NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 294

TOXICOLOGY AND CARCINOGENESIS STUDIES OF CHLORINATED TRISODIUM PHOSPHATE

(CAS NO. 56082-99-4)

IN B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

NATIONAL TOXICOLOGY PROGRAM

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

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF CHLORINATED TRISODIUM PHOSPHATE

(CAS NO. 56082-99-4)

IN B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

December 1986

NTP TR 294

NIH Publication No. 87-2550

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

NOTE TO THE READER

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

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

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

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

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

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

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

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$(Na_3PO_4 \cdot 12H_2O)_4 \cdot NaOCl$

Chlorinated trisodium phosphate
(Sodium hypochlorite phosphate)

ABSTRACT

Two-year toxicology and carcinogenesis studies of chlorinated trisodium phosphate, an inclusion complex of trisodium phosphate and sodium hypochlorite used in various cleaning compounds, were conducted by administering 0, 500, or 1,000 mg/kg (dose volume: 10 ml/kg) of the chemical in water by gavage, 5 days per week for 103 weeks, to groups of 50 male and 50 female $B6C3F_1$ mice. Groups of mice receiving 250 mg/kg were included in these studies but were removed after 6 months because of a lack of toxicity in the 500 and 1,000 mg/kg groups. Two-year studies were begun in male and female F344/N rats at doses of 0, 500, 1,000, or 2,000 mg/kg of chlorinated trisodium phosphate in water by gavage (10 ml/kg). The 2,000 mg/kg groups were killed at 15 weeks because of poor survival, and the other groups were killed at 35 weeks because of toxicity in the 1,000 mg/kg group. The doses selected for the 2-year studies were based on the general lack of adverse effects seen in the 14-day and 13-week studies in which rats received 0-1,000 mg/kg and mice received 0-2,000 mg/kg by gavage in water.

No compound-related histopathologic effects were observed in the 14-day or the 13-week studies in mice. In the 2-year studies, survival and mean body weights of dosed and vehicle control male mice groups were comparable (survival--vehicle control, 39/50; low dose, 35/50; high dose, 32/50). Survival of the dosed female mice was lower than that of the vehicle controls (30/50; 16/50; 21/50), although at week 80 survival of female mice was 42/50, 39/50, and 36/50. The mean body weights of the high dose female mice were lower than those of the vehicle control mice, primarily after week 32; final body weights were 11% lower in the high dose group compared with that in the vehicle controls. The lower survival and mean body weights of the dosed female mice may have been due to the greater incidence of uterine/ovarian infections in these mice rather than to a direct toxic effect of chlorinated trisodium phosphate. Nine of 20 vehicle control, 20/34 low dose, and 21/29 high dose female mice that died before the end of the studies had such infections. This reduced survival decreased the sensitivity of the study of female mice for detecting the presence or absence of carcinogenic effects.

At no site was the incidence of neoplasms considered to be related to the administration of chlorinated trisodium phosphate. Minimal necrosis and fatty changes were observed in the livers of male mice. Kidneys in male mice were characterized by small, multifocal areas of mineralization, primarily in the cortex but not at the corticomedullary junction or in the tubules of the medulla. Neither effect was considered compound related. Five different types of ovarian neoplasms were found in six dosed female mice; because these lesions were from tissues of different embryonic origin, they were considered unrelated to administration of chlorinated trisodium phosphate.

Chlorinated trisodium phosphate was weakly mutagenic in strain TA1535 of *Salmonella typhimurium* in the presence of Aroclor 1254-induced male Sprague-Dawley rat or male Syrian hamster liver S9. This compound was not mutagenic in strains TA97, TA98, or TA100.

An audit of the experimental data was conducted for these 2-year studies of chlorinated trisodium phosphate. No data discrepancies were found that influenced the final interpretation of these experiments.

Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenicity** for either male or female $B6C3F_1$ mice given chlorinated trisodium phosphate by gavage in water for 103 weeks at doses of 500 or 1,000 mg. Survival of dosed female mice was 78% and 72% after 80 weeks and 32% and 42% at the termination of the study. The studies in male and female F344/N rats were considered to be *inadequate studies of carcinogenicity* because the experiments were terminated at 35 weeks due to poor survival.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.

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The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Chlorinated Trisodium Phosphate is based on the 13-week studies that began in September 1979 and ended in December 1979 and the 2-year studies that began in June 1980 and ended in June 1982 at EG&G Mason Research Institute.

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

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF CHLORINATED TRISODIUM PHOSPHATE

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

Dr. C. Whitmire, NTP, began by describing the study design, results, and proposed conclusions (inadequate studies in rats; no evidence of carcinogenicity in male and female mice).

Dr. Davis, a principal reviewer, did not attend the meeting but submitted written comments, which were read by Dr. Hook, Panel Chair. Dr. Davis stated that the study results did not fully justify the conclusions. In her opinion, survival was not sufficient to reach conclusions for either the rat or mouse studies. She recommended doing the experiments again and using the results of the current studies to estimate more appropriate dosage regimens.

As a second principal reviewer, Dr. Van Ryzin agreed with the conclusions. He thought the 2-year studies in mice were adequate based on the survival and weight curves, although he thought new experiments could be designed due to the inadequacy of the 2-year studies in rats. He noted that 91.75% of the study material is trisodium phosphate, for which little toxicity data exist.

As a third principal reviewer, Mr. Beliczky stated that the studies were less than adequate to draw reasonable conclusions and felt that additional studies were needed to determine the carcinogenicity of chlorinated trisodium phosphate. He questioned the inclusion complex used and cited problems associated with the water gavage, such as differential solubility and excessive dose volumes.

Dr. Hook commented that the issue was whether survival in the mice was adequate. Dr. J. Haseman, NIEHS, said that survival in all groups of mice was above 50% at 18 months. Dr. Kociba said that some laboratories conduct mouse studies for only 18 months. Dr. J. Huff, NTP, noted that only the female mice were at issue, since 24-month survival of all male groups was above 60%. Dr. Turnbull observed that poor survival was generally more of an issue with a negative study, as was the case here. Dr. Hook said that there seemed to be a consensus for considering the mouse studies adequate but that the conclusions should indicate percent survival in females at 18 months.

Dr. Van Ryzin moved that the Technical Report on the toxicology and carcinogenesis studies of chlorinated trisodium phosphate be accepted with the parenthetical inclusion of 18- and 24-month percentage survival for the female mouse study in the conclusions. Dr. Kociba seconded the motion and the report was approved by nine affirmative votes. There was one negative vote (Mr. Beliczky).

I. INTRODUCTION

I. INTRODUCTION

$(Na_3PO_4 \cdot 12H_2O)_4 \cdot NaOCl$

Chlorinated trisodium phosphate
(Sodium hypochlorite phosphate)

Chlorinated trisodium phosphate, an inclusion complex of trisodium phosphate and sodium hypochlorite in variable proportions, is used as a cleaner and bacteriocide in dairies and food processing plants and as a component of dishwashing compounds, scouring powders, denture cleaners, and laundry bleaches (Merck, 1976; Kirk-Othmer, 1978; Hawley, 1981; Gosselin et al., 1976; Lahl et al., 1982). Trisodium phosphate is used as a preservative, sequesterent, and texturizer in foods (Merck, 1983; USCFR, 1974). Production figures for chlorinated trisodium phosphate in 1977 were 10-50 million pounds (EPA public posting TSCA inventory of chemicals in commerce for 1977).

Chlorinated trisodium phosphate is a skin and eye irritant (Hawley, 1981) and is an irritant to humans when inhaled or ingested (Sax, 1979). The oral LD_{50} value of chlorinated trisodium phosphate in rats (strain not specified) is 7.4 g/kg (Smyth et al., 1969).

Because toxicity data for chlorinated trisodium phosphate are sparse, much of the following information concerns its two constituents, sodium hypochlorite and trisodium phosphate. Sodium hypochlorite (0.05 ml, 10% effective chlorine administered 45 times over 245 days) promoted skin neoplasms in ddy female mice dermally administered 4-nitroquinoline-1-oxide 20 times with 500 mg per application in 0.25% (w/v) benzene over 50 days (Hayatsu et al., 1971). Of 32 dosed mice, 3 had squamous cell carcinomas, 1 had a fibrosarcoma, and 5 had benign skin neoplasms, as compared with no skin neoplasms in 27 control mice dosed with sodium hypochlorite 60 times over 30 days. A third group dosed only with 4-nitroquinoline (as the cocarcinogen) developed no skin tumors.

In contrast, Kurokawa et al. (1984) reported sodium hypochlorite was inactive either as a promoter or a complete carcinogen in female Sencar mice. In the promotion studies, groups of 20 female mice were initiated with DMBA and received dermal applications of sodium hypochlorite in acetone twice weekly for 51 weeks. Although statistically not significant, 30% of the mice dosed with sodium hypochlorite developed skin tumors, and five of these six mice had squamous cell carcinomas, with the first skin tumor appearing in week 17. In the complete carcinogenicity test, a group of 20 female Sencar mice received dermal applications of sodium hypochlorite in acetone twice weekly for 51 weeks; no skin tumors were observed.

Chloroform and other halogenated organic compounds are reaction products of chlorine in water purification and in the gut and contribute to the toxicity of chlorinated trisodium phosphate and its breakdown products (Lahl et al., 1982). Trichloroacetic acid, dichloroacetic acid, dichloroacetonitrile, and chloroform were found in the gut and/or plasma of fasted and unfasted male Sprague-Dawley rats 1 hour after administration of 140 mg sodium hypochlorite/kg body weight in distilled water by gavage (Mink et al., 1983). Chloroform was present in the blood, brain, liver, kidney, and fat 1.5 hours after administration of sodium hypochlorite (5 ml containing 80 mg equivalent free chlorine) by gavage to Sprague-Dawley rats (Vogt et al., 1979). Relative kidney weight was increased in female Wistar rats administered sodium hypochlorite in milk (200 mg available chlorine/liter) twice per day by gavage (Cunningham, 1980).

Chlorinated trisodium phosphate was weakly mutagenic in strain TA1535 of *Salmonella typhimurium* in the presence of Aroclor 1254-induced male Sprague-Dawley rat or male Syrian hamster liver S9 (Appendix J). Rosenkranz (1973) demonstrated that sodium hypochlorite, formed by chlorinated trisodium phosphate in water, caused DNA damage in the *Escherichia coli* pol A assay. Kawachi et al. (1980), however, reported that sodium hypochlorite did not cause DNA damage in the *Bacillus subtilis* rec assay.

Sodium hypochlorite was mutagenic in Salmonella strains TA1535 (Wlodkowski and Rosenkranz, 1975) and TA100 (Kawachi et al., 1980). In addition, Kawachi et al. (1980) reported that sodium hypochlorite induced chromosomal aberrations in hamster fibroblasts in the presence of S9 but did not induce chromosomal aberrations in human fibroblasts in vitro or in rat bone marrow cells in vivo; however, these investigators reported that sodium hypochlorite induced sister-chromatid exchanges in human fibroblasts in vitro. Abernethy et al. (1983) reported that sodium hypochlorite did not induce morphologic transformation of C3H/10T½ cells. In summary, chlorinated trisodium phosphate is a weak base-pair substitution mutagen in Salmonella, as is sodium hypochlorite; in addition, sodium hypochlorite causes cytogenetic damage in some but not all of the mammalian cell systems in which it has been tested.

Study Rationale

Chlorinated trisodium phosphate was nominated by the National Cancer Institute as a part of a soap and detergent class study because of its widespread use and the lack of testing for carcinogenicity. Gavage in water was chosen as the route of administration to ensure systemic exposure at controlled doses and because water is the likeliest medium for human exposure to this compound.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF CHLORINATED TRISODIUM PHOSPHATE

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

- Study Design
- Source and Specifications of Animals
- Animal Maintenance
- Clinical Examinations and Pathology
- Statistical Methods

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF CHLORINATED TRISODIUM PHOSPHATE

Chlorinated trisodium phosphate (sodium hypochlorite phosphate), a complex chemical compound of indefinite composition, was obtained from Textile Chemical Company (Baltimore, MD) in one lot (Lot no. QJOK6). Purity analyses (elemental analyses, titration for available chlorine and phosphorus, Karl Fischer water analysis, and spark source mass spectrometry) and identity analyses (infrared and ultraviolet/visible spectroscopy) were conducted at Midwest Research Institute (Appendix D). According to the manufacturer, a typical lot of chlorinated trisodium phosphate contains 91.75% trisodium phosphate dodecahydrate ($Na_3PO_4 \cdot 12H_2O$), 5% sodium chloride (NaCl), and 3.25% sodium hypochlorite (NaOCl).

Results of elemental analyses showed that all values were within ± 6% of the manufacturer's specifications. A typical lot has 3.68% available chlorine and 18.0% phosphorus as P_2O_5. The major impurities detected by spark source mass spectrometry were sulfur (0.16%), potassium (0.07%), fluorine (0.05%), silicon (0.05%), and magnesium (0.01%). Water content, as water of crystallization, was 52.6%. Available chlorine (as Cl_2) was present at 3.6%, and phosphorus (as P_2O_5) was present at 17.7%. According to these data, the lot used for study was representative of typical commercially available material.

Chlorinated trisodium phosphate was found to be stable for 2 weeks at 25° C (Appendix D). The material used in these studies was stored at 5° C. Periodic characterization of the bulk chemical by infrared spectroscopy and titration for available chlorine indicated that no detectable deterioration occurred over the course of the studies.

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

A mixture of chlorinated trisodium phosphate at a concentration of 12.2% (w/v) in distilled water was found to be stable for 14 days in the dark at room temperature (Appendix E).

Formulations of chlorinated trisodium phosphate in water (Table 1) were periodically analyzed to estimate the accuracy with which formulations were prepared over the course of the studies (Appendix F). In addition to the analyses of dose mixtures performed by the study laboratory, a split referee sample was sent to the analytical chemistry laboratory for analysis twice each year during the 2-year studies. For the first year of the studies, the method of analysis was titration for available chlorine. For the second year of the studies, analysis was by ultraviolet spectroscopy. Comparability of the methods was established by the analytical laboratory.

TABLE 1. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF CHLORINATED TRISODIUM PHOSPHATE

	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation	Mixed with tap water for 20 min on a stirring plate	Compound and deionized water mixed by inversion in ground glass-stoppered graduated cylinders to visual homogeneity. Tissue homogenizer used at highest dose	Same as 13-wk studies, but tissue homogenizer not used
Maximum Storage Time	14 d	14 d	14 d
Storage Conditions	4° C	4° C	0° ± 5° C (in the dark)

Dose mixtures prepared for the 13-week studies were within 10% of the target concentrations (Appendix G, Table G1). Samples were analyzed at approximately 8-week intervals during the 2-year studies (Table 2; Appendix G, Table G2). The proportion of analyzed mixtures within ± 10% of the target concentration was used to estimate the overall number of mixes prepared within specifications throughout the study. Because 2 of 30 samples analyzed were not within ± 10% of the target concentration, the dose preparations were estimated to have been within specifications 94% of the time.

FOURTEEN-DAY STUDIES

Male and female F344/N rats and $B6C3F_1$ mice were obtained from Charles River Breeding Laboratories and held for 20 days before the study began. Animals were housed five per cage. Feed and water were available ad libitum. Details of animal maintenance are presented in Table 3.

Groups of five male and five female rats were administered 0, 62.5, 125, 250, 500, or 1,000 mg/kg (5 ml/kg body weight) chlorinated trisodium phosphate in tap water by gavage for 14 consecutive days. Groups of five male and five female mice were administered 0, 125, 250, 500, 1,000, or 2,000 mg/kg of the compound (10 ml/kg body weight) on the same schedule. The maximal solubility of chlorinated trisodium phosphate in water (20%) determined the highest dose that was used.

The rats and mice were observed twice per day and were weighed on days 0, 14, and 16. A necropsy was performed on all animals on day 16.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative effects of repeated administration of chlorinated trisodium phosphate in rats and mice and to determine the doses to be used in the 2-year studies.

Four- to five-week old F344/N rats and 3- to 6-week-old male and female $B6C3F_1$ mice were obtained from Charles River Breeding Laboratories, observed for 20 days, and then assigned to cages such that average cage weights were approximately equal.

Groups of 10 animals of each species and sex were administered chlorinated trisodium phosphate in deionized water by gavage (rats: 0, 62, 125, 250, 500, or 1,000 mg/kg in 5 ml/kg body weight; mice: 0, 31, 62, 125, 250, or 500 mg/kg in 10 ml/kg), 5 days per week for 13 weeks. Animals were housed five per cage by species and by sex in polycarbonate cages. Feed and water were available ad libitum. Further experimental details are summarized in Table 3.

Animals were checked twice daily, and moribund animals were killed. Individual animal weights were recorded weekly. At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 3.

TABLE 2. SUMMARY OF RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED TRISODIUM PHOSPHATE

	Concentration of Chlorinated Trisodium Phosphate in Water for Target Concentration			
	25 mg/ml	50 mg/ml	100 mg/ml	200 mg/ml
Mean (mg/ml)	19.9	47.7	100.0	195.0
Range (mg/ml)	1.9-24.8	23.7-52.3	97.3-101.9	194.0-196.0
Standard deviation	10.07	7.01	1.29	1.41
Coefficient of variation (percent)	(a) 50.6	(a) 14.7	1.3	0.7
Number of samples	5	14	14	2

(a) Variation due primarily to one sample that was out of specification; that sample was not used in the animal studies.

TABLE 3. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF CHLORINATED TRISODIUM PHOSPHATE

	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN			
Study Laboratory	EG&G Mason Research Institute	Same as 14-d studies	Same as 14-d studies
Size of Study Group	5 males and 5 females	10 males and 10 females	50 males and 50 females
Doses	Rats--0, 62.5, 125, 250, 500, or 1,000 mg/kg chlorinated trisodium phosphate in tap water by gavage; mice--0, 125, 250, 500, 1,000, or 2,000 mg/kg; dose vol--rats: 5 ml/kg; mice: 10 ml/kg	Rats--0, 62, 125, 250, 500, or 1,000 mg/kg; 0, 31, 62, 125, 250, or 500 mg/kg chlorinated trisodium phosphate in deionized water by gavage; dose vol--rats: 5 ml/kg; mice: 10 ml/kg	Rats--0, 500, 1,000, or 2,000 mg/kg; mice--0, 250, 500, or 1,000 mg/kg chlorinated trisodium phosphate in deionized water by gavage; dose vol--10 ml/kg
Date of First Dose	7/2/79	Rats--9/9/79; mice--9/10/79	Rats--5/23/80; mice--6/10/80
Date of Last Dose	7/15/79	12/7/79	Rats--high dose 9/10/80, other groups 1/16/81; mice--6/4/82
Duration of Dosing	14 consecutive days	5 d/wk for 13 wk	Rats--5 d/wk: high dose 16 wk, other groups 35 wk; mice--5 d/wk for 103 wk; 250 mg/kg group removed from studies at 6 mo
Type and Frequency of Observation	Observed 2 × d; animals weighed on d 0, 14, and 16	Checked 2 × d; weighed on d 0 and every week thereafter	Observed 2 × d; weighed every week for 12 wk; monthly thereafter
Necropsy and Histologic Examination	Necropsy performed on all animals. Kidneys from vehicle control and high dose mice were examined microscopically	Necropsy performed on all animals; the following tissues from the vehicle control and high dose groups were examined histologically: gross lesions and tissue masses, mandibular lymph node, mammary gland, skin, salivary gland, sternebrae, thyroid gland, parathyroids, small intestine, colon, liver, prostate/testes or ovaries/uterus, gallbladder (mice), lungs and bronchi, heart, esophagus, stomach, brain, thymus, trachea, pancreas, spleen, kidneys, adrenal glands, urinary bladder, and pituitary gland	Necropsy performed on all animals; the following tissues were examined histologically: tissue masses, abnormal regional lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, bone marrow, costochondral junction, thymus, trachea, lungs and bronchi, heart, thyroid gland, parathyroids, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenal glands, urinary bladder, seminal vesicles/prostate/testes or ovaries/uterus, brain, and pituitary gland
ANIMALS AND ANIMAL MAINTENANCE			
Strain and Species	F344/N rats; B6C3F$_1$ mice	Same as 14-d studies	Same as 14-d studies
Animal Source	Charles River Breeding Laboratories (Portage, MI)	Same as 14-d studies	Same as 14-d studies

TABLE 3. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF CHLORINATED TRISODIUM PHOSPHATE (Continued)

	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)			
Time Held Before Study	20 d	Same as 14-d studies	14 d (rats); 19 d (mice)
Age When Placed on Study	Rats--7 wk; mice--6-7 wk	Rats--7-9 wk; mice--6-9 wk	Rats--6-7 wk; mice--9 wk
Age When Killed	Rats--9 wk; mice--8-10 wk	Rats--20-22 wk; mice--19-22 wk	Rats--high dose 23-24 wk, other groups 39-40 wk; mice--113-114 wk
Necropsy Dates	7/17/79	12/11/79-12/12/79	Rats--9/11/80; 1/16/81; mice--6/8/82-6/16/82
Method of Animal Distribution	Assigned so that average cage weights were approximately equal	Same as 14-d studies	Assigned to cages by a table of random numbers; then to groups by another table of random numbers
Animal Identification	Ear punch	Ear punch	Ear punch
Feed	Wayne Lab Blox® meal (Allied Mills, Chicago, IL); available ad libitum	Same as 14-d studies	NIH 07 Rat and Mouse Ration (Zeigler Brothers, Gardners, PA); available ad libitum
Bedding	Aspen Bed (American Excelsior, Baltimore, MD)	Same as 14-d studies and Betta chips (Agway, Inc., Syracuse, NY)	Same as 14-d studies
Water	Edstrom Automatic Watering System (Edstrom Industries, Waterford, WI); available ad libitum	Same as 14-d studies	Same as 14-d studies
Cages	Polycarbonate (Lab Products, Rochelle Park, NJ)	Same as 14-d studies	Same as 14-d studies
Cage Filters	Nonwoven fiber (Lab Products, Rochelle Park, NJ)	Nonwoven fiber (Snow Filtration, Cincinnati, OH)	Same as 14-d studies
Animals per Cage	5	5	5
Animal Room Enviroment	10 room air changes/h; temp--21°-30° C; fluorescent light 12 h/d; humidity--34%-80%	10-12 room air changes/h; temp--20.6°-27.8° C, mean 22.8° C; fluorescent light 12 h/d; humidity--9%-80%, mean 41%	12 room air changes/h; temp--17.2°-30.0° C, time-averaged mean 23° C; fluorescent light 12h/d; humidity--11%-78%, time-averaged mean 65%
Other Chemicals on Study in the Same Room	None	None	None

II. MATERIALS AND METHODS

TWO-YEAR STUDIES

Study Design

Groups of 50 rats of each sex were administered 0, 500, 1,000, or 2,000 mg/kg chlorinated trisodium phosphate in deionized water by gavage, 5 days per week (10 ml/kg body weight). The original design called for administration for 103 weeks to two dose groups and vehicle controls; the high dose group was terminated at 16 weeks and the other groups at 35 weeks. Groups of 50 mice of each sex were administered 0, 500, or 1,000 mg/kg chlorinated trisodium phosphate in deionized water by gavage, 5 days per week for 103 weeks. Groups of 50 mice of each sex administered 250 mg/kg were eliminated from the study at 6 months, at which time there was no toxicity at the two higher doses (500 and 1,000 mg/kg).

Source and Specifications of Animals

The male and female F344/N rats and $B6C3F_1$ (C57BL/6N, female, × C3H/HeN MTV^-, male) mice used in this study were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the Carcinogenesis Program. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Rats were shipped to the study laboratory at 4-5 weeks of age and mice at 6 weeks of age. The rats were quarantined at the study facility for 14 days and the mice for 19 days. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The mice were placed on study at 9 weeks of age and rats at 6-7 weeks of age. The health of the animals was monitored during the course of the study according to the protocols of the NTP Sentinel Animal Program (Appendix H).

A quality control skin grafting program has been in effect since early 1978 to monitor the genetic integrity of the inbred mice used to produce the hybrid $B6C3F_1$ study animal. In mid-1981, data were obtained that showed incompatibility between the NIH C3H reference colony and the C3H colony from a Program supplier. In August 1981, inbred parental lines of mice were further tested for genetic integrity via isozyme and protein electrophoresis profiles that demonstrate phenotype expressions of known genetic loci.

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

Male mice from the C3H colony and female mice from the C57BL/6 colony were used as parents for the hybrid $B6C3F_1$ mice used in these studies. The influence of the potential genetic nonuniformity in the hybrid mice on these results is not known. The results of the studies are not affected because concurrent controls were included in each study.

Animal Maintenance

Rats and mice were housed five per cage by species and sex in polycarbonate cages. Feed and water were freely available. Details of animal maintenance are summarized in Table 3.

Clinical Examinations and Pathology

All animals were observed twice daily, and clinical signs were recorded once per week. Body weights by cage were recorded once per week for the first 12 weeks of the study and once per month thereafter. Mean body weights were calculated for each group. Moribund animals were killed, as were animals that survived to the end of the study. A necropsy was performed on all animals, including those found dead unless they were excessively autolyzed or cannibalized. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study in each group.

Examinations for grossly visible lesions were performed on major tissues or organs. Tissues

were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissues examined microscopically are listed in Table 3.

When the pathology examination was completed, the slides, individual animal data records, and summary tables were sent to an independent quality assurance laboratory. Individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assurance pathologist. Slides of all target tissues and those about which the original and quality assurance pathologists disagreed were submitted to the Chairperson of the Pathology Working Group (PWG) for evaluation. Representative coded slides selected by the Chairperson were reviewed by PWG pathologists, who reached a consensus and compared their findings with the original and quality assurance diagnoses. When diagnostic differences were found, the PWG sent the appropriate slides and comments to the original pathologist for review. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final diagnoses represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent evaluations, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

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

Statistical Methods

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

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

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

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

For studies in which compound administration has little effect on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by

the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death. All reported P values for tumor analyses are one-sided.

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

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

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

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

III. RESULTS

RATS

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

FOURTEEN-DAY STUDIES

One female rat at the 1,000 mg/kg dose died on day 3 (Table 4). No other dosed or vehicle control rat died before the scheduled termination date. Notable weight depression was seen only in male rats dosed with 1,000 mg/kg (13% lower than vehicle controls) and females dosed with 500 mg/kg (8% lower than vehicle controls). One male rat receiving 62.5 mg/kg and one male and one female receiving 1,000 mg/kg had red coloration at the corticomedullary border. Transient rales were observed in one male and one female at 250 mg/kg, two males and one female at 500 mg/kg, and one male and three females at 1,000 mg/kg. No rales were recorded for vehicle control rats.

THIRTEEN-WEEK STUDIES

One female rat (62 mg/kg) died during the study, but the death was not considered to be chemically related (Table 5). A 6% lower final mean body weight was seen in female rats receiving 1,000 mg/kg. No gross or histopathologic findings were attributed to the administration of chlorinated trisodium phosphate.

Dose Selection Rationale: No adverse compound-related effects were observed at 500 mg/kg for 13 weeks or at 1,000 mg/kg for 14 days (other than weight differential); therefore, doses selected for the 2-year studies were 500, 1,000, or 2,000 mg/kg chlorinated trisodium phosphate in water, to be administered by gavage. After 6 months, one of the dose groups was to be removed from the study.

TWO-YEAR STUDIES

The 2-year studies in rats were terminated after 35 weeks due to toxicity. After 16 weeks on study, 36 male and 30 female high dose (2,000 mg/kg) rats had died and the remaining animals were killed. Histopathologic examinations showed mineralization of the kidneys and severe necrotic lesions of the trachea. By the 27th week, 13/50 male and 12/50 female mid dose (1,000 mg/kg) rats had died and showed histopathologic effects similar to those of the high dose rats. The rat studies were terminated after

TABLE 4. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FOURTEEN-DAY GAVAGE STUDIES OF CHLORINATED TRISODIUM PHOSPHATE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Mean Body Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	158 ± 4	214 ± 5	+56 ± 4	--
62	5/5	158 ± 4	217 ± 5	+59 ± 3	101
125	5/5	157 ± 3	211 ± 6	+54 ± 3	99
250	5/5	158 ± 3	210 ± 5	+52 ± 2	98
500	5/5	159 ± 4	203 ± 5	+44 ± 3	95
1,000	5/5	160 ± 5	186 ± 8	+26 ± 9	87
FEMALE					
0	5/5	123 ± 1	145 ± 3	+22 ± 3	--
62	5/5	122 ± 2	148 ± 1	+26 ± 2	102
125	5/5	122 ± 2	144 ± 5	+22 ± 4	99
250	5/5	124 ± 2	147 ± 2	+23 ± 1	101
500	5/5	122 ± 2	133 ± 8	+11 ± 8	92
1,000	(d) 4/5	119 ± 2	141 ± 4	+23 ± 5	97

(a) Number surviving/number initially in the group
(b) Initial mean group body weight. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean weight change of the survivors of the group ± standard error of the mean
(d) Day of death: 3

TABLE 5. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF CHLORINATED TRISODIUM PHOSPHATE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final (c)	Change (d)	Final Mean Body Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	140 ± 3	319 ± 6	+179 ± 5	--
62	10/10	140 ± 3	318 ± 3	+178 ± 5	100
125	10/10	140 ± 3	324 ± 5	+184 ± 5	102
250	10/10	140 ± 2	321 ± 6	+181 ± 6	101
500	10/10	140 ± 3	319 ± 4	+179 ± 4	100
1,000	10/10	140 ± 3	317 ± 3	+177 ± 3	99
FEMALE					
0	10/10	113 ± 2	198 ± 2	+ 85 ± 2	--
62	(e) 9/10	114 ± 2	196 ± 4	+ 81 ± 4	99
125	10/10	114 ± 2	195 ± 2	+ 81 ± 2	98
250	10/10	114 ± 1	193 ± 3	+ 79 ± 3	97
500	10/10	114 ± 1	198 ± 4	+ 84 ± 2	100
1,000	10/10	114 ± 2	187 ± 2	+ 73 ± 3	94

(a) Number surviving/number initially in the group
(b) Initial mean group body weight. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Final body weights are those recorded during week 12, the last time period for which individual body weights are available.
(d) Mean weight change of the survivors of the group ± standard error of the mean
(e) Week of death: 4

35 weeks because of the lack of a sufficient number of animals to constitute an adequate study.

Toxic effects (lesions of the trachea) observed in the rats at the two highest doses were consequences of the concentration of chlorinated trisodium phosphate in the dose mixture being near its threshold of solubility in water. It was necessary to increase the volume administered to rats from 5 ml/kg to 10 ml/kg to achieve the high dose (2,000 mg/kg). All rats were administered the same dose volume so that results would be comparable. This dose volume was apparently too great for young rats, and the excess dose mixture may have remained in the esophagus and might have been aspirated. Inflammatory lesions in the trachea and/or lungs of the rats receiving the two high doses (1,000 and 2,000 mg/kg) were dose related and associated with early death. The lesions were not typical of gavage accidents. Location and distribution suggested that small amounts of highly irritating material were aspirated by the animals that died. At the two highest doses, there may have been particles in suspension, which would account for the increased local toxicity on aspiration into the trachea. These lesions were not observed in animals killed at the end of the study or in the low dose (500 mg/kg) group.

The rat portion of this study was not restarted; the mouse studies were continued as a part of the soap and detergent class study for the National Cancer Institute.

FOURTEEN-DAY STUDIES

Four of five male mice that received 2,000 mg/kg died before the end of the study (Table 6). Male mice that received 125-2,000 mg/kg and females that received 250-2,000 mg/kg gained less weight than did the vehicle controls. Transient rales were present in 1/5 males and 0/5 females that received 500 mg/kg, in 0/5 males and 3/5 females that received 1,000 mg/kg, and in 2/5 males and 2/5 females that received 2,000 mg/kg. Although the kidneys of 4/5 males and 3/5 females that received 2,000 mg/kg had red coloration at the corticomedullary border, no compound-related effects were noted in the kidneys of mice examined microscopically.

Based on these results, 500 mg/kg was selected as the highest dose to be given in the 13-week studies in male and female mice.

THIRTEEN-WEEK STUDIES

Deaths of two female mice before the end of the studies were not considered dose related (one in the 31 mg/kg group during week 7 and one in the 62 mg/kg group during week 12) (Table 7). Final mean body weights (relative to those of the vehicle controls) were minimally lower (2.7% for males and 3.7% for females) in mice administered 500 mg/kg. No compound-related histopathologic effects were observed.

Dose Selection Rationale: Other than weight differential, no adverse compound-related effects were observed at 500 mg/kg for 13 weeks or at 1,000 mg/kg for 14 days; therefore, doses selected for the 2-year studies were 250, 500, and 1,000 mg/kg chlorinated trisodium phosphate in water, to be administered by gavage. After 6 months, the 250 mg/kg dose group was removed, without histopathologic examination, from the studies due to the lack of toxicity in the two higher doses.

TABLE 6. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FOURTEEN-DAY GAVAGE STUDIES OF CHLORINATED TRISODIUM PHOSPHATE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Mean Body Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	27.3 ± 0.9	29.0 ± 1.3	+1.7 ± 0.4	--
125	5/5	27.5 ± 0.8	28.6 ± 0.5	+1.1 ± 0.5	98.6
250	5/5	27.4 ± 0.8	27.8 ± 0.7	+0.4 ± 0.3	95.9
500	5/5	27.1 ± 0.4	27.2 ± 0.2	+0.1 ± 0.2	93.8
1,000	5/5	27.0 ± 0.5	27.2 ± 0.6	+0.2 ± 0.5	93.8
2,000	(d) 1/5	27.1 ± 0.6	26.0	−0.6	89.7
FEMALE					
0	5/5	20.9 ± 0.6	22.2 ± 0.6	+1.3 ± 0.3	--
125	5/5	20.6 ± 0.4	22.2 ± 0.7	+1.6 ± 0.9	100.0
250	5/5	20.3 ± 0.5	21.2 ± 0.7	+0.9 ± 0.2	95.5
500	5/5	20.8 ± 0.5	21.0 ± 0.7	+0.2 ± 0.4	94.6
1,000	5/5	20.8 ± 0.5	20.2 ± 1.2	−0.6 ± 1.0	91.0
2,000	5/5	21.2 ± 0.4	21.6 ± 0.5	+0.4 ± 0.2	97.3

(a) Number surviving/number initially in the group
(b) Initial mean group body weight. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean weight change of the survivors of the group ± standard error of the mean
(d) Days of death: 2, 6, 12, 15

TABLE 7. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF CHLORINATED TRISODIUM PHOSPHATE (a)

Dose (mg/kg)	Survival (b)	Mean Body Weights (grams) Initial (c)	Final	Change (d)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	26.4 ± 0.5	33.3 ± 0.6	+6.9 ± 0.5	--
31	10/10	26.3 ± 0.5	34.2 ± 0.8	+7.9 ± 0.3	102.7
62	10/10	26.4 ± 0.6	34.8 ± 1.5	+8.4 ± 1.1	104.5
125	10/10	26.3 ± 0.6	33.0 ± 1.0	+6.7 ± 0.6	99.1
250	10/10	26.3 ± 0.6	33.3 ± 1.1	+7.0 ± 0.8	100.0
500	10/10	26.2 ± 0.6	32.4 ± 0.7	+6.2 ± 0.4	97.3
FEMALE					
0	10/10	20.9 ± 0.4	26.8 ± 0.6	+5.9 ± 0.4	--
31	(e) 9/10	21.2 ± 0.3	26.8 ± 0.5	+5.6 ± 0.4	100.0
62	(f) 9/10	21.1 ± 0.4	25.9 ± 1.1	+4.9 ± 0.8	96.6
125	10/10	21.1 ± 0.4	25.9 ± 0.5	+4.8 ± 0.2	96.6
250	10/10	21.3 ± 0.3	26.6 ± 0.7	+5.3 ± 0.4	99.3
500	10/10	21.6 ± 0.4	25.8 ± 0.4	+4.2 ± 0.3	96.3

(a) Final body weights are those from week 12, the last study week for which individual weights are available.
(b) Number surviving/number initially in the group
(c) Initial mean group body weight. Subsequent calculations are based on those animals surviving to week 12.
(d) Mean weight change of the survivors of the group ± standard error of the mean
(e) Week of death: 7
(f) Week of death: 12

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed male mice were generally comparable with those of the vehicle control male mice (Table 8 and Figure 1). Mean body weights of high dose female mice were generally lower than those of the vehicle controls after week 32; final body weights were 11% lower than those of the vehicle controls. No compound-related clinical signs were observed.

TABLE 8. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED TRISODIUM PHOSPHATE

Weeks on Study	Vehicle Control		500 mg/kg			1,000 mg/kg		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors
MALE								
0	26	50	25	96.2	50	26	100.0	50
1	28	50	27	96.4	50	27	96.4	50
2	28	50	27	96.4	50	28	100.0	50
3	29	50	29	100.0	50	29	100.0	50
4	30	50	31	103.3	50	31	103.3	50
5	31	50	31	100.0	50	32	103.2	50
6	32	50	31	96.9	50	32	100.0	50
7	32	50	33	103.1	50	33	103.1	50
8	33	50	33	100.0	50	33	100.0	50
9	33	50	34	103.0	50	34	103.0	50
10	34	50	34	100.0	50	34	100.0	50
11	34	50	35	102.9	50	35	102.9	50
12	34	50	34	100.0	50	34	100.0	50
16	36	50	38	105.6	50	38	105.6	50
20	38	50	39	102.6	50	40	105.3	50
24	38	50	40	105.3	50	40	105.3	50
28	39	50	41	105.1	50	41	105.1	50
32	40	50	41	102.5	50	41	102.5	49
36	41	50	42	102.4	50	42	102.4	49
40	41	50	42	102.4	50	42	102.4	49
44	42	50	44	104.8	50	42	100.0	48
48	40	50	43	107.5	50	42	105.0	47
52	41	49	42	102.4	50	41	100.0	47
56	40	49	42	105.0	50	41	102.5	46
60	41	49	43	104.9	50	41	100.0	44
64	40	48	43	107.5	50	41	102.5	44
68	40	48	42	105.0	50	41	102.5	44
72	41	48	42	102.4	50	41	100.0	43
76	41	48	43	104.9	50	42	102.4	42
80	42	46	42	100.0	48	42	100.0	41
84	40	46	42	105.0	48	42	105.0	41
88	41	45	43	104.9	47	41	100.0	39
92	41	45	42	102.4	45	41	100.0	38
96	40	42	42	105.0	41	41	102.5	36
100	39	41	43	110.3	38	41	105.1	35
104	39	39	39	100.0	36	39	100.0	32
FEMALE								
0	19	50	19	100.0	50	19	100.0	50
1	20	50	21	105.0	50	20	100.0	50
2	20	50	21	105.0	50	21	105.0	50
3	21	50	22	104.8	50	22	104.8	50
4	22	50	23	104.5	50	23	104.5	50
5	23	50	24	104.3	50	23	100.0	50
6	23	50	24	104.3	50	24	104.3	50
7	24	50	24	100.0	50	24	100.0	50
8	24	50	25	104.2	50	24	100.0	50
9	25	50	25	100.0	50	26	104.0	50
10	24	50	25	104.2	50	25	104.2	50
11	25	50	25	100.0	50	26	104.0	50
12	26	50	25	96.2	50	25	96.2	50
16	27	50	28	103.7	50	28	103.7	49
20	29	50	30	103.4	50	32	110.3	49
24	31	50	32	103.2	50	31	100.0	49
28	33	50	33	100.0	50	33	100.0	49
32	35	50	35	100.0	50	32	91.4	49
36	37	50	36	97.3	50	35	94.6	49
40	38	50	37	97.4	50	35	92.1	49
44	39	50	39	100.0	50	37	94.9	49
48	37	50	38	102.7	50	36	97.3	49
52	39	50	38	97.4	50	37	94.9	49
56	38	50	38	100.0	50	38	100.0	48
60	41	50	41	100.0	50	38	92.7	48
64	41	50	41	100.0	49	38	92.7	48
68	41	47	41	100.0	48	38	92.7	47
72	42	46	42	100.0	45	37	88.1	44
76	43	45	43	100.0	41	39	90.7	40
80	44	42	44	100.0	39	42	95.5	36
84	43	42	44	102.3	35	42	97.7	33
88	44	41	45	102.3	28	42	95.5	30
92	44	39	46	104.5	25	42	95.5	27
96	45	35	45	100.0	23	43	95.6	23
100	45	32	44	97.8	18	41	91.1	22
104	44	30	41	93.2	16	39	88.6	21

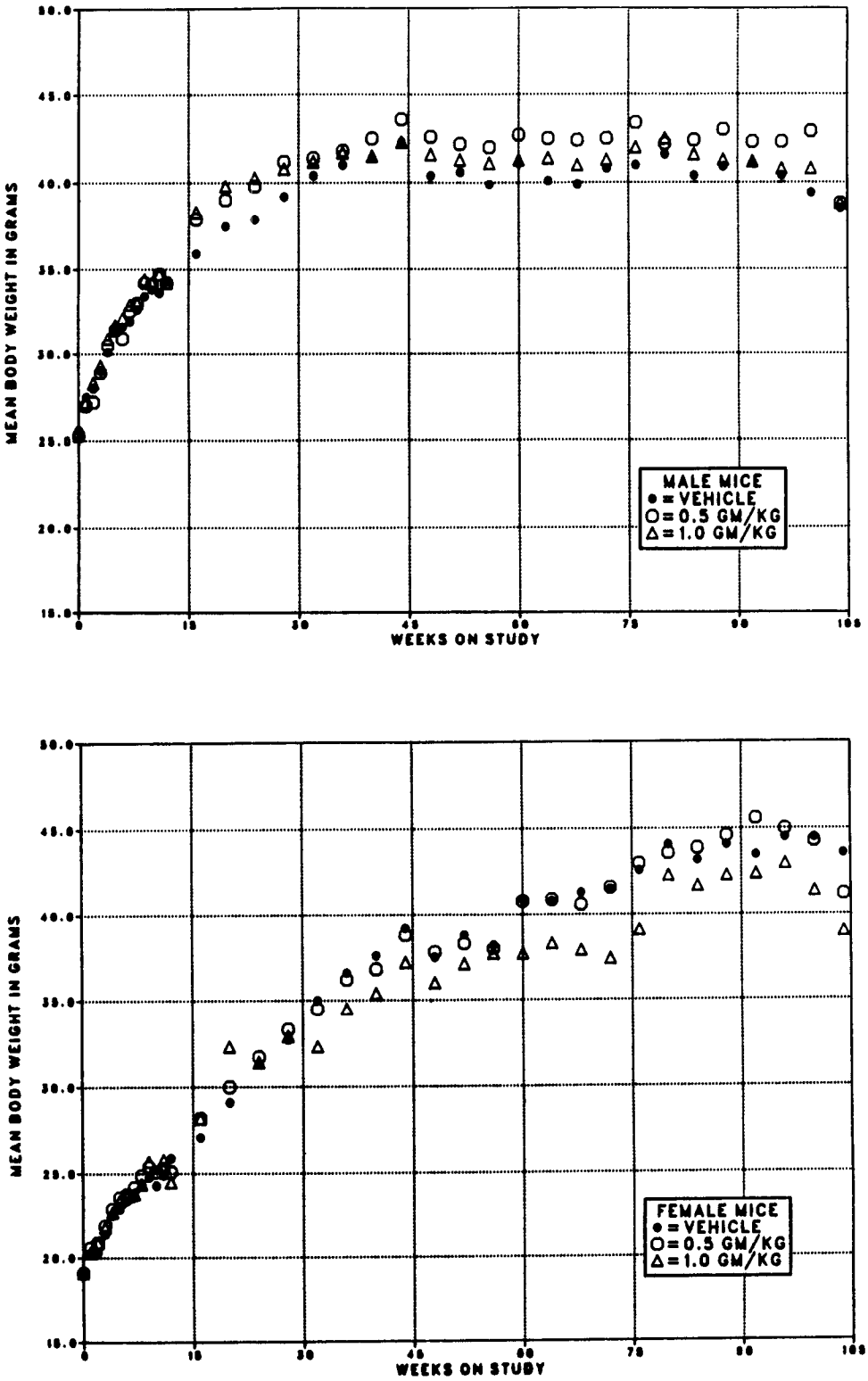

FIGURE 1. GROWTH CURVES FOR MICE ADMINISTERED CHLORINATED TRISODIUM PHOSPHATE IN WATER BY GAVAGE FOR TWO YEARS

III. RESULTS: MICE

Survival

Estimates of the probabilities of survival for male and female mice administered chlorinated trisodium phosphate at the doses used in these studies and for vehicle controls are shown in the Kaplan and Meier curves in Figure 2. The survival of the low dose group of female mice after week 88 was significantly lower than that of the vehicle control group (Table 9). Survival of high dose female mice was marginally but not significantly lower than that of the vehicle controls at the end of the study.

Pathology and Statistical Analyses of Results

This section describes significant or noteworthy changes in the numbers of animals with neoplastic or nonneoplastic lesions of the liver, kidney, ovary, uterus, hematopoietic system, subcutaneous tissue, and adrenal gland. Histopathologic findings on neoplasms in mice are summarized in Appendix A (Tables A1 and A2); Appendix A (Tables A3 and A4) also gives the survival and tumor status for individual male and female mice. Findings on nonneoplastic lesions are summarized in Appendix B (Tables B1 and B2). Appendix C (Tables C1 and C2) contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix C (footnotes). Historical incidences in control animals are given in Appendix K.

TABLE 9. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED TRISODIUM PHOSPHATE

	Vehicle Control	500 mg/kg	1,000 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	10	14	18
Accidentally killed	1	0	0
Killed at termination	39	35	32
Died during termination period	0	1	0
Survival P values (c)	0.073	0.529	0.099
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	20	34	29
Killed at termination	30	16	21
Survival P values (c)	0.049	0.007	0.061

(a) Terminal-kill period: male--weeks 104-105; female--week 105
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

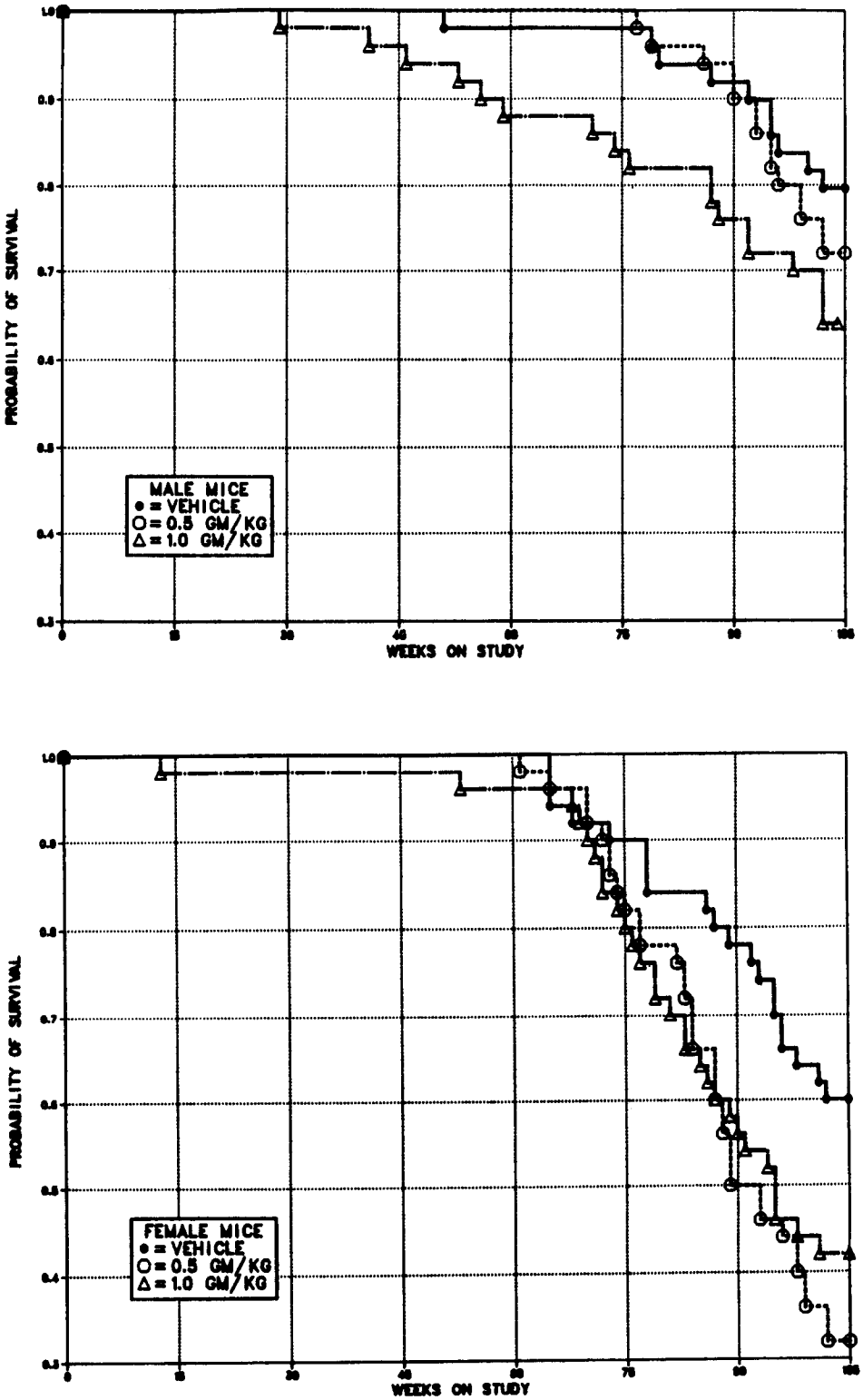

FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED CHLORINATED TRISODIUM PHOSPHATE IN WATER BY GAVAGE FOR TWO YEARS

Liver: Liver necrosis and fatty metamorphosis were observed at increased incidences in dosed male mice (necrosis: vehicle control, 8/50; low dose, 21/50; high dose, 16/50; fatty metamorphosis: 1/50; 3/50; 9/50). These liver lesions were not observed at increased incidence in dosed female mice.

Kidney: Kidney mineralization occurred at increased incidences in male mice (vehicle control, 16/50; low dose, 27/50; high dose, 33/50). These lesions were characterized by small, multifocal areas of mineralization, primarily in the cortex and not at the corticomedullary junction or in the tubules of the medulla as is sometimes seen in other studies. The foci of mineralization were small, often just one tubular epithelial cell. Other foci appeared to involve two or three cells and the basement membrane. Small laminated structures were seen in the lumen of some tubules of the cortex. The degree of severity was minimal to very minimal. Some kidneys had one small focus; others, just two to four such foci. This lesion was not considered compound related.

Ovary/Uterus: Ovarian abscesses, uterine abscesses, necrotizing inflammation of the ovary or uterus, or acute inflammation of the ovary was observed in 11/49 vehicle control, 21/50 low dose, and 24/49 high dose female mice, primarily in animals that died between week 70 and the end of the studies. The infection frequently spread throughout the abdominal cavity. The effects observed were probably due to an infection with Klebsiella. (Klebsiella was confirmed by culture from the uterus.) The incidence of ovarian neoplasms in female mice is given in Table 10.

Hematopoietic System: Lymphocytic lymphomas and lymphomas (all types) in male mice occurred with significant positive trends; the incidences in the dosed groups were not significantly greater than those in the vehicle controls (Table 11). These lesions did not occur at increased incidence in dosed female mice (vehicle control, 12/50; low dose, 13/50; high dose, 11/50).

Subcutaneous Tissue: The incidence of sarcomas, NOS, in low dose female mice was greater than that in the vehicle controls by the life table test (Table 12). In male mice, fibrosarcomas occurred with a negative trend, and the incidences in the dosed groups were significantly lower than that in the vehicle controls; but the incidence of fibromas, fibrosarcomas, or neurofibrosarcomas (combined) in dosed male mice was not significantly different from that in the vehicle controls.

Adrenal Gland: Cortical adenomas in male mice occurred with a significant ($P = 0.042$) positive trend (vehicle control, 0/49; low dose, 1/50; high dose, 3/49); the incidences in the dosed groups were not significantly greater than that in the vehicle controls. Adrenal cortical hyperplasia occurred with a negative trend (vehicle control, 3/49; low dose, 1/50; high dose, 0/49).

TABLE 10. INCIDENCE OF OVARIAN NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED TRISODIUM PHOSPHATE

Neoplasm	Vehicle Control	500 mg/kg	1,000 mg/kg
Papillary cystadenoma	0	0	1
Luteoma	0	1	0
Granulosa cell tumor	0	0	(a) 2
Tubular adenoma	0	1	0
Teratoma	0	1	0
No. mice examined	48	50	48

(a) One of the mice with a granulosa cell tumor also had the papillary cystadenoma.

TABLE 11. ANALYSIS OF LYMPHOMAS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED TRISODIUM PHOSPHATE (a)

	Vehicle Control	500 mg/kg	1,000 mg/kg
Malignant Lymphoma, Lymphocytic Type			
Overall Rates	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted Rates	0.0%	0.0%	8.7%
Terminal Rates	0/39 (0%)	0/36 (0%)	2/32 (6%)
Life Table Tests	P=0.027	(b)	P=0.092
Incidental Tumor Tests	P=0.035	(b)	P=0.112
Malignant Lymphoma, Mixed Type			
Overall Rates	1/50 (2%)	1/50 (2%)	4/50 (8%)
Adjusted Rates	2.6%	2.5%	11.9%
Terminal Rates	1/39 (3%)	0/36 (0%)	3/32 (9%)
Life Table Tests	P=0.073	P=0.749	P=0.131
Incidental Tumor Tests	P=0.062	P=0.707N	P=0.126
Lymphoma, All Malignant (c)			
Overall Rates	4/50 (8%)	4/50 (8%)	9/50 (18%)
Adjusted Rates	9.0%	10.3%	24.7%
Terminal Rates	2/39 (5%)	2/36 (6%)	6/32 (19%)
Life Table Tests	P=0.047	P=0.616	P=0.073
Incidental Tumor Tests	P=0.099	P=0.564	P=0.149

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix C (footnotes).
(b) No P value is reported because no tumors were observed in the 500 mg/kg and vehicle control groups.
(c) Historical incidence in NTP water gavage studies (mean): 7/150 (4.7%); historical incidence in NTP untreated controls: 280/2,343 (12%); historical incidence in NTP corn oil gavage controls: 126/1,040 (12%)

TABLE 12. ANALYSIS OF SUBCUTANEOUS TUMORS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED TRISODIUM PHOSPHATE

	Vehicle Control	500 mg/kg	1,000 mg/kg
MALE			
Fibrosarcoma			
Overall Rates	6/50 (12%)	1/50 (2%)	0/50 (0%)
Adjusted Rates	13.5%	2.3%	0.0%
Terminal Rates	2/39 (5%)	0/36 (0%)	0/32 (0%)
Life Table Tests	P=0.008N	P=0.070N	P=0.032N
Incidental Tumor Tests	P=0.003N	P=0.026N	P=0.019N
Fibroma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates	7/50 (14%)	3/50 (6%)	2/50 (4%)
Adjusted Rates	15.9%	7.8%	5.7%
Terminal Rates	3/39 (8%)	2/36 (6%)	0/32 (0%)
Life Table Tests	P=0.084N	P=0.188N	P=0.135N
Incidental Tumor Tests	P=0.054N	P=0.108N	P=0.095N
FEMALE			
Sarcoma, NOS			
Overall Rates	0/50 (0%)	4/50 (8%)	0/50 (0%)
Adjusted Rates	0.0%	15.1%	0.0%
Terminal Rates	0/30 (0%)	0/16 (0%)	0/21 (0%)
Life Table Tests	P=0.519	P=0.032	(a)
Incidental Tumor Tests	P=0.588N	P=0.124	(a)

(a) No P value is reported because no tumors were observed in the 1,000 mg/kg and vehicle control groups.

IV. DISCUSSION AND CONCLUSIONS

IV. DISCUSSION AND CONCLUSIONS

Two-year toxicology and carcinogenesis studies of chlorinated trisodium phosphate were conducted by administering 0, 500 or 1,000 mg/kg of the chemical in water by gavage, 5 days per week for 103 weeks, to groups of 50 male and 50 female $B6C3F_1$ mice. Dose selection for mice was based on 13-week studies in which no adverse compound-related effects or marked body weight differences were observed at 500 mg/kg and on 14-day studies in which 4/5 males that received 2,000 mg/kg died and animals that received 1,000 mg/kg showed slightly lower body weights than did the vehicle controls. No compound-related histopathologic effects were observed in either the 14-day or 13-week studies.

Carcinogenesis studies were also begun in groups of 50 male and 50 female F344/N rats at doses of 0, 500, 1,000, or 2,000 mg/kg by gavage in water. After 16 weeks on study, more than half the animals in the high dose groups had died, apparently from toxic effects of the chemical, and the remaining animals were killed. By the 27th week, 13/50 male and 12/50 female mid dose (1,000 mg/kg) rats had died and showed histopathologic effects similar to those in the high dose rats (severe necrotic lesions of the esophagus and mineralization of the kidney). The rat studies were terminated after 35 weeks because of the lack of a sufficient number of animals to constitute an adequate study.

In the 2-year studies, the survival of the dosed female mice was lower than that of the vehicle controls. The mean body weights of the high dose female mice were 11% lower than those of the vehicle control mice, primarily after week 32. The lower survival and mean body weights of the dosed female mice may have been due to the greater incidence of uterine/ovarian Klebsiella infections in these mice rather than to a toxic effect of chlorinated trisodium phosphate. Because the number of dosed female mice surviving to the end of the study was low (low dose, 32%; high dose, 42%), the study is less sensitive for determining the presence or absence of a carcinogenic effect. Survival and mean body weights of dosed and vehicle control male mice were comparable.

Nonneoplastic effects were observed in the liver and kidney of male, but not female, mice. Increased incidences of fatty metamorphosis and necrosis of the liver were observed in dosed male mice; however, these minimal effects were not considered related to chlorinated trisodium phosphate administration. In most animals, the necrosis or fatty metamorphosis was a secondary effect related to the presence of a primary hepatocellular lesion; most of these lesions were very minimal and focal and did not have the zonal pattern expected for a toxic effect. Mineralization of the kidney, observed in male mice, was characterized by small, multifocal areas of mineralization, primarily in the cortex and not at the corticomedullary junction or in the tubules of the medulla as is sometimes seen in other studies. The foci of mineralization were small, often involving just one tubular epithelial cell. Other foci appeared to involve two or three cells and the basement membrane. Small laminated structures were seen in the lumen of some tubules of the cortex. The severity of these lesions was very slight, and the lesions were not considered to be compound related.

At no site was the incidence of neoplasms considered to be related to administration of chlorinated trisodium phosphate. Five different types of ovarian neoplasms were observed microscopically in six dosed mice, and no ovarian neoplasms were observed in the vehicle controls (see Table 10). Because no single tumor type was observed in more than two animals and because these tumor types arise from tissues of differing embryonic origin (hence not combinable for purposes of analysis), these ovarian lesions are considered unrelated to the administration of chlorinated trisodium phosphate.

The incidence of malignant lymphomas was increased in high dose male mice relative to vehicle controls (vehicle control, 4/50; low dose, 4/50; high dose, 9/50). Because this increase was marginally significant ($P = 0.047$) only by the trend test and not by pairwise comparison, because no similar effect was observed in females, and because the incidence in the high dose group was within the ranges observed in both untreated controls and corn oil gavage controls throughout the Program (Appendix K, Table K1), this effect was considered unrelated to chlorinated trisodium phosphate.

Adenomas of the adrenal cortex occurred with a marginally significant (P = 0.042) positive trend in male mice (vehicle control, 0/49; low dose, 1/50; high dose, 3/49); however, adrenal cortical hyperplasia decreased in dosed male mice (3/49; 1/50; 0/49). The adrenal cortical hyperplasia and adenomas represent a spectrum of lesions that should be considered together when analyzing for a compound-related effect. In this case, the combined incidence is virtually identical in all groups, so the increased incidence of adenomas does not represent an effect of chlorinated trisodium phosphate.

As discussed in the Introduction, chlorinated trisodium phosphate is a weak base-pair substitution mutagen in Salmonella (Appendix J); however, it has not been studied in any additional short-term tests. Furthermore, chlorinated trisodium phosphate was mutagenic in strain TA1535 of Salmonella only when more (30%) S9 fraction was used than the usual amount (10%). Based on these limited data, only weak mutagenic activity was observed even at high doses (over 6 mg/plate).

Conclusions: Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenicity** for either male or female $B6C3F_1$ mice given chlorinated trisodium phosphate by gavage in water for 103 weeks at doses of 500 or 1,000 mg. Survival of dosed female mice was 78% and 72% after 80 weeks and 32% and 42% at the termination of the study. The studies in male and female F344/N rats were considered to be *inadequate studies of carcinogenicity* because the experiments were terminated at 35 weeks due to poor survival.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.

V. REFERENCES

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED TRISODIUM PHOSPHATE

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED TRISODIUM PHOSPHATE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
CARCINOMA, NOS		1 (2%)	
SQUAMOUS CELL CARCINOMA		2 (4%)	
*SUBCUTANEOUS TISSUE	(50)	(50)	(50)
MALIGNANT MELANOMA		1 (2%)	
FIBROMA	2 (4%)	1 (2%)	
FIBROSARCOMA	6 (12%)	1 (2%)	
NEUROFIBROSARCOMA		1 (2%)	2 (4%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(49)
HEPATOCELLULAR CARCINOMA, METAST	2 (4%)	4 (8%)	3 (6%)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)	8 (16%)	6 (12%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	6 (12%)	4 (8%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	1 (2%)	1 (2%)	
MALIG. LYMPHOMA, UNDIFFER TYPE	1 (2%)	1 (2%)	
MALIG. LYMPHOMA, LYMPHOCYTIC TYPE			3 (6%)
MALIG. LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)	1 (2%)	3 (6%)
#SPLEEN	(50)	(49)	(49)
MALIG. LYMPHOMA, UNDIFFER TYPE			1 (2%)
#LYMPH NODE	(50)	(48)	(46)
ALVEOLAR/BRONCHIOLAR CA, METASTA		1 (2%)	
MALIGNANT LYMPHOMA, NOS	1 (2%)		
MALIGNANT LYMPHOMA, MIXED TYPE			1 (2%)
#LIVER	(50)	(50)	(50)
MALIG. LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
CIRCULATORY SYSTEM			
#SPLEEN	(50)	(49)	(49)
HEMANGIOSARCOMA			1 (2%)
ANGIOSARCOMA			1 (2%)
#LYMPH NODE	(50)	(48)	(46)
HEMANGIOMA		1 (2%)	
#LIVER	(50)	(50)	(50)
HEMANGIOMA	1 (2%)		
HEMANGIOSARCOMA	1 (2%)		
ANGIOSARCOMA	1 (2%)		
DIGESTIVE SYSTEM			
*INTESTINAL TRACT	(50)	(50)	(50)
ADENOCARCINOMA, NOS		1 (2%)	
#LIVER	(50)	(50)	(50)
HEPATOCELLULAR ADENOMA	6 (12%)	5 (10%)	11 (22%)
HEPATOCELLULAR CARCINOMA	9 (18%)	11 (22%)	7 (14%)
#STOMACH	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)	1 (2%)	

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED TRISODIUM PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#FORESTOMACH	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	2 (4%)	1 (2%)	
#JEJUNUM	(50)	(49)	(47)
ADENOCARCINOMA, NOS		1 (2%)	
URINARY SYSTEM			
*PROSTATIC URETHRA	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(47)	(45)	(48)
ADENOMA, NOS		2 (4%)	1 (2%)
#ADRENAL	(49)	(50)	(49)
CORTICAL ADENOMA		1 (2%)	3 (6%)
PHEOCHROMOCYTOMA	2 (4%)	1 (2%)	
#ADRENAL/CAPSULE	(49)	(50)	(49)
ADENOMA, NOS	2 (4%)		3 (6%)
#THYROID	(47)	(50)	(49)
FOLLICULAR-CELL ADENOMA	2 (4%)		
FOLLICULAR-CELL CARCINOMA	1 (2%)		
#PANCREATIC ISLETS	(50)	(49)	(48)
ISLET-CELL ADENOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(50)	(50)	(50)
CARCINOMA, NOS	1 (2%)		
NERVOUS SYSTEM			
*CHOROID PLEXUS	(50)	(50)	(50)
CARCINOMA, NOS		1 (2%)	
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
ADENOMA, NOS	3 (6%)	3 (6%)	
CYSTADENOMA, NOS		2 (4%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PLEURAL CAVITY	(50)	(50)	(50)
MESOTHELIOMA, MALIGNANT		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
MESOTHELIOMA, METASTATIC		1 (2%)	
FOOT			
FIBROMA	1		

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED TRISODIUM PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	3	8	9
MORIBUND SACRIFICE	7	7	9
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	39	35	32
DOSING ACCIDENT			
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS	1		
ANIMAL MISSING			
ANIMAL MISSEXED			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	35	37	30
TOTAL PRIMARY TUMORS	54	56	45
TOTAL ANIMALS WITH BENIGN TUMORS	19	21	19
TOTAL BENIGN TUMORS	25	27	24
TOTAL ANIMALS WITH MALIGNANT TUMORS	27	23	18
TOTAL MALIGNANT TUMORS	29	29	21
TOTAL ANIMALS WITH SECONDARY TUMORS##	2	6	3
TOTAL SECONDARY TUMORS	2	6	3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED TRISODIUM PHOSPHATE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SUBCUTANEOUS TISSUE	(50)	(50)	(50)
SARCOMA, NOS		4 (8%)	
FIBROSARCOMA	1 (2%)		1 (2%)
OSTEOSARCOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
CARCINOMA, NOS, METASTATIC			1 (2%)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (6%)	2 (4%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	3 (6%)		1 (2%)
PHEOCHROMOCYTOMA, METASTATIC	1 (2%)		
OSTEOSARCOMA, METASTATIC	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS		3 (6%)	
MALIG. LYMPHOMA, UNDIFFER TYPE	2 (4%)	1 (2%)	1 (2%)
MALIG. LYMPHOMA, LYMPHOCYTIC TYPE	5 (10%)	4 (8%)	5 (10%)
MALIG. LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE	4 (8%)	4 (8%)	3 (6%)
#LYMPH NODE	(48)	(49)	(49)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
MALIG. LYMPHOMA, UNDIFFER TYPE			1 (2%)
CIRCULATORY SYSTEM			
*ABDOMINAL CAVITY	(50)	(50)	(50)
HEMANGIOMA			1 (2%)
*SUBCUTANEOUS TISSUE	(50)	(50)	(50)
HEMANGIOSARCOMA	1 (2%)		
#SPLEEN	(49)	(49)	(48)
HEMANGIOSARCOMA	1 (2%)		
#LIVER	(50)	(50)	(50)
HEMANGIOSARCOMA		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
HEPATOCELLULAR ADENOMA	6 (12%)	7 (14%)	5 (10%)
HEPATOCELLULAR CARCINOMA		1 (2%)	1 (2%)
#DUODENUM	(46)	(48)	(46)
ADENOCARCINOMA, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR CA, METASTA	1 (2%)		

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED TRISODIUM PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(45)	(48)	(47)
ADENOMA, NOS	8 (18%)	8 (17%)	10 (21%)
#PITUITARY INTERMEDIA	(45)	(48)	(47)
ADENOMA, NOS			1 (2%)
#ADRENAL	(48)	(50)	(50)
FIBROSARCOMA, INVASIVE			1 (2%)
#ADRENAL/CAPSULE	(48)	(50)	(50)
ADENOMA, NOS		2 (4%)	1 (2%)
#ADRENAL MEDULLA	(48)	(50)	(50)
PHEOCHROMOCYTOMA, MALIGNANT	1 (2%)		
#THYROID	(48)	(49)	(48)
FOLLICULAR-CELL ADENOMA	1 (2%)		2 (4%)
#PANCREATIC ISLETS	(48)	(49)	(46)
ISLET-CELL ADENOMA			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS			1 (2%)
FIBROADENOMA	2 (4%)	1 (2%)	1 (2%)
#UTERUS	(49)	(50)	(49)
LEIOMYOSARCOMA		1 (2%)	
ENDOMETRIAL STROMAL POLYP	1 (2%)		
#OVARY	(48)	(50)	(48)
PAPILLARY CYSTADENOMA, NOS			1 (2%)
LUTEOMA		1 (2%)	
GRANULOSA-CELL TUMOR			2 (4%)
TUBULAR ADENOMA		1 (2%)	
TERATOMA, NOS		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
CARCINOMA, NOS	1 (2%)		2 (4%)
ADENOMA, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
NEOPLASM, NOS, METASTATIC		1 (2%)	
CARCINOMA, NOS, METASTATIC	1 (2%)		
OSTEOSARCOMA, METASTATIC		1 (2%)	

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED TRISODIUM PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	9	10	20
MORIBUND SACRIFICE	11	24	9
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	30	16	21
DOSING ACCIDENT			
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS			
ANIMAL MISSING			
ANIMAL MISSEXED			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	29	31	29
TOTAL PRIMARY TUMORS	42	43	46
TOTAL ANIMALS WITH BENIGN TUMORS	13	18	20
TOTAL BENIGN TUMORS	21	22	26
TOTAL ANIMALS WITH MALIGNANT TUMORS	19	18	18
TOTAL MALIGNANT TUMORS	21	20	18
TOTAL ANIMALS WITH SECONDARY TUMORS##	4	2	3
TOTAL SECONDARY TUMORS	4	2	3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	2
TOTAL UNCERTAIN TUMORS		1	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED TRISODIUM PHOSPHATE: VEHICLE CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	105	080	095	102	095	105	105	051	062	105	105	105	105	105	105	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+
Fibroma			X																						
Fibrosarcoma					X	X																			
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																									
Alveolar/bronchiolar adenoma																							X		
Alveolar/bronchiolar carcinoma	X	X																				X		X	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS										X															
Thymus	−	+	+	−	−	−	−	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	−	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma					X				X																
Hepatocellular carcinoma			X				X					X													
Hemangioma																									
Hemangiosarcoma																									
Angiosarcoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																						X			
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																			X						
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Pheochromocytoma	X																								
Thyroid	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																					X	X			
Follicular cell carcinoma																								X	
Parathyroid	+	+	+	+	−	+	+	−	+	−	+	−	−	−	+	−	+	−	+	+	−	−	−	−	−
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS								X																	
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																							X		
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS																									
Malignant lymphoma, undiffer type									X																
Malignant lymphoma, mixed type																			X						
Foot, NOS																									
Fibroma																									

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed

: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

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

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	105	105	105	096	105	105	079	105	105	105	105	105	105	105	092	087	105	105	105	100	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma			X																							2
Fibrosarcoma			X												X	X							X			6
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic		X																	X							2
Alveolar/bronchiolar adenoma											X															2
Alveolar/bronchiolar carcinoma													X	X												6
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, NOS																										1
Thymus	+	−	+	+	+	+	−	+	+	−	+	−	+	+	−	−	+	+	−	−	+	−	+	−	+	31
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X									X											X			X		6
Hepatocellular carcinoma		X					X					X					X		X					X		9
Hemangioma																						X				1
Hemangiosarcoma																				X						1
Angiosarcoma																		X								1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma			X											X												3
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	−	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urethra	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																										1
ENDOCRINE SYSTEM																										
Pituitary	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS	X																								X	2
Pheochromocytoma																						X				2
Thyroid	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Follicular cell adenoma																										2
Follicular cell carcinoma																										1
Parathyroid	−	−	−	+	+	+	+	−	−	−	−	−	−	−	+	−	−	+	+	+	−	+	+	+	+	24
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	48
Prostate	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																		X				X				3
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS							X																			1
Malignant lymphoma, undiffer type																										1
Malignant lymphoma, mixed type																										1
Foot, NOS																										
Fibroma		X																								1

* Animals necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED TRISODIUM PHOSPHATE: LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	093	095	104	104	104	104	105	104	105	104	105	093	102	099	096	105	105	104	105	086	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+
Carcinoma, NOS																									
Squamous cell carcinoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+
Malignant melanoma																									
Fibroma																									
Fibrosarcoma		X																							
Neurofibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic									X					X											
Alveolar/bronchiolar adenoma			X						X								X			X					
Alveolar/bronchiolar carcinoma	X													X											
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma metastatic	X																								
Hemangioma															X										
Thymus	−	−	−	+	+	−	+	+	−	−	−	−	+	+	−	+	−	+	+	−	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma								X	X																
Hepatocellular carcinoma	X								X			X		X	X							X	X		
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	N	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma						X																			
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																								X	
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS								X																	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	+	+	−	+	+	+	+	−	+	−	−	−	+	−	+	+	−	+	+	−	+	+	−	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																				X					
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Choroid plexus																									
Carcinoma, NOS	X																								
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																			X	X					
Cystadenoma, NOS											X					X									
BODY CAVITIES																									
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, malignant																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, metastatic																									
Malignant lymphoma, NOS																									
Malignant lymphoma, undiffer type																									
Malignant lymphoma, histiocytic type																									
Malignant lymphoma, mixed type														X											
Intestinal tract																									
Adenocarcinoma, NOS																									

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

ANIMAL NUMBER	06	07	08	09	00	01	02	03	04	05	06	07	08	09	00	01	02	03	04	05	06	07	08	09	00	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	104	104	104	095	104	090	104	104	102	090	104	105	104	104	099	104	104	079	077	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Carcinoma, NOS														X												1
Squamous cell carcinoma		X													X											2
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Malignant melanoma																								X		1
Fibroma										X																1
Fibrosarcoma																										1
Neurofibrosarcoma																	X									1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic								X			X															4
Alveolar/bronchiolar adenoma		X					X					X									X					8
Alveolar/bronchiolar carcinoma																X							X			4
Trachea	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar carcinoma metast																										1
Hemangioma																										1
Thymus	+	−	+	+	−	+	−	+	−	−	−	−	−	−	+	+	+	+	+	+	+	+	+	−	−	28
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma													X								X				X	5
Hepatocellular carcinoma								X			X											X			X	11
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																		X								2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS																										1
Large intestine	+	+	+	+	+	+	+	−	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	45
Adenoma, NOS									X																	2
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																X										1
Pheochromocytoma											X															1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid	+	+	+	+	−	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	36
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Prostate	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	48
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Choroid plexus																										*
Carcinoma, NOS																										1
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS										X																3
Cystadenoma, NOS																										2
BODY CAVITIES																										
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, malignant																							X			1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, metastatic																							X			1
Malignant lymphoma, NOS												X														1
Malignant lymphoma, undiffer type						X																				1
Malignant lymphoma, histiocytic type																				X						1
Malignant lymphoma, mixed type																										1
Intestinal tract																										
Adenocarcinoma, NOS						X																				1

* Animals necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED TRISODIUM PHOSPHATE: HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	104	102	076	104	102	087	104	104	053	104	104	104	104	104	104	104	104	104	104	104	104	104	041	092	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurofibrosarcoma		X			X																				
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic						X																			
Alveolar/bronchiolar adenoma	X							X		X	X							X	X						
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Angiosarcoma			X																						
Malignant lymphoma, undiffer type															X										
Lymph nodes	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Malignant lymphoma, mixed type																									
Thymus	+	−	+	−	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	−	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma	X		X		X					X			X		X										
Hepatocellular carcinoma						X								X				X							
Malignant lymphoma, histiocytic type									X																
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+
Pancreas	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Adenoma, NOS																									
Adrenal	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																				X					
Cortical adenoma											X														X
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	+	−	+	+	−	−	+	+	−	−	+	+	−	−	+	−	−	−	−	−	−	+	+	−
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, lymphocytic type																X									
Malignant lymphoma, mixed type	X																	X							

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

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	092	104	087	104	074	088	104	071	104	104	029	104	104	056	104	104	104	104	104	102	046	059	098	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	*50
Neurofibrosarcoma																										2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	49
Hepatocellular carcinoma, metastatic					X			X																		3
Alveolar/bronchiolar adenoma																										6
Alveolar/bronchiolar carcinoma																						X				1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	49
Hemangiosarcoma								X																		1
Angiosarcoma																										1
Malignant lymphoma, undiffer type																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	46
Malignant lymphoma, mixed type																									X	1
Thymus	+	+	+	+	+	+	+	−	−	−	+	+	−	+	+	+	−	+	+	−	+	−	−	−	−	34
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma							X					X			X			X							X	11
Hepatocellular carcinoma	X				X			X																	X	7
Malignant lymphoma, histiocytic type																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	N	+	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	46
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	48
Adenoma, NOS															X											1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS														X					X							3
Cortical adenoma																			X							3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	49
Parathyroid	−	−	+	−	+	−	+	−	−	+	+	+	−	−	−	−	−	−	+	+	+	+	+	−	+	23
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	48
Prostate	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	48
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, lymphocytic type			X												X											3
Malignant lymphoma, mixed type									X																	3

* Animals necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED TRISODIUM PHOSPHATE: VEHICLE CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	065	098	095	087	095	089	105	105	105	105	105	105	105	105	105	105	105	105	105	096	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																						X			
Hemangiosarcoma																							X		
Osteosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma									X																
Alveolar/bronchiolar carcinoma								X																	
Pheochromocytoma, metastatic																									
Osteosarcoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																							X		
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma			X					X		X															X
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma metastatic																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
Adenoma, NOS		X							X		X							X							X
Adrenal	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
Follicular cell adenoma																									
Parathyroid	+	+	−	+	+	−	−	+	+	+	+	−	−	−	+	−	−	+	−	+	+	+	−	−	−
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	N	+	N	+	+	N	N	N	+	+	N	+	N	+	N	+	N	+	+	N	+	N
Fibroadenoma			X																						
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																									X
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
NERVOUS SYSTEM																									
Brain	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS		X																							
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS, metastatic		X																							
Malignant lymphoma, undifferentiated type							X																		
Malignant lymphoma, lymphocytic type																	X			X	X	X			
Malignant lymphoma, histiocytic type				X																					
Malignant lymphoma, mixed type						X																			

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed

: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

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

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	105	068	092	105	096	105	065	105	102	105	065	078	073	105	105	105	078	105	093	078	105	105	086	101	105	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																										1
Hemangiosarcoma																										1
Osteosarcoma							X																			1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X									X									3
Alveolar/bronchiolar carcinoma										X	X															3
Pheochromocytoma, metastatic																								X		1
Osteosarcoma, metastatic							X																			1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Lymph nodes	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	48
Thymus	+	−	+	+	−	+	+	+	−	+	−	−	−	+	−	+	+	+	−	+	+	+	+	+	+	40
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma								X							X											6
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	46
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma metastat											X															1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	45
Adenoma, NOS						X								X	X											8
Adrenal	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma, malignant																								X		1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	48
Follicular cell adenoma														X												1
Parathyroid	+	+	−	+	+	−	−	+	−	+	+	−	+	+	+	+	+	−	−	+	+	−	+	−	−	28
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	N	N	N	+	N	N	N	+	N	N	N	+	+	+	N	+	N	+	N	N	N	+	N	*50
Fibroadenoma														X												2
Uterus	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endometrial stromal polyp																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	48
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS, metastatic																										1
Malignant lymphoma, undiffer type						X																				2
Malignant lymphoma, lymphocytic type	X																									5
Malignant lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type			X						X												X					4

* Animals necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED TRISODIUM PHOSPHATE: LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	098	105	084	096	070	088	084	105	083	098	093	105	089	077	105	070	105	105	105	105	065	105	105	099
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									X
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X																		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS				X																					
Thymus	+	+	+	−	−	−	−	−	+	+	−	+	+	+	+	+	+	+	+	−	+	+	−	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma	X								X															X	
Hepatocellular carcinoma																									
Hemangiosarcoma																	X								
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Large intestine	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	−	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS							X		X		X				X						X			X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS			X										X												
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	+	+	+	−	−	+	+	+	+	+	+	+	+	−	+	−	−	+	+	−	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	+	N	+	N	N	N	N	N	N	+	N	N	+	N	N	+	+	N	N	N	N	N
Fibroadenoma						X																			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma	X																								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Luteoma																					X				
Tubular adenoma																				X					
Teratoma, NOS																						X			
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Neoplasm, NOS, metastatic																									
Osteosarcoma, metastatic																									
Malignant lymphoma, NOS														X											
Malignant lymphoma, undiffer type																			X						
Malignant lymphoma, lymphocytic type	X																								
Malignant lymphoma, mixed type										X						X					X				

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

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	083	073	072	105	102	105	073	061	084	088	075	077	087	099	105	082	087	087	074	105	089	089	093	102	105	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS					X							X					X									4
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																					X					2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, NOS																										1
Thymus	+	−	−	+	+	+	+	−	−	+	+	−	−	−	+	−	−	−	−	+	+	+	+	+	+	31
CIRCULATORY SYSTEM																										
Heart	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma				X	X														X						X	7
Hepatocellular carcinoma																								X		1
Hemangiosarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	N	+	+	+	N	N	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	45
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	44
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS	X																			X						8
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																										2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid	+	+	+	+	+	−	−	−	+	+	−	+	+	+	+	+	+	+	−	−	+	−	+	+	−	36
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	+	+	+	+	N	N	+	N	N	N	N	N	N	+	N	N	+	N	N	N	+	+	*50
Fibroadenoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Luteoma																										1
Tubular adenoma																										1
Teratoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Neoplasm, NOS, metastatic														X												1
Osteosarcoma, metastatic	X																									1
Malignant lymphoma, NOS									X										X							3
Malignant lymphoma, undiffer type																										1
Malignant lymphoma, lymphocytic type		X			X																				X	4
Malignant lymphoma, mixed type				X																						4

* Animals necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED TRISODIUM PHOSPHATE: HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	098	105	053	105	105	086	087	075	105	077	105	068	105	083	105	072	105	105	081	105	094	095	095	105	013
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																				X					
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic																		X							
Adenocarcinoma, NOS, metastatic										X															
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma	X																								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, undifferentiated type																									
Thymus	−	+	+	+	+	+	−	−	+	+	+	−	+	−	+	−	+	−	−	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma									X		X											X			
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	N	+	+	+	+	N	+	+	+	N	+	+	N	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS								X																	
Large intestine	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS		X		X																X			X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS									X																
Fibrosarcoma, invasive																				X					
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma													X												
Parathyroid	+	−	+	−	−	+	+	+	−	+	+	−	−	+	−	+	+	+	−	+	+	+	+	+	−
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	N	N	N	N	N	+	+	+	N	+	+	+	N	N	+	N	+	N	+	N	N	N
Adenocarcinoma, NOS										X															
Fibroadenoma																						X			
Uterus	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary cystadenoma, NOS									X																
Granulosa cell tumor									X																
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																		X				X			
Adenoma, NOS																									
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangioma																X									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, undiffer type																							X		
Malignant lymphoma, lymphocytic type			X			X							X												
Malignant lymphoma, histiocytic type																									
Malignant lymphoma, mixed type				X							X														

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

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	079	105	083	071	105	085	070	105	072	105	069	079	091	105	089	105	105	105	105	105	101	074	095	076	090	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, metastatic																										1
Adenocarcinoma, NOS, metastatic																										1
Alveolar/bronchiolar adenoma	X															X										2
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	46
Spleen	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, undiffer type																X										1
Thymus	−	+	−	−	+	+	−	+	−	+	−	+	+	+	−	+	+	−	+	+	−	+	+	−	−	31
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma													X				X									5
Hepatocellular carcinoma		X																								1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	+	N	N	+	N	N	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	−	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Esophagus	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	46
Adenocarcinoma, NOS																										1
Large intestine	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	47
Adenoma, NOS		X			X			X		X			X	X						X						11
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																										1
Fibrosarcoma, invasive																										1
Thyroid	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma																				X						2
Parathyroid	−	−	−	+	+	−	−	−	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	−	−	31
Pancreatic islets	−	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Islet cell adenoma		X																								1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	+	+	N	N	N	N	N	+	N	+	N	N	+	+	+	+	N	N	N	+	N	*50
Adenocarcinoma, NOS																										1
Fibroadenoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Papillary cystadenoma, NOS																										1
Granulosa cell tumor																X										2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										2
Adenoma, NOS																						X				1
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangioma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, undiffer type																										1
Malignant lymphoma, lymphocytic type			X																X							5
Malignant lymphoma, histiocytic type																					X					1
Malignant lymphoma, mixed type										X																3

* Animals necropsied

APPENDIX B

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED TRISODIUM PHOSPHATE

TABLE B1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED TRISODIUM PHOSPHATE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST	1 (2%)		
INFLAMMATION, NECROTIZING	4 (8%)	3 (6%)	4 (8%)
INFLAMMATION, ACUTE		1 (2%)	1 (2%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
FIBROSIS		1 (2%)	
NECROSIS, NOS	1 (2%)	1 (2%)	1 (2%)
NECROSIS, FOCAL		1 (2%)	
HYPERTROPHY, NOS		1 (2%)	
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, BASAL CELL		1 (2%)	
*SUBCUTANEOUS TISSUE	(50)	(50)	(50)
MINERALIZATION	1 (2%)		
EPIDERMAL INCLUSION CYST			1 (2%)
INFLAMMATION, NOS	2 (4%)		1 (2%)
INFLAMMATION, ACUTE		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC	†4 (8%)	2 (4%)	3 (6%)
FIBROSIS	3 (6%)	1 (2%)	3 (6%)
OSTEOARTHRITIS	1 (2%)		
NECROSIS, NOS	1 (2%)	3 (6%)	1 (2%)
METAPLASIA, OSSEOUS	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(50)	(50)	(49)
INFLAMMATION, NOS			1 (2%)
#LUNG/BRONCHIOLE	(50)	(50)	(49)
METAPLASIA, NOS	1 (2%)		
#LUNG	(50)	(50)	(49)
MINERALIZATION	2 (4%)		
CONGESTION, NOS	2 (4%)	5 (10%)	1 (2%)
HEMORRHAGE	7 (14%)	7 (14%)	3 (6%)
INFLAMMATION, NOS		3 (6%)	1 (2%)
INFLAMMATION, ACUTE	2 (4%)	1 (2%)	1 (2%)
INFLAMMATION, ACUTE FOCAL			1 (2%)
INFLAMMATION, ACUTE/CHRONIC	2 (4%)	1 (2%)	1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	
PNEUMONIA INTERSTITIAL CHRONIC		1 (2%)	
NECROSIS, NOS		2 (4%)	
INFARCT, NOS		1 (2%)	
ALVEOLAR MACROPHAGES	3 (6%)	8 (16%)	3 (6%)
HYPERPLASIA, EPITHELIAL	1 (2%)	3 (6%)	3 (6%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
HEMATOPOIESIS	7 (14%)	12 (24%)	3 (6%)
MYELOID METAPLASIA	2 (4%)	2 (4%)	2 (4%)
#BONE MARROW	(49)	(49)	(47)
HEMATOPOIESIS	3 (6%)	1 (2%)	
#SPLEEN	(50)	(49)	(49)
ANGIECTASIS	2 (4%)		1 (2%)
HYPERPLASIA, LYMPHOID	2 (4%)	2 (4%)	3 (6%)
HEMATOPOIESIS	23 (46%)	12 (24%)	15 (31%)
#SPLENIC CAPSULE	(50)	(49)	(49)
ADHESION, NOS			1 (2%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED TRISODIUM PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#LYMPH NODE	(50)	(48)	(46)
INFLAMMATION, NOS	1 (2%)	1 (2%)	
ANGIECTASIS	25 (50%)	30 (63%)	17 (37%)
PLASMACYTOSIS	1 (2%)	2 (4%)	
HYPERPLASIA, LYMPHOID	1 (2%)	1 (2%)	1 (2%)
MASTOCYTOSIS	1 (2%)		
HEMATOPOIESIS	11 (22%)	16 (33%)	14 (30%)
#LIVER	(50)	(50)	(50)
HEMATOPOIESIS	4 (8%)	2 (4%)	
#PEYER'S PATCH	(50)	(49)	(47)
HYPERPLASIA, LYMPHOID	13 (26%)	13 (27%)	7 (15%)
CIRCULATORY SYSTEM			
*FOOT	(50)	(50)	(50)
THROMBOSIS, NOS	1 (2%)		
#LUNG	(50)	(50)	(49)
THROMBOSIS, NOS		1 (2%)	
#HEART	(50)	(50)	(49)
THROMBUS, MURAL			1 (2%)
INFLAMMATION, GRANULOMATOUS			1 (2%)
*AORTA	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
PERIVASCULITIS	1 (2%)		
*PANCREATIC ARTERY	(50)	(50)	(50)
PERIVASCULITIS			1 (2%)
#LIVER	(50)	(50)	(50)
THROMBOSIS, NOS	2 (4%)	2 (4%)	
DIGESTIVE SYSTEM			
*INTESTINAL TRACT	(50)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
NECROSIS, NOS		1 (2%)	
#LIVER	(50)	(50)	(50)
MINERALIZATION	1 (2%)	2 (4%)	3 (6%)
CONGESTION, NOS	1 (2%)		
INFLAMMATION, ACUTE	1 (2%)		
ABSCESS, NOS		1 (2%)	
NECROSIS, NOS	1 (2%)	3 (6%)	3 (6%)
NECROSIS, FOCAL	4 (8%)	11 (22%)	12 (24%)
NECROSIS, ISCHEMIC	3 (6%)	7 (14%)	1 (2%)
INFARCT, NOS			1 (2%)
METAMORPHOSIS, FATTY	1 (2%)	3 (6%)	9 (18%)
CYTOPLASMIC CHANGE, NOS		1 (2%)	
FOCAL CELLULAR CHANGE		2 (4%)	
EOSINOPHILIC CYTO CHANGE	1 (2%)		
CLEAR-CELL CHANGE	2 (4%)	1 (2%)	1 (2%)
ANGIECTASIS	4 (8%)		1 (2%)
*GALLBLADDER	(50)	(50)	(50)
INFLAMMATION, NOS		2 (4%)	1 (2%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
#PANCREAS	(50)	(49)	(48)
DILATATION/DUCTS		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	
FIBROSIS	1 (2%)	1 (2%)	
METAPLASIA, SQUAMOUS		1 (2%)	

TABLE B1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED TRISODIUM PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#PANCREATIC ACINUS	(50)	(49)	(48)
ATROPHY, NOS	1 (2%)	2 (4%)	1 (2%)
ATROPHY, FOCAL			1 (2%)
HYPERTROPHY, FOCAL	1 (2%)		
HYPERPLASIA, NOS			1 (2%)
#STOMACH	(50)	(50)	(50)
MINERALIZATION		1 (2%)	
INFLAMMATION, NOS	3 (6%)	3 (6%)	
INFLAMMATION, ACUTE		2 (4%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	1 (2%)
NECROSIS, NOS	1 (2%)		
NECROSIS, FOCAL	1 (2%)		
HYPERPLASIA, BASAL CELL		1 (2%)	
HYPERKERATOSIS	2 (4%)	3 (6%)	
ACANTHOSIS		1 (2%)	
ANGIECTASIS		1 (2%)	
#FORESTOMACH	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL			1 (2%)
HYPERKERATOSIS	2 (4%)	1 (2%)	1 (2%)
*RECTUM	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
NECROSIS, NOS		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
MINERALIZATION	16 (32%)	27 (54%)	33 (66%)
HYDRONEPHROSIS	1 (2%)		1 (2%)
INFLAMMATION, NOS	1 (2%)		
INFLAMMATION, ACUTE		1 (2%)	3 (6%)
PYELONEPHRITIS, NOS	1 (2%)		
NEPHROPATHY	6 (12%)	5 (10%)	6 (12%)
DEGENERATION, NOS	1 (2%)		
GLOMERULOSCLEROSIS, NOS	1 (2%)		
#RENAL PAPILLA	(50)	(50)	(50)
MINERALIZATION			3 (6%)
NECROSIS, NOS			2 (4%)
#KIDNEY/TUBULE	(50)	(50)	(50)
MINERALIZATION		1 (2%)	1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
DEGENERATION, NOS	2 (4%)	2 (4%)	2 (4%)
NECROSIS, NOS	1 (2%)		1 (2%)
ANGIECTASIS	1 (2%)		
#KIDNEY/PELVIS	(50)	(50)	(50)
NECROSIS, NOS		1 (2%)	
#URINARY BLADDER	(50)	(50)	(49)
CALCULUS,UNKN GROSS OR MICRO	6 (12%)	3 (6%)	2 (4%)
INFLAMMATION, ACUTE			1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)	1 (2%)	
NECROSIS, NOS			1 (2%)
HYPERPLASIA, EPITHELIAL			1 (2%)
*PROSTATIC URETHRA	(50)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(47)	(45)	(48)
HYPERPLASIA, NOS	1 (2%)	1 (2%)	1 (2%)
#PITUITARY INTERMEDIA	(47)	(45)	(48)
HYPERTROPHY, FOCAL		1 (2%)	
#ADRENAL	(49)	(50)	(49)
CYST, NOS	1 (2%)		

TABLE B1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED TRISODIUM PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#ADRENAL/CAPSULE	(49)	(50)	(49)
HYPERPLASIA, NOS	27 (55%)	11 (22%)	22 (45%)
#ADRENAL CORTEX	(49)	(50)	(49)
HYPERTROPHY, NOS	3 (6%)	2 (4%)	2 (4%)
HYPERTROPHY, FOCAL			1 (2%)
HYPERPLASIA, NOS	3 (6%)	1 (2%)	
#ADRENAL MEDULLA	(49)	(50)	(49)
HYPERPLASIA, NOS	11 (22%)	4 (8%)	2 (4%)
#THYROID	(47)	(50)	(49)
FOLLICULAR CYST, NOS	1 (2%)	2 (4%)	
INFLAMMATION, NOS	1 (2%)		
INFLAMMATION, CHRONIC	2 (4%)		
HYPERPLASIA, FOLLICULAR-CELL	3 (6%)	1 (2%)	3 (6%)
REPRODUCTIVE SYSTEM			
*PREPUCE	(50)	(50)	(50)
INFLAMMATION, NECROTIZING	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
HYPERKERATOSIS	1 (2%)		
*PREPUTIAL GLAND	(50)	(50)	(50)
MINERALIZATION		3 (6%)	1 (2%)
EPIDERMAL INCLUSION CYST	1 (2%)		
CYSTIC DUCTS	4 (8%)	3 (6%)	
INFLAMMATION, NOS	6 (12%)	3 (6%)	
INFLAMMATION, NECROTIZING	1 (2%)		1 (2%)
ABSCESS, NOS	2 (4%)	5 (10%)	3 (6%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)	7 (14%)	7 (14%)
NECROSIS, NOS	3 (6%)		1 (2%)
HYPERPLASIA, NOS	1 (2%)	3 (6%)	1 (2%)
HYPERKERATOSIS	4 (8%)	3 (6%)	2 (4%)
#PROSTATE	(48)	(48)	(48)
HEMORRHAGE			1 (2%)
INFLAMMATION, NOS	3 (6%)		1 (2%)
INFLAMMATION, NECROTIZING			1 (2%)
INFLAMMATION, ACUTE			1 (2%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
FIBROSIS			1 (2%)
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)		
#TESTIS	(48)	(46)	(48)
MINERALIZATION	3 (6%)	2 (4%)	4 (8%)
ATROPHY, NOS			2 (4%)
#TESTIS/TUBULE	(48)	(46)	(48)
MINERALIZATION			3 (6%)
ATROPHY, FOCAL		1 (2%)	
NERVOUS SYSTEM			
*CHOROID PLEXUS	(50)	(50)	(50)
HYPERPLASIA, NOS		1 (2%)	
#BRAIN	(50)	(50)	(49)
MINERALIZATION		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
CALCIFICATION, FOCAL			1 (2%)
#CEREBELLUM	(50)	(50)	(49)
METAMORPHOSIS FATTY		1 (2%)	

TABLE B1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED TRISODIUM PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
INFLAMMATION, NOS	1 (2%)	1 (2%)	
MUSCULOSKELETAL SYSTEM			
*RIB	(50)	(50)	(50)
NECROSIS, NOS		1 (2%)	
BODY CAVITIES			
*PERITONEUM	(50)	(50)	(50)
NECROSIS, FAT			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
CONGESTION, NOS			2 (4%)
INFLAMMATION, NOS	1 (2%)	1 (2%)	
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
FIBROSIS	1 (2%)		
ANGIECTASIS			1 (2%)
LEG			
OSTEOARTHRITIS	1		
OMENTUM			
MINERALIZATION	1		
INFLAMMATION, ACUTE/CHRONIC			1
FIBROSIS			1
NECROSIS, FAT	1		
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED			1

* NUMBER OF ANIMALS RECEIVING COMPLETE NECROPSY EXAMINATION; ALL GROSS LESIONS INCLUDING MASSES EXAMINED MICROSCOPICALLY.
# NUMBER OF ANIMALS EXAMINED MICROSCOPICALLY AT THIS SITE
† MULTIPLE OCCURRENCE OF MORPHOLOGY IN THE SAME ORGAN; TISSUE IS COUNTED ONCE ONLY.

TABLE B2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED TRISODIUM PHOSPHATE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
HYPERPLASIA, NOS	1 (2%)		
*SUBCUTANEOUS TISSUE	(50)	(50)	(50)
MINERALIZATION	1 (2%)		
INFLAMMATION, NECROTIZING		1 (2%)	
NECROSIS, NOS	1 (2%)	1 (2%)	
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(50)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, FOCAL			1 (2%)
#LUNG	(50)	(50)	(50)
CONGESTION, NOS		1 (2%)	
HEMORRHAGE	3 (6%)	4 (8%)	
INFLAMMATION, NOS	3 (6%)	1 (2%)	2 (4%)
INFLAMMATION, ACUTE		1 (2%)	
NECROSIS, NOS			1 (2%)
ALVEOLAR MACROPHAGES	6 (12%)		1 (2%)
HYPERPLASIA, EPITHELIAL			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
LEUKEMOID REACTION			1 (2%)
HEMATOPOIESIS	14 (28%)	25 (50%)	25 (50%)
MYELOID METAPLASIA	2 (4%)	2 (4%)	1 (2%)
#SPLEEN	(49)	(49)	(48)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
FIBROSIS		1 (2%)	
ADHESION, NOS		1 (2%)	
NECROSIS, NOS	1 (2%)	1 (2%)	
ANGIECTASIS	1 (2%)		
HYPERPLASIA, LYMPHOID	4 (8%)	1 (2%)	1 (2%)
HEMATOPOIESIS	16 (33%)	12 (24%)	13 (27%)
MYELOID METAPLASIA		1 (2%)	
#LYMPH NODE	(48)	(49)	(49)
INFLAMMATION, NOS	2 (4%)	5 (10%)	3 (6%)
LYMPHOID DEPLETION			1 (2%)
ANGIECTASIS	3 (6%)	3 (6%)	1 (2%)
PLASMACYTOSIS	2 (4%)	5 (10%)	7 (14%)
HYPERPLASIA, LYMPHOID			2 (4%)
HEMATOPOIESIS	2 (4%)	2 (4%)	
#LIVER	(50)	(50)	(50)
HEMATOPOIESIS	1 (2%)	2 (4%)	1 (2%)
MYELOID METAPLASIA		1 (2%)	
#PEYER'S PATCH	(46)	(48)	(46)
HYPERPLASIA, LYMPHOID	6 (13%)	4 (8%)	5 (11%)
#OVARY	(48)	(50)	(48)
PLASMACYTOSIS	1 (2%)		
#THYMUS	(40)	(31)	(31)
NECROSIS, NOS			1 (3%)
LYMPHOID DEPLETION			1 (3%)
HYPERPLASIA, LYMPHOID			1 (3%)

TABLE B2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED TRISODIUM PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
#HEART	(50)	(49)	(50)
MINERALIZATION	1 (2%)		1 (2%)
ENDOCARDITIS, BACTERIAL		2 (4%)	
FIBROSIS	1 (2%)		
#LIVER	(50)	(50)	(50)
THROMBOSIS, NOS		1 (2%)	1 (2%)
#STOMACH	(50)	(48)	(49)
PERIVASCULITIS		1 (2%)	
#KIDNEY	(50)	(50)	(50)
PERIVASCULITIS		1 (2%)	
#UTERUS	(49)	(50)	(49)
THROMBOSIS, NOS			1 (2%)
#OVARY	(48)	(50)	(48)
THROMBOSIS, NOS		1 (2%)	
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(50)	(48)	(48)
HYPERTROPHY, NOS	1 (2%)		
#LIVER	(50)	(50)	(50)
HEMORRHAGE	1 (2%)		
INFLAMMATION, NOS	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
FIBROSIS			1 (2%)
NECROSIS, NOS			1 (2%)
NECROSIS, FOCAL	12 (24%)	8 (16%)	5 (10%)
NECROSIS, ISCHEMIC	1 (2%)	7 (14%)	3 (6%)
INFARCT, NOS			1 (2%)
METAMORPHOSIS FATTY	3 (6%)	7 (14%)	1 (2%)
CYTOPLASMIC CHANGE, NOS		4 (8%)	
FOCAL CELLULAR CHANGE	2 (4%)		
CLEAR-CELL CHANGE	1 (2%)		
ANGIECTASIS		4 (8%)	
#PANCREAS	(48)	(49)	(46)
HEMORRHAGE		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
NECROSIS, NOS		1 (2%)	
ANGIECTASIS			1 (2%)
#PANCREATIC ACINUS	(48)	(49)	(46)
ATROPHY, NOS	1 (2%)	5 (10%)	3 (7%)
HYPERPLASIA, NOS	2 (4%)	1 (2%)	
#STOMACH	(50)	(48)	(49)
MINERALIZATION			1 (2%)
INFLAMMATION, NOS	1 (2%)	1 (2%)	
HYPERPLASIA, EPITHELIAL			1 (2%)
HYPERKERATOSIS	1 (2%)	4 (8%)	3 (6%)
#GLANDULAR STOMACH	(50)	(48)	(49)
INFLAMMATION, NOS		1 (2%)	
FIBROSIS		1 (2%)	
HYPERPLASIA, NOS		1 (2%)	1 (2%)
#FORESTOMACH	(50)	(48)	(49)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)	2 (4%)
HYPERKERATOSIS	8 (16%)	9 (19%)	10 (20%)
ACANTHOSIS		2 (4%)	1 (2%)
#PEYER'S PATCH	(46)	(48)	(46)
NECROSIS, FOCAL	1 (2%)		

TABLE B2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED TRISODIUM PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
MINERALIZATION	2 (4%)	6 (12%)	1 (2%)
HYDRONEPHROSIS	2 (4%)		
CONGESTION, NOS		1 (2%)	
GLOMERULONEPHRITIS, NOS	7 (14%)	12 (24%)	8 (16%)
PYELONEPHRITIS, NOS		3 (6%)	1 (2%)
INFLAMMATION, NOS	2 (4%)		
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
FIBROSIS, DIFFUSE		1 (2%)	
NEPHROPATHY	3 (6%)	1 (2%)	
GLOMERULOSCLEROSIS, NOS	2 (4%)		2 (4%)
METAPLASIA, OSSEOUS		1 (2%)	2 (4%)
#RENAL PAPILLA	(50)	(50)	(50)
MINERALIZATION	3 (6%)		2 (4%)
INFLAMMATION, ACUTE		1 (2%)	
DEGENERATION, NOS			1 (2%)
NECROSIS, NOS		3 (6%)	
#KIDNEY/TUBULE	(50)	(50)	(50)
DEGENERATION, NOS	3 (6%)		2 (4%)
#URINARY BLADDER/MUSCULARIS	(49)	(49)	(48)
INFLAMMATION, ACUTE FOCAL		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(45)	(48)	(47)
CYST, NOS			1 (2%)
HYPERPLASIA, NOS	7 (16%)	9 (19%)	3 (6%)
HYPERPLASIA, FOCAL		1 (2%)	
ANGIECTASIS	3 (7%)	5 (10%)	2 (4%)
#ADRENAL	(48)	(50)	(50)
CONGESTION, NOS		1 (2%)	
#ADRENAL/CAPSULE	(48)	(50)	(50)
HYPERPLASIA, NOS	33 (69%)	31 (62%)	23 (46%)
#ADRENAL CORTEX	(48)	(50)	(50)
NECROSIS, NOS	1 (2%)		
HYPERTROPHY, NOS			1 (2%)
#ADRENAL MEDULLA	(48)	(50)	(50)
HYPERPLASIA, NOS	1 (2%)	1 (2%)	
#THYROID	(48)	(49)	(48)
INFLAMMATION, CHRONIC	1 (2%)		
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)		3 (6%)
#PANCREATIC ISLETS	(48)	(49)	(46)
HYPERPLASIA, NOS			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
NECROSIS, NOS		1 (2%)	
#UTERUS	(49)	(50)	(49)
HYDROMETRA	26 (53%)	13 (26%)	21 (43%)
INFLAMMATION, NOS	6 (12%)	2 (4%)	4 (8%)
INFLAMMATION, NECROTIZING		1 (2%)	
ABSCESS, NOS		1 (2%)	1 (2%)
NECROSIS, NOS		2 (4%)	
POLYP		1 (2%)	

TABLE B2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED TRISODIUM PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)			
#UTERUS/ENDOMETRIUM	(49)	(50)	(49)
HEMORRHAGE		1 (2%)	
HYPERPLASIA, NOS	1 (2%)	3 (6%)	1 (2%)
HYPERPLASIA, CYSTIC	30 (61%)	16 (32%)	22 (45%)
#OVARY	(48)	(50)	(48)
MINERALIZATION		1 (2%)	2 (4%)
EPIDERMAL INCLUSION CYST			1 (2%)
PAROVARIAN CYST	6 (13%)	7 (14%)	6 (13%)
HEMORRHAGE			1 (2%)
HEMORRHAGIC CYST	1 (2%)		
INFLAMMATION, NOS	1 (2%)		
ABSCESS, NOS	10 (21%)	20 (40%)	24 (50%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)	1 (2%)	
NECROSIS, NOS	1 (2%)		
CALCIFICATION, NOS		1 (2%)	
ANGIECTASIS		1 (2%)	1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
INFLAMMATION, NOS			2 (4%)
FIBROSIS			1 (2%)
NECROSIS, NOS	1 (2%)		2 (4%)
MUSCULOSKELETAL SYSTEM			
*COSTOCHONDRAL SYNCHO	(50)	(50)	(50)
INFLAMMATION, NECROTIZING		1 (2%)	
BODY CAVITIES			
*THORACIC CAVITY	(50)	(50)	(50)
INFLAMMATION, NECROTIZING		1 (2%)	1 (2%)
*ABDOMINAL CAVITY	(50)	(50)	(50)
MINERALIZATION			1 (2%)
INFLAMMATION, NECROTIZING		1 (2%)	4 (8%)
*PERITONEUM	(50)	(50)	(50)
INFLAMMATION, NOS	2 (4%)	4 (8%)	6 (12%)
*PLEURA	(50)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		
INFLAMMATION, NECROTIZING		1 (2%)	1 (2%)
*PERICARDIUM	(50)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		

TABLE B2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED TRISODIUM PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
INFLAMMATION, NOS	4 (8%)	10 (20%)	10 (20%)
INFLAMMATION, NECROTIZING		2 (4%)	1 (2%)
BACTERIAL SEPTICEMIA	1 (2%)		
AMYLOIDOSIS	1 (2%)		
OMENTUM			
NECROSIS, FAT	1	1	
SPECIAL MORPHOLOGY SUMMARY			
NONE			

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

APPENDIX C

ANALYSES OF PRIMARY TUMORS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED TRISODIUM PHOSPHATE

TABLE C1. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED TRISODIUM PHOSPHATE

	Vehicle Control	500 mg/kg	1,000 mg/kg
Skin: Carcinoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	0.0%	7.4%	0.0%
Terminal Rates (c)	0/39 (0%)	1/36 (3%)	0/32 (0%)
Life Table Tests (d)	P=0.595	P=0.119	(e)
Incidental Tumor Tests (d)	P=0.632	P=0.152	(e)
Cochran-Armitage Trend Test (d)	P=0.640		
Fisher Exact Test		P=0.121	(e)
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	6/50 (12%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	13.5%	2.3%	0.0%
Terminal Rates (c)	2/39 (5%)	0/36 (0%)	0/32 (0%)
Life Table Tests (d)	P=0.008N	P=0.070N	P=0.032N
Incidental Tumor Tests (d)	P=0.003N	P=0.026N	P=0.019N
Cochran-Armitage Trend Test (d)	P=0.005N		
Fisher Exact Test		P=0.056N	P=0.013N
Subcutaneous Tissue: Fibroma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (a)	7/50 (14%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	15.9%	7.8%	5.7%
Terminal Rates (c)	3/39 (8%)	2/36 (6%)	0/32 (0%)
Life Table Tests (d)	P=0.084N	P=0.188N	P=0.135N
Incidental Tumor Tests (d)	P=0.054N	P=0.108N	P=0.095N
Cochran-Armitage Trend Test (d)	P=0.049N		
Fisher Exact Test		P=0.159N	P=0.080N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	2/50 (4%)	8/50 (16%)	6/49 (12%)
Adjusted Rates (b)	5.1%	21.1%	18.8%
Terminal Rates (c)	2/39 (5%)	7/36 (19%)	6/32 (19%)
Life Table Tests (d)	P=0.068	P=0.038	P=0.078
Incidental Tumor Tests (d)	P=0.074	P=0.037	P=0.078
Cochran-Armitage Trend Test (d)	P=0.121		
Fisher Exact Test		P=0.046	P=0.128
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	6/50 (12%)	4/50 (8%)	1/49 (2%)
Adjusted Rates (b)	15.4%	9.2%	2.9%
Terminal Rates (c)	6/39 (15%)	1/36 (3%)	0/32 (0%)
Life Table Tests (d)	P=0.073N	P=0.405N	P=0.095N
Incidental Tumor Tests (d)	P=0.058N	P=0.334N	P=0.098N
Cochran-Armitage Trend Test (d)	P=0.044N		
Fisher Exact Test		P=0.370N	P=0.059N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	8/50 (16%)	12/50 (24%)	7/49 (14%)
Adjusted Rates (b)	20.5%	28.8%	21.1%
Terminal Rates (c)	8/39 (21%)	8/36 (22%)	6/32 (19%)
Life Table Tests (d)	P=0.481	P=0.189	P=0.563
Incidental Tumor Tests (d)	P=0.505N	P=0.223	P=0.558
Cochran-Armitage Trend Test (d)	P=0.467N		
Fisher Exact Test		P=0.227	P=0.517N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	0.0%	0.0%	8.7%
Terminal Rates (c)	0/39 (0%)	0/36 (0%)	2/32 (6%)
Life Table Tests (d)	P=0.027	(e)	P=0.092
Incidental Tumor Tests (d)	P=0.035	(e)	P=0.112
Cochran-Armitage Trend Test (d)	P=0.037		
Fisher Exact Test		(e)	P=0.121

TABLE C1. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED TRISODIUM PHOSPHATE (Continued)

	Vehicle Control	500 mg/kg	1,000 mg/kg
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	1/50 (2%)	1/50 (2%)	4/50 (8%)
Adjusted Rates (b)	2.6%	2.5%	11.9%
Terminal Rates (c)	1/39 (3%)	0/36 (0%)	3/32 (9%)
Life Table Tests (d)	P=0.073	P=0.749	P=0.131
Incidental Tumor Tests (d)	P=0.062	P=0.707N	P=0.126
Cochran-Armitage Trend Test (d)	P=0.101		
Fisher Exact Test		P=0.753N	P=0.181
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	4/50 (8%)	4/50 (8%)	9/50 (18%)
Adjusted Rates (b)	9.0%	10.3%	24.7%
Terminal Rates (c)	2/39 (5%)	2/36 (6%)	6/32 (19%)
Life Table Tests (d)	P=0.047	P=0.616	P=0.073
Incidental Tumor Tests (d)	P=0.099	P=0.564	P=0.149
Cochran-Armitage Trend Test (d)	P=0.078		
Fisher Exact Test		P=0.643N	P=0.117
Circulatory System: Hemangioma, Hemangiosarcoma, or Angiosarcoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	7.4%	2.4%	4.9%
Terminal Rates (c)	2/39 (5%)	0/36 (0%)	0/32 (0%)
Life Table Tests (d)	P=0.464N	P=0.331N	P=0.574N
Incidental Tumor Tests (d)	P=0.302N	P=0.218N	P=0.403N
Cochran-Armitage Trend Test (d)	P=0.399N		
Fisher Exact Test		P=0.309N	P=0.500N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	6/50 (12%)	5/50 (10%)	11/50 (22%)
Adjusted Rates (b)	14.8%	13.9%	29.6%
Terminal Rates (c)	5/39 (13%)	5/36 (14%)	7/32 (22%)
Life Table Tests (d)	P=0.051	P=0.552N	P=0.076
Incidental Tumor Tests (d)	P=0.092	P=0.515N	P=0.129
Cochran-Armitage Trend Test (d)	P=0.102		
Fisher Exact Test		P=0.500N	P=0.143
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	9/50 (18%)	11/50 (22%)	7/50 (14%)
Adjusted Rates (b)	21.5%	25.9%	18.3%
Terminal Rates (c)	7/39 (18%)	6/36 (17%)	3/32 (9%)
Life Table Tests (d)	P=0.511N	P=0.361	P=0.543N
Incidental Tumor Tests (d)	P=0.445N	P=0.491	P=0.474N
Cochran-Armitage Trend Test (d)	P=0.348N		
Fisher Exact Test		P=0.401	P=0.393N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	14/50 (28%)	14/50 (28%)	17/50 (34%)
Adjusted Rates (b)	32.9%	33.3%	42.6%
Terminal Rates (c)	11/39 (28%)	9/36 (25%)	10/32 (31%)
Life Table Tests (d)	P=0.144	P=0.517	P=0.168
Incidental Tumor Tests (d)	P=0.231	P=0.508N	P=0.280
Cochran-Armitage Trend Test (d)	P=0.293		
Fisher Exact Test		P=0.588N	P=0.333
Stomach: Squamous Cell Papilloma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	7.7%	5.6%	0.0%
Terminal Rates (c)	3/39 (8%)	2/36 (6%)	0/32 (0%)
Life Table Tests (d)	P=0.111N	P=0.537N	P=0.158N
Incidental Tumor Tests (d)	P=0.111N	P=0.537N	P=0.158N
Cochran-Armitage Trend Test (d)	P=0.082N		
Fisher Exact Test		P=0.500N	P=0.121N

TABLE C1. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED TRISODIUM PHOSPHATE (Continued)

	Vehicle Control	500 mg/kg	1,000 mg/kg
Adrenal: Cortical Adenoma			
Overall Rates (a)	0/49 (0%)	1/50 (2%)	3/49 (6%)
Adjusted Rates (b)	0.0%	2.8%	9.4%
Terminal Rates (c)	0/39 (0%)	1/36 (3%)	3/32 (9%)
Life Table Tests (d)	P=0.042	P=0.484	P=0.088
Incidental Tumor Tests (d)	P=0.042	P=0.484	P=0.088
Cochran-Armitage Trend Test (d)	P=0.060		
Fisher Exact Test		P=0.505	P=0.121
Adrenal Capsule: Adenoma			
Overall Rates (a)	2/49 (4%)	0/50 (0%)	3/49 (6%)
Adjusted Rates (b)	5.1%	0.0%	9.4%
Terminal Rates (c)	2/39 (5%)	0/36 (0%)	3/32 (9%)
Life Table Tests (d)	P=0.321	P=0.256N	P=0.410
Incidental Tumor Tests (d)	P=0.321	P=0.256N	P=0.410
Cochran-Armitage Trend Test (d)	P=0.390		
Fisher Exact Test		P=0.242N	P=0.500
Thyroid: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	3/47 (6%)	0/50 (0%)	0/49 (0%)
Adjusted Rates (b)	8.1%	0.0%	0.0%
Terminal Rates (c)	3/37 (8%)	0/36 (0%)	0/32 (0%)
Life Table Tests (d)	P=0.045N	P=0.126N	P=0.147N
Incidental Tumor Tests (d)	P=0.045N	P=0.126N	P=0.147N
Cochran-Armitage Trend Test (d)	P=0.034N		
Fisher Exact Test		P=0.110N	P=0.113N
Harderian Gland: Adenoma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	7.7%	7.5%	0.0%
Terminal Rates (c)	3/39 (8%)	2/36 (6%)	0/32 (0%)
Life Table Tests (d)	P=0.137N	P=0.634	P=0.158N
Incidental Tumor Tests (d)	P=0.126N	P=0.631	P=0.158N
Cochran-Armitage Trend Test (d)	P=0.101N		
Fisher Exact Test		P=0.661	P=0.121N
Harderian Gland: Adenoma or Cystadenoma			
Overall Rates (a)	3/50 (6%)	5/50 (10%)	0/50 (0%)
Adjusted Rates (b)	7.7%	13.0%	0.0%
Terminal Rates (c)	3/39 (8%)	4/36 (11%)	0/32 (0%)
Life Table Tests (d)	P=0.185N	P=0.322	P=0.158N
Incidental Tumor Tests (d)	P=0.173N	P=0.319	P=0.158N
Cochran-Armitage Trend Test (d)	P=0.133N		
Fisher Exact Test		P=0.357	P=0.121N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill.
(d) Beneath the vehicle control incidence are the P values associated with the trend tests. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the vehicle control and dosed groups.

TABLE C2. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED TRISODIUM PHOSPHATE

	Vehicle Control	500 mg/kg	1,000 mg/kg
Subcutaneous Tissue: Sarcoma, NOS			
Overall Rates (a)	0/50 (0%)	4/50 (8%)	0/50 (0%)
Adjusted Rates (b)	0.0%	15.1%	0.0%
Terminal Rates (c)	0/30 (0%)	0/16 (0%)	0/21 (0%)
Life Table Tests (d)	P=0.519	P=0.032	(e)
Incidental Tumor Tests (d)	P=0.588N	P=0.124	(e)
Cochran-Armitage Trend Test (d)	P=0.622		
Fisher Exact Test		P=0.059	(e)
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	8.7%	6.8%	7.3%
Terminal Rates (c)	2/30 (7%)	0/16 (0%)	1/21 (5%)
Life Table Tests (d)	P=0.535N	P=0.677N	P=0.619N
Incidental Tumor Tests (d)	P=0.324N	P=0.371N	P=0.482N
Cochran-Armitage Trend Test (d)	P=0.406N		
Fisher Exact Test		P=0.500N	P=0.500N
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted Rates (b)	8.5%	0.0%	4.3%
Terminal Rates (c)	2/30 (7%)	0/16 (0%)	0/21 (0%)
Life Table Tests (d)	P=0.259N	P=0.203N	P=0.410N
Incidental Tumor Tests (d)	P=0.224N	P=0.175N	P=0.368N
Cochran-Armitage Trend Test (d)	P=0.176N		
Fisher Exact Test		P=0.121N	P=0.309N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	6/50 (12%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	17.0%	6.8%	11.3%
Terminal Rates (c)	4/30 (13%)	0/16 (0%)	1/21 (5%)
Life Table Tests (d)	P=0.307N	P=0.305N	P=0.393N
Incidental Tumor Tests (d)	P=0.149N	P=0.105N	P=0.268N
Cochran-Armitage Trend Test (d)	P=0.169N		
Fisher Exact Test		P=0.134N	P=0.243N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	5/50 (10%)	4/50 (8%)	5/50 (10%)
Adjusted Rates (b)	15.8%	19.2%	16.6%
Terminal Rates (c)	4/30 (13%)	2/16 (13%)	2/21 (10%)
Life Table Tests (d)	P=0.365	P=0.456	P=0.434
Incidental Tumor Tests (d)	P=0.491	P=0.564	P=0.619
Cochran-Armitage Trend Test (d)	P=0.568		
Fisher Exact Test		P=0.500N	P=0.630N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	4/50 (8%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (b)	11.1%	20.9%	14.3%
Terminal Rates (c)	1/30 (3%)	3/16 (19%)	3/21 (14%)
Life Table Tests (d)	P=0.518	P=0.365	P=0.619
Incidental Tumor Tests (d)	P=0.469N	P=0.578N	P=0.486N
Cochran-Armitage Trend Test (d)	P=0.424N		
Fisher Exact Test		P=0.643N	P=0.500N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	12/50 (24%)	13/50 (26%)	11/50 (22%)
Adjusted Rates (b)	33.2%	50.0%	39.6%
Terminal Rates (c)	7/30 (23%)	6/16 (38%)	6/21 (29%)
Life Table Tests (d)	P=0.288	P=0.106	P=0.345
Incidental Tumor Tests (d)	P=0.501N	P=0.542	P=0.537N
Cochran-Armitage Trend Test (d)	P=0.453N		
Fisher Exact Test		P=0.500	P=0.500N

TABLE C2. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORINATED TRISODIUM PHOSPHATE (Continued)

	Vehicle Control	500 mg/kg	1,000 mg/kg
Liver: Hepatocellular Adenoma			
Overall Rates (a)	6/50 (12%)	7/50 (14%)	5/50 (10%)
Adjusted Rates (b)	18.9%	36.6%	20.5%
Terminal Rates (c)	5/30 (17%)	5/16 (31%)	3/21 (14%)
Life Table Tests (d)	P=0.408	P=0.131	P=0.510
Incidental Tumor Tests (d)	P=0.480	P=0.192	P=0.600
Cochran-Armitage Trend Test (d)	P=0.439N		
Fisher Exact Test		P=0.500	P=0.500N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	6/50 (12%)	8/50 (16%)	6/50 (12%)
Adjusted Rates (b)	18.9%	40.3%	24.9%
Terminal Rates (c)	5/30 (17%)	5/16 (31%)	4/21 (19%)
Life Table Tests (d)	P=0.280	P=0.073	P=0.365
Incidental Tumor Tests (d)	P=0.341	P=0.130	P=0.449
Cochran-Armitage Trend Test (d)	P=0.558		
Fisher Exact Test		P=0.387	P=0.620
Pituitary: Adenoma			
Overall Rates (a)	8/45 (18%)	8/48 (17%)	10/47 (21%)
Adjusted Rates (b)	26.4%	34.3%	46.3%
Terminal Rates (c)	7/29 (24%)	4/16 (25%)	8/19 (42%)
Life Table Tests (d)	P=0.089	P=0.214	P=0.100
Incidental Tumor Tests (d)	P=0.150	P=0.438	P=0.131
Cochran-Armitage Trend Test (d)	P=0.381		
Fisher Exact Test		P=0.552N	P=0.437
Harderian Gland: Adenoma or Carcinoma			
Overall Rates (a)	1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	3.0%	0.0%	10.6%
Terminal Rates (c)	0/30 (0%)	0/16 (0%)	1/21 (5%)
Life Table Tests (d)	P=0.128	P=0.581N	P=0.214
Incidental Tumor Tests (d)	P=0.141	P=0.477N	P=0.250
Cochran-Armitage Trend Test (d)	P=0.176		
Fisher Exact Test		P=0.500N	P=0.309

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill.
(d) Beneath the vehicle control incidence are the P values associated with the trend tests. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the 1,000 mg/kg and vehicle control group.

APPENDIX D

CHEMICAL CHARACTERIZATION OF CHLORINATED TRISODIUM PHOSPHATE

APPENDIX D. CHEMICAL CHARACTERIZATION

I. Identity and Purity Determinations of Lot No. QJOK6 Performed by the Analytical Chemistry Laboratory

A. Physical properties

Appearance: Fluffy, colorless solid

B. Spectral data

	Determined	Literature Values
1. Infrared		
Instrument:	Beckman IR-12	
Cell:	Nujol mull between sodium chloride plates	
Results:	See Figure 3	No literature spectrum was found. Consistent with a compound containing ionic phosphate.
2. Ultraviolet/visible		
Instrument:	Cary 118	
Solvent:	Water	
Results:	λ_{max} (nm) / ε_{max}: 291.5 / 0.189 ± 0.008 (δ)	No literature spectrum was found. Consistent with the proposed structure and composition.

C. Titrations

1. Hypochlorite (available chlorine)

Method: Oxidation of added I^- to I_2 by OCl^-, and titration of I_2 generated with standardized $S_2O_3^{2-}$

Results (as Cl_2): Four titrations indicated 3.57% ± 0.02 (δ)%

2. Phosphate as P_2O_5

Method: Potentiometric titration of the $H_2PO_4^-$ ion with 1 N NaOH

Results: Four titrations indicated a concentration of 17.68% ± 0.04 (δ)%

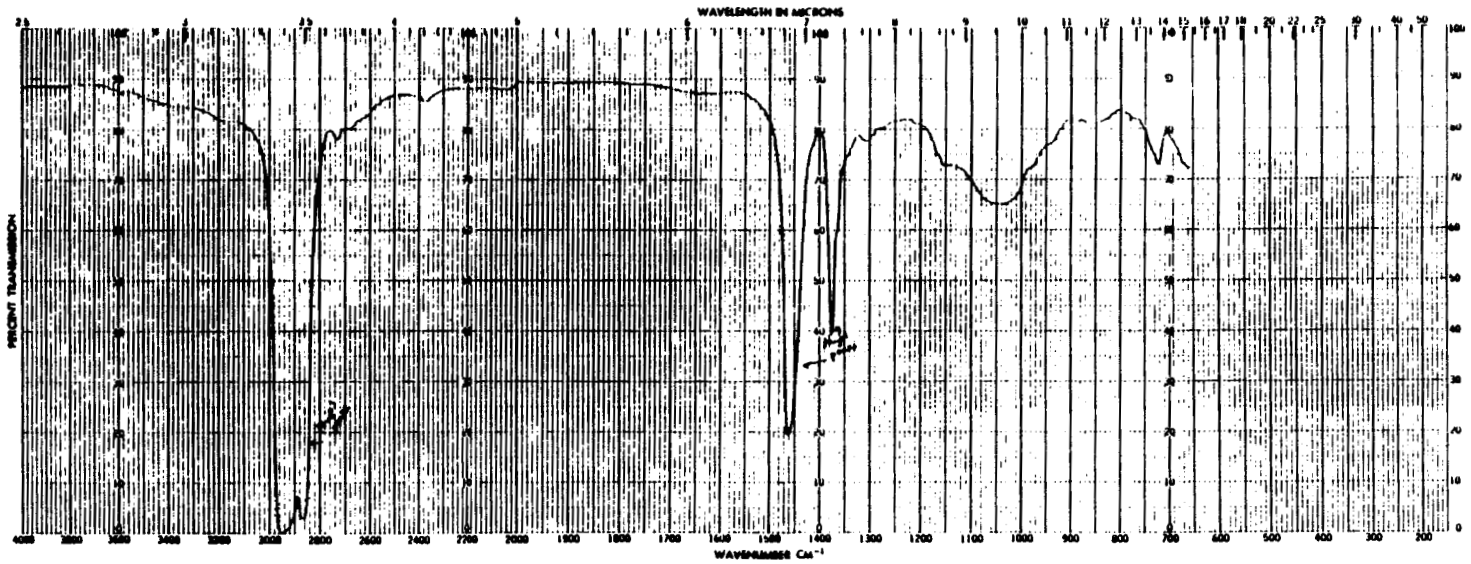

FIGURE 3. INFRARED ABSORPTION SPECTRUM OF CHLORINATED TRISODIUM PHOSPHATE (LOT NO. QJOK6)

D. Water analysis (Karl Fischer): 52.6% ± 0.7 (δ)%

E. Elemental analysis

Element	Phosphorus (percent)	Hydrogen (percent)	Sodium (percent)	Chlorine (percent)
Manufacturer's specifications	7.48	5.84	19.62	4.57
Determined	7.90	5.42	18.32	4.72
	7.62	5.57	18.40	4.91

F. Spark source mass spectrometry--element concentrations in parts per million (ppm) by weight (a)

Uranium	58	Rubidium	8.2
Lead	4.9	Bromine	14
Rhenium	Internal standard	Arsenic	<0.61
Tungsten	<0.62	Nickel	0.50
Tantalum	(b) 0.51	Iron	53
Hafnium	<1.1	Vanadium	21
Samarium	<0.66	Calcium	51
Neodymium	<0.58	Potassium	690
Praseodymium	0.74	Chlorine	Major
Lanthanum	1.2	Sulfur	≃1,600
Barium	5.9	Phosphorus	Major
Cesium	0.37	Silicon	530
Iodine	51	Aluminum	16
Indium	Internal standard	Magnesium	100
Molybdenum	2.0	Sodium	Major
Niobium	0.56	Fluorine	450
Strontium	<0.51	Boron	25
Lithium	3.2	Beryllium	<0.80

(a) All not listed are present at less than 0.5 ppm.
(b) Possible source contamination

G. Summary of analytical data: Based on the manufacturer's specifications, the elemental analyses were high for phosphorus and chlorine and low for hydrogen and sodium. Spark source mass spectrometry indicated that the major impurities were sulfur, potassium, fluorine, silicon, and magnesium. The range of these impurities was 0.01%-0.30% (w/w). The water content was 52.6% ± 0.7 (δ)% by Karl Fischer titrimetry. Titrations indicated an available chlorine (as Cl_2) concentration of 3.57% ± 0.02 (δ)% and a phosphorus content (as P_2O_5) of 17.7% ± 0.04 (δ)%. (Manufacturer's quote for a typical lot is 3.68% available chlorine and 18.00% phosphorus as P_2O_5.) Infrared and ultraviolet/visible spectra were consistent with the proposed composition.

II. Stability Study of Lot No. QJOK6 Performed by the Analytical Chemistry Laboratory

A. Sample storage: Samples were stored for 2 weeks in 4-oz amber jars with Poly-Seal® lids at temperatures of −20°, 5°, 25°, or 60° C.

B. Analytical method: Three samples from each storage temperature were analyzed by two titrimetric methods (see I.C.1.a. and I.C.2.a.).

C. Results

Storage Temperature	Percent Compound (normalized to −20° C sample--P_2O_5)	Percent Compound (normalized to −20° C sample--available Cl_2)
−20° C	100.0 ± 1.0	100.0 ± 2.1
5° C	99.7 ± 1.0	101.0 ± 2.1
25° C	100.1 ± 1.0	100.4 ± 2.1
60° C	Not determined	2.9 ± 2.1

D. Conclusions: The compound was stable, when stored as the bulk chemical, for 2 weeks at temperatures up to 25° C. The compound was unstable at 60° C, losing chlorine. At 60° C, the solid compound liquefied. This phenomenon was probably caused by a change of the water of hydration into water of solution, with Cl_2 being lost more readily in this state.

III. Stability Study of Lot No. QJOK6 Performed by the Study Laboratory

Periodic reanalysis of study and reference samples of the chemical by infrared spectroscopy confirmed the identity and gross purity of the chemical during storage at the study laboratory. Reanalysis by titration showed that the bulk chlorinated trisodium phosphate underwent no decomposition but the reference sample stored at −20° C lost chlorine. Results are summarized below.

Date	Percent Chlorine	
	Bulk	Reference
8/2/79	3.40	Bulk received 6/22/79
10/29/79	3.42	2.31
2/27/80	3.41	2.16
5/28/80	3.41	2.83
9/30/80	3.39	2.10
1/23/81	3.36	3.16
5/21/81	3.27	2.60
9/18/81	3.16	2.68
1/20/82	3.24	2.59
5/26/82	3.29	2.49

IV. Special Bulk Chemical Studies

Because analyses at the study laboratory indicated a drop in the available chlorine content for the −20° C sample relative to the material stored at room temperature, analysis of Midwest Research Institute's −20° C reference sample was performed to determine if a decrease in available chlorine had occurred since the original analysis. Analysis of the −20° C reference samples stored at Midwest Research Institute indicated no change in the available chlorine content since the original analysis (i.e., 3.68% ± 0.07 (δ)%; 3.57% ± 0.02 (δ)% originally). Therefore, no definitive explanation for the lower values of reference standards can be given. However, whatever happened to the reference material must have occurred during the initial sampling, since no measurable change could be seen for all subsequent analyses. Despite the difference from the reference sample data, the bulk chemical showed no change throughout the toxicity studies.

APPENDIX E

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

Studies Conducted at the Analytical Chemistry Laboratory

I. Stability Study Parameters

Concentration: 122 mg/ml
Vehicle: Water
Duration: 14 days
Temperature: 5° C, room temperature
Analysis times: 25° C storage; 0, 0 + 3 hours, 1, 7, 13, and 14 days
5° C storage; 0, 7, and 14 days

II. Sample Preparation and Storage

A 122.0-g quantity of chlorinated trisodium phosphate was dissolved in about 750 ml of water and diluted to 1,000 ml. After the solution was thoroughly mixed, eight 60-ml septum vials were filled with approximately 35 ml of the solution. One of the vials was used for the zero-time analyses, and another was left open and exposed to light at room temperature for 3 hours before being analyzed.

The remaining six vials were sealed and subdivided into two groups. Four vials were stored in the dark at room temperature (~25° C) for analysis after 1, 7, 13, and 14 days' storage. The remaining two vials were stored in the dark at 5° C for analysis after 7 and 14 days' storage.

Available chlorine determination: On each analysis day, one of the septum vials was opened. An 8.0-ml aliquot of study solution, equivalent to 0.976 g of chlorinated trisodium phosphate, was pipetted into a 250-ml Erlenmeyer flask and diluted with 25 ml of distilled water.

Potassium iodide solution (10 ml of 10% (w/v) solution) was added while the solution was being stirred; then 5 ml of dilute hydrochloric acid (1:1) was added. The liberated iodine was titrated immediately with standardized sodium thiosulfate solution until most of the iodine was consumed (light yellow in solution).

Starch solution (3 ml, 1% w/v) was added, and the titration was continued until the blue color was completely discharged.

The percent available chlorine in the sample was calculated as:

$$\text{Percent available chlorine} = \frac{\text{milliliters thiosulfate} \times \text{normality} \times 35.45 \times 100}{\text{grams of sample used} \times 1{,}000}$$

III. Quality Control Protocols

Sample analyses were run in triplicate on each test day. The normality of the sodium thiosulfate was determined in quadruplicate initially and was monitored by checking the normality in triplicate on each test day. In order to minimize sampling variations, the same pipette was used to draw samples at each testing period.

IV. Results

	14-Day Stability in Water (percent available chlorine)	Percent Recovery Relative to Zero-Time Sample
Storage time at room temperature (days)		
0	3.543 ± 0.013	100.0 ± 0.37
0 + 3 h exposure to air and light	3.514 ± 0.012	99.2 ± 0.34
1	3.529 ± 0.017	99.6 ± 0.48
7	3.515 ± 0.005	99.2 ± 0.14
13	3.527 ± 0.003	99.5 ± 0.09
14	3.526 ± 0.007	99.5 ± 0.20
Storage time at 5° C (days)		
7	3.512 ± 0.002	99.1 ± 0.06
13	3.530 ± 0.005	99.6 ± 0.14
14	3.537 ± 0.010	99.8 ± 0.28

V. Conclusion

A water gavage solution of chlorinated trisodium phosphate at a concentration of 12.2% w/v showed about 0.5% loss of available chlorine after 14 days' storage at room temperature in the dark. Since this loss was approximately equal to the test error (0.6%), it was not considered significant. Exposure to light for 3 hours at ambient temperature was equivalent to 2 weeks' storage in the dark.

APPENDIX F

METHODS OF ANALYSIS OF DOSE MIXTURES

APPENDIX F. METHODS OF ANALYSIS

I. Study Laboratory

A. Procedure through 5/7/81

Duplicate volumes of 5 ml, 10 ml, and 20 ml from the 100, 50, and 25 mg/ml formulations, respectively, were used for analysis. The variable volumes were calculated to provide approximately 0.5 g of the study compound for determining available chlorine by titrating with standardized 0.1 N $Na_2S_2O_3$ solution.

B. Procedure from 6/26/81

Duplicate 1-ml aliquots were diluted to 25 ml with water in 25-ml volumetric flasks and mixed. The absorbance of the samples and standards were measured in 1-cm quartz cells at 292 nm in the Perkin-Elmer Lambda 3® spectrophotometer.

II. Analytical Chemistry Laboratory

A. Preparation of standard spiked water: Two working standard solutions of chlorinated trisodium phosphate in distilled water were prepared independently. These solutions were further diluted with distilled water to make standard solutions bracketing the specified dose range of the referee sample. One 500-ml volumetric flask containing 5 ml of undosed water was treated with 5 ml of distilled water for use as a blank. The spiked waters and the water blank were analyzed immediately by the procedure described below.

B. Preparation of the referee sample: Three portions (5 ml each) of the dosed referee water sample were transferred to volumetric flasks. Distilled water (5 ml) was pipetted into each flask; then the referee samples were analyzed immediately by the procedure described below.

C. Analysis procedure: Each sample was diluted to volume with distilled water and thoroughly mixed. The chlorinated trisodium phosphate content of the samples was determined by reading the absorbance of the solutions at 292 nm on a Cary 118 or 219 spectrophotometer in 1-cm quartz cells versus distilled water.

D. Quality assurance measures: The dosed referee water sample was analyzed in triplicate, and the water blank sample was analyzed once. Individually spiked portions of undosed water (six levels) prepared from two independently weighed standards were used for obtaining standard curve data. The dosed referee water samples, spiked water standards, and water blank sample were all extracted and analyzed by the same procedure.

Results were computed from the linear regression equation obtained by plotting the absorbance of each spiked water sample versus the milligrams of chemical in the respective spiked water sample. The linearity of the standard curve data was evaluated by the regression equation.

APPENDIX G

RESULTS OF ANALYSIS OF DOSE MIXTURES

TABLE G1. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK GAVAGE STUDIES OF CHLORINATED TRISODIUM PHOSPHATE (a)

Target concentration (mg/ml)	6.2	12.5	25	50	100	200
Determined concentration (mg/ml)	5.8	12.0	24.4	49.3	101.5	194.5

(a) Date mixed: 9/17/79

TABLE G2. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED TRISODIUM PHOSPHATE (a)

Date Mixed	Concentration (a) of Chlorinated Trisodium Phosphate in Water for Target Concentration (mg/ml)			
	25 mg/ml	50 mg/ml	100 mg/ml	200 mg/ml
06/27/80	24.3	(b) 23.7	99.5	194.0
07/02/80		(c) 49.5		
07/25/80	24.6	48.9	100.4	196.0
10/03/80	(b) 1.9	49.6	101.3	
10/08/80	(c) 25.1			
12/05/80	23.9	48.6	98.3	
01/02/81	24.8	49.8	99.4	
04/10/81		49.0	100.4	
05/07/81		48.3	101.7	
06/26/81		50.5	99.7	
09/25/81		52.3	101.9	
11/27/81		48.1	97.3	
12/23/81		49.0	100.3	
02/26/82		51.8	100.7	
04/23/82		49.3	98.8	
05/28/82		48.4	100.3	
Mean (mg/ml)	19.9	47.7	100.0	195.0
Range (mg/ml)	1.9-24.8	23.7-52.3	97.3-101.9	194.0-196.0
Standard deviation	10.07	7.01	1.29	1.41
Coefficient of variation (percent)	50.6	14.7	1.3	0.7
Number of samples	5	14	14	2

(a) Results of duplicate analysis
(b) Out of specifications. Remixed.
(c) Remix. Not included in mean.

TABLE G3. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED TRISODIUM PHOSPHATE

Date Mixed	Target Concentration (mg/ml)	Concentration Found (mg/ml)	
		Study Laboratory	Referee Laboratory
07/25/80	50	48.9	50.69
12/05/80	25	23.9	22.66
05/07/81	100	101.7	101.9
11/27/81	50	48.1	48.9
05/28/82	100	100.3	101.2

APPENDIX H

SENTINEL ANIMAL PROGRAM

APPENDIX H. SENTINEL ANIMAL PROGRAM

I. Methods

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

Fifteen $B6C3F_1$ mice 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. Data from animals surviving 24 months were collected from 5/50 randomly selected control animals of each sex. The blood from each animal is collected and clotted, and the serum is separated. The serum is cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral antibody titers. The following tests are performed:

	Hemagglutination Inhibition	Complement Fixation	ELISA
Mice	PVM (pneumonia virus of mice) Reo 3 (reovirus type 3) GDVII (Theiler's encephalomyelitis virus) Poly (polyoma virus) MVM (minute virus of mice) Ectro (infectious ectromelia) Sendai	M.Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus)	MHV (mouse hepatitis virus)

II. Results

TABLE H1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORINATED TRISODIUM PHOSPHATE (a)

Interval (months)	No. of Animals	Positive Serologic Reaction for
6	10/10	PVM
	10/10	Sendai
12	1/10	Reo 3
	7/7	Sendai
18	5/6	PVM
	5/6	Sendai
24	6/6	Sendai
	6/10	MHV

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

APPENDIX I

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

Meal Diet: March 1980-April 1982

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

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
Brewer's dried yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Pre-mixes (vitamins and minerals) (c)	0.25

(a) Prepared according to NIH, 1978; NCI, 1976
(b) Ingredients ground to pass through a U.S. Standard Screen #16 before mixing.
(c) Details given in Table I2

TABLE I2. VITAMINS AND MINERALS IN NIH 07 RATION (a)

	Amount	Source
Vitamins		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D_3	4,600,000 IU	D-activated animal sterol
K_3	2.8 g	Menadione activity
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	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	*d*-Biotin
Minerals		
Cobalt	0.4 g	Cobalt carbonate
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide

(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	No of Samples
Crude protein (percent by weight)	24.30 ± 1.04	22.9 - 26.3	24
Crude fat (percent by weight)	4.92 ± 0.43	4.4 - 6.0	24
Crude fiber (percent by weight)	3.36 ± 0.59	1.4 - 4.2	24
Ash (percent by weight)	6.71 ± 0.44	5.97 - 7.42	24
Vitamins			
Vitamin A (IU/kg)	10,800 ± 2,250	7,900 - 17,000	24
Vitamin D (IU/kg)	6,300		(a) 1
α-Tocopherol (ppm)	37.6	31.1 - 44.0	(a) 2
Thiamine (ppm)	17.3 ± 0.61	7.3 - 26.0	(b) 23
Riboflavin (ppm)	6.9	6.1 - 7.4	(a) 2
Niacin (ppm)	75	65 - 85	(a) 2
Pantothenic acid (ppm)	30.2	29.8 - 30.5	(a) 2
Pyridoxine (ppm)	7.2	5.6 - 8.8	(a) 2
Folic acid (ppm)	2.1	1.8 - 2.4	(a) 2
Biotin (ppm)	0.24	0.21 - 0.27	(a) 2
Vitamin B_{12} (ppb)	12.8	10.6 - 15.0	(a) 2
Choline (ppm)	3,315	3,200 - 3,430	(a) 2
Minerals			
Calcium	1.30 ± 0.20	0.81 - 1.6	24
Phosphorus	1.01 ± 0.09	0.82 - 1.10	24
Potassium	0.809	0.772 - 0.846	(a) 2
Chloride	0.557	0.479 - 0.635	(a) 2
Sodium	0.304	0.258 - 0.349	(a) 2
Magnesium	0.172	0.166 - 0.177	(a) 2
Sulfur	0.278	0.270 - 0.285	(a) 2
Iron (ppm)	418	409 - 426	(a) 2
Manganese (ppm)	90.8	86.0 - 95.5	(a) 2
Zinc (ppm)	55.1	54.2 - 56.0	(a) 2
Copper (ppm)	12.68	9.65 - 15.70	(a) 2
Iodine (ppm)	2.58	1.52 - 3.64	(a) 2
Chromium (ppm)	1.86	1.79 - 1.93	(a) 2
Cobalt (ppm)	0.57	0.49 - 0.65	(a) 2
Essential Amino Acids			
Arginine	1.260	1.21 - 1.31	(a) 2
Cystine	0.395	0.39 - 0.40	(a) 2
Glycine	1.175	1.15 - 1.20	(a) 2
Histidine	0.553	0.530 - 0.576	(a) 2
Isoleucine	0.908	0.881 - 0.934	(a) 2
Leucine	1.905	1.85 - 1.96	(a) 2
Lysine	1.250	1.20 - 1.30	(a) 2
Methionine	0.310	0.306 - 0.314	(a) 2
Phenylalanine	0.967	0.960 - 0.974	(a) 2
Threonine	0.834	0.827 - 0.840	(a) 2
Tryptophan	0.175	0.171 - 0.178	(a) 2
Tyrosine	0.587	0.566 - 0.607	(a) 2
Valine	1.085	1.05 - 1.12	(a) 2
Essential Fatty Acids			
Linoleic	2.37		(a) 1
Linolenic	0.308		(a) 1
Arachidonic	0.008		(a) 1

(a) Analyses were done on batches of diet manufactured in January and/or April 1983.
(b) One batch was not analyzed for thiamine.

TABLE I4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminant	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.36 ± 0.18	<0.05 - 0.93	24
Cadmium (ppm) (a)	0.11	<0.1-0.40	24
Lead (ppm)	1.03 ± 0.61	0.57 - 2.62	24
Mercury (ppm) (b)	<0.05		24
Selenium (ppm)	0.29 ± 0.08	0.10 - 0.48	24
Aflatoxins (ppb) (b,c)	<10		24
Nitrate nitrogen (ppm) (d,e)	7.30 ± 4.14	<0.1 - 13.0	24
Nitrite nitrogen (ppm) (d,e)	1.77 ± 1.28	<0.1 - 3.7	24
BHA (ppm) (f,g)	3.51 ± 2.83	<0.4 - 11.0	24
BHT (ppm) (f)	2.72 ± 1.22	1.2 - 5.3	24
Aerobic plate count (CFU/g) (h)	70,896 ± 50,153	7,000 - 210,000	24
Coliform (MPN/g) (i,j)	96 ± 119	<3 - 460	16
Coliform (MPN/g) (k)	593 ± 814	<3-2,400	24
E. coli (MPN/g)	7.50 ± 7.68	<3 - 23	24
Total nitrosamines (ppb) (l)	7.12 ± 6.56	<1.8 - 24.5	22
Total nitrosamines (ppb) (m)	14.93 ± 27.23	<1.8 - 101.6	24
N-Nitrosodimethylamine (ppb) (n)	5.37 ± 5.98	0.7 - 20.0	22
N-Nitrosodimethylamine (ppb) (o)	13.13 ± 26.89	0.7 - 101.6	24
N-Nitrosopyrrolidine (ppb)	1.27 ± 0.80	<0.5 - 3.5	24
Pesticides (ppm)			
α-BHC (b,p)	<0.01		24
β-BHC (b)	<0.02		24
γ-BHC-lindane (b)	<0.01		24
δ-BHC (b)	<0.01		24
Heptachlor (b)	<0.01		24
Aldrin (b)	<0.01		24
Heptachlor epoxide (b)	<0.01		24
DDE (q)	<0.01	0.05 (7/14/81)	24
DDD (b)	<0.01		24
DDT (b)	<0.01		24
HCB (b)	<0.01		24
Mirex (b)	<0.01		24
Methoxychlor (q)	<0.05	0.13 (8/25/81)	24
Dieldrin (b)	<0.01		24
Endrin (b)	<0.01		24
Telodrin (b)	<0.01		24
Chlordane (b)	<0.05		24
Toxaphene (b)	<0.1		24
Estimated PCB's (b)	<0.2		24
Ronnel (b)	<0.01		24
Ethion (b)	<0.02		24
Trithion (b)	<0.05		24
Diazinon (b)	<0.1		24
Methyl parathion (b)	<0.02		24
Ethyl parathion (b)	<0.02		24
Malathion (r)	0.08 ± 0.05	<0.05-0.25	24
Endosulfan I (b)	<0.01		24
Endosulfan II (b)	<0.01		24
Endosulfan sulfate (b)	<0.03		24

TABLE I4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION (Continued)

(a) Two batches contained more than 0.1 ppm.
(b) All values were less than the detection limit given in the table as the mean.
(c) Detection limit reduced from 10 ppb to 5 ppb after 7/81
(d) Source of contamination: alfalfa, grains, and fish meal
(e) Two batches contained less than 0.2 ppm.
(f) Source of contamination: soy oil and fish meal
(g) Three batches contained less than 0.5 ppm.
(h) CFU = colony-forming unit
(i) MPN = most probable number
(j) Mean, standard deviation, and range exclude eight very high values in the range 1,100-2,400 obtained for batches produced on 11/25/80, 12/16/80, 5/26/81, 7/14/81, 9/25/81, 10/23/81, 11/27/81, and 4/26/82
(k) Mean, standard deviation, and range include the values listed in footnote (j).
(l) All values were corrected for percent recovery; mean, standard deviation, and range exclude two very high values of 101.6 and 103.2 ppb for batches produced on 1/26/81 and 4/27/81.
(m) All values were corrected for percent recovery; mean, standard deviation, and range include the two very high values given in footnote (l).
(n) All values were corrected for percent recovery; mean, standard deviation, and range exclude two very high values of 101.6 and 103 ppb for batches produced on 1/26/81 and 4/27/81.
(o) All values were corrected for percent recovery; mean, standard deviation, and range include the two very high values given in footnote (n).
(p) BHC = hexachlorocyclohexane or benzene hexachloride.
(q) One observation was above the detection limit. The value and the date it was obtained are listed under the range.
(r) Eight batches contained more than 0.05 ppm.

APPENDIX J

MUTAGENICITY OF CHLORINATED TRISODIUM PHOSPHATE IN SALMONELLA

TABLE J1. MUTAGENICITY OF CHLORINATED TRISODIUM PHOSPHATE IN SALMONELLA

Strain	Dose (µg/plate)	Revertants/plate (a) −S9	+S9 (rat)	+S9 (hamster)
TA100	0	90 ± 2.6	116 ± 5.2	100 ± 9.2
	10	89 ± 9.0	---	---
	33	74 ± 3.7	---	---
	100	85 ± 2.5	97 ± 8.5	103 ± 0.6
	333	93 ± 4.7	109 ± 3.4	94 ± 8.7
	666	104 ± 10.3	---	---
	1,000	---	116 ± 12.0	117 ± 0.9
	3,333	---	164 ± 6.2	156 ± 1.5
	6,666	---	Toxic	Toxic
TA1535	0	21 ± 2.0	11 ± 0.9	11 ± 0.6
	10	19 ± 1.5	---	---
	33	22 ± 2.6	---	---
	100	18 ± 0.9	12 ± 1.0	8 ± 2.1
	333	21 ± 3.7	12 ± 1.2	15 ± 1.9
	666	25 ± 2.6	---	---
	1,000	---	15 ± 2.2	13 ± 0.6
	3,333	---	17 ± 2.4	32 ± 0.7
	6,666	---	23 ± 4.9	31 ± 2.8
TA97	0	91 ± 4.1	170 ± 13.4	146 ± 5.4
	10	92 ± 6.8	---	---
	33	88 ± 5.4	---	---
	100	87 ± 9.1	164 ± 11.3	144 ± 1.2
	333	92 ± 8.8	184 ± 6.7	134 ± 8.8
	666	92 ± 2.2	---	---
	1,000	---	199 ± 16.4	153 ± 3.2
	3,333	---	232 ± 6.6	165 ± 9.6
	6,666	---	104 ± 5.9	Toxic
TA98	0	18 ± 0.9	24 ± 2.8	25 ± 3.3
	10	22 ± 0.3	---	---
	33	19 ± 2.1	---	---
	100	16 ± 2.1	29 ± 2.7	23 ± 2.1
	333	15 ± 1.7	22 ± 2.0	26 ± 2.6
	666	17 ± 0.3	---	---
	1,000	---	24 ± 2.7	30 ± 0.3
	3,333	---	28 ± 1.7	20 ± 2.0
	6,666	---	13 ± 0.6	Toxic

(a) The S9 fractions were prepared from the liver of Aroclor 1254-induced male Sprague-Dawley rats and male Syrian hamsters. Cells and study compound or solvent (water) were incubated for 20 minutes at 37° C in the presence of either S9 or buffer. After the addition of soft agar, the contents of each tube were poured onto minimal medium, and the plates were incubated at 37° C for 48 hours (Haworth et al., 1983). The analysis was performed twice, each in triplicate; because the results were similar, data from only one experiment are shown. The S9 mix contained 30% S9.

APPENDIX K

HISTORICAL INCIDENCE OF TUMORS IN $B6C3F_1$ MICE

TABLE K1. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN MALE B6C3F$_1$ MICE

Study	Incidence In Vehicle Controls		
	Lymphoma	Leukemia	Lymphoma or Leukemia
Historical Incidence in Animals Administered Water by Gavage			
Pyridine (a)	1/50	0/50	1/50
Chlorinated trisodium phosphate (b)	4/50	0/50	4/50
THPS (c)	2/50	0/50	2/50
	7/150 (4.7%)	0/150 (0%)	7/150 (4.7%)
Overall Historical Incidence in Untreated Animals (d)			
	280/2,343 (12.0%)	17/2,343 (0.7%)	297/2,343 (12.7%)
Range (e)			
High	16/50	5/48	16/50
Low	1/49	0/50	1/49
Overall Historical Incidence in Animals Administered Corn Oil by Gavage (d)			
	126/1,040 (12.1%)	6/1,040 (0.6%)	132/1,040 (12.7%)
Range (e)			
High	11/50	5/48	13/48
Low	1/48	0/50	0/50

(a) Historical incidence at Gulf South Research Institute
(b) Historical incidence at EG&G Mason Research Institute
(c) Historical incidence at Battelle Columbus Laboratories
(d) Data as of March 16, 1983, for studies of at least 104 weeks
(e) Range presented for groups of 35 or more animals.

APPENDIX L

DATA AUDIT SUMMARY

APPENDIX L. DATA AUDIT SUMMARY

An audit was conducted on the archival data and pathology materials for the study of the chronic toxicity of chlorinated trisodium phosphate in mice. The data available on uncompleted studies in rats were also reviewed. These animal studies were performed at EG&G Mason Research Institute, Worcester, Massachusetts, under a subcontract with Tracor Jitco, Inc., from the National Cancer Institute. The 2-year studies were conducted from May 1980 to June 1982 and were initiated before the requirement of compliance to Good Laboratory Practices by NTP in October 1981. The audit was conducted at the NTP Archives, Rockville, Maryland, and involved the following Dynamac personnel: C. Dippel, M.S.; F. Garner, D.V.M.; C. Lunchick, M.S.; J. Plautz, M.S.; C. Sexsmith, B.S.; and P. Wennerberg, D.V.M. Additional participants were : A. Grant (NTP) and M. Pielmeier (Tracor Jitco, Inc.).

The audit consisted of an indepth review of the data and pathology materials collected during the conduct of the studies as well as a review of the correspondence (e.g., protocol and amendments) and 13-week studies. For the inlife toxicology data, this review involved examination of 100% of the records on animal receipt and husbandry, mortality, environmental conditions, sentinel animals, and dosing. Data for 10% of the animals were examined for body weight and clinical observations. In the review of the chemistry portion of the studies, all of the records were examined pertaining to receipt and use of the chemical, analysis of the bulk chemical and dose mixtures by the contract laboratory, and characterization of the bulk chemical and analysis of the dose mixtures by the reference laboratory. The audit of the pathology materials included review of 100% of the Individual Animal Data Records (IADRs) for correlation between gross observations and microscopic diagnoses and for clerical errors, examination of the wet tissues of 10% of the animals for unidentified lesions and correct identification, correlation of slides and tissue blocks for six of the eight groups of mice, and verification of the reported pathologic effects on a 10% sample of the animals.

Review of the toxicology data found some discrepancies regarding recordkeeping practices prevalent at the time the studies were conducted. For example, documentation of the disposition of extra animals, of observations during the quarantine period, and of the randomization of animals was not present. Communication with laboratory personnel confirmed that these operations were carried out according to the study protocol or the laboratory's standard procedures. Not every death was recorded in the inlife records; the laboratory's procedures called for the IADRs to serve as the primary record of mortality. No problems in animal identification or in the collection of body weight or clinical observation data were found. Dosing was performed as required (5 days per week). Environmental conditions were not always within specifications, and the few occasions of high temperatures or low humidity were not associated with any deaths.

Review of the chemistry data identified three minor problems that could not be resolved from the available data. There was no indication in the records that the dose mixtures were mixed continuously during the gavaging of the animals, three of the dose mixtures prepared during the first 4 months of the study did not contain the proper concentration of study material and had to be remixed, and a 2-kg discrepancy was noted between the amount of chemical received by the laboratory and the amount indicated by the shipping label.

Review of the pathology data noted that some gross lesions on the IADRs were not followed by microscopic diagnosis; examination of the microscopic sections found no significant lesions associated with these gross findings, which were mostly changes in color or organ size. Descriptions of 13 of the gross lesions observed suggested that they were neoplastic lesions, but microscropic sections were not available for review. These gross lesions were, in general, evenly distributed among the groups. Few gavage-related deaths occurred in the studies, and the audits of animal identification and slide/block match found no problems. Three other untrimmed lesions were found in wet tissues from organs that were not routinely sampled.

Overall, the audit identified no substantive problems that would have an adverse effect on the studies. Although some problems and discrepancies were identified as discussed in the audit report, these were adequately resolved or were determined not to affect the outcome of the studies. In conclusion, the data examined in this audit are considered adequate to meet the objectives of the studies.

☆U.S. GOVERNMENT PRINTING OFFICE: 1986-181-296:41255