered to rats. Despite the higher doses, mortality and body weights were similar among dosed groups of male and female mice and their respective controls. Nevertheless, approximately 80% of the high-dose (350 mg/kg) mice had renal lesions, specifically, nuclear enlargement (karyomegaly) of tubule epithelial cells. Thus, although somewhat higher doses may have been tolerated by mice, toxic effects were achieved by the doses administered in the 2-year studies.

The mechanism for the induction of karyomegaly by TRCP may be interference with cell division with continued DNA synthesis, as occurs with the administration of lysinoalanine in the rat (Richardson and Woodard, 1986). Rats are considered to be one of the most sensitive species for the induction of karyomegaly, although karyomegaly is induced by pyrrolizidine alkaloids in swine but not in rats (Peckham *et al.*, 1974). In the TRCP studies, karyomegaly was seen in mice but not in rats, perhaps because the rat doses were approximately one-fourth of those administered to mice.

Karyomegaly in the kidney has been associated with a variety of chemicals studied by the NTP including trichloroethylene (NTP, 1988), tetrachloroethylene (NTP, 1986), bromodichloromethane (NTP, 1987), and ochratoxin (NTP, 1989). Many, but not all, chemicals that cause tubule cell karyomegaly are kidney carcinogens. In mice given TRCP, the evaluation of single sections of left and right kidneys identified tubule cell adenomas in one control male, one low-dose female, and one high-dose male, and an adenocarcinoma was seen in another high-dose male. Because of the occurrence of TRCP- related kidney neoplasms in rats, the association of karyomegaly with kidney neoplasms with other chemicals, and the low spontaneous incidence of kidney neoplasms in historical controls, additional sections of the kidneys of mice were prepared and evaluated to provide more data for comparison of the dosed and control groups. In the step-sections two additional adenomas were observed in high-dose males and one in a low-dose male. Focal hyperplasia was observed in one additional control male and four additional high-dose males (two from the 66-week interim and two from the 2-year group). Although the slight increase in tubule cell neoplasms was not statistically significant, the marginal increase in both tubule cell hyperplasia and tubule cell neoplasms is suggestive of a chemical-related effect. Thus, the data were considered to represent equivocal evidence of carcinogenic activity for male mice.

The incidence of harderian gland neoplasms, primarily adenomas, was marginally increased in high-dose female mice relative to concurrent controls. This marginal increase was considered equivocal evidence of carcinogenic activity. Further comparisons of the incidence rates in dosed females with NTP historical controls were not made because harderian glands of historical controls were examined microscopically only if they were observed to be grossly enlarged at necropsy. In the TRCP studies, since three harderian gland neoplasms were observed in dosed females at the 66-week interim evaluation, an attempt was made to section and microscopically examine harderian glands from all mice. Only four of the harderian gland neoplasms in these studies were observed grossly. Therefore, the incidence rates in historical controls may substantially underestimate the true rates.

The increased liver weights in high-dose (700 mg/kg) male mice in the 16-week study suggest that the liver is also a target site for TRCP. In the 2-year studies, there was a marginal increase in the incidence of foci of cytologic alteration, particularly eosinophilic foci, and of hepatocellular adenomas in male mice. However, there was no increase in the incidence of hepatocellular carcinomas, and the combined incidence of adenomas and carcinomas in the dosed males was not significantly different from that in controls. In female mice, there was no increase in the incidence of either hepatocellular foci or hepatocellular neoplasms. Therefore, the

marginal increase in the incidence of hepatocellular adenomas in male mice was not considered related to chemical administration.

Of the three trisalkyl phosphate flame retardants studied by the NTP, TBP produced the broadest spectrum of carcinogenic activity. Dietary administration of TBP caused a marked increase in: renal tubule cell neoplasms, primarily adenomas, in male and female rats (similar to TRCP); squamous cell papillomas and carcinomas of the forestomach and alveolar/bronchiolar adenomas and carcinomas of the lung in male and female mice; renal tubule adenomas and carcinomas in male mice; and hepatocellular adenomas and carcinomas in female mice. Karyomegaly of tubule epithelial cells, diagnosed as tubule dysplasia, was also observed in mice receiving TBP, similar to the observations made in mice receiving TRCP. TEHP, however, produced only a marginal increase in pheochromocytomas in male rats, indicating equivocal evidence of carcinogenicity, and an increase in hepatocellular carcinomas in female mice, representing some evidence of carcinogenicity.

The carcinogenic activity of the two flame retardants studied earlier might be related to the alkyl portions of the respective phosphate esters. The major metabolite of TBP, 2,3-dibromopropanol (Nomeir and Matthews, 1981), is a relatively potent carcinogen, causing tumors in numerous organs following dermal exposure (NTP, unpublished data). However, studies of several compounds [di(2-ethylhexyl) phthalate, di(2-ethylhexyl)adipate, 2-ethylhexyl sulfate] containing 2-ethylhexanol, the anticipated metabolite of TEHP, indicate that this metabolite is a weak carcinogen for the mouse liver (Kluwe *et al.*, 1985). In contrast, there does not appear to be any similarity in the carcinogenic activity of TRCP and 2-chloroethanol, the hydrolysis product of TRCP, which was found in a dermal study in rats and mice to be noncarcinogenic (NTP, 1985).

Conclusions: Under the conditions of these 2-year gavage studies, there was *clear evidence of carcinogenic activity** for male and female F344/N rats receiving tris(2-chloroethyl) phosphate as shown by increased incidences of renal tubule adenomas. Thyroid follicular cell neoplasms and mononuclear cell leukemia in male and female rats may have been related to chemical administration. There was *equivocal evidence of carcinogenic activity* for male $B6C3F_1$ mice as shown by a marginally increased incidence of renal tubule cell neoplasms. There was *equivocal evidence of carcinogenic activity* for female $B6C3F_1$ mice as shown by a marginally increased incidence of harderian gland adenomas.

Renal tubule cell hyperplasia in male and female rats and gliosis, hemorrhage, pigmentation (hemosiderin accumulation), and mineralization in the brains of female rats were associated with the administration of tris(2-chloroethyl) phosphate. Karyomegaly of tubule epithelial cells of the kidney of male and female mice was also chemical related.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 8. A summary of peer review comments and the public discussion on this Technical Report appear on page 10.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR GAVAGE STUDY OF TRIS(2-CHLOROETHYL) PHOSPHATE

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate

	Vehicle Control	44 mg/kg	88 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
Scheduled sacrifice	9	10	10
Early deaths			
Dead	6	9	10
Moribund	5	7	14
Gavage death	4	1	
Accident			1
Survivors			
Terminal sacrifice	36	33	25
Animals examined microscopically	50	50	50
Alimentary System			
Intestine large, cecum	(50)	(47)	(48)
Intestine small, duodenum	(48)	(46)	(47)
Leiomyosarcoma		1 (2%)	
Intestine small, ileum	(48)	(46)	(47)
Liver	(50)	(50)	(50)
Hepatocellular carcinoma		1 (2%)	1 (2%)
Hepatocellular adenoma			1 (2%)
Sarcoma, metastatic, mesentery			1 (2%)
Sarcoma, metastatic, uncertain primary site		1 (2%)	
Mesentery	(13)	(8)	(10)
Sarcoma			1 (10%)
Pancreas	(49)	(48)	(50)
Sarcoma, metastatic, mesentery			1 (2%)
Acinus, adenocarcinoma		1 (2%)	
Acinus, adenoma			1 (2%)
Salivary glands	(50)	(49)	(49)
Sarcoma		1 (2%)	
Stomach, forestomach	(50)	(48)	(50)
Stomach, glandular	(50)	(48)	(50)
Cardiovascular System			
Heart	(50)	(50)	(50)
Endocrine System			
Adrenal gland	(50)	(50)	(50)
Pheochromocytoma benign		1 (2%)	
Adrenal gland, cortex	(50)	(50)	(49)
Carcinoma			1 (2%)
Adrenal gland, medulla	(43)	(47)	(44)
Pheochromocytoma malignant	2 (5%)	1 (2%)	5 (11%)
Pheochromocytoma benign	9 (21%)	14 (30%)	12 (27%)
Pheochromocytoma benign, multiple		1 (2%)	
Bilateral, pheochromocytoma benign	1 (2%)	5 (11%)	1 (2%)
Islets, pancreatic	(50)	(49)	(50)
Adenoma	1 (2%)	2 (4%)	3 (6%)
Carcinoma			1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	44 mg/kg	88 mg/kg
Endocrine System (continued)			
Pituitary gland	(49)	(46)	(48)
Pars distalis, adenoma	19 (39%)	16 (35%)	14 (29%)
Pars distalis, carcinoma	2 (4%)		
Thyroid gland	(50)	(48)	(50)
C-cell, adenoma	14 (28%)	8 (17%)	4 (8%)
C-cell, carcinoma		1 (2%)	2 (4%)
Follicular cell, adenoma	1 (2%)	2 (4%)	3 (6%)
Follicular cell, carcinoma			2 (4%)
Genital System			
Epididymis	(50)	(49)	(49)
Preputial gland	(42)	(47)	(42)
Adenoma	1 (2%)		1 (2%)
Carcinoma	3 (7%)	7 (15%)	6 (14%)
Prostate	(50)	(50)	(50)
Adenoma	1 (2%)		
Seminal vesicle	(50)	(48)	(50)
Sarcoma, metastatic, mesentery			1 (2%)
Testes	(50)	(50)	(49)
Bilateral, interstitial cell, adenoma	30 (60%)	30 (60%)	35 (71%)
Interstitial cell, adenoma	8 (16%)	11 (22%)	7 (14%)
Hematopoietic System			
Bone marrow	(50)	(49)	(50)
Lymph node	(50)	(49)	(50)
Mediastinal, sarcoma, metastatic			1 (2%)
Mediastinal, sarcoma, metastatic, mesentery			1 (2%)
Lymph node, mandibular	(44)	(42)	(47)
Lymph node, mesenteric	(48)	(43)	(43)
Spleen	(50)	(49)	(50)
Hemangiosarcoma			1 (2%)
Osteosarcoma, metastatic, bone		1 (2%)	
Sarcoma	1 (2%)		1 (2%)
Thymus	(37)	(38)	(39)
Integumentary System			
Mammary gland	(29)	(26)	(32)
Adenocarcinoma	1 (3%)		
Fibroadenoma	2 (7%)	1 (4%)	
Skin	(50)	(50)	(48)
Basal cell adenoma	1 (2%)	1 (2%)	1 (2%)
Basosquamous tumor benign		1 (2%)	
Keratoacanthoma		3 (6%)	2 (4%)
Papilloma squamous	1 (2%)		
Squamous cell carcinoma		2 (4%)	1 (2%)
Sebaceous gland, adenoma		1 (2%)	
Subcutaneous tissue, fibroma	1 (2%)	3 (6%)	6 (13%)
Subcutaneous tissue, fibrosarcoma	2 (4%)		
Subcutaneous tissue, lipoma, multiple		1 (2%)	
Subcutaneous tissue, sarcoma, metastatic			1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	44 mg/kg	88 mg/kg
Musculoskeletal System			
Bone		(3)	(3)
Femur, osteosarcoma		1 (33%)	
Humerus, osteosarcoma		1 (33%)	
Vertebra, chordoma			1 (33%)
Vertebra, sarcoma, metastatic			1 (33%)
Nervous System			
Brain	(50)	(49)	(50)
Carcinoma, metastatic, pituitary gland	1 (2%)		
Granular cell tumor benign			1 (2%)
Cerebellum, meninges, granular cell tumor benign			2 (4%)
Respiratory System			
Lung	(50)	(49)	(50)
Alveolar/bronchiolar adenoma			1 (2%)
Alveolar/bronchiolar carcinoma			1 (2%)
Carcinoma, metastatic, thyroid gland		1 (2%)	
Fibrosarcoma, metastatic, skin	1 (2%)		
Osteosarcoma, metastatic, bone		2 (4%)	
Pheochromocytoma malignant, metastatic, adrenal gland			2 (4%)
Sarcoma, metastatic, salivary glands		1 (2%)	
Sarcoma, metastatic, uncertain primary site		1 (2%)	
Special Senses System			
Zymbal's gland			(1)
Carcinoma			1 (100%)
Urinary System			
Kidney	(50)	(50)	(50)
Lipoma			1 (2%)
Renal tubule, adenoma	1 (2%)	4 (8%)	16 (32%)
Renal tubule, adenoma, multiple		1 (2%)	8 (16%)
Renal tubule, carcinoma	1 (2%)		1 (2%)
Urinary bladder	(49)	(49)	(50)
Systemic Lesions			
Multiple organs[a]	(50)	(50)	(50)
Leukemia mononuclear	5 (10%)	14 (28%)	13 (26%)
Mesothelioma benign		2 (4%)	1 (2%)
Mesothelioma malignant	1 (2%)	2 (4%)	3 (6%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	44 mg/kg	88 mg/kg
Tumor Summary			
Total animals with primary neoplasms[b]	48	48	49
Total primary neoplasms	109	141	163
Total animals with benign neoplasms	46	46	49
Total benign neoplasms	91	108	121
Total animals with malignant neoplasms	16	29	30
Total malignant neoplasms	18	33	42
Total animals with secondary neoplasms[c]	3	7	6
Total secondary neoplasms	3	11	11
Total animals with malignant neoplasms		1	

[a] The number in parentheses is the number of animals with any tissue examined microscopically
[b] Primary tumors: all tumors except metastatic tumors
[c] Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: Vehicle Control

Number of Days on Study	350	390	403	419	463	478	505	518	539	549	559	603	611	641	722	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	07 5	08 5	07 4	03 5	03 4	05 5	08 4	08 3	10 5	04 5	03 3	04 4	01 5	09 5	11 1	11 2	11 3	11 4	12 1	12 2	12 3	12 4	12 5	13 1	13 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	A	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery					+	+					+														
Pancreas	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant														X		X									
Pheochromocytoma benign																	X			X					
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X		X			X		X			X	X							X	X	X	X	
Pars distalis, carcinoma				X			X																		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma					X					X								X				X	X		X
Follicular cell, adenoma																									

+: Tissue examined
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: Vehicle Control (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 4 1	0 4 2	0 4 3	0 5 1	0 5 2	0 5 3	0 5 4	0 6 1	0 6 2	0 6 3	0 6 4	0 6 5	0 7 1	0 7 2	0 7 3	0 8 1	0 8 2	0 9 1	0 9 2	0 9 3	0 9 4	1 0 1	1 0 2	1 0 3	1 0 4	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	I	+	+	+	+	+	+	+	+	I	I	+	+	+	+	+	+	+	+	I	+	+	+	+	45
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery		+				+	+							+		+	+		+	+		+	+			13
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	M	M	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	43
Pheochromocytoma malignant																										2
Pheochromocytoma benign		X		X				X		X		X		X										X		9
Bilateral, pheochromocytoma benign															X											1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																									X	1
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X	X		X										X	X		X	X				X		X		19
Pars distalis, carcinoma																										2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X		X									X			X			X			X		X	X		14
Follicular cell, adenoma																									X	1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: Vehicle Control (continued)

Number of Days on Study	3 5 0	3 9 0	4 0 3	4 1 9	4 6 3	4 7 8	5 0 5	5 1 8	5 3 9	5 4 9	5 9 5	6 0 3	6 1 1	6 4 1	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 7 5	0 8 5	0 7 4	0 3 5	0 3 4	0 5 5	0 8 4	0 8 3	1 0 5	0 4 5	0 3 3	0 4 4	0 1 5	0 9 5	0 1 1	1 2 2	1 3 3	1 4 4	2 1 1	2 2 2	2 3 3	2 4 4	2 5 1	3 1 2
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes							X																	
Preputial gland	M	+	+	M	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+
Adenoma																		X						
Carcinoma																								
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell adenoma									X		X			X			X	X	X	X			X	X
Interstitial cell, adenoma							X					X			X	X					X	X		
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma															X									
Thymus	+	+	+	M	+	M	+	+	+	+	+	+	I	+	+	M	+	M	+	+	+	M	+	+
Integumentary System																								
Mammary gland	+	M	+	+	+	+	+	M	+	M	M	+	+	+	+	M	+	M	+	+	+	+	M	M
Adenocarcinoma	X																							
Fibroadenoma																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																	X							
Papilloma squamous																								
Subcutaneous tissue, fibroma																								
Subcutaneous tissue, fibrosarcoma												X											X	
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland				X																				
Spinal cord			+																					

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: Vehicle Control (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 4 1	0 4 2	0 4 3	0 5 1	0 5 2	0 5 3	0 5 4	0 6 1	0 6 2	0 6 3	0 6 4	0 6 5	0 7 1	0 7 2	0 7 3	0 8 1	0 8 2	0 9 1	0 9 2	0 9 3	0 9 4	1 0 1	1 0 2	1 0 3	1 0 4	**Total Tissues/ Tumors**
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																										1
Preputial gland	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	42
Adenoma																										1
Carcinoma	X											X					X									3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																								X		1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell adenoma	X		X	X	X	X	X	X	X	X		X	X	X		X	X	X	X	X	X		X	X	X	30
Interstitial cell, adenoma		X									X															8
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	M	M	+	+	M	M	37
Integumentary System																										
Mammary gland	M	M	+	M	+	M	+	+	M	+	+	M	+	M	M	+	+	M	M	+	+	M	+	M	M	29
Adenocarcinoma																										1
Fibroadenoma																					X		X			2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																										1
Papilloma squamous								X																		1
Subcutaneous tissue, fibroma																X										1
Subcutaneous tissue, fibrosarcoma																										2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																										1
Spinal cord																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: Vehicle Control (continued)

Number of Days on Study	350	399	403	419	463	478	505	518	539	549	559	603	611	641	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	07535	08554	07435	03545	03544	05545	08544	08543	10555	04555	03533	04544	01555	09551	11511	11512	11513	11514	12211	12212	12213	12214	12215	13111	13112
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin												X													
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye										+											+				
Harderian gland							+																		
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X		X										X				X
Mesothelioma malignant							X																		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: Vehicle Control (continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	04 1	04 2	04 3	05 1	05 2	05 3	05 4	06 1	06 2	06 3	06 4	06 5	07 1	07 2	07 3	08 1	08 2	09 1	09 2	09 3	09 4	10 1	10 2	10 3	10 4	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																						+				3
Harderian gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma								X																		1
Renal tubule, carcinoma	X																									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear															X											5
Mesothelioma malignant																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 44 mg/kg

Number of Days on Study	4 4 1	4 6 3	5 0 6	5 4 0	5 6 2	5 7 4	5 8 7	6 0 3	6 2 0	6 2 2	6 3 4	6 3 8	6 4 7	6 6 0	6 7 3	7 0 2	7 1 4	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	1 7 5	1 8 5	1 3 5	2 1 5	1 9 2	2 2 5	2 2 4	2 1 4	2 1 3	1 4 5	2 2 3	2 5 5	1 6 5	1 8 4	1 8 3	1 7 4	1 9 5	2 3 1	2 3 2	2 3 3	1 3 4	1 4 1	1 4 2	1 4 3	1 4 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Intestine large	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	A	+	+	+	+	A	A	+	+	+	+	+	+	+	+	I	I	+	+	I	I
Intestine small	+	+	+	+	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	A	+	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma		X																							
Intestine small, ileum	+	+	+	+	A	+	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	A	+	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma														X											
Mesothelioma malignant, metastatic, testes											X														
Sarcoma, metastatic, uncertain primary site																		X							
Mesentery																						+	+		
Pancreas	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenocarcinoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																			X						
Stomach	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	M	+
Pheochromocytoma malignant																									
Pheochromocytoma benign								X	X								X						X		
Pheochromocytoma benign, multiple															X										
Bilateral, pheochromocytoma, benign																						X			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	M	M	+	+	+	+	M	M	+	+	M	M	+	M	+	+	+	+	M	M	+	+
Pituitary gland	+	+	+	+	I	I	+	+	I	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X				X						X		X		X	X	X			X	X		
Thyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																						X			
C-cell, carcinoma						X																			
Follicular cell, adenoma						X																		X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 44 mg/kg (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	1 5 1	1 5 2	1 5 3	1 5 4	1 6 1	1 6 2	1 6 3	1 6 4	1 7 1	1 7 2	1 7 3	1 8 1	1 8 2	1 9 1	1 9 3	1 9 4	2 0 1	2 0 2	2 0 3	2 0 4	2 0 5	2 1 1	2 1 2	2 2 1	2 2 2	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Leiomyosarcoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										1
Mesothelioma malignant, metastatic, testes																										1
Sarcoma, metastatic, uncertain primary site																										1
Mesentery				+	+	+			+				+						+							8
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	48
Acinus, adenocarcinoma																				X						1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	49
Sarcoma																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign												X														1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pheochromocytoma malignant																X										1
Pheochromocytoma benign	X	X			X	X	X	X	X				X									X			X	14
Pheochromocytoma benign, multiple																										1
Bilateral, pheochromocytoma, benign											X				X			X				X				5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	49
Adenoma												X											X			2
Parathyroid gland	+	M	+	+	+	+	+	M	M	+	+	M	M	+	+	+	+	+	+	+	M	+	M		+	33
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pars distalis, adenoma						X			X				X			X	X			X				X		16
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	48
C-cell, adenoma			X									X	X			X					X	X			X	8
C-cell, carcinoma																										1
Follicular cell, adenoma																										2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 44 mg/kg (continued)

Number of Days on Study	4 4 1	4 6 3	5 0 6	5 4 0	5 6 2	5 7 4	5 8 7	6 0 3	6 2 0	6 2 2	6 3 4	6 3 8	6 4 7	6 6 0	6 7 3	7 0 2	7 1 4	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	1 7 5	1 8 5	1 3 5	2 1 5	1 9 2	2 2 5	2 2 4	2 1 4	2 1 3	2 4 5	2 2 3	1 5 5	1 6 5	1 8 4	1 8 3	1 7 4	1 9 5	1 3 1	1 3 2	1 3 3	1 3 4	1 4 1	1 4 2	1 4 3	1 4 4
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes											X													
Preputial gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma	X	X						X							X	X			X					
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma									X	X	X				X			X	X	X	X	X		X	X
Interstitial cell, adenoma				X			X	X						X		X	X								
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	M	+	+	+	+	M	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	M	+
Lymph node, mesenteric	+	+	I	+	M	+	M	+	+	A	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes											X													
Osteosarcoma, metastatic, bone				X																				
Thymus	+	+	+	+	M	+	M	M	+	+	+	M	M	+	+	+	+	+	+	+	M	+	M	+	+
Integumentary System																								
Mammary gland	M	+	M	+	M	M	+	+	+	+	M	+	+	M	M	M	+	+	+	+	+	+	M	M	+
Fibroadenoma																									X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Basosquamous tumor benign																									
Keratoacanthoma																									
Squamous cell carcinoma																									
Sebaceous gland, adenoma																									
Subcutaneous tissue, fibroma																					X				
Subcutaneous tissue, lipoma, multiple							X																		
Musculoskeletal System																									
Bone				+													+								
Femur, osteosarcoma				X																					
Humerus, osteosarcoma																	X								
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 44 mg/kg (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	15 1	15 2	15 3	15 4	16 1	16 2	16 3	16 4	17 1	17 2	17 3	18 1	18 2	19 1	19 3	19 4	20 1	20 2	20 3	20 4	20 5	21 1	21 2	22 1	22 2	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	49
Mesothelioma malignant, metastatic, testes																		X								2
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+		+	47
Carcinoma												X														7
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	48
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma		X	X	X	X	X	X	X		X	X	X		X	X		X		X	X	X	X	X		X	30
Interstitial cell, adenoma	X								X				X			X		X								11
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	49
Lymph node	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	49
Mesothelioma malignant, metastatic, testes																										1
Osteosarcoma, metastatic, bone																										1
Thymus	+	+	+	+	M	+	M	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	38
Integumentary System																										
Mammary gland	+	+	M	+	M	+	M	+	M	+	+	M	M	+	M	M	+	+	M	+	M	M	M		M	26
Fibroadenoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma									X																	1
Basosquamous tumor benign																				X						1
Keratoacanthoma			X		X	X																				3
Squamous cell carcinoma							X											X								2
Sebaceous gland, adenoma										X																1
Subcutaneous tissue, fibroma																		X				X				3
Subcutaneous tissue, lipoma, multiple																										1
Musculoskeletal System																										
Bone																		+								3
Femur, osteosarcoma																										1
Humerus, osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	49

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 44 mg/kg (continued)

Number of Days on Study	4 4 1	4 6 3	5 0 6	5 4 0	5 6 2	5 7 4	5 8 7	6 0 3	6 2 0	6 2 2	6 3 4	6 3 8	6 4 7	6 6 0	6 7 3	7 0 2	7 1 4	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	1 7 5	1 8 5	1 3 5	2 1 5	1 9 2	2 2 5	2 2 4	2 1 4	2 1 3	1 4 5	2 2 3	1 5 5	1 6 5	1 8 4	1 8 3	1 7 4	1 9 5	1 3 1	1 3 2	1 3 3	1 3 4	1 4 1	1 4 2	1 4 3	1 4 4
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland						X																			
Osteosarcoma, metastatic, bone				X													X								
Sarcoma, metastatic, salivary glands																			X						
Sarcoma, metastatic, uncertain primary site																		X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye		A		+																					+
Harderian gland		+																							
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Renal tubule, adenoma, multiple																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X					X				X			X		X	X	
Mesothelioma benign								X											X						
Mesothelioma malignant												X													

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 44 mg/kg (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	1 5 1	1 5 2	1 5 3	1 5 4	1 6 1	1 6 2	1 6 3	1 6 4	1 7 1	1 7 2	1 7 3	1 8 1	1 8 2	1 9 1	1 9 3	1 9 4	2 0 1	2 0 2	2 0 3	2 0 4	2 0 5	2 1 1	2 1 2	2 2 1	2 2 2	**Total Tissues/ Tumors**
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	49
Carcinoma, metastatic, thyroid gland																										1
Osteosarcoma, metastatic, bone																										2
Sarcoma, metastatic, salivary glands																										1
Sarcoma, metastatic, uncertain primary site																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	49
Special Senses System																										
Eye							+																	+		4
Harderian gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma		X							X													X		X		4
Renal tubule, adenoma, multiple																X										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X					X	X					X			X						X		X	14
Mesothelioma benign																										2
Mesothelioma malignant																		X								2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 88 mg/kg

Number of Days on Study	4 5 8	4 6 9	4 7 1	5 2 8	5 5 0	5 5 4	5 7 5	5 8 4	6 2 5	6 3 0	6 3 0	6 3 2	6 4 8	6 5 3	6 6 1	6 7 4	6 7 6	6 8 0	6 8 3	6 8 7	6 9 0	6 9 5	6 9 6	7 0 0	7 1 0
Carcass ID Number	2 5 3	2 9 5	2 7 5	3 2 5	2 8 5	3 2 4	2 7 4	3 4 5	2 9 4	2 6 5	3 3 5	3 1 5	2 9 3	2 9 2	2 7 3	3 0 4	3 4 4	2 8 4	3 0 5	3 3 4	3 1 4	2 9 1	3 3 3	3 3 2	2 6 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Hepatocellular adenoma																									
Sarcoma, metastatic, mesentery																							X		
Mesentery								+		+		+								+	+		+		
Sarcoma																							X		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery																							X		
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma						X																			
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	I	M	M	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign				X		X							X								X				
Bilateral, pheochromocytoma benign																									X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X	
Carcinoma										X															
Parathyroid gland	M	M	M	M	+	+	M	M	+	+	M	+	M	M	+	M	+	+	+	M	M	+	+	M	+
Pituitary gland	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X							X					X				X	X	X				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma											X														
C-cell, carcinoma																									
Follicular cell, adenoma																X									
Follicular cell, carcinoma																							X		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 88 mg/kg (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	251	252	254	255	261	262	263	271	272	281	282	283	301	302	303	311	312	313	321	322	323	331	341	342	343	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																								X		1
Hepatocellular adenoma								X																		1
Sarcoma, metastatic, mesentery																										1
Mesentery										+	+		+							+						10
Sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, mesentery																										1
Acinus, adenoma																			X							1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	44
Pheochromocytoma malignant							X			X						X			X	X						5
Pheochromocytoma benign					X							X	X				X	X	X			X		X		12
Bilateral, pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X																	X							3
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	M	+	+	M	+	+	+	M	M	+	+	M	+	M	+	30
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma		X				X				X		X		X					X		X			X		14
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma					X												X							X		4
C-cell, carcinoma						X														X						2
Follicular cell, adenoma																X					X					3
Follicular cell, carcinoma																			X							2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 88 mg/kg (continued)

Number of Days on Study	4 5 8	4 6 9	4 7 1	5 2 8	5 5 0	5 5 4	5 7 5	5 8 4	6 2 5	6 3 0	6 3 0	6 3 2	6 4 8	6 5 3	6 6 1	6 7 4	6 7 6	6 8 0	6 8 3	6 8 7	6 9 0	6 9 5	6 9 6	7 0 0	7 1 0
Carcass ID Number	2 5 3	2 9 5	2 7 5	3 2 5	2 8 5	3 2 4	2 7 4	3 4 5	2 9 4	2 6 5	3 3 5	3 1 5	2 9 3	2 9 2	2 7 3	3 0 4	3 4 4	3 8 4	3 0 5	3 3 4	3 1 4	2 9 1	3 3 3	3 3 2	2 6 4
General Body System																									
Tissue NOS																									
Genital System																									
Epididymis	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																	X				X				
Preputial gland	+	M	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	M	+	M	+	+	+	M	+
Adenoma																									
Carcinoma							X		X				X										X		X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery																								X	
Testes	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell adenoma	X				X			X	X				X	X		X	X	X		X		X	X	X	X
Interstitial cell, adenoma				X		X					X	X							X						
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, sarcoma, metastatic				X																					
Mediastinal, sarcoma, metastatic, mesentery																								X	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+		+
Lymph node, mesenteric	+	+	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									X
Sarcoma																X									
Thymus	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+	M	M	M	+	+	+	M	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	M	+	+	M	+	+	+	M	+	M	+	M	M	+	+	M	M	+	M
Skin	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Basal cell adenoma																									
Keratoacanthoma																							X	X	
Squamous cell carcinoma					X																				
Subcutaneous tissue, fibroma																X	X	X							X
Subcutaneous tissue, sarcoma, metastatic				X																					
Musculoskeletal System																									
Bone				+													+								
Vertebra, chordoma																	X								
Vertebra, sarcoma, metastatic				X																					

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 88 mg/kg (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	2 5 1	2 5 2	2 5 4	2 5 5	2 6 1	2 6 2	2 6 3	2 7 1	2 7 2	2 8 1	2 8 2	2 8 3	3 0 1	3 0 2	3 0 3	3 1 1	3 1 2	3 1 3	3 2 1	3 2 2	3 2 3	3 3 1	3 4 1	3 4 2	3 4 3	**Total Tissues/ Tumors**
General Body System																										
Tissue NOS																			+						1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant, metastatic, testes																										2
Preputial gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	42
Adenoma													X													1
Carcinoma										X																6
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, mesentery																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, interstitial cell adenoma	X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X		X	X		X	X	X	35
Interstitial cell, adenoma									X													X				7
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, sarcoma, metastatic																										1
Mediastinal, sarcoma, metastatic, mesentery																										1
Lymph node, mandibular	+			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric		+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	M	+	+	+	+	+	+	43
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Sarcoma																										1
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	M	+	M	+	+	+	+	39
Integumentary System																										
Mammary gland	M	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	M	M	+	M	M	M	+	+	M	32
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Basal cell adenoma																			X							1
Keratoacanthoma																										2
Squamous cell carcinoma																										1
Subcutaneous tissue, fibroma						X																X				6
Subcutaneous tissue, sarcoma, metastatic																										1
Musculoskeletal System																										
Bone																			+							3
Vertebra, chordoma																										1
Vertebra, sarcoma, metastatic																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 88 mg/kg (continued)

Number of Days on Study	4 5 8	4 6 9	4 7 1	5 2 8	5 5 0	5 5 4	5 7 5	5 8 4	6 2 5	6 3 0	6 3 0	6 3 2	6 4 8	6 5 3	6 6 1	6 7 4	6 7 6	6 8 0	6 8 3	6 8 7	6 9 0	6 9 5	6 9 6	7 0 0	7 1 0
Carcass ID Number	2 5 3	2 9 5	2 7 5	3 2 5	2 8 5	3 2 4	2 7 4	3 4 5	2 9 4	2 6 5	2 3 5	3 1 5	2 9 3	2 9 2	2 7 3	3 0 4	3 4 4	2 8 4	3 0 5	3 3 4	3 1 4	2 9 1	3 3 3	3 3 2	2 6 4
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor benign							X																		
Cerebellum, meninges, granular cell tumor benign																							X		
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																			X						
Alveolar/bronchiolar carcinoma																									
Pheochromocytoma malignant, metastatic, adrenal gland																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Renal tubule, adenoma							X				X		X		X							X	X		X
Renal tubule, adenoma, multiple																	X				X				
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X		X	X		X	X		X						X			
Mesothelioma benign																									
Mesothelioma malignant																	X					X			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 88 mg/kg (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	2 5 1	2 5 2	2 5 4	2 5 5	2 6 1	2 6 2	2 6 3	2 7 1	2 7 2	2 8 1	2 8 2	2 8 3	3 0 1	3 0 2	3 0 3	3 1 1	3 1 2	3 1 3	3 2 1	3 2 2	3 2 3	3 3 1	3 4 1	4 4 2	4 4 3	**Total Tissues/ Tumors**
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor benign																										1
Cerebellum, meninges, granular cell tumor benign																						X				2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma				X																						1
Pheochromocytoma malignant, metastatic, adrenal gland							X									X										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye														+					+							2
Zymbal's gland																								+		1
Carcinoma																								X		1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma													X													1
Renal tubule, adenoma		X					X	X			X	X			X	X						X			X	16
Renal tubule, adenoma, multiple													X	X			X	X	X	X						8
Renal tubule, carcinoma			X																							1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X		X			X									X			X		X			13
Mesothelioma benign					X																					1
Mesothelioma malignant									X																	3

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate

	Vehicle Control	44 mg/kg	88 mg/kg
Adrenal Gland (Medulla): Pheochromocytoma Benign			
Overall rates[a]	10/43 (23%)	20/47 (43%)	13/44 (30%)
Adjusted rates[b]	33.3%	55.0%	43.5%
Terminal rates[c]	10/30 (33%)	16/32 (50%)	8/23 (35%)
First incidence (days)	729 (T)	603	528
Life table tests[d]	P=0.103	P=0.033	P=0.137
Logistic regression tests[d]	P=0.305	P=0.058	P=0.341
Cochran-Armitage test[d]	P=0.306		
Fisher exact test[d]		P=0.042	P=0.337
Adrenal Gland (Medulla): Pheochromocytoma Malignant			
Overall rates	2/43 (5%)	1/47 (2%)	5/44 (11%)
Adjusted rates	5.9%	3.1%	21.7%
Terminal rates	1/30 (3%)	1/32 (3%)	5/23 (22%)
First incidence (days)	641	729 (T)	729 (T)
Life table tests	P=0.079	P=0.482N	P=0.135
Logistic regression tests	P=0.118	P=0.448N	P=0.204
Cochran-Armitage test	P=0.136		
Fisher exact		P=0.466N	P=0.226
Adrenal Gland (Medulla): Pheochromocytoma (Benign or Malignant)			
Overall rates	12/43 (28%)	21/47 (45%)	17/44 (39%)
Adjusted rates	38.4%	57.8%	58.6%
Terminal rates	11/30 (37%)	17/32 (53%)	12/23 (52%)
First incidence (days)	641	603	528
Life table tests	P=0.037	P=0.061	P=0.051
Logistic regression tests	P=0.170	P=0.108	P=0.199
Cochran-Armitage test	P=0.179		
Fisher exact test test		P=0.076	P=0.202
Brain (Granular Cell): Benign			
Overall rates	0/50 (0%)	0/49 (0%)	3/50 (6%)
Adjusted rates	0.0%	0.0%	9.5%
Terminal rates	0/36 (0%)	0/32 (0%)	1/25 (4%)
First incidence (days)			575
Life table tests	P=0.028	–[e]	P=0.094
Logistic regression tests	P=0.037	–[e]	P=0.119
Cochran-Armitage test test	P=0.038		
Fisher exact test test		–[e]	P=0.121
Preputial Gland: Carcinoma			
Overall rates	3/42 (7%)	7/47 (15%)	6/42 (14%)
Adjusted rates	9.1%	17.2%	17.6%
Terminal rates	3/33 (9%)	2/31 (6%)	1/23 (4%)
First incidence (days)	729 (T)	441	575
Life table tests	P=0.148	P=0.165	P=0.165
Logistic regression tests	P=0.195	P=0.192	P=0.239
Cochran-Armitage test	P=0.202		
Fisher exact test		P=0.208	P=0.241

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	44 mg/kg	88 mg/kg
Preputial Gland: Adenoma or Carcinoma			
Overall rates	4/42 (10%)	7/47 (15%)	7/42 (17%)
Adjusted rates	12.1%	17.2%	21.4%
Terminal rates	4/33 (12%)	2/31 (6%)	2/23 (9%)
First incidence (days)	729 (T)	441	575
Life table tests	P=0.145	P=0.263	P=0.157
Logistic regression tests	P=0.211	P=0.316	P=0.253
Cochran-Armitage test	P=0.214		
Fisher exact test		P=0.330	P=0.260
Islets, Pancreatic: Adenoma			
Overall rates	1/50 (2%)	2/49 (4%)	3/50 (6%)
Adjusted rates	2.8%	6.3%	11.4%
Terminal rates	1/36 (3%)	2/32 (6%)	2/25 (8%)
First incidence (days)	729 (T)	729 (T)	700
Life table tests	P=0.129	P=0.459	P=0.193
Logistic regression tests	P=0.168	P=0.459	P=0.253
Cochran-Armitage test	P=0.223		
Fisher exact test		P=0.492	P=0.309
Islets, Pancreatic: Adenoma or Carcinoma			
Overall rates	1/50 (2%)	2/49 (4%)	4/50 (8%)
Adjusted rates	2.8%	6.3%	13.6%
Terminal rates	1/36 (3%)	2/32 (6%)	2/25 (8%)
First incidence (days)	729 (T)	729 (T)	630
Life table tests	P=0.066	P=0.459	P=0.114
Logistic regression tests	P=0.108	P=0.459	P=0.174
Cochran-Armitage test	P=0.119		
Fisher exact test		P=0.492	P=0.181
Kidney (Renal Tubule): Adenoma			
Overall rates	1/50 (2%)	5/50 (10%)	24/50 (48%)
Adjusted rates	2.8%	15.2%	69.7%
Terminal rates	1/36 (3%)	5/33 (15%)	15/25 (60%)
First incidence (days)	729 (T)	729 (T)	575
Life table tests	P<0.001	P=0.083	P<0.001
Logistic regression tests	P<0.001	P=0.083	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.102	P<0.001
Kidney (Renal Tubule): Adenoma or Carcinoma			
Overall rates	2/50 (4%)	5/50 (10%)	25/50 (50%)
Adjusted rates	5.6%	15.2%	72.7%
Terminal rates	2/36 (6%)	5/33 (15%)	16/25 (64%)
First incidence (days)	729 (T)	729 (T)	575
Life table tests	P<0.001	P=0.181	P<0.001
Logistic regression tests	P<0.001	P=0.181	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.218	P<0.001

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	44 mg/kg	88 mg/kg
Mammary Gland: Fibroadenoma or Adenocarcinoma			
Overall rates	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted rates	7.4%	3.0%	0.0%
Terminal rates	2/36 (6%)	1/33 (3%)	0/25 (0%)
First incidence (days)	350	729 (T)	
Life table tests	P=0.089N	P=0.330N	P=0.168N
Logistic regression tests	P=0.070N	P=0.342N	P=0.144N
Cochran-Armitage test	P=0.060N		
Fisher exact test		P=0.309N	P=0.121N
Pituitary Gland (Pars Distalis): Adenoma			
Overall rates	19/49 (39%)	16/46 (35%)	14/48 (29%)
Adjusted rates	44.8%	41.4%	42.8%
Terminal rates	13/36 (36%)	11/33 (33%)	8/25 (32%)
First incidence (days)	403	506	471
Life table tests	P=0.440N	P=0.403N	P=0.477N
Logistic regression tests	P=0.182N	P=0.421N	P=0.213N
Cochran-Armitage test	P=0.187N		
Fisher exact test		P=0.425N	P=0.217N
Pituitary Gland: (Pars Distalis): Adenoma or Carcinoma			
Overall rates	21/49 (43%)	16/46 (35%)	14/48 (29%)
Adjusted rates	47.2%	41.4%	42.8%
Terminal rates	13/36 (36%)	11/33 (33%)	8/25 (32%)
First incidence (days)	403	506	471
Life table tests	P=0.292N	P=0.266N	P=0.327N
Logistic regression tests	P=0.102N	P=0.314N	P=0.127N
Cochran-Armitage test	P=0.096N		
Fisher exact test		P=0.276N	P=0.116N
Skin: Keratoacanthoma			
Overall rates	0/50 (0%)	3/50 (6%)	2/50 (4%)
Adjusted rates	0.0%	9.1%	7.1%
Terminal rates	0/36 (0%)	3/33 (9%)	0/25 (0%)
First incidence (days)		729 (T)	696
Life table tests	P=0.126	P=0.106	P=0.183
Logistic regression tests	P=0.178	P=0.106	P=0.237
Cochran-Armitage test	P=0.201		
Fisher exact test		P=0.121	P=0.247
Skin (Subcutaneous Tissue): Fibroma			
Overall rates	1/50 (2%)	3/50 (6%)	6/50 (12%)
Adjusted rates	2.8%	9.1%	19.1%
Terminal rates	1/36 (3%)	3/33 (9%)	2/25 (8%)
First incidence (days)	729 (T)	729 (T)	674
Life table tests	P=0.016	P=0.274	P=0.033
Logistic regression tests	P=0.030	P=0.274	P=0.055
Cochran-Armitage test	P=0.036		
Fisher exact test		P=0.309	P=0.056

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	44 mg/kg	88 mg/kg
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma			
Overall rates	3/50 (6%)	3/50 (6%)	6/50 (12%)
Adjusted rates	8.0%	9.1%	19.1%
Terminal rates	2/36 (6%)	3/33 (9%)	2/25 (8%)
First incidence (days)	603	729 (T)	674
Life table tests	P=0.103	P=0.636	P=0.159
Logistic regression tests	P=0.173	P=0.647N	P=0.243
Cochran-Armitage test	P=0.179		
Fisher exact test		P=0.661N	P=0.243
Testes: Adenoma			
Overall rates	38/50 (76%)	41/50 (82%)	42/49 (86%)
Adjusted rates	92.7%	95.3%	95.3%
Terminal rates	33/36 (92%)	31/33 (94%)	23/25 (92%)
First incidence (days)	505	540	458
Life table tests	P=0.004	P=0.166	P=0.006
Logistic regression tests	P=0.292	P=0.615	P=0.332
Cochran-Armitage test	P=0.134		
Fisher exact test		P=0.312	P=0.166
Thyroid Gland (C-cell): Adenoma			
Overall rates	14/50 (28%)	8/48 (17%)	4/50 (8%)
Adjusted rates	36.4%	25.0%	14.1%
Terminal rates	12/36 (33%)	8/32 (25%)	3/25 (12%)
First incidence (days)	463	729 (T)	630
Life table tests	P=0.029N	P=0.166N	P=0.043N
Logistic regression tests	P=0.006N	P=0.108N	P=0.009N
Cochran-Armitage test	P=0.006N		
Fisher exact test		P=0.135N	P=0.009N
Thyroid Gland (C-cell): Carcinoma or Adenoma			
Overall rates	14/50 (28%)	9/48 (19%)	6/50 (12%)
Adjusted rates	36.4%	26.7%	22.0%
Terminal rates	12/36 (33%)	8/32 (25%)	5/25 (20%)
First incidence (days)	463	574	630
Life table tests	P=0.110N	P=0.237N	P=0.147N
Logistic regression tests	P=0.028N	P=0.167N	P=0.038N
Cochran-Armitage test	P=0.029N		
Fisher exact test		P=0.200N	P=0.039N
Thyroid Gland (Follicular Cell): Adenoma			
Overall rates	1/50 (2%)	2/48 (4%)	3/50 (6%)
Adjusted rates	2.8%	5.3%	10.6%
Terminal rates	1/36 (3%)	1/32 (3%)	2/25 (8%)
First incidence (days)	729 (T)	574	674
Life table tests	P=0.159	P=0.486	P=0.213
Logistic regression tests	P=0.224	P=0.487	P=0.279
Cochran-Armitage test	P=0.224		
Fisher exact test		P=0.485	P=0.309

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	44 mg/kg	88 mg/kg
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma			
Overall rates	1/50 (2%)	2/48 (4%)	5/50 (10%)
Adjusted rates	2.8%	5.3%	17.6%
Terminal rates	1/36 (3%)	1/32 (3%)	3/25 (12%)
First incidence (days)	729 (T)	574	674
Life table tests	P=0.032	P=0.486	P=0.052
Logistic regression tests	P=0.060	P=0.487	P=0.087
Cochran-Armitage test	P=0.061		
Fisher exact test		P=0.485	P=0.102
All Organs: Leukemia (Mononuclear)			
Overall rates	5/50 (10%)	14/50 (28%)	13/50 (26%)
Adjusted rates	12.8%	39.6%	37.3%
Terminal rates	3/36 (8%)	12/33 (36%)	6/25 (24%)
First incidence (days)	539	620	584
Life table tests	P=0.010	P=0.017	P=0.018
Logistic regression tests	P=0.033	P=0.025	P=0.035
Cochran-Armitage test	P=0.033		
Fisher exact test		P=0.020	P=0.033
All Organs: Mesothelioma Benign or Malignant			
Overall rates	1/50 (2%)	4/50 (8%)	4/50 (8%)
Adjusted rates	2.3%	10.5%	13.8%
Terminal rates	0/36 (0%)	2/33 (6%)	2/25 (8%)
First incidence (days)	505	603	676
Life table tests	P=0.105	P=0.190	P=0.133
Logistic regression tests	P=0.144	P=0.148	P=0.177
Cochran-Armitage test	P=0.146		
Fisher exact test		P=0.181	P=0.181
All Organs: Benign Tumors			
Overall rates	46/50 (92%)	46/50 (92%)	49/50 (98%)
Adjusted rates	100.0%	100.0%	100.0%
Terminal rates	36/36 (100%)	33/33 (100%)	25/25 (100%)
First incidence (days)	403	506	458
Life table tests	P=0.008	P=0.404	P=0.013
Logistic regression tests	P=0.576	P=0.125N	P=0.769
Cochran-Armitage test	P=0.147		
Fisher exact test		P=0.643N	P=0.181
All Organs: Malignant Tumors			
Overall rates	16/50 (32%)	29/50 (58%)	31/50 (62%)
Adjusted rates	36.6%	65.4%	74.4%
Terminal rates	9/36 (25%)	18/33 (55%)	15/25 (60%)
First incidence (days)	350	441	528
Life table tests	P<0.001	P=0.016	P=0.001
Logistic regression tests	P=0.002	P=0.006	P=0.002
Cochran-Armitage test	P=0.002		
Fisher exact test		P=0.008	P=0.002

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	44 mg/kg	88 mg/kg
All Organs: Malignant and Benign Tumors			
Overall rates	48/50 (96%)	48/50 (96%)	49/50 (98%)
Adjusted rates	100.0%	100.0%	100.0%
Terminal rates	36/36 (100%)	33/33 (100%)	25/25 (100%)
First incidence (days)	350	441	458
Life table tests	P=0.025	P=0.419	P=0.035
Logistic regression tests	P=0.557N	P=0.458N	P=0.661N
Cochran-Armitage test	P=0.391		
Fisher exact test		P=0.691N	P=0.500

(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals necropsied or examined microscopically for this tumor type
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality.
[c] Observed 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 the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] No tumors in dosed group or control group, statistical test not performed.

TABLE A4a
Historical Incidence of Renal Tubule Adenoma or Adenocarcinoma in Male F344/N Rats Receiving Corn Oil Vehicle[a]

Study	Incidence in Controls	
	Renal Tubule Adenoma	Renule Tubule Adenoma or Adenocarcinoma
Historical Incidence at Microbiological Associates		
d-Limonene	0/50	0/50
Benzyl Alcohol	0/48	0/48
α-Methylbenzyl Alcohol	0/50	0/50
Total	0/148 (0%)	0/148 (0%)
Overall Historical Incidence		
Total	5/2,142 (0.2%)	12/2,142 (0.6%)
Standard deviation	0.6%	0.9%
Range	0%-2%	0%-2%

[a] Data as of 22 November 1989 for studies of at least 104 weeks

TABLE A4b
Historical Incidence of Thyroid Follicular Cell Adenoma or Carcinoma in Male F344/N Rats Receiving Corn Oil Vehicle[a]

Study	Incidence in Controls		
	Follicular Cell Adenoma[b]	Follicular Cell Carcinoma	Follicular Cell Adenoma or Carcinoma[b]
Historical Incidence at Microbiological Associates			
d-Limonene	0/48	1/48	1/48
Benzyl Alcohol	1/49	0/49	1/49
α-Methylbenzyl Alcohol	0/48	0/48	0/48
Total	1/145 (0.7%)	1/145 (0.7%)	2/145 (1.4%)
Overall Historical Incidence			
Total	21/2,106 (1.0%)	30/2,106 (1.4%)	51/2,106 (2.4%)
Standard deviation	1.7%	1.8%	2.3%
Range	0%-8%	0%-8%	0%-10%

[a] Data as of 22 November 1989 for studies of at least 104 weeks
[b] Includes two papillary adenomas and one cystadenoma

Table A4c
Historical Incidence of Mononuclear Cell Leukemia or All Leukemias in Male F344/N Rats Receiving Corn Oil Vehicle[a]

Study	Incidence in Controls	
	Mononuclear Cell Leukemia	All Leukemias[b]
Historical Incidence at Microbiological Associates		
d-Limonene	10/50	10/50
Benzyl Alcohol	15/50	15/50
α-Methylbenzyl Alcohol	15/50	15/50
Total	40/150 (27%)	40/150 (27%)
Overall Historical Incidence		
Total	321/2,149 (14.9%)	371/2,149 (17.3%)
Standard deviation	10.8%	8.9%
Range	0%-44%	2%-44%

[a] Data as of 22 November 1989 for studies of at least 104 weeks
[b] Includes mononuclear cell, NOS, undifferentiated, myelomonocytic, lymphocytic, granulocytic, and monocytic leukemias

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate

	Vehicle Control	44 mg/kg	88 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
Scheduled sacrifice	9	10	10
Early deaths			
Dead	6	9	10
Moribund	5	7	14
Gavage death	4	1	
Accident			1
Survivors			
Terminal sacrifice	36	33	25
Animals examined microscopically	50	50	50
Alimentary System			
Esophagus	(50)	(48)	(50)
Hemorrhage	1 (2%)	1 (2%)	
Inflammation, chronic	1 (2%)		1 (2%)
Inflammation, chronic active	1 (2%)		
Wall, foreign body	1 (2%)		
Intestine large, cecum	(50)	(47)	(48)
Hemorrhage			1 (2%)
Ulcer, multifocal			1 (2%)
Intestine large, colon	(50)	(47)	(49)
Inflammation, subacute		1 (2%)	
Intestine small, duodenum	(48)	(46)	(47)
Erosion		1 (2%)	
Artery, inflammation, chronic	1 (2%)		
Liver	(50)	(50)	(50)
Angiectasis	3 (6%)	1 (2%)	1 (2%)
Basophilic focus	13 (26%)	6 (12%)	2 (4%)
Congestion	2 (4%)	1 (2%)	1 (2%)
Degeneration, cystic		2 (4%)	1 (2%)
Eosinophilic focus		1 (2%)	
Fatty change, diffuse	2 (4%)	1 (2%)	4 (8%)
Fatty change, focal	2 (4%)	1 (2%)	2 (4%)
Fatty change, multifocal	1 (2%)	3 (6%)	2 (4%)
Fibrosis			1 (2%)
Hematopoietic cell proliferation		3 (6%)	1 (2%)
Hemorrhage		1 (2%)	
Hepatodiaphragmatic nodule	4 (8%)	2 (4%)	1 (2%)
Inflammation, granulomatous, multifocal	13 (26%)	6 (12%)	5 (10%)
Leukocytosis	1 (2%)		
Mixed cell focus		3 (6%)	
Pigmentation, hemosiderin	1 (2%)	2 (4%)	1 (2%)
Bile duct, hyperplasia	42 (84%)	46 (92%)	46 (92%)
Centrilobular, fatty change	3 (6%)		
Centrilobular, necrosis	3 (6%)	2 (4%)	5 (10%)
Periportal, fatty change	4 (8%)	2 (4%)	1 (2%)
Periportal, fibrosis	1 (2%)		
Mesentery	(13)	(8)	(10)
Thrombus			1 (10%)
Artery, inflammation, chronic			1 (10%)
Fat, necrosis, focal	11 (85%)	8 (100%)	8 (80%)
Fat, necrosis, multifocal	2 (15%)		

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	44 mg/kg	88 mg/kg
Alimentary System (continued)			
Pancreas	(49)	(48)	(50)
Ectopic tissue	1 (2%)		
Necrosis, focal	1 (2%)		
Acinus, atrophy	9 (18%)	10 (21%)	11 (22%)
Acinus, hyperplasia, focal		2 (4%)	4 (8%)
Acinus, hyperplasia, multifocal			1 (2%)
Artery, inflammation, chronic	1 (2%)	4 (8%)	2 (4%)
Salivary glands	(50)	(49)	(49)
Inflammation, chronic			1 (2%)
Adventitia, fibrosis			1 (2%)
Stomach, forestomach	(50)	(48)	(50)
Hyperplasia, focal	1 (2%)	1 (2%)	2 (4%)
Inflammation, acute			1 (2%)
Inflammation, chronic, focal	1 (2%)		4 (8%)
Inflammation, chronic active	1 (2%)		
Ulcer		1 (2%)	
Stomach, glandular	(50)	(48)	(50)
Degeneration, cystic	38 (76%)	33 (69%)	39 (78%)
Erosion			1 (2%)
Cardiovascular System			
Heart	(50)	(50)	(50)
Cardiomyopathy	25 (50%)	36 (72%)	31 (62%)
Dilatation			2 (4%)
Mineralization			1 (2%)
Aortic valve, inflammation, chronic			1 (2%)
Artery, inflammation, chronic			1 (2%)
Atrium, thrombus	2 (4%)	4 (8%)	2 (4%)
Epicardium, inflammation, subacute			1 (2%)
Myocardium, inflammation, subacute			1 (2%)
Endocrine System			
Adrenal gland	(50)	(50)	(50)
Atrophy	1 (2%)		
Adrenal gland, cortex	(50)	(50)	(49)
Hyperplasia, focal	4 (8%)	4 (8%)	1 (2%)
Hyperplasia, multifocal		1 (2%)	
Hypertrophy	1 (2%)		
Necrosis, focal			1 (2%)
Vacuolization cytoplasmic, diffuse	2 (4%)		
Vacuolization cytoplasmic, focal	8 (16%)	1 (2%)	1 (2%)
Vacuolization cytoplasmic, multifocal	1 (2%)	1 (2%)	2 (4%)
Bilateral, hyperplasia, focal	1 (2%)		
Bilateral, vacuolization cytoplasmic, focal			2 (4%)
Adrenal gland, medulla	(43)	(47)	(44)
Hyperplasia, focal	1 (2%)	4 (9%)	2 (5%)
Hyperplasia, multifocal		2 (4%)	1 (2%)
Bilateral, hyperplasia, focal			1 (2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	44 mg/kg	88 mg/kg
Endocrine System (continued)			
Pituitary gland	(49)	(46)	(48)
Angiectasis		1 (2%)	2 (4%)
Cyst	4 (8%)	3 (7%)	2 (4%)
Hemorrhage	1 (2%)	3 (7%)	1 (2%)
Pigmentation, hemosiderin		1 (2%)	
Pars distalis, hyperplasia, focal	4 (8%)	1 (2%)	6 (13%)
Thyroid gland	(50)	(48)	(50)
Ultimobranchial cyst			1 (2%)
C-cell, hyperplasia	3 (6%)	1 (2%)	3 (6%)
Follicle, cyst		1 (2%)	1 (2%)
General Body System			
Tissue NOS			(1)
Necrosis, fibrinoid			1 (100%)
Genital System			
Preputial gland	(42)	(47)	(42)
Hyperplasia			1 (2%)
Inflammation, chronic	2 (5%)		1 (2%)
Inflammation, chronic active	4 (10%)	6 (13%)	8 (19%)
Duct, ectasia	1 (2%)	1 (2%)	1 (2%)
Prostate	(50)	(50)	(50)
Cytoplasmic alteration		1 (2%)	1 (2%)
Hyperplasia, focal	7 (14%)	10 (20%)	3 (6%)
Hyperplasia, multifocal		3 (6%)	4 (8%)
Inflammation, chronic	3 (6%)		
Inflammation, chronic active		7 (14%)	10 (20%)
Inflammation, suppurative		1 (2%)	1 (2%)
Seminal vesicle	(50)	(48)	(50)
Infiltration cellular, lymphocytic			1 (2%)
Inflammation, chronic active	1 (2%)		
Artery, inflammation, chronic			1 (2%)
Testes	(50)	(50)	(49)
Giant cell			1 (2%)
Granuloma sperm	1 (2%)	1 (2%)	
Hypospermia	5 (10%)	8 (16%)	3 (6%)
Arteriole, inflammation, chronic	1 (2%)	1 (2%)	1 (2%)
Interstitial cell, hyperplasia	10 (20%)	11 (22%)	6 (12%)
Hematopoietic System			
Bone marrow	(50)	(49)	(50)
Atrophy	2 (4%)		
Necrosis		1 (2%)	
Lymph node	(50)	(49)	(50)
Inguinal, sinus, ectasia	1 (2%)		
Mediastinal, hemorrhage	7 (14%)	6 (12%)	9 (18%)
Mediastinal, pigmentation, hemosiderin		1 (2%)	2 (4%)
Mediastinal, sinus, ectasia	1 (2%)	1 (2%)	
Pancreatic, hyperplasia, lymphoid			1 (2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	44 mg/kg	88 mg/kg
Hematopoietic System (continued)			
Lymph node, mandibular	(44)	(42)	(47)
Hemorrhage	1 (2%)	2 (5%)	
Hyperplasia, lymphoid		1 (2%)	
Hyperplasia, plasma cell	1 (2%)	5 (12%)	3 (6%)
Pigmentation, hemosiderin		1 (2%)	
Adventitia, fibrosis			1 (2%)
Sinus, ectasia	1 (2%)	3 (7%)	2 (4%)
Lymph node, mesenteric	(48)	(43)	(43)
Hemorrhage	2 (4%)	5 (12%)	3 (7%)
Sinus, ectasia	6 (13%)	5 (12%)	5 (12%)
Spleen	(50)	(49)	(50)
Congestion	1 (2%)		
Depletion lymphoid		1 (2%)	
Fibrosis	4 (8%)	2 (4%)	
Hematopoietic cell proliferation	1 (2%)	2 (4%)	4 (8%)
Hyperplasia, re cell, focal			1 (2%)
Infarct		1 (2%)	
Necrosis			1 (2%)
Red pulp, atrophy		1 (2%)	
Thymus	(37)	(38)	(39)
Hemorrhage	3 (8%)	1 (3%)	2 (5%)
Epithelial cell, hyperplasia	19 (51%)	24 (63%)	18 (46%)
Integumentary System			
Mammary gland	(29)	(26)	(32)
Galactocele		1 (4%)	1 (3%)
Duct, ectasia	1 (3%)	3 (12%)	3 (9%)
Skin	(50)	(50)	(48)
Cyst epithelial inclusion	1 (2%)		1 (2%)
Fibrosis, focal	1 (2%)		1 (2%)
Hemorrhage			1 (2%)
Inflammation, chronic		1 (2%)	1 (2%)
Inflammation, chronic, focal			1 (2%)
Musculoskeletal System			
Bone		(3)	(3)
Cranium, fibrous osteodystrophy			1 (33%)
Femur, fibrous osteodystrophy			1 (33%)
Femur, proliferation, focal		1 (33%)	
Nervous System			
Brain	(50)	(49)	(50)
Brain stem, compression	4 (8%)	2 (4%)	4 (8%)
Brain stem, hemorrhage			1 (2%)
Brain stem, pigmentation, hemosiderin	1 (2%)		
Cerebrum, gliosis, focal			1 (2%)
Cerebrum, hemorrhage		1 (2%)	1 (2%)
Cerebrum, pigmentation, hemosiderin			1 (2%)
Pons, hemorrhage			3 (6%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	44 mg/kg	88 mg/kg
Respiratory System			
Lung	(50)	(49)	(50)
Congestion	6 (12%)	3 (6%)	6 (12%)
Hemorrhage	3 (6%)	3 (6%)	1 (2%)
Hyperplasia, lymphoid			1 (2%)
Infiltration cellular, histiocytic	25 (50%)	18 (37%)	22 (44%)
Inflammation, granulomatous, focal	1 (2%)		2 (4%)
Inflammation, granulomatous, multifocal	1 (2%)	7 (14%)	6 (12%)
Pigmentation	26 (52%)	19 (39%)	23 (46%)
Alveolar epithelium, hyperplasia, focal	13 (26%)	6 (12%)	8 (16%)
Alveolar epithelium, hyperplasia, multifocal	1 (2%)	3 (6%)	1 (2%)
Bronchiole, inflammation, suppurative	1 (2%)		1 (2%)
Interstitium, inflammation	2 (4%)	2 (4%)	1 (2%)
Peribronchiolar, alveolus, inflammation, suppurative	1 (2%)		1 (2%)
Nose	(50)	(50)	(50)
Congestion	1 (2%)		
Foreign body		2 (4%)	3 (6%)
Fungus	4 (8%)	4 (8%)	5 (10%)
Hemorrhage	2 (4%)		
Hyperkeratosis, focal		1 (2%)	1 (2%)
Inflammation, suppurative	10 (20%)	9 (18%)	13 (26%)
Trachea	(50)	(49)	(50)
Hemorrhage		1 (2%)	
Special Senses System			
Eye	(3)	(4)	(2)
Cataract	2 (67%)	4 (100%)	1 (50%)
Necrosis			1 (50%)
Retina, degeneration	2 (67%)	3 (75%)	1 (50%)
Sclera, metaplasia, osseous	2 (67%)	3 (75%)	
Harderian gland	(1)	(1)	
Pigmentation, porphyrin		1 (100%)	
Urinary System			
Kidney	(50)	(50)	(50)
Hydronephrosis		1 (2%)	
Necrosis		1 (2%)	1 (2%)
Nephropathy	45 (90%)	44 (88%)	43 (86%)
Bilateral, pelvis, inflammation, chronic active			1 (2%)
Papilla, mineralization			1 (2%)
Renal tubule, hyperplasia, focal		1 (2%)	1 (2%)
Renal tubule, mineralization		1 (2%)	
Renal tubule, epithelium, hyperplasia		1 (2%)	1 (2%)
Renal tubule, epithelium, hyperplasia, focal			18 (36%)
Renal tubule, epithelium, hyperplasia, multifocal			4 (8%)
Urinary bladder	(49)	(49)	(50)
Dilatation			2 (4%)
Hemorrhage			1 (2%)
Infiltration cellular, lymphocytic		2 (4%)	
Transitional epithelium, hyperplasia		1 (2%)	

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR GAVAGE STUDY OF TRIS(2-CHLOROETHYL) PHOSPHATE

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate

	Vehicle Control	44 mg/kg	88 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
Scheduled sacrifice	10	10	9
Early deaths			
Dead	9	4	7
Moribund	8	10	22
Accident	1		1
Gavage death		3	4
Survivors			
Died last week of study	1		
Terminal sacrifice	31	33	17
Animals examined microscopically	50	50	50
Alimentary System			
Liver	(50)	(49)	(50)
Sarcoma stromal, metastatic, uterus			1 (2%)
Mesentery	(4)	(4)	(1)
Sarcoma stromal, metastatic, uterus			1 (100%)
Pancreas	(49)	(49)	(50)
Sarcoma stromal, metastatic, uterus			1 (2%)
Salivary glands	(50)	(49)	(50)
Stomach, forestomach	(50)	(50)	(49)
Stomach, glandular	(50)	(50)	(50)
Tongue	(1)		
Papilloma squamous	1 (100%)		
Cardiovascular System			
Heart	(50)	(50)	(50)
Endocardium, schwannoma malignant	2 (4%)	1 (2%)	
Endocrine System			
Adrenal gland, cortex	(48)	(50)	(50)
Carcinoma	1 (2%)		
Adrenal gland, medulla	(43)	(41)	(45)
Pheochromocytoma benign		2 (5%)	
Islets, pancreatic	(50)	(50)	(50)
Adenoma			1 (2%)
Pituitary	(49)	(49)	(47)
Carcinoma		1 (2%)	
Pars distalis, adenoma	21 (43%)	14 (29%)	11 (23%)
Pars distalis, carcinoma	1 (2%)	1 (2%)	
Thyroid gland	(50)	(50)	(50)
Bilateral, c-cell, adenoma	2 (4%)		
C-cell, adenoma		2 (4%)	3 (6%)
C-cell, carcinoma	1 (2%)	1 (2%)	1 (2%)
Follicular cell, adenoma		1 (2%)	1 (2%)
Follicular cell, carcinoma		2 (4%)	3 (6%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	44 mg/kg	88 mg/kg
Genital System			
Clitoral gland	(34)	(35)	(32)
Adenoma	7 (21%)	3 (9%)	4 (13%)
Carcinoma	2 (6%)	4 (11%)	2 (6%)
Ovary	(49)	(50)	(50)
Uterus	(50)	(50)	(50)
Leiomyoma	1 (2%)		
Polyp stromal	9 (18%)	13 (26%)	11 (22%)
Polyp stromal, multiple	1 (2%)		1 (2%)
Sarcoma stromal			3 (6%)
Endometrium, adenoma		1 (2%)	1 (2%)
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Lymph node	(50)	(49)	(49)
Lymph node, mandibular	(47)	(45)	(47)
Lymph node, mesenteric	(48)	(45)	(49)
Spleen	(50)	(49)	(50)
Thymus	(37)	(42)	(39)
Integumentary System			
Mammary gland	(46)	(46)	(47)
Adenocarcinoma	3 (7%)	3 (7%)	3 (6%)
Adenoma		1 (2%)	1 (2%)
Fibroadenoma	14 (30%)	16 (35%)	13 (28%)
Fibroadenoma, multiple	3 (7%)	5 (11%)	5 (11%)
Skin	(50)	(49)	(49)
Sarcoma	1 (2%)		
Subcutaneous tissue, fibroma	1 (2%)		
Subcutaneous tissue, hemangiosarcoma	1 (2%)		1 (2%)
Subcutaneous tissue, schwannoma malignant	1 (2%)		
Musculoskeletal System			
Bone	(2)	(1)	(2)
Osteosarcoma		1 (100%)	1 (50%)
Nervous System			
Brain	(50)	(50)	(50)
Astrocytoma benign		1 (2%)	
Carcinoma, metastatic		1 (2%)	
Carcinoma, metastatic, pituitary gland	1 (2%)		
Glioma malignant			1 (2%)
Cerebellum, meninges, granular cell tumor benign		2 (4%)	
Cerebrum, oligodendroglioma malignant	1 (2%)		

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	44 mg/kg	88 mg/kg
Respiratory System			
Lung	(50)	(50)	(50)
Adenocarcinoma, metastatic, mammary gland	1 (2%)		
Alveolar/bronchiolar adenoma	1 (2%)	1 (2%)	1 (2%)
Carcinoma, metastatic, adrenal gland	1 (2%)		
Osteosarcoma, metastatic, bone		1 (2%)	
Nose	(50)	(50)	(50)
Squamous cell carcinoma			1 (2%)
Special Senses System			
Zymbal's gland	(1)		
Carcinoma	1 (100%)		
Urinary System			
Kidney	(50)	(50)	(50)
Renal tubule, adenoma		2 (4%)	5 (10%)
Transitional epithelium, carcinoma			1 (2%)
Urinary bladder	(49)	(49)	(48)
Systemic Lesions			
Multiple organs[a]	(50)	(50)	(50)
Leukemia monocytic	1 (2%)		
Leukemia mononuclear	14 (28%)	16 (32%)	20 (40%)
Lymphoma malignant		1 (2%)	
Tumor Summary			
Total animals with primary neoplasms[b]	45	46	44
Total primary neoplasms	91	95	95
Total animals with benign neoplasms	35	38	32
Total benign neoplasms	61	64	58
Total animals with malignant neoplasms	26	25	30
Total malignant neoplasms	30	31	37
Total animals with secondary neoplasms[c]	3	2	1
Total secondary neoplasms	3	2	3

[a] The number in parentheses is the number of animals with any tissue examined microscopically
[b] Primary tumors: all tumors except metastatic tumors
[c] Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: Vehicle Control

Number of Days on Study	1 6 1	3 3 5	3 4 3	4 0 3	4 3 8	4 8 9	5 8 2	5 9 7	6 1 9	6 3 3	6 3 4	6 8 3	6 9 5	7 0 2	7 0 3	7 1 1	7 1 7	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	4 3 5	4 2 5	4 1 5	4 2 4	4 1 4	3 8 4	4 0 5	4 6 5	4 1 3	3 9 5	3 8 3	4 4 5	4 2 3	4 6 4	3 7 5	4 5 5	3 7 1	4 4 4	3 7 2	3 7 3	3 7 4	3 8 1	3 8 2	3 8 5	3 9 1
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery		+																						
Pancreas	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																							+	
Papilloma squamous																							X	
Tooth																								
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocardium, schwannoma							X																	
Endocardium, schwannoma malignant																							X	
Endocrine System																								
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Carcinoma																								
Adrenal gland, medulla	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+
Pars distalis, adenoma										X	X				X		X	X	X		X	X	X	
Pars distalis, carcinoma				X																				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, c-cell, adenoma																								
C-cell, carcinoma																								X

+: Tissue Examined
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: Vehicle Control (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	3 9 2	3 9 3	3 9 4	4 0 1	4 0 2	4 0 3	4 0 4	4 1 1	4 1 2	4 2 1	4 2 2	4 3 1	4 3 2	4 3 3	4 3 4	4 4 1	4 4 2	4 4 3	4 5 1	4 5 2	4 5 3	4 5 4	4 6 1	4 6 2	4 6 3	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery		+							+								+									4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Papilloma squamous																										1
Tooth												+														1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocardium, schwannoma, Endocardium, schwannoma malignant																										2
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+		48
Carcinoma											X															1
Adrenal gland, medulla	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	43
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X					X					X	X			X	X	X	X		X	X		X	X		21
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, c-cell, adenoma					X										X											2
C-cell, carcinoma																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: Vehicle Control (continued)

Number of Days on Study	1 6 1	3 3 5	3 4 3	4 0 3	4 3 8	4 8 9	5 8 2	5 9 7	6 1 9	6 3 3	6 3 4	6 8 3	6 9 5	7 0 2	7 0 3	7 1 1	7 1 7	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	4 3 5	4 2 5	4 1 5	4 2 4	4 1 4	3 8 4	4 0 5	4 6 5	4 1 3	3 9 5	3 8 3	4 4 5	4 2 3	4 6 4	3 7 5	4 5 5	3 7 1	4 4 4	3 7 2	3 7 3	3 7 4	3 8 1	3 8 2	3 8 5	3 9 1
Genital System																									
Clitoral gland	M	+	+	+	+	+	+	+	M	M	+	+	+	M	M	+	M	M	+	+	+	M	+	+	M
Adenoma																								X	
Carcinoma											X					X									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																					X				
Polyp stromal												X													
Polyp stromal, multiple																				X					
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	M	M
Integumentary System																									
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+
Adenocarcinoma								X													X				
Fibroadenoma									X	X							X					X			
Fibroadenoma, multiple															X			X					X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, hemangiosarcoma																									
Subcutaneous tissue, schwannoma, malignant																									
Musculoskeletal System																									
Bone																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland				X																					
Cerebrum, oligodendroglioma, malignant					X																				

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: Vehicle Control (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	3 9 2	3 9 3	3 9 4	4 0 1	4 0 2	4 0 3	4 0 4	4 1 1	4 1 2	4 2 1	4 2 2	4 3 1	4 3 2	4 3 3	4 3 4	4 4 1	4 4 2	4 4 3	4 5 1	4 5 2	4 5 3	4 5 4	4 6 1	4 6 2	4 6 3	**Total Tissues/ Tumors**
Genital System																										
Clitoral gland	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	M	+	+	+	M	M	+	+	M	34
Adenoma									X	X	X		X										X	X		7
Carcinoma																										2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																										1
Polyp stromal						X				X		X				X		X	X	X		X				9
Polyp stromal, multiple																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	47
Lymph node, mesenteric	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	M	+	+	M	M	37
Integumentary System																										
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenocarcinoma							X																			3
Fibroadenoma			X	X	X	X		X						X		X	X						X	X		14
Fibroadenoma, multiple																										3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma	X																									1
Subcutaneous tissue, fibroma			X																							1
Subcutaneous tissue, hemangiosarcoma								X																		1
Subcutaneous tissue, schwannoma, malignant																			X							1
Musculoskeletal System																										
Bone										+												+				2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																										1
Cerebrum, oligodendroglioma, malignant																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: Vehicle Control (continued)

Number of Days on Study	1 6 1	3 3 5	3 4 3	4 0 3	4 3 8	4 8 9	5 8 2	5 9 7	6 1 9	6 3 3	6 3 4	6 8 3	6 9 5	7 0 2	7 0 3	7 1 1	7 1 7	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	4 3 5	4 2 5	4 1 5	4 2 4	4 1 4	4 8 4	3 0 5	4 6 5	4 1 3	3 9 5	3 8 3	4 4 5	4 2 3	4 6 4	3 7 5	4 5 5	3 7 1	4 4 4	3 7 2	3 7 3	3 7 4	3 8 1	3 8 2	3 8 5	3 9 1
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, mammary gland								X																	
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, adrenal gland																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye												+													
Harderian gland												+													
Zymbal's gland														+											
Carcinoma														X											
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monocytic																								X	
Leukemia mononuclear		X				X			X			X								X	X	X		X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: Vehicle Control (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	3 9 2	3 9 3	3 9 4	4 0 1	4 0 2	4 0 3	4 0 4	4 1 1	4 1 2	4 2 1	4 2 2	4 3 1	4 3 2	4 3 3	4 3 4	4 4 1	4 4 2	4 4 3	4 5 1	4 5 2	4 5 3	4 5 4	4 6 1	4 6 2	4 6 3	**Total Tissues/ Tumors**
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, mammary gland																										1
Alveolar/bronchiolar adenoma																			X							1
Carcinoma, metastatic, adrenal gland											X															1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+				+									+							+		+			6
Harderian gland																										1
Zymbal's gland																										
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia monocytic																										1
Leukemia mononuclear				X				X		X		X					X						X			14

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 44 mg/kg

Number of Days on Study	0 8 5	1 5 4	1 5 4	1 5 4	3 1 0	5 6 1	5 8 8	5 9 8	6 1 7	6 2 0	6 5 2	6 7 1	6 8 6	6 9 7	7 0 4	7 1 6	7 2 4	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	5 0 5	5 0 4	5 4 5	5 5 5	5 3 5	5 8 5	5 1 5	5 6 5	5 6 4	5 1 4	5 2 5	5 0 3	5 9 5	4 3 4	5 4 4	5 6 3	5 7 5	4 9 1	4 9 2	4 9 3	4 9 4	5 0 1	5 0 2	5 1 1	5 1 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery																									
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocardium, schwannoma malignant																									
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	M	+	+	+	M	+	+	+	+	+	M	+	+	+	M	+	M	+	+	+	+	+	+	+	M
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																	X								
Pars distalis, adenoma								X	X				X								X		X		
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																							X		
C-cell, carcinoma																									
Follicular cell, adenoma														X											
Follicular cell, carcinoma																									
Genital System																									
Clitoral gland	M	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	M	M	M
Adenoma													X												
Carcinoma					X															X	X				
Ovary																+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal									X	X						X	X			X		X			
Endometrium, adenoma																	X								

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 44 mg/kg (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	5 1 3	5 2 1	5 2 2	5 2 3	5 2 4	5 3 1	5 3 2	5 3 3	5 4 1	5 4 2	5 4 3	5 5 1	5 5 2	5 5 3	5 5 4	5 6 1	5 6 2	5 7 1	5 7 2	5 7 3	5 7 4	5 8 1	5 8 2	5 8 3	5 8 4	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	49
Mesentery					+					+		+											+			4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocardium, schwannoma malignant																		X								1
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	M	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	41
Pheochromocytoma benign	X						X																			2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	+	M	M	M	+	+	+	M	+	+	M	+	+	+	M	+	+	M	M	+	M	+	37
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																										1
Pars distalis, adenoma	X	X	X	X		X												X		X	X			X		14
Pars distalis, carcinoma																							X			1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																					X					2
C-cell, carcinoma																		X								1
Follicular cell, adenoma																										1
Follicular cell, carcinoma							X																	X		2
Genital System																										
Clitoral gland	+	+	+	+	M	+	+	+	+	M	+	+	M	+	+	+	+	M	+	+	M	M	M	M	+	35
Adenoma								X									X									3
Carcinoma							X																			4
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal								X	X	X					X						X	X		X		13
Endometrium, adenoma																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 44 mg/kg (continued)

Number of Days on Study	0 8 5	1 5 4	1 5 4	1 5 4	3 1 0	5 6 1	5 8 8	5 9 8	6 1 7	6 2 0	6 5 2	6 7 1	6 8 6	6 9 7	7 0 4	7 1 6	7 2 4	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	5 0 5	5 0 4	5 4 5	5 5 5	5 3 5	5 8 5	5 1 5	5 6 5	5 6 4	5 1 4	5 2 5	5 0 3	4 9 5	5 3 4	5 4 4	5 6 3	5 7 5	4 9 1	4 9 2	4 9 3	4 9 4	5 0 1	5 0 2	5 1 1	5 1 2
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	M	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	M	+
Integumentary System																									
Mammary gland	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Adenocarcinoma									X																
Adenoma																				X					
Fibroadenoma							X			X			X		X	X	X								
Fibroadenoma, multiple																									X
Skin	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone											+														
Osteosarcoma											X														
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma benign																									
Carcinoma, metastatic																	X								
Cerebellum, meninges, granular cell tumor, benign																		X							
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Osteosarcoma, metastatic, bone											X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																								+	
Urinary system																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X	X			X		X	X	X	X	X			X	X		X		X	
Lymphoma malignant	X																								

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 44 mg/kg (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	5 1 3	5 2 1	5 2 2	5 2 3	5 2 4	5 3 1	5 3 2	5 3 3	5 4 1	5 4 2	5 4 3	5 5 1	5 5 2	5 5 3	5 5 4	5 6 1	5 6 2	5 7 1	5 7 2	5 7 3	5 7 4	5 8 1	5 8 2	5 8 3	5 8 4	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mandibular	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	45
Lymph node, mesenteric	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	M	42
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenocarcinoma		X	X																							3
Adenoma																										1
Fibroadenoma			X		X	X	X			X			X	X		X		X	X							16
Fibroadenoma, multiple				X													X				X		X			5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Musculoskeletal System																										
Bone																										1
Osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma benign						X																				1
Carcinoma, metastatic																										1
Cerebellum, meninges, granular cell tumor, benign																	X									2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma												X														1
Osteosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																									+	2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma		X		X																						2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear							X				X												X	X		16
Lymphoma malignant																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 88 mg/kg

Number of Days on Study	1 5 4	2 8 8	3 9 4	4 3 1	4 6 9	4 7 0	4 9 2	5 1 9	5 3 4	5 3 4	5 3 6	5 4 7	5 5 5	5 7 6	5 8 1	5 8 8	5 9 2	5 9 6	6 0 4	6 1 0	6 1 0	6 1 2	6 1 7	6 3 4	6 6 0
Carcass ID Number	6 7 5	6 9 5	6 5 5	6 7 4	6 6 5	6 3 5	6 1 5	6 5 4	6 4 5	6 5 3	6 4 4	6 3 4	6 0 5	6 4 3	6 8 5	6 2 5	7 0 4	6 3 3	6 1 4	6 6 4	6 7 3	6 3 2	6 6 3	6 1 3	6 9 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	M	+	M	+	+	+	+	+	M	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal, metastatic, uterus																			X						
Mesentery																			+						
Sarcoma stromal, metastatic, uterus																			X						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal, metastatic, uterus																			X						
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	M	+	+	I	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Pars distalis, adenoma							X													X	X				X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma																									
Follicular cell, adenoma																									
Follicular cell, carcinoma																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 88 mg/kg (continued)

Number of Days on Study	6 7 5	6 8 7	6 8 7	7 0 4	7 0 4	7 1 0	7 1 8	7 2 4	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	6 9 3	6 2 4	6 8 4	6 1 2	6 4 2	6 2 3	7 0 2	6 9 1	6 1 1	6 2 1	6 2 2	6 3 1	6 4 1	6 5 1	6 5 2	6 6 1	6 6 2	6 7 1	6 7 2	6 8 1	6 8 2	6 8 3	6 9 2	7 0 1	7 0 3	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma stromal, metastatic, uterus																										1
Mesentery																										1
Sarcoma stromal, metastatic, uterus																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma stromal, metastatic, uterus																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	45
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma													X													1
Parathyroid gland	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	M	+	40
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	47
Pars distalis, adenoma					X				X	X				X		X			X						X	11
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																		X			X	X				3
C-cell, carcinoma																				X						1
Follicular cell, adenoma													X													1
Follicular cell, carcinoma							X												X	X						3

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 88 mg/kg (continued)

Number of Days on Study	1 5 4	2 8 8	3 9 4	4 3 1	4 6 9	4 7 0	4 9 2	5 1 9	5 3 4	5 3 4	5 3 6	5 3 7	5 4 5	5 5 6	5 7 1	5 8 8	5 9 2	5 9 6	6 0 4	6 1 0	6 1 0	6 1 2	6 1 7	6 3 4	6 6 0
Carcass ID Number	6 7 5	6 9 5	6 5 5	6 7 4	6 6 5	6 3 5	6 1 5	6 5 4	6 4 5	6 5 3	6 4 4	6 3 4	7 0 5	6 4 3	6 8 5	6 2 5	7 0 4	6 3 3	6 1 4	6 6 4	6 7 3	6 3 2	6 6 3	6 1 3	6 9 4
Genital System																									
Clitoral gland	M	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	M	+	+	+	+	M	+
Adenoma													X								X				
Carcinoma								X									X								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal			X				X					X	X			X									
Polyp stromal, multiple																								X	
Sarcoma stromal																			X						
Endometrium, adenoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Lymph node, mandibular	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	M	M	+	+	+
Integumentary System																									
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Adenocarcinoma																									
Adenoma																									
Fibroadenoma																		X			X				
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Subcutaneous tissue, hemangiosarcoma																									
Musculoskeletal System																									
Bone							+																		
Osteosarcoma							X																		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma malignant																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 88 mg/kg (continued)

Number of Days on Study	6 7 5	6 8 7	6 8 7	7 0 4	7 0 4	7 1 0	7 1 8	7 2 4	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	6 9 3	6 2 4	6 8 4	6 1 2	6 4 2	6 2 3	7 0 2	6 9 1	6 1 1	6 2 1	6 2 2	6 3 1	6 4 1	6 5 1	6 5 2	6 6 1	6 6 2	6 7 1	6 7 2	6 8 1	6 8 2	6 8 3	6 9 2	7 0 1	7 0 3	**Total Tissues/ Tumors**
Genital System																										
Clitoral gland	M	+	+	M	+	M	M	+	M	M	+	+	+	M	+	M	M	+	M	+	M	M	+	+	+	32
Adenoma					X			X																		4
Carcinoma																										2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal			X	X											X		X						X	X		11
Polyp stromal, multiple																										1
Sarcoma stromal		X																			X					3
Endometrium, adenoma								X																		1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	M	+	M	+	+	+	+	+	+	M	+	+	M	+	+	M	+	+	+	M	M	39
Integumentary System																										
Mammary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenocarcinoma		X			X												X									3
Adenoma																									X	1
Fibroadenoma	X	X						X			X		X	X	X			X				X		X	X	13
Fibroadenoma, multiple					X		X			X							X		X							5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcutaneous tissue, hemangiosarcoma																				X						1
Musculoskeletal System																										
Bone															+											2
Osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma malignant	X																									1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 88 mg/kg (continued)

Number of Days on Study	1 5 4	2 8 8	3 9 4	4 3 1	4 6 9	4 7 0	4 9 2	5 1 9	5 3 4	5 3 4	5 3 6	5 4 7	5 5 5	5 7 6	5 8 1	5 8 8	5 9 2	5 9 6	6 0 4	6 1 0	6 1 0	6 1 2	6 1 7	6 3 4	6 6 0
Carcass ID Number	6 7 5	6 9 5	6 5 5	6 7 4	6 6 5	6 3 5	6 1 5	6 5 4	6 4 5	6 5 3	6 4 4	6 3 4	7 0 5	6 4 3	6 8 5	6 2 5	7 0 4	6 3 3	6 1 4	6 6 4	6 7 3	6 3 2	6 6 3	6 1 3	6 9 4
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																		X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma															X										
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye				+											+					+					
Harderian gland				+																					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Transitional epithelium, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X	X						X		X								X	X		X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 88 mg/kg (continued)

Number of Days on Study	6 7 5	6 8 7	6 8 7	7 0 4	7 0 4	7 1 0	7 1 8	7 2 4	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	6 9 3	6 2 4	6 8 4	6 1 2	6 4 2	6 2 3	7 0 2	6 9 1	6 1 1	6 2 1	6 2 2	6 3 1	6 4 1	6 5 1	6 5 2	6 6 1	6 6 2	7 1 1	7 1 2	6 8 1	6 8 2	6 8 3	6 9 2	7 0 1	7 0 3	**Total Tissues/ Tumors**
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+		+			+	+																		8
Harderian gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																	X	X			X	X		X		5
Transitional epithelium, carcinoma									X																	1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X		X		X	X	X		X	X		X		X				X			X	X			20

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate

	Vehicle Control	44 mg/kg	88 mg/kg
Adrenal Gland (Medulla): Pheochromocytoma Benign			
Overall rates[a]	0/43 (0%)	2/41 (5%)	0/45 (0%)
Adjusted rates[b]	0.0%	6.9%	0.0%
Terminal rates[c]	0/28 (0%)	2/29 (7%)	0/16 (0%)
First incidence (days)		729 (T)	
Life table tests[d]	P=0.562	P=0.246	–[e]
Logistic regression tests[d]	P=0.562	P=0.246	–[e]
Cochran-Armitage test[d]	P=0.661N		
Fisher exact test[d]		P=0.235	–[e]
Clitoral Gland: Adenoma			
Overall rates	7/34 (21%)	3/35 (9%)	4/32 (13%)
Adjusted rates	30.4%	11.5%	15.2%
Terminal rates	7/23 (30%)	2/22 (9%)	0/9 (0%)
First incidence (days)	729 (T)	686	555
Life table tests	P=0.565N	P=0.166N	P=0.523
Logistic regression tests	P=0.370N	P=0.145N	P=0.534N
Cochran-Armitage test	P=0.213N		
Fisher exact test		P=0.141N	P=0.292N
Clitoral Gland: Carcinoma			
Overall rates	2/34 (6%)	4/35 (11%)	2/32 (6%)
Adjusted rates	5.3%	15.5%	5.2%
Terminal rates	0/23 (0%)	3/22 (14%)	0/9 (0%)
First incidence (days)	634	310	519
Life table tests	P=0.376	P=0.325	P=0.573
Logistic regression tests	P=0.589	P=0.356	P=0.688N
Cochran-Armitage test	P=0.561		
Fisher exact test		P=0.351	P=0.670
Clitoral Gland: Adenoma or Carcinoma			
Overall rates	9/34 (26%)	7/35 (20%)	6/32 (19%)
Adjusted rates	34.1%	26.4%	19.7%
Terminal rates	7/23 (30%)	5/22 (23%)	0/9 (0%)
First incidence (days)	634	310	519
Life table tests	P=0.427	P=0.423N	P=0.447
Logistic regression tests	P=0.338N	P=0.378N	P=0.467N
Cochran-Armitage test	P=0.269N		
Fisher exact test		P=0.363N	P=0.326N
Kidney (Renal Tubule): Adenoma			
Overall rates	0/50 (0%)	2/50 (4%)	5/50 (10%)
Adjusted rates	0.0%	6.1%	29.4%
Terminal rates	0/32 (0%)	2/33 (6%)	5/17 (29%)
First incidence (days)		729 (T)	729 (T)
Life table tests	P=0.001	P=0.245	P=0.003
Logistic regression tests	P=0.001	P=0.245	P=0.003
Cochran-Armitage test	P=0.017		
Fisher exact test		P=0.247	P=0.028

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	44 mg/kg	88 mg/kg
Mammary Gland: Adenocarcinoma			
Overall rates	3/50 (6%)	3/50 (6%)	3/50 (6%)
Adjusted rates	8.4%	8.3%	13.9%
Terminal rates	2/32 (6%)	2/33 (6%)	1/17 (6%)
First incidence (days)	597	617	687
Life table tests	P=0.344	P=0.651N	P=0.412
Logistic regression tests	P=0.505	P=0.658	P=0.563
Cochran-Armitage test	P=0.584		
Fisher exact test		P=0.661N	P=0.661N
Mammary Gland: Fibroadenoma			
Overall rates	17/50 (34%)	21/50 (42%)	18/50 (36%)
Adjusted rates	45.5%	53.6%	74.0%
Terminal rates	12/32 (38%)	15/33 (45%)	11/17 (65%)
First incidence (days)	619	588	596
Life table tests	P=0.017	P=0.312	P=0.019
Logistic regression tests	P=0.089	P=0.253	P=0.084
Cochran-Armitage test	P=0.458		
Fisher exact test		P=0.268	P=0.500
Mammary Gland: Adenoma, Fibroadenoma, or Adenocarcinoma			
Overall rates	20/50 (40%)	24/50 (48%)	18/50 (36%)
Adjusted rates	52.1%	59.7%	74.0%
Terminal rates	14/32 (44%)	17/33 (52%)	11/17 (65%)
First incidence (days)	597	588	596
Life table tests	P=0.052	P=0.323	P=0.059
Logistic regression tests	P=0.258	P=0.251	P=0.252
Cochran-Armitage test	P=0.382N		
Fisher exact test		P=0.273	P=0.418N
Pituitary Gland (Pars Distalis): Adenoma			
Overall rates	21/49 (43%)	14/49 (29%)	11/47 (23%)
Adjusted rates	57.9%	38.1%	47.6%
Terminal rates	16/31 (52%)	11/33 (33%)	6/16 (38%)
First incidence (days)	633	598	492
Life table tests	P=0.342N	P=0.081N	P=0.500N
Logistic regression tests	P=0.095N	P=0.091N	P=0.165N
Cochran-Armitage test	P=0.026N		
Fisher exact test		P=0.103N	P=0.035N
Pituitary Gland (Pars Distalis): Adenoma, Carcinoma, or Unspecified Site Carcinoma			
Overall rates	22/49 (45%)	16/49 (33%)	11/47 (23%)
Adjusted rates	58.8%	42.7%	47.6%
Terminal rates	16/31 (52%)	12/33 (36%)	6/16 (38%)
First incidence (days)	403	598	492
Life table tests	P=0.297N	P=0.125N	P=0.414N
Logistic regression tests	P=0.056N	P=0.147N	P=0.082N
Cochran-Armitage test	P=0.017N		
Fisher exact test		P=0.150N	P=0.022N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	44 mg/kg	88 mg/kg
Thyroid Gland (C-cell): Adenoma			
Overall rates	2/50 (4%)	2/50 (4%)	3/50 (6%)
Adjusted rates	6.3%	6.1%	17.6%
Terminal rates	2/32 (6%)	2/33 (6%)	3/17 (18%)
First incidence (days)	729 (T)	729 (T)	729 (T)
Life table tests	P=0.177	P=0.685N	P=0.226
Logistic regression tests	P=0.177	P=0.685N	P=0.226
Cochran-Armitage test	P=0.407		
Fisher exact test		P=0.691N	P=0.500
Thyroid Gland (C-cell): Adenoma or Carcinoma			
Overall rates	3/50 (6%)	3/50 (6%)	4/50 (8%)
Adjusted rates	9.4%	9.1%	23.5%
Terminal rates	3/32 (9%)	3/33 (9%)	4/17 (24%)
First incidence (days)	729 (T)	729 (T)	729 (T)
Life table tests	P=0.150	P=0.650N	P=0.182
Logistic regression tests	P=0.150	P=0.650N	P=0.182
Cochran-Armitage test	P=0.421		
Fisher exact test		P=0.661N	P=0.500
Thyroid Gland (Follicular Cell): Carcinoma			
Overall rates	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted rates	0.0%	6.1%	16.4%
Terminal rates	0/32 (0%)	2/33 (6%)	2/17 (12%)
First incidence (days)		729 (T)	718
Life table tests	P=0.021	P=0.245	P=0.040
Logistic regression tests	P=0.023	P=0.245	P=0.044
Cochran-Armitage test	P=0.082		
Fisher exact test		P=0.247	P=0.121
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma			
Overall rates	0/50 (0%)	3/50 (6%)	4/50 (8%)
Adjusted rates	0.0%	8.6%	22.0%
Terminal rates	0/32 (0%)	2/33 (6%)	3/17 (18%)
First incidence (days)	---	697	718
Life table tests	P=0.008	P=0.127	P=0.013
Logistic regression tests	P=0.011	P=0.120	P=0.014
Cochran-Armitage test	P=0.048		
Fisher exact test		P=0.121	P=0.059
Uterus: Stromal Polyp			
Overall rates	10/50 (20%)	13/50 (26%)	12/50 (24%)
Adjusted rates	30.0%	34.7%	40.6%
Terminal rates	9/32 (28%)	9/33 (27%)	4/17 (24%)
First incidence (days)	683	617	394
Life table tests	P=0.050	P=0.345	P=0.073
Logistic regression tests	P=0.249	P=0.311	P=0.321
Cochran-Armitage test	P=0.361		
Fisher exact test		P=0.318	P=0.405

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	44 mg/kg	88 mg/kg
Uterus: Stromal Sarcoma			
Overall rates	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted rates	0.0%	0.0%	12.6%
Terminal rates	0/32 (0%)	0/33 (0%)	1/17 (6%)
First incidence (days)			604
Life table tests	P=0.015	–[e]	P=0.057
Logistic regression tests	P=0.032	–[e]	P=0.099
Cochran-Armitage test	P=0.038		
Fisher exact test		–[e]	P=0.121
All Organs: Leukemia (Mononuclear)			
Overall rates	14/50 (28%)	16/50 (32%)	20/50 (40%)
Adjusted rates	37.4%	38.4%	64.4%
Terminal rates	10/32 (31%)	8/33 (24%)	7/17 (41%)
First incidence (days)	335	561	469
Life table tests	P=0.006	P=0.441	P=0.006
Logistic regression tests	P=0.076	P=0.399	P=0.093
Cochran-Armitage test	P=0.122		
Fisher exact test		P=0.414	P=0.146
All Organs: Benign Tumors			
Overall rates	35/50 (70%)	38/50 (76%)	32/50 (64%)
Adjusted rates	89.7%	90.4%	93.8%
Terminal rates	28/32 (88%)	29/33 (88%)	15/17 (88%)
First incidence (days)	619	588	394
Life table tests	P=0.003	P=0.410	P=0.005
Logistic regression tests	P=0.248	P=0.289	P=0.295
Cochran-Armitage test	P=0.294N		
Fisher exact test		P=0.326	P=0.335N
All Organs: Malignant Tumors			
Overall rates	26/50 (52%)	25/50 (50%)	30/50 (60%)
Adjusted rates	59.2%	54.2%	82.2%
Terminal rates	15/32 (47%)	12/33 (36%)	11/17 (65%)
First incidence (days)	335	85	469
Life table tests	P=0.010	P=0.478N	P=0.008
Logistic regression tests	P=0.214	P=0.492N	P=0.216
Cochran-Armitage test	P=0.242		
Fisher exact test		P=0.500N	P=0.273
All Organs: Malignant and Benign Tumors			
Overall rates	45/50 (90%)	46/50 (92%)	44/50 (88%)
Adjusted rates	95.7%	97.9%	100.0%
Terminal rates	30/32 (94%)	32/33 (97%)	17/17 (100%)
First incidence (days)	335	85	394
Life table tests	P=0.001	P=0.562	P=0.002
Logistic regression tests	P=0.557	P=0.308	P=0.587
Cochran-Armitage test	P=0.435N		
Fisher exact test		P=0.500	P=0.500N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals necropsied or examined microscopically for this tumor type
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality.
[c] Observed 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 the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] No tumors in dosed group or control group; statistical test not performed.

TABLE B4a
Historical Incidence of Renal Tubule Adenoma or Adenocarcinoma in Female F344/N Rats Receiving Corn Oil Vehicle[a]

Study	Incidence in Controls	
	Renal Tubule Adenoma	Renal Tubule Adenoma or Adenocarcinoma
Historical Incidence at Microbiological Associates		
d-Limonene	0/50	0/50
Benzyl Alcohol	0/48	0/48
α-Methylbenzyl Alcohol	0/50	0/50
Total	0/148 (0%)	0/148 (0%)
Overall Historical Incidence		
Total	1/2,144 (0.1%)	2/2,144 (0.1%)
Standard deviation	0.3%	0.4%
Range	0%-2%	0%-2%

[a] Data as of 22 November 1989 for studies of at least 104 weeks

TABLE B4b
Historical Incidence of Thyroid Follicular Cell Adenoma or Carcinoma in Female F344/N Rats Receiving Corn Oil Vehicle[a]

Study	Incidence in Controls		
	Follicular Cell Adenoma[b]	Follicular Cell Carcinoma	Follicular Cell Adenoma or Carcinoma[b]
Historical Incidence at Microbiological Associates			
d-Limonene	1/50	0/50	1/50
Benzyl Alcohol	0/49	0/49	0/49
α-Methylbenzyl Alcohol	0/47	1/47	1/47
Total	1/146 (0.7%)	1/146 (0.7%)	2/146 (1.4%)
Overall Historical Incidence			
Total	20/2,107 (0.9%)	14/2,107 (0.7%)	34/2,107 (1.6%)
Standard deviation	1.4%	1.2%	1.6%
Range	0%-6%	0%-4%	0%-6%

[a] Data as of 22 November 1989 for studies of at least 104 weeks
[b] Includes one papillary adenoma, two papillary cystadenomas, and two cystadenomas

TABLE B4c
Historical Incidence of Mononuclear Cell Leukemia or All Leukemias in Female F344/N Rats Receiving Corn Oil Vehicle[a]

Study	Incidence in Controls	
	Mononuclear Cell Leukemia	All Leukemias[b]
Historical Incidence at Microbiological Associates		
d-Limonene	10/50	10/50
Benzyl Alcohol	8/50	8/50
α-Methylbenzyl Alcohol	12/50	12/50
Total	30/150 (20%)	30/150 (20%)
Overall Historical Incidence		
Total	329/2,150 (15.3%)	422/2,150 (19.6%)
Standard deviation	10.6%	8.3%
Range	0%-38%	4%-42%

[a] Data as of 22 November 1989 for studies of at least 104 weeks
[b] Includes mononuclear cell, NOS, undifferentiated, myelomonocytic, lymphocytic, granulocytic, and monocytic leukemias

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate

	Vehicle Control	44 mg/kg	88 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
Scheduled sacrifice	10	10	9
Early deaths			
Dead	9	4	7
Moribund	8	10	22
Accident	1		1
Gavage death		3	4
Survivors			
Died last week of study	1		
Terminal sacrifice	31	33	17
Animals examined microscopically	50	50	50
Alimentary System			
Liver	(50)	(49)	(50)
Angiectasis	3 (6%)	1 (2%)	
Basophilic focus	16 (32%)	19 (39%)	9 (18%)
Congestion		1 (2%)	
Cyst	1 (2%)		
Fatty change, diffuse	2 (4%)	4 (8%)	3 (6%)
Fatty change, focal	1 (2%)	1 (2%)	2 (4%)
Fatty change, multifocal		2 (4%)	2 (4%)
Hematopoietic cell proliferation	5 (10%)	1 (2%)	2 (4%)
Hepatodiaphragmatic nodule	1 (2%)	3 (6%)	6 (12%)
Hepatodiaphragmatic nodule, multiple		2 (4%)	
Inflammation, granulomatous, multifocal	10 (20%)	14 (29%)	6 (12%)
Inflammation, necrotizing, focal		1 (2%)	
Necrosis, multifocal	1 (2%)	2 (4%)	2 (4%)
Pigmentation, hemosiderin		1 (2%)	
Regeneration		1 (2%)	
Bile duct, hyperplasia	24 (48%)	26 (53%)	28 (56%)
Centrilobular, degeneration			1 (2%)
Centrilobular, fatty change			2 (4%)
Centrilobular, necrosis	3 (6%)	1 (2%)	1 (2%)
Periportal, fatty change			1 (2%)
Mesentery	(4)	(4)	(1)
Fat, necrosis, focal	4 (100%)	4 (100%)	
Pancreas	(49)	(49)	(50)
Acinus, atrophy	6 (12%)	11 (22%)	7 (14%)
Stomach, forestomach	(50)	(50)	(49)
Hyperplasia, focal		1 (2%)	1 (2%)
Inflammation, acute			2 (4%)
Inflammation, chronic		1 (2%)	
Ulcer			2 (4%)
Stomach, glandular	(50)	(50)	(50)
Degeneration, cystic	34 (68%)	36 (72%)	36 (72%)
Erosion	1 (2%)		1 (2%)
Erosion, multifocal		1 (2%)	1 (2%)
Ulcer			1 (2%)
Submucosa, fibrosis			1 (2%)
Tooth	(1)		
Pulp, inflammation, necrotizing	1 (100%)		

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	44 mg/kg	88 mg/kg
Cardiovascular System			
Heart	(50)	(50)	(50)
Cardiomyopathy	11 (22%)	8 (16%)	15 (30%)
Coronary artery, inflammation, chronic		1 (2%)	
Endocardium, thrombus			1 (2%)
Epicardium, inflammation, chronic active	1 (2%)		
Myocardium, inflammation, subacute, multifocal	1 (2%)		
Endocrine System			
Adrenal gland	(50)	(50)	(50)
Accessory adrenal cortical nodule			1 (2%)
Adrenal gland, cortex	(48)	(50)	(50)
Angiectasis			2 (4%)
Hematopoietic cell proliferation			1 (2%)
Hemorrhage			1 (2%)
Hyperplasia, focal	4 (8%)	2 (4%)	4 (8%)
Hyperplasia, multifocal	1 (2%)		
Necrosis		1 (2%)	1 (2%)
Vacuolization cytoplasmic, diffuse			2 (4%)
Vacuolization cytoplasmic, focal	6 (13%)	5 (10%)	5 (10%)
Vacuolization cytoplasmic, multifocal	1 (2%)		1 (2%
Adrenal gland, medulla	(43)	(41)	(45)
Hematopoietic cell proliferation			1 (2%)
Hyperplasia, focal	1 (2%)	2 (5%)	
Hyperplasia, multifocal		2 (5%)	2 (4%)
Bilateral, hyperplasia, focal	1 (2%)		
Pituitary gland	(49)	(49)	(47)
Angiectasis	4 (8%)	10 (20%)	10 (21%)
Cyst	11 (22%)	14 (29%)	8 (17%)
Hemorrhage		1 (2%)	
Pigmentation, hemosiderin			2 (4%)
Pars distalis, angiectasis	1 (2%)		
Pars distalis, hyperplasia, focal	3 (6%)	5 (10%)	2 (4%)
Thyroid gland	(50)	(50)	(50)
Ultimobranchial cyst		1 (2%)	
C-cell, hyperplasia	8 (16%)	6 (12%)	5 (10%)
Follicle, cyst			1 (2%)
Follicular cell, hyperplasia	1 (2%)		1 (2%)
Genital System			
Clitoral gland	(34)	(35)	(32)
Hyperplasia		1 (3%)	3 (9%)
Inflammation, chronic	1 (3%)		
Inflammation, chronic active	3 (9%)		2 (6%)
Duct, ectasia	1 (3%)	4 (11%)	7 (22%)
Ovary	(49)	(50)	(50)
Cyst	2 (4%)		1 (2%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	44 mg/kg	88 mg/kg
Genital System (continued)			
Uterus	(50)	(50)	(50)
Decidual reaction		1 (2%)	
Hydrometra	1 (2%)		1 (2%)
Inflammation, suppurative			2 (4%)
Cervix, cyst		1 (2%)	
Endometrium, cyst		2 (4%)	2 (4%)
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Hyperplasia			1 (2%)
Lymph node	(50)	(49)	(49)
Bronchial, hemorrhage	1 (2%)		
Bronchial, hyperplasia, plasma cell			1 (2%)
Bronchial, hyperplasia, re cell	1 (2%)		
Mediastinal, hemorrhage	2 (4%)	5 (10%)	4 (8%)
Mediastinal, hyperplasia, plasma cell	1 (2%)		
Mediastinal, pigmentation, hemosiderin	1 (2%)		
Lymph node, mandibular	(47)	(45)	(47)
Hemorrhage	1 (2%)	3 (7%)	3 (6%)
Hyperplasia, lymphoid		1 (2%)	
Hyperplasia, plasma cell	2 (4%)	2 (4%)	3 (6%)
Pigmentation, hemosiderin		1 (2%)	
Lymph node, mesenteric	(48)	(45)	(49)
Hemorrhage	2 (4%)	2 (4%)	1 (2%)
Pigmentation	1 (2%)		
Sinus, ectasia			2 (4%)
Spleen	(50)	(49)	(50)
Hematopoietic cell proliferation	8 (16%)	2 (4%)	6 (12%)
Hemorrhage			1 (2%)
Necrosis	1 (2%)		2 (4%)
Capsule, fibrosis, focal		1 (2%)	
Thymus	(37)	(42)	(39)
Cyst			2 (5%)
Hemorrhage	1 (3%)	3 (7%)	5 (13%)
Epithelial cell, hyperplasia	22 (59%)	29 (69%)	20 (51%)
Integumentary System			
Mammary gland	(46)	(46)	(47)
Galactocele	2 (4%)	3 (7%)	2 (4%)
Hemorrhage	1 (2%)		
Duct, ectasia	6 (13%)	5 (11%)	2 (4%)
Skin	(50)	(49)	(49)
Cyst epithelial inclusion	1 (2%)		1 (2%)
Ulcer, multifocal		1 (2%)	
Musculoskeletal System			
Bone	(2)	(1)	(2)
Osteopetrosis	2 (100%)		1 (50%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	44 mg/kg	88 mg/kg
Nervous System			
Brain	(50)	(50)	(50)
Brain stem, compression	5 (10%)	7 (14%)	1 (2%)
Brain stem, gliosis	1 (2%)		15 (30%)
Brain stem, hemorrhage	1 (2%)		12 (24%)
Brain stem, mineralization			7 (14%)
Brain stem, necrosis			1 (2%)
Brain stem, pigmentation, hemosiderin	1 (2%)		17 (34%)
Cerebellum, gliosis	1 (2%)		
Cerebellum, hemorrhage	1 (2%)		2 (4%)
Cerebellum, necrosis			1 (2%)
Cerebellum, pigmentation, hemosiderin	1 (2%)		
Cerebrum, gliosis			19 (38%)
Cerebrum, hemorrhage	1 (2%)		17 (34%)
Cerebrum, mineralization			15 (30%)
Cerebrum, pigmentation, hemosiderin			22 (44%)
Meninges, hemorrhage			1 (2%)
Pons, hemorrhage		1 (2%)	
Pons, necrosis	1 (2%)		
Respiratory System			
Lung	(50)	(50)	(50)
Congestion	6 (12%)	1 (2%)	
Edema	1 (2%)		
Hemorrhage		3 (6%)	7 (14%)
Infiltration cellular, histiocytic	33 (66%)	26 (52%)	28 (56%)
Inflammation, granulomatous, multifocal	1 (2%)	3 (6%)	
Leukocytosis			1 (2%)
Pigmentation	33 (66%)	26 (52%)	28 (56%)
Alveolar epithelium, hyperplasia, focal	2 (4%)	8 (16%)	2 (4%)
Alveolar epithelium, hyperplasia, multifocal	2 (4%)	1 (2%)	1 (2%)
Interstitium, inflammation	1 (2%)	1 (2%)	1 (2%)
Peribronchiolar, foreign body		1 (2%)	2 (4%)
Pleura, inflammation, chronic active	1 (2%)		
Nose	(50)	(50)	(50)
Foreign body	2 (4%)		
Fungus	1 (2%)		
Hemorrhage		2 (4%)	1 (2%)
Inflammation, suppurative	3 (6%)	2 (4%)	3 (6%)
Ulcer		1 (2%)	1 (2%)
Special Senses System			
Eye	(6)	(2)	(8)
Cataract	2 (33%)	2 (100%)	4 (50%)
Necrosis			1 (13%)
Bilateral, cataract	2 (33%)		
Retina, degeneration	3 (50%)	2 (100%)	5 (63%)
Sclera, metaplasia, osseous	1 (17%)		
Harderian gland	(1)		(1)
Infiltration cellular, lymphocytic			1 (100%)
Pigmentation, porphyrin	1 (100%)		

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	44 mg/kg	88 mg/kg
Urinary System			
Kidney	(50)	(50)	(50)
Calculus micro observation only	2 (4%)		5 (10%)
Cyst	1 (2%)		
Nephropathy	27 (54%)	23 (46%)	32 (64%)
Pigmentation	2 (4%)	1 (2%)	
Pelvis, inflammation, chronic			1 (2%)
Renal tubule, epithelium, hyperplasia			4 (8%)
Renal tubule, epithelium, hyperplasia, focal		3 (6%)	11 (22%)
Renal tubule, epithelium, hyperplasia, multifocal			1 (2%)
Urinary bladder	(49)	(49)	(48)
Infiltration cellular, lymphocytic	2 (4%)	1 (2%)	
Transitional epithelium, hyperplasia, focal		2 (4%)	
Transitional epithelium, hyperplasia, papillary		1 (2%)	

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR GAVAGE STUDY OF TRIS(2-CHLOROETHYL) PHOSPHATE

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate

	Vehicle Control	175 mg/kg	350 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
Scheduled sacrifice	8	10	8
Early deaths			
Moribund	10	8	12
Dead	14	13	9
Gavage death	3	4	5
Survivors			
Terminal sacrifice	25	25	25
Missing			1
Animals examined microscopically	50	50	50
Alimentary System			
Intestine large	(50)	(26)	(47)
Intestine large, cecum	(47)	(25)	(46)
Intestine small, jejunum	(45)	(23)	(44)
Adenocarcinoma		1 (4%)	2 (5%)
Liver	(50)	(50)	(50)
Adenocarcinoma, metastatic, intestine small			1 (2%)
Fibrosarcoma, metastatic, skin			1 (2%)
Hemangiosarcoma	2 (4%)	4 (8%)	
Hemangiosarcoma, metastatic, spleen	1 (2%)		
Hepatoblastoma			1 (2%)
Hepatocellular carcinoma	7 (14%)	10 (20%)	8 (16%)
Hepatocellular carcinoma, multiple	3 (6%)		2 (4%)
Hepatocellular adenoma	12 (24%)	11 (22%)	11 (22%)
Hepatocellular adenoma, multiple	8 (16%)	7 (14%)	17 (34%)
Histiocytic sarcoma	1 (2%)		
Sarcoma, metastatic, spleen	1 (2%)		
Mesentery	(9)	(2)	(4)
Adenocarcinoma, metastatic, intestine small			1 (25%)
Fibrosarcoma, metastatic, skin			1 (25%)
Lipoma	1 (11%)		
Pancreas	(49)	(26)	(49)
Fibrosarcoma, metastatic, skin			1 (2%)
Salivary glands	(49)	(24)	(49)
Stomach, forestomach	(49)	(50)	(49)
Papilloma squamous		1 (2%)	1 (2%)
Glandular, mast cell tumor malignant, metastatic, skin			1 (2%)
Stomach, glandular	(50)	(47)	(47)
Adenocarcinoma, metastatic, intestine small			1 (2%)
Cardiovascular System			
Heart	(50)	(25)	(50)
Carcinoma, metastatic, uncertain primary site	1 (2%)		
Hepatocellular carcinoma, metastatic, liver		1 (4%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	175 mg/kg	350 mg/kg
Endocrine System			
Adrenal gland, cortex	(48)	(23)	(48)
Adrenal gland, medulla	(46)	(23)	(43)
Pheochromocytoma malignant			1 (2%)
Pheochromocytoma benign			1 (2%)
Islets, pancreatic	(49)	(25)	(49)
Adenoma			1 (2%)
Mast cell tumor malignant, metastatic, skin			1 (2%)
Thyroid gland	(49)	(23)	(49)
Follicular cell, adenoma			1 (2%)
Genital System			
Epididymis	(49)	(24)	(47)
Preputial gland	(7)	(3)	(5)
Carcinoma		1 (33%)	
Seminal vesicle	(48)	(26)	(50)
Testes	(50)	(24)	(50)
Interstitial cell, adenoma	2 (4%)		
Hematopoietic System			
Bone marrow	(50)	(25)	(49)
Hemangiosarcoma, metastatic	1 (2%)		
Hemangiosarcoma, metastatic, spleen	1 (2%)	1 (4%)	
Mast cell tumor malignant, metastatic, skin			1 (2%)
Lymph node	(50)	(27)	(49)
Lymph node, mandibular	(46)	(22)	(44)
Mast cell tumor malignant, metastatic, skin			1 (2%)
Lymph node, mesenteric	(48)	(24)	(44)
Histiocytic sarcoma	1 (2%)		
Spleen	(50)	(28)	(49)
Hemangioma		1 (4%)	
Hemangiosarcoma	3 (6%)		
Hemangiosarcoma, multiple		1 (4%)	
Histiocytic sarcoma	1 (2%)		
Mast cell tumor malignant, metastatic, skin			1 (2%)
Sarcoma	1 (2%)		
Thymus	(29)	(17)	(33)
Integumentary System			
Skin	(50)	(35)	(49)
Hemangiosarcoma, metastatic, spleen		1 (3%)	
Mast cell tumor malignant			1 (2%)
Subcutaneous tissue, fibroma		3 (9%)	
Subcutaneous tissue, fibroma, multiple			1 (2%)
Subcutaneous tissue, fibrosarcoma	1 (2%)	4 (11%)	2 (4%)
Subcutaneous tissue, fibrosarcoma, multiple			1 (2%)
Subcutaneous tissue, hemangiosarcoma		1 (3%)	
Subcutaneous tissue, sarcoma	1 (2%)		

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	175 mg/kg	350 mg/kg
Nervous System			
Brain	(50)	(25)	(50)
Respiratory System			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	7 (14%)	9 (18%)	7 (14%)
Alveolar/bronchiolar adenoma, multiple		2 (4%)	2 (4%)
Alveolar/bronchiolar carcinoma	3 (6%)	1 (2%)	2 (4%)
Carcinoma, metastatic, uncertain primary site	1 (2%)		
Fibrosarcoma, metastatic, skin		1 (2%)	1 (2%)
Hepatocellular carcinoma, metastatic, liver	2 (4%)	3 (6%)	2 (4%)
Histiocytic sarcoma	1 (2%)		
Mast cell tumor malignant, metastatic, skin			1 (2%)
Nose	(50)	(25)	(50)
Carcinoma, metastatic, harderian gland			1 (2%)
Special Senses System			
Eye	(6)	(5)	(7)
Mast cell tumor malignant, metastatic, skin			1 (14%)
Harderian gland	(48)	(49)	(47)
Adenoma	5 (10%)	8 (16%)	3 (6%)
Adenoma, mild			1 (2%)
Adenoma, multiple			1 (2%)
Carcinoma			1 (2%)
Bilateral, adenoma	1 (2%)		
Urinary System			
Kidney	(50)	(50)	(50)
Carcinoma, metastatic, uncertain primary site	1 (2%)		
Hemangiosarcoma	1 (2%)		
Hepatocellular carcinoma, metastatic, liver		1 (2%)	
Mast cell tumor malignant, metastatic, skin			1 (2%)
Renal tubule, adenoma	1 (2%)		1 (2%)
Renal tubule, carcinoma			1 (2%)
Urinary bladder	(50)	(24)	(49)
Systemic Lesions			
Multiple organs[a]	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)		
Lymphoma malignant mixed	2 (4%)	3 (6%)	1 (2%)
Lymphoma malignant undifferentiated cell	2 (4%)		

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	175 mg/kg	350 mg/kg
Tumor Summary			
Total animals with primary neoplasms[b]	38	39	42
Total primary neoplasms	64	68	71
Total animals with benign neoplasms	28	28	32
Total benign neoplasms	37	42	48
Total animals with malignant neoplasms	22	21	21
Total malignant neoplasms	27	26	23
Total animals with secondary neoplasms[c]	6	5	6
Total secondary neoplasms	9	8	18
Total animals with malignant neoplasms	1		
Uncertain primary site			

[a] The number in parentheses is the number of animals with any tissue examined microscopically
[b] Primary tumors: all tumors except metastatic tumors
[c] Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: Vehicle Control

Number of Days on Study	0 2 3	2 5 0	2 9 8	2 9 8	4 5 1	4 8 5	6 2 0	6 2 6	6 3 2	6 3 6	6 3 8	6 5 4	6 5 6	6 6 5	6 7 0	6 7 4	6 7 5	6 7 5	6 8 1	6 8 8	6 9 0	6 9 4	6 9 7	7 1 4	7 1 5	7 2 9
Carcass ID Number	1 0 0 1 5	0 2 5 5	0 5 4 5	0 5 4 5	0 4 5 5	0 4 4 4	0 7 5 5	0 8 5 5	1 0 4 4	0 7 4 3	0 7 7 3	0 2 4 4	0 5 3 3	0 1 5 5	0 1 6 5	1 0 3 3	0 3 5 5	0 9 5 5	0 5 2 2	0 2 3 3	0 8 4 0	1 0 2 4	0 1 4 4	0 2 2 4	0 2 1 5	0 1 1 9
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	M	+	A	A	+	M	A	A	+	+	+	+	+	A	+	+	+	+	M	+	M	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	A	+	+
Intestine small	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	M	M	A	M	A	M	M	+	A	M	M	+	M	+	+	M	+	+	M	M	M	M	A	+	M
Intestine small, ileum	A	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	M	M	A	+	+	+	+	A	+	+
Intestine small, jejunum	A	+	+	A	+	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma															X											
Hemangiosarcoma, metastatic									X																	
Hemangiosarcoma, metastatic, spleen									X																	
Hepatocellular carcinoma							X			X					X			X		X	X				
Hepatocellular carcinoma, multiple								X	X																	
Hepatocellular adenoma																		X			X		X	X	X	
Hepatocellular adenoma, multiple										X						X	X									
Histiocytic sarcoma																									X	
Sarcoma, metastatic, spleen																						X				
Mesentery														+					+		+		+			+
Lipoma																										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uncertain primary site							X																			

+: Tissue examined
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: Vehicle Control (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 1 2	0 1 3	0 3 1	0 3 2	0 3 3	0 3 4	0 4 1	0 4 2	0 4 3	0 5 1	0 6 1	0 6 2	0 6 3	0 6 4	0 7 1	0 7 2	0 8 1	0 8 2	0 8 3	0 9 1	0 9 2	0 9 3	0 9 4	1 0 1	**Total Tissues/ Tumors**
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	38
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	M	+	M	M	+	M	+	+	M	M	+	M	M	M	M	+	+	+	+	M	M	M	M	M	16
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma			X																						2
Hemangiosarcoma, metastatic																									1
Hemangiosarcoma, metastatic, spleen																									1
Hepatocellular carcinoma																				X					7
Hepatocellular carcinoma, multiple																	X								3
Hepatocellular adenoma						X				X		X	X					X		X				X	12
Hepatocellular adenoma, multiple	X				X						X				X				X						8
Histiocytic sarcoma																									1
Sarcoma, metastatic, spleen																									1
Mesentery					+	+	+			+															9
Lipoma							X																		1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, uncertain primary site																									1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: Vehicle Control (continued)

Number of Days on Study	0 2 3	2 9 7	2 9 8	2 9 8	4 5 1	4 8 5	6 2 0	6 2 6	6 3 2	6 3 6	6 3 8	6 5 4	6 5 6	6 6 5	6 7 0	6 7 4	6 7 5	6 7 5	6 8 1	6 8 8	6 9 0	6 9 4	6 9 7	7 1 4	7 1 5	7 2 9
Carcass ID Number	1 0 5	1 1 5	0 5 4	0 5 5	0 4 5	0 4 4	0 7 5	0 8 5	1 0 4	0 7 4	0 7 3	0 2 4	0 5 3	0 1 5	0 1 6	0 6 5	1 0 3	0 3 5	0 9 5	0 5 2	0 2 3	0 8 4	1 0 2	0 1 4	0 2 2	0 2 1	0 1 1
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Parathyroid gland	+	M	+	+	M	+	+	+	M	+	M	M	+	+	M	M	+	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland															+	+		+	+							
Prostate	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																						X				
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic									X										X							
Hemangiosarcoma, metastatic, spleen									X																	
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma									X				X						X							
Histiocytic sarcoma																									X	
Sarcoma																							X			
Thymus	+	+	+	M	+	+	M	+	M	M	+	+	+	+	M	+	+	+	+	M	M	+	+	+	M	M
Integumentary System																										
Mammary gland	M	M	M	+	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	+	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																										
Subcutaneous tissue, sarcoma																										
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: Vehicle Control (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 1 2	0 1 3	0 3 1	0 3 2	0 3 3	0 3 4	0 4 1	0 4 2	0 4 3	0 5 1	0 6 1	0 6 2	0 6 3	0 6 4	0 7 1	0 7 2	0 8 1	0 8 2	0 8 3	0 9 1	0 9 2	0 9 3	0 9 4	1 0 1	Total Tissues/ Tumors
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	M	M	M	+	+	M	M	+	+	M	+	+	+	+	+	+	36
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	45
Thyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Genital System																									
Epididymis	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland												+	+											+	7
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	48
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma												X													2
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic																									2
Hemangiosarcoma, metastatic, spleen																									1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	48
Histiocytic sarcoma																									1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																									3
Histiocytic sarcoma																									1
Sarcoma																									1
Thymus	M	+	M	+	+	M	+	M	M	+	M	M	M	M	M	+	+	+	+	+	+	+	M	M	29
Integumentary System																									
Mammary gland	M	M	M	M	+	M	+	M	M	+	+	M	M	M	M	+	M	M	+	M	M	M	M	M	9
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma								X																	1
Subcutaneous tissue, sarcoma																					X				1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: Vehicle Control (continued)

Number of Days on Study	0 2 3	2 5 0	2 9 8	2 9 8	4 5 1	4 8 5	6 2 0	6 2 6	6 3 2	6 3 6	6 3 8	6 5 4	6 5 6	6 6 5	6 7 0	6 7 4	6 7 5	6 7 5	6 8 1	6 8 8	6 9 0	6 9 4	6 9 7	7 1 4	7 1 5	7 2 9
Carcass ID Number	1 0 5	0 2 5	0 5 4	0 5 5	0 4 5	0 4 4	0 7 5	0 8 5	1 0 4	0 7 4	0 7 3	0 2 4	0 5 3	0 1 5	0 6 5	1 0 3	0 3 5	0 9 5	0 5 2	0 2 3	0 8 4	1 0 2	0 1 4	0 0 2	0 2 1	0 1 1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																										X
Alveolar/bronchiolar carcinoma										X																
Carcinoma, metastatic, uncertain primary site							X																			
Hepatocellular carcinoma, metastatic, liver								X											X							
Histiocytic sarcoma																									X	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Ear																										
Eye	+	+	+	+	+																		+			
Harderian gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X			X	X			
Bilateral, adenoma																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uncertain primary site							X																			
Hemangiosarcoma																										
Renal tubule, adenoma																										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X	
Lymphoma malignant mixed												X														
Lymphoma malignant undifferentiated cell type																						X		X		

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: Vehicle Control (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 1 2	0 1 3	0 3 1	0 3 2	0 3 3	0 3 4	0 4 1	0 4 2	0 4 3	0 5 1	0 6 1	0 6 2	0 6 3	0 6 4	0 7 1	0 7 2	0 8 1	0 8 2	0 8 3	0 9 1	0 9 2	0 9 3	0 9 4	1 0 1	**Total Tissues/ Tumors**
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X				X				X	X	X			X		7
Alveolar/bronchiolar carcinoma						X																X			3
Carcinoma, metastatic, uncertain primary site																									1
Hepatocellular carcinoma, metastatic, liver																									2
Histiocytic sarcoma																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																									
Ear						+													+						2
Eye																									6
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	48
Adenoma					X																	X			5
Bilateral, adenoma																			X						1
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, uncertain primary site																									1
Hemangiosarcoma																						X			1
Renal tubule, adenoma																	X								1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																									1
Lymphoma malignant mixed																				X					2
Lymphoma malignant undifferentiated cell type																									2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 175 mg/kg

Number of Days on Study	0 0 3	2 8 9	2 9 7	3 8 9	4 8 0	5 3 2	5 7 2	6 2 0	6 2 3	6 2 6	6 2 6	6 3 8	6 4 9	6 5 3	6 5 5	6 6 3	6 6 3	6 6 4	6 6 9	6 7 3	6 7 9	6 8 8	6 9 4	7 1 2	7 1 8	7 2 9
Carcass ID Number	2 1 5	1 9 5	1 4 5	1 7 5	1 5 5	1 8 5	1 8 4	1 7 4	1 3 5	1 6 5	2 0 5	1 5 4	2 2 5	1 5 3	2 2 4	1 5 2	1 6 4	1 9 4	2 0 4	2 0 3	2 2 3	2 1 4	1 4 4	1 9 3	2 1 3	1 3 1
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	
Gallbladder	+	A	+	A	M	M	+	+	+	+	+	M	+	M	+	+	+	M	M	M	+	+	M	+	M	
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	
Intestine small, duodenum	+	M	M	A	A	A	+	M	A	M	M	M	M	A	+	M	M	+	M	M	M	+	M	+	+	
Intestine small, ileum	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	M	+	+	+	+	+	+	+	
Intestine small, jejunum	+	+	+	+	+	A	+	+	A	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	
Adenocarcinoma																										
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma									X			X														X
Hepatocellular carcinoma						X	X	X						X		X						X				
Hepatocellular adenoma												X					X	X	X				X		X	
Hepatocellular adenoma, multiple									X															X		
Mesentery																										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																										
Stomach, glandular	+	+	+	+	+	A	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hepatocellular carcinoma, metastatic, liver																						X				
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Parathyroid gland	M	M	+	+	+	M	+	+	+	+	M	+	+	M	+	+	+	M	M	+	+	+	+	+	+	
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+	+	
Thyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 175 mg/kg (continued)

Number of Days on Study	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	13 2	13 3	13 4	14 1	14 2	14 3	15 1	16 1	16 2	16 3	17 1	17 2	17 3	18 1	18 2	18 3	19 1	19 2	20 1	20 2	21 1	21 2	22 1	22 2	**Total Tissues/ Tumors**
Alimentary System																									
Esophagus																									23
Gallbladder																									14
Intestine large											+														26
Intestine large, cecum											+														25
Intestine large, colon											+														26
Intestine large, rectum											+														26
Intestine small									+		+														25
Intestine small, duodenum											M														7
Intestine small, ileum											+														23
Intestine small, jejunum									+		+														23
Adenocarcinoma									X																1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma			X																						4
Hepatocellular carcinoma			X			X	X													X					10
Hepatocellular adenoma							X		X			X	X		X										11
Hepatocellular adenoma, multiple					X			X		X				X								X			7
Mesentery								+												+					2
Pancreas																									26
Salivary glands																									24
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous													X												1
Stomach, glandular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Tooth																									25
Cardiovascular System																									
Heart																									25
Hepatocellular carcinoma, metastatic, liver																									1
Endocrine System																									
Adrenal gland																									23
Adrenal gland, cortex																									23
Adrenal gland, medulla																									23
Islets, pancreatic																									25
Parathyroid gland																									18
Pituitary gland																									22
Thyroid gland																									23

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 175 mg/kg (continued)

Number of Days on Study	0 2 2 3 4 5 5 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 7 7 7 0 8 9 8 8 3 7 2 2 2 2 3 4 5 5 6 6 6 6 7 7 8 9 1 1 2 3 9 7 9 0 2 2 0 3 6 6 8 9 3 5 3 3 4 9 3 9 8 4 2 8 9
Carcass ID Number	2 1 1 1 1 1 1 1 1 1 2 1 2 1 2 1 1 1 2 2 2 2 1 1 2 1 1 9 4 7 5 8 8 7 3 6 0 5 2 5 2 5 6 9 0 0 2 1 4 9 1 3 5 5 5 5 5 5 4 4 5 5 5 4 5 3 4 2 4 4 4 3 3 4 4 3 3 1
Genital System	
Epididymis	+ M +
Preputial gland	+ +
Carcinoma	X
Prostate	+ + + + + + + M + + + + + + + + + M + + + + + + + + +
Seminal vesicle	+ +
Testes	+ M +
Hematopoietic System	
Bone marrow	+ +
Hemangiosarcoma, metastatic spleen	X
Lymph node	+ +
Lymph node, mandibular	+ + + + M + + + + + + + + + + + + + + + M + + M +
Lymph node, mesenteric	+ + + + + + + + + M + M + + M + + + + + + + + + + +
Spleen	+ +
Hemangioma	
Hemangiosarcoma, multiple	X
Thymus	+ + M + + M M + M + + + + M + + M + M + + + M + + +
Integumentary System	
Mammary gland	+ + M M M M M M M M M + M M M M M M M + M M M M M +
Skin	+ + + + + + + + + + + + + + M + + + + + + + + + + +
Hemangiosarcoma, metastatic, spleen	X
Subcutaneous tissue, fibroma	X
Subcutaneous tissue, fibrosarcoma	X X X X
Subcutaneous tissue, hemangiosarcoma	
Musculoskeletal System	
Bone	+ +
Skeletal muscle	+ +

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 175 mg/kg (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	1 3 2	1 3 3	1 3 4	1 4 1	1 4 2	1 4 3	1 5 1	1 6 1	1 6 2	1 6 3	1 7 1	1 7 2	1 7 3	1 8 1	1 8 2	1 8 3	1 9 1	1 9 2	2 0 1	2 0 2	2 1 1	2 1 2	2 2 1	2 2 2	**Total Tissues/ Tumors**
Genital System																									
Epididymis																									24
Preputial gland																									3
Carcinoma																									1
Prostate																									23
Seminal vesicle																		+							26
Testes																									24
Hematopoietic System																									
Bone marrow																									25
Hemangiosarcoma, metastatic spleen																									1
Lymph node																	+								27
Lymph node, mandibular																									22
Lymph node, mesenteric																	+								24
Spleen														+			+							+	28
Hemangioma																	X								1
Hemangiosarcoma, multiple																									1
Thymus																									17
Integumentary System																									
Mammary gland					+																				6
Skin			+	+	+			+	+	+	+	+	+					+							35
Hemangiosarcoma, metastatic, spleen																									1
Subcutaneous tissue, fibroma												X	X												3
Subcutaneous tissue, fibrosarcoma																									4
Subcutaneous tissue, hemangiosarcoma			X																						1
Musculoskeletal System																									
Bone																									25
Skeletal muscle																									25

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 175 mg/kg (continued)

Number of Days on Study	0 2 2 3 4 5 5 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 7 7 7 0 8 9 8 8 3 7 2 2 2 2 3 4 5 5 6 6 6 6 7 7 8 9 1 1 2 3 9 7 9 0 2 2 0 3 6 6 8 9 3 5 3 3 4 9 3 9 8 4 2 8 9
Carcass ID Number	2 1 1 1 1 1 1 1 1 1 2 1 2 1 2 1 1 1 2 2 2 2 1 1 2 1 1 9 4 7 5 8 8 7 3 6 0 5 2 5 2 5 6 9 0 0 2 1 4 9 1 3 5 5 5 5 5 5 4 4 5 5 5 4 5 3 4 2 4 4 4 3 3 4 4 3 3 1
Nervous System	
Brain	+ +
Spinal cord	+
Respiratory System	
Lung	+ +
Alveolar/bronchiolar adenoma	X
Alveolar/bronchiolar adenoma, multiple	X
Alveolar/bronchiolar carcinoma	X
Fibrosarcoma, metastatic, skin	X
Hepatocellular carcinoma, liver	X X
Nose	+ +
Trachea	+ + + + + + + + + + + + + + + + + M + + + + + + +
Special Senses System	
Ear	+
Eye	+ + + + + +
Harderian gland	+ +
Adenoma	X X X X
Urinary System	
Kidney	+ +
Hepatocellular carcinoma, metastatic	X
Hepatocellular carcinoma, metastatic, liver	X
Urinary bladder	+ I + + +
Systemic Lesions	
Multiple organs	+ +
Lymphoma malignant mixed	X X X

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 175 mg/kg (continued)

Number of Days on Study	729	729	729	730	700	730	700	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	13 2	13 3	13 4	14 1	14 2	14 3	15 1	16 1	16 2	16 3	17 1	17 2	17 3	18 1	18 2	18 3	19 1	19 2	20 1	20 2	21 1	21 2	22 1	22 2	Total Tissues/ Tumors
Nervous System																									
Brain																									25
Spinal cord																									1
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X	X							X		X		X		X						X		X	9
Alveolar/bronchiolar adenoma, multiple						X																			2
Alveolar/bronchiolar carcinoma																									1
Fibrosarcoma, metastatic, skin																									1
Hepatocellular carcinoma, metastatic, liver						X																			3
Nose																									25
Trachea																									24
Special Senses System																									
Ear																									1
Eye																									5
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma				X	X								X											X	8
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																									1
Hepatocellular carcinoma, metastatic, liver																									1
Urinary bladder																									24
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																									3

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 350 mg/kg

Number of Days on Study	0 6 0	1 2 2	1 3 4	2 9 3	4 6 9	5 1 1	5 7 1	5 8 8	5 9 9	6 0 4	6 2 7	6 3 4	6 3 5	6 6 6	6 6 6	6 6 6	6 7 3	6 7 3	6 9 8	6 9 9	7 0 6	7 1 2	7 1 7	7 1 9	7 3 0
Carcass ID Number	3 2 5	3 5 5	2 9 5	3 0 5	3 1 5	2 8 5	2 8 4	2 5 5	3 4 5	2 5 4	2 7 5	3 1 4	3 1 3	2 5 3	2 7 4	2 9 4	2 6 5	2 9 3	3 4 4	3 4 3	3 2 4	3 1 2	3 2 3	3 3 4	3 5 1
Alimentary System																									
Esophagus	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+		A	A	+	A	M	M	+	M	+	+	+	+	+	M	M	+	+	+	M	+	+	+	M
Intestine large	+		A	+	+	+	+	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A		A	+	+	+	+	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+		A	+	+	+	+	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+		A	M	+	+	+	A	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+		A	+	+	A	+	A	+	A	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A		A	A	M	A	+	A	M	A	M	M	M	M	M	M	M	M	+	+	M	M	+	M	M
Intestine small, ileum	A		A	A	+	A	+	A	+	A	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+
Intestine small, jejunum	A		A	+	+	A	+	A	+	A	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																								X	
Liver	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, intestine small																								X	
Fibrosarcoma, metastatic, skin																X									
Hepatoblastoma									X																
Hepatocellular carcinoma					X	X	X	X				X													
Hepatocellular carcinoma, multiple																					X				
Hepatocellular adenoma							X		X										X						
Hepatocellular adenoma, multiple													X	X	X		X		X			X		X	
Mesentery																+								+	
Adenocarcinoma, metastatic, intestine small																								X	
Fibrosarcoma, metastatic, skin																X									
Pancreas	+		A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																X									
Salivary glands	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+		A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+		A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Glandular, mast cell tumor malignant, metastatic, skin														X											
Stomach, glandular	+		A	A	+	+	+	+	+	+	+	+	+			+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, intestine small																								X	
Tooth	+		+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 350 mg/kg (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	2 5 2	2 6 1	2 6 2	2 6 3	2 6 4	2 7 1	2 7 2	2 7 3	2 8 1	2 8 2	2 8 3	2 9 1	2 9 2	3 0 1	3 0 2	3 0 3	3 1 1	3 1 2	3 2 1	3 2 2	3 3 1	3 3 2	3 3 3	3 4 1	3 4 2	**Total Tissues/ Tumors**
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	+	+	M	+	M	+	M	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	32
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, duodenum	+	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	+	+	M	+	M	M	M	9
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Adenocarcinoma															X										2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma, metastatic, intestine small																									1
Fibrosarcoma, metastatic, skin																									1
Hepatoblastoma																									1
Hepatocellular carcinoma				X										X	X										8
Hepatocellular carcinoma, multiple					X																				2
Hepatocellular adenoma	X			X		X					X				X	X			X	X					11
Hepatocellular adenoma, multiple		X	X		X		X		X	X				X									X	X	16
Mesentery											+						+								4
Adenocarcinoma, metastatic, intestine small																									1
Fibrosarcoma, metastatic, skin																									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Fibrosarcoma, metastatic, skin																									1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Papilloma squamous																		X							1
Glandular, mast cell tumor malignant, metastatic, skin																									1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenocarcinoma, metastatic, intestine small																									1
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 350 mg/kg (continued)

Number of Days on Study	0 6 0	1 2 2	1 3 4	2 9 3	4 6 9	5 1 1	5 7 1	5 8 8	5 9 9	6 0 4	6 2 7	6 3 4	6 3 5	6 6 6	6 6 6	6 6 6	6 7 3	6 7 3	6 9 8	6 9 9	7 0 6	7 1 2	7 1 7	7 1 9	7 3 0
Carcass ID Number	3 2 5	3 5 5	2 9 5	3 0 5	3 1 5	2 8 5	2 8 4	2 5 5	3 4 5	2 5 4	2 7 5	3 1 4	3 1 3	2 5 3	2 7 4	2 9 4	2 6 5	2 9 3	3 4 4	3 4 3	3 2 4	3 1 2	3 2 3	3 3 4	3 5 1
Cardiovascular System																									
Heart	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+		+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+		+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+		+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	M	+	M	M	+
Pheochromocytoma malignant																									
Pheochromocytoma benign																									
Islets, pancreatic	+		A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Mast cell tumor malignant, metastatic, skin														X											
Parathyroid gland	M		M	+	+	+	M	+	M	+	M	+	+	M	M	M	+	+	+	+	+	+	M	+	+
Pituitary gland	M		+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
Genital System																									
Epididymis	+		+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland				+								+													
Prostate	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+
Seminal vesicle	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Blood											+														
Bone marrow	M		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, skin														X											
Lymph node	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+		+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+
Mast cell tumor malignant, metastatic, skin														X											
Lymph node, mesenteric	+		M	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	I	+	+	+
Spleen	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, skin														X											
Thymus	+		M	+	+	+	+	M	+	M	M	+	M	+	M	M	+	+	+	+	M	M	M	+	+
Integumentary System																									
Mammary gland	M		M	M	+	M	M	+	M	M	M	+	M	M	+	+	M	+	M	+	M	M	+	+	M
Skin	+		+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant														X											
Subcutaneous tissue, fibroma, multiple																									
Subcutaneous tissue, fibrosarcoma													X			X									
Subcutaneous tissue, fibrosarcoma multiple											X														

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 350 mg/kg (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	2 5 2	2 6 1	2 6 2	2 6 3	2 6 4	2 7 1	2 7 2	2 7 3	2 8 1	2 8 2	2 8 3	2 9 1	2 9 2	3 0 1	3 0 2	3 0 3	3 1 1	3 2 1	3 2 2	3 3 1	3 3 2	3 3 3	3 4 1	3 4 2	**Total Tissues/ Tumors**
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adrenal gland, cortex	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adrenal gland, medulla	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	41
Pheochromocytoma malignant																					X				1
Pheochromocytoma benign																						X			1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma																									1
Mast cell tumor malignant, metastatic skin																									1
Parathyroid gland	M	M	+	+	+	M	M	M	M	+	+	+	M	+	M	+	+	+	M	+	M	+	M	+	28
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	47
Follicular cell, adenoma																		X							1
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+		+	+	+	45
Preputial gland				+						+				+											5
Prostate	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hematopoietic System																									
Blood																									1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Mast cell tumor malignant, metastatic, skin																									1
Lymph node	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	42
Mast cell tumor malignant, metastatic, skin																									1
Lymph node, mesenteric	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Spleen	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Mast cell tumor malignant, metastatic, skin																									1
Thymus	+	+	+	+	+	M	+	+	+	M	+	+	M	+	+	+	M	+	+	+	+	+	+	M	33
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	+	+	+	M	+	M	M	M	M	14
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Mast cell tumor malignant																									1
Subcutaneous tissue, fibroma, multiple									X																1
Subcutaneous tissue, fibrosarcoma																									2
Subcutaneous tissue, fibrosarcoma, multiple																									1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 350 mg/kg (continued)

Number of Days on Study	0 6 0	1 2 2	1 3 4	2 9 3	4 6 9	5 1 1	5 7 1	5 8 8	5 9 9	6 0 4	6 2 7	6 3 4	6 3 5	6 6 6	6 6 6	6 6 6	6 7 3	6 7 3	6 9 8	6 9 9	7 0 6	7 1 2	7 1 7	7 1 9	7 3 0
Carcass ID Number	3 2 5	3 5 5	2 9 5	3 0 5	3 1 5	2 8 5	2 8 4	2 5 5	3 4 5	2 5 4	2 7 5	3 1 4	3 1 3	2 5 3	2 7 4	2 9 4	2 6 5	2 9 3	3 4 4	3 4 3	3 2 4	3 1 2	3 2 3	3 3 4	2 5 1
Musculoskeletal System																									
Bone	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X																			
Alveolar/bronchiolar adenoma, multiple														X											
Alveolar/bronchiolar carcinoma										X															
Fibrosarcoma, metastatic, skin																X									
Hepatocellular carcinoma, metastatic, liver						X															X				
Mast cell tumor malignant, metastatic, skin														X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland																			X						
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Eye	+			+	+									+					+						
Mast cell tumor malignant, metastatic, skin														X											
Harderian gland	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X													
Adenoma, mild																									X
Adenoma, multiple																									
Carcinoma																			X						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, skin														X											
Renal tubule, adenoma																									X
Renal tubule, carcinoma																	X								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed														X											

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 350 mg/kg (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	2 5 2	2 6 1	2 6 2	2 6 3	2 6 4	2 7 1	2 7 2	2 7 3	2 8 1	2 8 2	2 8 3	2 9 1	2 9 2	3 0 1	3 0 2	3 0 3	3 1 1	3 1 2	3 2 2	3 2 3	3 3 1	3 3 2	3 3 3	3 4 1	3 4 2	**Total Tissues/ Tumors**
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar adenoma					X									X						X		X	X			6
Alveolar/bronchiolar adenoma, multiple																X										2
Alveolar/bronchiolar carcinoma																						X				2
Fibrosarcoma, metastatic, skin																										1
Hepatocellular carcinoma, metastatic, liver																										2
Mast cell tumor malignant, metastatic skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, harderian gland																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Special Senses System																										
Ear																				+						1
Eye							+													+						7
Mast cell tumor malignant, metastatic, skin																										1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma						X										X										3
Adenoma, mild																										1
Adenoma, multiple																	X									1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mast cell tumor malignant, metastatic, skin																										1
Renal tubule, adenoma																										1
Renal tubule, carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant mixed																										1

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate

	Vehicle Control	175 mg/kg	350 mg/kg
Adrenal Gland (Medulla): Pheochromocytoma (Benign or Malignant)			
Overall rates[a]	0/46 (0%)	0/23 (0%)	2/43 (5%)
Adjusted rates[b]	0.0%	0.0%	8.7%
Terminal rates[c]	0/24 (0%)	0/0	2/23 (9%)
First incidence (days)			729 (T)
Life table tests[d]	P=0.135	–[e]	P=0.228
Logistic regression tests[d]	P=0.135	–[e]	P=0.228
Cochran-Armitage test[d]	P=0.107		
Fisher exact test test[d]		–[e]	P=0.231
Harderian Gland: Adenoma			
Overall rates	6/50 (12%)	8/50 (16%)	5/50 (10%)
Adjusted rates	20.6%	26.0%	18.2%
Terminal rates	3/25 (12%)	4/25 (16%)	4/25 (16%)
First incidence (days)	681	638	634
Life table tests	P=0.441N	P=0.369	P=0.493N
Logistic regression tests	P=0.448N	P=0.372	P=0.508N
Cochran-Armitage test	P=0.440N		
Fisher exact test		P=0.387	P=0.500N
Harderian Gland: Adenoma or Carcinoma			
Overall rates	6/50 (12%)	8/50 (16%)	6/50 (12%)
Adjusted rates	20.6%	26.0%	20.8%
Terminal rates	3/25 (12%)	4/25 (16%)	4/25 (16%)
First incidence (days)	681	638	634
Life table tests	P=0.550N	P=0.369	P=0.603N
Logistic regression tests	P=0.550	P=0.372	P=0.614
Cochran-Armitage test	P=0.558		
Fisher exact test		P=0.387	P=0.620N
Liver: Hepatocellular Adenoma			
Overall rates	20/50 (40%)	18/50 (36%)	28/50 (56%)
Adjusted rates	60.0%	53.5%	79.2%
Terminal rates	12/25 (48%)	10/25 (40%)	18/25 (72%)
First incidence (days)	636	623	571
Life table tests	P=0.087	P=0.460N	P=0.103
Logistic regression tests	P=0.045	P=0.450N	P=0.055
Cochran-Armitage test	P=0.065		
Fisher exact test		P=0.418N	P=0.080
Liver: Hepatocellular Carcinoma			
Overall rates	10/50 (20%)	10/50 (20%)	10/50 (20%)
Adjusted rates	26.2%	28.5%	27.8%
Terminal rates	2/25 (8%)	4/25 (16%)	4/25 (16%)
First incidence (days)	620	532	469
Life table tests	P=0.528	P=0.555	P=0.573
Logistic regression tests	P=0.548	P=0.598	P=0.598
Cochran-Armitage test	P=0.550		
Fisher exact test		P=0.598N	P=0.598N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	175 mg/kg	350 mg/kg
Liver: Hepatocellular Carcinoma or Hepatoblastoma			
Overall rates	10/50 (20%)	10/50 (20%)	11/50 (22%)
Adjusted rates	26.2%	28.5%	29.6%
Terminal rates	2/25 (8%)	4/25 (16%)	4/25 (16%)
First incidence (days)	620	532	469
Life table tests	P=0.438	P=0.555	P=0.481
Logistic regression tests	P=0.449	P=0.598	P=0.500
Cochran-Armitage test	P=0.451		
Fisher exact test		P=0.598N	P=0.500
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rates	26/50 (52%)	27/50 (54%)	33/50 (66%)
Adjusted rates	67.6%	68.3%	81.7%
Terminal rates	13/25 (52%)	13/25 (52%)	18/25 (72%)
First incidence (days)	620	532	469
Life table tests	P=0.149	P=0.454	P=0.168
Logistic regression tests	P=0.073	P=0.488	P=0.087
Cochran-Armitage test	P=0.094		
Fisher exact test		P=0.500	P=0.111
Lung: Alveolar/bronchiolar Adenoma			
Overall rates	7/50 (14%)	11/50 (22%)	9/50 (18%)
Adjusted rates	28.0%	39.7%	30.0%
Terminal rates	7/25 (28%)	9/25 (36%)	6/25 (24%)
First incidence (days)	729 (T)	655	571
Life table tests	P=0.345	P=0.197	P=0.393
Logistic regression tests	P=0.336	P=0.182	P=0.381
Cochran-Armitage test	P=0.348		
Fisher exact test		P=0.218	P=0.393
Lung: Alveolar/bronchiolar Carcinoma			
Overall rates	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted rates	10.2%	2.4%	6.3%
Terminal rates	2/25 (8%)	0/25 (0%)	1/25 (4%)
First incidence (days)	636	626	604
Life table tests	P=0.417N	P=0.316N	P=0.516N
Logistic regression tests	P=0.402N	P=0.306N	P=0.504N
Cochran-Armitage test	P=0.399N		
Fisher exact test		P=0.309N	P=0.500N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rates	10/50 (20%)	12/50 (24%)	10/50 (20%)
Adjusted rates	37.6%	41.1%	31.7%
Terminal rates	9/25 (36%)	9/25 (36%)	6/25 (24%)
First incidence (days)	636	626	571
Life table tests	P=0.542	P=0.388	P=0.594
Logistic regression tests	P=0.537	P=0.368	P=0.589
Cochran-Armitage test	P=0.549N		
Fisher exact test		P=0.405	P=0.598N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	175 mg/kg	350 mg/kg
Skin (Subcutaneous Tissue): Fibroma			
Overall rates	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted rates	0.0%	10.0%	4.0%
Terminal rates	0/25 (0%)	2/25 (8%)	1/25 (4%)
First incidence (days)		480	729 (T)
Life table tests	P=0.378	P=0.124	P=0.500
Logistic regression tests	P=0.377	P=0.121	P=0.500
Cochran-Armitage test	P=0.378		
Fisher exact test		P=0.121	P=0.500
Skin (Subcutaneous Tissue): Fibrosarcoma			
Overall rates	1/50 (2%)	4/50 (8%)	3/50 (6%)
Adjusted rates	4.0%	11.0%	7.6%
Terminal rates	1/25 (4%)	0/25 (0%)	0/25 (0%)
First incidence (days)	729 (T)	626	627
Life table tests	P=0.252	P=0.176	P=0.300
Logistic regression tests	P=0.251	P=0.179	P=0.303
Cochran-Armitage test	P=0.252		
Fisher exact test		P=0.181	P=0.309
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma			
Overall rates	1/50 (2%)	7/50 (14%)	4/50 (8%)
Adjusted rates	4.0%	19.9%	11.3%
Terminal rates	1/25 (4%)	2/25 (8%)	1/25 (4%)
First incidence (days)	729 (T)	480	627
Life table	P=0.183	P=0.035	P=0.179
Logistic regression tests	P=0.177	P=0.033	P=0.177
Cochran-Armitage test	P=0.178		
Fisher exact test		P=0.030	P=0.181
Skin (Subcutaneous Tissue): Fibrosarcoma or Sarcoma			
Overall rates	2/50 (4%)	4/50 (8%)	3/50 (6%)
Adjusted rates	8.0%	11.0%	7.6%
Terminal rates	2/25 (8%)	0/25 (0%)	0/25 (0%)
First incidence (days)	729 (T)	626	627
Life table tests	P=0.411	P=0.329	P=0.491
Logistic regression tests	P=0.414	P=0.335	P=0.497
Cochran-Armitage test	P=0.417		
Fisher exact test		P=0.339	P=0.500
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma			
Overall rates	2/50 (4%)	7/50 (14%)	4/50 (8%)
Adjusted rates	8.0%	19.9%	11.3%
Terminal rates	2/25 (8%)	2/25 (8%)	1/25 (4%)
First incidence (days)	729 (T)	480	627
Life table tests	P=0.298	P=0.084	P=0.333
Logistic regression tests	P=0.294	P=0.081	P=0.332
Cochran-Armitage test	P=0.297		
Fisher exact test		P=0.080	P=0.339

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	175 mg/kg	350 mg/kg
All Organs: Hemangiosarcoma			
Overall rates	6/50 (12%)	5/50 (10%)	0/50 (0%)
Adjusted rates	17.6%	15.7%	0.0%
Terminal rates	2/25 (8%)	2/25 (8%)	0/25 (0%)
First incidence (days)	632	623	
Life table tests	P=0.023N	P=0.528N	P=0.022N
Logistic regression tests	P=0.018N	P=0.503N	P=0.018N
Cochran-Armitage test	P=0.017N		
Fisher exact test		P=0.500N	P=0.013N
All Organs: Hemangioma or Hemangiosarcoma			
Overall rates	6/50 (12%)	6/50 (12%)	0/50 (0%)
Adjusted rates	17.6%	19.4%	0.0%
Terminal rates	2/25 (8%)	3/25 (12%)	0/25 (0%)
First incidence (days)	632	623	
Life table tests	P=0.027N	P=0.590	P=0.022N
Logistic regression tests	P=0.022N	P=0.618	P=0.018N
Cochran-Armitage test	P=0.021N		
Fisher exact test		P=0.620N	P=0.013N
All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, Mixed, NOS, or Undifferentiated Cell Type)			
Overall rates	4/50 (8%)	3/50 (6%)	1/50 (2%)
Adjusted rates	13.0%	9.0%	2.7%
Terminal rates	1/25 (4%)	1/25 (4%)	0/25 (0%)
First incidence (days)	654	532	666
Life table tests	P=0.140N	P=0.518N	P=0.183N
Logistic regression tests	P=0.134N	P=0.501N	P=0.182N
Cochran-Armitage test	P=0.133N		
Fisher exact test		P=0.500N	P=0.181N
All Organs: Benign Tumors			
Overall rates	28/50 (56%)	28/50 (56%)	32/50 (64%)
Adjusted rates	79.8%	79.4%	88.4%
Terminal rates	18/25 (72%)	18/25 (72%)	21/25 (84%)
First incidence (days)	636	480	571
Life table tests	P=0.263	P=0.533	P=0.295
Logistic regression tests	P=0.176	P=0.531	P=0.196
Cochran-Armitage test	P=0.239		
Fisher exact test		P=0.580N	P=0.270
All Organs: Malignant Tumors			
Overall rates	22/50 (44%)	21/50 (42%)	21/50 (42%)
Adjusted rates	54.2%	50.2%	49.6%
Terminal rates	7/25 (28%)	6/25 (24%)	6/25 (24%)
First incidence (days)	620	532	469
Life table tests	P=0.483N	P=0.548N	P=0.509N
Logistic regression tests	P=0.470N	P=0.503N	P=0.512N
Cochran-Armitage test	P=0.460N		
Fisher exact test		P=0.500N	P=0.500N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	175 mg/kg	350 mg/kg
All Organs: Malignant And Benign Tumors			
Overall rates	38/50 (76%)	39/50 (78%)	42/50 (84%)
Adjusted rates	90.4%	88.4%	93.2%
Terminal rates	21/25 (84%)	20/25 (80%)	22/25 (88%)
First incidence (days)	620	480	469
Life table tests	P=0.288	P=0.442	P=0.317
Logistic regression tests	P=0.127	P=0.497	P=0.150
Cochran-Armitage test	P=0.194		
Fisher exact test		P=0.500	P=0.227

(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals necropsied or examined microscopically for this tumor type
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality.
[c] Observed 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 the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] No tumors in dosed group or control group; statistical test not performed.

TABLE C4
Historical Incidence of Renal Tubule Adenoma or Adenocarcinoma in Male B6C3F$_1$ Mice Receiving Corn Oil Vehicle[a]

	Incidence in Controls	
	Renal Tubule Adenoma[b]	Renule Tubule Adenoma or Adenocarcinoma[b]
Overall Historical Incidence		
Total	5/2,183 (0.2%)	8/2,183 (0.4%)
Standard deviation	0.6%	0.7%
Range	0%-2%	0%-2%

[a] Data as of 22 November 1989 for studies of at least 104 weeks
[b] No reported incidence for this tumor morphology in historical corn oil vehicle controls at the study laboratory

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate

	Vehicle Control	175 mg/kg	350 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
Scheduled sacrifice	8	10	8
Early deaths			
Moribund	10	8	12
Dead	14	13	9
Gavage death	3	4	5
Survivors			
Terminal sacrifice	25	25	25
Missing			1
Animals examined microscopically	50	50	50
Alimentary System			
Esophagus	(48)	(23)	(50)
Perforation	1 (2%)		
Periesophageal tissue, foreign body	1 (2%)	3 (13%)	1 (2%)
Periesophageal tissue, inflammation, acute	3 (6%)	3 (13%)	1 (2%)
Periesophageal tissue, inflammation, chronic		2 (9%)	
Periesophageal tissue, inflammation, granulomatous	1 (2%)	1 (4%)	
Intestine large, cecum	(47)	(25)	(46)
Inflammation, acute			1 (2%)
Intestine large, colon	(48)	(26)	(47)
Inflammation, acute		1 (4%)	
Intestine small, duodenum	(16)	(7)	(11)
Inflammation, chronic		1 (14%)	
Inflammation, necrotizing			1 (9%)
Intestine small, ileum	(43)	(23)	(41)
Hyperplasia, lymphoid		1 (4%)	
Intestine small, jejunum	(45)	(23)	(44)
Ulcer			1 (2%)
Liver	(50)	(50)	(50)
Amyloid deposition		1 (2%)	
Angiectasis			2 (4%)
Basophilic focus	1 (2%)	2 (4%)	1 (2%)
Clear cell focus	4 (8%)	1 (2%)	5 (10%)
Cytomegaly			1 (2%)
Eosinophilic focus		3 (6%)	8 (16%)
Hematopoietic cell proliferation	2 (4%)	1 (2%)	
Hyperplasia, lymphoid, chronic		1 (2%)	
Inflammation, subacute	1 (2%)		
Mitotic alteration			1 (2%)
Mixed cell focus		2 (4%)	1 (2%)
Necrosis, coagulative	2 (4%)	4 (8%)	4 (8%)
Vacuolization cytoplasmic	4 (8%)	2 (4%)	4 (8%)
Mesentery	(9)	(2)	(4)
Hemorrhage			1 (25%)
Inflammation, acute	1 (11%)		
Fat, necrosis	5 (56%)	2 (100%)	1 (25%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	175 mg/kg	350 mg/kg
Alimentary System (continued)			
Pancreas	(49)	(26)	(49)
Inflammation, acute	1 (2%)		
Acinus, atrophy	10 (20%)	3 (12%)	8 (16%)
Acinus, basophilic focus			1 (2%)
Acinus, hyperplasia			1 (2%)
Acinus, vacuolization cytoplasmic	1 (2%)		1 (2%)
Salivary glands	(49)	(24)	(49)
Inflammation, chronic	8 (16%)	1 (4%)	13 (27%)
Stomach, forestomach	(49)	(50)	(49)
Hyperplasia		1 (2%)	
Hyperplasia, squamous	2 (4%)	3 (6%)	6 (12%)
Infiltration cellular, mast cell		1 (2%)	
Inflammation, acute		2 (4%)	
Ulcer		1 (2%)	
Stomach, glandular	(50)	(47)	(47)
Inflammation, acute	2 (4%)		2 (4%)
Mucosa, dilatation	1 (2%)	1 (2%)	1 (2%)
Tooth	(50)	(25)	(49)
Dysplasia	21 (42%)	6 (24%)	18 (37%)
Inflammation, acute	3 (6%)		2 (4%)
Cardiovascular System			
Heart	(50)	(25)	(50)
Inflammation, acute	1 (2%)		
Inflammation, subacute	1 (2%)		2 (4%)
Mineralization		1 (4%)	
Atrium, thrombus	1 (2%)	1 (4%)	2 (4%)
Myocardium, degeneration			1 (2%)
Endocrine System			
Adrenal gland, cortex	(48)	(23)	(48)
Atrophy	1 (2%)		4 (8%)
Degeneration, ballooning	4 (8%)		
Hyperplasia	1 (2%)		
Hyperplasia, focal	1 (2%)	1 (4%)	
Hypertrophy	1 (2%)		
Hypertrophy, focal			2 (4%)
Spindle cell, hyperplasia		1 (4%)	
Adrenal gland, medulla	(46)	(23)	(43)
Hyperplasia		1 (4%)	1 (2%)
Pituitary gland	(45)	(22)	(48)
Pars distalis, cyst	1 (2%)		
Thyroid gland	(49)	(23)	(49)
Inflammation, acute	1 (2%)		
Ultimobranchial cyst		1 (4%)	1 (2%)
Follicle, cyst		1 (4%)	
Follicular cell, hyperplasia	3 (6%)		6 (12%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	175 mg/kg	350 mg/kg
Genital System			
Preputial gland	(7)	(3)	(5)
Inflammation, chronic	6 (86%)		2 (40%)
Prostate	(49)	(23)	(47)
Inflammation, acute	1 (2%)		
Inflammation, chronic	1 (2%)		
Seminal vesicle	(48)	(26)	(50)
Concretion		1 (4%)	
Inflammation, chronic	1 (2%)		
Testes	(50)	(24)	(50)
Interstitial cell, hyperplasia	2 (4%)		
Seminiferous tubule, atrophy		1 (4%)	1 (2%)
Hematopoietic System			
Bone marrow	(50)	(25)	(49)
Atrophy	2 (4%)		
Lymph node	(50)	(27)	(49)
Mediastinal, inflammation, acute		1 (4%)	
Renal, hyperplasia, lymphoid			1 (2%)
Lymph node, mandibular	(46)	(22)	(44)
Infiltration cellular, plasma cell			1 (2%)
Lymph node, mesenteric	(48)	(24)	(44)
Angiectasis			1 (2%)
Hyperplasia, lymphoid		1 (4%)	
Inflammation, acute	1 (2%)		
Inflammation, chronic		1 (4%)	
Thrombus	1 (2%)		
Spleen	(50)	(28)	(49)
Amyloid deposition		1 (4%)	
Angiectasis			1 (2%)
Atrophy			3 (6%)
Hematopoietic cell proliferation	3 (6%)	4 (14%)	2 (4%)
Hyperplasia, lymphoid	2 (4%)	2 (7%)	1 (2%)
Thymus	(29)	(17)	(33)
Cyst	3 (10%)		2 (6%)
Thymocyte, necrosis		3 (18%)	1 (3%)
Integumentary System			
Skin	(50)	(35)	(49)
Acanthosis	1 (2%)	1 (3%)	1 (2%)
Edema	1 (2%)		
Fibrosis	1 (2%)		
Hyperplasia, basal cell			1 (2%)
Inflammation	1 (2%)		1 (2%)
Inflammation, acute	2 (4%)	2 (6%)	2 (4%)
Inflammation, chronic	1 (2%)	1 (3%)	4 (8%)
Pigmentation	1 (2%)		
Face, foreign body	1 (2%)		
Face, inflammation, acute	1 (2%)		1 (2%)
Subcutaneous tissue, abscess	1 (2%)	2 (6%)	2 (4%)
Subcutaneous tissue, foreign body		1 (3%)	

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	175 mg/kg	350 mg/kg
Musculoskeletal System			
Bone	(50)	(25)	(49)
Fracture healed	1 (2%)		
Tibia, hyperostosis		1 (4%)	
Skeletal muscle	(50)	(25)	(50)
Fibrosis	1 (2%)		
Inflammation, acute	1 (2%)		
Inflammation, chronic	1 (2%)		1 (2%)
Head, inflammation, acute			2 (4%)
Nervous System			
Brain	(50)	(25)	(50)
Meninges, inflammation, chronic	1 (2%)		
Thalamus, mineralization	17 (34%)	14 (56%)	26 (52%)
Respiratory System			
Lung	(50)	(50)	(50)
Congestion	3 (6%)	1 (2%)	2 (4%)
Edema	1 (2%)		
Foreign body	2 (4%)		3 (6%)
Hemorrhage		1 (2%)	1 (2%)
Inflammation, acute		1 (2%)	
Inflammation, chronic	3 (6%)	1 (2%)	3 (6%)
Leukocytosis			1 (2%)
Alveolar epithelium, hyperplasia	4 (8%)	3 (6%)	3 (6%)
Alveolus, foreign body	3 (6%)		
Alveolus, infiltration cellular	1 (2%)		
Alveolus, infiltration cellular, histiocytic	2 (4%)	5 (10%)	3 (6%)
Mediastinum, foreign body	5 (10%)	2 (4%)	3 (6%)
Mediastinum, inflammation, acute	5 (10%)	2 (4%)	5 (10%)
Pleura, foreign body	1 (2%)		
Pleura, inflammation, acute	3 (6%)	2 (4%)	
Pleura, inflammation, granulomatous	2 (4%)		1 (2%)
Nose	(50)	(25)	(50)
Foreign body	1 (2%)	1 (4%)	
Inflammation, acute			1 (2%)
Nasolacrimal duct, inflammation, subacute			1 (2%)
Trachea	(49)	(24)	(49)
Peritracheal tissue, inflammation, acute	1 (2%)		
Special Senses System			
Ear	(2)	(1)	(1)
Inflammation, acute		1 (100%)	
Middle ear, inflammation, acute	1 (50%)		
Pinna, hyperplasia			1 (100%)
Eye	(6)	(5)	(7)
Lens, cataract		1 (20%)	1 (14%)
Harderian gland	(48)	(49)	(47)
Hyperplasia	3 (6%)	3 (6%)	5 (11%)
Inflammation, chronic	1 (2%)		

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	175 mg/kg	350 mg/kg
Urinary System			
Kidney	(50)	(50)	(50)
Amyloid deposition		1 (2%)	
Infarct	1 (2%)	2 (4%)	
Inflammation, chronic			1 (2%)
Metaplasia, osseous	2 (4%)	5 (10%)	3 (6%)
Nephropathy	9 (18%)	7 (14%)	13 (26%)
Glomerulus, dilatation	1 (2%)		1 (2%)
Pelvis, inflammation, acute	3 (6%)		1 (2%)
Proximal convoluted renal tubule, dilatation			2 (4%)
Renal tubule, hyperplasia			1 (2%)
Renal tubule, karyomegaly	2 (4%)	16 (32%)	39 (78%)
Renal tubule, necrosis, coagulative	1 (2%)		
Renal tubule, pigmentation			1 (2%)
Urinary bladder	(50)	(24)	(49)
Hemorrhage	1 (2%)		
Inflammation, acute	2 (4%)		1 (2%)
Inflammation, chronic	2 (4%)		

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR GAVAGE STUDY OF TRIS(2-CHLOROETHYL) PHOSPHATE

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate

	Vehicle Control	175 mg/kg	350 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
Scheduled sacrifice	9	10	10
Early deaths			
Moribund	7	5	5
Dead	6	6	8
Gavage death	6	2	2
Accident	1		
Survivors			
Terminal sacrifice	31	37	35
Animals examined microscopically	50	50	50
Alimentary System			
Gallbladder	(41)	(8)	(43)
Histiocytic sarcoma			1 (2%)
Intestine large, cecum	(49)	(10)	(49)
Liver	(50)	(50)	(50)
Hepatocellular carcinoma	2 (4%)	2 (4%)	3 (6%)
Hepatocellular adenoma	3 (6%)	2 (4%)	4 (8%)
Hepatocellular adenoma, multiple		1 (2%)	1 (2%)
Histiocytic sarcoma			1 (2%)
Mesentery	(7)	(9)	(9)
Fibrosarcoma, metastatic, skin			1 (11%)
Hemangiosarcoma, metastatic, skeletal muscle		1 (11%)	
Pancreas	(49)	(13)	(48)
Fibrosarcoma, metastatic, skin		1 (8%)	
Histiocytic sarcoma			1 (2%)
Salivary glands	(50)	(13)	(48)
Mast cell tumor malignant, metastatic, spleen		1 (8%)	
Stomach, forestomach	(49)	(49)	(48)
Papilloma squamous	1 (2%)		1 (2%)
Cardiovascular System			
Heart	(50)	(13)	(49)
Endocrine System			
Adrenal gland	(49)	(12)	(50)
Adrenal gland, cortex	(49)	(12)	(50)
Adrenal gland, medulla	(49)	(12)	(48)
Pheochromocytoma benign			1 (2%)
Pituitary gland	(48)	(14)	(44)
Pars distalis, adenoma	4 (8%)	3 (21%)	1 (2%)
Thyroid gland	(50)	(12)	(49)
Follicular cell, adenoma		1 (8%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	175 mg/kg	350 mg/kg
Genital System			
Ovary	(37)	(16)	(35)
Cystadenoma		1 (6%)	
Uterus	(50)	(43)	(50)
Deciduoma benign		1 (2%)	
Histiocytic sarcoma			1 (2%)
Cervix, hemangiosarcoma			1 (2%)
Endometrium, adenocarcinoma			1 (2%)
Endometrium, polyp stromal		1 (2%)	3 (6%)
Hematopoietic System			
Bone marrow	(49)	(13)	(50)
Histiocytic sarcoma			1 (2%)
Mast cell tumor malignant			1 (2%)
Lymph node	(49)	(17)	(50)
Lymph node, mandibular	(47)	(12)	(47)
Fibrosarcoma, metastatic, ear			1 (2%)
Mast cell tumor malignant			1 (2%)
Lymph node, mesenteric	(45)	(16)	(48)
Histiocytic sarcoma	1 (2%)		1 (2%)
Mast cell tumor malignant, metastatic, spleen		1 (6%)	
Spleen	(50)	(20)	(48)
Fibrosarcoma, metastatic, skin			1 (2%)
Hemangiosarcoma		1 (5%)	
Histiocytic sarcoma			1 (2%)
Mast cell tumor malignant		1 (5%)	
Thymus	(45)	(8)	(40)
Mast cell tumor malignant			1 (3%)
Integumentary System			
Mammary gland	(48)	(33)	(45)
Adenocarcinoma			3 (7%)
Fibroadenoma	1 (2%)		
Skin	(50)	(48)	(50)
Mast cell tumor malignant, metastatic, spleen		1 (2%)	
Trichoepithelioma		1 (2%)	
Subcutaneous tissue, fibrosarcoma		1 (2%)	2 (4%)
Subcutaneous tissue, fibrosarcoma, multiple			1 (2%)
Musculoskeletal System			
Skeletal muscle	(49)	(14)	(50)
Hemangiosarcoma		1 (7%)	
Nervous System			
Brain	(50)	(13)	(49)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	175 mg/kg	350 mg/kg
Respiratory System			
Lung	(50)	(50)	(49)
Alveolar/bronchiolar adenoma	2 (4%)	2 (4%)	5 (10%)
Alveolar/bronchiolar carcinoma	1 (2%)		
Fibrosarcoma, metastatic, skin		1 (2%)	1 (2%)
Hepatocellular carcinoma, metastatic, liver	2 (4%)		1 (2%)
Histiocytic sarcoma	1 (2%)		1 (2%)
Squamous cell carcinoma, metastatic, ear	1 (2%)		1 (2%)
Nose	(49)	(14)	(50)
Special Senses System			
Ear	(2)		(3)
Fibrosarcoma			1 (33%)
Squamous cell carcinoma			1 (33%)
External ear, squamous cell carcinoma	1 (50%)		
Pinna, fibrosarcoma			1 (33%)
Harderian gland	(49)	(49)	(49)
Adenoma	3 (6%)	6 (12%)	7 (14%)
Adenoma, multiple		1 (2%)	
Carcinoma		1 (2%)	
Urinary System			
Kidney	(50)	(49)	(50)
Histiocytic sarcoma			1 (2%)
Renal tubule, adenoma		1 (2%)	
Urinary bladder	(49)	(12)	(49)
Systemic Lesions			
Multiple organs[a]	(50)[a]	(50)[a]	(50)[a]
Histiocytic sarcoma	1 (2%)		2 (4%)
Leukemia		1 (2%)	
Lymphoma malignant lymphocytic	3 (6%)	2 (4%)	
Lymphoma malignant mixed	7 (14%)	5 (10%)	3 (6%)
Mesothelioma malignant		1 (2%)	
Tumor Summary			
Total animals with primary neoplasms[b]	25	26	37
Total primary neoplasms	29	37	45
Total animals with benign neoplasms	14	16	19
Total benign neoplasms	14	21	23
Total animals with malignant neoplasms	14	15	20
Total malignant neoplasms	15	16	22
Total animals with secondary neoplasms[c]	3	3	4
Total secondary neoplasms	3	6	6

[a] The number in parentheses is the number of animals with any tissue examined microscopically
[b] Primary tumors: all tumors except metastatic tumors
[c] Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: Vehicle Control

Number of Days on Study	2 3 6	3 0 2	3 0 2	3 0 4	3 0 0	3 6 5	3 6 5	4 9 7	5 6 9	5 3 7	5 4 0	5 4 4	6 1 0	6 3 2	6 3 9	6 6 9	6 6 9	7 0 0	7 1 6	7 1 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	4 1 5	3 8 5	4 2 5	4 3 5	4 0 5	4 4 5	4 6 5	4 0 4	4 5 5	4 5 4	4 6 4	4 9 5	3 5 4	4 6 3	4 6 4	4 1 4	4 2 4	3 8 4	3 8 3	3 7 5	3 7 1	3 7 2	3 7 3	3 7 4	3 8 1	3 8 2
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	A	M	+	+	+	+	A	A	+	A	M	+	M	+	+	A	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	A	A	+	+	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	M	A	A	A	M	M	M	A	A	A	M	A	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Intestine small, ileum	+	A	A	A	+	+	+	A	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	A	+	+	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																				X						X
Hepatocellular adenoma																						X				
Mesentery							+					+		+												
Pancreas	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																										
Stomach, glandular	+	+	+	A	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	+	M	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma											X															
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Genital System																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	M	M	+	+	M	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+: Tissue examined
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: Vehicle Control (continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	391	392	393	394	401	402	403	411	412	413	421	422	423	431	432	433	434	441	442	443	451	452	453	461	462	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	M	M	+	M	M	M	+	+	M	+	+	M	M	M	M	+	M	M	M	M	M	+	M	+	M	8
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										2
Hepatocellular adenoma														X						X						3
Mesentery		+			+							+										+				7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma squamous						X																				1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	39
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma					X				X			X														4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Genital System																										
Ovary	+	M	M	+	+	+	+	+	+	M	+	M	M	+	M	+	+	+	+	+	+	+	M	+	M	37
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: Vehicle Control (continued)

Number of Days on Study	2 3 6	3 0 2	3 0 2	3 0 4	3 0 5	3 6 5	3 6 7	4 6 9	5 3 7	5 4 0	5 4 4	6 1 0	6 3 2	6 3 9	6 6 9	6 6 9	7 0 0	7 1 6	7 1 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	4 1 5	3 8 5	4 2 5	4 3 5	4 0 5	4 4 5	4 6 5	4 0 4	4 5 5	4 5 4	4 6 4	3 9 5	4 5 4	4 6 3	4 1 4	4 2 4	3 8 4	3 8 3	3 7 5	3 7 1	3 7 2	3 7 3	3 7 4	3 8 1	3 8 2
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Lymph node, mesenteric	+	M	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X		X										
Alveolar/bronchiolar carcinoma																									
Hepatocellular carcinoma, metastatic, liver																			X						X
Histiocytic sarcoma																									X
Squamous cell carcinoma, metastatic, ear							X																		
Nose	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear						+	+																		
External ear, squamous cell carcinoma							X																		
Eye	+	+	+		+	+	+	+	+																
Harderian gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																				X					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Lymphoma malignant lymphocytic												X		X				X							
Lymphoma malignant mixed									X				X			X									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: Vehicle Control (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	3 9 1	3 9 2	3 9 3	3 9 4	4 0 1	4 0 2	4 0 3	4 1 1	4 1 2	4 1 3	4 2 1	4 2 2	4 2 3	4 3 1	4 3 2	4 3 3	4 3 4	4 4 1	4 4 2	4 4 3	4 5 1	4 5 2	4 5 3	4 6 1	4 6 2	**Total Tissues/ Tumors**
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	45
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	48
Fibroadenoma																			X							1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										2
Alveolar/bronchiolar carcinoma																	X									1
Hepatocellular carcinoma, metastatic, liver																										2
Histiocytic sarcoma																										1
Squamous cell carcinoma, metastatic, ear																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										2
External ear, squamous cell carcinoma																										1
Eye																										8
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma								X														X				3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant lymphocytic																										3
Lymphoma malignant mixed							X	X												X			X			7

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 175 mg/kg

Number of Days on Study	3 2 4	6 1 4	6 2 2	6 2 6	6 4 2	6 5 4	6 5 8	6 6 6	6 6 6	6 6 9	6 7 0	6 9 0	6 9 4	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	4 9 5	5 4 5	5 3 5	5 2 2	5 8 5	5 7 5	5 1 5	5 3 4	5 5 5	5 6 5	5 5 4	5 7 4	5 5 3	5 9 1	4 9 2	4 9 3	4 9 4	5 0 1	5 0 2	5 0 3	5 0 4	5 0 5	5 1 1	5 1 2	5 1 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+												
Gallbladder	+	M	A	+	A	A	+	+	+	+	+	+	M												
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+												
Intestine large, cecum	+	+	A	A	+	+	+	+	+	+	+	M	+												
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+												
Intestine large, rectum	+	+	+	A	+	+	+	+	+	+	+	M	+												
Intestine small	+	+	+	+	+	A	+	+	+	+	+	+	+												
Intestine small, duodenum	M	+	A	+	A	A	M	M	M	M	M	M	M												
Intestine small, ileum	+	+	A	M	A	A	+	+	+	+	+	+	+												
Intestine small, jejunum	+	+	+	+	+	A	+	+	+	+	+	+	+												
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma		X									X														
Hepatocellular adenoma																				X					
Hepatocellular adenoma, multiple				X																					
Mesentery			+	+						+	+								+	+					
Hemangiosarcoma, metastatic, skeletal muscle																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+												
Fibrosarcoma, metastatic, skin			X																						
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+												
Mast cell tumor malignant, metastatic, spleen				X																					
Stomach	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+												
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+												
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	M	+	+	+												
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	M	+	+	+												
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	M	+	+	+												
Islets, pancreatic	+	+	+	+	+	+	+	+	M	+	+	+	+												
Parathyroid gland	+	+	+	+	+	M	+	+	M	+	+	+	+												
Pituitary gland	+	+	M	+	+	+	+	+	+	M	+	+	+												
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+												
Follicular cell, adenoma									X																

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 175 mg/kg (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	5 1 4	5 2 1	5 2 3	5 2 4	5 2 5	5 3 1	5 3 2	5 3 3	5 4 1	5 4 2	5 4 3	5 4 4	5 5 1	5 5 2	5 6 1	5 6 2	5 6 3	5 6 4	5 7 1	5 7 2	5 7 3	5 8 1	5 8 2	5 8 3	5 8 4	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus																										13
Gallbladder																										8
Intestine large																										13
Intestine large, cecum																										10
Intestine large, colon																										13
Intestine large, rectum																										11
Intestine small																										12
Intestine small, duodenum																										2
Intestine small, ileum																										9
Intestine small, jejunum																										12
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										2
Hepatocellular adenoma																					X					2
Hepatocellular adenoma, multiple																										1
Mesentery							+														+			+		9
Hemangiosarcoma, metastatic, skeletal muscle																								X		1
Pancreas																										13
Fibrosarcoma, metastatic, skin																										1
Salivary glands																										13
Mast cell tumor malignant, metastatic, spleen																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth																										13
Cardiovascular System																										
Heart																										13
Endocrine System																										
Adrenal gland																										12
Adrenal gland, cortex																										12
Adrenal gland, medulla																										12
Islets, pancreatic																										12
Parathyroid gland																										11
Pituitary gland	+								+															+		14
Pars distalis, adenoma	X								X															X		3
Thyroid gland																										12
Follicular cell, adenoma																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 175 mg/kg (continued)

Number of Days on Study	3 2 4	6 1 4	6 2 2	6 2 6	6 4 2	6 5 4	6 5 8	6 6 6	6 6 6	6 6 9	6 7 0	6 9 0	6 9 4	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	4 9 5	5 4 5	5 3 5	5 2 2	5 8 5	5 7 5	5 1 5	5 3 4	5 5 5	5 6 5	5 5 4	5 7 4	5 5 3	5 9 1	4 9 2	4 9 3	4 9 4	5 0 1	5 0 2	5 0 3	5 0 4	5 0 5	5 1 1	5 1 2	5 1 3
Genital System																									
Ovary	+	+	+	+	+	+	+	M	+	+	+	M	+					+							
Cystadenoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+
Deciduoma benign																							X		
Endometrium, polyp stromal															X										
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+												
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+												
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+												
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	M	+												
Mast cell tumor malignant, metastatic, spleen				X																					
Spleen	+	+	+	+	+	+	+	+	+	M	+	+	+		+	+								+	+
Hemangiosarcoma																									X
Mast cell tumor malignant				X																					
Thymus	+	M	+	+	+	M	M	I	+	M	+	+	+												
Integumentary System																									
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+		+			+			+	+	+	+	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, spleen				X																					
Trichoepithelioma																									
Subcutaneous tissue, fibrosarcoma			X																						
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+												
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+												
Hemangiosarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+												

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 175 mg/kg (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	51 4	52 1	52 3	52 4	52 5	53 1	53 2	53 3	54 1	54 2	54 3	54 4	55 1	55 2	56 1	56 2	56 3	56 4	57 1	57 2	57 3	58 1	58 2	58 3	58 4	Total Tissues/ Tumors
Genital System																										
Ovary					+				+		+						+									16
Cystadenoma																	X									1
Uterus		+	+			+	+	+		+	+	+	+	+	+	+			+	+	+	+	+	+	+	43
Deciduoma benign																										1
Endometrium, polyp stromal																										1
Hematopoietic System																										
Bone marrow																										13
Lymph node							+										+				+			+		17
Lymph node, mandibular																										12
Lymph node, mesenteric							+										+				+			+		16
Mast cell tumor malignant, metastatic, spleen																										1
Spleen							+										+				+			+		20
Hemangiosarcoma																										1
Mast cell tumor malignant																										1
Thymus																										8
Integumentary System																										
Mammary gland				+	+	+	+				+	+	+	+	+	+	+	+	+	+	+					33
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	48
Mast cell tumor malignant, metastatic, spleen																										1
Trichoepithelioma														X												1
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone																										13
Skeletal muscle																								+		14
Hemangiosarcoma																								X		1
Nervous System																										
Brain																										13

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 175 mg/kg (continued)

Number of Days on Study	3 2 4	6 1 4	6 2 2	6 2 6	6 4 2	6 5 4	6 5 8	6 6 6	6 6 6	6 6 9	6 7 0	6 9 0	6 9 4	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	4 9 5	5 4 5	5 3 5	5 2 2	5 8 5	5 7 5	5 1 5	5 3 4	5 5 5	5 6 5	5 5 4	5 7 4	5 5 3	4 9 1	4 9 2	4 9 3	4 9 4	5 0 1	5 0 2	5 0 3	5 0 4	5 0 5	5 1 1	5 1 2	5 1 3
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Fibrosarcoma, metastatic, skin			X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+												
Trachea	+	+	+	+	+	M	+	+	+	+	+	+	+												
Special Senses System																									
Eye															+										
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X								X					X					
Adenoma, multiple														X											
Carcinoma																								X	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma									X																
Urinary bladder	+	+	+	+	+	+	+	M	+	+	+	+	+												
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia																									
Lymphoma malignant lymphocytic						X			X																
Lymphoma malignant mixed							X					X	X												
Mesothelioma malignant											X														

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 175 mg/kg (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	5 1 4	5 2 1	5 2 3	5 2 4	5 2 5	5 3 1	5 3 2	5 3 3	5 4 1	5 4 2	5 4 3	5 4 4	5 5 1	5 5 2	5 6 1	5 6 2	5 6 3	5 6 4	5 7 1	5 7 2	5 7 3	5 8 1	5 8 2	5 8 3	5 8 4	**Total Tissues/ Tumors**
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma												X											X			2
Fibrosarcoma, metastatic, skin																										1
Nose													+													14
Trachea																										12
Special Senses System																										
Eye																										1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma					X							X												X		6
Adenoma, multiple																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Renal tubule, adenoma																										1
Urinary bladder																										12
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia													X													1
Lymphoma malignant lymphocytic																										2
Lymphoma malignant mixed							X														X					5
Mesothelioma malignant																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 350 mg/kg

Number of Days on Study	0 7 2	4 8 2	4 8 9	5 1 9	5 3 7	5 8 3	6 2 7	6 6 4	6 7 0	6 7 6	6 7 6	6 9 6	6 9 8	7 0 6	7 1 9	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	6 2 5	6 1 5	6 1 4	6 6 5	6 7 5	6 6 4	6 9 5	6 5 1	7 0 5	6 2 4	7 0 4	6 5 5	6 2 3	6 8 5	6 9 4	6 1 1	6 1 2	6 1 3	6 2 1	6 2 2	6 3 1	6 3 2	6 3 3	6 3 4	6 3 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	A	M	M	+	+	+	+	+	A	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M
Intestine small	A	A	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	A	M	A	M	A	M	A	M	M	A	+	M	M	M	M	+	M	+	M	M	+	M	M	M
Intestine small, ileum	A	A	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	A	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma						X		X																	
Hepatocellular adenoma																						X	X		
Hepatocellular adenoma, multiple												X													
Histiocytic sarcoma																									
Mesentery							+				+		+												
Fibrosarcoma, metastatic, skin							X																		
Pancreas	+	+	I	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Salivary glands	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Stomach, glandular	+	+	M	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																				X					
Islets, pancreatic	+	+	I	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	M	M	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 350 mg/kg (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	6 4 1	6 4 2	6 4 3	6 4 4	6 4 5	6 5 2	6 5 3	6 5 4	6 6 1	6 6 2	6 6 3	6 7 1	6 7 2	6 7 3	6 7 4	6 8 1	6 8 2	6 8 3	6 8 4	6 9 1	6 9 2	6 9 3	7 0 1	7 0 2	7 0 3	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Histiocytic sarcoma													X													1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	+	+	M	7
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma									X																	3
Hepatocellular adenoma		X																				X				4
Hepatocellular adenoma, multiple																										1
Histiocytic sarcoma													X													1
Mesentery		+																+	+		+	+		+		9
Fibrosarcoma, metastatic, skin																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma													X													1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Papilloma squamous													X													1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	M	+	M	+	+	+	+	+	+	+	M	+	+	M	41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	44
Pars distalis, adenoma																			X							1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	49

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 350 mg/kg (continued)

Number of Days on Study	0 7 2	4 8 2	4 8 9	5 1 9	5 3 7	5 8 3	6 2 7	6 6 4	6 7 0	6 7 6	6 7 6	6 9 6	6 9 8	7 0 6	7 1 9	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	6 2 5	6 1 5	6 1 4	6 6 5	6 7 5	6 6 4	6 9 5	6 5 1	7 0 5	6 2 4	7 0 4	6 5 5	6 2 3	6 8 5	6 9 4	6 1 1	6 1 2	6 1 3	6 2 1	6 2 2	6 3 1	6 3 2	6 3 3	6 3 4	6 3 5
Genital System																									
Ovary	+	+	+	+	M	M	+	+	M	M	+	+	+	+	+	+	M	+	M	+	M	M	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Cervix, hemangiosarcoma																									
Endometrium, adenocarcinoma																									
Endometrium, polyp stromal				X											X										
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Mast cell tumor malignant					X																				
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, ear		X																							
Mast cell tumor malignant					X																				
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Spleen	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin							X																		
Histiocytic sarcoma																									
Thymus	+	+	M	+	+	M	+	+	+	+	+	+	+	M	M	+	+	+	+	M	M	+	+	+	+
Mast cell tumor malignant					X																				
Integumentary System																									
Mammary gland	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Adenocarcinoma													X												
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma							X																		X
Subcutaneous tissue, fibrosarcoma multiple														X											

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 350 mg/kg (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	6 4 1	6 4 2	6 4 3	6 4 4	6 4 5	6 5 2	6 5 3	6 5 4	6 6 1	6 6 2	6 6 3	6 7 1	6 7 2	6 7 3	6 7 4	6 8 1	6 8 2	6 8 3	6 8 4	6 9 1	6 9 2	6 9 3	7 0 1	7 0 2	7 0 3	**Total Tissues/ Tumors**
Genital System																										
Ovary	+	M	+	+	+	M	M	M	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	35
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma								X																		1
Cervix, hemangiosarcoma																									X	1
Endometrium, adenocarcinoma																				X						1
Endometrium, polyp stromal																						X				3
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma													X													1
Mast cell tumor malignant																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	47
Fibrosarcoma, metastatic, ear																										1
Mast cell tumor malignant																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma													X													1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrosarcoma, metastatic, skin																										1
Histiocytic sarcoma													X													1
Thymus	+	+	+	+	+	+	M	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	40
Mast cell tumor malignant																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	45
Adenocarcinoma			X												X											3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										2
Subcutaneous tissue, fibrosarcoma, multiple																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 350 mg/kg (continued)

Number of Days on Study	0 7 2	4 8 2	4 8 9	5 1 9	5 3 7	5 8 3	6 2 7	6 6 4	6 7 0	6 7 6	6 7 6	6 9 6	6 9 8	6 0 6	7 1 9	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	6 2 5	6 1 5	6 1 4	6 6 5	6 7 5	6 6 4	6 9 5	6 5 1	7 0 5	6 2 4	7 0 4	6 5 5	6 2 3	6 8 5	6 9 4	6 1 1	6 1 2	6 1 3	6 2 1	6 2 2	6 3 1	6 3 2	6 3 3	6 3 4	6 3 5
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																						X			
Fibrosarcoma, metastatic, skin							X																		
Hepatocellular carcinoma, metastatic, liver								X																	
Histiocytic sarcoma																									
Squamous cell carcinoma, metastatic, ear									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear		+							+		+														
Fibrosarcoma											X														
Squamous cell carcinoma									X																
Pinna, fibrosarcoma		X																							
Eye			+	+	+																				
Harderian gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X						X				X			X	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant mixed																		X	X						

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate: 350 mg/kg (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	6 4 1	6 4 2	6 4 3	6 4 4	6 4 5	6 5 2	6 5 3	6 5 4	6 6 1	6 6 2	6 6 3	6 7 1	6 7 2	6 7 3	6 7 4	6 8 1	6 8 2	6 8 3	6 8 4	6 9 1	6 9 2	6 9 3	7 0 1	7 0 2	7 0 3	**Total Tissues/ Tumors**
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma	X	X								X							X								5
Fibrosarcoma, metastatic, skin																										1
Hepatocellular carcinoma, metastatic, liver																										1
Histiocytic sarcoma													X													1
Squamous cell carcinoma, metastatic ear																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										3
Fibrosarcoma																										1
Squamous cell carcinoma																										1
Pinna, fibrosarcoma																										1
Eye																										3
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma							X					X										X				7
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma													X													1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma								X					X													2
Lymphoma malignant mixed																		X								3

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate

	Vehicle Control	175 mg/kg	350 mg/kg
Harderian Gland: Adenoma			
Overall rates[a]	3/50 (6%)	7/50 (14%)	7/50 (14%)
Adjusted rates[b]	9.7%	18.1%	19.2%
Terminal rates[c]	3/31 (10%)	6/37 (16%)	6/35 (17%)
First incidence (days)	729 (T)	658	676
Life table tests[d]	P=0.183	P=0.240	P=0.214
Logistic regression tests[d]	P=0.184	P=0.232	P=0.214
Cochran-Armitage test[d]	P=0.135		
Fisher exact test[d]		P=0.159	P=0.159
Harderian Gland: Adenoma or Carcinoma			
Overall rates	3/50 (6%)	8/50 (16%)	7/50 (14%)
Adjusted rates	9.7%	20.8%	19.2%
Terminal rates	3/31 (10%)	7/37 (19%)	6/35 (17%)
First incidence (days)	729 (T)	658	676
Life table tests	P=0.192	P=0.165	P=0.214
Logistic regression tests	P=0.193	P=0.157	P=0.214
Cochran-Armitage test	P=0.141		
Fisher exact test		P=0.100	P=0.159
Liver: Hepatocellular Adenoma			
Overall rates	3/50 (6%)	3/50 (6%)	5/50 (10%)
Adjusted rates	9.7%	7.4%	13.7%
Terminal rates	3/31 (10%)	2/37 (5%)	4/35 (11%)
First incidence (days)	729 (T)	626	696
Life table tests	P=0.340	P=0.576N	P=0.426
Logistic regression tests	P=0.339	P=0.592N	P=0.430
Cochran-Armitage test	P=0.283		
Fisher exact test		P=0.661N	P=0.357
Liver: Hepatocellular Carcinoma			
Overall rates	2/50 (4%)	2/50 (4%)	3/50 (6%)
Adjusted rates	6.3%	4.5%	7.2%
Terminal rates	1/31 (3%)	0/37 (0%)	1/35 (3%)
First incidence (days)	718	614	583
Life table tests	P=0.468	P=0.624N	P=0.561
Logistic regression tests	P=0.397	P=0.687N	P=0.521
Cochran-Armitage test	P=0.406		
Fisher exact test		P=0.691N	P=0.500
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rates	5/50 (10%)	5/50 (10%)	8/50 (16%)
Adjusted rates	15.6%	11.6%	20.2%
Terminal rates	4/31 (13%)	2/37 (5%)	5/35 (14%)
First incidence (days)	718	614	583
Life table tests	P=0.300	P=0.511N	P=0.367
Logistic regression tests	P=0.257	P=0.562N	P=0.351
Cochran-Armitage test	P=0.221		
Fisher exact test		P=0.630N	P=0.277

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	175 mg/kg	350 mg/kg
Lung: Alveolar/bronchiolar Adenoma			
Overall rates	2/50 (4%)	2/50 (4%)	5/49 (10%)
Adjusted rates	5.3%	5.4%	14.3%
Terminal rates	0/31 (0%)	2/37 (5%)	5/35 (14%)
First incidence (days)	632	729 (T)	729 (T)
Life table tests	P=0.181	P=0.631N	P=0.273
Logistic regression tests	P=0.172	P=0.675N	P=0.254
Cochran-Armitage test	P=0.140		
Fisher exact test		P=0.691N	P=0.210
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rates	3/50 (6%)	2/50 (4%)	5/49 (10%)
Adjusted rates	8.4%	5.4%	14.3%
Terminal rates	1/31 (3%)	2/37 (5%)	5/35 (14%)
First incidence (days)	632	729 (T)	729 (T)
Life table tests	P=0.327	P=0.424N	P=0.428
Logistic regression tests	P=0.319	P=0.455N	P=0.413
Cochran-Armitage test	P=0.265		
Fisher exact test		P=0.500N	P=0.346
Mammary Gland: Adenocarcinoma			
Overall rates	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted rates	0.0%	0.0%	8.2%
Terminal rates	0/31 (0%)	0/37 (0%)	2/35 (6%)
First incidence (days)			698
Life table tests	P=0.043	–[e]	P=0.145
Logistic regression tests	P=0.042	–[e]	P=0.144
Cochran-Armitage test	P=0.037		
Fisher exact test		–[e]	P=0.121
Mammary Gland: Adenocarcinoma or Fibroadenoma			
Overall rates	1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted rates	3.2%	0.0%	8.2%
Terminal rates	1/31 (3%)	0/37 (0%)	2/35 (6%)
First incidence (days)	729 (T)		698
Life table tests	P=0.199	P=0.465N	P=0.350
Logistic regression tests	P=0.200	P=0.465N	P=0.353
Cochran-Armitage test	P=0.176		
Fisher exact test		P=0.500N	P=0.309
Pituitary Gland (Pars Distalis): Adenoma			
Overall rates	4/48 (8%)	3/14 (21%)	1/44 (2%)
Adjusted rates	12.6%	100.0%	3.0%
Terminal rates	3/29 (10%)	3/3 (100%)	1/33 (3%)
First incidence (days)	544	729 (T)	729 (T)
Life table tests	P=0.125N	P=0.046	P=0.145N
Logistic regression tests	P=0.141N	P=0.150	P=0.177N
Cochran-Armitage test	P=0.193N		
Fisher exact test		P=0.184	P=0.209N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	175 mg/kg	350 mg/kg
Skin (Subcutaneous Tissue): Fibrosarcoma			
Overall rates	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rates	0.0%	2.1%	7.6%
Terminal rates	0/31 (0%)	0/37 (0%)	1/35 (3%)
First incidence (days)		622	627
Life table tests	P=0.073	P=0.547	P=0.148
Logistic regression tests	P=0.057	P=0.450	P=0.128
Cochran-Armitage test	P=0.060		
Fisher exact test		P=0.500	P=0.121
Uterus: Stromal Polyp			
Overall rates	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rates	0.0%	2.7%	7.6%
Terminal rates	0/31 (0%)	1/37 (3%)	1/35 (3%)
First incidence (days)		729 (T)	519
Life table tests	P=0.072	P=0.535	P=0.148
Logistic regression tests	P=0.057	P=0.535	P=0.113
Cochran-Armitage test	P=0.060		
Fisher exact test		P=0.500	P=0.121
All Organs: Malignant Lymphoma (Lymphocytic and Mixed)			
Overall rates	10/50 (20%)	7/50 (14%)	3/50 (6%)
Adjusted rates	26.0%	16.2%	8.6%
Terminal rates	4/31 (13%)	2/37 (5%)	3/35 (9%)
First incidence (days)	537	654	729 (T)
Life table tests	P=0.018N	P=0.196N	P=0.027N
Logistic regression tests	P=0.024N	P=0.278N	P=0.029N
Cochran-Armitage test	P=0.028N		
Fisher exact test		P=0.298N	P=0.036N
All Organs: Benign Tumors			
Overall rates	14/50 (28%)	16/50 (32%)	19/50 (38%)
Adjusted rates	40.5%	39.4%	48.3%
Terminal rates	11/31 (35%)	13/37 (35%)	15/35 (43%)
First incidence (days)	544	626	519
Life table tests	P=0.296	P=0.528N	P=0.343
Logistic regression tests	P=0.273	P=0.572N	P=0.320
Cochran-Armitage test	P=0.169		
Fisher exact test		P=0.414	P=0.198
All Organs: Malignant Tumors			
Overall rates	14/50 (28%)	15/50 (30%)	20/50 (40%)
Adjusted rates	35.1%	32.1%	44.7%
Terminal rates	6/31 (19%)	6/37 (16%)	11/35 (31%)
First incidence (days)	397	614	482
Life table tests	P=0.261	P=0.457N	P=0.302
Logistic regression tests	P=0.116	P=0.498	P=0.161
Cochran-Armitage test	P=0.120		
Fisher exact test		P=0.500	P=0.146

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	175 mg/kg	350 mg/kg
All Organs: Benign and Malignant			
Overall rates	25/50 (50%)	26/50 (52%)	37/50 (74%)
Adjusted rates	60.7%	56.2%	78.6%
Terminal rates	15/31 (48%)	17/37 (46%)	25/35 (71%)
First incidence (days)	397	614	482
Life table tests	P=0.096	P=0.339N	P=0.124
Logistic regression tests	P=0.019	P=0.497N	P=0.026
Cochran-Armitage test	P=0.010		
Fisher exact test		P=0.500	P=0.011

(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals necropsied or examined microscopically for this tumor type
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality.
[c] Observed 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 the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] No tumors in dosed group or control group; statistical test not performed.

TABLE D4
Historical Incidence of Harderian Gland Tumors in Female B6C3F$_1$ Mice Receiving Corn Oil Vehicle[a]

Study	Incidence in Controls Harderian Gland Adenoma or Carcinoma
Historical Incidence at Microbiological Associates	
d-Limonene	3/50 (6%)
Benzyl alcohol	3/50 (6%)
Succinic anhydride	0/50 (0%)
α-Methylbenzyl alcohol	2/50 (4%)
Total	8/200 (4%)
Overall Historical Incidence	
Overall	53/2,193 (2.4%)
Standard deviation	2.4%
Range	0%-10%

[a] Data as of 22 November 1989 for studies of at least 104 weeks

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate

	Vehicle Control	175 mg/kg	350 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
Scheduled sacrifice	9	10	10
Early deaths			
Moribund	7	5	5
Dead	6	6	8
Gavage death	6	2	2
Accident	1		
Survivors			
Terminal sacrifice	31	37	35
Animals examined microscopically	50	50	50
Alimentary System			
Esophagus	(50)	(13)	(49)
Periesophageal tissue, foreign body	1 (2%)		
Periesophageal tissue, inflammation, acute	3 (6%)		
Wall, inflammation, necrotizing	1 (2%)		
Intestine small, ileum	(43)	(9)	(46)
Hyperplasia, lymphoid	2 (5%)		
Intestine small, jejunum	(45)	(12)	(46)
Hyperplasia, lymphoid	1 (2%)		
Liver	(50)	(50)	(50)
Angiectasis		1 (2%)	
Clear cell focus			1 (2%)
Eosinophilic focus	1 (2%)	3 (6%)	1 (2%)
Hematopoietic cell proliferation	1 (2%)	1 (2%)	3 (6%)
Inflammation, chronic	1 (2%)	1 (2%)	1 (2%)
Inflammation, subacute			2 (4%)
Necrosis, coagulative		3 (6%)	4 (8%)
Vacuolization cytoplasmic	3 (6%)	4 (8%)	1 (2%)
Mesentery	(7)	(9)	(9)
Infiltration cellular, mast cell	1 (14%)		
Fat, necrosis	3 (43%)	8 (89%)	8 (89%)
Pancreas	(49)	(13)	(48)
Inflammation, chronic			1 (2%)
Acinus, atrophy	4 (8%)	2 (15%)	6 (13%)
Acinus, basophilic focus	1 (2%)	1 (8%)	1 (2%)
Acinus, necrosis, coagulative	1 (2%)		
Duct, ectasia		1 (8%)	
Salivary glands	(50)	(13)	(48)
Inflammation, chronic	8 (16%)	1 (8%)	5 (10%)
Stomach, forestomach	(49)	(49)	(48)
Hyperplasia, squamous	4 (8%)	1 (2%)	8 (17%)
Infiltration cellular, mast cell	1 (2%)		
Inflammation, acute	1 (2%)		
Stomach, glandular	(48)	(49)	(47)
Infiltration cellular, mast cell	1 (2%)		
Mucosa, dilatation	1 (2%)		1 (2%)
Mucosa, hyperplasia	1 (2%)		
Tooth	(49)	(13)	(50)
Inflammation, acute	2 (4%)		1 (2%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	175 mg/kg	350 mg/kg
Cardiovascular System			
Heart	(50)	(13)	(49)
Inflammation, chronic		1 (8%)	
Inflammation, subacute			1 (2%)
Atrium, thrombus		1 (8%)	
Epicardium, inflammation, acute	4 (8%)	1 (8%)	
Myocardium, necrosis, zenkers			1 (2%)
Endocrine System			
Adrenal gland, cortex	(49)	(12)	(50)
Atrophy	1 (2%)		
Degeneration, ballooning	1 (2%)		1 (2%)
Hematopoietic cell proliferation			1 (2%)
Hypertrophy, focal	1 (2%)		
Adrenal gland, medulla	(49)	(12)	(48)
Hyperplasia	2 (4%)		
Pituitary gland	(48)	(14)	(44)
Pars distalis, angiectasis	4 (8%)		4 (9%)
Pars distalis, hyperplasia	6 (13%)	1 (7%)	5 (11%)
Pars distalis, hypertrophy, focal	1 (2%)		
Thyroid gland	(50)	(12)	(49)
Inflammation, acute	1 (2%)		
Inflammation, chronic	2 (4%)		
Follicle, cyst		1 (8%)	
Follicular cell, hyperplasia	6 (12%)		6 (12%)
Genital System			
Ovary	(37)	(16)	(35)
Cyst	14 (38%)	6 (38%)	7 (20%)
Periovarian tissue, inflammation, chronic			1 (3%)
Uterus	(50)	(43)	(50)
Hydrometra		1 (2%)	
Inflammation, chronic	1 (2%)		
Endometrium, hyperplasia, cystic	49 (98%)	42 (98%)	48 (96%)
Endometrium, inflammation, acute		2 (5%)	1 (2%)
Hematopoietic System			
Bone marrow	(49)	(13)	(50)
Hyperplasia, reticulum cell			1 (2%)
Myelofibrosis	12 (24%)		14 (28%)
Lymph node	(49)	(17)	(50)
Iliac, hemorrhage	1 (2%)		
Iliac, hyperplasia, plasma cell	1 (2%)		
Inguinal, infiltration cellular, mast cell	1 (2%)		
Mediastinal, hyperplasia, lymphoid		1 (6%)	1 (2%)
Lymph node, mandibular	(47)	(12)	(47)
Hematopoietic cell proliferation			1 (2%)
Hyperplasia, lymphoid			2 (4%)
Hyperplasia, plasma cell	1 (2%)		
Infiltration cellular, mast cell	1 (2%)		

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	175 mg/kg	350 mg/kg
Hematopoietic System (continued)			
Lymph node, mesenteric	(45)	(16)	(48)
Ectasia	1 (2%)		
Hematopoietic cell proliferation		1 (6%)	1 (2%)
Hyperplasia, lymphoid	1 (2%)		3 (6%)
Inflammation, chronic		1 (6%)	
Spleen	(50)	(20)	(48)
Atrophy	1 (2%)		
Hematopoietic cell proliferation	2 (4%)	5 (25%)	5 (10%)
Hyperplasia, lymphoid	2 (4%)	3 (15%)	6 (13%)
Hyperplasia, plasma cell	1 (2%)		
Thymus	(45)	(8)	(40)
Cyst	1 (2%)		3 (8%)
Hyperplasia, lymphoid	1 (2%)		1 (3%)
Mediastinum, foreign body	1 (2%)		
Mediastinum, inflammation, acute	3 (7%)	1 (13%)	
Thymocyte, necrosis	1 (2%)	1 (13%)	
Integumentary System			
Mammary gland	(48)	(33)	(45)
Hyperplasia, cystic	3 (6%)	3 (9%)	5 (11%)
Duct, ectasia			1 (2%)
Duct, hyperplasia		1 (3%)	1 (2%)
Skin	(50)	(48)	(50)
Fibrosis		1 (2%)	
Foreign body	1 (2%)		
Inflammation, acute	1 (2%)	3 (6%)	
Inflammation, chronic	1 (2%)		2 (4%)
Inflammation, granulomatous	1 (2%)		
Face, inflammation, acute			2 (4%)
Subcutaneous tissue, abscess	2 (4%)		
Subcutaneous tissue, necrosis		1 (2%)	
Musculoskeletal System			
Skeletal muscle	(49)	(14)	(50)
Hemorrhage	1 (2%)		
Inflammation, chronic			1 (2%)
Head, inflammation, acute	1 (2%)		1 (2%)
Nervous System			
Brain	(50)	(13)	(49)
Hemorrhage	1 (2%)		
Necrosis, liquifactive		1 (8%)	
Meninges, inflammation, chronic	1 (2%)		1 (2%)
Thalamus, inflammation	1 (2%)		
Thalamus, mineralization	21 (42%)	6 (46%)	23 (47%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Tris(2-Chloroethyl) Phosphate (continued)

	Vehicle Control	175 mg/kg	350 mg/kg
Respiratory System			
Lung	(50)	(50)	(49)
Congestion	2 (4%)	1 (2%)	1 (2%)
Foreign body	1 (2%)	1 (2%)	
Hemorrhage	2 (4%)		
Inflammation, acute	1 (2%)		1 (2%)
Inflammation, chronic	2 (4%)	4 (8%)	2 (4%)
Leukocytosis			1 (2%)
Thrombus			1 (2%)
Alveolar epithelium, hyperplasia		2 (4%)	3 (6%)
Alveolus, foreign body		3 (6%)	
Alveolus, infiltration cellular, histiocytic	1 (2%)		
Arteriole, hyperplasia			1 (2%)
Fat, mediastinum, necrosis		1 (2%)	
Mediastinum, foreign body	4 (8%)	1 (2%)	3 (6%)
Mediastinum, inflammation, acute	2 (4%)	1 (2%)	2 (4%)
Mediastinum, inflammation, chronic			1 (2%)
Pleura, inflammation, acute	2 (4%)	1 (2%)	
Nose	(49)	(14)	(50)
Infiltration cellular, mast cell	1 (2%)		
Inflammation, acute	1 (2%)		
Nasolacrimal duct, foreign body			1 (2%)
Nasolacrimal duct, inflammation, acute		1 (7%)	1 (2%)
Respiratory epithelium, inflammation, acute	1 (2%)		
Trachea	(50)	(12)	(50)
Glands, dilatation			1 (2%)
Peritracheal tissue, foreign body	2 (4%)	1 (8%)	
Peritracheal tissue, inflammation, acute	2 (4%)		
Special Senses System			
Harderian gland	(49)	(49)	(49)
Hyperplasia	1 (2%)	4 (8%)	2 (4%)
Inflammation, chronic	1 (2%)		
Urinary System			
Kidney	(50)	(49)	(50)
Infarct		3 (6%)	2 (4%)
Inflammation, chronic			1 (2%)
Metaplasia, osseous	1 (2%)	1 (2%)	1 (2%)
Mineralization		1 (2%)	
Nephropathy	8 (16%)	1 (2%)	9 (18%)
Cortex, necrosis, coagulative			1 (2%)
Glomerulus, amyloid deposition	1 (2%)		
Medulla, inflammation, acute		1 (2%)	
Renal tubule, karyomegaly		5 (10%)	44 (88%)
Urinary bladder	(49)	(12)	(49)
Inflammation, chronic	1 (2%)		1 (2%)

APPENDIX E
ORGAN WEIGHTS
AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE E1
Organ Weights for Rats in the 16-Day Gavage Studies of Tris(2-Chloroethyl) Phosphate[a]

Weight (g)	0 mg/kg	22 mg/kg	44 mg/kg	88 mg/kg	175 mg/kg	350 mg/kg
Male						
Necropsy body wt	203 ± 4.47	203 ± 2.86	198 ± 7.47	199 ± 3.15	209 ± 3.65	202 ± 5.57
Brain	1.91 ± 0.02	1.88 ± 0.02	1.87 ± 0.02	1.87 ± 0.02	1.91 ± 0.02	1.89 ± 0.02
Heart	0.77 ± 0.02	0.75 ± 0.03	0.72 ± 0.02	0.75 ± 0.01	0.80 ± 0.02	0.78 ± 0.01
R. Kidney	1.00 ± 0.03	1.04 ± 0.01	0.99 ± 0.05	1.03 ± 0.01	1.12 ± 0.04*	1.10 ± 0.03*
Liver	10.4 ± 0.36	10.7 ± 0.43	9.80 ± 0.37	10.1 ± 0.22	11.2 ± 0.45	10.9 ± 0.45
Lung	1.36 ± 0.04	1.60 ± 0.15	1.38 ± 0.06	1.47 ± 0.12	1.43 ± 0.10	1.37 ± 0.04
Thymus	0.52 ± 0.02	0.45 ± 0.02*	0.47 ± 0.02	0.51 ± 0.01	0.48 ± 0.02	0.48 ± 0.01
Female						
Necropsy body wt	140 ± 2.50	140 ± 3.90	139 ± 4.40	140 ± 4.21	139 ± 4.14	144 ± 6.61
Brain	1.82 ± 0.02	1.80 ± 0.03	1.73 ± 0.02*	1.74 ± 0.03*	1.75 ± 0.02*	1.75 ± 0.01*
Heart	0.63 ± 0.03	0.61 ± 0.01	0.53 ± 0.01	0.61 ± 0.03	0.55 ± 0.02	0.61 ± 0.05
R. Kidney	0.74 ± 0.02	0.75 ± 0.01	0.70 ± 0.02	0.71 ± 0.03	0.75 ± 0.03	0.76 ± 0.03
Liver	6.21 ± 0.15	6.24 ± 0.25	6.15 ± 0.24	6.45 ± 0.29	6.42 ± 0.21	7.25 ± 0.46*
Lung	1.32 ± 0.05	1.20 ± 0.03	1.37 ± 0.14	1.08 ± 0.03**	1.08 ± 0.05**	1.10 ± 0.04**
Thymus	0.45 ± 0.02	0.43 ± 0.03	0.38 ± 0.01	0.42 ± 0.02	0.37 ± 0.01*	0.45 ± 0.05

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error; n=5 for all groups except 88 mg/kg males (n=4).

TABLE E2
Organ-Weight-to-Body-Weight Ratios for Rats in the 16-Day Gavage Studies of Tris(2-Chloroethyl) Phosphate[a]

Ratio (mg/g)	0 mg/kg	22 mg/kg	44 mg/kg	88 mg/kg	175 mg/kg	350 mg/kg
Male						
Necropsy body wt	203 ± 4.47	203 ± 2.86	198 ± 7.47	199 ± 3.15	209 ± 3.65	202 ± 5.57
Brain	9.43 ± 0.27	9.24 ± 0.05	9.52 ± 0.31	9.37 ± 0.18	9.13 ± 0.17	9.34 ± 0.17
Heart	3.79 ± 0.08	3.70 ± 0.09	3.64 ± 0.08	3.77 ± 0.05	3.82 ± 0.04	3.88 ± 0.09
R. Kidney	4.95 ± 0.11	5.15 ± 0.08	4.99 ± 0.07	5.22 ± 0.09	5.35 ± 0.14*	5.46 ± 0.09**
Liver	51.2 ± 1.31	52.7 ± 1.50	49.6 ± 0.96	51.1 ± 0.55	53.5 ± 1.51	53.7 ± 1.23
Lung	6.72 ± 0.11	7.88 ± 0.77	7.00 ± 0.13	7.59 ± 0.82	6.89 ± 0.56	6.78 ± 0.14
Thymus	2.58 ± 0.11	2.21 ± 0.07*	2.36 ± 0.08	2.53 ± 0.11	2.30 ± 0.08	2.37 ± 0.03
Female						
Necropsy body wt	140 ± 2.50	140 ± 3.90	139 ± 4.40	140 ± 4.21	139 ± 4.14	144 ± 6.61
Brain	13.0 ± 0.13	12.9 ± 0.34	12.4 ± 0.36	12.5 ± 0.36	12.6 ± 0.42	12.3 ± 0.55
Heart	4.45 ± 0.16	4.40 ± 0.14	3.81 ± 0.09*	4.33 ± 0.14	3.98 ± 0.05	4.20 ± 0.27
R. Kidney	5.30 ± 0.10	5.36 ± 0.06	5.05 ± 0.20	5.07 ± 0.14	5.42 ± 0.14	5.26 ± 0.09
Liver	44.2 ± 0.50	44.5 ± 0.80	44.1 ± 0.75	46.0 ± 0.85	46.3 ± 0.88	50.2 ± 0.15**
Lung	9.43 ± 0.36	8.62 ± 0.27	9.79 ± 0.86	7.75 ± 0.17**	7.76 ± 0.25**	7.66 ± 0.14**
Thymus	3.20 ± 0.06	3.05 ± 0.11	2.70 ± 0.09*	2.98 ± 0.10	2.68 ± 0.06**	3.10 ± 0.19

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error; n=5 for all groups except 88 mg/kg males (n=4).

TABLE E3
Organ Weights for Rats in the 16-Week Gavage Studies of Tris(2-Chloroethyl) Phosphate[a]

Weight (g)	0 mg/kg	22 mg/kg	44 mg/kg	88 mg/kg	175 mg/kg	350 mg/kg
Male						
Necropsy body wt	360 ± 4.37	366 ± 7.23	352 ± 4.73	348 ± 6.65	358 ± 10.7	352 ± 11.1
Brain	2.05 ± 0.02	2.07 ± 0.02	2.04 ± 0.02	2.01 ± 0.02	2.05 ± 0.02	2.07 ± 0.05
Heart	1.13 ± 0.02	1.13 ± 0.02	1.08 ± 0.02	1.17 ± 0.02	1.11 ± 0.04	1.10 ± 0.07
R. Kidney	1.28 ± 0.03	1.25 ± 0.03	1.30 ± 0.03	1.28 ± 0.03	1.32 ± 0.04	1.56 ± 0.07**
Liver	13.4 ± 0.27	13.5 ± 0.74	13.2 ± 0.33	13.2 ± 0.40	14.4 ± 0.31*	15.7 ± 0.50**
Lung	2.15 ± 0.15	2.31 ± 0.13	2.25 ± 0.10	1.93 ± 0.05	1.88 ± 0.08	2.35 ± 0.08
L. Testis	1.49 ± 0.03	1.56 ± 0.03	–[b]	1.47 ± 0.03	1.50 ± 0.03	–
Thymus	0.30 ± 0.01	0.29 ± 0.02	0.35 ± 0.02	0.30 ± 0.01	0.31 ± 0.01	0.32 ± 0.01
Female						
Necropsy body wt	191 ± 1.68	187 ± 3.21	189 ± 2.36	185 ± 2.48	199 ± 6.97	230 ± 16.7
Brain	1.83 ± 0.01	1.81 ± 0.01	1.81 ± 0.01	1.80 ± 0.01	1.84 ± 0.02	1.94 ± 0.05
Heart	0.63 ± 0.01	0.61 ± 0.01	0.62 ± 0.01	0.61 ± 0.01	0.64 ± 0.03	0.75 ± 0.06
R. Kidney	0.71 ± 0.01	0.72 ± 0.02	0.76 ± 0.01**	0.76 ± 0.01**	0.83 ± 0.02**	1.04 ± 0.07**
Liver	6.10 ± 0.14	6.34 ± 0.19	6.85 ± 0.14**	6.52 ± 0.08**	7.56 ± 0.37**	11.2 ± 1.34**
Lung	1.26 ± 0.06	1.39 ± 0.10	1.32 ± 0.05*	1.27 ± 0.04	1.32 ± 0.04*	1.48 ± 0.02**
Thymus	0.22 ± 0.01	0.22 ± 0.01	0.21 ± 0.01	0.22 ± 0.01	0.22 ± 0.02	0.21 ± 0.02

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error; n=10 for all groups except 22 mg/kg males (n=9), 175 mg/kg and 350 mg/kg males (n=4), 22 mg/kg and 175 mg/kg females (n=8), and 350 mg/kg females (n=5).
[b] No means calculated since less than two measurements were available.

Table E4
Organ-Weight-to-Body-Weight Ratios for Rats in the 16-Week Gavage Studies of Tris(2-Chloroethyl) Phosphate[a]

Ratio (mg/g)	0 mg/kg	22 mg/kg	44 mg/kg	88 mg/kg	175 mg/kg	350 mg/kg
Male						
Necropsy body wt	360 ± 4.37	366 ± 7.23	352 ± 4.73	348 ± 6.65	358 ± 10.7	352 ± 11.1
Brain	5.71 ± 0.10	5.67 ± 0.09	5.80 ± 0.06	5.78 ± 0.10	5.75 ± 0.17	5.88 ± 0.08
Heart	3.14 ± 0.03	3.08 ± 0.06	3.08 ± 0.03	3.38 ± 0.04**	3.33 ± 0.12*	3.13 ± 0.09
R. Kidney	3.54 ± 0.08	3.42 ± 0.07	3.68 ± 0.04	3.68 ± 0.04	3.65 ± 0.09	4.42 ± 0.07**
Liver	37.1 ± 0.64	36.8 ± 1.55	37.4 ± 0.60	38.2 ± 1.23	39.3 ± 1.43	44.5 ± 0.29**
Lung	5.99 ± 0.41	6.29 ± 0.30	6.37 ± 0.25	5.56 ± 0.12	5.65 ± 0.42	6.69 ± 0.28
L. Testis	4.14 ± 0.12	4.26 ± 0.05	–[b]	4.23 ± 0.08	4.33 ± 0.08	–
Thymus	0.84 ± 0.03	0.78 ± 0.04	0.98 ± 0.06	0.88 ± 0.04	0.89 ± 0.05	0.92 ± 0.02
Female						
Necropsy body wt	191 ± 1.68	187 ± 3.21	189 ± 2.36	185 ± 2.48	199 ± 6.97	230 ± 16.7
Brain	9.57 ± 0.09	9.69 ± 0.16	9.60 ± 0.13	9.75 ± 0.12	9.33 ± 0.22	8.53 ± 0.48
Heart	3.32 ± 0.05	3.29 ± 0.07	3.30 ± 0.04	3.30 ± 0.04	3.21 ± 0.05	3.25 ± 0.02
R. Kidney	3.69 ± 0.04	3.83 ± 0.06	4.03 ± 0.04**	4.10 ± 0.07**	4.18 ± 0.06**	4.51 ± 0.06**
Liver	32.0 ± 0.57	33.9 ± 0.73*	36.2 ± 0.58**	35.3 ± 0.30**	38.0 ± 0.60**	48.2 ± 2.49**
Lung	6.59 ± 0.31	7.41 ± 0.50	6.98 ± 0.24	6.90 ± 0.21	6.69 ± 0.13	6.55 ± 0.48
Thymus	1.14 ± 0.04	1.17 ± 0.05	1.12 ± 0.05	1.17 ± 0.05	1.10 ± 0.04	0.92 ± 0.05*

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error; n=10 for all groups except 22 mg/kg males (n=9), 175 mg/kg and 350 mg/kg males (n=4), 22 mg/kg and 175 mg/kg females (n=8), 350 mg/kg females (n=5), where noted.
[b] No means calculated since less than two measurements were available.

TABLE E5
Organ Weights for Rats at the 66-Week Interim Sacrifice in the 2-Year Gavage Studies of Tris(2-Chloroethyl) Phosphate[a]

Weight (g)	0 mg/kg	44 mg/kg	88 mg/kg
Male			
Necropsy body wt	465 ± 14.5	477 ± 8.0	471 ± 6.1
Brain	2.20 ± 0.04	2.13 ± 0.03	2.20 ± 0.03
R. Kidney	1.52 ± 0.06	1.60 ± 0.03	1.73 ± 0.03**
Liver	14.9 ± 0.84	16.2 ± 0.33	17.9 ± 0.35**
Female			
Necropsy body wt	286 ± 4.4	269 ± 4.4*	278 ± 5.4
Brain	1.93 ± 0.05	1.93 ± 0.01	1.93 ± 0.02
R. Kidney	0.87 ± 0.04	0.88 ± 0.03	0.92 ± 0.02
Liver	8.86 ± 0.26	8.62 ± 0.20	9.13 ± 0.26

** Significantly different ($P \leq 0.01$) from the control group by Dunn's or Shirley's test
[a] Mean ± standard error; n=10 for all groups except control males and 88 mg/kg females (n=9).

TABLE E6
Organ-Weight-to-Body-Weight Ratios for Rats at the 66-Week Interim Sacrifice in the 2-Year Gavage Studies of Tris(2-Chloroethyl) Phosphate[a]

Ratio (mg/g)	0 mg/kg	44 mg/kg	88 mg/kg
Male			
Necropsy body wt	465 ± 14.5	477 ± 8.0	471 ± 6.1
Brain	4.76 ± 0.13	4.47 ± 0.06	4.66 ± 0.09
R. Kidney	3.28 ± 0.12	3.37 ± 0.06	3.68 ± 0.06**
Liver	31.9 ± 1.11	34.0 ± 0.34*	37.9 ± 0.50**
Female			
Necropsy body wt	286 ± 4.4	269 ± 4.4*	278 ± 5.4
Brain	6.75 ± 0.18	7.20 ± 0.15	6.97 ± 0.14
R. Kidney	3.03 ± 0.14	3.26 ± 0.13	3.31 ± 0.12
Liver	31.1 ± 0.96	32.0 ± 0.77	32.8 ± 0.70

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error; n=10 for all groups except control males and 88 mg/kg females (n=9).

TABLE E7
Organ Weights for Mice in the 16-Day Gavage Studies of Tris(2-Chloroethyl) Phosphate[a]

Weight (g)	0 mg/kg	44 mg/kg	88 mg/kg	175 mg/kg	350 mg/kg	700 mg/kg
Male						
Necropsy body wt	23.9 ± 0.58	24.6 ± 0.45	24.9 ± 0.91	25.2 ± 0.86	24.5 ± 0.26	25.1 ± 0.41
Brain	0.54 ± 0.01	0.50 ± 0.01	0.50 ± 0.01	0.49 ± 0.00	0.50 ± 0.01	0.51 ± 0.02
Heart	0.19 ± 0.02	0.13 ± 0.01	0.13 ± 0.01*	0.17 ± 0.01	0.14 ± 0.01	0.15 ± 0.01
R. Kidney	0.23 ± 0.01	0.20 ± 0.00	0.21 ± 0.02	0.22 ± 0.02	0.23 ± 0.03	0.23 ± 0.01
Liver	1.31 ± 0.10	1.10 ± 0.04	1.18 ± 0.04	1.23 ± 0.08	1.25 ± 0.06	1.35 ± 0.04
Lung	0.27 ± 0.05	0.21 ± 0.01	0.23 ± 0.01	0.24 ± 0.01	0.23 ± 0.02	0.24 ± 0.01
Thymus	0.08 ± 0.01	0.07 ± 0.013	0.06 ± 0.00	0.08 ± 0.01	0.05 ± 0.00	0.06 ± 0.01
Female						
Necropsy body wt	21.3 ± 0.45	21.3 ± 0.34	22.0 ± 0.46	21.6 ± 0.68	22.1 ± 0.36	20.9 ± 0.43
Brain	0.54 ± 0.01	0.52 ± 0.03	0.52 ± 0.01	0.56 ± 0.02	0.53 ± 0.01	0.54 ± 0.02
Heart	0.15 ± 0.01	0.14 ± 0.01	0.13 ± 0.01	0.16 ± 0.02	0.14 ± 0.01	0.16 ± 0.01
R. Kidney	0.18 ± 0.01	0.20 ± 0.01	0.18 ± 0.02	0.21 ± 0.02	0.20 ± 0.01	0.21 ± 0.01
Liver	1.22 ± 0.02	1.25 ± 0.04	1.21 ± 0.06	1.18 ± 0.04	1.26 ± 0.03	1.29 ± 0.03
Lung	0.25 ± 0.01	0.22 ± 0.01	0.25 ± 0.03	0.25 ± 0.01	0.27 ± 0.02	0.27 ± 0.02
Thymus	0.07 ± 0.00	0.09 ± 0.01	0.08 ± 0.01	0.08 ± 0.01	0.09 ± 0.01	0.09 ± 0.01

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
[a] Mean ± standard error; n=5 for all groups except 175 mg/kg males, 350 mg/kg males, and 700 mg/kg females (n=4).

TABLE E8
Organ-Weight-to-Body-Weight Ratios for Mice in the 16-Day Gavage Studies of Tris(2-Chloroethyl) Phosphate[a]

Ratio (mg/g)	0 mg/kg	44 mg/kg	88 mg/kg	175 mg/kg	350 mg/kg	700 mg/kg
Male						
Necropsy body wt	23.9 ± 0.58	24.6 ± 0.45	24.9 ± 0.91	25.2 ± 0.86	24.5 ± 0.26	25.1 ± 0.41
Brain	22.5 ± 0.48	20.5 ± 0.64*	20.2 ± 0.91*	19.6 ± 0.76*	20.4 ± 0.33*	20.4 ± 0.84*
Heart	7.74 ± 0.72	5.43 ± 0.25*	5.32 ± 0.25*	6.61 ± 0.63	5.83 ± 0.58	5.99 ± 0.27
R. Kidney	9.47 ± 0.24	8.22 ± 0.22	8.36 ± 0.66	8.55 ± 0.91	9.21 ± 1.07	9.34 ± 0.41
Liver	54.7 ± 3.73	44.6 ± 1.15*	47.5 ± 0.75	48.6 ± 1.84	51.1 ± 2.98	53.8 ± 2.22
Lung	11.4 ± 2.06	8.5 ± 0.48	9.2 ± 0.23	9.6 ± 0.45	9.2 ± 0.70	9.7 ± 0.43
Thymus	3.22 ± 0.52	2.75 ± 0.35	2.44 ± 0.20	3.18 ± 0.59	2.14 ± 0.19	2.47 ± 0.30
Female						
Necropsy body wt	21.3 ± 0.45	21.3 ± 0.34	22.0 ± 0.46	21.6 ± 0.68	22.1 ± 0.36	20.9 ± 0.43
Brain	25.3 ± 0.35	24.3 ± 1.25	23.5 ± 1.02	26.0 ± 1.02	23.8 ± 0.37	25.7 ± 0.95
Heart	6.88 ± 0.40	6.66 ± 0.38	6.09 ± 0.43	7.46 ± 0.92	6.42 ± 0.29	7.43 ± 0.21
R. Kidney	8.37 ± 0.54	9.19 ± 0.52	8.05 ± 0.68	9.65 ± 0.56	9.25 ± 0.57	10.2 ± 0.54*
Liver	57.2 ± 1.53	58.7 ± 1.33	54.7 ± 1.76	54.7 ± 1.27	57.0 ± 1.42	61.8 ± 0.73
Lung	11.7 ± 0.49	10.2 ± 0.50	11.2 ± 1.09	11.5 ± 0.56	12.2 ± 0.73	12.7 ± 1.19
Thymus	3.49 ± 0.23	4.31 ± 0.67	3.64 ± 0.33	3.92 ± 0.46	4.23 ± 0.43	4.06 ± 0.44

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
[a] Mean ± standard error; n=5 for all groups except 175 mg/kg males, 350 mg/kg males, and 700 mg/kg females (n=4).

TABLE E9
Organ Weights for Mice in the 16-Week Gavage Studies of Tris(2-Chloroethyl) Phosphate[a]

Weight (g)	0 mg/kg	44 mg/kg	88 mg/kg	175 mg/kg[b]	350 mg/kg[b]	700 mg/kg
Male						
Necropsy body wt	34.3 ± 0.68	34.6 ± 0.66	35.5 ± 0.77	37.5 ± 1.05	36.7 ± 0.95	32.1 ± 0.98
Brain	0.47 ± 0.01	0.47 ± 0.01	0.48 ± 0.01	0.48 ± 0.02	0.48 ± 0.01	0.49 ± 0.01
Heart	0.19 ± 0.01	0.19 ± 0.01	0.22 ± 0.02	0.19 ± 0.01	0.19 ± 0.01	0.17 ± 0.00
R. Kidney	0.31 ± 0.01	0.32 ± 0.01	0.31 ± 0.01	0.30 ± 0.01	0.28 ± 0.01	0.25 ± 0.00**
Liver	1.58 ± 0.04	1.57 ± 0.06	1.83 ± 0.08*	1.70 ± 0.05	1.79 ± 0.11	1.66 ± 0.04
Lung	0.21 ± 0.01	0.22 ± 0.01	0.30 ± 0.05	0.20 ± 0.01	0.28 ± 0.01**	0.21 ± 0.00
L. Testis	0.12 ± 0.00	0.13 ± 0.00	–[b]	0.13 ± 0.00	–	0.10 ± 0.00**
Thymus	0.04 ± 0.00	0.05 ± 0.00	0.05 ± 0.00	0.05 ± 0.00**	0.05 ± 0.00**	0.05 ± 0.00*
Female						
Necropsy body wt	25.8 ± 0.23	26.8 ± 0.61	27.2 ± 0.68	26.5 ± 0.47	26.6 ± 0.46	25.6 ± 0.59
Brain	0.47 ± 0.01	0.47 ± 0.01	0.47 ± 0.00	0.47 ± 0.01	0.47 ± 0.01	0.46 ± 0.01
Heart	0.12 ± 0.00	0.12 ± 0.00	0.12 ± 0.00	0.12 ± 0.00	0.12 ± 0.00	0.11 ± 0.00
R. Kidney	0.18 ± 0.00	0.18 ± 0.00	0.20 ± 0.01	0.20 ± 0.00	0.19 ± 0.00	0.18 ± 0.00
Liver	1.07 ± 0.03	1.11 ± 0.04	1.16 ± 0.03	1.22 ± 0.04*	1.29 ± 0.04**	1.21 ± 0.02**
Lung	0.22 ± 0.01	0.22 ± 0.01	0.23 ± 0.01	0.22 ± 0.01	0.20 ± 0.01	0.20 ± 0.00*
Thymus	0.04 ± 0.00	0.04 ± 0.00	0.05 ± 0.00	0.04 ± 0.00	0.05 ± 0.00	0.04 ± 0.00

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error; n=10 for all groups except 175 mg/kg, 350 mg/kg, and 700 mg/kg males (n=9) and 175 mg/kg and 350 mg/kg females (n=9).
[b] No means calculated since less than two measurements were available.

TABLE E10
Organ-Weight-to-Body-Weight Ratios for Mice in the 16-Week Gavage Studies of Tris(2-Chloroethyl) Phosphate[a]

Ratio (mg/g)	0 mg/kg	44 mg/kg	88 mg/kg	175 mg/kg	350 mg/kg	700 mg/kg
Male						
Necropsy body wt	34.3 ± 0.68	34.6 ± 0.66	35.5 ± 0.77	37.5 ± 1.05	36.7 ± 0.95	32.1 ± 0.98
Brain	13.7 ± 0.29	13.6 ± 0.22	13.7 ± 0.33	12.8 ± 0.84	13.2 ± 0.37	15.3 ± 0.42
Heart	5.59 ± 0.24	5.35 ± 0.21	6.14 ± 0.44	5.06 ± 0.19	5.30 ± 0.13	5.23 ± 0.19
R. Kidney	9.14 ± 0.17	9.35 ± 0.33	8.80 ± 0.23	7.92 ± 0.19**	7.67 ± 0.25**	7.85 ± 0.15**
Liver	46.2 ± 0.59	45.4 ± 1.38	51.3 ± 1.49*	45.4 ± 0.92	48.6 ± 2.20	51.8 ± 1.14**
Lung	6.14 ± 0.22	6.31 ± 0.31	8.34 ± 1.20	5.47 ± 0.21	7.78 ± 0.33*	6.56 ± 0.20
L. Testis	3.61 ± 0.11	3.69 ± 0.08	–[b]	3.41 ± 0.15	–	3.01 ± 0.10**
Thymus	1.26 ± 0.04	1.37 ± 0.08	1.37 ± 0.11	1.39 ± 0.05	1.45 ± 0.07	1.46 ± 0.09*
Female						
Necropsy body wt	25.8 ± 0.23	26.8 ± 0.61	27.2 ± 0.68	26.5 ± 0.47	26.6 ± 0.46	25.6 ± 0.59
Brain	18.3 ± 0.12	17.4 ± 0.22*	17.3 ± 0.48	17.7 ± 0.24	17.8 ± 0.25	18.1 ± 0.39
Heart	4.66 ± 0.06	4.46 ± 0.11	4.54 ± 0.14	4.47 ± 0.05	4.46 ± 0.07	4.36 ± 0.07**
R. Kidney	7.09 ± 0.14	6.85 ± 0.09	7.20 ± 0.30	7.43 ± 0.09	7.23 ± 0.08	7.04 ± 0.11
Liver	41.5 ± 1.15	41.7 ± 1.58	42.8 ± 1.27	45.9 ± 1.23*	48.6 ± 1.35**	47.4 ± 1.04**
Lung	8.71 ± 0.13	8.05 ± 0.20*	8.29 ± 0.35	8.29 ± 0.18	7.69 ± 0.26**	7.98 ± 0.18**
Thymus	1.68 ± 0.07	1.51 ± 0.07	1.67 ± 0.09	1.65 ± 0.09	1.77 ± 0.08	1.51 ± 0.11

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error; n=10 for all groups except 175 mg/kg, 350 mg/kg, and 700 mg/kg males (n=9) and 175 mg/kg and 350 mg/kg females (n=9).
[b] No means calculated since less than two measurements were available.

APPENDIX F
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA PROTOCOL

Testing was performed as reported by Ames *et al.* (1975) with modifications as listed below and described in greater detail in Haworth *et al.* (1983). Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, TX). The study chemical was incubated with the *Salmonella typhimurium* tester strain (TA98, TA100, TA1535, TA1537, and/or TA97) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C prior to the addition of soft agar supplemented with *l*-histidine and *d*-biotin, and subsequent plating on minimal glucose agar plates. Incubation continued for an additional 48 hours.

Each test consisted of triplicate plates of concurrent positive and negative controls and of at least 5 doses of test chemical. High dose was limited by toxicity or solubility, but did not exceed 3,333 μg/plate. All negative assays were repeated and all positive assays were repeated under the conditions which elicited the positive response.

A positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants which was not dose-related, not reproducible, or of insufficient magnitude to support a determination of mutagenicity. A negative response was obtained when no increase in revertant colonies was observed following chemical treatment.

CHINESE HAMSTER OVARY CYTOGENETICS ASSAYS

Testing was performed as reported by Galloway *et al.* (1985, 1987) and presented briefly below. Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, TX). Chemicals were tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCE) and chromosomal aberrations both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least 3 doses of test chemical; the high dose was limited by toxicity or solubility, but did not exceed 1,600 μg/mL.

In the SCE test without S9 metabolic activation, CHO cells were incubated for 26 hours with the study chemical in McCoy's 5A medium supplemented with 10% fetal bovine serum, *l*-glutamine (2 mM), and antibiotics. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing the test chemical was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 more hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9 metabolic activation, cells were incubated with the chemical, serum-free medium, and S9 mix for 2 hours. The medium was then removed and replaced with medium containing BrdU and no test chemical and incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 hours. Harvesting and staining was the same as for cells treated without S9 metabolic activation.

In the chromosome aberration (Abs) test without S9 metabolic activation, cells were incubated in McCoy's 5A medium with the study chemical for 12 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9 metabolic activation, cells were treated with the study chemical and S9 mix for 2 hours, after which the treatment medium was removed and the cells incubated for 12 hours

in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9 mix.

For the SCE test, if significant chemical-induced cell cycle delay was seen, incubation time was lengthened to ensure a sufficient number of scorable cells. The harvest time for the Abs test was based on the cell cycle information obtained in the SCE test: if cell cycle delay was anticipated, the incubation period was extended approximately 5 hours.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind and those from a single test were read by the same person. For the SCE test, usually 50 second-division metaphase cells were scored for frequency of SCE per cell from each dose level; 100 first-division metaphase cells were scored at each dose level for the Abs test. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Statistical analyses were conducted on both the slopes of the dose-response curves (SCE/chromosome or percent aberrant cells vs. the log of the concentration of the test chemical) and the individual dose points. An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. Chromosomal aberration data are presented as percentage of cells with aberrations. A statistically significant ($P<0.003$) effect on the slope of the dose-response curve or on a dose point ($P<0.05$) was sufficient for a conclusion of positive for a test.

RESULTS

Tris(2-chloroethyl) phosphate (TRCP) was not mutagenic when tested up to toxic levels in *Salmonella typhimurium* strains TA100, TA1535, TA1537, and TA98 in a preincubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat liver S9 (Table F1; Haworth *et al.*, 1983). In cytogenetic tests with Chinese hamster ovary (CHO) cells, tris(2-chloroethyl) phosphate did not induce a significant increase in chromosomal aberrations in either the presence or the absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 (Galloway *et al.*, 1987; Table F3). Results of the CHO cell SCE test were equivocal (Galloway *et al.*, 1987; Table F2). No increase in SCE was observed without S9 metabolic activation. In the presence of S9 metabolic activation, one trial showed a significant response at the two highest doses tested, but the second trial, conducted up to the same maximum test concentration, was negative. The overall call for the test was concluded to be equivocal.

TABLE F1
Mutagenicity of Tris(2-Chloroethyl) Phosphate in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA100	0	107 ± 11.2	130 ± 3.1	119 ± 7.7	126 ± 2.5	115 ± 8.5	105 ± 5.3
	10	140 ± 13.4					
	33	131 ± 7.3	138 ± 15.1	131 ± 7.5	144 ± 14.1	123 ± 4.2	111 ± 4.3
	100	123 ± 7.5	129 ± 9.6	108 ± 8.6	133 ± 4.4	104 ± 10.9	108 ± 4.4
	333	117 ± 4.9	135 ± 10.6	118 ± 3.5	147 ± 2.8	127 ± 15.2	126 ± 5.9
	1,000	129 ± 10.4	127 ± 1.5	136 ± 12.2	154 ± 4.5	121 ± 3.8	130 ± 5.5
	3,333		98 ± 11.1[c]	61 ± 8.1[c]	57 ± 56.5[c]	111 ± 17.9	27 ± 10.8[c]
Trial Summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[d]		530 ± 5.4	641 ± 13.0	1078 ± 7.5	1088 ± 9.3	439 ± 9.7	423 ± 3.6
TA1535	0	19 ± 1.5	32 ± 3.6	12 ± 1.5	10 ± 1.2	7 ± 1.5	11 ± 3.1
	10	19 ± 1.5					
	33	19 ± 0.6	31 ± 3.6	6 ± 0.7	10 ± 3.4	10 ± 2.5	8 ± 0.3
	100	23 ± 5.0	24 ± 2.5	11 ± 2.7	10 ± 1.5	7 ± 0.9	11 ± 1.5
	333	22 ± 2.5	23 ± 2.4	14 ± 0.6	12 ± 3.2	8 ± 0.6	9 ± 1.7
	1,000	17 ± 1.7	30 ± 3.5	16 ± 1.3	18 ± 1.0	15 ± 0.3	10 ± 2.1
	3,333		13 ± 8.9[c]	11 ± 3.2[c]	8 ± 1.9[c]	11 ± 2.7	0 ± 0.0[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[d]		423 ± 11.4	564 ± 14.2	550 ± 11.9	477 ± 5.5	190 ± 16.3	157 ± 15.9
TA1537	0	5 ± 0.3	6 ± 1.7	5 ± 1.8	12 ± 2.6	9 ± 1.7	8 ± 2.0
	10	13 ± 6.5					
	33	5 ± 1.9	5 ± 0.7	8 ± 1.3	7 ± 1.3	4 ± 1.9	6 ± 1.5
	100	4 ± 0.3	6 ± 1.2	8 ± 1.3	9 ± 1.3	8 ± 0.3	4 ± 0.9
	333	5 ± 1.5	4 ± 0.6	9 ± 1.5	6 ± 0.9	7 ± 2.7	8 ± 2.9
	1,000	4 ± 0.3	4 ± 1.5	5 ± 1.5	10 ± 2.3	8 ± 2.5	5 ± 0.7
	3,333		Toxic	3 ± 1.0[c]	2 ± 1.5[c]	6 ± 3.2	2 ± 1.2[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[d]		89 ± 16.9	126 ± 10.8	390 ± 17.9	341 ± 21.2	156 ± 4.5	98 ± 9.0

TABLE F1
Mutagenicity of Tris(2-Chloroethyl) Phosphate in *Salmonella typhimurium*[a] (continued)

Strain	Dose (μg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA98	0	17 ± 1.7	26 ± 0.9	30 ± 3.2	33 ± 3.2	28 ± 2.7	37 ± 5.2
	10	17 ± 0.9					
	33	17 ± 0.6	16 ± 1.2	22 ± 3.4	30 ± 3.3	22 ± 2.7	23 ± 2.4
	100	15 ± 1.7	15 ± 2.1	24 ± 2.0	21 ± 2.0	19 ± 1.5	31 ± 1.2
	333	14 ± 3.3	23 ± 1.5	29 ± 1.7	27 ± 3.7	26 ± 7.7	23 ± 3.2
	1,000	9 ± 2.3	16 ± 1.9	22 ± 1.8	31 ± 4.2	22 ± 5.5	21 ± 3.8
	3,333		Toxic	21 ± 4.2[c]	15 ± 3.4[c]	22 ± 3.4	7 ± 7.0[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[d]		839 ± 23.2	874 ± 21.3	910 ± 46.2	844 ± 41.5	317 ± 18.3	294 ± 21.5

[a] Study performed at SRI International. The detailed protocol is presented in Haworth *et al.* (1983). Cells and study compound or solvent (dimethylsulfoxide) were incubated in the absence of exogenous metabolic activation (-S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague-Dawley rat liver. High dose was limited by toxicity or solubility, but did not exceed 3,333 μg/plate; 0 μg/plate dose is the solvent control.

[b] Revertants presented as mean ± standard error from 3 plates.

[c] Slight toxicity

[d] Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was tested on TA98, sodium azide was tested on TA100 and TA1535, and 9-aminoacridine was tested on TA1537.

TABLE F2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Tris(2-Chloroethyl) Phosphate[a]

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCE/ Chromosome	SCE/ Cell	Hrs in BrdU	Rel. SCEs/ Chromosome (%)[b]
-S9[c]								
Trial 1--Summary: Negative								
Dimethylsulfoxide		50	1,049	474	0.45	9.5	26.0	
Mitomycin-C	0.0050	25	525	616	1.17	24.6	26.0	159.67
Tris(2-chloroethyl) phosphate								
	5	50	1,031	537	0.52	10.7	26.0	15.27
	16	50	1,045	518	0.49	10.4	26.0	9.70
	50	50	1,038	516	0.49	10.3	26.0	10.01
	160	50	1,043	532	0.51	10.6	26.0	12.88
								P=0.087[d]
+S9[e]								
Trial 1--Summary: Positive								
Dimethylsulfoxide		50	1,046	414	0.39	8.3	26.0	
Cyclophosphamide	1.5	50	1,046	1,130	1.08	22.6	26.0	172.95
Tris(2-chloroethyl) phosphate								
	160	50	1,049	458	0.43	9.2	26.0	10.31
	500	50	1,035	503	0.48	10.1	26.0	22.79*
	1,600	50	1,034	495	0.47	9.9	26.0	20.95*
								P<0.001
Trial 2--Summary: Negative								
Dimethylsulfoxide		50	1,049	460	0.43	9.2	26.0	
Cyclophosphamide	1.0	50	1,048	1,061	1.01	21.2	26.0	130.87
Tris(2-Chloroethyl) Phosphate								
	1,200	50	1,050	467	0.44	9.3	26.0	1.43
	1,400	50	1,050	506	0.48	10.1	26.0	9.89
	1,600	50	1,051	531	0.50	10.6	26.0	15.22
								P=0.006

TABLE F2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Tris(2-Chloroethyl) Phosphate[a] (continued)

* Positive (≥20% increase over solvent control)
[a] Study performed at Columbia University. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway *et al.* (1987). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethylsulfoxide) as described below, and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air-dried, and stained.
[b] Percentage increase in SCEs/chromosome of culture exposed to study chemical relative to those of culture exposed to solvent.
[c] In the absence of S9, cells were incubated with study compound or solvent for 26 hours at 37° C. Then BrdU was added and incubation was continued for 2 hours.
[d] Significance of relative SCEs/chromosome tested by linear regression vs. log of the dose
[e] In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. The cells were then washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with Colcemid present for the final 2 hours. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats.

TABLE F3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Tris(2-Chloroethyl) Phosphate[a]

-S9[b]					+S9[c]				
Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Cells with Abs (%)	Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs[d]
Trial 1--Harvest time: 14.0 hours					**Trial 2--Harvest time: 14.0 hours**				
Dimethylsulfoxide					Dimethylsulfoxide				
	100	6	0.06	6.0		100	4	0.04	4.0
Mitomycin-C					Cyclophosphamide				
0.1500	50	32	0.64	38.0	15	100	29	0.29	24.0
Tris(2-chloroethyl) phosphate					Tris(2-Chloroethyl) Phosphate				
160	100	10	0.10	10.0	160	100	11	0.11	10.0
500	100	11	0.11	10.0	500	100	9	0.09	7.7
1,600	100	9	0.09	9.0	1,600	100	10	0.10	8.8
				P=0.239					P=0.218

[a] Study performed at Columbia University. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway *et al.* (1987). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethylsulfoxide) as indicated below. Cells were arrested in the first metaphase by addition of Colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.

[b] In the absence of S9, cells were incubated with study compound or solvent for 12 hours at 37° C. Cells were then washed and fresh medium containing Colcemid was added for an additional 2 hours followed by harvest.

[c] In the presence or 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 12 hours. Colcemid was added for the last 2 hours of incubation before harvest. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats.

[d] Significance of percent cells with aberrations tested by linear regression trend test vs. log of the dose

APPENDIX G
SERUM CHOLINESTERASE ACTIVITY IN THE 16-DAY AND 16-WEEK GAVAGE STUDIES

SERUM CHOLINESTERASE ACTIVITY ANALYSES

PROTOCOL

During the 16-day and 16-week studies of the effects of tris (2-chloroethyl) phosphate on male and female F344/N rats and B6C3F$_1$ mice, serum cholinesterase activity studies were performed on the sera of all animals surviving until scheduled sacrifice. Blood was collected by aortic puncture, and sera were prepared and assayed according to the method of Ellman *et al.* (1961). Cholinesterase levels were determined on individual fresh serum samples on the day of blood collection (Tables G1, G2, G3, and G4).

TABLE G1
Serum Cholinesterase Activity in Rats in the 16-Day Gavage Studies of Tris(2-Chloroethyl) Phosphate

Dose (mg/kg)	n	Enzyme Activity[a]	Relative Enzyme Activity (% of control)
Male			
0	5	688 ± 20	
22	5	715 ± 28	104
44	5	673 ± 22	98
88	5	724 ± 36	105
175	5	747 ± 30	109
350	5	723 ± 18	105
Female			
0	5	1,545 ± 97	
22	5	1,480 ± 29	96
44	5	1,495 ± 52	96
88	5	1,630 ± 82	105
175	5	1,232 ± 47**	80
350	5	1,264 ± 145*	82

* Significantly different from the control group (P≤0.05)
** Significantly different from the control group (P≤0.01)
[a] nM acetylcholine/mL serum per minute; mean ± standard error

TABLE G2
Serum Cholinesterase Activity in Rats in the 16-Week Gavage Studies of Tris(2-Chloroethyl) Phosphate

Dose (mg/kg)	n	Enzyme Activity[a]	Relative Enzyme Activity (% of control)
Male			
0	7	719 ± 18	
22	9	706 ± 15	98
44	10	678 ± 17	94
88	10	734 ± 22	102
175	9	756 ± 18	105
350	4	696 ± 43	97
Female			
0	10	2,064 ± 112	
22	8	1,946 ± 125	94
44	10	1,808 ± 105	88
88	10	1,873 ± 105	91
175	8	1,550 ± 104**	75
350	5	1,226 ± 28**	59

** Significantly different from the control group ($P \leq 0.01$)
[a] nM acetylcholine/mL serum per minute; mean ± standard error

TABLE G3
Serum Cholinesterase Activity in Mice in the 16-Day Gavage Studies of Tris(2-Chloroethyl) Phosphate

Dose (mg/kg)	n	Enzyme Activity[a]	Relative Enzyme Activity (% of control)
Male			
0	5	3,271 ± 100	
44	5	3,109 ± 246	95
88	5	2,961 ± 85	91
175	4	3,022 ± 109	92
350	4	4,094 ± 101	125
700	5	3,127 ± 196	95
Female			
0	5	3,513 ± 142	
44	5	3,464 ± 175	98
88	5	2,085 ± 516	59
175	5	2,736 ± 276	78
350	5	2,938 ± 304	84
700	4	3,179 ± 228	90

[a] nM acetylcholine/mL serum per minute; mean ± standard error

TABLE G4
Serum Cholinesterase Activity in Mice in the 16-Week Gavage Studies of Tris(2-Chloroethyl) Phosphate

Dose (mg/kg)	n	Enzyme Activity[a]	Relative Enzyme Activity (% of control)
Male			
0	10	2,276 ± 99	
44	10	2,471 ± 97	109
88	10	2,339 ± 57	103
175	9	2,548 ± 91	112
350	9	2,428 ± 60	107
700	9	2,264 ± 54	99
Female			
0	10	3,662 ± 104	
44	10	3,821 ± 91	104
88	10	3,500 ± 74	96
175	9	3,681 ± 147	101
350	9	3,735 ± 93	102
700	10	3,776 ± 76	103

[a] nM acetylcholine/mL serum per minute; mean ± standard error

APPENDIX H
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION

PROCUREMENT AND CHARACTERIZATION OF TRIS(2-CHLOROETHYL) PHOSPHATE

Tris(2-chloroethyl) phosphate (TRCP) was manufactured by Stauffer Chemical Company (Westpoint, CT) and was obtained in one lot (lot no. 0101F-1-3). Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, MO). MRI reports on analyses performed in support of the TRCP studies are on file at the National Institute of Environmental Health Sciences.

The study chemical, a clear transparent liquid, was identified as TRCP by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. Infrared and nuclear magnetic resonance spectra (Figures H1 and H2) were consistent with the spectra in the literature, and ultraviolet/visible spectra were consistent with the chemical structure.

The purity of lot no. 0101F-1-3 was determined by elemental analysis, Karl Fischer water analysis, titration of acidic components with 0.01 N isopropyl alcoholic potassium hydroxide using *p*-naphtholbenzein as an indicator, thin-layer chromatography, and gas chromatography. Thin-layer chromatography was performed on silica gel plates with two solvent systems: anhydrous diethyl ether (system 1) and hexanes:methylene chloride:methanol (70:25:5) (system 2). The samples were visualized under ultraviolet light (254 nm) and with an iodine spray. Gas chromatography was performed with flame ionization detection, using a 3% SP-2401 on 100/120 Supelcoport column (system 1) or a 3% SP-2100 on 100/120 Supelcoport column (system 2) with nitrogen as the carrier at 70 mL/minute.

Elemental analysis for carbon, hydrogen, phosphorus, and chlorine was in agreement with the theoretical values. Karl Fischer analysis indicated the presence of 0.129% water. Acid number was 0.019 ± .001 mg of KOH/g. Thin layer chromatography by two systems indicated only one spot. Gas chromatography with system 1 indicated one impurity with an area of 0.55% relative to the major peak area, and three additional impurities with relative peak areas < 0.1% that of the major peak area. Gas chromatography with system 2 indicated 4 impurities with a combined area of 1.83% relative to the major peak area, and 2 additional impurities with peak areas < 0.1% of the major peak area. The overall purity was estimated at approximately 98%.

Stability studies on the bulk chemical performed by gas chromatography using a 3% SP-2401 on 80/100 Supelcoport column with helium as a carrier at 70 mL/minute indicated that TRCP was stable for at least 2 weeks at temperatures up to 25° C. The stability of the bulk chemical was also monitored throughout the course of the studies by infrared spectroscopy and titration for acid number. No changes in the bulk chemical were observed by infrared spectroscopy, and the data from the titration of the acid number remained within the maximum value specified by the manufacturer. The bulk chemical was stored at -4° C throughout the studies.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

Dose formulations were prepared by mixing the appropriate quantities of TRCP and corn oil. Stability studies on the dose formulations were conducted at the analytical laboratory. The dose formulations were extracted with methanol, and *n*-butyl phthalate in methylene chloride was added as an internal standard. Analyses performed by gas chromatography with a 3% OV-25 on 100/125 Supelcoport column indicated that tris(2 chloroethyl) phosphate was stable in corn oil at a concentration of 8 mg/mL when stored sealed in darkness for up to three weeks at 5° C or at room temperature.

Periodic analysis of TRCP/corn oil dose formulations was conducted at the study laboratory by extraction of the mixtures with methanol and analysis by gas chromatography. Dose formulations were analyzed two times during the 13-week studies (Table H2). During the 2-year studies, the dose formulations were analyzed at approximately 8-week intervals by gas chromatography after methanol extraction. The mixtures were formulated within ± 10% of the target concentrations throughout the course of the 2-year studies (Table H3). Results of periodic referee analyses performed by MRI indicated good agreement with the results from the study laboratory (Table H4).

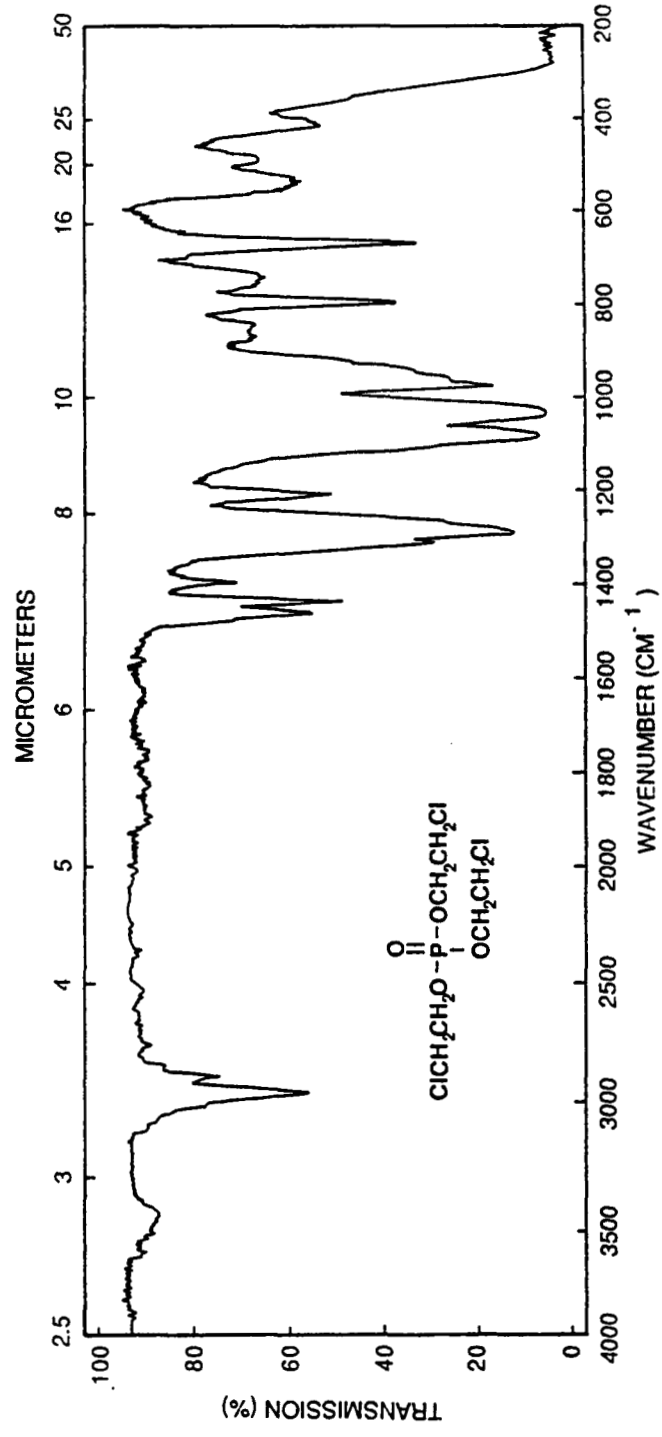

FIGURE H1
Infrared Spectrum of Tris(2-Chloroethyl) Phosphate

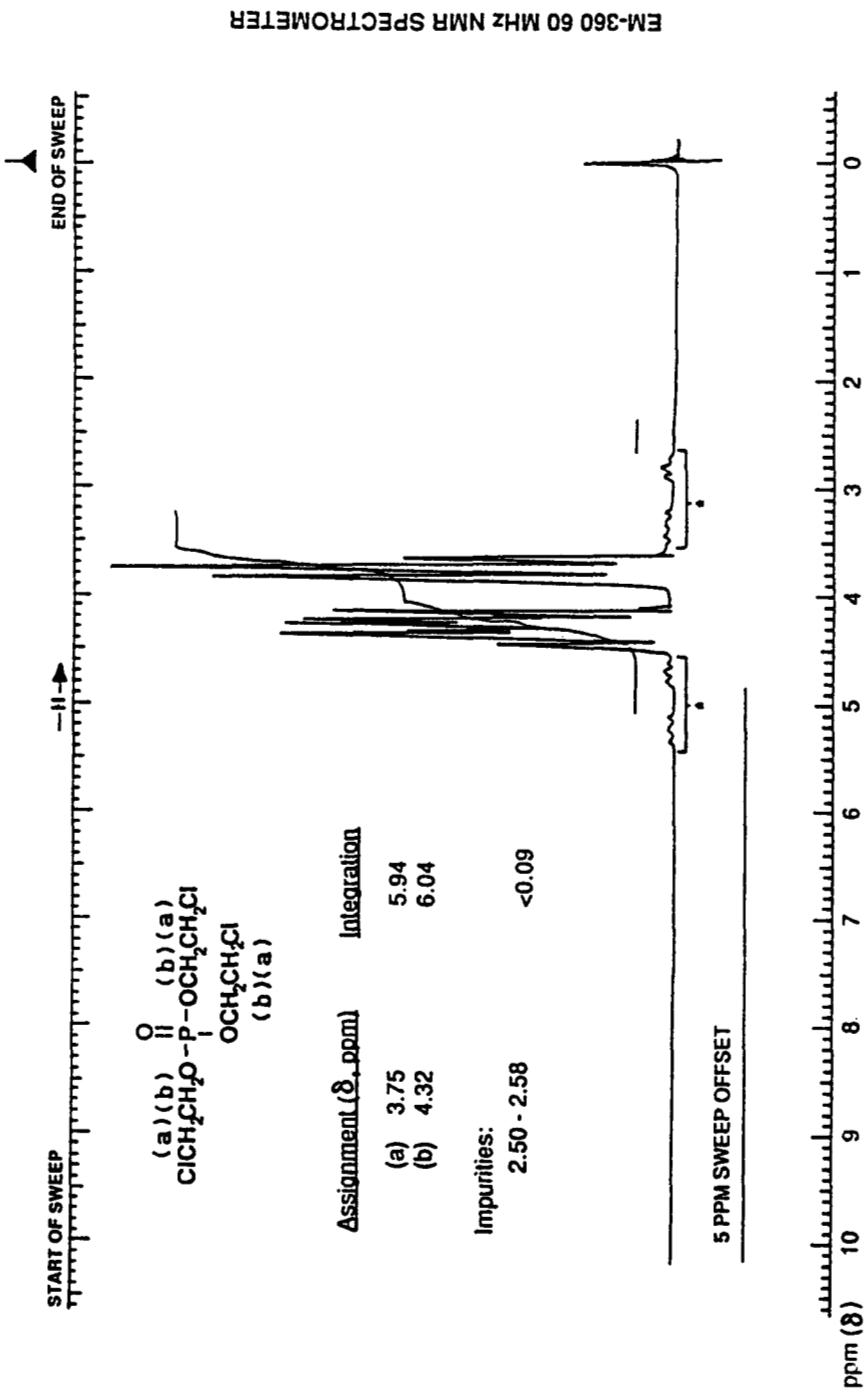

FIGURE H2
Nuclear Magnetic Resonance Spectrum of Tris(2-Chloroethyl) Phosphate

TABLE H1
Preparation and Storage of Dose Formulations in the Gavage Studies of Tris(2-Chloroethyl) Phosphate

16-Day Studies	16-Week Studies	2-Year Studies
Preparation		
Similar to 2-year studies	Similar to 2-year studies	The appropriate volume of TRCP was dispensed into a two liter volumetric flask. The flask was filled 3/4 full with corn oil and shaken well. The flask was then filled to the mark with corn oil, shaken, and an amount necessary to cover the bottom of each dosing bottle (250 or 500 mL) was dispensed into the bottles to free volume from the neck area of the flask to facilitate better mixing. The flask was then shaken and the solution distributed to the appropriate bottles.
Maximum Storage Time		
2 weeks	2 weeks	2 weeks
Storage Conditions		
0° ± 5° C	0° ± 5° C	0° ± 5° C

TABLE H2
Results of Analysis of Dose Formulations in the 16-Week Gavage Studies of Tris(2-Chloroethyl) Phosphate

Date Mixed	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	Percent of Target
18 August 1981	4.4	4.13	93.8
	8.8	8.29	94.3
	17.5	17.09	97.7
	35.0	35.53	101.5
	70.0	70.78	101.1
29 October 1981	4.4	4.20	95.4
	8.8	8.33	94.7
	17.5	16.51	94.4
	35.0	26.26	75.0
		32.76	93.2[b]
	70.0	63.12	90.2

[a] Results of duplicate analysis
[b] Remix; first preparation not used in animal studies.

TABLE H3
Results of Dose Formulation Analyses for Rats During the 2-Year Gavage Studies of Tris(2-Chloroethyl) Phosphate

Date Mixed	Determined Concentration of Tris(2-Chloroethyl) Phosphate	
	target 8.8 mg/mL	target 17.5 mg/mL
1 September 1982	8.41	18.00
27 October 1982	8.64	18.64
27 October 1982[a]	8.89	19.21
21 December 1982	8.93	18.12
16 February 1983	9.21	17.68
13 April 1983	8.60	17.70
8 June 1983	8.56	17.62
3 August 1983	8.83	17.69
3 August 1983[a]	8.91	17.33
28 September 1983	8.33	16.55
24 November 1983	8.26	16.89
18 January 1984	8.22	17.00
14 March 1984	8.39	16.49
14 March 1984[a]	8.46	17.57
9 May 1984	8.72	17.16
9 May 1984	9.24	18.61
3 July 1984	9.24	18.61
Mean (mg/mL)	8.70	17.64
Standard deviation	0.338	0.757
Coefficient of variation (%)	4	4
Range (mg/mL)	8.22-9.24	16.49-19.21
Number of samples	17	17

[a] Animal room samples

TABLE H4
Results of Dose Formulation Analyses for Mice During the 2-Year Gavage Studies of Tris(2-Chloroethyl) Phosphate

Date Mixed	Determined Concentration of Tris(2-Chloroethyl) Phosphate	
	target 17.5 mg/mL	target 35.0 mg/mL
8 September 1982	18.12	37.17
27 October 1982	18.65	38.02
27 October 1982[a]	19.21	37.35
21 December 1982	18.12	37.49
16 February 1983	17.68	35.87
13 April 1983	17.70	34.75
8 June 1983	17.62	33.28
3 August 1983	17.69	34.75
3 August 1983[a]	17.44	35.21
28 September 1983[a]	16.89	33.36
24 November 1983[a]	16.58	34.14
18 January 1984	17.18	36.36
14 March 1984	16.49	35.51
14 March 1984[a]	17.57	33.98
9 May 1984	17.16	34.95
9 May 1984	18.61	36.40
3 July 1984	18.61	36.40
Mean (mg/mL)	17.72	35.59
Standard deviation	0.76	1.46
Coefficient of variation (%)	4	4
Range (mg/mL)	16.49-19.21	33.28-38.02
Number of samples	17	17

[a] Animal room samples

TABLE H5
Results of Referee Analysis of Dose Formulations in the 2-Year Gavage Studies of Tris(2-Chloroethyl) Phosphate

Date Mixed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	
		Study Laboratory[a]	Referee Laboratory[b]
1 September 1982	8.8	8.41	8.77
13 April 1983	17.5	17.70	16.80
24 November 1983	35.0	34.10	33.00
9 May 1984	8.8	8.72	8.35

[a] Results of duplicate analysis
[b] Results of triplicate analysis

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

TABLE I1
Ingredients of NIH-07 Rat and Mouse Ration[a]

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

[a] NCI, 1976; NIH, 1978
[b] Ingredients ground to pass through a U.S. Standard Screen No. 16 before being mixed.

TABLE I2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration

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

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

TABLE I3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	23.13 ± 1.08	21.3 – 26.3	25
Crude fat (% by weight)	5.13 ± 0.59	3.3 – 6.3	25
Crude fiber (% by weight)	3.47 ± 0.53	2.8 – 5.6	25
Ash (% by weight)	6.63 ± 0.38	5.7 – 7.3	25
Amino Acids (% of total diet)			
Arginine	1.320 ± 0.072	1.310 – 1.390	5
Cystine	0.319 ± 0.088	0.218 – 0.400	5
Glycine	1.146 ± 0.063	1.060 – 1.210	5
Histidine	0.571 ± 0.025	0.531 – 0.603	5
Isoleucine	0.914 ± 0.030	0.881 – 0.944	5
Leucine	1.946 ± 0.056	1.850 – 1.990	5
Lysine	1.280 ± 0.067	1.200 – 1.370	5
Methionine	0.436 ± 0.165	0.306 – 0.699	5
Phenylalanine	0.938 ± 0.158	0.665 – 1.050	5
Threonine	0.855 ± 0.035	0.824 – 0.898	5
Tryptophan	0.277 ± 0.221	0.156 – 0.671	5
Tyrosine	0.618 ± 0.086	0.564 – 0.769	5
Valine	1.108 ± 0.043	1.050 – 1.170	5
Essential Fatty Acids (% of total diet)			
Linoleic	2.290 ± 0.313	1.830 – 2.520	5
Linolenic	0.258 ± 0.040	0.210 – 0.308	5
Vitamins			
Vitamin A (IU/kg)	12,584 ± 4,612	4,100 – 24,000	25
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 – 6,300	4
α–Tocopherol (ppm)	43.58 ± 6.92	31.1 – 48.0	5
Thiamine (ppm)	17.60 ± 3.80	12.0 – 27.0	25
Riboflavin (ppm)	7.60 ± 0.85	7.58 – 8.20	5
Niacin (ppm)	97.80 ± 31.68	65.0 – 150.0	5
Pantothenic acid (ppm)	30.06 ± 4.31	23.0 – 34.0	5
Pyridoxine (ppm)	7.68 ± 1.31	5.60 – 8.80	5
Folic acid (ppm)	2.62 ± 0.89	1.80 – 3.70	5
Biotin (ppm)	0.254 ± 0.053	0.19 – 0.32	5
Vitamin B_{12} (ppb)	24.21 ± 12.66	10.6 – 38.0	5
Choline (ppm)	3,122 ± 416.8	2,400 – 3,430	5
Minerals			
Calcium (%)	1.30 ± 0.13	1.11 – 1.63	25
Phosphorus (%)	0.97 ± 0.06	0.87 – 1.10	25
Potassium (%)	0.900 ± 0.098	0.772 – 0.971	3
Chloride (%)	0.513 ± 0.114	0.380 – 0.635	5
Sodium (%)	0.323 ± 0.043	0.258 – 0.371	5
Magnesium (%)	0.167 ± 0.012	0.151 – 0.181	5
Sulfur (%)	0.304 ± 0.064	0.268 – 0.420	5
Iron (ppm)	410.3 ± 94.04	262.0 – 523.0	5
Manganese (ppm)	90.29 ± 7.15	81.70 – 99.40	5
Zinc (ppm)	52.78 ± 4.94	46.10 – 58.20	5
Copper (ppm)	10.72 ± 2.76	8.090 – 15.39	5
Iodine (ppm)	2.95 ± 1.05	1.52 – 3.82	4
Chromium (ppm)	1.85 ± 0.25	1.44 – 2.09	5
Cobalt (ppm)	0.681 ± 0.14	0.490 – 0.780	4

TABLE I4
Contaminant Levels in NIH-07 Rat and Mouse Ration

	Mean ± Standard Deviation[a]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.53 ± 0.15	0.17 – 0.77	25
Cadmium (ppm)	<0.10		25
Lead (ppm)	0.74 ± 0.62	0.33 – 3.37	25
Mercury (ppm)	<0.05		25
Selenium (ppm)	0.32 ± 0.07	0.13 – 0.42	25
Aflatoxins (ppb)	<5.0		25
Nitrate nitrogen (ppm)	9.20 ± 4.64	0.10 – 22.0	25
Nitrite nitrogen (ppm)	1.37 ± 1.69	0.10 – 7.20	25
BHA (ppm)	4.08 ± 4.76	2.00 – 17.00	25
BHT (ppm)	2.80 ± 2.57	1.00 – 12.00	25
Aerobic plate count (CFU/g)[b]	46,112 ± 34,525	6,600 – 130,000	25
Coliform (MPN/g)[c]	49.20 ± 125	3.00 – 460	25
E. coli (MPN/g)	<3.00		25
Total nitrosamines (ppb)[d]	5.67 ± 5.81	1.80 – 30.90	25
N-Nitrosodimethylamine (ppb)[d]	4.61 ± 5.77	0.80 – 30.00	25
N-Nitrosopyrrolidine (ppb)[d]	1.06 ± 0.26	0.81 – 1.70	25
Pesticides (ppm)			
α-BHC[e]	<0.01		25
β-BHC	<0.02		25
γ-BHC	<0.01		25
δ-BHC	<0.01		25
Heptachlor	<0.01		25
Aldrin	<0.01		25
Heptachlor epoxide	<0.01		25
DDE	<0.01		25
DDD	<0.01		25
DDT	<0.01		25
HCB	<0.01		25
Mirex	<0.01		25
Methoxychlor	<0.05		25
Dieldrin	<0.01		25
Endrin	<0.01		25
Telodrin	<0.01		25
Chlordane	<0.05		25
Toxaphene	<0.1		25
Estimated PCBs	<0.2		25
Ronnel	<0.01		25
Ethion	<0.02		25
Trithion	<0.05		25
Diazinon	<0.1		25
Methyl parathion	<0.02		25
Ethyl parathion	<0.02		25
Malathion[f]	0.12 ± 0.09	0.05 – 0.45	25
Endosulfan I	<0.01		25
Endosulfan II	<0.01		25
Endosulfan sulfate	<0.03		25

[a] All values were less than the detection limit, given in the table as the mean.
[b] CFU = colony forming unit
[c] MPN = most probable number
[d] All values were corrected for percent recovery.
[e] BHC = hexachlorocyclohexane or benzene hexachloride
[f] Fifteen lots contained more than 0.05 ppm.

APPENDIX J
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

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 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 tris(2-chloroethyl) phosphate.

RATS

Upon arrival, 5 male and 5 female rats were sacrificed and their blood collected for the evaluation of the general health status of the animals. Fifteen F344/N rats of each sex were selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group were killed at 6, 12, and 18 months on study. The blood from each animal was collected and clotted, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the antibody titers. The following tests were performed:

Time and Method	Time of Analysis
Complement Fixation	
RCV (rat coronavirus)	Preinitiation and 6 months
Sendai virus	Preinitiation
ELISA	
RCV/SDA (sialodacryoadenitis virus)	12 and 18 months
Mycoplasma pulmonis	Preinitiation, 6, and 12 months
Hemagglutination Inhibition	
PVM (pneumonia virus of mice)	
KRV (Kilham rat virus)	
H-1 (Toolan's H-1 virus)	
Sendai	6, 12, and 18 months

Results are presented in Table J1.

MICE

Upon arrival, 10 B6C3F$_1$ mice were sacrificed and their blood collected for the evaluation of the general health status of the animals. Eight animals at 6 months and 7 animals at 12 and 18 months were sacrificed for serological analysis. The blood from each animal was collected and clotted, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the antibody titers. The following tests were performed:

Time and Method	Time of Analysis
Complement Fixation	
Sendai	Preinitiation
Mouse adenoma virus	
LCM (lymphocytic choriomeningitis virus)	
ELISA	
MHV (mouse hepatitis virus)	
Mycoplasma pulmonis	Preinitiation, 6, 12, and 18 months
Hemagglutination Inhibition	
PVM (pneumonia virus of mice)	
Reovirus	
GDVII (mouse encephalomyelitis virus)	
MVM (minute virus of mice)	
Ectromelia virus (mouse pox)	
Sendai	6, 12, and 18 months

Results are presented in Table J1.

TABLE J1
Murine Virus Antibody Determinations for Rats and Mice in the 2-Year Gavage Studies of Tris(2-Chloroethyl) Phosphate

Interval (months)	Number of Animals	Positive Serologic Reaction for
Rats		
0	0/10	–[a]
6	0/10	–
12	0/10	–[b]
18	0/10	–
Mice		
0	0/10	–[c]
6	0/8	–
12	0/7	–
18	0/7	–

[a] Equivocal results for 1/10 rats, ELISA (*M. pulmonis*)
[b] Equivocal results for 3/10 rats, ELISA (*M. pulmonis*)
[c] Equivocal results for 3/10 mice, ELISA (*M. pulmonis*)

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TR No.	CHEMICAL
201	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Dermal)
206	1,2-Dibromo-3-chloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butyl Benzyl 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)
243	Trichloroethylene (Rats and Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
246	Chrysotile Asbestos (Hamsters)
247	L-Ascorbic Acid
248	4,4'-Methylenedianiline Dihydrochloride
249	Amosite Asbestos (Hamsters)
250	Benzyl Acetate
251	2,4- & 2,6-Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
254	Dichloromethane (Methylene Chloride)
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
266	Monuron
267	1,2-Propylene Oxide
269	1,3-Dichloropropane (Telone II®)
271	HC Blue No. 1
272	Propylene
273	Trichloroethylene (Four Rat Strains)
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
277	Tremolite
278	2,6-Xylidine
279	Amosite Asbestos
280	Crocidolite Asbestos
281	HC 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(hydroxymethyl) phosphonium Sulfate & Tetrakis(hydroxymethyl) 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 (Methylene Chloride)
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
313	Mirex
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
320	Rotenone
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
323	Dimethyl Methylphosphonate
324	Boric Acid
325	Pentachloronitrobenzene
326	Ethylene Oxide
327	Xylenes (Mixed)
328	Methyl Carbamate
329	1,2-Epoxybutane
330	4-Hexylresorcinol
331	Malonaldehyde, Sodium Salt
332	2-Mercaptobenzothiazole
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol
335	C.I. Acid Orange 3
336	Penicillin VK
337	Nitrofurazone

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TR No.	CHEMICAL
338	Erythromycin Stearate
339	2-Amino-4-nitrophenol
340	Iodinated Glycerol
341	Nitrofurantoin
342	Dichlorvos
343	Benzyl Alcohol
344	Tetracycline Hydrochloride
345	Roxarsone
346	Chloroethane
347	D-Limonene
348	*a*-Methyldopa Sesquihydrate
349	Pentachlorophenol
350	Tribromomethane
351	*p*-Chloroaniline Hydrochloride
352	N-Methylolacrylamide
353	2,4-Dichlorophenol
354	Dimethoxane
355	Diphenhydramine Hydrochloride
356	Furosemide
357	Hydrochlorothiazide
358	Ochratoxin A
359	8-Methoxypsoralen
360	N,N-Dimethylaniline
361	Hexachloroethane
362	4-Vinyl-1-Cyclohexene Diepoxide
363	Bromoethane (Ethyl Bromide)
364	Rhodamine 6G (C.I. Basic Red 1)
365	Pentaerythritol Tetranitrate
366	Hydroquinone
367	Phenylbutazone
368	Nalidixic Acid
369	Alpha-Methylbenzyl Alcohol
370	Benzofuran
371	Toluene
372	3,3'-Dimethoxybenzidine Dihydrochloride
373	Succinic Anhydride
374	Glycidol
375	Vinyl Toluene
376	Allyl Glycidyl Ether
377	*o*-Chlorobenzalmalononitrile
378	Benzaldehyde
379	2-Chloroacetophenone
380	Epinephrine Hydrochloride
381	*d*-Carvone
382	Furfural
386	Tetranitromethane
393	Sodium Fluoride

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