NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 433

TOXICOLOGY AND CARCINOGENESIS STUDIES OF TRICRESYL PHOSPHATE

(CAS NO. 1330-78-5)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE AND FEED STUDIES)

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

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

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

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NTP TECHNICAL REPORT

ON THE

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NATIONAL TOXICOLOGY PROGRAM
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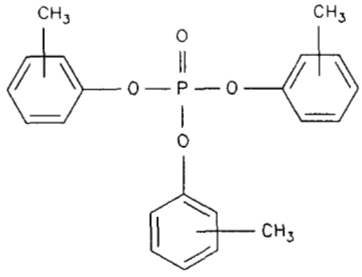
ABSTRACT



TRICRESYL PHOSPHATE

CAS No. 1330-78-5

Chemical Formula: $C_{21}H_{21}O_4P$ Molecular Weight: 368.36

Tricresyl phosphate is an organophosphate plasticizer widely used in vinyl plastics and as a fire retardant additive for hydraulic fluids. Toxicology and carcinogenesis studies were conducted by administering a mixed isomer preparation of 79% tricresyl phosphate esters (consisting of 21% tri-*m*-cresyl phosphate, 4% tri-*p*-cresyl phosphate, less than 1% tri-*o*-cresyl phosphate, and other unidentified tricresyl phosphate esters) by gavage to groups of F344/N rats and $B6C3F_1$ mice for 16 days and 13 weeks, and in feed to groups of F344/N rats and $B6C3F_1$ mice for 13 weeks and 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium* and cultured Chinese hamster ovary cells.

16-Day Gavage Study in Rats

Groups of 10 male and 10 female rats received tricresyl phosphate in corn oil by gavage at doses of 0, 360, 730, 1,450, 2,900, or 5,800 mg/kg body weight, 5 days per week, for a total of 13 or 14 doses in a 16-day period. One female receiving 1,450 mg/kg and five males and eight females receiving 2,900 mg/kg died before the end of the study. Final mean body weights of male and female rats that received 1,450, 2,900, or 5,800 mg/kg were significantly lower than those of the controls. Necrosis of the mandibular lymph node, spleen, and thymus occurred primarily in rats receiving 2,900 and 5,800 mg/kg. Diffuse aspermatogenesis occurred in the testes of male rats that received 2,900 and 5,800 mg/kg. Changes in neurobehavioral parameters in groups that received 1,450, 2,900, or 5,800 mg/kg were confounded by mortality and reduced body weights and were not attributed to a direct neurotoxic response.

16-Day Gavage Study in Mice

Groups of 10 male and 10 female mice received tricresyl phosphate in corn oil by gavage at doses of 0, 360, 730, 1,450, 2,900, or 5,800 mg/kg body weight, 5 days per week, for a total of 13 or 14 doses in a 16-day period. Five males and all females that received 1,450 mg/kg, all mice that received 2,900 mg/kg, and four males and one female that received 5,800 mg/kg died before the end of the study. Final mean body weights of male mice that received 1,450 and 5,800 mg/kg were significantly lower than that of the controls. Final mean body weights of female mice that received 360, 730, or 5,800 mg/kg were significantly greater than that of the controls. Necrosis of the mandibular lymph node, thymus, and spleen occurred primarily in mice receiving 2,900 and 5,800 mg/kg. Hindlimb grip strengths of male mice that received 360 and 1,450 mg/kg and male and female mice that received 730 and 5,800 mg/kg were significantly lower than those of the controls at the end of the study.

13-Week Gavage Study in Rats

Groups of 10 male and 10 female rats received tricresyl phosphate in corn oil by gavage at doses of 0, 50, 100, 200, 400, or 800 mg/kg body weight. All rats survived to the end of the study. Final mean body weights of male rats receiving 200, 400, and 800 mg/kg were significantly lower than that of the controls. Cytoplasmic vacuolization of the adrenal cortex occurred in all dosed groups and the severity increased with dose. Ovarian interstitial cell hypertrophy occurred in all dosed groups of females. Atrophy of the seminiferous tubules occurred in male rats that received 400 and 800 mg/kg. There were no biologically significant changes in neurobehavioral parameters in rats.

13-Week Gavage Study in Mice

Groups of 10 male and 10 female mice received tricresyl phosphate in corn oil by gavage at doses of 0, 50, 100, 200, 400, or 800 mg/kg body weight. All mice survived to the end of the study. Final mean body weights of male mice receiving 200 mg/kg and of male and female mice receiving 400 and 800 mg/kg were significantly lower than those of the controls. Cytoplasmic vacuolization of the adrenal cortex occurred in all dosed groups of mice and the severity increased with dose. Ovarian interstitial cell hypertrophy was present in all dosed groups of female mice. Multifocal degeneration of the spinal cord occurred in males and females that received 100, 200, 400, and 800 mg/kg, and multifocal degeneration of the sciatic nerve occurred in males that received 200, 400, and 800 mg/kg and females that received 100, 200, 400, and 800 mg/kg. Hindlimb grip strengths of male mice that received 200, 400, or 800 mg/kg were significantly lower than that of the controls at the end of the study.

13-Week Feed Study in Rats

Groups of 10 male and 10 female rats were fed diets containing 0, 900, 1,700, 3,300, 6,600, or 13,000 ppm of tricresyl phosphate. All rats survived to the end of the study. Final mean body weights of males and females exposed to 6,600 and 13,000 ppm and females exposed to 3,300 ppm were significantly lower than those of controls. Feed consumption by male and female rats exposed to 13,000 ppm was lower than that by controls during the first week of the study. Dietary levels of 900, 1,700, 3,300, 6,600 or 13,000 ppm tricresyl phosphate were estimated to deliver daily doses of 55, 120, 220, 430, or 750 mg/kg body weight (males) and 65, 120, 230, 430, or 770 mg/kg (females). There were no biologically significant changes in neurobehavioral parameters in rats.

Cytoplasmic vacuolization of the adrenal cortex occurred in all exposed groups of rats. Hyperplasia of ovarian interstitial cells and inflammation of the ovarian interstitium occurred in all exposed groups of females. Renal papillary edema and renal papillary necrosis occurred in 13,000 ppm males and females and in 6,600 ppm females. Basophilic hypertrophy of the pituitary gland pars distalis and atrophy of the seminiferous tubules occurred in 6,600 and 13,000 ppm males.

Dose selection for the 2-year study in rats was based on lower mean body weights; toxic responses observed in the kidney, pituitary gland, and testis of males and the kidney of females exposed to 6,600 and 13,000 ppm; the presence of cytoplasmic vacuolization of the adrenal cortex in exposed males and females; and the occurrence of ovarian interstitial cell hyperplasia in females exposed to 900 and 1,700 ppm.

13-Week Feed Study in Mice

Groups of 10 male and 10 female mice were fed diets containing 0, 250, 500, 1,000, 2,100, or 4,200 ppm of tricresyl phosphate. All mice survived to the end of the study. Mean body weights of 4,200 ppm males and of females exposed to 2,100 and 4,200 ppm were lower than those of controls throughout the study. Feed consumption by females exposed to 1,000, 2,100, or 4,200 ppm was lower than that by controls during week 12. Dietary levels of 250, 500, 1,000, 2,100, or 4,200 ppm tricresyl phosphate were estimated to deliver average daily doses of 45, 110, 180, 380, or 900 mg/kg body weight (males) and 65, 130, 230, 530, or 1,050 mg/kg (females). Interpretation of grip strength changes observed in groups receiving 2,100 or 4,200 ppm were confounded by the reduced body weights of these groups.

Cytoplasmic vacuolization of the adrenal cortex occurred in all exposed groups of male and female mice with the exception of 250 ppm males. Papillary hyperplasia of the gallbladder mucosa occurred in male mice exposed to 500 ppm or more and in female mice exposed to 1,000 ppm or more. Axonal

degeneration occurred in males and females exposed to 2,100 and 4,200 ppm and females exposed to 1,000 ppm. Renal tubule regeneration occurred in all 4,200 ppm male mice.

Dose selection for the 2-year study in mice was based on the presence of axonal degeneration at concentrations of 1,000 ppm or more and cytoplasmic vacuolization of the adrenal cortex at concentrations of 500 ppm or more in males and in all exposed groups of females.

2-Year Feed Study in Rats

Groups of 95 male and 95 female rats were fed diets containing 0, 75, 150, or 300 ppm of tricresyl phosphate. An additional group of 95 male and 95 female rats were fed diets containing 600 ppm of tricresyl phosphate for 22 weeks and then received only control feed. After 3, 9, and 15 months of chemical exposure, up to 15 males and 15 females per group were evaluated for forelimb and hindlimb grip strength, then necropsied and evaluated for histopathologic lesions.

Survival, Mean Body Weights, and Feed Consumption

Survival of exposed rats was similar to that of controls. The final mean body weights of all exposed groups of males and females were similar to those of the controls. Feed consumption by exposed groups of male and female rats was similar to that by the controls. Dietary levels of 75, 150, or 300 ppm tricresyl phosphate were estimated to deliver average daily doses of 3, 6, or 13 mg/kg body weight (males) and 4, 7, or 15 mg/kg (females).

Pathology Findings

There were no chemical-related increased incidences of neoplasms in rats. Cytoplasmic vacuolization of the adrenal cortex occurred in 600 ppm males and 150, 300, and 600 ppm females at the 3-month interim evaluation. At 9 and 15 months, cytoplasmic vacuolization occurred only in female rats, primarily in the 300 ppm group. Cytoplasmic vacuolization of the adrenal cortex and ovarian interstitial cell hyperplasia occurred in female rats exposed to 300 ppm throughout the 2-year study and the incidence and severity were significantly increased at the end of the study.

2-Year Feed Study in Mice

Groups of 95 male and 95 female mice were fed diets containing 0, 60, 125, or 250 ppm of tricresyl phosphate. After 3, 9, and 15 months of chemical exposure, up to 15 males and 15 females per group were evaluated for forelimb and hindlimb grip strength, then necropsied and evaluated for histopathologic lesions.

Survival, Mean Body Weights, and Feed Consumption

Survival of exposed groups of male and female mice was similar to that of the controls. The final mean body weights of males and females receiving tricresyl phosphate were similar to those of controls. Feed consumption by exposed groups of male and female mice was similar to that by the controls. Dietary levels of 60, 125, or 250 ppm tricresyl phosphate were estimated to deliver average daily doses of 7, 13, or 27 mg/kg body weight (males) and 8, 18, or 37 mg/kg (females).

Pathology Findings

There were no chemical-related increased incidences of neoplasms in mice. Ceroid pigmentation of the adrenal cortex occurred in all groups of mice throughout most of the 2-year study, with the exception of 60 and 125 ppm females at the 3-month interim evaluation; however, the severity was markedly increased in female mice receiving 250 ppm. Incidences of clear cell foci, fatty change, and ceroid pigmentation of the liver were significantly increased in male mice that received 125 or 250 ppm.

Genetic Toxicology

Tricresyl phosphate was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537, nor did it induce chromosomal aberrations or sister chromatid exchanges in cultured Chinese hamster ovary cells. These *in vitro* assays were all conducted with and without exogenous metabolic activation (S9).

Conclusions

Under the conditions of these 2-year feed studies, there was *no evidence of carcinogenic activity** of tricresyl phosphate in male or female F344/N rats that received 75, 150, or 300 ppm. There was *no*

evidence of carcinogenic activity of tricresyl phosphate in male or female B6C3F$_1$ mice that received 60, 125, or 250 ppm.

Nonneoplastic lesions associated with exposure to tricresyl phosphate included cytoplasmic vacuolization of the adrenal cortex and ovarian interstitial cell hyperplasia in female rats, increased incidences of clear cell focus, fatty change, and ceroid pigmentation of the liver in male mice, and increased severity of ceroid pigmentation of the adrenal cortex in female mice.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this report appears on page 12.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Tricresyl Phosphate

Variable	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 75, 150, or 300 ppm in feed (Approximately 3, 6, or 13 mg/kg)	0, 75, 150, or 300 ppm in feed (Approximately 4, 7, or 15 mg/kg)	0, 60, 125, or 250 ppm in feed (Approximately 7, 13, or 27 mg/kg)	0, 60, 125, or 250 ppm in feed (Approximately 8, 18, or 37 mg/kg)
Body weights	Exposed groups similar to controls	Exposed groups similar to controls	Exposed groups similar to controls	Exposed groups similar to controls
2-Year survival rates	32/51, 30/50, 35/50, 28/50	34/51, 38/53, 30/50, 26/49	43/51, 43/49, 44/49, 42/50	41/50, 38/50, 42/48, 45/51
Nonneoplastic effects	None	Adrenal cortex: cytoplasmic vacuolization (14/51, 12/53, 16/50, 36/50); Ovary: interstitial hyperplasia (0/51, 0/53, 0/50, 15/50)	Liver: ceroid pigmentation (0/52, 0/49, 30/49, 28/50); clear cell focus (5/52, 8/49, 17/49, 12/50); fatty change (6/52, 10/49, 23/49, 22/50)	Adrenal cortex: ceroid pigmentation (severity grades - 1.2, 1.6, 2.5, 3.9)
Neoplastic effects	None	None	None	None
Level of evidence of carcinogenic activity	No evidence	No evidence	No evidence	No evidence
Genetic toxicology				
Salmonella typhimurium gene mutation:	Negative with and without S9 in strains TA98, TA100, TA1535, and TA1537			
Sister chromatid exchanges				
Chinese hamster ovary cells *in vitro*:	Negative with and without S9			
Chromosomal aberrations				
Chinese hamster ovary cells *in vitro*:	Negative with and without S9			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such lesions to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

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

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

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on tricresyl phosphate on June 22, 1993, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

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

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On June 22, 1993, the draft Technical Report on the toxicology and carcinogenesis studies of tricresyl phosphate received public review by the National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. R.D. Irwin, NIEHS, introduced the toxicology and carcinogenesis studies of tricresyl phosphate by discussing the uses and rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related nonneoplastic lesions in rats and mice. The proposed conclusions were *no evidence of carcinogenic activity* of tricresyl phosphate in male or female rats or mice.

Dr. van Zwieten, a principal reviewer, agreed with the proposed conclusions. He thought the description of the rationale for maximum tolerated dose was extremely well done.

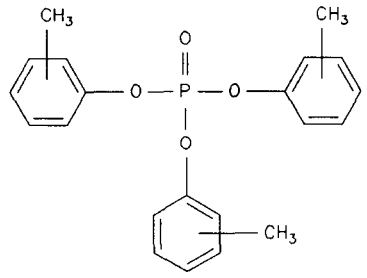
Dr. Davidson, the second principal reviewer, agreed with the proposed conclusions. She asked for an explanation why there was high mortality in male and female rats that received 2,900 mg/kg in the 16-day gavage study, while at double that dose there was no mortality. Similar results were observed in mice. Dr. Irwin said the higher dose was pure tricresyl phosphate, which is a liquid, while the lower dose was the chemical diluted with an equal amount of corn oil. He speculated that the corn oil may have enhanced the absorption. Because dosed feed was used in the 2-year studies, this observation was not pursued further.

Dr. Bailey, the third principal reviewer, also agreed with the proposed conclusions. He said that mention needed to be made in the introductory toxicity section that tricresyl phosphate esters with only one *ortho*-cresyl substituent are much more potent neurotoxicants than the tri-*ortho*-cresyl ester. He provided a reference.

Dr. Ryan inquired as to why extensive neurotoxicity testing was reported in an appendix but there was little discussion of the results. Dr. Irwin replied that neurotoxicity was considered to be a possible complicating factor that might interfere with evaluation of carcinogenic potential. Tests such as measurement of grip strength in response to acoustic and thermal stimuli were intended to determine whether there was neurotoxicity present. In public comments, Dr. Mary Barth, Mobil Oil Corporation, reported that there are several unpublished studies that indicate tricresyl phosphate is somewhat more toxic with corn oil as a vehicle than with mineral oil as a vehicle.

Dr. van Zwieten moved that the Technical Report on tricresyl phosphate be accepted with the revision discussed and with the conclusions as written for male and female rats and mice, *no evidence of carcinogenic activity*. Dr. Bailey seconded the motion, which was accepted unanimously with nine votes.

INTRODUCTION



TRICRESYL PHOSPHATE

CAS No. 1330-78-5

Chemical Formula: $C_{21}H_{21}O_4P$ Molecular Weight: 368.36

PHYSICAL AND CHEMICAL PROPERTIES

Tricresyl phosphate is a clear, colorless, viscous liquid with a specific gravity of 1.15 to 1.16, a freezing point of −33° C, and boiling point of 240° to 250° C at 4 mm Hg (*Merck Index*, 1976). Structurally, tricresyl phosphate is a triester of cresol and phosphoric acid. Cresol can exist as three isomers (ortho-, meta-, and para-) depending on the relative positions of the methyl and phenolic hydroxyl groups, resulting in 10 structurally distinguishable triesters of cresol and phosphoric acid.

PRODUCTION, USE, AND HUMAN EXPOSURE

The most common method for the synthesis of tricresyl phosphate involves the reaction of phosphorus oxychloride with a preparation of cresols composed of a mixture of the three isomers. Therefore, the composition of the final product depends on the isomeric composition of the cresol preparation and may include a certain percentage of each of the ten distinguishable triesters. A common source of cresol preparations has been the high-boiling phenolic fractions obtained during petroleum refining. More recently, however, the petroleum feedstocks which are often contaminated with other phenolic compounds have been replaced by cresols prepared synthetically, which produce a more uniform product (IPCS, 1990).

Tricresyl phosphate is primarily used as a vinyl plasticizer in the manufacture of vinyl plastics for automotive interiors and as a fire-retardant and anti-wear additive to industrial lubricants such as hydraulic fluids, extreme pressure fluids, cutting oils, machine oils, automotive transmission fluids, and certain cooling lubricants. Current production figures for tricresyl phosphate are unavailable; however, the use of tricresyl phosphate in these applications has declined considerably over the last 5 years because of its replacement by lower cost synthetic triaryl (tri-isopropylphenyl- and tri-*t*-butylphenyl-) phosphates and high water-based oil emulsions in hydraulic and industrial fluids (Chemical and Economics Handbook, 1988).

Tricresyl phosphate has been detected in air, soil, sediment, water, and various aquatic organisms, with the greatest contamination present in heavily industrialized areas. Concentrations measured in the air over production facilities in the U.S. ranged from 0.01 to 2 ng/m^3, however levels as high as 26 to 70 ng/m^3 have been detected over the Japanese city of Matsuyama. Tricresyl phosphate has been detected at low concentrations in surface water near production sites. Although it is not very soluble in water, it is readily absorbed into sediment; levels of 400 to 600 ng/g have been measured in sediment from Baltimore Harbor and 230 to 1,300 ng/g in sediments from the Detroit River. Tricresyl phosphate has been detected at concentrations of up to 40 ng/g of tissue

in sturgeon from the Columbia River and 2 to 5 ng/g of tissue in fish inhabiting lakes and rivers near tricresyl phosphate manufacturing facilities (IPCS, 1990).

METABOLISM, EXCRETION, DISTRIBUTION, AND ABSORPTION

Studies of the metabolism, distribution, and pharmacokinetics of tricresyl phosphate published to date have examined isomerically pure triesters in which only a single cresol isomer was esterified to phosphoric acid. There have been no studies which have attempted to characterize the metabolism of tricresyl phosphate prepared from mixed isomers.

Tri-*o*-cresyl phosphate is the most widely studied tricresyl phosphate. The metabolism of this compound has been examined in rats (Casida *et al.*, 1961; Abou-Donia and Nomeir, 1986; Somkuti and Abou-Donia, 1990), chickens (Abou-Donia *et al.*, 1990), and cats (Nomeir and Abou-Donia, 1986) and can be described by the pathways shown in Figure 1. However, there are species specific quantitative differences in the relative amounts of various metabolites produced and in the rate of their formation and excretion. The initial step appears to involve oxidation of the ring methyl group of one or more of the three *o*-cresyl groups to produce an *o*-hydroxy benzyl alcohol (saligenin) residue (Eto *et al.*, 1962). This reaction occurs in the liver and is catalyzed by mixed function oxidases. The product of the reaction then cyclizes via an internal group displacement reaction in which the hydroxyl group of an ortho-hydroxy benzyl alcohol residue displaces a neighboring cresol/*o*-benzyl alcohol group. This reaction, and hence the formation of the cyclic phosphate has been shown to occur only with tri-*o*-cresyl phosphate; however, in theory it could occur whenever one of the cresol groups esterified to phosphoric acid was *o*-cresol. The position of the methyl group in *m*- or *p*-cresol is such that the corresponding benzyl alcohol residue cannot participate in this type of internal cyclization when these latter compounds are esterified to phosphoric acid. Since no $^{14}CO_2$ is formed when the label is in the cresol ring, the ring is not degraded, and the final product of the pathway is *o*-hydroxy benzoic acid, which is excreted in the urine either free or as a conjugate.

The metabolism of tri-*p*-cresyl phosphate has been evaluated in Wistar rats (Kurebayashi *et al.*, 1985) and the pathways leading to the formation of the major metabolites are shown in Figure 2. Once again the initial reaction is the oxidation of a ring methyl group to form a *p*-hydroxy benzyl alcohol residue; however, as mentioned above this metabolite does not cyclize like the corresponding metabolite of the *o*-cresol triester. The final product of the degradation pathway is *p*-hydroxy benzoic acid which is excreted in the urine. The metabolism of tri-*m*-cresyl phosphate has not been evaluated.

The distribution and excretion of ^{14}C-labeled isomerically pure tri-*o*-, tri-*m*- and tri-*p*-cresyl phosphates has been examined in F344/N rats (NTP, unpublished). Groups of male rats were administered 2, 20, or 200 mg/kg of the respective ^{14}C-labeled isomerically pure tricresyl phosphate in corn oil by gavage, or 20 mg/kg was administered intravenously. All three compounds were well absorbed after oral administration; however, the pattern of excretion of each of the three triesters was different. Tri-*o*-cresyl phosphate was excreted primarily in the urine with approximately 70% of the label appearing in urine and 20% in feces within 24 hours for all three dose levels administered. Tri-*m*-cresyl phosphate was excreted primarily in the feces at all four dose levels administered (0.5, 2, 20, or 200 mg/kg); however, as the dose increased the percentage excreted in the feces also increased and that excreted in urine decreased. Tri-*p*-cresyl phosphate exhibited yet a different excretion pattern; at low doses (0.5 or 2 mg/kg) the primary route of excretion was the urine, whereas at higher doses (20 or 200 mg/kg) the primary route of excretion was the feces.

Evaluation of biliary excretion following intravenous administration indicated that after administration of 2 or 20 mg/kg tri-*o*-cresyl phosphate or tri-*m*-cresyl phosphate approximately 40% to 60% of the label was excreted in the bile within the first 6 hours. However, tri-*p*-cresyl phosphate exhibited a dose dependent increase which represented an approximate doubling of biliary excretion between the 2 mg/kg and 20 mg/kg doses. The percentage of administered label appearing in feces was less than that excreted in bile for all three triesters, suggesting that substantial enterohepatic recycling occurs. Within 3 days after administration essentially 100% of the label of all three isomers had been excreted. All three isomers were rapidly distributed to muscle and liver and then redistributed to adipose tissue and skin; however, the parent compounds were

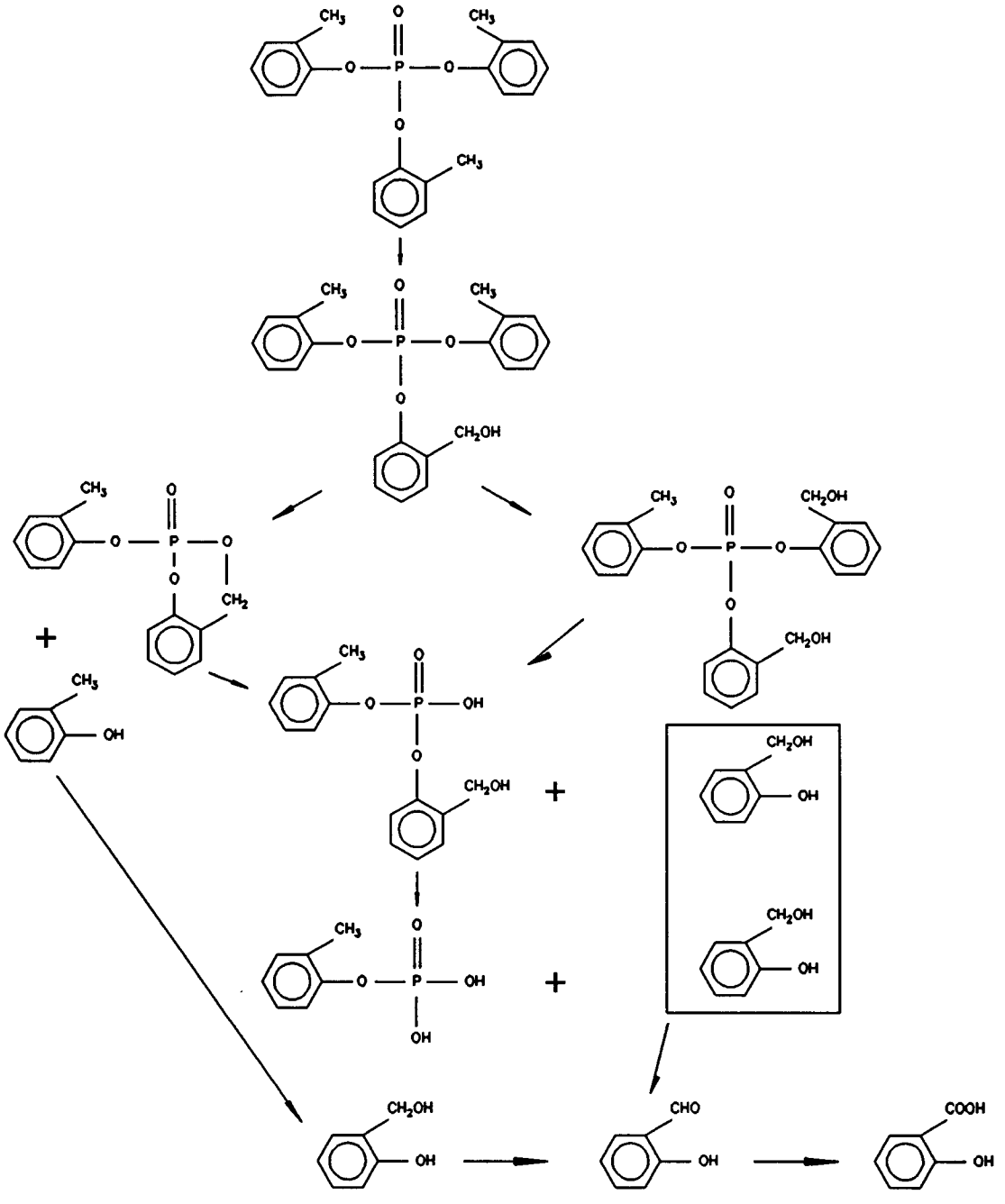


FIGURE 1
Metabolic Pathway of Tri-*o*-cresyl Phosphate

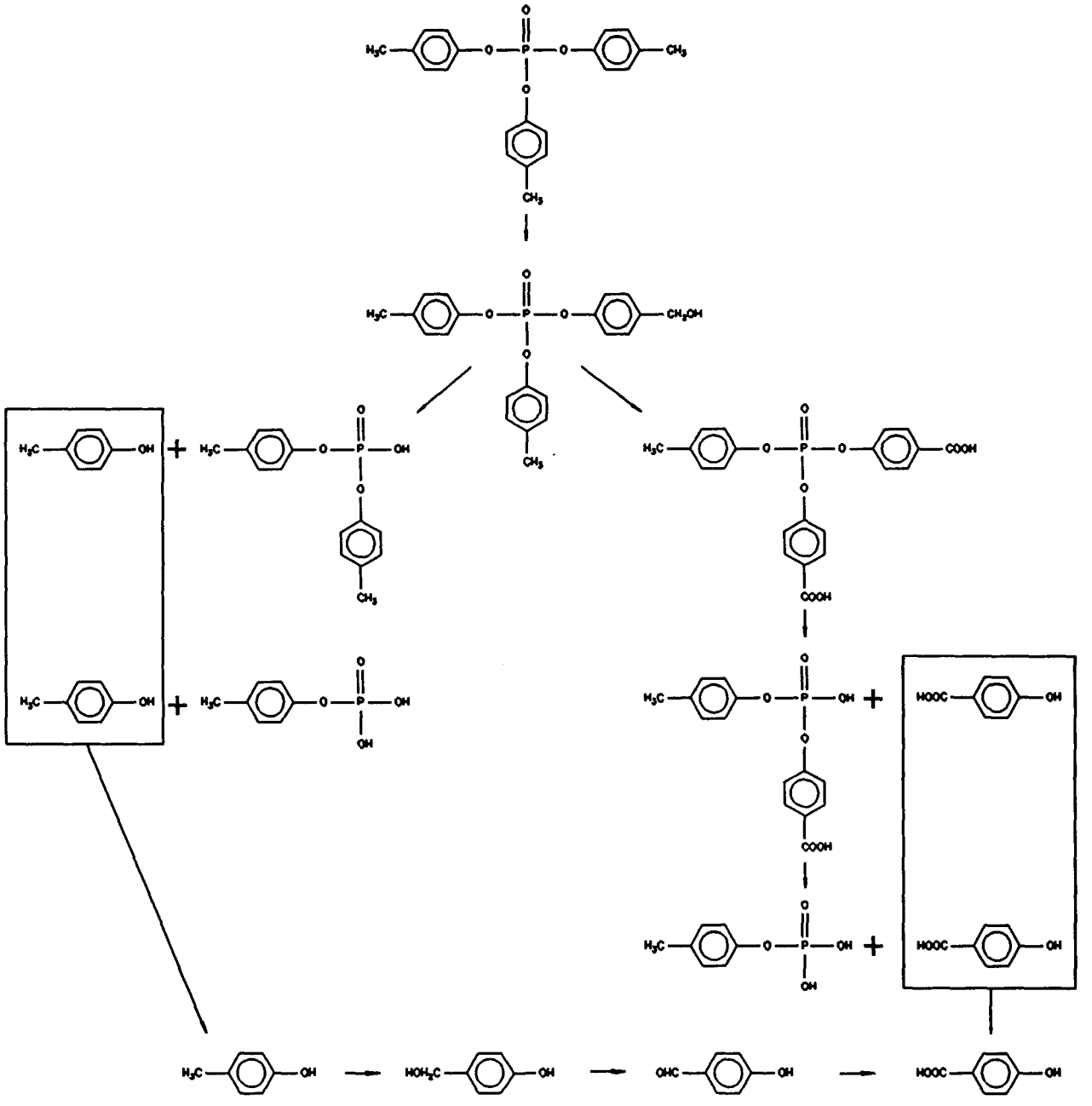


FIGURE 2
Metabolic Pathway of Tri-*p*-cresyl Phosphate

rapidly cleared with no tendency to bioaccumulate in specific organs or tissues.

Within 12 hours of dermal administration of a 50 mg/kg dose of ^{14}C-tri-*o*-cresyl phosphate to the intrascapular region of cats, 73% of the radioactivity had disappeared from the site of application, and within 24 hours it reached its maximum concentration in all organs and tissues examined (Nomeir and Abou-Donia, 1986). Within 10 days after administration, 28% of the applied radioactivity had been excreted in the urine and 20% in the feces. Although studies of skin absorption have not been conducted with other isomeric tricresyl phosphate esters, the similarity of structure and physical properties (solubility, etc.) make it likely that these compounds are also absorbed through the skin.

TOXICITY

Experimental Animals

The values reported for the LD_{50} of tricresyl phosphate prepared from mixed cresol isomers show considerable variation as illustrated in Table 1. As the values for the pure isomers suggest, the ortho-isomer is more toxic than the meta- or para- isomer.

The central and peripheral nervous systems have been identified as target organs sensitive to tricresyl phosphate toxicity. Neurotoxicity caused by exposure to tri-*o*-cresyl phosphate (and other neurotoxic organophosphates) is characterized by a delay in the development of symptoms until 1 to 3 weeks after the initial exposure. As a result it is commonly referred to as delayed neurotoxicity or organophosphate-induced delayed neurotoxicity (OPIDN) (Davies, 1963; Abou-Donia and Nomeir, 1986). In sensitive animal species such as the chicken or cat, the clinical course usually begins with ataxia approximately 1 week after exposure and progressively develops into complete paralysis of the hind limbs. Following the development of complete paralysis, there is usually a period of partial clinical recovery which may be minimal in severe cases of poisoning.

The other major site of tricresyl phosphate toxicity is the reproductive system. Tricresyl phosphate (mixed isomers) administered orally reduced fertility in both rats and mice and caused testicular and ovarian toxicity. Exposure to tricresyl phosphate prior to and during mating caused a significant reduction of the fertility index and mean litter size in Long-Evans rats (Carlton *et al.*, 1987). Among F_0 males there was a dose-related decrease in epididymal weight and a marked increase in the percentage of sperm with abnormal morphology in each dose group. In the high-dose group, sperm concentration, motility, and progressive linear movement were significantly lower than that in the controls. Exposure to tricresyl phosphate prior to and during a 98-day continuous breeding study did not reduce the fertility index of Swiss (CD-1®) mice; however, the number of litters per breeding pair decreased with dose and the proportion of live-born pups and mean pup weight were significantly decreased in groups receiving the highest dose of tricresyl phosphate (0.2% in feed; Chapin *et al.*, 1988). A crossover mating trial revealed impaired fertility in both males and females. Epididymal weights of high-dose F_0 males were significantly reduced and histopathologic examination indicated dose-related atrophy of the seminiferous tubules. There were no chemical-associated histopathologic lesions found in the reproductive tract of F_0 females. The last litter born during the continuous breeding study was reared to 74 days of age and pairs within the same dose groups were allowed to mate. The fertility index and the number and proportion of live pups born were decreased in animals from the high-dose group. Among F_1 males sperm concentration and morphology were normal; however, motility was lower than that of controls in tricresyl phosphate exposure groups.

Humans

The central and peripheral nervous systems of humans are also a site of tricresyl phosphate toxicity. The first indication that tricresyl phosphate was a neurotoxin dates back to 1896 when neurological symptoms were reported in tuberculosis patients treated with phosphocreosote. However, the most definitive studies were those reported by Smith and Elvove (1930) involving an outbreak of paralysis associated with the consumption of beverages containing a ginger extract. United States Pharmacopeia fluid extracts of ginger contained a high content of alcohol (up to 75% by volume); however, during prohibition the Prohibition Bureau considered it a non-potable beverage and therefore not subject to regulation. Not surprisingly, it became very popular for use as a beverage base, especially in rural areas of Ohio, Tennessee, and Kentucky, and was often rebottled and distributed locally under several

TABLE 1
The Acute Toxicity of Tricresyl Phosphate to Different Species[a]

Compounds	Route of Administration	Species	LD_{50} (mg/kg)	Reference
Tricresyl phosphate	oral	rat	5,190	Marhold (1972)
(mixed isomers)	oral	rat	> 15,800	Johannsen (1977)
	oral	mouse	3,900	Izmerov (1982)
	oral	chicken	> 10,000	Johannsen *et al.* (1977)
	dermal	rabbit	> 7,900	Johannsen *et al.* (1977)
	dermal	cat	1,500	Abou-Donia *et al.* (1980)
Tri-*o*-cresyl phosphate	oral	rat	8,400	Johannsen *et al.* (1977)
	oral	rat	1,150	Varonesi *et al.* (1984)
	oral	rabbit	3,700	Johannsen *et al.* (1977)
	oral	chicken	500	Kimmerle and Loeser (1974)
	oral	chicken	100-200	Smith *et al.* (1932)
Tri-*p*-cresyl phosphate	oral	rabbit	> 3,000	Smith *et al.* (1932)
		chicken	> 1,000	Smith *et al.* (1932)
Tri-*m*-cresyl phosphate	oral	rabbit	> 3,000	Smith *et al.* (1932)
	oral	chicken	> 2,000	Smith *et al.* (1932)

[a] From IPCS (1990).

different brand names. It was in association with the consumption of a particular lot of beverage that several hundred cases of paralysis were reported beginning in February 1930. In subsequent investigations, Smith (1930) was able to identify the offending substance in the beverage as tricresyl phosphate, and in particular tri-*o*-cresol phosphate, which was added as a flavoring agent. Since then, tens of thousands of people have suffered varying degrees of neurotoxicity as a result of exposure to tricresyl phosphate. In most cases the exposure has resulted from accidental ingestion of hydraulic fluid, lubricating oil, mineral oil, or some similar fluid which contained tricresyl phosphate. Cooking oil contaminated with hydraulic fluid or lubricating oil has been the source of several large scale human exposures which have resulted in the development of polyneuropathy (IPCS, 1990).

In sensitive animal species, symptoms of tricresyl phosphate neurotoxicity or that caused by other neurotoxic organophosphates develop 1 to 3 weeks after the initial exposure. In humans, the first noticeable symptom is soreness and/or weakness of the leg muscles which may begin from 5 days to 2 weeks after exposure (IPCS, 1990). Over the next several days the symptoms may progress to partial paralysis of the extremities in mild cases or complete paralysis in more severe cases. As in sensitive animal species, the development of complete paralysis may be followed by a period of partial clinical recovery that may be minimal in severe cases of poisoning. Follow-up studies conducted after several large scale human exposures have indicated that neurological disorders may persist for many years; for instance, of the 11 survivors of the 1930 poisoning in the southwest U.S. still living 47 years later, all exhibited spasticity and abnormal reflexes characteristic of an upper motor neuron syndrome (Morgan and Penovich, 1978).

In both humans and sensitive animal species, the onset of delayed neurotoxicity is associated with the presence of a distal axonopathy which is most prominent in long, large diameter myelinated axons of peripheral nerves and long spinal tracts (Cavanagh and Patangia, 1965; Bouldin and Cavanagh, 1979a; 1979b). The axonopathy begins initially as a nonterminal focal lesion resembling a transection of the axon; the portion of the severed axon distal to the site of transection then degenerates followed by degeneration of the myelin sheath surrounding this distal portion of the neuron. During the period of

clinical recovery, peripheral nerve fibers regenerate relatively quickly (weeks), however recovery of long spinal tracts occurs much more slowly or not at all. The strong correlation between the development of symptoms of delayed neurotoxicity and the appearance and progression of the axonopathy suggest a causal relationship.

Only tricresyl phosphates in which at least one of the cresol residues is an ortho-isomer are neurotoxic; triesters which contain only meta- or para- isomers (or both) are not neurotoxic. Since metabolism of the ortho residue leads to the formation of a reactive cyclic phosphate which cannot form from meta- or para- cresol residues, the reaction of the cyclic phosphate with a particular target molecule(s) has been proposed as a critical step in the ultimate development of axonopathy and, hence, neurotoxicity. Moreover, the cyclic phosphate, when administered directly, is much more neurotoxic than an equivalent amount of parent tri-*o*-cresyl phosphate, providing further support for its importance in the development of axonopathy (Jortner and Ehrich, 1987). Henschler (1958) examined the neurotoxicity of tricresyl phosphate containing various isomeric compositions, and the results indicated that preparations in which *o*-cresol was present predominantly as a mono-ester, with the remaining two positions being occupied by *m*- and/or *p*-cresol, were more neurotoxic to chickens than preparations containing predominantly tri-*o*-cresyl phosphate. Therefore, preparations composed of *o*-cresol containing mixed triesters exhibit toxicity similar to that usually associated with tri-*o*-cresyl phosphate.

CARCINOGENICITY

Experimental Animals

There are no published studies which have evaluated the carcinogenic potential of tricresyl phosphate or the consequences of long-term exposure in animals.

Humans

No case reports or epidemiological studies considered pertinent to an assessment of human carcinogenicity were found in the literature.

GENETIC TOXICOLOGY

Tricresyl phosphate did not induce gene mutations in *Salmonella typhinurium* strains, with or without S9 (Haworth *et al.*, 1983)

STUDY RATIONALE

Because of the documented sensitivity of humans to tricresyl phosphate, its use in functional fluids and the associated potential for occupational exposure, the possibility of increased environmental contamination, and the absence of information about the consequences of long-term exposure, tricresyl phosphate was selected as a representative organophosphate for in-depth toxicologic testing and evaluation of its carcinogenic potential. Since the toxicity of isomerically mixed preparations had not been well characterized, the prechronic studies were conducted by two routes of administration: gavage and dosed feed.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF TRICRESYL PHOSPHATE

Tricresyl phosphate was obtained as a clear, colorless liquid from Stauffer Chemical Company (Westport, CT) in one lot (1202A-2-7) which was used throughout the 16-day, 13-week, and 2-year studies in rats and mice. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Confirmatory analyses were conducted by Radian Corporation (Austin, TX).

The chemical was characterized by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. Purity was determined by elemental analyses, Karl Fischer water analysis, thin-layer chromatography, and gas chromatography. Elemental analyses for carbon, hydrogen, and phosphorus were in agreement with the theoretical values for tricresyl phosphate. Karl Fischer water analysis indicated 0.072% water. Thin-layer chromatography indicated only one major spot in each system. Gas chromatography indicated 28 components, with nine of these having peak areas greater than 2% of the total chromatographic peak area. The concentrations of tri-*m*-cresyl phosphate and tri-*p*-cresyl phosphate were estimated at 21% and 4% of the total. The concentration of tri-*o*-cresyl phosphate was estimated at less than 0.1%.

Special analyses using gas chromatography and mass spectrometry were performed to identify the other seven components of tricresyl phosphate, which represent greater than 2% of the total chromatographic peak area. Two peaks representing 24% and 30% of the total chromatographic peak area were identified as tricresyl phosphate esters whose isomeric compositions could not be confirmed. The remaining five peaks (2%, 3%, 3%, 4%, and 5%) were identified as dicresyl phosphate esters, but again the isomeric composition could not be confirmed.

To summarize, the test chemical is a complex mixture consisting of 18% dicresyl phosphate esters and 79% tricresyl phosphate esters. Two of the tricresyl phosphate esters were identified as tri-*m*-cresyl phosphate (21%) and tri-*p*-cresyl phosphate (4%) with no detectable tri-*o*-cresyl phosphate (<0.1%).

Stability studies were performed by the analytical chemistry laboratory using gas chromatography. These studies indicated that tricresyl phosphate, based on the four major components, was stable as a bulk chemical for at least 2 weeks when stored protected from light at temperatures up to 60° C. The stability of the bulk chemical was monitored periodically at the study laboratory with ultraviolet spectroscopy and gas chromatography methods similar to those described above. No degradation of the bulk chemical was observed.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulation suspensions for the gavage studies were prepared by mixing tricresyl phosphate in USP grade corn oil, except the high dose in the 16-day studies, which was given neat. Dose formulations for the feed studies were prepared by mixing tricresyl phosphate with feed in a blender (Patterson-Kelley Twin Shell with intensifier bar) for 15 minutes (Table I1). Dose formulations were prepared once for the 16-day studies and weekly for the 13-week and 2-year studies. The stability of the gavage dose formulations was confirmed, based on the four major components, for at least 2 weeks at room temperature when stored in the dark, and for 3 hours when exposed to air and light. For the feed studies, homogeneity was confirmed and the stability of the dose formulations was established, again based on the four major components, for at least 2 weeks when stored in the dark at 23° C.

Periodic analyses of the dose formulations of tricresyl phosphate were conducted by the study laboratory using ultraviolet spectroscopy (16-day and 13-week gavage studies), high performance liquid chromatography (13-week feed studies), and gas chromatography (13-week and 2-year feed studies). All dose formulations were analyzed during the 16-day studies (Table I2). During the 13-week studies, the dose

formulations were analyzed at the beginning, midpoint, and end of the studies (Tables I3 and I4). During the 2-year studies, the dose formulations were analyzed every 6 to 10 weeks (Table I5). In the 2-year studies all dose formulations (89/89) were within 10% of the target concentrations. Results of the periodic referee analyses performed by the analytical chemistry laboratory were in agreement with the results obtained by the study laboratory (Tables I6 and I7).

16-Day Gavage Studies

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories (Kingston, NY). At receipt the rats were 30 days old and mice were 40 days old. The animals were quarantined for 20 to 22 days before dosing began. During this time two males and two females of each species were randomly selected and evaluated for evidence of disease.

Groups of 10 male and 10 female rats and mice received tricresyl phosphate gavage at doses of 0, 360, 730, 1,450, or 2,900 mg/kg body weight (in corn oil), or 5,800 mg/kg body weight (neat) for 13 or 14 days. Animals were housed five per cage; water and feed were available *ad libitum*. Clinical findings were recorded once daily. Animals were weighed at study initiation, once a week, and at the end of the studies. Details of study design and animal maintenance are summarized in Table 2.

Neurobehavioral assessments were performed one week before the beginning of the studies and the day before scheduled necropsy. All rats and mice were tested for spontaneous motor activity, forelimb and hindlimb grip strength, startle response, and paw-lick latency. Further details are provided in Appendix H.

A gross necropsy was performed on all rats and mice. The brain, heart, right kidney, liver, lung, right testis, and thymus of rats and mice were weighed. Tissues for microscopic examination were embedded in paraffin, sectioned to a thickness of 4 to 6 μm, and stained with hematoxylin and eosin. Histopathologic examinations were conducted on all rats receiving 5,800 mg/kg, all rats dying early, and all mice receiving 2,900 mg/kg. In addition, the mandibular lymph node, spleen, and thymus of all controls, rats and surviving male mice that received 1,450 mg/kg, rats that received 2,900 mg/kg, and surviving mice that received 5,800 mg/kg were examined. The tissues examined microscopically are listed in Table 2.

13-Week Gavage Studies

The 13-week gavage studies were conducted to evaluate the cumulative toxic effects of repeated exposure to tricresyl phosphate.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Simonsen Laboratories, Inc. (Gilroy, CA); rats were 40 days old and mice were 41 days old upon receipt. Rats were quarantined 27 to 30 days and mice were quarantined 19 to 22 days before dosing began. At this time, five males and five females of each species were randomly selected and evaluated for evidence of disease. At the end of the study, serology samples were collected from five male and five female control rats for murine virus antibody determinations (Appendix L).

Groups of 10 male and 10 female rats and mice received tricresyl phosphate in corn oil by gavage at doses of 0, 50, 100, 200, 400, or 800 mg/kg body weight 5 days per week for 13 weeks. Rats and mice were housed five per cage; water and feed were available *ad libitum*. Clinical findings were recorded once weekly. The animals were weighed at study initiation and weekly thereafter. Further details of study design and animal maintenance are summarized in Table 2.

Neurobehavioral assessments of spontaneous motor activity, forelimb and hindlimb grip strength, startle response, and paw-lick latency were performed on all rats and mice one week before dosing began and again on the day prior to scheduled necropsy. Further details are provided in Appendix H.

At the end of the 13-week gavage studies, blood was collected from the vena cava (rats) or by cardiac puncture (mice) for hematology and clinical chemistry analyses. The parameters measured are listed in Table 2.

A necropsy was performed on all animals. The brain, heart, right kidney, liver, lung, left testis, and thymus of rats and mice were weighed. Tissues for microscopic examination were embedded in paraffin, sectioned to a thickness of 4 to 6 μm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on all controls, all

animals dying early, and all rats and mice receiving 800 mg/kg. In addition, the adrenal gland, ovary, and spinal cord and sciatic nerve of all dosed rats and mice and testes of rats were examined microscopically. The tissues examined microscopically are listed in Table 2.

13-WEEK FEED STUDIES

The 13-week feed studies were conducted to evaluate the cumulative toxic effects of repeated exposure to tricresyl phosphate and to determine the appropriate doses to be used in the 2-year studies.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Frederick Cancer Research Facility (Frederick, MD); all rats and mice were 28 days old upon receipt. The animals were quarantined for 15 or 16 days before exposure began. At this time, five males and five females of each species were randomly selected and evaluated for evidence of disease. At the end of the studies, serology samples were collected from five rats and mice of each control group for murine virus antibody determinations (Appendix L).

Groups of 10 male and 10 female rats were fed diets containing 0, 900, 1,700, 3,300, 6,600, or 13,000 ppm of tricresyl phosphate 7 days per week for 13 weeks; groups of 10 male and 10 female mice were fed diets containing 0, 250, 500, 1,000, 2,100, or 4,200 ppm of tricresyl phosphate 7 days per week for 13 weeks. Rats were housed five per cage; mice were housed individually. Water and feed were available *ad libitum*. Feed consumption was measured once weekly, and clinical findings were recorded once weekly. The animals were weighed at study initiation and weekly thereafter. Further details of study design and animal maintenance are summarized in Table 2.

Neurobehavioral assessments of forelimb and hindlimb grip strength were performed on all rats and mice the day before the beginning of the studies, and again on the day prior to scheduled necropsy. Further details are provided in Appendix H.

At the end of the 13-week feed studies, blood was collected from the orbital sinus of all animals for hematology analyses and from the vena cava (rats) or by cardiac puncture (mice) for clinical chemistry analyses. The parameters measured are listed in Table 2.

A necropsy was performed on all animals. The brain, heart, right kidney, liver, lung, right testis, and thymus of rats and mice were weighed. Tissues for microscopic examination were embedded in paraffin, sectioned to a thickness of 4 to 6 μm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on all controls, rats exposed to 13,000 ppm, and mice exposed to 4,200 ppm. In addition, the adrenal gland, epididymis, kidney, ovary, pituitary gland (males), and testis of rats exposed to 900, 1,700, 3,300, or 6,600 ppm and the adrenal gland, gallbladder, kidney, ovary, sciatic nerve, and spinal cord of mice exposed to 250, 500, 1,000, or 2,100 ppm were examined. Table 2 lists the tissues and organs routinely examined microscopically.

2-YEAR FEED STUDIES

Study Design

Groups of 95 male and 95 female rats were fed diets containing 0, 75, 150, or 300 ppm of tricresyl phosphate for 104 weeks; groups of 95 male and 95 female mice were fed diets containing 0, 60, 125, or 250 ppm of tricresyl phosphate for 105 weeks. Fifteen male and 15 female rats and mice per exposure group were randomly selected for interim evaluations after 3, 9, and 15 months of chemical administration. An additional group of 95 male and 95 female rats were fed diets containing 600 ppm of tricresyl phosphate for 22 weeks and then received only control feed. Based on the findings at the 3-month interim evaluation, the core group of male and female rats receiving 600 ppm were killed and discarded; the remaining 30 male and 30 female rats fed 600 ppm were examined at the 9- and 15-month interim evaluations.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Simonsen Laboratories, Incorporated (Gilroy, CA) for use in the 2-year feed studies. Rats and mice were quarantined for 11 to 14 days before the beginning of the studies. Five rats and five mice of each sex were randomly selected and evaluated for evidence of disease. Serology samples were collected for viral screening. Rats and mice were 6 weeks old at the beginning of the 2-year studies. The health of the animals was monitored during the studies according to the NTP Sentinel Animal Program (Appendix L).

Animal Maintenance

Rats were housed five per cage; mice were housed individually. Feed and water were available *ad libitum*, and feed consumption was measured once monthly (Appendix J). Cages were rotated every 2 weeks. Further details of animal maintenance are given in Table 2. Information on feed composition and contaminants is provided in Appendix K.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings and body weights were recorded initially, weekly for 13 weeks, then monthly and at the interim evaluations. Neurobehavioral assessments were performed before exposure began and prior to necropsy at the 3-, 9-, and 15-month interim evaluations. Further details are given in Appendix H. Blood was collected from the orbital sinus of all animals at the 3-, 9-, and 15-month interim evaluations for hematology and clinical chemistry. The parameters measured are listed in Table 2. The left and right adrenal gland, brain, left and right kidney, liver, and left and right testis of rats and mice were weighed at the 3-, 9-, and 15-month interim evaluations.

A necropsy was performed on all animals. At necropsy, all organs and tissues were examined for gross lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic examination. In addition, up to five male and female rats and mice per dose group were selected for special neuropathology at the interim evaluations. The animals were anaesthetized with sodium pentobarbital and total body perfusion was accomplished with 2% heparinized Ringer's solution followed by 2.5% glutaraldehyde. The brain, sciatic nerve, and spinal cord were removed and placed in 10% neutral buffered formalin, processed as described above, and stained with hematoxylin and eosin, luxol fast blue/cresyl fast violet, and Bodian's stain. Complete histopathologic examinations were performed on all rats and mice and on all tissues with grossly visible lesions. Tissues examined are listed in Table 2.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The microscopic slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and histotechnique was evaluated. The quality assessment pathologist reviewed the pituitary gland and liver of male rats and the adrenal cortex, ovary, and liver of female rats to verify the incidence and severity of selected nonneoplastic lesions. Neoplasms of the pituitary gland pars distalis, skeletal muscles, and liver of male rats and neoplasms of the liver of female rats were also reviewed to verify the diagnoses. The spleen and liver of male and female rats were also reviewed to verify the incidences of mononuclear cell leukemia. For mice, the quality assessment pathologist reviewed the adrenal gland of males and females and the liver of males to verify the incidence and severity of selected nonneoplastic lesions. Further, neoplasms of the adrenal medulla and harderian gland of male and female mice, neoplasms of the small intestine, pancreatic islets, and gallbladder of male mice, and neoplasms of the liver, pituitary gland pars intermedia, skeletal muscle, and ovary of female mice were reviewed to verify the diagnoses.

The quality assessment report and slides were submitted to the NTP Pathology Working Group (PWG) chair. Representative histopathology slides containing examples of disagreements in diagnosis between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chair to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of dose groups or previously rendered diagnoses. When the consensus opinion of the PWG differed from that of the laboratory pathologist, the diagnosis was changed. Thus, the final diagnoses represent a consensus of contractor pathologists and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analyses of pathology data, the diagnosed lesions for each tissue type were evaluated separately or combined according to the guidelines of McConnell *et al.* (1986).

Statistical Methods

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses if they were found dead of other than natural causes or were missing; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions as presented in Tables A1, A4, B1, B5, C1, C5, D1, and D5 are given as the number of animals bearing such lesions at a specific anatomic site and the number of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the ratio of the number of affected animals to the number of animals with the site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., skin, intestine, harderian gland, and mammary gland) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Neoplasm Incidences

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

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

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

Analysis of Nonneoplastic Lesion Incidences

Because all nonneoplastic lesions in these studies were considered to be incidental to the cause of death or not rapidly lethal, the primary statistical analysis used was a logistic regression analysis in which lesion prevalence was modeled as a logistic function of chemical exposure and time. For lesions detected at the interim evaluation, the Fisher exact test was used, a procedure based on the overall proportion of affected animals.

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 neoplasm incidence. Consequently, neoplasm incidences from the NTP historical control database (Haseman *et al.*, 1984, 1985) are included in the NTP reports for neoplasms appearing to show compound-related effects.

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between dosed and

control groups in the analysis of continuous variables. Organ and body weight data, which have approximately normal distributions, were analyzed using the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Clinical chemistry, hematology, and neurobehavioral data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Dunn (1964) and Shirley (1977). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-response trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-response trend (Dunnett's or Dunn's test). Average severity values were analyzed for significance using the Mann-Whitney U test (Hollander and Wolfe, 1973).

Quality Assurance Methods

The 13-week and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, they were audited retrospectively by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and staff review draft of this NTP Technical Report were conducted. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff so that all discrepancies had been resolved or were otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICOLOGY

The genetic toxicity of tricresyl phosphate was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium* and chromosomal damage in cultured Chinese hamster ovary cells. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies of tricresyl phosphate are part of a larger effort by the NTP to develop a database that would permit the evaluation of carcinogenicity in experimental animals from the structure of the chemical and its responses in short-term *in vitro* and *in vivo* genetic toxicity tests. These genetic toxicity tests were originally developed to study mechanisms of chemically induced DNA damage and to predict carcinogenicity in animals, based on the electrophilic theory of chemical carcinogenesis and the somatic mutation theory (Miller and Miller, 1977; Straus, 1981; Crawford, 1985).

There is a strong correlation between a chemical's potential electrophilicity (structural alert to DNA reactivity), mutagenicity in *Salmonella*, and carcinogenicity in rodents. The combination of electrophilicity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in rats and mice and/or at multiple tissue sites (Ashby and Tennant, 1991). Other *in vitro* genetic toxicity tests do not correlate well with rodent carcinogenicity (Tennant *et al.*, 1987; Zeiger *et al.*, 1990), although these other tests can provide information on the types of DNA and chromosome effects that can be induced by the chemical being investigated. Data from the NTP studies show that a positive response in *Salmonella* is currently the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens were rodent carcinogens), and that there is no complimentarity among the *in vitro* genetic toxicity tests. That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone. The predictivity for carcinogenicity of a positive response in bone marrow chromosome aberration or micronucleus tests is not yet defined.

TABLE 2
Experimental Design and Materials and Methods in the Studies of Tricresyl Phosphate

16-Day Gavage Studies	13-Week Gavage Studies	13-Week Feed Studies	2-Year Feed Studies
Study Laboratory			
Battelle Columbus (Columbus, OH)	Battelle Columbus (Columbus, OH)	Battelle Columbus (Columbus, OH)	Battelle Columbus (Columbus, OH)
Strain and Species			
Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$
Animal Source			
Charles River Breeding Laboratories (Kingston, NY)	Simonsen Laboratories, Inc. (Gilroy, CA)	Frederick Cancer Research Facility (Frederick, MD)	Simonsen Laboratories, Inc. (Gilroy, CA)
Time Held Before Studies			
20 days (male) 21 or 22 days (female)	Rats: 27 to 30 days Mice: 19 to 22 days	15 or 16 days	11 to 14 days
Average Age When Studies Began			
Rats: 8 weeks Mice: 9 weeks	Rats: 10 weeks Mice: 9 weeks	6 weeks	6 weeks
Date of First Dose			
Rats: 12 April 1982 (male) 13-14 April 1982 (female) Mice: 19 April 1982 (male) 20-21 April 1982 (female)	Rats: 27-28 December 1982 (male) 29-30 December 1982 (female) Mice: 18-19 October 1982 (male) 20-21 October 1982 (female)	Rats: 28-29 November 1984 Mice: 5-6 December 1984	Rats: Core - 29 September 1986 Stop exposure - 18 September 1986 Mice: 13 October 1986
Duration of Dosing			
13 or 14 days	90 days	90 days	Rats: Core - 104 weeks Stop exposure 22 weeks Mice: 105 weeks
Date of Last Dose			
Rats: 26-27 April 1982 (male) 28-29 April 1982 (female) Mice: 3-4 May 1982 (male) 5-6 May 1982 (female)	Rats: 28-29 March 1983 (male) 30-31 March 1983 (female) Mice: 17-18 January 1983 (male) 19-20 January 1982 (female)	Rats: 26-27 February 1985 Mice: 5-6 March 1985	Rats: Core- 19 September 1988 Stop exposure 20 February 1987 Mice: 10 October 1988

TABLE 2
Experimental Design and Materials and Methods in the Studies of Tricresyl Phosphate (continued)

16-Day Gavage Studies	13-Week Gavage Studies	13-Week Feed Studies	2-Year Feed Studies
Necropsy Dates			
Rats: 27-28 April 1982 (male) 29-30 April 1982 (female) Mice: 4-5 May 1982 (male) 6-7 May 1982 (female)	Rats: 29-30 March 1983 (male) 31 March-1 April 1983 (female) Mice: 18-19 January 1983 (male) 20-21 January 1983 (female)	Rats: 26-27 February 1985 Mice: 5-6 March 1985	Rats: 26-29 September 1988 Mice: 17-21 October 1988
Average Age at Necropsy			
Rats: 10 weeks Mice: 11 weeks	Rats: 23 weeks Mice: 22 weeks	19 weeks	Rats: 110 weeks Mice: 112 weeks
Size of Study Groups			
10 males and 10 females	10 males and 10 females	10 males and 10 females	95 males and 95 females
Method of Distribution			
Animals randomized according to body weight using a table of random numbers.	Same as the 16-day studies	Animals randomized according to body weight using a computer generated table of random numbers.	Same as the 13-week feed studies
Animals per Cage			
5	5	Rats: 5 Mice: 1	Rats: 5 Mice: 1
Method of Animal Identification			
Ear tag	Ear tag	Ear tag	Ear tag and toe clip
Diet			
NIH-07 open formula pelleted diet (Zeigler Bros., Inc., Gardners, PA), available *ad libitum*	Same as the 16-day studies	NIH-07 open formula meal diet (Zeigler Bros., Inc., Gardners, PA), available *ad libitum*	Same as the 13-week feed studies
Maximum Storage Time for Feed			
Not available	Not available	120 days after milling	120 days after milling
Water			
City of Columbus, OH, municipal water supply, via automatic watering system (Edstrom Industries, Inc., Waterford, WI), available *ad libitum*	Same as the 16-day studies	Same as the 16-day studies	Same as the 16-day studies
Cages			
Polycarbonate (Lab Products, Inc., Rochelle, NJ), changed twice weekly	Same as the 16-day studies	Polycarbonate (Lab Products, Inc., Garfield, NJ), changed twice weekly	Polycarbonate (Lab Products, Inc., Maywood, NJ), changed twice weekly

TABLE 2
Experimental Design and Materials and Methods in the Studies of Tricresyl Phosphate (continued)

16-Day Gavage Studies	13-Week Gavage Studies	13-Week Feed Studies	2-Year Feed Studies
Bedding			
Not available	Ab-Sorb-Dri® hardwood chips (Ab-Sorb-Dri, Inc.), changed twice weekly	BetaChips®, heat-treated hardwood chips (Northeastern Products, Inc., Warrensburg, NY), changed twice weekly	BetaChips®, heat-treated hardwood chips (Northeastern Products, Inc., Warrensburg, NY) until 21 May 1988, then SaniChips, hardwood chips (P.J. Murphy Forest Products Corp., Montville, NJ), changed twice weekly
Cage Filters			
Spun-bonded polyester (DuPont 2024), changed once every two weeks	Same as the 16-day studies	Spun-bonded polyester (Snow Filtration, Co., Cincinnati, OH), changed once every two weeks	Same as the 13-week feed studies
Racks			
Stainless steel (Lab Products, Inc., Rochelle, NJ), changed once every two weeks	Same as the 16-day studies	Stainless steel (Lab Products, Inc., Garfield, NJ), changed once every two weeks	Stainless steel (Lab Products, Inc., Maywood, NJ), changed once every two weeks
Animal Room Environment			
Temperature: 21°-23° C Relative humidity: 40%-60% Fluorescent light: 12 hours/day Room air changes: 15 changes/hour	Temperature: 21°-23° C Relative humidity: 40%-60% Fluorescent light: 12 hours/day Room air changes: 15 changes/hour	Average temperature: 22° C Relative humidity: 45%-56% (rats) 46%-57% (mice) Fluorescent light: 12 hours/day Room air changes: 15 changes/hour	Average temperature: 22° C Average relative humidity: 49% Fluorescent light: 12 hours/day Room air changes: 15 changes/hour
Doses			
0, 360, 730, 1,450, or 2,900, in corn oil by gavage or 5,800 mg/kg neat by gavage	0, 50, 100, 200, 400, or 800 mg/kg in corn oil by gavage	Rats: 0, 900, 1,700, 3,300, 6,600, or 13,000 ppm in feed Mice: 0, 250, 500, 1,000, 2,100, or 4,200 ppm in feed	Rats: 0, 75, 150, or 300 ppm in feed Stop-exposure rats: 600 ppm in feed Mice: 0, 60, 125, or 250 ppm in feed
Type and Frequency of Observation			
Observed once daily; animals weighed initially, weekly, and at the end of the studies.	Observed twice daily; clinical findings recorded weekly; animals weighed initially, weekly, and at the end of the studies.	Observed twice daily; clinical findings recorded weekly; animals weighed initially, weekly, and at the end of the studies; feed consumption measured weekly.	Observed twice daily; clinical findings and animal weights recorded weekly for first 13 weeks and monthly thereafter; feed consumption measured monthly.
Method of Sacrifice			
Carbon dioxide	Pentobarbital injection	Carbon dioxide	Carbon dioxide

TABLE 2
Experimental Design and Materials and Methods in the Studies of Tricresyl Phosphate (continued)

16-Day Gavage Studies	13-Week Gavage Studies	13-Week Feed Studies	2-Year Feed Studies
Necropsy			
Necropsy was performed on all animals. Organ weights were recorded for brain, heart, right kidney, liver, lung, right testis, and thymus.	Necropsy was performed on all animals. Organ weights were recorded for brain, heart, right kidney, liver, lung, left testis, and thymus.	Necropsy was performed on all animals. Organ weights recorded for brain, heart, right kidney, liver, lung, right testis, and thymus.	Necropsy was performed on all animals. Organ weights recorded for left and right adrenal gland, brain, left and right kidney, liver, and left and right testis at the 3-, 9-, and 15-month interim evaluations.
Clinical Pathology			
None	Blood was collected from the vena cava (rats) or by cardiac puncture (mice) for hematology and clinical chemistry. *Hematology:* erythrocytes, hemoglobin, hematocrit, mean erythrocyte hemoglobin, mean erythrocyte hemoglobin concentration, mean erythrocyte volume, and total and differential leukocyte counts *Clinical chemistry:* cholinesterase	Blood was collected from the orbital sinus of all animals for hematology, and vena cava (rats) or by cardiac puncture (mice) for clinical chemistry. *Hematology:* erythrocytes, hemoglobin, hematocrit, mean erythrocyte hemoglobin, mean erythrocyte hemoglobin concentration, mean erythrocyte volume, platelets, reticulocytes, and total and differential leukocyte counts *Clinical chemistry:* cholinesterase	Blood was collected from the orbital sinus of all animals for hematology and clinical chemistry at the 3-, 9-, and 15-month interim evaluations. *Hematology:* erythrocytes, hemoglobin, hematocrit, mean erythrocyte hemoglobin, mean erythrocyte hemoglobin concentration, mean erythrocyte volume, platelets, reticulocytes, nucleated erythrocytes, and total and differential leukocyte counts *Clinical chemistry:* cholinesterase
Neurobehavioral Studies			
Spontaneous motor activity, forelimb and hindlimb grip strength, startle response, and paw-lick latency were measured in all rats and mice one week before dosing began and on the day before necropsy.	Spontaneous motor activity, forelimb and hindlimb grip strength, startle response, and paw-lick latency were measured in all rats and mice one week before dosing began and on the day before necropsy.	Forelimb and hindlimb grip strength measured in all rats and mice before exposure and on the day before necropsy.	Forelimb and hindlimb grip strength measured in all rats and mice before exposure and prior to necropsy at the 3-, 9-, and 15-month interim evaluations.

TABLE 2
Experimental Design and Materials and Methods in the Studies of Tricresyl Phosphate (continued)

16-Day Gavage Studies	13-Week Gavage Studies	13-Week Feed Studies	2-Year Feed Studies
Histopathology			
Histopathologic examinations were conducted on all rats receiving 5,800 mg/kg, all rats dying early, and all mice receiving 2,900 mg/kg. In addition, the mandibular lymph node, spleen, and thymus of all controls, rats and surviving male mice that received 1,450 mg/kg, rats that received 2,900 mg/kg, and surviving mice that received 5,800 mg/kg were examined.	Complete histopathology was performed on all controls, all animals dying early, and all rats and mice receiving 800 mg/kg. In addition to gross lesions, the tissues examined included: adrenal gland, bone (including marrow), brain, clitoral gland (rats), epididymis, esophagus, gallbladder (mice), heart, kidney, large intestine (cecum, colon, rectum), liver, lung, mandibular and mesenteric lymph node, mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland (rats), prostate gland, salivary gland, sciatic nerve, seminal vesicle, skin, small intestine (duodenum, jejunum, ileum), spinal cord, spleen, stomach, testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. In addition, the adrenal gland, ovary, and spinal cord and sciatic nerve of all dosed rats and mice and testis of dosed rats were examined.	Complete histopathology was performed on all control and high-dose rats and mice. In addition to gross lesions, the tissues examined included: adrenal gland, bone (including marrow), brain, clitoral gland (rats), epididymis, esophagus, gallbladder (mice), heart, kidney, large intestine (cecum, colon, rectum), liver, lung, mandibular and mesenteric lymph node, mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland (rats), prostate gland, salivary gland, sciatic nerve, seminal vesicle, skin, small intestine (duodenum, jejunum, ileum), spinal cord, spleen, stomach, testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. In addition, the adrenal gland, epididymis, kidney, ovary, pituitary gland (males), and testis of rats exposed to 900, 1,700, 3,300, or 6,600 ppm and the adrenal gland, gallbladder, kidney, ovary, sciatic nerve, and spinal cord of mice exposed to 250, 500, 1,000, or 2,100 ppm were examined.	Complete histopathology was performed on all rats and mice. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, brain, bone and marrow, clitoral gland (rats), large intestine (cecum, colon, rectum), epididymis, esophagus, gallbladder (mice), heart, kidney, liver, lung, mandibular and mesenteric lymph nodes, mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland (rats), prostate gland, salivary gland, sciatic nerve, seminal vesicle, skin, small intestine (duodenum, jejunum, ileum), spinal cord, spleen, stomach (forestomach and glandular), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus.

RESULTS

RATS

16-DAY GAVAGE STUDY

One control male and one control female rat, one male receiving 730 mg/kg, one female receiving 1,450 mg/kg, and five males and eight females receiving 2,900 mg/kg died during the study (Table 3). Reduced survival in the 2,900 mg/kg groups was related to chemical administration. The final mean body weights and mean body weight gains of male and female rats that received 1,450, 2,900, and 5,800 mg/kg were significantly lower than those of the controls. The only clinical finding related to chemical administration was diarrhea, which occurred in six males receiving 730 mg/kg and all males and females receiving 1,450, 2,900, or 5,800 mg/kg.

The deaths of one control male, one control female, one male that received 730 mg/kg, and one male and one female that received 2,900 mg/kg were due to improper gavage technique and the introduction of gavage fluid into the lungs. Lesions compatible with sialodacryoadenitis virus infection were observed in

TABLE 3
Survival and Mean Body Weights of Rats in the 16-Day Gavage Study of Tricresyl Phosphate

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	9/10[c]	158 ± 3	214 ± 6	55 ± 4	
360	10/10	160 ± 2	209 ± 4	49 ± 2	98
730	9/10[d]	160 ± 2	199 ± 4	40 ± 2	93
1,450	10/10	158 ± 3	178 ± 5**	20 ± 4**	83
2,900	5/10[e]	162 ± 3	164 ± 16**	4 ± 13**	76
5,800	10/10	163 ± 3	168 ± 9**	5 ± 9**	78
Female					
0	9/10[d]	121 ± 3	148 ± 2	28 ± 1	
360	10/10	123 ± 1	154 ± 2	31 ± 2	104
730	10/10	127 ± 3	153 ± 4	26 ± 2	103
1,450	9/10[f]	123 ± 3	136 ± 4*	14 ± 5**	92
2,900	2/10[g]	125 ± 2	122 ± 7**	−4 ± 2**	83
5,800	10/10	124 ± 2	125 ± 5**	2 ± 4**	85

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on the number of animals surviving to the end of the study.
[c] Day of death: 6
[d] Day of death: 12
[e] Day of death: 6, 10, 12, 12, 16
[f] Day of death: 13
[g] Day of death: 9, 10, 11, 11, 11, 12, 14, 14

one female that received 1,450 mg/kg and five males that received 2,900 mg/kg and may have contributed to their deaths. Deaths of other animals were considered to be the result of chemical exposure.

Total activity recorded at the end of the 16-day study decreased with dose among groups of male rats but was not significantly different from that of the controls (Table H1). Among females, total activity for groups that received 1,450, 2,900, or 5,800 mg/kg was significantly lower than that of the controls, and the change in group mean total activity (activity at day 14 minus activity at day 0) was significantly greater than the change in activity recorded for the controls. Slight differences were noted in startle response latency for a few groups, but the differences were small in magnitude and not considered biologically meaningful. Significant increases in startle response amplitude occurred in females that received 1,450 mg/kg and males and females that received 2,900 or 5,800 mg/kg. Paw-lick latency in males was unaffected by chemical administration, but latency was significantly increased in females that received 1,450, 2,900, or 5,800 mg/kg. Forelimb grip strengths were significantly reduced at the end of the study in females that received 1,450 mg/kg and males and females that received 2,900 or 5,800 mg/kg, and hindlimb grip strengths were significantly reduced at the end of the study in males that received 2,900 mg/kg and males and females that received 5,800 mg/kg.

Almost all significant changes in neurobehavioral measures occurred in groups that received 1,450, 2,900, or 5,800 mg/kg, doses that were also associated with mortality and/or lower mean body weights. Therefore, it was not possible to distinguish changes due to a direct chemical effect on the nervous system from changes resulting from toxicity.

Absolute thymus weights of males and absolute and relative thymus weights of females that received 1,450 mg/kg, and absolute and relative thymus weights of males and females that received 2,900 or 5,800 mg/kg were significantly lower than those of controls (Table F1). Relative liver weights of all groups of dosed males and absolute and relative liver weights of all groups of dosed females were significantly greater than those of the controls. Other differences in organ weights were considered to be due to the lower final mean body weights of rats that received 1,450, 2,900, and 5,800 mg/kg.

There were no gross lesions observed at necropsy that were considered to be related to chemical administration. Diffuse aspermatogenesis was present in the testes of male rats that received 2,900 and 5,800 mg/kg. Mild necrosis of the spleen and mandibular lymph node was observed in male rats receiving 5,800 mg/kg, and mild thymic lymphoid depletion was observed in female rats receiving 5,800 mg/kg. Necrosis of the mandibular lymph node and spleen, and necrosis and lymphoid depletion of the thymus were observed in male and female rats that received 2,900 mg/kg (Table 4).

Dose selection rationale: Due to dose-related decreases in final mean body weights in rats receiving 1,450, 2,900, and 5,800 mg/kg, chemical-related deaths in rats receiving 2,900 mg/kg, and chemical-related microscopic lesions in rats receiving 2,900 and 5,800 mg/kg, the high dose selected for the 13-week gavage study was 800 mg/kg. The other doses selected were 50, 100, 200, and 400 mg/kg.

TABLE 4
Selected Incidences of Nonneoplastic Lesions in Rats in the 16-Day Gavage Study of Tricresyl Phosphate

Dose (mg/kg)	0	730	1,450	2,900	5,800
Male					
n[a]	10	1	10	10	10
Harderian Gland					
Necrosis, Multifocal[b]	-[c]	-	-	2 (1.5)[d]	0
Mandibular Lymph Node					
Necrosis, Multifocal	0	1 (3.0)	0	2 (1.0)	6**(1.8)
Nasolacrimal Duct					
Inflammation, Acute, Multifocal	-	-	-	1 (2.0)	0
Necrosis, Diffuse	-	-	-	1 (4.0)	0
Salivary Gland					
Necrosis, Diffuse	-	-	-	2 (4.0)	0
Spleen					
Necrosis, Multifocal	0	1 (2.0)	0	4*(2.3)	5*(1.8)
Testis					
Aspermatogenesis, Diffuse	-	-	-	5 (3.0)	10 (4.0)
Thymus					
Necrosis, Multifocal	0	-	0	4*(1.5)	0
Lymphoid Depletion, Diffuse	0	-	0	6**(3.7)	0

(continued)

TABLE 4
Selected Incidences of Nonneoplastic Lesions in Rats in the 16-Day Gavage Study of Tricresyl Phosphate
(continued)

Dose (mg/kg)	0	730	1,450	2,900	5,800
Female					
n	10		10	10	10
Harderian Gland					
Necrosis, Diffuse	-		-	1 (3.0)	0
Necrosis, Multifocal	-		-	4 (2.3)	0
Mandibular Lymph Node					
Necrosis, Multifocal	0		1 (2.0)	6**(2.2)	0
Nasolacrimal Duct					
Inflammation, Acute, Multifocal	-		0	3 (2.0)	0
Necrosis, Diffuse	-		0	2 (2.5)	0
Necrosis, Multifocal	-		1 (3.0)[e]	0	0
Salivary Gland					
Necrosis, Diffuse	-		0	5 (4.0)	0
Necrosis, Multifocal	-		1 (2.0)[e]	4 (1.5)	0
Spleen					
Necrosis, Diffuse	0		1 (3.0)	5*(3.0)	0
Thymus					
Necrosis, Diffuse	0		1 (4.0)	8**(4.1)	0
Lymphoid Depletion, Diffuse	0		2 (3.5)	7**(3.9)	2 (1.5)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] Number of animals examined microscopically; females receiving 730 mg/kg not examined microscopically.
[b] Number of animals with lesion
[c] Organ not examined in this dose group
[d] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked, 5 = severe.
[e] n=1

13-WEEK GAVAGE STUDY

All rats survived to the end of the study (Table 5). There were no clinical findings clearly related to tricresyl phosphate administration. Mean body weights of male rats that received 800 mg/kg were lower than those of the controls throughout the study, whereas mean body weights of males that received 200 or 400 mg/kg were lower than those of controls during the latter half of the study. The final mean body weights and mean body weight gains of males receiving 200, 400, and 800 mg/kg were significantly lower than those of the controls. The final mean body weights of dosed groups of female rats were similar to that of the controls. Average daily feed consumption by male and female rats that received 800 mg/kg was slightly greater than feed consumption by controls; however, feed consumption by groups receiving lower doses was similar to consumption by controls.

TABLE 5
Survival and Body Weights of Rats in the 13-Week Gavage Study of Tricresyl Phosphate

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	199 ± 5	373 ± 6	174 ± 4	
50	10/10	191 ± 4	361 ± 5	170 ± 5	97
100	10/10	195 ± 4	362 ± 8	167 ± 5	97
200	10/10	193 ± 4	346 ± 7**	153 ± 5**	93
400	10/10	191 ± 4	343 ± 5**	152 ± 6**	92
800	10/10	195 ± 4	324 ± 5**	129 ± 5**	87
Female					
0	10/10	144 ± 2	205 ± 5	60 ± 3	
50	10/10	146 ± 2	208 ± 3	62 ± 2	102
100	10/10	144 ± 2	208 ± 2	64 ± 2	102
200	10/10	147 ± 2	212 ± 3	65 ± 2	104
400	10/10	143 ± 3	205 ± 3	63 ± 3	100
800	10/10	145 ± 2	213 ± 3	68 ± 2*	104

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Number of animals surviving at 13 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error.

Absolute and relative liver weights of male rats that received 800 mg/kg and female rats that received 400 or 800 mg/kg were significantly greater than those of controls, whereas the absolute and relative thymus weights of males and females and the absolute and relative testis weights of males decreased with dose (Table F2). Several organ weight to body weight ratios of males receiving 200, 400, or 800 mg/kg were significantly different from controls; however, the lower final mean body weights of these groups tend to obscure any possible association between these differences and a toxic response.

Hemoglobin concentration and erythrocyte counts in males that received 400 or 800 mg/kg and the hemoglobin concentration in females that received 200 or 800 mg/kg were significantly lower than those of the controls (Table G1). However, the magnitude of the decreases were small and not indicative of toxicity to the blood or hematopoietic system. There were also significant, dose-related decreases in the serum cholinesterase activity in all dosed groups of males and females. The only neurobehavioral measure affected by chemical exposure in the 13-week gavage study was hindlimb grip strength, which was significantly reduced in female rats that received 400 or 800 mg/kg. However, the magnitude of the reduction was small, and the difference between group mean grip strength recorded on study day 0 and that recorded at week 13 did not differ significantly from the corresponding difference measured for the control group.

The principal lesions associated with administration of tricresyl phosphate by gavage for 13 weeks occurred in the testis, ovary, and adrenal gland (Table 6). Atrophy of the testis was observed in all males receiving 400 or 800 mg/kg and was characterized by focal to diffuse loss of spermatogenic cells from the seminiferous tubules. The most severely affected tubules had only a thin layer of Sertoli cells remaining. Hypertrophy of ovarian interstitial cells occurred in all female rats receiving tricresyl phosphate. The interstitial cells were enlarged by abundant foamy cytoplasm, apparently due to lipid accumulation. While the change primarily appeared to be enlargement of the interstitial cells, it was uncertain if there was also an increased number of cells (hyperplasia). Diffuse vacuolization of the zona glomerulosa and zona fasciculata of the adrenal cortex also occurred in all male and female rats receiving tricresyl phosphate, and the degree of vacuolization increased with dose.

TABLE 6
Selected Incidences of Nonneoplastic Lesions in Rats in the 13-Week Gavage Study of Tricresyl Phosphate

Doses (mg/kg)	0	50	100	200	400	800
Male						
Adrenal Cortex[a]	10	10	10	10	10	10
Cytoplasmic Vacuolization[b]	0	10**(2.5)[c]	10**(2.7)	10**(2.9)	10**(3.1)	10**(3.9)
Testis	10	10	10	10	10	10
Seminiferous Tubule Atrophy	0	0	0	0	10**(2.2)	10**(3.6)
Female						
Adrenal Cortex	10	10	10	10	10	10
Cytoplasmic Vacuolization	0	10**(1.0)	10**(1.0)	10**(1.3)	10**(1.6)	10**(2.2)
Ovary	10	10	10	10	10	10
Interstitial Cell Hypertrophy	0	10**(3.0)	10**(3.9)	10**(3.9)	10**(3.2)	10**(3.8)

** Significantly different (P≤0.01) from the control group by the Fisher exact test
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked, 5 = severe.

13-WEEK FEED STUDY

All rats survived to the end of the study (Table 7). Final mean body weights and mean body weight gains of females exposed to 3,300 ppm and males and females exposed to 6,600 or 13,000 ppm were significantly lower than those of the controls. During the first week of the study feed consumption by groups of male and female rats exposed to 13,000 ppm was 58% and 50% lower than that by the controls and remained somewhat lower than the controls throughout the study, indicating reduced palatability of feed containing tricresyl phosphate at this concentration. Feed consumption by males exposed to 6,600 ppm was 16% lower than that by controls during the first week of the study. Dietary levels of 900, 1,700, 3,300, 6,600, and 13,000 ppm tricresyl phosphate were estimated to deliver daily doses of 55, 120, 220, 430, and 750 mg/kg body weight to males and 65, 120, 230, 430, and 770 mg/kg to females. The only chemical-related clinical finding was emaciation, which was observed by day 23 in males and by day 10 in females exposed to 13,000 ppm.

There were no biologically significant changes in the neurobehavioral measurements of rats exposed to tricresyl phosphate (Table H3). Relative liver weights of males and females exposed to 1,700, 3,300, 6,600, and 13,000 ppm and absolute liver weights of 6,600 ppm males and females and of 13,000 ppm females were significantly greater than those of controls (Table F3). Absolute and relative right testis weights of males exposed to 6,600 and 13,000 ppm were significantly lower than those of the controls. Other organ weight differences were most likely due to the reduced body weights of groups

TABLE 7
Survival, Mean Body Weights, and Feed Consumption of Rats in the 13-Week Feed Study of Tricresyl Phosphate

Dose (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Feed Consumption[c]	
		Initial	Final	Change		Week 1	Week 12
Male							
0	10/10	151 ± 4	359 ± 7	209 ± 6		16.1	16.2
900	10/10	149 ± 4	355 ± 8	206 ± 10	99	14.0	16.1
1,700	10/10	150 ± 4	363 ± 6	213 ± 5	101	19.7	15.9
3,300	10/10	147 ± 4	340 ± 4	193 ± 5	95	16.4	16.1
6,600	10/10	142 ± 5	327 ± 8**	185 ± 5**	91	13.5	16.8
13,000	10/10	136 ± 4*	242 ± 8**	106 ± 5**	67	6.8	15.0
Female							
0	10/10	117 ± 2	198 ± 3	81 ± 2		11.1	9.7
900	10/10	116 ± 2	191 ± 4	75 ± 3	97	11.5	10.5
1,700	10/10	118 ± 2	192 ± 3	74 ± 3	97	11.5	9.5
3,300	10/10	116 ± 2	187 ± 3*	71 ± 3**	94	11.4	9.3
6,600	10/10	112 ± 2	177 ± 3**	65 ± 3**	89	10.1	8.7
13,000	10/10	107 ± 2**	175 ± 3**	68 ± 3**	88	5.6	11.1

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Number of animals surviving at 13 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error.
[c] Feed consumption is expressed as grams per animal per day.

exposed to 3,300, 6,600, and 13,000 ppm. There were no differences in the hematological parameters which were considered to be related to chemical exposure. Significant dose-related decreases in the serum cholinesterase activity was present in all exposed groups of rats (Table G2).

At necropsy adrenal gland enlargement was observed in two males and four females exposed to 6,600 ppm and four males and six females exposed to 13,000 ppm. In addition, small testes were observed in one 6,600 ppm and four 13,000 ppm males. Microscopic lesions associated with chemical exposure were present in the testis, epididymis, adrenal gland, pituitary gland, and kidney of males, and the ovary, adrenal gland, and kidney of females (Table 8).

The lesions in the testis, ovary, and adrenal gland were similar to those observed in the 13-week gavage study. Small focal accumulations of mononuclear inflammatory cells (chronic inflammation) were also observed in the ovary of some exposed females but the incidence and severity did not increase with dose. Small groups of lymphocytes were also observed in the adrenal cortex of some male and female rats exposed to tricresyl phosphate.

Hypertrophy of basophils of the pars distalis of the pituitary gland was observed in several males exposed to 3,300, 6,600, or 13,000 ppm tricresyl phosphate. Scattered individual basophils were enlarged and had pale staining or clear cytoplasm. This effect is consistent with the testicular atrophy observed in males, and may be due to loss of feedback inhibition of secretion of gonadotropin releasing hormone (GnRH) in the hypothalamus with a consequent stimulation of pituitary secretion of gonadotropins. A similar effect has been observed in castrated males.

Edema and/or necrosis of the renal papilla was observed in nearly all male and female rats exposed to 13,000 ppm and most rats exposed to 6,600 ppm. The interstitium was distended, presumably from edema, and there was coagulative necrosis of the epithelium lining the papillary ducts and thin limbs of the loop of Henle with no accompanying inflammatory response. One or a few scattered foci of tubule regeneration consistent with an early stage of nephropathy were also observed in the kidney of most rats in the 13,000 ppm groups, but not in the controls.

Dose selection rationale: Diets containing 6,600 or 13,000 ppm tricresyl phosphate were initially unpalatable to male and female rats, and groups receiving these diets had significantly lower final mean body weights and mean body weight gains. Histopathologic lesions consistent with very early stages of nephropathy and papillary necrosis were also observed in males and females exposed to 6,600 and 13,000 ppm. Over the duration of the 2-year study, the renal lesions and lower mean body weight gain could become life threatening; therefore these concentrations were considered too high for the high exposure level in a 2-year feed study. At exposure levels of 3,300 ppm and lower, the most significant lesion was cytoplasmic vacuolization of the adrenal cortex. The severity of this lesion increased with exposure level and occurred in all exposed groups of rats but not in controls, and therefore was clearly associated with chemical exposure. Even at the lowest exposure level (900 ppm) the lesion was present in all males and females, with average severity grades of 1.6 (males) and 1.4 (females). While the biological significance of this lesion was unknown, accumulation of cytoplasmic vacuoles was believed to represent an alteration in steroid metabolism. Since adrenal cortical steroids are essential for normal functioning of several organ systems, this change was considered potentially life threatening. Based on this assessment, 900 ppm was considered too high for the high exposure level in a 2-year feed study. Therefore, the decision was made to begin the 2-year feed study with exposure levels of 75, 150, 300, and 600 ppm. After 13 weeks, 10 animals per group would be evaluated for the presence of adrenal gland lesions; if lesions were present in the 600 ppm group then this group would be terminated. If no adrenal gland lesions were present in the 600 ppm group, then the 75 ppm group would be terminated. If adrenal gland lesions were present in all groups, a decision would be made based on the incidence and severity of the lesions in the various groups.

TABLE 8
Selected Incidences of Nonneoplastic Lesions in Rats in the 13-Week Feed Study of Tricresyl Phosphate

Dose (ppm)	0	900	1,700	3,300	6,600	13,000
Male						
n[a]	10	10	10	10	10	10
Adrenal Cortex						
Cytoplasmic Vacuolization, Bilateral[b]	0	10**(1.6)[c]	10**(2.9)	10**(3.0)	10**(4.0)	10**(4.0)
Kidney						
Nephropathy	0	0	0	0	0	9**(1.0)
Renal Papilla, Edema	0	0	0	0	1	10**
Renal Papilla, Necrosis	0	0	0	0	0	9**
Pituitary Gland (Pars Distalis)						
Basophilic Hypertrophy	0	0	0	6**	8**	8**
Testis						
Seminiferous Tubules, Atrophy, Bilateral	0	0	0	0	10**(2.2)	10**(4.0)
Female						
n	10	10	10	10	10	10
Adrenal Cortex						
Cytoplasmic Vacuolization, Bilateral	0	10**(1.4)	10**(2.7)	10**(3.0)	10**(4.0)	10**(4.0)
Kidney						
Nephropathy	0	0	0	0	2 (1.0)	10**(1.0)
Renal Papilla, Edema	0	0	0	0	9**	9**
Renal Papilla, Necrosis	0	0	0	0	6**	9**
Ovary						
Interstitial Cells, Hypertrophy	0	9**(4.0)	10**(4.0)	10**(3.9)	9**(4.0)	10**(4.0)
Interstitium, Inflammation, Chronic, Bilateral	0	8**(2.3)	4*(1.8)	4*(1.5)	6**(1.7)	4*(1.3)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] Number of animals examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked, 5 = severe.

2-YEAR FEED STUDY

Survival

Estimates of survival probabilities for male and female rats are shown in Table 9 and in the Kaplan-Meier curves in Figure 3. Survival of exposed rats was similar to that of the controls.

Body Weights, Feed and Compound Consumption, and Clinical Findings

The mean body weights of exposed groups of male and female rats were similar to those of controls throughout the study (Tables 10 and 11 and Figure 4). Feed consumption by exposed groups of male and female rats was similar to that by controls (Tables J1 and J2). Dietary levels of 75, 150, and 300 ppm tricresyl phosphate were estimated to deliver average daily doses of 3, 6, or 13 mg/kg body weight to males and 4, 7, or 15 mg/kg to females. There were no chemical-related clinical findings noted in male or female rats.

TABLE 9
Survival of Rats in the 2-Year Feed Study of Tricresyl Phosphate

	0 ppm	75 ppm	150 ppm	300 ppm
Male				
Animals initially in study	95	95	95	95
3-Month interim evaluation[a]	15	15	15	15
9-Month interim evaluation[a]	14	15	15	15
15-Month interim evaluation[a]	15	15	15	15
Natural deaths	5	4	4	6
Moribund kills	14	16	11	16
Animals surviving to study termination	32[e]	30	35	28
Percent probability of survival at end of study[b]	63	61	71	56
Mean survival (days)[c]	494	489	492	493
Survival analysis[d]	P=0.664	P=0.868	P=0.604N	P=0.606
Female				
Animals initially in study	95	95	95	95
3-Month interim evaluation[a]	15	15	15	14
9-Month interim evaluation[a]	15	14	15	15
15-Month interim evaluation[a]	14	13	15	15
Natural deaths	3	3	5	5
Moribund kills	14	12	15	18
Accidental deaths[a]	0	0	0	1
Missing[a]	0	0	0	1
Animals surviving to study termination	34	38[e]	30	26
Percent probability of survival at end of study	67	73	60	54
Mean survival (days)	488	496	499	478
Survival analysis	P=0.141	P=0.681N	P=0.877	P=0.357

[a] Censored from survival analyses
[b] Kaplan-Meier determinations based on the number of animals alive on the first day of terminal sacrifice
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the dosed columns. A lower mortality in a dose group is indicated by N.
[e] Includes one animal that died during the last week of the study.

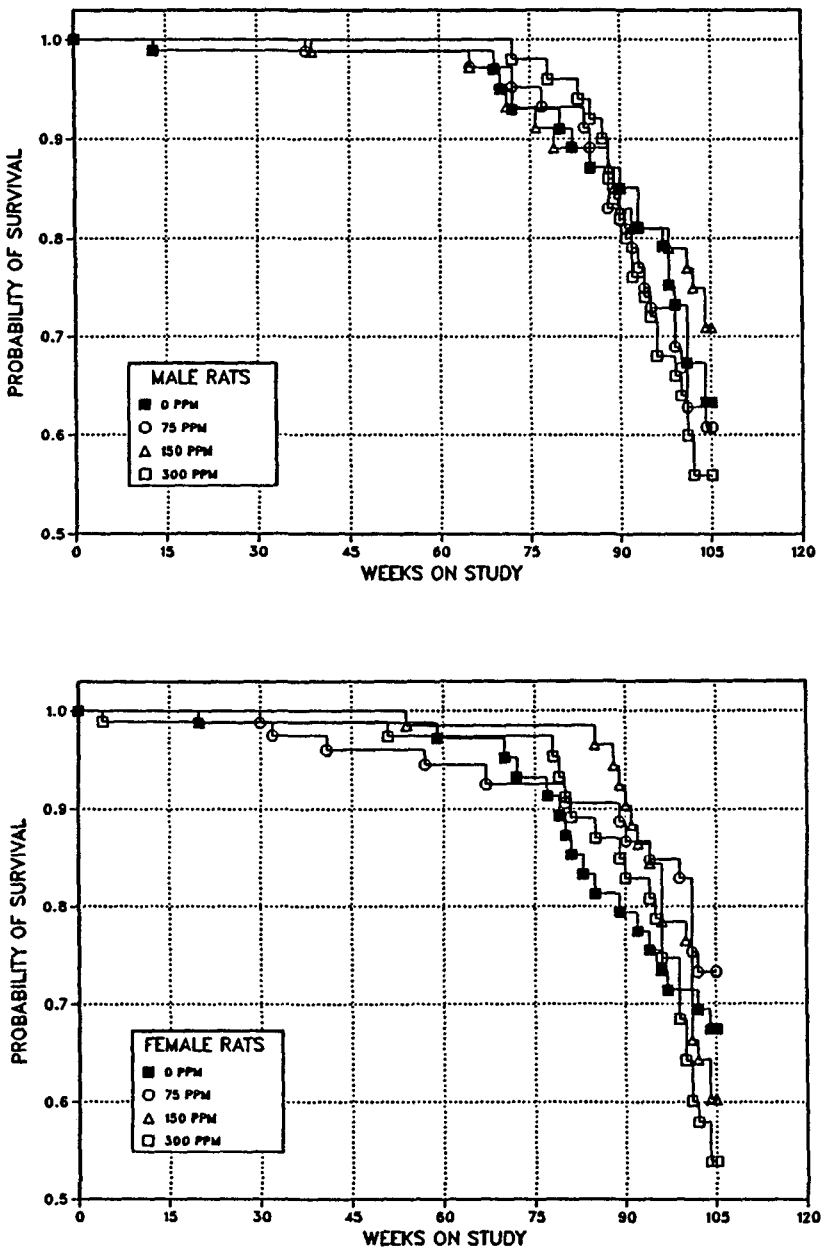


FIGURE 3
Kaplan-Meier Survival Curves for Male and Female Rats Administered Tricresyl Phosphate in Feed for 2 Years

TABLE 10
Mean Body Weights and Survival of Male Rats in the 2-Year Feed Study of Tricresyl Phosphate

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	75 ppm Av. Wt. (g)	75 ppm Wt. (% of controls)	75 ppm No. of Survivors	150 ppm Av. Wt. (g)	150 ppm Wt. (% of controls)	150 ppm No. of Survivors	300 ppm Av. Wt. (g)	300 ppm Wt. (% of controls)	300 ppm No. of Survivors
1	105	95	103	98	95	106	101	95	102	97	95
2	140	95	138	99	95	139	99	95	137	98	95
3	175	95	170	97	95	174	99	95	173	99	95
4	205	95	202	99	95	204	100	95	203	99	95
5	230	95	225	98	95	230	100	95	228	99	95
6	250	95	246	98	95	250	100	95	248	99	95
7	264	95	264	100	95	266	101	95	263	100	95
8	274	95	278	102	95	279	102	95	276	101	95
9	289	95	291	101	95	292	101	95	289	100	95
10	299	95	302	101	95	301	101	95	299	100	95
11	309	95	311	101	95	314	102	95	310	100	95
12	315	95	318	101	95	320	102	95	315	100	95
13	323	94	326	101	94	323	100	94	323	100	94
17[a]	354	79	352	100	80	353	100	80	352	100	80
20	377	79	378	100	80	380	101	80	374	99	80
21	373	79	373	100	80	366	98	80	365	98	80
24	394	79	399	101	80	401	102	80	392	100	80
25	385	79	393	102	80	381	99	80	380	99	80
28	411	79	411	100	80	412	100	80	403	98	80
29	404	79	400	99	80	398	99	80	396	98	80
32	423	79	420	99	80	429	101	80	418	99	80
33	408	79	410	100	80	404	99	80	401	98	80
36	429	79	426	99	80	434	101	80	420	98	80
37	415	79	417	100	80	408	98	80	406	98	80
40[a]	431	65	442	103	64	436	101	64	432	100	65
41	423	65	427	101	64	415	98	64	414	98	65
44	441	65	440	100	64	449	102	64	446	101	65
45	429	65	430	100	64	418	97	64	419	98	65
48	455	65	452	99	64	454	100	64	455	100	65
49	438	65	441	101	64	429	98	64	426	97	65
52	455	65	453	100	64	458	101	64	456	100	65
53	429	65	446	104	64	428	100	64	422	98	65
56	453	65	456	101	64	455	101	64	454	100	65
57	438	65	443	101	64	432	98	64	426	97	65
60	457	65	460	101	64	458	100	64	460	101	65
61	442	65	444	100	64	435	98	64	429	97	65
64	467	65	464	100	64	462	99	64	466	100	65
65[a]	441	50	450	102	49	436	99	49	431	98	50
69	442	49	450	102	48	434	98	48	433	98	50
73	445	47	453	102	47	441	99	46	437	98	49
77	445	47	450	101	47	444	100	45	436	98	49
81	443	46	450	102	46	441	100	44	436	99	48
85	444	45	444	100	45	439	99	44	427	96	46
89	445	44	443	99	41	436	98	43	421	95	43
93	432	43	435	101	39	434	101	40	428	99	38
97	437	40	440	101	36	433	99	40	430	98	34
101	421	35	426	101	32	428	102	38	417	99	32
104	412	33	421	102	31	424	103	35	419	102	28
Mean for weeks											
1-13	244		244	100		246	101		244	100	
14-52	414		415	100		413	100		409	99	
53-104	441		446	101		439	100		434	98	

[a] Interim evaluations occurred during weeks 14, 40, and 65.

TABLE 11
Mean Body Weights and Survival of Female Rats in the 2-Year Feed Study of Tricresyl Phosphate

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	75 ppm Av. Wt. (g)	75 ppm Wt. (% of controls)	75 ppm No. of Survivors	150 ppm Av. Wt. (g)	150 ppm Wt. (% of controls)	150 ppm No. of Survivors	300 ppm Av. Wt. (g)	300 ppm Wt. (% of controls)	300 ppm No. of Survivors
1	91	95	91	99	95	92	100	95	90	99	95
2	111	95	110	99	95	112	101	95	110	99	94
3	126	95	125	99	95	128	101	95	126	100	94
4	140	95	139	99	95	141	101	95	140	100	94
5	150	95	149	100	95	152	101	95	150	100	93
6	158	95	159	101	95	160	101	95	158	100	93
7	164	95	168	102	95	168	102	95	166	101	93
8	170	95	173	102	95	173	102	95	171	101	93
9	174	95	175	101	95	177	102	95	175	101	93
10	179	95	179	100	95	181	101	95	179	100	93
11	182	95	181	99	95	183	101	95	183	101	93
12	182	95	184	101	95	186	102	95	183	100	93
13	185	94	186	101	94	188	102	94	186	101	92
17[a]	196	80	195	99	80	199	101	80	197	101	78
20	208	80	211	102	80	204	98	80	206	99	78
21	204	79	203	99	80	207	102	80	201	99	78
24	215	79	219	102	80	210	98	80	213	99	78
25	210	79	209	100	80	214	102	80	210	100	78
28	220	79	226	103	80	218	99	80	218	99	78
29	216	79	213	99	80	222	103	80	214	99	78
32	225	79	230	102	79	226	100	80	226	100	78
33	220	79	219	100	78	224	102	80	221	100	78
36	231	79	229	99	78	228	99	80	229	99	78
37	228	79	224	98	78	232	102	80	226	100	78
40[a]	236	64	241	102	64	235	99	65	237	100	63
41	234	64	232	99	64	239	102	65	234	100	63
44	241	64	246	102	63	244	101	65	242	101	63
45	242	64	237	98	63	248	103	65	241	100	63
48	256	64	262	102	63	260	101	65	255	100	63
49	252	64	249	99	63	259	103	65	249	99	63
52	261	64	274	105	63	270	103	65	264	101	62
53	262	64	256	98	63	258	99	65	257	98	62
56	264	64	281	106	63	275	104	64	268	102	62
57	268	64	263	98	63	274	102	64	264	98	62
60	275	63	288	105	62	283	103	64	282	103	62
61	279	63	273	98	62	285	102	64	270	97	62
64	286	63	301	105	62	297	104	64	298	104	62
65[a]	289	49	285	99	49	297	103	49	286	99	47
69	299	49	294	98	48	303	101	49	292	98	47
73	310	47	304	98	48	312	101	49	304	98	47
77	312	47	308	99	48	317	102	49	307	99	47
81	319	44	315	99	47	324	101	49	312	98	44
85	325	42	322	99	47	332	102	49	318	98	43
89	323	41	323	100	47	328	101	47	317	98	42
93	326	39	330	101	45	335	103	43	324	99	40
97	328	36	331	101	44	336	102	39	319	97	36
101	319	36	327	103	42	332	104	38	312	98	31
104	315	34	320	102	38	332	106	30	313	99	26
Mean for weeks											
1-13	155		155	100		157	101		155	100	
14-52	228		229	100		230	101		227	100	
53-104	300		301	100		307	102		297	99	

[a] Interim evaluations occurred during weeks 14, 40, and 65.

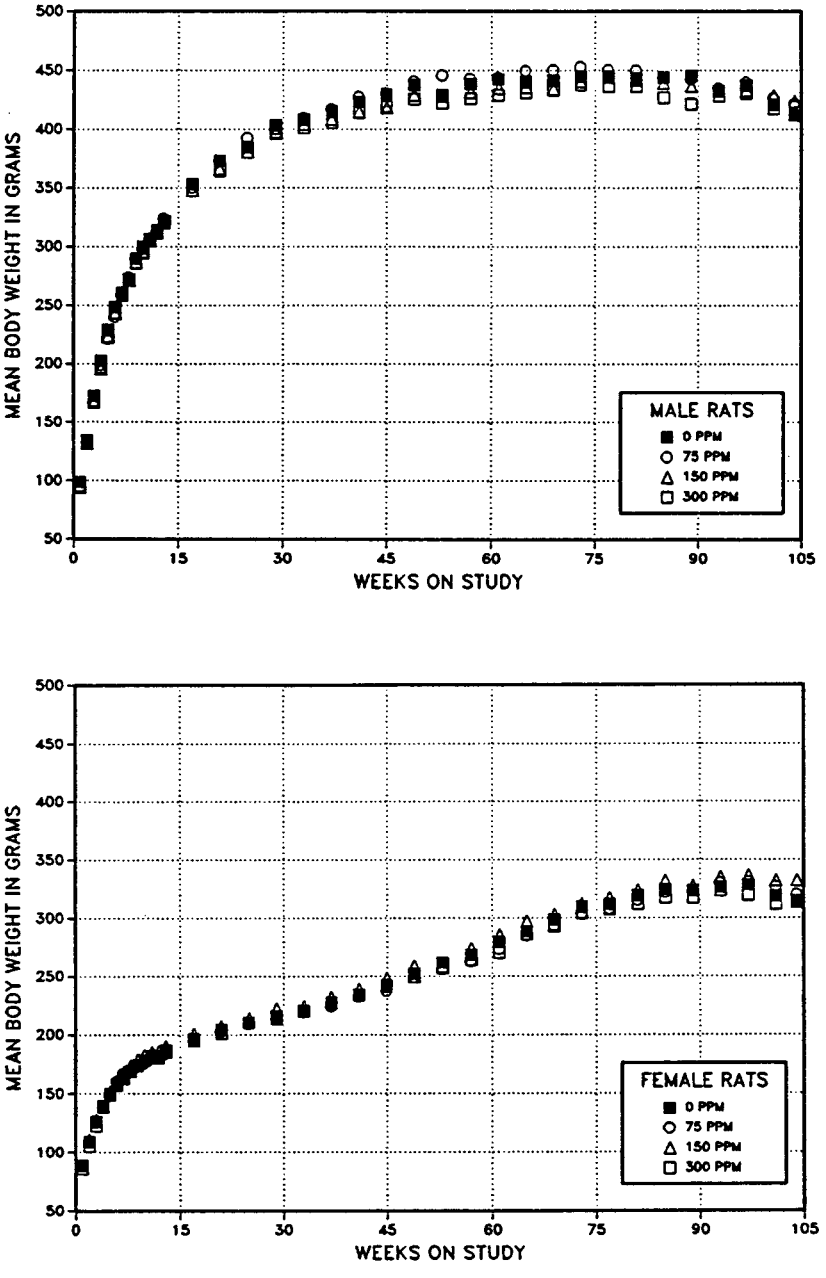


FIGURE 4
Growth Curves for Male and Female Rats
Administered Tricresyl Phosphate in Feed for 2 Years

Hematology, Clinical Chemistry, and Neurobehavioral Results

There were no significant differences in hematology parameters measured at the 3-, 9-, or 15-month interim evaluations that could be related to chemical exposure (Tables G3, G4, and G5). Serum cholinesterase activity in females that were exposed to 150 ppm and in males and females that were exposed to 300 or 600 ppm were significantly lower than those in the controls at the 3-month interim evaluation. At the 9-month evaluation, serum cholinesterase activity of 150 ppm males and females and 300 ppm females were significantly lower than those of controls. At the 15-month evaluation, serum cholinesterase activities in all exposed groups of female rats and in 300 ppm male rats were significantly lower than those in the controls.

Hindlimb grip strengths in 300 ppm males and in males and females exposed to 600 ppm were significantly lower than those of controls at the 3-month interim evaluation (Table H4). The change in group mean hindlimb grip strength in 300 ppm males was significantly lower than that of the controls. There were no significant changes in neurobehavioral measurements among any groups of rats at the 9- and 15-month interim evaluations (Tables H5 and H6).

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of nonneoplastic lesions of the adrenal gland, ovary, and kidney and in the incidence of mononuclear cell leukemia. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, and statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group are presented in Appendix A for male rats and Appendix B for female rats. Historical control incidences for leukemia in female rats appear in Appendix B.

Adrenal gland: At the 3-month interim evaluation, the absolute and relative adrenal gland weights of females exposed to 300 or 600 ppm were significantly greater than those of controls (Table F4). Cytoplasmic vacuolization of the adrenal cortex was observed in one 150 ppm female, all 300 ppm females and 600 ppm males, and nine 600 ppm females (Tables 12 and B5). The lesion was most severe in females exposed to 300 and 600 ppm, and was characterized by increased numbers of small, fine vacuoles in the cortical cells of the zona fasciculata, resulting in a ground glass appearance and an increase in cell size. Cells of the zona reticularis in exposed rats were more compact than those in controls and sinusoids were less apparent, giving the impression that the size of cells in the zona fasciculata might have caused some compression. In 300 ppm females, the fine cytoplasmic vacuoles were still present to a minimal degree; however, cell size in the zona fasciculata was not increased to the same degree as that observed in 600 ppm females, and therefore, compression of the zona reticularis was less apparent. Based on these results, the decision was made to stop chemical exposure of the 600 ppm groups and maintain these animals on control feed.

At the 9-month interim evaluation, all females exposed to 300 ppm and three 150 ppm females had cytoplasmic vacuolization of the adrenal cortex; however, the severity of the lesions was less than that observed at the 3-month evaluation (Tables 12 and B5). At the 15-month interim evaluation cytoplasmic vacuolization of the adrenal cortex was observed in all 300 ppm females, but the severity was minimal. At the end of the 2-year study, the incidence of cytoplasmic vacuolization of the adrenal cortex was significantly increased in females exposed to 300 ppm (Tables 12 and B5). Although the lesion was also present in controls (Plate 1), the pathology working group considered the severity of the lesion in the 300 ppm group (Plate 2) to be slightly greater than and distinguishable from that in the controls.

Ovary: Minimal to mild interstitial cell hyperplasia was present in female rats exposed to 150 or 300 ppm at the 3-, 9-, and 15-month interim evaluations and in 600 ppm females at 9 months (Tables 12 and B5). This lesion occurred with moderate severity in 600 ppm females at 3 months. The lesion was the same as that diagnosed as hypertrophy in the 13-week studies. At the end of the 2-year study the incidence of interstitial cell hyperplasia was significantly increased in female rats exposed to 300 ppm. The lesion was characterized by an increase in size and possibly number of interstitial cells (Plates 3 to 6). There was no particular alteration of ovarian architecture, but rather an enhanced prominence of interstitial cells in animals with this lesion.

TABLE 12
Selected Incidences of Nonneoplastic Lesions in Rats in the 2-Year Feed Study of Tricresyl Phosphate

Doses (ppm)	0	75	150	300	600
Male					
Adrenal Cortex					
Cytoplasmic Vacuolization					
3-Month interim evaluation	0/10[a]	0/10	0/10	0/10	10/10**(1.0)[b]
9-Month interim evaluation	0/9	0/10	0/10	0/10	0/10
15-Month interim evaluation	0/10	0/10	0/10	0/10	0/10
2-Year study	0/50	0/49	0/50	0/49	
Female					
Adrenal Cortex					
Cytoplasmic Vacuolization					
3-Month interim evaluation	0/10	0/10	1/10 (1.0)	10/10**(1.9)	9/10**(1.8)
9-Month interim evaluation	1/10 (1.0)	0/10	3/10 (1.0)	10/10**(1.0)	0/10
15-Month interim evaluation	0/9	0/8	0/10	10/10**(1.1)	0/8
2-Year study	14/51 (1.0)	12/53 (1.2)	16/50 (1.0)	36/50**(1.0)	
Ovary					
Interstitium, Hyperplasia					
3-Month interim evaluation	0/10	0/10	6/10**(1.0)	10/10**(1.6)	10/10**(2.6)
9-Month interim evaluation	0/10	0/10	1/10 (1.0)	10/10**(1.1)	4/10 (1.0)
15-Month interim evaluation	0/9	0/8	3/10 (1.0)	9/10**(1.0)	0/9
2-Year study	0/51	0/53	0/50	15/50**(1.1)	

** Significantly different ($P \leq 0.01$) from the control group by the Fisher exact test (interim evaluations) or the logistic regression test (2-year study)
[a] Number of animals with lesion per number of animals with organ examined microscopically
[b] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.

Kidney: The incidence of nephropathy in males was unaffected by chemical exposure (0 ppm, 47/51; 75 ppm, 48/50; 150 ppm, 46/50; 300 ppm, 45/50; Table A4). However, there was a decreased incidence of nephropathy in exposed groups of female rats (38/51, 34/53, 29/50 22/50; Table B5).

All organs: There was an increased incidence of mononuclear cell leukemia in female rats that received 150 and 300 ppm (8/51, 8/53, 13/50, 15/50; Table B3). The incidence in the control and the 75 ppm groups was considerably lower than the incidence in historical controls from recent NTP feed studies (324/1,251, 26%; range 14%-52%; Table B4), but the incidence in the 150 and 300 ppm groups was similar to that of the historical controls.

MICE

16-DAY GAVAGE STUDY

Five male mice and all female mice receiving 1,450 mg/kg, all male and female mice receiving 2,900 mg/kg, and four male mice and one female mouse receiving 5,800 mg/kg died before the end of the study (Table 13); these deaths were attributed to chemical administration. The final mean body weights of males that received 1,450 and 5,800 mg/kg were significantly lower than that of the controls, while the final mean body weights and mean body weight gains of females that received 360, 730, and 5,800 mg/kg were significantly greater than those of the controls. The primary clinical observation was rough hair coat which occurred in seven males receiving 1,450 mg/kg and 10 males and four females receiving 5,800 mg/kg.

Total spontaneous activity at day 14 in male mice that received 1,450 and 5,800 mg/kg was significantly lower than that in controls (Table H7). Startle response latency in male mice receiving 730, 1,450, and 5,800 mg/kg was significantly longer than that of controls at day 14. Forelimb grip strengths of male mice that received 1,450 mg/kg and of males and females that received 5,800 mg/kg were significantly lower than those of controls at day 14. Hindlimb grip strengths of 360 mg/kg males, 730 mg/kg males and females, 1,450 mg/kg males, and 5,800 mg/kg males and females were significantly lower than those of the controls on day 14 of the study. The absolute and relative thymus weights of males and females receiving 5,800 mg/kg were significantly lower than those of the controls (Table F7). Absolute liver weights of males that received 360 or 730 mg/kg and

TABLE 13
Survival and Mean Body Weights of Mice in the 16-Day Gavage Study of Tricresyl Phosphate

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	26.0 ± 0.4	27.4 ± 0.3	1.4 ± 0.3	
360	10/10	25.8 ± 0.3	27.9 ± 0.3	2.1 ± 0.2	102
730	10/10	25.0 ± 0.4	27.8 ± 0.6	2.8 ± 0.3*	101
1,450	5/10[c]	26.0 ± 0.5	24.5 ± 0.6*	−1.7 ± 0.8**	89
2,900	0/10[d]	26.3 ± 0.3	–	–	–
5,800	6/10[e]	26.2 ± 0.4	26.3 ± 1.0*	−0.1 ± 0.7	96
Female					
0	10/10	19.9 ± 0.4	20.8 ± 0.3	0.9 ± 0.3	
360	10/10	20.3 ± 0.2	22.6 ± 0.3**	2.3 ± 0.2**	109
730	10/10	20.4 ± 0.4	24.3 ± 0.4**	3.9 ± 0.4**	117
1,450	0/10[f]	19.9 ± 0.3	–	–	–
2,900	0/10[g]	20.8 ± 0.4	–	–	–
5,800	9/10[h]	20.8 ± 0.2	23.3 ± 0.4**	2.4 ± 0.3**	112

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Number of animals surviving at 16 days/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on the number of animals surviving to the end of the study. No data calculated for groups with 100% mortality.
[c] Day of death: 14, 15, 15, 16, 16
[d] Day of death: 6, 6, 7, 9, 10, 11, 11, 12, 13, 15
[e] Day of death: 15, 15, 16, 16
[f] Day of death: 13, 13, 13, 14, 14, 14, 14, 14, 14, 15
[g] Day of death: 3, 4, 8, 9, 9, 10, 10, 12, 12, 12
[h] Day of death: 5

all dosed groups of females were significantly greater than those of the controls; relative liver weights of all dosed groups of males and females were significantly greater than those of the controls.

No gross lesions observed at necropsy were related to chemical administration. Microscopic lesions including lymphoid depletion and/or necrosis of the mandibular lymph node, spleen, and thymus were observed primarily in males and females that received 2,900 mg/kg (Table 14). Male and female mice receiving 2,900 mg/kg had increased incidences of lymphoid depletion and necrosis of the spleen and thymus and necrosis of the mandibular lymph node; the severity of these lesions ranged from mild to marked. Lymphoid depletion and necrosis of the spleen and thymus also occurred in a few males and females that received 5,800 mg/kg, but the severity ranged from minimal to moderate. Mild lymphoid depletion of the thymus was also observed in four males receiving 1,450 mg/kg.

Dose selection rationale: Due to reduced survival and the occurrence of lymphoid depletion of the spleen and thymus in male and female mice receiving 1,450, 2,900, and 5,800 mg/kg, these doses were considered too high for the high dose in a 13-week gavage study. Therefore, 800 mg/kg was selected as the high dose for the 13-week gavage study, with the remaining doses being 50, 100, 200, and 400 mg/kg.

TABLE 14
Selected Incidences of Nonneoplastic Lesions in Mice in the 16-Day Gavage Study of Tricresyl Phosphate

Doses (mg/kg)	0	1,450	2,900	5,800
Male				
n[a]	10	5	10	6
Mandibular Lymph Node				
Necrosis, Multifocal[b]	0	0	5*(2.0)[c]	0
Spleen				
Necrosis, Multifocal	0	0	9**(2.4)	0
Lymphoid Depletion, Diffuse	0	0	10**(3.5)	2 (2.0)
Thymus				
Necrosis, Diffuse	0	0	3 (3.7)	0
Necrosis, Multifocal	0	0	3 (3.0)	0
Lymphoid Depletion, Diffuse	0	4**(2.3)	6**(3.7)	3*(2.3)
Female				
n	10		10	9
Mandibular Lymph Node				
Necrosis, Multifocal	0		8**(2.4)	0
Spleen				
Necrosis, Multifocal	0		10**(2.4)	0
Lymphoid Depletion, Diffuse	0		10**(3.4)	0
Thymus				
Necrosis, Diffuse	0		8**(3.9)	0
Necrosis, Multifocal	0		0	1 (1.0)
Lymphoid Depletion, Diffuse	0		8**(3.3)	1 (2.0)

* Significantly different (P≤0.05) from the control group by the Fisher exact test
** P≤0.01
[a] Number of animals with organ examined microscopically; males and females receiving 360 and 730 mg/kg and females receiving 1,450 mg/kg not examined microscopically.
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked, 5 = severe.

13-WEEK GAVAGE STUDY

All mice survived to the end of the study (Table 15). The final mean body weights and mean body weight gains of male mice that received 200, 400, and 800 mg/kg were significantly lower than those of the controls, and the final mean body weights and mean body weight gains of female mice that received 400 and 800 mg/kg were significantly lower than those of controls. Feed consumption by groups of exposed mice was similar to that by controls.

Clinical findings related to chemical administration consisted of hindlimb weakness and hindlimb tremors, which were observed in all male and female mice receiving 800 mg/kg beginning at approximately day 60. Hindlimb weakness was also observed in all females receiving 400 mg/kg (Table H8). Absolute and relative liver weights in female mice that received 200, 400, or 800 mg/kg were significantly greater than those of the controls; however, other organ weight differences were most likely related to lower final mean body weights of these groups (Table F8). There were no differences in hematologic parameters related to chemical administration (Table G6). There were significant, dose-related decreases in serum cholinesterase activity in all dosed groups of males and females.

TABLE 15
Survival and Body Weights of Mice in the 13-Week Gavage Study of Tricresyl Phosphate

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	26.5 ± 0.5	38.6 ± 0.5	12.1 ± 0.8	
50	10/10	25.5 ± 0.5	39.7 ± 0.8	14.2 ± 0.8	103
100	10/10	25.1 ± 0.7	40.6 ± 0.8	15.5 ± 0.9	105
200	10/10	26.0 ± 0.5	35.3 ± 0.7**	9.3 ± 0.5**	91
400	10/10	25.0 ± 0.5	33.9 ± 0.5**	8.9 ± 0.6**	88
800	10/10	25.3 ± 0.5	29.3 ± 0.5**	4.0 ± 0.5**	76
Female					
0	10/10	18.8 ± 0.3	27.9 ± 0.7	9.1 ± 0.6	
50	10/10	19.3 ± 0.5	28.1 ± 1.4	8.8 ± 1.1	101
100	10/10	19.6 ± 0.4	29.3 ± 0.7	9.7 ± 0.7	105
200	10/10	19.3 ± 0.3	27.2 ± 0.3	7.9 ± 0.4	97
400	10/10	20.0 ± 0.5	24.7 ± 0.5**	4.7 ± 0.3**	89
800	10/10	19.5 ± 0.2	22.6 ± 0.3**	3.1 ± 0.2**	81

** Significantly different ($P \leq 0.01$) from the control group by Williams' or Dunnett's test
[a] Number of animals surviving at 13 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error.

The total activity of male and female mice that received 800 mg/kg was significantly lower than that of controls at the end of the study. Although the change in group mean activity was significant for females that received 800 mg/kg, it was not significant for 800 mg/kg males. Post-exposure startle response latency was significantly longer in groups of males and females that received 400 or 800 mg/kg than that measured for controls. Forelimb and hindlimb grip strength of 400 and 800 mg/kg males and females was significantly lower than that measured for controls. Forelimb and hindlimb grip strength of 200 mg/kg females and hindlimb grip strength of 200 mg/kg males were also significantly lower than that measured for controls.

The principal lesions associated with administration of tricresyl phosphate occurred in the adrenal gland, ovary, spinal cord, and sciatic nerve (Table 16). The lesions in the ovary and adrenal gland were similar to those described for rats. Multifocal axonal degeneration of the spinal cord and sciatic nerve was observed in mice that received 100 mg/kg or greater. The lesions were characterized by scattered swollen axons or clear vacuoles representing dilated myelin sheaths. The number of affected axons generally increased with dose. There were also occasional aggregates of mononuclear inflammatory cells observed in the sciatic nerve of some of the affected mice.

TABLE 16
Selected Incidences of Nonneoplastic Lesions in Mice in the 13-Week Gavage Study of Tricresyl Phosphate

Doses (mg/kg)	0	50	100	200	400	800
Male						
Spinal Cord[a]	10	10	10	10	10	10
Multifocal Axonal Degeneration[b]	0	0	2 (1.0)[c]	9**(1.2)	9**(1.3)	10**(2.1)
Sciatic Nerve	10	10	10	10	9	10
Multifocal Axonal Degeneration	0	0	0	6**(1.0)	9**(1.5)	10**(3.0)
Adrenal Cortex	10	10	10	10	10	10
Cytoplasmic Vacuolization	0	10**(1.5)	10**(1.4)	10**(2.0)	10**(2.0)	10**(3.0)
Female						
Spinal Cord	10	9	10	10	10	10
Multifocal Axonal Degeneration	0	0	5*(1.0)	9**(1.5)	10**(2.2)	10**(2.2)
Sciatic Nerve	10	9	10	10	10	10
Multifocal Axonal Degeneration	0	0	1 (1.0)	10**(1.5)	10**(1.6)	9**(2.7)
Adrenal Cortex	10	10	10	10	10	10
Cytoplasmic Vacuolization	0	10**(1.0)	10**(2.4)	10**(3.0)	10**(3.0)	10**(4.0)
Ovary	10	10	10	10	10	10
Interstitial Cell Hypertrophy	0	9**(1.2)	10**(1.5)	10**(1.7)	10**(2.3)	10**(2.6)

* Significantly different (P≤0.05) from the control group by the Fisher exact test
** P≤0.01
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked, 5 = severe.

13-WEEK FEED STUDY

All mice survived to the end of the study (Table 17). The final mean body weights and mean body weight gains of 2,100 ppm females and males and females exposed to 4,200 ppm were significantly lower than those of the controls. At week 12, feed consumption by female mice was progressively less with increasing concentration, and consumption by the 4,200 ppm group was less than at week 1. Feed consumption by other exposed groups of mice was similar to that by the controls. Dietary levels of 250, 500, 1,000, 2,100, and 4,200 ppm tricresyl phosphate were estimated to deliver average daily doses of 45, 110, 180, 380, and 900 mg/kg body weight to males and 65, 130, 230, 530, and 1,050 mg/kg to females. The only clinical findings considered to be related to chemical exposure were tremors, which occurred on day 86 in two males and three females exposed to 4,200 ppm.

TABLE 17
Survival, Mean Body Weights, and Feed Consumption of Mice in the 13-Week Feed Study of Tricresyl Phosphate

Dose (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Feed Consumption[c]	
		Initial	Final	Change		Week 1	Week 12
Male							
0	10/10	21.3 ± 0.4	31.4 ± 1.0	10.1 ± 0.7		4.1	4.9
250	10/10	21.4 ± 0.2	32.4 ± 0.8	11.0 ± 0.7	103	5.3	4.4
500	10/10	21.2 ± 0.4	31.1 ± 0.7	9.8 ± 0.4	99	5.9	5.5
1,000	10/10	21.5 ± 0.4	31.4 ± 0.9	9.9 ± 0.7	100	4.2	5.2
2,100	10/10	21.3 ± 0.5	30.0 ± 0.6	8.8 ± 0.4	96	4.6	4.6
4,200	10/10	20.9 ± 0.3	25.9 ± 0.2**	5.0 ± 0.3**	82	5.3	4.7
Female							
0	10/10	17.1 ± 0.3	28.2 ± 0.9	11.1 ± 0.8		5.1	6.5
250	10/10	16.6 ± 0.3	28.1 ± 0.6	11.6 ± 0.6	100	5.0	6.4
500	10/10	17.1 ± 0.4	27.6 ± 0.7	10.5 ± 0.4	98	5.2	6.2
1,000	10/10	17.1 ± 0.3	27.0 ± 0.9	9.9 ± 0.8	96	4.2	5.9
2,100	10/10	16.9 ± 0.3	24.1 ± 0.5**	7.2 ± 0.4**	86	5.0	5.4
4,200	10/10	16.5 ± 0.3	22.6 ± 0.3**	6.1 ± 0.3**	80	5.3	4.2

** Significantly different (P≤0.01) from the control group by Williams' or Dunnett's test
[a] Number of animals surviving at 13 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error.
[c] Feed consumption is expressed as grams per animal per day.

Forelimb grip strength of male and female mice exposed to 2,100 and 4,200 ppm and hindlimb grip strength of 2,100 ppm females and of males and females exposed to 4,200 ppm were significantly lower than those of controls (Table H9). Differences in organ weights were most likely due to the lower final mean body weights (Table F9). Slight decreases in hemoglobin and mean erythrocyte hemoglobin concentration were observed in male mice exposed to 4,200 ppm, and greater numbers of segmented neutrophils were observed in 2,100 and 4,200 ppm males than in the controls (Table G7). However, these slight differences were not considered to be related to chemical exposure. There was a significant dose-related decrease in the serum cholinesterase values in all exposed groups of male and female mice.

Lesions associated with chemical exposure occurred in the spinal cord, sciatic nerve, adrenal gland, gallbladder, ovary, and kidney (Table 18). Axonal degeneration was observed in both the spinal cord and sciatic nerve, but appeared to be more severe in the sciatic nerve (Plate 7). The lesion was similar to that observed in mice in the 13-week gavage study. While there also appeared to be some loss of myelin sheaths, this was difficult to determine from the routine paraffin embedded sections. The adrenal gland and ovary lesions were also similar to those seen in mice in the 13-week gavage study. Cytoplasmic vacuolization of the adrenal cortex occurred in all exposed groups of female mice and in male mice exposed to 500, 1,000, 2,100, and 4,200 ppm. Scattered individual or multiple small foci of tubule regeneration were observed in the kidney of all 4,200 ppm male mice; none were observed in female mice or in controls.

Hyperplasia of the mucosal epithelium of the gallbladder was observed in male mice exposed to 500 ppm or more and in female mice exposed to 1,000 ppm or more tricresyl phosphate. The hyperplasia was characterized by enlargement and crowding of the epithelial cells to form short, blunt, mucosal folds.

Dose selection rationale: The occurrence of axonal degeneration in male and female mice exposed to 1,000, 2,100, and 4,200 ppm indicated that these concentrations were too high for the highest exposure level in a 2-year feed study. Because of the presence of adrenal cortex lesions in males and females receiving 500 ppm and the cumulative and potentially irreversible nature of axonal degeneration from continued chemical exposure, 500 ppm was not considered to be an appropriate high exposure level for the 2-year feed study. Since the adrenal cortex lesions were minimal in females and absent in males that received 250 ppm, this was selected as the highest exposure level for the 2-year feed study.

TABLE 18
Selected Incidences of Nonneoplastic Lesions in Mice in the 13-Week Feed Study of Tricresyl Phosphate

Doses (ppm)	0	250	500	1,000	2,100	4,200
Male						
Adrenal Cortex[a]	10	10	10	10	10	10
Cytoplasmic Vacuolization, Bilateral[b]	0	0	10**(1.1)[c]	10**(1.3)	10**(2.1)	10**(3.0)
Gallbladder	9	9	10	10	10	9
Mucosa, Hyperplasia, Papillary	0	0	4 (1.5)	6**(1.2)	3 (2.3)	3 (1.7)
Kidney	10	10	10	10	10	10
Renal Tubules, Regeneration[d]	0	0	0	0	0	10**(1.0)
Sciatic Nerve	10	10	10	10	10	10
Axonal Degeneration	0	0	0	0	3 (2.7)	10**(2.7)
Spinal Cord	10	10	10	10	10	10
Axonal Degeneration	0	0	0	0	3 (1.0)	4*(1.0)
Female						
Adrenal Cortex	10	10	10	10	10	10
Cytoplasmic Vacuolization, Bilateral	0	10**(3.0)	10**(3.0)	10**(3.8)	10**(4.0)	10**(4.0)
Gallbladder	10	9	9	10	10	10
Mucosa, Hyperplasia, Papillary	0	0	0	10**(2.2)	7**(2.1)	8**(2.4)
Ovary	10	10	10	10	10	10
Interstitial Cells, Cytoplasmic Vacuolization, Bilateral	0	0	0	2 (1.0)	5*(1.0)	10**(1.0)
Sciatic Nerve	9	9	10	10	10	10
Axonal Degeneration	0	0	0	4 (1.0)	10**(2.7)	8**(3.0)
Spinal Cord	10	10	10	10	10	10
Axonal Degeneration	0	0	0	0	6**(1.0)	6**(1.0)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] Number of animals examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked, 5 = severe.
[d] Diagnosed as cytoplasmic alteration by the laboratory pathologist

2-YEAR FEED STUDY

Survival

Estimates of survival probabilities for male and female mice are shown in Table 19 and in the Kaplan-Meier curves in Figure 5. Survival of exposed groups was similar to that of the controls.

Body Weights, Feed and Compound Consumption, and Clinical Findings

The mean body weights of male and female mice exposed to tricresyl phosphate were similar to those of the controls throughout the study (Tables 20 and 21 and Figure 6). The final mean body weights of all exposed groups of mice were similar to those of the controls. Feed consumption by exposed groups of male and female mice was similar to that by controls (Tables J3 and J4). Dietary levels of 60, 125, and 250 ppm tricresyl phosphate were estimated to deliver average daily doses of 7, 13, or 27 mg/kg body weight to males and 8, 18, or 37 mg/kg to females. No chemical-related clinical findings of toxicity were noted in male or female mice.

TABLE 19
Survival of Mice in the 2-Year Feed Study of Tricresyl Phosphate

	0 ppm	60 ppm	125 ppm	250 ppm
Male				
Animals initially in study	95	95	95	95
3-Month interim evaluation[a]	13	15	15	15
9-Month interim evaluation[a]	15	15	15	15
15-Month interim evaluation[a]	15	15	15	15
Natural deaths	4	5	4	6
Moribund kills	4	1	1	2
Accidental deaths[a]	1	0	0	0
Missing[a]	0	1	1	0
Animals surviving to study termination	43	43	44	42
Percent probability of survival at end of study[b]	86	88	90	85
Mean survival (days)[c]	504	504	509	504
Survival analysis[d]	P=0.979	P=0.763N	P=0.551N	P=0.807
Female				
Animals initially in study	95	95	95	95
3-Month interim evaluation[a]	15	15	15	15
9-Month interim evaluation[a]	15	15	15	15
15-Month interim evaluation[a]	15	15	15	14
Natural deaths	5	7	2	3
Moribund kills	4	5	4	3
Missing[a]	0	0	2	0
Animals surviving to study termination	41[e]	38[e]	42	45
Percent probability of survival at end of study	82	77	88	89
Mean survival (days)	508	504	499	507
Survival analysis	P=0.263N	P=0.607	P=0.603N	P=0.570N

[a] Censored from survival analyses
[b] Kaplan-Meier determinations based on the number of animals alive on the first day of terminal sacrifice
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the dosed columns. A negative trend or a lower mortality in a dose group is indicated by N.
[e] Includes one animal that died during the last week of the study.

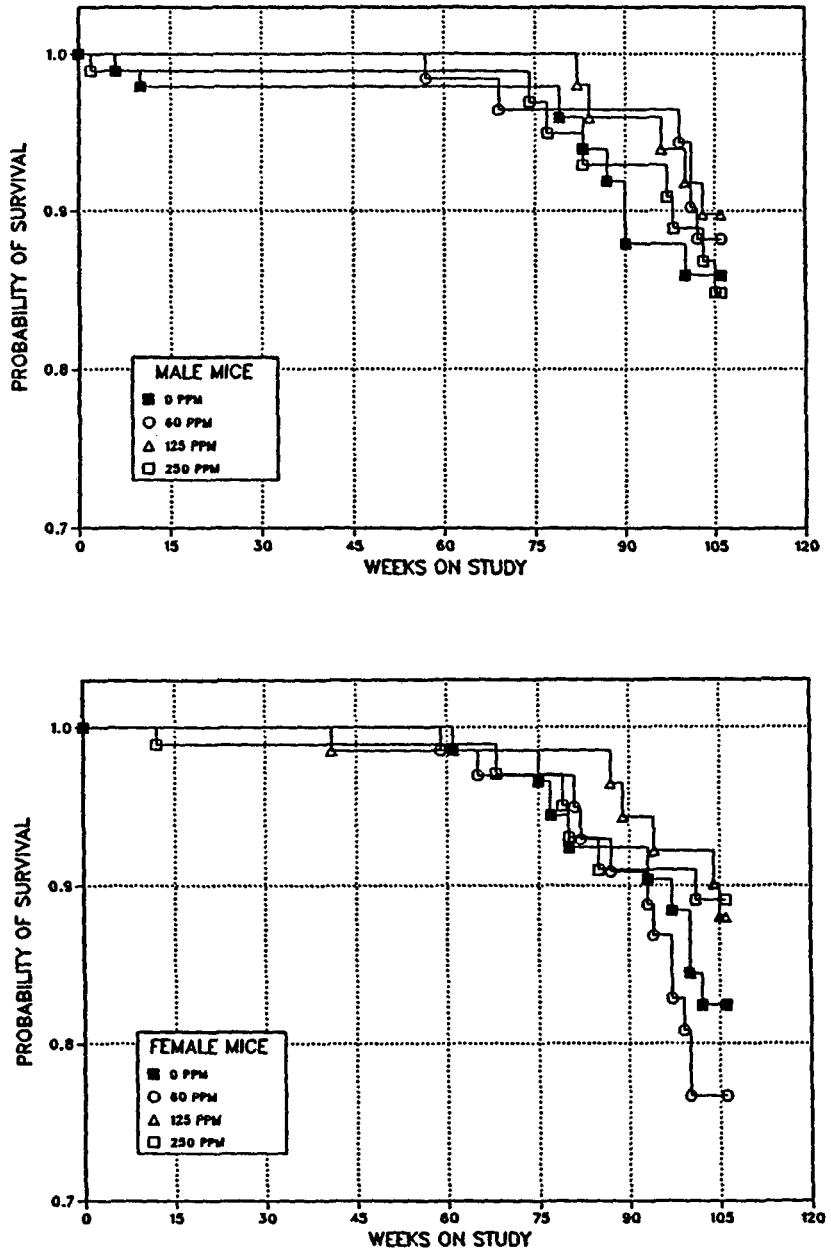


FIGURE 5
Kaplan-Meier Survival Curves for Male and Female Mice Administered Tricresyl Phosphate in Feed for 2 Years

TABLE 20
Mean Body Weights and Survival of Male Mice in the 2-Year Feed Study of Tricresyl Phosphate

Weeks on Study	0 ppm		60 ppm			125 ppm			250 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	22.2	95	22.3	101	95	22.1	100	95	22.2	100	95
2	23.6	95	23.5	100	95	23.4	99	95	23.5	100	95
3	24.4	95	24.2	99	95	24.4	100	95	24.4	100	94
4	25.6	95	25.5	100	95	25.4	99	95	25.5	100	94
5	26.3	95	26.1	99	95	26.4	100	95	26.3	100	94
6	27.2	95	27.3	100	95	27.3	100	95	27.3	100	94
7	27.9	94	27.7	99	95	27.7	99	95	28.1	101	94
8	28.6	94	28.5	100	95	28.6	100	95	28.8	101	94
9	29.4	94	29.4	100	94	29.3	100	95	29.4	100	94
10	29.9	94	30.1	101	95	30.1	101	95	30.3	101	94
11	30.4	93	30.1	99	94[a]	30.1	99	95[a]	30.3	100	94[a]
12	31.8	93	31.7	100	94	31.4	99	95	31.8	100	94
13	32.0	93	32.0	100	94	31.9	100	95	32.3	101	94
17[b]	34.6	79	34.6	100	79	35.0	101	80	35.5	103	79
21	36.5	79	36.4	100	79	36.8	101	80	37.2	102	79
25	38.3	79	38.5	101	79	38.9	102	80	39.7	104	79
29	39.6	79	39.5	100	79	39.8	101	80	40.8	103	79
33	41.0	79	40.9	100	79	41.4	101	80	41.9	102	79
37	42.9	79	43.1	101	79	43.5	101	79	44.1	103	79
41[b]	42.9	64	42.4	99	64	42.8	100	64	44.1	103	64
45	43.6	64	43.9	101	64	44.3	102	64	45.7	105	64
49	45.3	64	45.5	100	64	45.7	101	64	47.3	104	64
53	45.2	64	45.8	101	64	46.3	102	64	47.4	105	64
57	46.2	64	46.4	100	64	46.3	100	64	47.9	104	64
61	46.4	64	47.0	101	63	47.7	103	64	48.3	104	64
65	47.2	64	47.8	101	63	48.4	103	64	48.6	103	64
69[b]	48.0	49	47.7	99	48	49.1	102	49	48.7	102	49
73	46.5	49	47.6	102	47	49.0	105	49	48.1	103	49
77	48.0	49	48.8	102	47	50.2	105	49	49.6	103	47
81	47.3	48	48.5	103	47	50.1	106	49	49.2	104	47
85	46.3	47	47.7	103	47	49.0	106	47	47.7	103	46
89	47.3	46	48.7	103	47	50.1	106	47	49.2	104	46
93	46.6	44	46.9	101	47	49.1	105	47	48.3	104	46
97	47.2	44	47.4	100	47	48.7	103	46	48.5	103	46
101	46.1	43	45.8	99	44	48.6	105	45	46.9	102	44
105	44.7	43	43.7	98	43	47.0	105	44	44.3	99	43
Mean for weeks											
1-13	27.6		27.5	100		27.6	100		27.7	100	
14-52	40.5		40.5	100		40.9	101		41.8	103	
53-105	46.6		47.1	101		48.5	104		48.1	103	

[a] The number of animals weighed for this week is fewer than the number of animals surviving.
[b] Interim evaluations occurred during weeks 14, 40, and 66.

TABLE 21
Mean Body Weights and Survival of Female Mice in the 2-Year Feed Study of Tricresyl Phosphate

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	60 ppm Av. Wt. (g)	60 ppm Wt. (% of controls)	60 ppm No. of Survivors	125 ppm Av. Wt. (g)	125 ppm Wt. (% of controls)	125 ppm No. of Survivors	250 ppm Av. Wt. (g)	250 ppm Wt. (% of controls)	250 ppm No. of Survivors
1	18.4	95	18.5	101	95	18.4	100	95	18.3	100	95
2	19.8	95	19.8	100	95	19.7	100	95	19.6	99	95
3	20.7	95	20.9	101	95	20.9	101	95	20.7	100	95
4	22.2	95	22.2	100	95	22.1	100	94	21.8	98	95
5	22.8	95	23.1	101	95	23.1	101	94	23.0	101	95
6	24.0	95	24.1	100	95	24.3	101	94	24.1	100	95
7	24.6	95	25.0	102	95	24.9	101	94	24.8	101	95
8	25.5	95	26.1	102	95	25.9	102	94	25.9	102	95
9	26.3	95	26.7	102	95	26.9	102	94	26.3	100	95
10	27.3	95	27.6	101	95	27.7	102	94	27.0	99	95
11	28.1	95[a]	29.1	104	95[a]	28.6	102	94[a]	28.1	100	95[a]
12	28.4	95	29.3	103	95	29.1	103	94	28.6	101	94
13	29.1	95	29.7	102	95	29.9	103	94	29.2	100	94
17[b]	31.9	80	33.3	104	80	33.2	104	79	32.9	103	79
21	34.8	80	35.7	103	80	35.5	102	79	35.2	101	79
25	37.1	80	38.3	103	80	38.3	103	79	37.5	101	79
29	38.6	80	39.3	102	80	39.2	102	79	39.0	101	79
33	40.0	80	41.0	103	80	40.9	102	79	40.5	101	79
37	41.6	80	42.9	103	80	42.4	102	79	42.3	102	79
41[b]	42.1	65	41.7	99	65	41.7	99	63	41.6	99	64
45	43.0	65	43.9	102	65	43.8	102	62	43.8	102	64
49	44.9	65	45.0	100	65	45.7	102	62	45.5	101	64
53	45.2	65	45.8	101	65	45.5	101	62	46.3	102	64
57	45.6	65	46.4	102	65	45.9	101	62	46.5	102	64
61	47.0	65	47.9	102	64	47.8	102	62	47.9	102	64
65	47.8	64	49.1	103	64	49.1	103	62	49.0	103	64
69[b]	49.0	49	50.3	103	48	50.2	102	47	49.7	101	49
73	48.8	49	50.0	103	48	50.1	103	47	49.6	102	49
77	50.9	48	51.6	101	48	51.1	100	47	50.9	100	49
81	50.8	46	51.6	102	47	51.3	101	47	51.6	102	47
85	49.7	46	50.9	102	46	50.4	101	47	50.1	101	47
89	50.8	46	51.7	102	45	51.1	101	46	51.3	101	46
93	50.3	45	51.1	102	44	50.6	101	45	50.5	100	46
97	50.2	45	50.6	101	42	49.7	99	44	50.8	101	46
101	49.1	42	50.4	103	38	49.0	100	44	48.9	100	46
105	46.7	41	47.0	101	38	47.1	101	42	46.0	99	45
Mean for weeks											
1-13	24.4		24.8	102		24.7	101		24.4	100	
14-52	39.3		40.1	102		40.1	102		39.8	101	
53-105	48.7		49.6	102		49.2	101		49.2	101	

[a] The number of animals weighed for this week is fewer than the number of animals surviving.
[b] Interim evaluations occurred during weeks 14, 40, and 66.

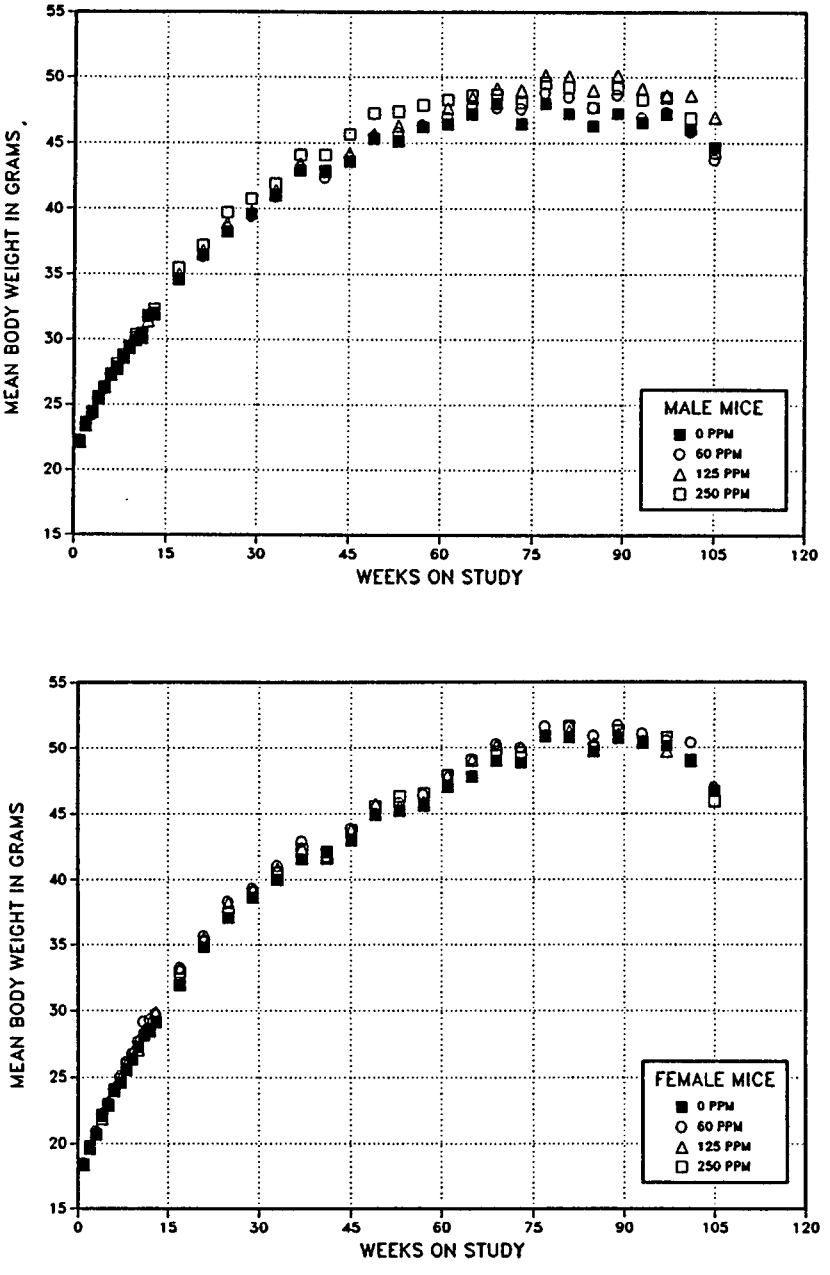


FIGURE 6
Growth Curves for Male and Female Mice Administered Tricresyl Phosphate in Feed for 2 Years

Hematology, Clinical Chemistry, and Neurobehavioral Results

There were no biologically significant differences in hematology parameters measured at the 3-, 9- or 15-month interim evaluations (Tables G8, G9, and G10). There were significant dose-related decreases in the serum cholinesterase activity in all groups of exposed mice at the 3-, 9-, and 15-month interim evaluations. Hindlimb grip strength in 250 ppm female mice was significantly lower than that in the controls at the 3-month interim evaluation (Table H10). At the 9- and 15-month interim evaluations, the hindlimb and forelimb grip strengths of exposed male and female mice were similar to those of the controls (Tables H11 and H12).

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions of the adrenal gland, liver, and harderian gland. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for liver and harderian gland neoplasms are presented in Appendix C for male mice and Appendix D for female mice.

Adrenal gland: An increase in the severity of ceroid pigmentation in the adrenal cortex of most exposed groups of male and female mice was first noted at the 9-month interim evaluation (Tables 22, C5, and D5). At the 15-month interim evaluation, the absolute and relative adrenal gland weights of 250 ppm males were significantly lower than those of the controls (Table F12), and the absolute and relative adrenal gland weights of 250 ppm females were significantly greater than those of the controls. There was a dose-related increase in the severity of ceroid pigmentation of the adrenal cortex in females at the 15-month interim evaluation (Tables 22, C5, and D5). At the end of the 2-year study, ceroid pigmentation of the adrenal cortex was present in most exposed and control mice; however, a dose-related increase in the severity of yellow-brown ceroid pigmentation was present in the innermost area of the zona reticularis of the adrenal cortex in exposed male and female

TABLE 22
Incidences of Nonneoplastic Lesions of the Adrenal Cortex of Mice in the 2-Year Feed Study of Tricresyl Phosphate

Doses (ppm)	0	60	125	250
Male				
Ceroid Pigmentation				
3-Month interim evaluation	0/8[a]	3/10 (1.0)[b]	3/10 (1.0)	6/10*(1.0)
9-Month interim evaluation	10/10 (1.0)	10/10 (1.0)	10/10 (1.1)	10/10 (1.6)
15-Month interim evaluation	10/10 (1.2)	10/10 (1.1)	10/10 (1.0)	10/10 (1.3)
2-Year study	48/52 (1.0)	47/49 (1.0)	49/49 (1.1)	49/50 (1.2)
Female				
Ceroid Pigmentation				
3-Month interim evaluation	0/10	0/10	0/10	1/10 (1.0)
9-Month interim evaluation	9/10 (1.0)	10/10 (1.0)	10/10 (1.8)	10/10 (3.1)
15-Month interim evaluation	10/10 (1.0)	10/10 (1.0)	10/10 (2.0)	9/9 (3.8)
2-Year study	49/50 (1.2)	49/49 (1.6)	47/48 (2.5)	51/51 (3.9)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
[a] Number of animals with lesion per number of number of animals with adrenal cortex examined microscopically
[b] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.

mice (Plates 8 and 9). The lesion consisted of macrophages and/or epithelial cells in various stages of distension from the accumulation of yellow-brown cytoplasmic pigment (Plates 10 and 11). The severity of pigmentation was minimal to mild in exposed groups of male mice and moderate to marked in exposed groups of female mice, especially those receiving 125 and 250 ppm.

Liver: At the end of the 2-year study, the incidences of clear cell focus, fatty change, and ceroid pigmentation were significantly increased in male mice receiving 125 and 250 ppm (Tables 23 and C5).

Clear cell foci were usually smaller than the size of one lobule and showed partial compression of adjacent liver cells. Cells within foci were enlarged and contained one or more medium to large clear spaces in the cytoplasm. The fatty change consisted of small vacuoles in individual hepatocytes, randomly distributed throughout the liver. The severity increased with exposure level but was never considered to be more than moderate in any group.

Ceroid pigmentation consisted of cells containing fine, yellow-brown granules in their cytoplasm. In mice exposed to 250 ppm, the cells were enlarged and grouped into clusters. Periodic acid-Schiff and oil red O staining were done in an attempt to further characterize the pigment; the results confirmed the presence of lipid in the affected cells consistent with identification of the pigment as ceroid or acid fast lipofuscin.

TABLE 23
Incidences of Nonneoplastic Lesions of the Liver of Mice in the 2-Year Feed Study of Tricresyl Phosphate

Doses (ppm)	0	60	125	250
Male				
9-Month Interim Evaluation				
Liver[a]	10	10	10	10
Clear Cell Focus[b]	0	0	1	0
Ceroid Pigmentation	0	0	0	1 (1.0)[c]
15-Month Interim Evaluation				
Liver	10	10	10	10
Clear Cell Focus	0	1	0	0
Fatty Change	1 (2.0)	3 (1.7)	5 (1.8)	5 (1.8)
Ceroid Pigmentation	0	0	4*(1.0)	2 (1.0)
2-Year Study				
Liver	52	49	49	50
Clear Cell Focus	5	8	17**	12*
Fatty Change	6 (1.3)	10 (1.1)	23**(1.3)	22**(2.0)
Ceroid Pigmentation	0	0	30**(1.0)	28**(1.1)

(continued)

TABLE 23
Incidences of Nonneoplastic Lesions of the Liver of Mice in the 2-Year Feed Study of Tricresyl Phosphate
(continued)

Doses (ppm)	0	60	125	250
Female				
9-Month Interim Evaluation				
Liver	10	10	10	10
Basophilic Focus	0	1	0	0
15-Month Interim Evaluation				
Liver	10	10	10	9
Basophilic Focus	0	1	0	0
Clear Cell Focus	0	0	0	1
Eosinophilic Focus	0	0	0	1
2-Year Study				
Liver	50	50	48	51
Basophilic Focus	4	1	1	0
Clear Cell Focus	0	0	0	3
Eosinophilic Focus	8	4	5	6
Mixed Cell Focus	1	0	2	2

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test (interim evaluations) or by the logistic regression test (2-year study)
** $P \leq 0.01$
[a] Number of animals with liver examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.

Harderian gland: The incidence of harderian gland adenoma was marginally increased in 250 ppm male mice, but the incidence of adenoma or carcinoma combined was not significantly increased in males, and actually decreased in females (Tables 24, C3, and D3). Harderian gland carcinomas occurred in one control male, one 60 ppm male, and two 125 ppm males. Hyperplasia occurred in both control and exposed males and females, however the incidence and severity were similar in all groups. The incidence of harderian gland adenoma in control male B6C3F$_1$ mice from recent NTP feed studies is 66/1,374 (5%) with a range of 0% to 18% (Table C4b). The incidence of harderian gland adenoma or carcinoma (combined) in historical control male B6C3F$_1$ mice is 74/1,374 (5%) with a range of 0% to 20% (Table C4b). Therefore, the incidences of adenoma or carcinoma observed in males in the present study are well within the historical control ranges for these neoplasms.

TABLE 24
Incidences of Neoplasms and Nonneoplastic Lesions of the Harderian Gland of Mice in the 2-Year Feed Study of Tricresyl Phosphate

Doses (ppm)	0	60	125	250
Male				
15-Month Interim Evaluation				
Harderian Gland[a]	10	5	9	6
Adenoma[b]	0	1	0	0
2-Year Study				
Harderian Gland	43	40	37	37
Hyperplasia	2 (2.0)[c]	1 (2.0)	0	0
Adenoma				
Overall rate[d]	0/52 (0%)	1/49 (2%)	2/49 (4%)	5/50 (10%)
Logistic regression test[e]	P=0.007	P=0.500	P=0.244	P=0.031
Carcinoma				
Overall rate	1/52 (2%)	1/49 (2%)	2/49 (4%)	0/50 (0%)
Logistic regression test	P=0.372N	P=0.762	P=0.508	P=0.505N
Adenoma or Carcinoma[f]				
Overall rate	1/52 (2%)	2/49 (4%)	3/49 (6%)	5/50 (10%)
Logistic regression test	P=0.048	P=0.500	P=0.314	P=0.098

(continued)

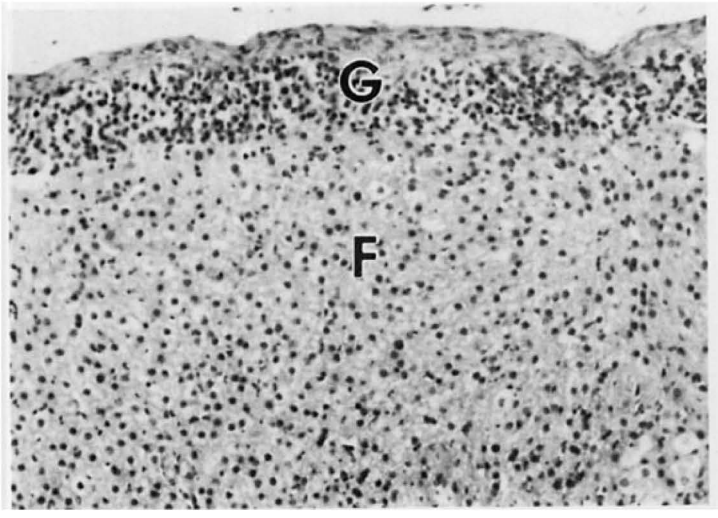


PLATE 1
Adrenal cortex from a control female F344/N rat in the 2-year feed study of tricresyl phosphate. Note the zona glomerulosa (G) and zona fasciculata (F). H&E, 50×

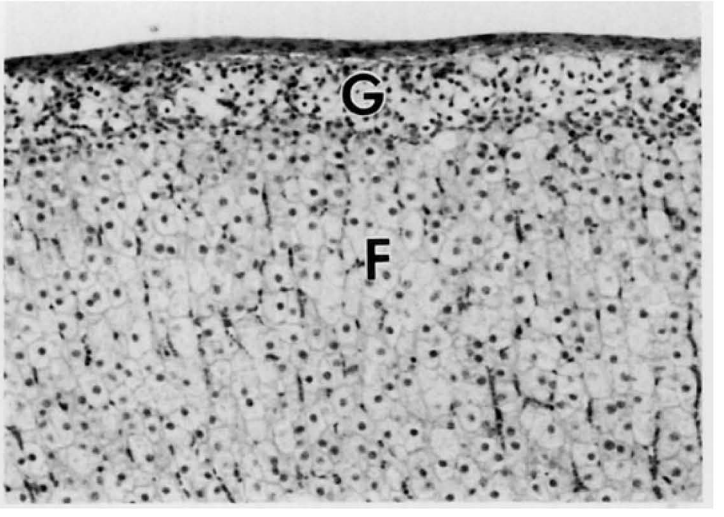


PLATE 2
Cytoplasmic vacuolation of cortical cells in the zona glomerulosa (G) and zona fasciculata (F) in a female F344/N rat exposed to 300 ppm tricresyl phosphate in the 2-year feed study. H&E, 50×

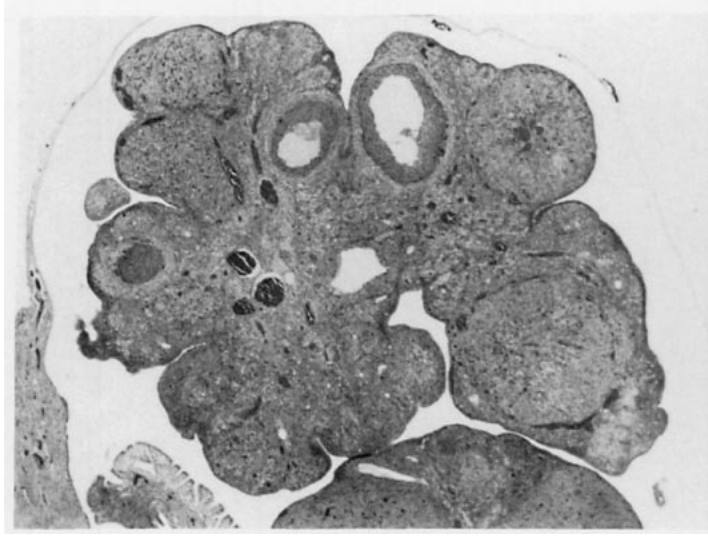


PLATE 3
Ovary from a control female F344/N rat in the 2-year feed study of tricresyl phosphate. H&E, 8×

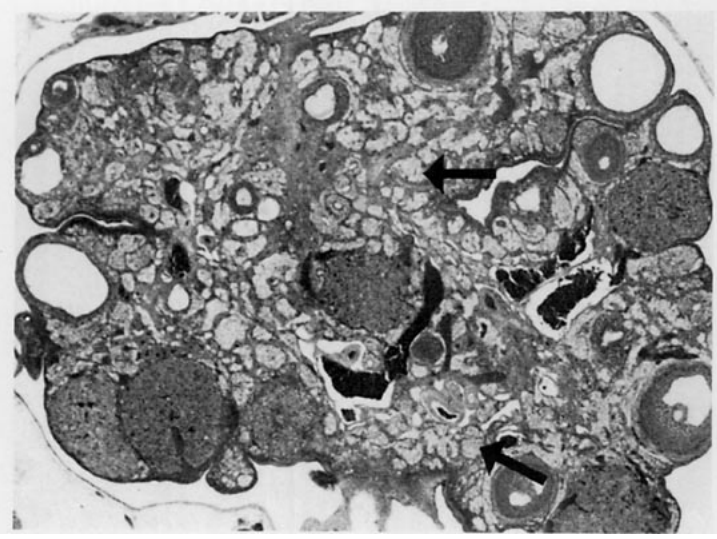


PLATE 4
Interstitial cell hyperplasia (arrows) in a female F344/N rat exposed to 300 ppm tricresyl phosphate in the 2-year feed study. H&E, 8×

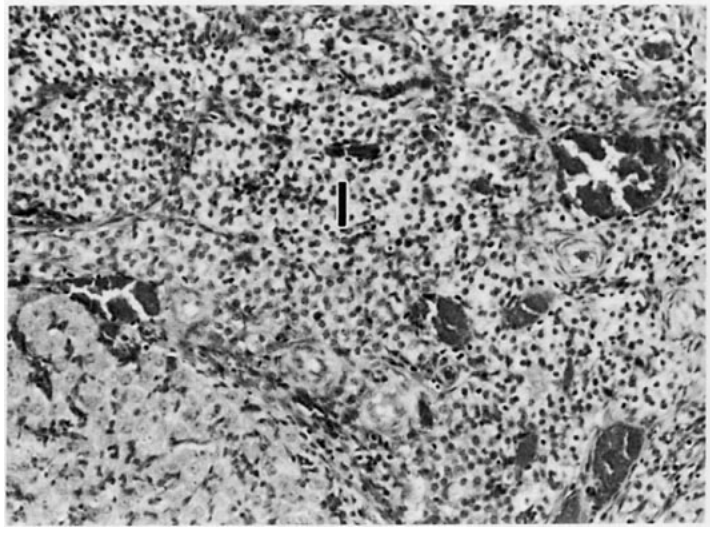


PLATE 5
Higher magnification of an ovary from a control female F344/N rat in the 2-year feed study of tricresyl phosphate. Note interstitial cells (I). H&E, 50×

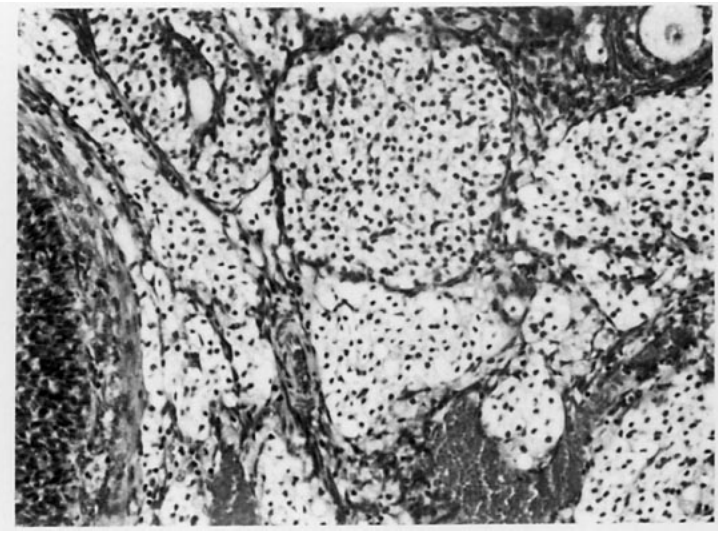


PLATE 6
Higher magnification of interstitial cell hyperplasia in a female F344/N rat exposed to 300 ppm tricresyl phosphate in the 2-year feed study. Compared to Plate 5, the interstitial cells are increased in number and enlarged with abundant foamy (clear) cytoplasm. H&E; 50×

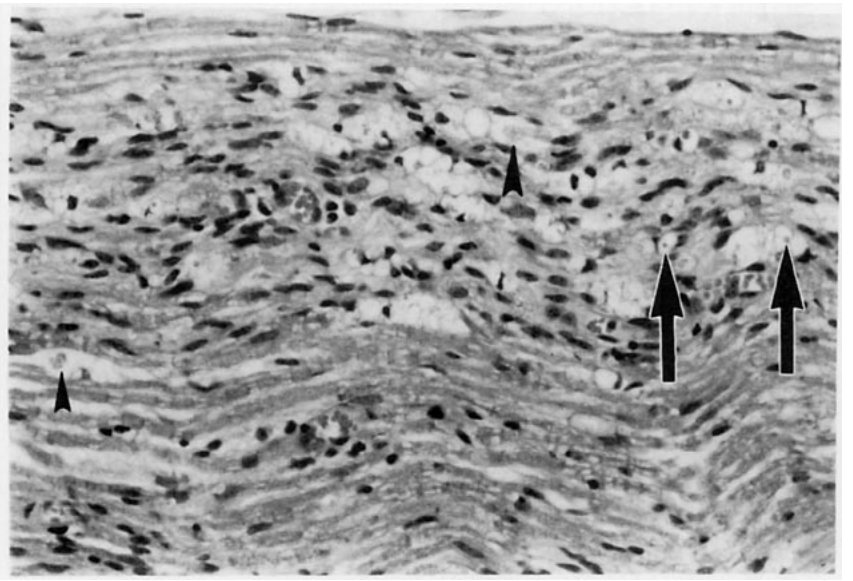


PLATE 7
Multifocal axonal degeneration with dilatation of myelin sheaths of the sciatic nerve in a female B6C3F$_1$ mouse exposed to 4,200 ppm tricresyl phosphate in the 13-week feed study. Note occasional shrunken axons (arrows) and swollen axons (arrow heads). H&E, 80×

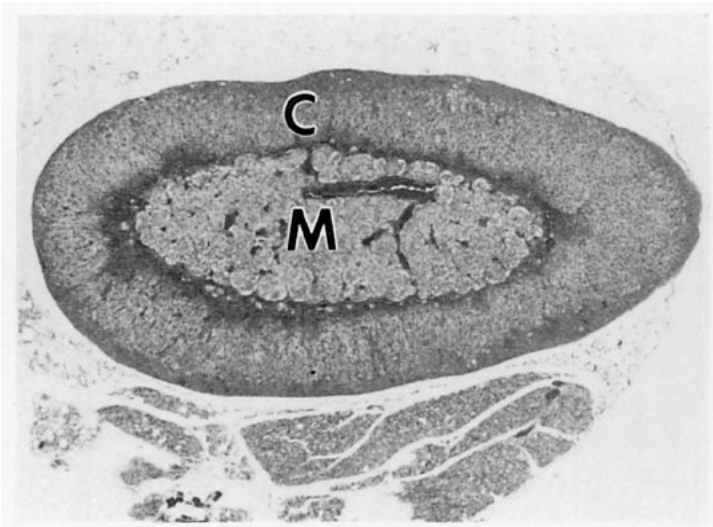


PLATE 8
Adrenal gland showing the cortex (C) and medulla (M) from a control female B6C3F$_1$ mouse in the 2-year feed study of tricresyl phosphate. H&E, 50×

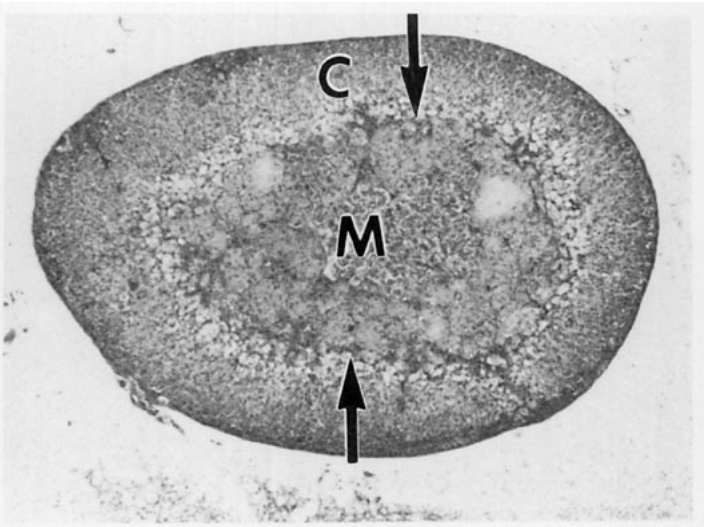


PLATE 9
Ceroid pigmentation in the cytoplasm of cortical cells within the zona reticularis (arrows) in a female B6C3F$_1$ mouse exposed to 250 ppm tricresyl phosphate in the 2-year feed study. H&E, 50×

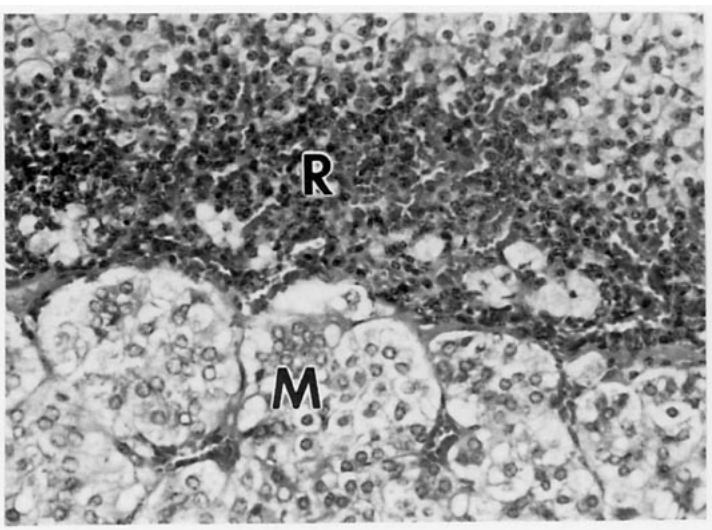


PLATE 10
Higher magnification of cortical cells within the zona reticularis (R) from a control female B6C3F$_1$ mouse in the 2-year feed study of tricresyl phosphate. Note the adjacent medulla (M). H&E, 66×

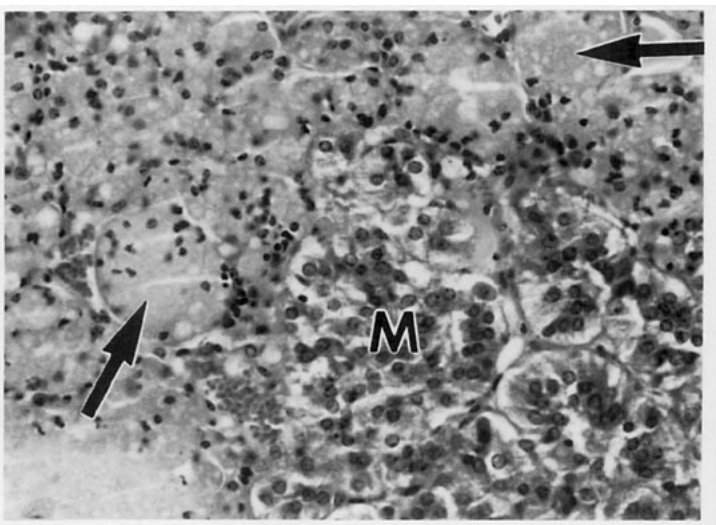


PLATE 11
Higher magnification of cortical cells in the zona reticularis containing fine granular ceroid pigment (arrows) in a female B6C3F$_1$ mouse exposed to 250 ppm tricresyl phosphate in the 2-year feed study. Note cells within the adjacent medulla (M) lack ceroid pigment. H&E; 66×

TABLE 24
Incidences of Neoplasms and Nonneoplastic Lesions of the Harderian Gland of Mice in the 2-Year Feed Study of Tricresyl Phosphate (continued)

Doses (ppm)	0	60	125	250
Female				
15-Month Interim Evaluation				
Harderian Gland	7	4	5	8
Hyperplasia	1 (1.0)	0	0	0
2-Year Study				
Harderian Gland	47	38	29	36
Hyperplasia	2 (2.5)	1 (1.0)	1 (1.0)	0
Adenoma				
Overall rate	5/50 (10%)	3/50 (6%)	0/48 (0%)	0/51 (0%)
Logistic regression test	P=0.007N	P=0.365N	P=0.031N	P=0.026N
Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	1/48 (2%)	0/51 (0%)
Logistic regression test	P=0.693	–[g]	P=0.495	–
Adenoma or Carcinoma[h]				
Overall rate	5/50 (10%)	3/50 (6%)	1/48 (2%)	0/51 (0%)
Logistic regression test	P=0.012N	P=0.365N	P=0.098N	P=0.026N

[a] Number of animals with harderian gland examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.
[d] Number of animals with neoplasm per number of animals necropsied
[e] In the control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to pairwise comparisons between the controls and that exposure group. The logistic regression test regards these lesions as nonfatal. A negative trend or a lower incidence in an exposure group is indicated by N.
[f] Historical incidence for 2-year feed studies with untreated control groups (mean ± standard deviation): 74/1,374 (5.4% ± 4.5%); range 0%-20%
[g] Not applicable; no neoplasms in animal group
[h] Historical incidence: 55/1,371 (4.0% ± 3.2%); range 0%-10%

GENETIC TOXICOLOGY

Tricresyl phosphate (100 to 10,000 μg/plate) was tested by two laboratories for the induction of gene mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 with and without S9 (Table E1; Haworth *et al.*, 1983). No induction of gene mutations was observed by either laboratory in any of the four tester strains. Precipitation of tricresyl phosphate was noted at concentrations of 3,333 μg/plate and above in the study conducted at SRI, International.

In cytogenicity tests with cultured Chinese hamster ovary cells, tricresyl phosphate did not induce sister chromatid exchanges (Table E2) or chromosomal aberrations (Table E3), with or without Aroclor 1254-induced male Sprague-Dawley rat liver S9. The highest concentration tested in all trials except the sister chromatid exchange trial was 5,000 μg/mL. In the sister chromatid exchange trials in the absence of S9, the highest concentration of tricresyl phosphate for which results could be obtained was 16 μg/mL. No tricresyl phosphate-induced cell cycle delay was observed in either of these two assays.

DISCUSSION AND CONCLUSIONS

Tricresyl phosphate is a widely used vinyl plasticizer and fire retardant additive for functional fluids such as hydraulic and brake fluids. It was nominated by the National Cancer Institute as a representative aromatic organophosphate plasticizer. It has been known since the 1930's that tri-*ortho*-cresyl phosphate (TOCP), one of the isomeric components of tricresyl phosphate, produces peripheral neuropathy in humans and experimental animals after acute exposure to sufficiently high concentrations. However, the toxicity of industrial preparations composed of isomeric mixtures of tricresyl phosphates had not been examined in detail. Moreover, the consequences of long-term exposure to low doses, as might occur in an occupational setting, had not been investigated. The present studies examine the toxic response of F344/N rats and B6C3F$_1$ mice to short-term and long-term exposures involving a broad range of concentrations.

Tricresyl phosphate is well absorbed through the skin and lungs and from the gastrointestinal tract and can reach systemic circulation through any of these exposure routes. Administration in the diet was selected for the long-term studies because this would provide daily exposure to low concentrations similar to what might occur in an occupational setting. Since it was unclear whether enough tricresyl phosphate would be consumed by this route to enable the toxicity to be well characterized, the 13-week studies were conducted using administration by gavage in corn oil vehicle and exposure by dosed feed.

During the 13-week gavage and feed studies, tricresyl phosphate produced a similar spectrum of lesions in rats and mice involving primarily the adrenal cortex and gonads. Cytoplasmic vacuolization of the adrenal cortex occurred in all exposed groups of male and female rats and mice, with the exception of 250 ppm mice; the severity increased with exposure level. Since the lesion was not observed in control animals, it was considered to be related to chemical exposure. Ovarian interstitial cell hypertrophy/hyperplasia and inflammation of the interstitium occurred in all exposed groups of female rats and female mice in the 13-week feed studies. Aspermatogenesis and atrophy of the seminiferous tubules, reduced caudal and epididymal weights, reduced sperm motility, and abnormal sperm head morphology occurred in exposed groups of male rats. Although no histopathologic lesions were observed in the testes of male mice, reduced caudal and epididymal weights, reduced sperm motility, and abnormal sperm head morphology occurred in groups that received the highest concentrations of tricresyl phosphate (NTP, 1983, 1985). Microscopic lesions in nervous tissue occurred only in exposed groups of mice; degenerative lesions occurred in the lumbar spinal cord and sciatic nerve of male mice exposed to 2,100 and 4,200 ppm and female mice exposed to 1,000 ppm or more.

As a means of monitoring the potential neurotoxicity of tricresyl phosphate, several neurobehavioral parameters were evaluated during the 16-day and 13-week studies. In most instances, treatment-related differences were observed only at concentrations that caused mortality, lower mean body weights, or other indications of toxicity. Therefore it was not possible to distinguish between specific effects on the nervous system and other types of toxicity. However, the reductions in hindlimb grip strength of male mice administered 363 or 726 mg/kg in the 16-day gavage study or 200 mg/kg in the 13-week gavage study were not confounded by body weight differences or other indications of toxicity and appeared to be treatment-related effects. Based on these results, grip strength appeared to be the parameter most useful for monitoring potential neurotoxicity and was the only neurobehavioral parameter evaluated in the feed studies. During the 13-week feed studies significant reductions in hindlimb grip strength occurred only at the highest concentrations where interpretation was confounded by lower mean body weights.

The selection of exposure levels for the 2-year feed studies was complicated by the fact that a no-effect level was not achieved in the 13-week studies. Cytoplasmic vacuolization of the adrenal cortex was present in all exposed groups of rats and mice, with the exception of male mice exposed to 250 ppm. In each sex and species, lesion severity increased with exposure level, and the most severe lesions occurred

in exposed females. This lesion was not observed in control animals. Although it was difficult to judge the character or the potential for progression, those regions of the adrenal cortex involved are major sites of steroid hormone production and are essential for life. Partial or complete loss of their function over the duration of a 2-year study would be potentially life threatening. Therefore, the 2-year rat study was designed with five exposure concentrations: 0, 75, 150, 300, or 600 ppm.

After 3 months of exposure, up to 10 male and 10 female rats per group were evaluated for the presence of adrenal cortex lesions. None were found in animals exposed to 75 ppm and the lesion occurred in only one 150 ppm female. However, it occurred at a high incidence in females exposed to 300 or 600 ppm and in 600 ppm males. To determine whether the lesion would persist and/or progress in the absence of continued chemical exposure, groups that received diets containing 600 ppm for the first 3 months of the study were fed control diets for the remainder of the study, while groups that had received 75, 150, or 300 ppm continued to receive these same diets. Interim evaluations were conducted during months 9 and 15 of the 2-year studies.

Selection of exposure levels for mice was based primarily on the occurrence of lesions of the adrenal cortex and nervous system. Axonal degeneration occurred in female mice exposed to 1,000 ppm or more and in males exposed to 2,100 ppm or more. Although axonal degeneration was not observed at lower exposure levels, subtle axonal lesions are difficult to detect histopathologically. In the presence of continued exposure to tricresyl phosphate, lesions that were below the limit of detection at 13 weeks could become debilitating during a 2-year study. Therefore, 500 ppm was considered too close to 1,000 ppm for the high exposure concentration in a 2-year feed study. Cytoplasmic vacuolization of the adrenal cortex occurred in male and female mice exposed to 500 ppm or more and in 250 ppm females. As a result, 250 ppm was selected as the high exposure level for the mouse study; other exposure levels selected were 60 and 125 ppm.

Analysis of the lot of tricresyl phosphate used in the present studies indicated that it was composed of 79% tricresyl phosphate esters and 18% dicresyl phosphate esters (Table I2). The tricresyl phosphate esters contained 21% tri-*m*-cresyl phosphate and 4% tri-*p*-cresyl phosphate; the remaining 75% was mixed triesters. Analysis of the bulk chemical failed to detect the presence of tri-*o*-cresyl phosphate (TOCP), indicating that if present, it could be present at most at a concentration of less than 0.1% (Table I2). However, the toxic responses observed in the 13-week feed and gavage studies, especially the axonal degeneration that occurred in the spinal cord and sciatic nerve of mice and the testicular lesions that occurred in male rats, were essentially the same as those observed for isomerically pure TOCP. Neither tri-*m*-cresyl nor tri-*p*-cresyl phosphate produce these types of lesions.

Based on the results of a 63-day study in which pure TOCP was administered in corn oil by gavage to male F344/N rats, Somkuti *et al.* (1987a,b) estimated that the minimum effective dose for observable testicular toxicity was between 10 and 25 mg/kg per day. In the 13-week gavage study reported here, atrophy of the seminiferous tubules occurred in the male rats that received 400 mg/kg per day, but no testicular lesions were observed at lower doses. Therefore, less than a 20-fold difference in dose between pure TOCP and the isomerically mixed tricresyl phosphate sample used for the present studies produced a similar result.

In the 13-week gavage study in mice, multifocal axonal degeneration was present in the spinal cord of male and female mice that received 100 mg/kg per day or greater. If 0.1% of the administered mixed isomer preparation was TOCP, 100 mg/kg per day would correspond to 0.1 mg/kg per day of TOCP, a no-effect dose even in as sensitive species as the chicken. Therefore, the axonal degeneration and other signs of neurotoxicity observed in the present study cannot be attributed to the potential presence of undetectable quantities of TOCP. Veronesi *et al.* (1991) produced axonal degeneration in the spinal cord of Swiss (CD-1®) mice evaluated 14 days after administering single gavage doses of TOCP ranging from 580 to 2,320 mg/kg. Although the two studies cannot be directly compared, the doses are similar enough (even when the comparison is based on the total cumulative dose administered during the 13-week study) to illustrate that the effects produced with the mixed isomer preparation cannot be explained by the presence of contaminating TOCP. However, the toxicity of the mixed isomer preparation may be due to the presence of *o*-cresol groups in the mixed triester fraction.

During the 2-year feed studies, survival rates, mean body weights, and feed consumption of exposed groups of rats and mice were similar to those of controls. There were no clinical findings observed during the 2-year studies that were considered to be associated with exposure to tricresyl phosphate.

The hindlimb grip strengths of male rats exposed to 300 or 600 ppm, 600 ppm female rats, and 250 ppm female mice were significantly lower than those of controls at 3 months. However, at the 9- and 15-month interim evaluations forelimb and hindlimb grip strengths of exposed groups of rats and mice were similar to those of the controls. Moreover, no histopathologic lesions of the spinal cord or sciatic nerve in rats or mice were associated with chemical exposure. Therefore, it is difficult to judge the significance of the transient decrease in hindlimb and forelimb grip strengths observed at the 3-month interim evaluations.

Somkuti *et al.* (1988) administered TOCP (10 to 100 mg/kg) to male F344 rats daily by gavage for 63 days. Although the activities of brain neurotoxic esterase (NTE) and acetylcholinesterase were inhibited in a dose-dependent fashion in treated animals, no consistent differences occurred in forelimb/hindlimb grip strength, spontaneous motor activity, tremor, or response to a thermal stimulus. No toxic lesions were observed histopathologically in the spinal cord or peripheral nerves. The authors concluded that the F344 rat was insensitive to the delayed neurotoxic effect of TOCP. In another report, Veronesi (1984) found spinal cord lesions in Long-Evans rats following daily administration of a similar dose (116 mg/kg) for 6 weeks. Therefore, rats appear to exhibit strain differences in sensitivity to TOCP neurotoxicity.

Although no neurobehavioral data on the response of mice to TOCP were found in the literature, spinal cord lesions and inhibition of NTE activity have also been reported in Swiss (CD-1®) mice receiving a single oral dose of TOCP ranging from 580 to 3,480 mg/kg (Veronesi *et al.*, 1991). The results observed in the present studies are, therefore, consistent with previous observations.

Consumption of tricresyl phosphate in feed for 2 years did not increase the incidence of neoplasms in rats. The increased incidence of mononuclear cell leukemia in female rats exposed to 150 or 300 ppm was not considered to be associated with chemical exposure for several reasons. The concurrent control incidence is lower than the historical control incidence, while the incidences in the 150 and 300 ppm groups are comparable to historical control incidences. In addition, the incidences for all groups fall within the historical control range. The severity of mononuclear cell leukemia did not increase in exposed female rats and there was no indication of reduced latency associated with the increased incidences of mononuclear cell leukemia. Moreover, the survival rate of 300 ppm female rats was similar to that of the controls. Therefore, the increased incidence may be the result of the variability of mononuclear cell leukemia among the treatment groups rather than an effect of chemical exposure.

Chemical exposure also did not increase the incidence of neoplasms in mice. There was a significant positive trend in the incidence of harderian gland adenomas and the incidence was significantly increased in 250 ppm males, but there were no increased incidences of hyperplasia. Harderian gland carcinomas occurred in one control male, one 60 ppm male, and two 125 ppm males; however, no carcinomas occurred in 250 ppm males and the incidence of harderian gland adenomas or carcinomas (combined) was not increased significantly. In exposed groups of females, there was a decreased incidence of harderian gland adenomas or carcinomas (combined). Therefore, the increased incidence of harderian gland adenomas in males was not attributed to chemical exposure.

Nonneoplastic lesions similar to those found in the 13-week studies occurred in rats during the 2-year feed study. At the 3-month interim evaluation, cytoplasmic vacuolization of the adrenal cortex occurred in 600 ppm male rats and in 300 and 600 ppm female rats. At the 9- and 15-month interim evaluations, this lesion occurred only in female rats, primarily in the 300 ppm group. At the end of the 2-year study, this lesion was present in control and exposed groups of females, but the incidence and severity were significantly increased only in 300 ppm females. Although there was a suggestion of inflammation of the adrenal cortex in some animals from the 13-week studies, there was no evidence of inflammation or degenerative processes occurring during the 2-year feed study. Therefore, over the duration of the study, the adrenal cortex lesion was not related to cytotoxicity, although

the increased incidence was clearly related to tricresyl phosphate exposure.

Ovarian interstitial cell hyperplasia occurred in 150 and 300 ppm female rats at the 3- and 9-month interim evaluations, but at the end of the 2-year study the lesion occurred only in the 300 ppm group. This lesion was not observed in control rats.

Nonneoplastic lesions also occurred in mice during the 2-year study. Ceroid pigmentation of the adrenal cortex occurred in several animals in the control and exposed groups at the 3-, 9-, and 15-month interim evaluations; however, at the end of the 2-year study the severity of pigmentation in exposed groups was greater than in controls, especially in females.

There were significantly increased incidences of liver lesions in male mice exposed to 125 or 250 ppm. These lesions included clear cell foci, fatty change, and ceroid pigmentation.

Overall, the most consistent biological response associated with exposure to tricresyl phosphate was increased cytoplasmic vacuolization of cells of the zona glomerulosa and zona fasciculata of the adrenal cortex. These regions are actively involved in the biotransformation of cholesterol into steroid hormones. Several reactions involved in the formation of these products are catalyzed by cytochrome P-450-containing enzymes, and these tissues contain significant levels of P-450 activity. Therefore, tricresyl phosphate may be activated directly in the adrenal cortex by an endogenous enzyme resulting in disruption or partial inhibition of one or more biosynthetic reactions and, ultimately, accumulation of lipid-containing vacuoles. A disruption in lipid metabolism could also account for the lesions observed in the livers of male mice; however, a similar response would have been expected in female mice, but was not observed.

Another consistent finding was involvement of the gonads. During 13-week studies the testes/epididymides of male rats were severely affected by exposure to tricresyl phosphate, resulting in atrophy and cessation of spermatogenesis. Male mice did not exhibit degeneration of the testes and epididymides; however, sperm motility was markedly reduced and abnormal sperm were present (NTP, 1983, 1985). Somkuti *et al.* (1987a,b) have shown that after oral administration of TOCP, the cyclic saligenin phosphate metabolite is present in the testis of male F344 rats at a 4-fold higher concentration than in the blood. Chapin *et al.* (1990, 1991) have demonstrated *in vitro* that Leydig cells, sites of active steroidogenesis, can metabolize TOCP to the cyclic phosphate intermediate, which then produces toxicity in Sertoli cells. Therefore, there is good evidence that the testicular toxicity of tricresyl phosphate is the result of testicular metabolism by Leydig cells.

Ovarian interstitial cells also possess significant steroidogenic activity and, therefore, may also be able to metabolize tricresyl phosphate to active intermediates. However, the hyperplasia or hypertrophy that occurred was not regenerative as would be expected for the repair of a cytotoxic insult, nor was there other indication of cytotoxicity in the ovarian interstitium.

In view of the complex control of adrenal cortical and gonadal function by the anterior pituitary and hypothalamus, altered hormonal regulation may have also contributed to development of the observed lesions. Smallridge *et al.* (1991) studied the effect of diisopropylfluorophosphate (DFP) on the levels of several pituitary gland hormones in an effort to evaluate the contribution of cholinergic pathways to hormone secretion in the anterior pituitary gland. DFP is a neurotoxic organophosphate ester that also produces testicular damage in rodents. Within 1 hour after administering an intraperitoneal dose of DFP (0.6 mg/kg) to F344 rats, serum levels of adrenocorticotropic hormone (ACTH) were increased 2.5-fold, corticosterone was increased 4-fold, and luteinizing hormone (LH) was increased 3-fold over control values. Moreover, the concentrations of ACTH and corticosterone remained elevated for 9 to 18 hours.

Administration of higher doses of DFP, in addition to increasing ACTH and corticosterone, suppressed LH, thyroid stimulating hormone (TSH), and prolactin (PRL) concentrations. Adrenalectomy abolished the DFP-stimulated increase in corticosterone but had no effect on the suppression of TSH, LH, or PRL, thus eliminating the possibility that the high corticosterone levels were responsible for suppression of TSH, LH, and PRL secretion. In DFP-treated animals, secretion of corticosterone caused by corticotropin releasing factor (CRF) was similar to that observed in controls. Therefore DFP did not alter the ability of the pituitary gland to respond to

hypothalamic releasing hormones. Administration of atropine prior to DFP eliminated the increase in corticosterone, suggesting the involvement of muscarinic receptors in the secretion of CRF. This observation was consistent with previous reports that cholinergic agonists activate ACTH secretion by stimulating CRF release through a mechanism involving primarily muscarinic receptors (Smallridge *et al.*, 1991). The authors suggest that because of the long duration of pituitary-adrenal gland stimulation, repeated long-term exposure to low doses of a cholinesterase inhibitor could produce biologically significant impairment of pituitary function. In the present studies, serum cholinesterase activity was significantly decreased at the 3-, 9-, and 15-month interim evaluations in all exposed groups of mice, in 300 ppm male rats, and 150 and 300 ppm female rats. This raises the possibility that ACTH secretion may have been increased in these groups throughout the 2-year study.

Adrenocorticotropic hormone acts on the adrenal cortex to increase the activity of cholesterol side chain cleavage enzyme, a mitochondrial enzyme which catalyzes the first and primary regulatory step in the steroid biosynthetic pathway. Therefore, increased secretion of ACTH might lead to increased lipid content in the adrenal cortex, and, in fact, this has been observed in rats receiving daily doses of ACTH for 14 days (Szabo *et al.*, 1992). If LH were also increased as observed by Smallridge *et al.* (1987), then the increase could conceivably be partially responsible for the ovarian interstitial cell hyperplasia observed in female rats.

Mice did not exhibit the same sensitivity to tricresyl phosphate toxicity as rats in spite of the greater extent of serum cholinesterase inhibition. Moreover, ovarian lesions were not observed in female mice in the 2-year study although they occurred in female mice at the higher exposure levels used in the 13-week study. Clearly, the response of rats and mice is somewhat different. However, cytoplasmic vacuolization occurred in the adrenal cortex in the 13-week studies and ceroid occurred in the adrenal cortex of exposed animals during the 2-year studies. Ceroid is the generic name given to a family of lipopigments that accumulate in association with lipid degeneration or lipid excess (Harman, 1989; Jolly and Dalefield, 1989) and is considered an indication of the presence of an ongoing pathologic process. Therefore, its greater accumulation and earlier appearance in exposed mice during the 2-year study is consistent with an increase in steroidogenesis, albeit not as obvious as that observed in rats.

Two other organophosphate esters have been evaluated in NTP 2-year studies. Dimethyl methylphosphonate (methyl phosphonic acid dimethyl ester), was administered in corn oil by gavage at doses of 500 or 1,000 mg/kg to F344/N rats and 1,000 or 2,000 mg/kg to $B6C3F_1$ mice for 2 years (NTP, 1987). The incidences of renal transitional cell papillomas and renal tubule cell adenomas were increased in male rats, but there were no treatment-related neoplasms or nonneoplastic lesions in female rats or mice.

Dichlorvos (2,2-dichlorovinyl dimethyl phosphate) was administered in corn oil by gavage at doses of 4 or 8 mg/kg to F344/N rats, 10 or 20 mg/kg to male $B6C3F_1$ mice, and 20 or 40 mg/kg to female $B6C3F_1$ mice (NTP, 1989). Dichlorvos administration was associated with increased incidences of mononuclear cell leukemia in male rats, fibroadenomas in female rats, and pancreatic adenomas in male and female rats. The most significant response was an increased incidence of squamous cell papillomas of the forestomach in male and female mice. Although mice did not develop any treatment-related nonneoplastic lesions in the 2-year study, increased incidences of cytoplasmic vacuolization of the adrenal cortex occurred in male and female rats.

Based on the doses used in the 2-year studies, the toxicity of dichlorvos appears to be more like that of tricresyl phosphate than does the toxicity of dimethyl methylphosphonate. However, dose selection for the 2-year studies of dichlorvos was based on mortality and lower mean body weights; there were no compound-related microscopic lesions observed in the 13-week studies. Therefore, there appears to be very little similarity in the toxic response observed for the three compounds.

The biological and toxicological significance of responses such as those observed in the present studies is particularly difficult to judge in the context of selecting doses or evaluating the adequacy of exposure. A chemical-related lesion that has the potential to markedly alter the function or integrity of the adrenal cortex must be considered a toxic effect. In cells actively involved in steroid biosynthesis the accumulation of lipid-containing cytoplasmic vacuoles could signal inhibition or disruption of normal

biosynthetic processes that could eventually result in cell death.

At the concentrations used in the 2-year studies, the adrenal gland lesions did not become noticeably cytotoxic and were not present in male rats at the end of the study. However, it is difficult to judge what might have happened at higher concentrations. In 300 ppm female rats and 250 ppm female mice, the severity of adrenal gland lesions was significantly increased, and it is doubtful that these groups could have tolerated a doubling of the concentration. At the 3-month interim evaluations in the 2-year studies, cytoplasmic vacuolization was present in the adrenal cortex of 600 ppm male rats, but was not present in males exposed to lower concentrations; therefore, it is possible that male rats may have been able to tolerate concentrations up to 600 ppm. Even if higher concentrations had been administered to male rats, it is still unlikely that a carcinogenic or preneoplastic response would have occurred. The highest concentration that did not cause mortality or lower mean body weights in male rats during the 13-week study was 1,700 ppm, a 5-fold increase over the high concentration in the 2-year study. At this concentration, the adrenal cortex and testes were the major sites of toxicity with essentially no response in any organ system that could be considered preneoplastic.

In male mice, cytoplasmic vacuolization of the adrenal cortex did not occur in the 250 ppm group, but was present in the 500 ppm group at the end of the 13-week feed study. However, degenerative lesions occurred in the sciatic nerve of mice receiving 1,000 ppm; therefore, it is questionable whether male mice could have tolerated concentrations up to 500 ppm for 2 years without complications associated with lesions in the nervous system. Exposure levels greater than 500 ppm would clearly have been unacceptable for mice.

Therefore, dose selection in these studies was limited by the presence of toxic lesions in organs/tissues involved in functions critical for life. The potential hazard associated with the presence of these lesions dictated that concentrations be selected to minimize their severity. Moreover, the dose response was such that the lesions would have become debilitating or fatal at concentrations high enough to elicit more conventional toxic responses such as lower mean body weights.

CONCLUSIONS

Under the conditions of these 2-year feed studies, there was *no evidence of carcinogenic activity** of tricresyl phosphate in male or female F344/N rats that received 75, 150, or 300 ppm. There was *no evidence of carcinogenic activity* of tricresyl phosphate in male or female B6C3F$_1$ mice that received 60, 125 or 250 ppm.

Nonneoplastic lesions associated with exposure to tricresyl phosphate included cytoplasmic vacuolization of the adrenal cortex and ovarian interstitial cell hyperplasia in female rats, increased incidences of clear cell focus, fatty change, and ceroid pigmentation of the liver in male mice, and increased severity of ceroid pigmentation of the adrenal cortex in female mice.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this report appears on page 12.

REFERENCES

Abou-Donia, M.B., and Nomeir, A.A. (1986). The role of pharmacokinetics and metabolism in species sensitivity to neurotoxic agents. *Fundam. Appl. Toxicol.* **6**, 190-207.

Abou-Donia, M.B., Varga, P.A., Graham, D.G., and Kinnes, C.G. (1980). Delayed neurotoxicity of a single dermal administration of o-ethyl o-4-nitrophenyl phenylphosphonothioate and tri-o-cresyl phosphate to cats. *Toxicol. Lett.* **1**, 141.

Abou-Donia, M.B., Suwita, E., and Nomeir, A.A. (1990). Absorption, distribution, and elimination of a single oral dose of [^{14}C]tri-*o*-cresyl phosphate in hens. *Toxicology* **61**, 13-25.

Armitage, P. (1971). *Statistical Methods in Medical Research*, pp. 362-365. John Wiley and Sons, New York.

Ashby, J., and Tennant, R.W. (1991). Definitive relationships among chemical structure, carcinogenicity, and mutagenicity for 301 chemicals tested by the U.S. NTP. *Mutat. Res.* **257**, 229-306.

Boorman, G.A., Montgomery, C.A., Jr., Eustis, S.L., Wolfe, M.J., McConnell, E.E., and Hardisty, J.F. (1985). Quality assurance in pathology for rodent carcinogenicity studies. In *Handbook of Carcinogen Testing* (H.A. Milman and E.K. Weisburger, Eds.), pp. 345-357. Noyes Publications, Park Ridge, NJ.

Bouldin, T.W., and Cavanagh, J.B. (1979a). A teased-fiber study of the spatio-temporal spread of axonal degeneration. *Am. J. Pathol.* **94**, 241-252.

Bouldin, T.W., and Cavanagh, J.B. (1979b). A fine-structural study of the early stages of axonal degeneration. *Am. J. Pathol.* **94**, 253-270.

Carlton, B.D., Basaran, A.H., Mezza, L.E., and Smith, M.K. (1987). Examination of the reproductive effects of tricresyl phosphate administered to Long-Evans rats. *Toxicology* **46**, 321-328.

Casida, J.E., Eto, M., and Baron, R.L. (1961). Biological activity of a tri-*o*-cresyl phosphate metabolite. *Nature (Lond.)* **191**, 1396-1397.

Cavanagh, J.B., and Patangia, G.N. (1965). Changes in the central nervous system in the cat as the result of tri-*o*-cresyl phosphate poisoning. *Brain* **38**, 165-180.

Chapin R.E., George, J.D., and Lamb, J.C., IV (1988). Reproductive toxicity of tricresyl phosphate in a continuous breeding protocol in Swiss (CD-1) mice. *Fundam. Appl. Toxicol.* **10**, 344-354.

Chapin, R.E., Phelps, J.L., Somkuti, S.G., Heindel, J.J., and Burka, L.T. (1990). The interaction of Sertoli and Leydig cells in the testicular toxicity of tri-*o*-cresyl phosphate. *Toxicol. Appl. Pharmacol.* **104**, 483-495.

Chapin, R.E., Phelps, J.L., Burka, L.T., Abou-Donia, M.B., and Heindel, J.J. (1991). The effects of tri-*o*-cresyl phosphate and metabolites on rat Sertoli cell function in primary culture. *Toxicol. Appl. Pharmacol.* **108**, 194-204.

Chemical and Economics Handbook (1988). SRI International, Menlo Park, CA.

Code of Federal Regulations (CFR) **21**, Part 58.

Cox, D.R. (1972). Regression models and life-tables. *J. R. Stat. Soc.* **B34**, 187-220.

Crawford, B.D. (1985). Perspectives on the somatic mutation model of carcinogenesis. In *Advances in Modern Environmental Toxicology* (M.A. Mehlman, W.G. Flamm, and R.J. Lorentzen, Eds.), pp. 13-59. Princeton Scientific Publishing Co., Inc., Princeton, NJ.

Davies, D.R. (1963). Neurotoxicity of organophosphorous compounds. In *Handbuch der Experimentallen Pharmakologie* (G. Koelle, Ed.).

Dinse, G.E., and Haseman, J.K. (1986). Logistic regression analysis of incidental-tumor data from animal carcinogenicity experiments. *Fundam. Appl. Toxicol.* **6**, 44-52.

Dinse, G.E., and Lagakos, S.W. (1983). Regression analysis of tumour prevalence data. *Appl. Statist.* **32**, 236-248.

Dunn, O.J. (1964). Multiple comparisons using rank sums. *Technometrics* **6**, 241-252.

Dunnett, C.W. (1955). A multiple comparison procedure for comparing several treatments with a control. *J. Am. Stat. Assoc.* **50**, 1095-1121.

Eto, M., Casida, J.E., and Eto, T. (1962). Hydroxylation and cyclization reactions involved in the metabolism of tri-*o*-cresyl phosphate. *Biochem. Pharmacol.* **11**, 337-352.

Galloway, S.M., Armstrong, M.J., Reuben, C., Colman, S., Brown, B., Cannon, C., Bloom, A.D., Nakamura, F., Ahmed, M., Duk, S., Rimpo, J., Margolin, B.H., Resnick, M.A., Anderson, B., and Zeiger, E. (1987). Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: Evaluations of 108 chemicals. *Environ. Mol. Mutagen.* **10** (Suppl. 10), 1-175.

Gart, J.J., Chu, K.C., and Tarone, R.E. (1979). Statistical issues in interpretation of chronic bioassay tests for carcinogenicity. *J. Natl. Cancer Inst.* **62**, 957-974.

Harman, D. (1989). Lipofuscin and ceroid formation: The cellular recycling system. *Adv. Exp. Med. Biol.* **266**, 3-16.

Haseman, J.K. (1984). Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies. *Environ. Health Perspect.* **58**, 385-392.

Haseman, J.K., Huff, J., and Boorman, G.A. (1984). Use of historical control data in carcinogenicity studies in rodents. *Toxicol. Pathol.* **12**, 126-135.

Haseman, J.K., Huff, J.E., Rao, G.N., Arnold, J.E., Boorman, G.A., and McConnell, E.E. (1985). Neoplasms observed in untreated and corn oil gavage control groups of F344/N rats and (C57BL/6N × C3H/HeN)F_1 (B6C3F_1) mice. *JNCI* **75**, 975-984.

Haworth, S., Lawlor, T., Mortelmans, K., Speck, W., and Zeiger, E. (1983). *Salmonella* mutagenicity test results for 250 chemicals. *Environ. Mutagen.* **5** (Suppl. 1), 3-142.

Henschler, D. (1958). Relationships between the chemical structure and the paralyzing action of triaryl phosphates. (Besiehungen zwischen chemischer struktur und lahmungawirkung von triaryl-phosphaten.) *Naunyn-Schmiedeberg's Arch. Exp. Path. U. Pharmak.*, Vol. 237, pp. 459-472.

Hollander, M., and Wolfe, D.A. (1973). *Nonparametric Statistical Methods*, pp. 120-123. John Wiley and Sons, New York.

International Programme on Chemical Safety (IPCS) (1990). Environmental Health Criteria 110: Tricresyl Phosphate. World Health Organization, Geneva.

Izmerov, N.F., Sanotsky, I.V., and Sidorov, K.K. (1982). *Toxicometric Parameters of Industrial Toxic Chemicals Under Single Exposure.* Moscow, Centre of International Projects, GKNT, p. 114.

Johannsen, F.R., Wright, P.L., Gordon, D.E., Levinskas, G.J., Radue, R.W., and Graham, P.R. (1977). Evaluation of delayed neurotoxicity and dose-response relationships of phosphate esters in the adult hen. *Toxicol. Appl. Pharmacol.* **41**, 291-304.

Jolly, R.D., and Dalefield, R.R. (1989). Lipopigments in veterinary pathology: Pathogenesis and terminology. *Adv. Exp. Med. Biol.* **266**, 157-168.

Jonckheere, A.R. (1954). A distribution-free *k*-sample test against ordered alternatives. *Biometrika* **41**, 133-145.

Jortner, B.S., and Ehrich, M. (1987). Neuropathological effects of phenyl saligenin phosphate in chickens. *Neurotoxicology* **8**, 303-314.

Jortner, B.S., Shell, L., El-Fawal, H., and Ehrich, M. (1989). Myelinated nerve fiber regeneration following organophosphorus ester-induced delayed neuropathy. *Neurotoxicology* **10**, 717-726.

Kaplan, E.L., and Meier, P. (1958). Nonparametric estimation from incomplete observations. *J. Am. Stat. Assoc.* **53**, 457-481.

Kimmerle, G., and Loeser, E. (1974). Delayed neurotoxicity of organophosphorus compounds and copper concentration in the serum of hens. *Environ. Qual. Saf.* **3**, 174-178.

Kurebayashi, H., Tanaka, A., and Yamaha, T. (1985). Metabolism and disposition of the flame retardant plasticizer, tri-p-cresyl phosphate, in the rat. *Toxicol. Appl. Pharmacol.* **77**, 395-404.

Marhold, J.V. (1972). *Collection of Results of Toxicological Assessments of Compounds and Formulations Tested at the Department of Toxicology, Research Institute for Organic Syntheses.* Prague, Institute for Management Training in the Chemical Industry.

McConnell, E.E., Solleveld, H.A., Swenberg, J.A., and Boorman, G.A. (1986). Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. *JNCI* **76**, 283-289.

McKnight, B., and Crowley, J. (1984). Tests for differences in tumor incidence based on animal carcinogenesis experiments. *J. Am. Stat. Assoc.* **79**, 639-648.

Maronpot, R.R., and Boorman, G.A. (1982). Interpretation of rodent hepatocellular proliferative alterations and hepatocellular tumors in chemical safety assessment. *Toxicol. Pathol.* **10**, 71-80.

The Merck Index. (1976). 9th ed. (M. Windholz, Ed.). Merck and Co., Rahway, NJ.

Meyer, O.A., Tilson, H.A., Byrd, W.C., and Riley, M.T. (1979). A method for the routine assessment of fore- and hindlimb grip strength of rats and mice. *Neurobehav. Toxicol.* **1**, 233-236.

Miller, R.G. (1981). *Simultaneous Statistical Inference*, p. 67. Springer-Verlag, New York.

Miller, J.A., and Miller, E.C. (1977). Ultimate chemical carcinogens as reactive mutagenic electrophiles. In *Origins of Human Cancer* (H.H. Hiatt, J.D. Watson, and J.A. Winsten, Eds.), pp. 605-627. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.

Morgan, J.P., and Penovich, P. (1978). Jamaica Ginger Paralysis: Forty-seven-year follow-up. *Arch. Neurol.* **35**, 530-532.

National Cancer Institute (NCI) (1976). Guidelines for Carcinogen Bioassay in Small Rodents. Technical Report Series No. 1. NIH Publication No. 76-801. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

National Institutes of Health (NIH) (1978). Open Formula Rat and Mouse Ration (NIH-07). Specification NIH-11-1335. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

National Toxicology Program (NTP) (1983). Report on Sperm Morphology and Vaginal Cytology in Rats and Mice Administered Tricresyl Phosphate (Gavage Studies). U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1985). Report on sperm morphology and vaginal cytology in rats and mice administered tricresyl phosphate (Feed Studies). U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1987). Toxicology and Carcinogenesis Studies of Dimethyl Methylphosphonate (CAS No. 756-79-6) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies). Technical Report Series No. 323. NIH Publication No. 88-2579. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1989). Toxicology and Carcinogenesis Studies of Dichlorvos (CAS No. 62-73-7) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies). Technical Report Series No. 342. NIH Publication No. 89-2598. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

Nomeir, A.A., and Abou-Donia, M.B. (1986). Studies on the metabolism of the neurotoxic tri-*o*-cresyl phosphate, distribution, excretion, and metabolism in male cats after a single, dermal application. *Toxicology* **38**, 15-33.

Sadtler Standard Spectra. UV No. 10. Sadtler Research Laboratories, Philadelphia, PA.

Shirley, E. (1977). A non-parametric equivalent of Williams' test for contrasting increasing dose levels of a treatment. *Biometrics* **33**, 386-389.

Smallridge, R.C., Carr, F.E., and Fein, H.G. (1991). Diisopropylfluorophosphate (DFP) reduces serum prolactin, thyrotropin, luteinizing hormone, and growth hormone and increases adrenocorticotropin and corticosterone in rats: Involvement of dopaminergic and somatostatinergic as well as cholinergic pathways. *Toxicol. Appl. Pharmacol.* **108**, 284-295.

Smallridge, R.C. (1987). Thyrotropin-secreting pituitary tumors. *Endocrinol. Metab. Clin. North Am.* **16**, 765-792.

Smith, M.I., and Elvove, E. (1930). Pharmacological and chemical studies of the cause of so-called ginger paralysis. *Public Health Rep.* **45**, 1703- .

Smith, M.I., Engel, E.W., and Stohlman, F.F. (1932). Further studies on the pharmacology of certain phenol esters with special reference to the relation of chemical constitution and physiologic action. *Natl. Inst. Health Bull.* **160**, 1-53.

Somkuti, S.G, and Abou-Donia, M.B. (1990). Disposition, elimination, and metabolism of tri-*o*-cresyl phosphate following daily oral administration in Fischer 344 male rats. *Arch. Toxicol.* **64**

Somkuti, S.G., Lapadula, D.M., Chapin, R.E., Lamb, J.C., IV, and Abou-Donia, M.B. (1987a). Reproductive tract lesions resulting from subchronic administration (63 days) of tri-*o*-cresyl phosphate in male rats. *Toxicol. Appl. Pharmacol.* **89**, 49-63.

Somkuti, S.G., Lapadula, D.M., Chapin, R.E., Lamb, J.C., IV, and Abou-Donia, M.B. (1987b). Time course of the tri-*o*-cresyl phosphate-induced testicular lesion in F-344 rats: Enzymatic, hormonal, and sperm parameter studies. *Toxicol. Appl. Pharmacol.* **89**, 64-72.

Somkuti, S.G., Tilson, H.A., Brown, H.R., Campbell, G.A., Lapadula, D.M., and Abou-Donia, M.B. (1988). Lack of delayed neurotoxic effect after tri-*o*-cresyl phosphate treatment in male Fischer 344 rats: Biochemical, neurobehavioral, and neuropathological studies. *Fundam. Appl. Toxicol.* **10**, 199-205.

Straus, D.S. (1981). Somatic mutation, cellular differentiation, and cancer causation. *JNCI* **67**, 233.

Szabó, D., Czakó, F., Tóth, I.E., Szalay, K.Sz., Krasznai, K., and Stark, E. (1992). Effect of chronic ACTH treatment on the physical state of lipid droplets in rat adrenocortical cells. *J. Steroid Biochem. Mol. Biol.* **41**, 781-784.

Tarone, R.E. (1975). Tests for trend in life table analysis. *Biometrika* **62**, 679-682.

Tennant, R.W., Margolin, B.H., Shelby, M.D., Zeiger, E., Haseman, J.K., Spalding, J., Caspary, W., Resnick, M., Stasiewicz, S., Anderson, B., and Minor, R. (1987). Prediction of chemical carcinogenicity in rodents from *in vitro* genetic toxicity assays. *Science* **236**, 933-941.

Veronesi B. (1984). Effect of metabolic inhibition with piperonyl butoxide on rodent sensitivity to tri-*ortho*-cresyl phosphate. *Exp. Neurol.* **85**, 651-660.

Veronesi, B., Newland, D., and Inman, A. (1984). The effect of metabolic interference on rodent-sensitivity to tri-ortho-cresyl phosphate. *Toxicologist* **4**, 55. (Abstr.)

Veronesi, B., Padilla, S., Blackmon, K., and Pope, C. (1991). Murine susceptibility to organophosphorus-induced delayed neuropathy (OPIDN). *Toxicol. Appl. Pharmacol.* **107**, 311-324.

Williams, D.A. (1971). A test for differences between treatment means when several dose levels are compared with a zero dose control. *Biometrics* **27**, 103-117.

Williams, D.A. (1972). The comparison of several dose levels with a zero dose control. *Biometrics* **28**, 519-531.

Zeiger, E., Haseman, J.K., Shelby, M.D., Margolin, B.H., and Tennant, R.W. (1990). Evaluation of four *in vitro* genetic toxicity tests for predicting rodent carcinogenicity: Confirmation of earlier results with 41 additional chemicals. *Environ. Mol. Mutagen.* **16** (Suppl. 18), 1-14.

APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR FEED STUDY OF TRICRESYL PHOSPHATE

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TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Tricresyl Phosphate[a]

	0 ppm	75 ppm	150 ppm	300 ppm
Disposition Summary				
Animals initially in study	95	95	95	95
3-Month interim evaluation[b]	15	15	15	15
9-Month interim evaluation[b]	14	15	15	15
15-Month interim evaluation[b]	15	15	15	15
Early deaths				
Moribund	14	16	11	16
Natural deaths	5	4	4	6
Survivors				
Died last week of study	1			
Terminal sacrifice	31	30	35	28
Animals examined microscopically	95	95	95	95
Systems Examined at 3, 9, and 15 Months With No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				
2-Year Study				
Alimentary System				
Intestine small, jejunum	(49)	(49)	(48)	(49)
Mast cell tumor benign	1 (2%)			1 (2%)
Liver	(50)	(50)	(49)	(50)
Hepatocellular adenoma		1 (2%)	1 (2%)	1 (2%)
Mesentery	(4)	(8)	(5)	(6)
Liposarcoma				1 (17%)
Schwannoma malignant	1 (25%)			
Pancreas	(51)	(50)	(49)	(50)
Stomach, forestomach	(51)	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)			
Cardiovascular System				
Heart	(51)	(50)	(50)	(50)
Endocrine System				
Adrenal cortex	(50)	(49)	(50)	(49)
Adenoma	1 (2%)	2 (4%)	2 (4%)	3 (6%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	75 ppm	150 ppm	300 ppm
2-Year Study (continued)				
Endocrine System (continued)				
Adrenal medulla	(50)	(50)	(50)	(50)
Ganglioneuroma	1 (2%)			
Pheochromocytoma malignant	1 (2%)	1 (2%)		
Pheochromocytoma benign	5 (10%)	7 (14%)	5 (10%)	4 (8%)
Bilateral, pheochromocytoma complex	1 (2%)			
Bilateral, pheochromocytoma benign			4 (8%)	1 (2%)
Islets, pancreatic	(51)	(50)	(49)	(50)
Adenoma	2 (4%)		3 (6%)	1 (2%)
Carcinoma		1 (2%)		
Pituitary gland	(51)	(50)	(50)	(50)
Pars distalis, adenoma	7 (14%)	11 (22%)	14 (28%)	3 (6%)
Pars distalis, adenoma, multiple	1 (2%)	1 (2%)		1 (2%)
Pars intermedia, adenoma			1 (2%)	
Thyroid gland	(51)	(50)	(50)	(49)
Bilateral, C-cell, adenoma	1 (2%)	2 (4%)		2 (4%)
C-cell, adenoma	11 (22%)	7 (14%)	6 (12%)	6 (12%)
C-cell, carcinoma		1 (2%)		
General Body System				
None				
Genital System				
Epididymis	(51)	(50)	(50)	(50)
Preputial gland	(50)	(49)	(49)	(50)
Adenoma	4 (8%)	3 (6%)	3 (6%)	2 (4%)
Carcinoma		1 (2%)		
Seminal vesicle	(51)	(50)	(50)	(50)
Testes	(51)	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma	40 (78%)	40 (80%)	39 (78%)	41 (82%)
Interstitial cell, adenoma	8 (16%)	5 (10%)	7 (14%)	8 (16%)
Hematopoietic System				
Lymph node	(4)	(6)	(5)	(5)
Lymph node, mandibular	(49)	(50)	(50)	(49)
Lymph node, mesenteric	(51)	(49)	(50)	(50)
Spleen	(50)	(50)	(50)	(50)
Sarcoma				1 (2%)
Thymus	(51)	(47)	(47)	(49)
Integumentary System				
Mammary gland	(46)	(48)	(45)	(45)
Fibroadenoma		3 (6%)	2 (4%)	2 (4%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	75 ppm	150 ppm	300 ppm
2-Year Study (continued)				
Integumentary System (continued)				
Skin	(51)	(50)	(50)	(50)
Basal cell adenoma	1 (2%)			
Basosquamous tumor benign	1 (2%)			
Fibroma	1 (2%)			
Keratoacanthoma	2 (4%)			
Squamous cell carcinoma	1 (2%)			
Subcutaneous tissue, fibroma		1 (2%)		
Subcutaneous tissue, fibrosarcoma	1 (2%)			1 (2%)
Subcutaneous tissue, fibrous histiocytoma	1 (2%)			
Subcutaneous tissue, lipoma				1 (2%)
Subcutaneous tissue, sarcoma			1 (2%)	
Subcutaneous tissue, schwannoma malignant	1 (2%)			
Musculoskeletal System				
None				
Nervous System				
Brain	(51)	(50)	(50)	(50)
Astrocytoma benign	1 (2%)			
Granular cell tumor benign	1 (2%)			
Oligodendroglioma benign			1 (2%)	
Peripheral nerve	(51)	(50)	(50)	(50)
Spinal cord	(51)	(50)	(50)	(49)
Respiratory System				
Lung	(51)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma	1 (2%)			
Nose	(51)	(50)	(50)	(50)
Squamous cell carcinoma				1 (2%)
Special Senses System				
Ear			(1)	(1)
Pinna, fibrosarcoma				1 (100%)
Zymbal's gland	(1)	(1)	(1)	(1)
Carcinoma	1 (100%)	1 (100%)	1 (100%)	1 (100%)
Urinary System				
Kidney	(51)	(50)	(50)	(50)
Urinary bladder	(51)	(50)	(50)	(50)
Systemic Lesions				
Multiple organs[c]	(51)	(50)	(50)	(50)
Leukemia mononuclear	20 (39%)	18 (36%)	16 (32%)	20 (40%)
Mesothelioma malignant	1 (2%)		1 (2%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	75 ppm	150 ppm	300 ppm
Neoplasm Summary				
Total animals with primary neoplasms[d]	50	49	49	50
Total primary neoplasms	120	106	107	103
Total animals with benign neoplasms	49	48	48	50
Total benign neoplasms	90	83	88	77
Total animals with malignant neoplasms	28	23	19	24
Total malignant neoplasms	30	23	19	26
Total animals with metastatic neoplasms	1			
Total metastatic neoplasms	2			

[a] Number of animals examined microscopically at site and number of animals with neoplasm
[b] Includes up to five animals per dose group subjected to total body perfusion for special neuropathology
[c] Number of animals with any tissue examined microscopically
[d] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Tricresyl Phosphate: 0 ppm

Number of Days on Study	0 8 7	4 7 8	4 8 6	5 0 0	5 5 8	5 7 2	5 9 2	6 2 5	6 4 7	6 4 7	6 7 3	6 8 0	6 8 3	6 9 0	7 0 1	7 0 1	7 0 2	7 2 2	7 2 5	7 3 0	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2
Carcass ID Number	0 0 9	4 8 1	5 1 3	5 2 1	5 3 0	4 9 1	4 8 7	5 1 2	4 8 8	5 1 7	5 2 7	5 2 3	5 2 2	5 9 6	5 0 6	5 0 9	5 2 9	5 1 1	4 9 0	5 0 2	4 8 2	4 8 3	4 8 4	4 8 5	4 8 6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor benign																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Mesentery							+			+															
Schwannoma malignant																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, lung						X																			
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Ganglioneuroma																									
Pheochromocytoma malignant																									
Pheochromocytoma benign																							X		
Bilateral, pheochromocytoma complex																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X							
Parathyroid gland	M	+	+	M	+	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma															X					X		X		X	
Pars distalis, adenoma, multiple									X																
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, lung						X																			
Bilateral, C-cell, adenoma													X												
C-cell, adenoma										X							X		X					X	X
General Body System																									
None																									

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Tricresyl Phosphate: 0 ppm (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	4 8 9	4 9 2	4 9 3	4 9 4	4 9 5	4 9 7	4 9 8	4 9 9	5 0 0	5 0 1	5 0 3	5 0 4	5 0 5	5 0 7	5 0 8	5 1 0	5 1 4	5 1 5	5 1 6	5 1 8	5 1 9	5 2 0	5 2 4	5 2 5	5 2 6	5 2 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mast cell tumor benign																						X				1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery						+							+													4
Schwannoma malignant						X																				1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Squamous cell papilloma																						X				1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Mesothelioma malignant, metastatic, lung																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ganglioneuroma					X																					1
Pheochromocytoma malignant																								X		1
Pheochromocytoma benign			X			X	X							X												5
Bilateral, pheochromocytoma complex																				X						1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma																									X	2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pars distalis, adenoma		X			X				X																	7
Pars distalis, adenoma, multiple																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Mesothelioma malignant, metastatic, lung																										1
Bilateral, C-cell, adenoma																										1
C-cell, adenoma				X						X		X		X						X		X				11
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Tricresyl Phosphate: 0 ppm (continued)

Number of Days on Study	0 8 7	4 7 8	4 8 6	5 0 0	5 5 8	5 7 2	5 9 2	6 2 5	6 4 7	6 4 7	6 7 3	6 8 0	6 8 3	6 9 0	7 0 1	7 0 1	7 0 2	7 2 2	7 2 5	7 3 0	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2
Carcass ID Number	0 0 9	4 8 1	5 1 3	5 2 1	5 3 0	4 9 1	4 8 7	5 1 2	4 8 8	5 1 7	5 2 7	5 2 3	5 2 3	5 9 2	5 0 6	5 0 6	5 2 9	5 1 9	4 9 0	5 0 2	4 8 2	4 8 3	4 8 4	4 8 5	4 8 6
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Adenoma					X																				
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma						X	X		X	X	X	X	X	X	X	X	X	X	X		X	X		X	X
Interstitial cell, adenoma		X		X				X												X			X		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+								+	+		+											
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																					X				
Basosquamous tumor benign																									
Fibroma																									
Keratoacanthoma															X										
Squamous cell carcinoma																									
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, fibrous histiocytoma															X										
Subcutaneous tissue, schwannoma malignant																	X								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																	+								
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma benign																			X						
Granular cell tumor benign													X												
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Tricresyl Phosphate: 0 ppm (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	4 8 9	4 9 2	4 9 3	4 9 4	4 9 5	4 9 7	4 9 8	4 9 9	5 0 0	5 0 1	5 0 3	5 0 4	5 0 5	5 0 7	5 0 8	5 1 0	5 1 4	5 1 5	5 1 6	5 1 8	5 1 9	5 2 0	5 2 4	5 2 5	5 2 6	5 2 8	Total Tissues/ Tumors
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X										X									X						4
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Bilateral, interstitial cell, adenoma	X		X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	40
Interstitial cell, adenoma		X				X				X																	8
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node																											4
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	46
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Basal cell adenoma																											1
Basosquamous tumor benign											X																1
Fibroma				X																							1
Keratoacanthoma											X																2
Squamous cell carcinoma																									X		1
Subcutaneous tissue, fibrosarcoma					X																						1
Subcutaneous tissue, fibrous histiocytoma																											1
Subcutaneous tissue, schwannoma malignant																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Skeletal muscle																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Astrocytoma benign																											1
Granular cell tumor benign																											1
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar carcinoma											X																1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Tricresyl Phosphate: 0 ppm (continued)

Number of Days on Study	0	4	4	5	5	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	
	8	7	8	0	5	7	9	2	4	4	7	8	8	9	0	0	0	2	2	3	3	3	3	3	
	7	8	6	0	8	2	2	5	7	7	3	0	3	0	1	1	2	2	5	0	1	1	2	2	2
Carcass ID Number	0	4	5	5	5	4	4	5	4	5	5	5	5	4	5	5	5	5	4	5	4	4	4	4	4
	0	8	1	2	3	9	8	1	8	1	2	2	2	9	0	0	2	1	9	0	8	8	8	8	8
	9	1	3	1	0	1	7	2	8	7	7	3	2	6	6	9	9	1	0	2	2	3	4	5	6
Special Senses System																									
Eye		+	+				+												+						+
Zymbal's gland		+																							
Carcinoma		X																							
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X			X	X	X	X	X	X		X	X	X		X				X	X		X
Mesothelioma malignant						X																			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Tricresyl Phosphate: 0 ppm (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	4 8 9	4 9 2	4 9 3	4 9 4	4 9 5	4 9 7	4 9 8	4 9 9	5 0 0	5 0 1	5 0 3	5 0 4	5 0 5	5 0 7	5 0 8	5 1 0	5 1 4	5 1 5	5 1 6	5 1 8	5 1 9	5 2 0	5 2 4	5 2 5	5 2 6	5 2 8	Total Tissues/ Tumors
Special Senses System																											
Eye			+																				+				7
Zymbal's gland																											1
Carcinoma																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Leukemia mononuclear								X	X	X			X												X		20
Mesothelioma malignant																											1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Tricresyl Phosphate: 75 ppm

Number of Days on Study	2 6 3	4 5 5	4 9 8	5 3 7	5 8 6	5 9 0	6 1 1	6 1 4	6 1 4	6 3 5	6 4 0	6 4 8	6 5 2	6 6 2	6 9 0	6 9 1	6 9 9	7 0 1	7 0 2	7 2 5	7 3 0	7 3 0	7 3 0	7 3 1
Carcass ID Number	5 6 7	5 6 6	5 7 2	5 3 2	5 3 7	5 3 1	5 6 9	5 3 3	5 7 0	5 3 9	5 5 4	5 6 4	5 7 9	5 3 8	5 4 8	5 4 5	5 3 1	5 7 1	5 6 1	5 5 6	5 3 5	5 3 4	5 4 6	5 4 0	5 4 1	5 4 2
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Intestine large, colon	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																										
Mesentery								+				+														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X											
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant												X														
Pheochromocytoma benign					X								X													
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																										
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma									X															X	X	
Pars distalis, adenoma, multiple																										
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma									X				X													
C-cell, adenoma					X	X		X																		
C-cell, carcinoma																										X
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X																		X
Carcinoma																										
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma			X		X	X	X	X	X	X	X	X	X				X	X	X	X	X	X	X	X		X
Interstitial cell, adenoma		X													X	X										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Tricresyl Phosphate: 75 ppm (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	5 4 3	5 4 4	5 4 5	5 4 6	5 4 7	5 4 9	5 5 0	5 5 1	5 5 2	5 5 3	5 5 7	5 5 8	5 5 9	5 6 0	5 6 2	5 6 3	5 6 5	5 6 8	5 7 3	5 7 4	5 7 5	5 7 6	5 7 7	5 7 8	5 8 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																				X						1
Mesentery		+			+				+					+					+					+		8
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma						X																				2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign					X					X										X				X	X	7
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma							X																			1
Parathyroid gland	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma				X	X							X		X		X	X	X							X	11
Pars distalis, adenoma, multiple																					X					1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma																										2
C-cell, adenoma					X													X		X					X	7
C-cell, carcinoma																										1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Adenoma														X												3
Carcinoma																	X									1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X		X	X		X	X	X	X	40
Interstitial cell, adenoma																	X		X							5

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Tricresyl Phosphate: 75 ppm (continued)

Number of Days on Study	2	4	4	5	5	5	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7
	6	5	9	3	8	9	1	1	1	3	4	4	5	6	9	9	9	0	0	2	3	3	3	3	3
	3	5	8	7	6	0	1	4	4	5	0	8	2	2	0	1	9	1	2	5	0	0	0	0	1
Carcass ID Number	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	6	6	7	3	3	3	6	3	7	3	5	6	7	3	4	3	7	6	5	5	3	3	4	4	4
	7	6	2	2	7	1	9	3	0	9	4	4	9	8	8	5	1	1	6	5	4	6	0	1	2
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node											+				+		+	+	+						
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma			X						X												X				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																		X							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle			+																						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Special Senses System																									
Eye						+						+													
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X		X	X	X	X			X	X		X	X	X	X	X	X	X						

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Tricresyl Phosphate: 75 ppm (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	5 4 3	5 4 4	5 4 5	5 4 6	5 4 7	5 4 9	5 5 0	5 5 1	5 5 2	5 5 3	5 5 7	5 5 8	5 5 9	5 6 0	5 6 2	6 6 3	6 6 5	6 7 8	7 7 3	7 7 4	7 7 5	7 7 6	7 7 7	7 7 8	5 8 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																							+			6
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	47
Integumentary System																										
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibroadenoma																										3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye					+																					3
Zymbal's gland																									+	1
Carcinoma																									X	1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear									X	X			X										X			18

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Tricresyl Phosphate: 150 ppm

Number of Days on Study	2 6 9	4 5 4	4 8 8	4 9 1	5 2 9	5 5 3	6 1 4	6 1 8	6 2 4	6 3 8	6 8 2	7 0 1	7 1 1	7 2 2	7 2 2	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	6 1 8	5 9 7	5 9 5	6 1 7	6 0 2	5 8 2	6 0 8	6 3 0	5 8 4	6 0 6	6 1 9	5 8 1	6 2 2	6 0 7	6 0 9	5 8 3	5 8 5	5 8 6	5 8 7	5 8 8	5 8 9	5 9 0	5 9 1	5 9 2	5 9 3
Alimentary System																									
Esophagus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	A	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	A	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	M	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+
Hepatocellular adenoma																				X					
Mesentery		+											+		+								+		
Pancreas	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																				+					
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X													
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																								X	
Bilateral, pheochromocytoma benign														X	X		X				X				
Islets, pancreatic	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X	X						X			
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X			X					X	X					X				X					
Pars intermedia, adenoma											X														
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																		X				X			
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X							
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma							X	X	X		X	X	X	X		X	X	X	X	X	X	X	X	X	X
Interstitial cell, adenoma				X		X				X					X										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Tricresyl Phosphate: 150 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	5 9 4	5 9 6	5 9 8	5 9 9	6 0 0	6 0 1	6 0 3	6 0 4	6 0 5	6 1 0	6 1 1	6 1 2	6 1 3	6 1 4	6 1 5	6 1 6	6 2 0	6 2 1	6 2 3	6 2 4	6 2 5	6 2 6	6 2 7	6 2 8	6 2 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma																										1
Mesentery																							+			5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma											X															2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign			X				X			X							X									5
Bilateral, pheochromocytoma benign																										4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										3
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X		X									X						X			X		X	X	X	14
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X	X							X											X						6
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																					X			X		3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma		X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	39
Interstitial cell, adenoma	X											X	X													7

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Tricresyl Phosphate: 150 ppm (continued)

Number of Days on Study	2 6 9	4 5 4	4 8 8	4 9 1	5 2 9	5 5 3	6 1 4	6 1 8	6 2 4	6 3 8	6 8 2	7 0 1	7 1 1	7 2 2	7 2 2	7 2 2	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	6 1 8	5 9 7	5 9 5	6 1 7	6 0 2	5 8 2	6 0 8	6 3 0	5 8 4	6 0 6	6 1 9	5 8 1	6 2 1	6 0 2	6 0 7	6 0 9	5 8 3	5 8 5	5 8 6	5 8 7	5 8 8	5 8 9	5 9 0	5 9 1	5 9 2	5 9 3
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node							+	+		+					+										
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, sarcoma									X																
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle									+																
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma benign				X																					
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear	+																								
Eye																									
Zymbal's gland			+																						
Carcinoma			X																						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X	X	X		X			X	X	X										X
Mesothelioma malignant																							X		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Tricresyl Phosphate: 150 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	5 9 4	5 9 6	5 9 8	5 9 9	6 0 0	6 0 1	6 0 3	6 0 4	6 0 5	6 1 0	6 1 1	6 1 2	6 1 3	6 1 4	6 1 5	6 1 6	6 2 0	6 2 1	6 2 3	6 2 4	6 2 5	6 2 6	6 2 7	6 2 8	6 2 9	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node													+													5
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	45
Fibroadenoma						X		X																		2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Oligodendroglioma benign																										1
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Ear																										1
Eye																						+				1
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X							X			X			X			X			X		X		16
Mesothelioma malignant																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Tricresyl Phosphate: 300 ppm

Number of Days on Study	4 9 8	5 4 2	5 7 8	5 8 9	6 0 5	6 1 4	6 1 4	6 1 8	6 2 8	6 3 1	6 3 8	6 4 0	6 5 6	6 6 2	6 7 0	6 7 0	6 9 1	6 9 7	7 0 2	7 0 5	7 1 1	7 1 2	7 2 9	7 2 9	7 2 9
Carcass ID Number	6 6 3	6 4 0	6 5 4	6 3 1	6 6 5	6 4 5	6 7 8	6 4 6	6 6 6	6 5 2	6 4 8	6 8 0	6 6 7	6 5 7	6 5 6	6 6 4	6 5 9	6 3 5	6 7 9	6 3 7	6 6 9	6 7 5	6 3 2	6 3 3	6 3 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor benign																									
Intestine small, ileum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery							+							+											
Liposarcoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign													X											X	
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X	
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X																						X		
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma				X																					
C-cell, adenoma								X						X											
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X	X		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma		X	X	X	X	X		X	X	X	X	X	X	X	X		X	X	X		X	X		X	X
Interstitial cell, adenoma							X									X				X			X		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Tricresyl Phosphate: 300 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	6 3 6	6 3 8	6 3 9	6 4 1	6 4 2	6 4 3	6 4 4	6 4 7	6 4 9	6 5 0	6 5 1	6 5 3	6 5 5	6 5 8	6 6 0	6 6 1	6 6 2	6 6 8	6 7 0	6 7 1	6 7 2	6 7 3	6 7 4	6 7 6	6 7 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mast cell tumor benign																			X							1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																								X		1
Mesentery								+										+				+		+		6
Liposarcoma								X																		1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																		+				+				2
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma		X													X										X	3
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign				X												X										4
Bilateral, pheochromocytoma benign	X																									1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma								X																		3
Pars distalis, adenoma, multiple																						X				1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, C-cell, adenoma				X																						2
C-cell, adenoma											X					X	X	X								6
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	41
Interstitial cell, adenoma				X			X														X	X				8

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Tricresyl Phosphate: 300 ppm (continued)

Number of Days on Study	4 9 8	5 4 2	5 7 8	5 8 9	6 0 5	6 1 4	6 1 4	6 1 8	6 2 8	6 3 1	6 3 8	6 4 0	6 5 6	6 6 2	6 7 0	6 7 0	6 9 1	6 9 7	7 0 2	7 0 5	7 1 1	7 1 2	7 2 9	7 2 9	7 2 9
Carcass ID Number	6 6 3	6 4 0	6 5 4	6 3 1	6 6 5	6 4 5	6 7 8	6 4 6	6 6 6	6 5 2	6 4 8	6 8 0	6 6 7	6 5 7	6 5 6	6 6 4	6 5 9	6 3 5	6 7 9	6 3 7	6 6 9	6 7 5	6 3 2	6 3 3	6 3 4
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+						+	+	+		+												
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma		X																							
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	M	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Fibroadenoma						X													X						
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																				X					
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma		X																							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear							+																		
Pinna, fibrosarcoma							X																		
Eye					+																				
Zymbal's gland															+										
Carcinoma															X										
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X	X			X	X	X	X	X	X	X	X		X	X			X	X			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Tricresyl Phosphate: 300 ppm (continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	63 6	63 8	63 9	64 1	64 2	64 3	64 4	64 7	64 9	65 0	65 1	65 3	65 5	65 8	66 0	66 1	66 2	66 8	67 0	67 1	67 2	67 3	67 4	67 6	67 7	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										5
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Fibroadenoma																										2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, lipoma															X											1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Pinna, fibrosarcoma																										1
Eye																										1
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear									X		X					X		X					X			20

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Tricresyl Phosphate

	0 ppm	75 ppm	150 ppm	300 ppm
Adrenal Cortex: Adenoma				
Overall rate[a]	1/51 (2%)	2/50 (4%)	2/50 (4%)	3/50 (6%)
Adjusted rate[b]	3.1%	6.0%	5.3%	10.7%
Terminal rate[c]	1/32 (3%)	1/30 (3%)	1/35 (3%)	3/28 (11%)
First incidence (days)	729 (T)	690	701	729 (T)
Life table test[d]	P=0.197	P=0.479	P=0.527	P=0.257
Logistic regression test[d]	P=0.208	P=0.480	P=0.503	P=0.257
Cochran-Armitage test[d]	P=0.227			
Fisher exact test[d]		P=0.492	P=0.492	P=0.301
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate	5/51 (10%)	7/50 (14%)	9/50 (18%)	5/50 (10%)
Adjusted rate	15.6%	20.6%	24.3%	16.5%
Terminal rate	5/32 (16%)	5/30 (17%)	7/35 (20%)	4/28 (14%)
First incidence (days)	729 (T)	586	722	656
Life table test	P=0.510	P=0.339	P=0.246	P=0.549
Logistic regression test	P=0.547	P=0.347	P=0.229	P=0.564
Cochran-Armitage test	P=0.541N			
Fisher exact test		P=0.366	P=0.183	P=0.617
Mammary Gland: Fibroadenoma				
Overall rate	0/51 (0%)	3/50 (6%)	2/50 (4%)	2/50 (4%)
Adjusted rate	0.0%	7.5%	5.7%	5.4%
Terminal rate	0/32 (0%)	1/30 (3%)	2/35 (6%)	0/28 (0%)
First incidence (days)	–[e]	498	729 (T)	614
Life table test	P=0.312	P=0.119	P=0.258	P=0.232
Logistic regression test	P=0.301	P=0.106	P=0.258	P=0.220
Cochran-Armitage test	P=0.319			
Fisher exact test		P=0.118	P=0.243	P=0.243
Pancreatic Islets: Adenoma				
Overall rate	2/51 (4%)	0/50 (0%)	3/49 (6%)	1/50 (2%)
Adjusted rate	6.0%	0.0%	8.3%	3.6%
Terminal rate	1/32 (3%)	0/30 (0%)	2/35 (6%)	1/28 (4%)
First incidence (days)	722	–	722	729 (T)
Life table test	P=0.600N	P=0.257N	P=0.539	P=0.553N
Logistic regression test	P=0.595N	P=0.255N	P=0.521	P=0.550N
Cochran-Armitage test	P=0.562N			
Fisher exact test		P=0.252N	P=0.481	P=0.508N
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	2/51 (4%)	1/50 (2%)	3/49 (6%)	1/50 (2%)
Adjusted rate	6.0%	3.3%	8.3%	3.6%
Terminal rate	1/32 (3%)	1/30 (3%)	2/35 (6%)	1/28 (4%)
First incidence (days)	722	729 (T)	722	729 (T)
Life table test	P=0.519N	P=0.526N	P=0.539	P=0.553N
Logistic regression test	P=0.516N	P=0.529N	P=0.521	P=0.550N
Cochran-Armitage test	P=0.481N			
Fisher exact test		P=0.508N	P=0.481	P=0.508N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	75 ppm	150 ppm	300 ppm
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	8/51 (16%)	12/50 (24%)	14/50 (28%)	4/50 (8%)
Adjusted rate	22.8%	38.1%	34.9%	12.5%
Terminal rate	6/32 (19%)	11/30 (37%)	10/35 (29%)	3/28 (11%)
First incidence (days)	647	614	454	498
Life table test	P=0.168N	P=0.176	P=0.156	P=0.243N
Logistic regression test	P=0.129N	P=0.178	P=0.106	P=0.187N
Cochran-Armitage test	P=0.132N			
Fisher exact test		P=0.213	P=0.104	P=0.188N
Preputial Gland: Adenoma				
Overall rate	4/50 (8%)	3/49 (6%)	3/49 (6%)	2/50 (4%)
Adjusted rate	11.6%	9.1%	8.6%	6.9%
Terminal rate	3/31 (10%)	2/29 (7%)	3/35 (9%)	1/28 (4%)
First incidence (days)	558	614	729 (T)	712
Life table test	P=0.294N	P=0.529N	P=0.448N	P=0.381N
Logistic regression test	P=0.270N	P=0.512N	P=0.506N	P=0.335N
Cochran-Armitage test	P=0.272N			
Fisher exact test		P=0.511N	P=0.511N	P=0.339N
Preputial Gland: Adenoma or Carcinoma				
Overall rate	4/50 (8%)	4/49 (8%)	3/49 (6%)	2/50 (4%)
Adjusted rate	11.6%	12.4%	8.6%	6.9%
Terminal rate	3/31 (10%)	3/29 (10%)	3/35 (9%)	1/28 (4%)
First incidence (days)	558	614	729 (T)	712
Life table test	P=0.253N	P=0.612	P=0.448N	P=0.381N
Logistic regression test	P=0.231N	P=0.631	P=0.506N	P=0.335N
Cochran-Armitage test	P=0.232N			
Fisher exact test		P=0.631	P=0.511N	P=0.339N
Skin: Keratoacanthoma, Basal Cell Adenoma, or Squamous Cell Carcinoma				
Overall rate	4/51 (8%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
Adjusted rate	11.8%	0.0%	0.0%	0.0%
Terminal rate	3/32 (9%)	0/30 (0%)	0/35 (0%)	0/28 (0%)
First incidence (days)	701	–	–	–
Life table test	P=0.022N	P=0.075N	P=0.055N	P=0.083N
Logistic regression test	P=0.021N	P=0.071N	P=0.060N	P=0.076N
Cochran-Armitage test	P=0.021N			
Fisher exact test		P=0.061N	P=0.061N	P=0.061N
Testes: Adenoma				
Overall rate	48/51 (94%)	45/50 (90%)	46/50 (92%)	49/50 (98%)
Adjusted rate	100.0%	93.7%	100.0%	100.0%
Terminal rate	32/32 (100%)	27/30 (90%)	35/35 (100%)	28/28 (100%)
First incidence (days)	478	455	491	542
Life table test	P=0.177	P=0.561N	P=0.216N	P=0.189
Logistic regression test	P=0.346	P=0.314N	P=0.602N	P=0.781N
Cochran-Armitage test	P=0.185			
Fisher exact test		P=0.346N	P=0.489N	P=0.316

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	75 ppm	150 ppm	300 ppm
Thyroid Gland (C-cell): Adenoma				
Overall rate	12/51 (24%)	9/50 (18%)	6/50 (12%)	8/49 (16%)
Adjusted rate	32.8%	23.0%	17.1%	23.6%
Terminal rate	8/32 (25%)	4/30 (13%)	6/35 (17%)	5/28 (18%)
First incidence (days)	647	586	729 (T)	589
Life table test	P=0.236N	P=0.374N	P=0.073N	P=0.329N
Logistic regression test	P=0.197N	P=0.333N	P=0.090N	P=0.255N
Cochran-Armitage test	P=0.204N			
Fisher exact test		P=0.331N	P=0.105N	P=0.258N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	12/51 (24%)	10/50 (20%)	6/50 (12%)	8/49 (16%)
Adjusted rate	32.8%	26.0%	17.1%	23.6%
Terminal rate	8/32 (25%)	5/30 (17%)	6/35 (17%)	5/28 (18%)
First incidence (days)	647	586	729 (T)	589
Life table test	P=0.213N	P=0.467N	P=0.073N	P=0.329N
Logistic regression test	P=0.175N	P=0.430N	P=0.090N	P=0.255N
Cochran-Armitage test	P=0.182N			
Fisher exact test		P=0.426N	P=0.105N	P=0.258N
All Organs: Mononuclear Cell Leukemia				
Overall rate	20/51 (39%)	18/50 (36%)	16/50 (32%)	20/50 (40%)
Adjusted rate	44.3%	39.7%	37.7%	44.9%
Terminal rate	8/32 (25%)	4/30 (13%)	9/35 (26%)	5/28 (18%)
First incidence (days)	486	455	553	578
Life table test	P=0.427	P=0.514N	P=0.250N	P=0.441
Logistic regression test	P=0.472	P=0.446N	P=0.291N	P=0.528
Cochran-Armitage test	P=0.494			
Fisher exact test		P=0.449N	P=0.292N	P=0.549
All Organs: Benign Neoplasms				
Overall rate	50/51 (98%)	48/50 (96%)	48/50 (96%)	50/50 (100%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	32/32 (100%)	30/30 (100%)	35/35 (100%)	28/28 (100%)
First incidence (days)	87	455	454	498
Life table test	P=0.248	P=0.497	P=0.235N	P=0.247
Logistic regression test	P=0.580	P=0.400N	P=0.401N	P=0.641
Cochran-Armitage test	P=0.301			
Fisher exact test		P=0.492N	P=0.492N	P=0.505
All Organs: Malignant Neoplasms				
Overall rate	28/51 (55%)	23/50 (46%)	19/50 (38%)	24/50 (48%)
Adjusted rate	58.9%	50.3%	42.7%	51.1%
Terminal rate	13/32 (41%)	8/30 (27%)	10/35 (29%)	6/28 (21%)
First incidence (days)	478	455	488	542
Life table test	P=0.406N	P=0.358N	P=0.074N	P=0.461N
Logistic regression test	P=0.311N	P=0.239N	P=0.068N	P=0.311N
Cochran-Armitage test	P=0.294N			
Fisher exact test		P=0.243N	P=0.066N	P=0.310N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	75 ppm	150 ppm	300 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	51/51 (100%)	49/50 (98%)	49/50 (98%)	50/50 (100%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	32/32 (100%)	30/30 (100%)	35/35 (100%)	28/28 (100%)
First incidence (days)	87	455	454	498
Life table test	P=0.315	P=0.497	P=0.243N	P=0.302
Logistic regression test	P=0.420N	P=0.301N	P=0.305N	–[f]
Cochran-Armitage test	P=0.598			
Fisher exact test		P=0.495N	P=0.495N	P=1.000N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, pancreas, pituitary gland, preputial gland, testes, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Tricresyl Phosphate[a]

	0 ppm	75 ppm	150 ppm	300 ppm
Disposition Summary				
Animals initially in study	95	95	95	95
3-Month interim evaluation[b]	15	15	15	15
9-Month interim evaluation[b]	14	15	15	15
15-Month interim evaluation[b]	15	15	15	15
Early deaths				
Moribund	14	16	11	16
Natural deaths	5	4	4	6
Survivors				
Died last week of study	1			
Terminal sacrifice	31	30	35	28
Animals examined microscopically	95	95	95	95
3-Month Interim Evaluation				
Cardiovascular System				
Heart	(10)	(10)	(10)	(10)
Myocardium, degeneration	3 (30%)	3 (30%)	5 (50%)	3 (30%)
Genital System				
Epididymis	(10)	(10)	(10)	(10)
Hypospermia			1 (10%)	
Preputial gland	(10)	(10)	(8)	(10)
Inflammation, chronic		3 (30%)		2 (20%)
Testes	(10)	(10)	(10)	(10)
Hypospermia			1 (10%)	
Seminiferous tubule, atrophy			1 (10%)	
Systems Examined With No Lesions Observed				
Alimentary System				
Endocrine System				
General Body System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] Includes up to five animals per dose group subjected to total body perfusion for special neuropathology

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Tricresyl Phosphate
(continued)

	0 ppm	75 ppm	150 ppm	300 ppm
9-Month Interim Evaluation				
Nervous System				
Spinal cord	(5)	(5)	(5)	(5)
Cyst	2 (40%)			
Systems Examined With No Lesions Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Respiratory System				
Special Senses System				
Urinary System				
15-Month Interim Evaluation				
Nervous System				
Spinal cord	(5)	(5)	(5)	(5)
Cyst		1 (20%)		
Systems Examined With No Lesions Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Respiratory System				
Special Senses System				
Urinary System				
2-Year Study				
Alimentary System				
Intestine large, colon	(50)	(49)	(49)	(49)
Parasite metazoan	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Intestine large, rectum	(51)	(49)	(48)	(49)
Parasite metazoan	6 (12%)	1 (2%)	8 (17%)	8 (16%)
Intestine small, jejunum	(49)	(49)	(48)	(49)
Ulcer		1 (2%)		1 (2%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Tricresyl Phosphate
(continued)

	0 ppm	75 ppm	150 ppm	300 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Intestine small, ileum	(49)	(49)	(48)	(49)
Ulcer			1 (2%)	
Venule, parasite metazoan	1 (2%)			
Liver	(50)	(50)	(49)	(50)
Angiectasis				1 (2%)
Basophilic focus	2 (4%)	7 (14%)	6 (12%)	7 (14%)
Clear cell focus	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Degeneration, cystic	6 (12%)	1 (2%)	7 (14%)	5 (10%)
Eosinophilic focus	7 (14%)	4 (8%)	7 (14%)	6 (12%)
Fatty change	1 (2%)	1 (2%)	1 (2%)	
Hepatodiaphragmatic nodule	5 (10%)	4 (8%)	5 (10%)	5 (10%)
Hyperplasia		2 (4%)	2 (4%)	
Mixed cell focus	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Necrosis	1 (2%)		2 (4%)	2 (4%)
Mesentery	(4)	(8)	(5)	(6)
Inflammation, chronic		1 (13%)		
Artery, inflammation, chronic				1 (17%)
Fat, necrosis	3 (75%)	7 (88%)	4 (80%)	4 (67%)
Pancreas	(51)	(50)	(49)	(50)
Acinus, atrophy	20 (39%)	23 (46%)	22 (45%)	19 (38%)
Acinus, hyperplasia		2 (4%)		
Stomach, forestomach	(51)	(50)	(50)	(50)
Ulcer	2 (4%)		1 (2%)	
Stomach, glandular	(51)	(50)	(50)	(50)
Ulcer	2 (4%)	2 (4%)	3 (6%)	3 (6%)
Tongue			(1)	(2)
Epithelium, hyperplasia			1 (100%)	
Mucosa, epithelium, hyperplasia				2 (100%)
Cardiovascular System				
Heart	(51)	(50)	(50)	(50)
Artery, inflammation, chronic		1 (2%)		
Atrium, dilatation	1 (2%)			1 (2%)
Atrium, thrombosis	2 (4%)	1 (2%)	2 (4%)	
Intima, hyperplasia	1 (2%)			
Myocardium, degeneration	38 (75%)	42 (84%)	40 (80%)	38 (76%)
Endocrine System				
Adrenal cortex	(50)	(49)	(50)	(49)
Hyperplasia	7 (14%)	15 (31%)	8 (16%)	11 (22%)
Adrenal medulla	(50)	(50)	(50)	(50)
Hyperplasia	10 (20%)	4 (8%)	6 (12%)	10 (20%)
Islets, pancreatic	(51)	(50)	(49)	(50)
Hyperplasia	1 (2%)	2 (4%)		3 (6%)
Pituitary gland	(51)	(50)	(50)	(50)
Cyst	1 (2%)	2 (4%)		1 (2%)
Pars distalis, degeneration, focal		1 (2%)		
Pars distalis, hyperplasia	2 (4%)	5 (10%)	8 (16%)	10 (20%)
Pars distalis, inflammation, chronic		1 (2%)		

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Tricresyl Phosphate
(continued)

	0 ppm	75 ppm	150 ppm	300 ppm
2-Year Study (continued)				
Endocrine System (continued)				
Thyroid gland	(51)	(50)	(50)	(49)
C-cell, hyperplasia	25 (49%)	34 (68%)	39 (78%)	33 (67%)
Follicle, dilatation		3 (6%)		
General Body System				
None				
Genital System				
Preputial gland	(50)	(49)	(49)	(50)
Hyperplasia	1 (2%)	1 (2%)		
Inflammation, chronic	9 (18%)	14 (29%)	11 (22%)	5 (10%)
Prostate	(51)	(50)	(50)	(50)
Abscess		1 (2%)		
Inflammation, chronic			1 (2%)	2 (4%)
Seminal vesicle	(51)	(50)	(50)	(50)
Inflammation, chronic		1 (2%)		1 (2%)
Testes	(51)	(50)	(50)	(50)
Interstitial cell, hyperplasia	1 (2%)			
Seminiferous tubule, atrophy		2 (4%)	1 (2%)	2 (4%)
Hematopoietic System				
Lymph node, mandibular	(49)	(50)	(50)	(49)
Hyperplasia, lymphoid				1 (2%)
Lymph node, mesenteric	(51)	(49)	(50)	(50)
Cyst			1 (2%)	
Inflammation, granulomatous		1 (2%)		
Spleen	(50)	(50)	(50)	(50)
Congestion	1 (2%)			
Fibrosis	3 (6%)	2 (4%)	2 (4%)	6 (12%)
Hematopoietic cell proliferation		1 (2%)	2 (4%)	
Hyperplasia, lymphoid		1 (2%)		
Infarct		2 (4%)		
Capsule, inflammation, chronic				1 (2%)
Integumentary System				
Mammary gland	(46)	(48)	(45)	(45)
Hyperplasia, cystic			2 (4%)	
Skin	(51)	(50)	(50)	(50)
Abscess		1 (2%)		
Acanthosis				1 (2%)
Cyst epithelial inclusion			1 (2%)	
Hyperkeratosis				1 (2%)
Inflammation, chronic		1 (2%)		
Ulcer		1 (2%)	1 (2%)	1 (2%)
Dermis, mineralization	1 (2%)			

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Tricresyl Phosphate
(continued)

	0 ppm	75 ppm	150 ppm	300 ppm
2-Year Study (continued)				
Musculoskeletal System				
Bone	(51)	(50)	(50)	(50)
Inflammation, chronic				1 (2%)
Nervous System				
Brain	(51)	(50)	(50)	(50)
Hydrocephalus		1 (2%)		
Infarct		1 (2%)		
Hypothalamus, compression	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Peripheral nerve	(51)	(50)	(50)	(50)
Axon, degeneration		1 (2%)		
Spinal cord	(51)	(50)	(50)	(49)
Cyst				1 (2%)
Nerve, degeneration				1 (2%)
Respiratory System				
Lung	(51)	(50)	(50)	(50)
Erythrophagocytosis			1 (2%)	
Hemorrhage				1 (2%)
Inflammation, chronic	3 (6%)	4 (8%)	1 (2%)	3 (6%)
Nose	(51)	(50)	(50)	(50)
Inflammation, suppurative	2 (4%)	2 (4%)	3 (6%)	2 (4%)
Nares, hemorrhage	1 (2%)			
Special Senses System				
Ear			(1)	(1)
Pinna, ulcer			1 (100%)	
Eye	(7)	(3)	(1)	(1)
Inflammation, chronic	1 (14%)			
Phthisis bulbi			1 (100%)	
Lens, cataract	3 (43%)	3 (100%)		
Lens, cataract, focal				1 (100%)
Urinary System				
Kidney	(51)	(50)	(50)	(50)
Hydronephrosis				1 (2%)
Infarct		1 (2%)		
Nephropathy	47 (92%)	48 (96%)	46 (92%)	45 (90%)
Urinary bladder	(51)	(50)	(50)	(50)
Inflammation, chronic		1 (2%)		
Mucosa, ulcer				1 (2%)

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR FEED STUDY OF TRICRESYL PHOSPHATE

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TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Tricresyl Phosphate[a]

	0 ppm	75 ppm	150 ppm	300 ppm
Disposition Summary				
Animals initially in study	95	95	95	95
3-Month interim evaluation[b]	15	15	15	14
9-Month interim evaluation[b]	15	14	15	15
15-Month interim evaluation[b]	14	13	15	15
Early deaths				
Accidental deaths				1
Moribund	14	12	15	18
Natural deaths	3	3	5	5
Survivors				
Died last week of study		1		
Terminal sacrifice	34	37	30	26
Missing				1
Animals examined microscopically	95	95	95	94
3-Month Interim Evaluation				
Integumentary System				
Mammary gland	(9)	(10)	(9)	(10)
Adenoma		1 (10%)		
Systems Examined With No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				
9-Month Interim Evaluation				
Integumentary System				
Mammary gland	(10)	(10)	(10)	(10)
Adenocarcinoma		1 (10%)		
Nervous System				
Brain	(10)	(10)	(10)	(10)
Astrocytoma malignant	1 (10%)			

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	75 ppm	150 ppm	300 ppm
9-Month Interim Evaluation (continued)				
Systems Examined With No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Musculoskeletal System				
Respiratory System				
Special Senses System				
Urinary System				
15-Month Interim Evaluation				
Endocrine System				
Pituitary gland	(9)	(8)	(10)	(10)
Pars distalis, adenoma		1 (13%)	2 (20%)	1 (10%)
Thyroid gland	(9)	(8)	(10)	(10)
C-cell, adenoma	1 (11%)	1 (13%)	1 (10%)	
Follicle, adenoma			1 (10%)	
Genital System				
Uterus	(9)	(8)	(10)	(10)
Polyp stromal	1 (11%)	1 (13%)		
Integumentary System				
Skin	(9)	(8)	(10)	(10)
Fibrosarcoma			1 (10%)	
Trichoepithelioma				1 (10%)
Systems Examined With No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
General Body System				
Hematopoietic System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	75 ppm	150 ppm	300 ppm
2-Year Study				
Alimentary System				
Liver	(51)	(53)	(50)	(50)
Mesentery	(3)	(7)	(4)	(4)
Histiocytic sarcoma		1 (14%)		
Tooth	(1)	(1)		
Gingiva, squamous cell carcinoma	1 (100%)			
Cardiovascular System				
Heart	(51)	(53)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Rhabdomyoma			1 (2%)	
Endocrine System				
Adrenal cortex	(51)	(53)	(50)	(50)
Adenoma	1 (2%)	1 (2%)		1 (2%)
Adrenal medulla	(51)	(53)	(50)	(50)
Pheochromocytoma malignant				1 (2%)
Pheochromocytoma benign	1 (2%)	2 (4%)	2 (4%)	
Bilateral, pheochromocytoma benign			1 (2%)	
Islets, pancreatic	(51)	(53)	(50)	(50)
Adenoma			1 (2%)	
Carcinoma		1 (2%)		
Pituitary gland	(51)	(53)	(50)	(50)
Pars distalis, adenoma	30 (59%)	25 (47%)	25 (50%)	23 (46%)
Thyroid gland	(51)	(53)	(50)	(50)
Bilateral, C-cell, adenoma	1 (2%)			
C-cell, adenocarcinoma				1 (2%)
C-cell, adenoma	8 (16%)	7 (13%)	2 (4%)	11 (22%)
Follicle, adenoma		1 (2%)	1 (2%)	
General Body System				
None				
Genital System				
Clitoral gland	(51)	(53)	(49)	(49)
Adenoma	1 (2%)	2 (4%)	3 (6%)	3 (6%)
Carcinoma	1 (2%)	1 (2%)		
Bilateral, adenoma		2 (4%)	1 (2%)	
Ovary	(51)	(53)	(50)	(50)
Adenoma	1 (2%)			
Granulosa cell tumor benign	1 (2%)			1 (2%)
Granulosa-theca tumor malignant		1 (2%)		
Granulosa-theca tumor benign			1 (2%)	
Uterus	(51)	(53)	(50)	(50)
Adenocarcinoma	1 (2%)			
Leiomyosarcoma			1 (2%)	
Polyp stromal	6 (12%)	1 (2%)	8 (16%)	9 (18%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	75 ppm	150 ppm	300 ppm
2-Year Study (continued)				
Hematopoietic System				
Lymph node	(2)	(2)	(2)	(2)
Lymph node, mandibular	(51)	(53)	(49)	(50)
Squamous cell carcinoma, metastatic, skin				1 (2%)
Lymph node, mesenteric	(51)	(52)	(50)	(49)
Spleen	(51)	(53)	(50)	(50)
Integumentary System				
Mammary gland	(49)	(53)	(50)	(49)
Adenoma	2 (4%)			1 (2%)
Adenoma, multiple	1 (2%)			
Fibroadenoma	13 (27%)	13 (25%)	18 (36%)	14 (29%)
Fibroadenoma, multiple	2 (4%)	3 (6%)	3 (6%)	1 (2%)
Skin	(51)	(53)	(50)	(50)
Fibrosarcoma			1 (2%)	
Squamous cell carcinoma	1 (2%)			1 (2%)
Subcutaneous tissue, fibroma				1 (2%)
Subcutaneous tissue, fibrous histiocytoma			1 (2%)	
Musculoskeletal System				
Bone	(51)	(53)	(50)	(50)
Osteosarcoma				1 (2%)
Skeletal muscle		(1)		
Hemangioma		1 (100%)		
Nervous System				
Brain	(51)	(53)	(50)	(50)
Spinal cord	(51)	(52)	(50)	(50)
Hemangiosarcoma		1 (2%)		
Respiratory System				
Lung	(51)	(53)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)			1 (2%)
Alveolar/bronchiolar carcinoma			1 (2%)	1 (2%)
Histiocytic sarcoma		1 (2%)		
Pheochromocytoma malignant, metastatic, adrenal medulla				1 (2%)
Nose	(51)	(53)	(50)	(50)
Chondrosarcoma	1 (2%)			
Special Senses System				
Ear				(1)
Pinna, fibrosarcoma				1 (100%)
Zymbal's gland		(2)		
Carcinoma		2 (100%)		

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	75 ppm	150 ppm	300 ppm
2-Year Study (continued)				
Urinary System				
Kidney	(51)	(53)	(50)	(50)
Urinary bladder	(51)	(53)	(50)	(50)
Systemic Lesions				
Multiple organs[c]	(51)	(53)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Leukemia mononuclear	8 (16%)	8 (15%)	13 (26%)	15 (30%)
Neoplasm Summary				
Total animals with primary neoplasms[d]				
3-Month interim evaluation		1		
9-Month interim evaluation	1	1		
15-Month interim evaluation	2	3	5	2
2-Year study	47	39	43	46
Total primary neoplasms				
3-Month interim evaluation		1		
9-Month interim evaluation	1	1		
15-Month interim evaluation	2	3	5	2
2-Year study	82	74	84	87
Total animals with benign neoplasms				
3-Month interim evaluation		1		
15-Month interim evaluation	2	3	4	2
2-Year study	45	32	38	42
Total benign neoplasms				
3-Month interim evaluation		1		
15-Month interim evaluation	2	3	4	2
2-Year study	69	59	67	66
Total animals with malignant neoplasms				
9-Month interim evaluation	1	1		
15-Month interim evaluation			1	
2-Year study	13	15	17	20
Total malignant neoplasms				
9-Month interim evaluation	1	1		
15-Month interim evaluation			1	
2-Year study	13	15	17	21
Total animals with metastatic neoplasms				
2-Year study				2
Total metastatic neoplasms				
2-Year study				2

[a] Number of animals examined microscopically at site and number of animals with neoplasm
[b] Includes up to five animals per dose group subjected to total body perfusion for special neuropathology
[c] Number of animals with any tissue examined microscopically
[d] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Tricresyl Phosphate: 0 ppm

Number of Days on Study	1 3 4	4 1 2	4 8 8	5 0 2	5 3 7	5 5 3	5 5 7	5 6 4	5 7 8	5 9 2	6 1 9	6 3 8	6 5 2	6 6 7	6 7 5	7 1 2	7 2 2	7 3 1	7 3 2	7 3 3	7 3 4	7 3 5	7 3 6	7 3 7	7 3 2
Carcass ID Number	7 7 2	2 4 0	7 5 2	7 7 7	7 3 2	7 3 9	7 7 5	7 6 4	7 6 3	7 6 0	7 4 2	7 7 1	7 7 0	7 3 8	7 5 5	7 5 1	7 3 3	7 3 1	7 3 4	7 3 5	7 3 6	7 3 7	7 4 0	7 4 1	7 4 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery			+																						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Gingiva, squamous cell carcinoma																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X		X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma				X	X						X			X					X						
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X			
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Granulosa cell tumor benign																			X						
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma		X																							
Polyp stromal														X											X

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Tricresyl Phosphate: 0 ppm
(continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	7 4 4	7 4 5	7 4 6	7 4 7	7 4 8	7 4 9	7 5 0	7 5 3	7 5 4	7 5 6	7 5 7	7 5 8	7 5 9	7 6 1	7 6 2	7 6 5	7 6 6	7 6 7	7 6 8	7 6 9	7 7 3	7 7 4	7 7 6	7 7 8	7 7 9	7 8 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Mesentery					+																	+				3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Tooth																								+		1
Gingiva, squamous cell carcinoma																								X		1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma																							X			1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pheochromocytoma benign				X																						1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pars distalis, adenoma			X		X			X	X	X	X		X	X	X			X			X	X		X		30
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Bilateral, C-cell, adenoma						X																				1
C-cell, adenoma			X				X										X									8
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma																										1
Carcinoma		X																								1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma																									X	1
Granulosa cell tumor benign																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenocarcinoma																										1
Polyp stromal	X																X		X						X	6

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Tricresyl Phosphate: 0 ppm
(continued)

Number of Days on Study	1 3 4	4 1 2	4 8 8	5 0 2	5 3 7	5 5 3	5 5 7	5 6 4	5 7 8	5 9 2	6 1 9	6 3 8	6 5 2	6 6 7	6 7 5	7 1 2	7 2 2	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2
Carcass ID Number	7 7 2	7 4 0	7 5 2	7 7 7	7 3 2	7 3 9	7 7 5	7 6 4	7 6 3	7 6 0	7 4 2	7 7 1	7 7 0	7 3 8	7 5 5	7 5 1	7 3 3	7 3 1	7 3 4	7 3 5	7 3 6	7 4 7	7 4 0	7 4 1	7 4 3
Hematopoietic System																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node															+										
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adenoma, multiple																									
Fibroadenoma							X	X				X	X			X	X			X					X
Fibroadenoma, multiple										X															
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chondrosarcoma				X																					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																						+			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear															X			X		X					

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Tricresyl Phosphate: 0 ppm
(continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	7 4 4	7 4 5	7 4 6	7 4 7	7 4 8	7 4 9	7 5 0	7 5 3	7 5 4	7 5 6	7 5 7	7 5 8	7 5 9	7 6 1	7 6 2	7 6 5	7 6 6	7 6 7	7 6 8	7 6 9	7 7 3	7 7 4	7 7 6	7 7 8	7 7 9	7 8 0	Total Tissues/ Tumors
Hematopoietic System																											
Blood													+														1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node				+																							2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	48
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	49
Adenoma												X													X		2
Adenoma, multiple			X																								1
Fibroadenoma		X							X				X								X					X	13
Fibroadenoma, multiple					X																						2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Squamous cell carcinoma																							X				1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma											X																1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Chondrosarcoma																											1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Special Senses System																											
Eye																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Leukemia mononuclear	X			X										X								X		X			8

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Tricresyl Phosphate: 75 ppm

Number of Days on Study	2 0 4	2 2 2	2 8 5	3 9 7	4 6 4	5 5 8	6 2 0	6 2 4	6 5 3	6 8 7	7 0 1	7 0 5	7 0 5	7 0 7	7 1 2	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	2 8 8	3 0 9	2 9 7	8 0 7	8 0 5	8 2 5	8 1 3	8 0 8	8 0 6	7 8 6	8 2 6	8 1 6	8 2 3	8 9 5	8 2 9	7 9 2	7 8 1	7 8 2	7 8 3	7 8 4	7 8 5	7 8 7	7 8 8	8 8 9	9 9 0
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery				+							+		+			+									
Histiocytic sarcoma											X														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Tooth				+																					
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma											X														
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X								
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign							X																		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma															X										
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X	X			X		X	X	X	X		X				X	X	X	X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																					X		X		
Follicle, adenoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Bilateral, adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor malignant																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																					X				

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Tricresyl Phosphate: 75 ppm
(continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	7 9 1	7 9 3	7 9 4	7 9 6	7 9 7	7 9 8	7 9 9	8 0 0	8 0 1	8 0 2	8 0 3	8 0 4	8 0 9	8 1 0	8 1 1	8 1 2	8 1 4	8 1 5	8 1 7	8 1 8	8 1 9	8 2 0	8 2 1	8 2 2	8 2 4	8 2 7	8 2 8	8 3 0	Total Tissues/ Tumors
Alimentary System																													
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	52
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Mesentery	+							+	+																				7
Histiocytic sarcoma																													1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Tongue																						+							1
Tooth																													1
Cardiovascular System																													
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Histiocytic sarcoma																													1
Endocrine System																													
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma																													1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pheochromocytoma benign																									X				2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Carcinoma																													1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	M	M	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pars distalis, adenoma		X		X	X		X					X				X						X	X	X	X	X	X		25
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
C-cell, adenoma						X	X			X							X							X				7
Follicle, adenoma																								X					1
General Body System																													
None																													
Genital System																													
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma		X										X																	2
Carcinoma				X																									1
Bilateral, adenoma																X	X												2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Granulosa-theca tumor malignant	X																												1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Polyp stromal																													1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Tricresyl Phosphate: 75 ppm
(continued)

Number of Days on Study	2	2	2	3	4	5	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	2	8	9	6	5	2	2	5	8	0	0	0	0	1	2	3	3	3	3	3	3	3	3
	4	2	5	7	4	8	0	4	3	7	1	5	5	7	2	9	0	0	0	0	1	1	1	1
Carcass ID Number	2	3	2	8	8	8	8	8	8	7	8	8	8	7	8	7	7	7	7	7	7	7	7	7
	8	0	9	0	0	2	1	0	0	8	2	1	2	9	2	9	8	8	8	8	8	8	8	9
	9	9	7	7	5	5	3	8	6	6	6	6	3	5	9	2	1	2	3	4	5	7	8	9	0
Hematopoietic System																								
Blood													+											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node														+										
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma									X			X			X				X		X		X	X
Fibroadenoma, multiple													X											
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																					+			
Hemangioma																					X			
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma		X																						
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma											X													
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye				+																	+		+	
Harderian gland																								
Zymbal's gland				+						+														
Carcinoma				X						X														
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma											X													
Leukemia mononuclear					X				X					X		X						X		

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Tricresyl Phosphate: 75 ppm
(continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	7 9 1	7 9 3	7 9 4	7 9 6	7 9 7	7 9 8	7 9 9	8 0 0	8 0 1	8 0 2	8 0 3	8 0 4	8 0 9	8 1 0	8 1 1	8 1 2	8 1 4	8 1 5	8 1 7	8 1 8	8 1 9	8 2 0	8 2 1	8 2 2	8 2 4	8 2 7	8 2 8	8 3 0	Total Tissues/ Tumors
Hematopoietic System																													
Blood																													1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node													+																2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Thymus	+	+	+	+	+	M	+	+	M	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	M	+	+	47
Integumentary System																													
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Fibroadenoma		X		X	X	X		X					X																13
Fibroadenoma, multiple										X		X																	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Musculoskeletal System																													
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Skeletal muscle																													1
Hemangioma																													1
Nervous System																													
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Hemangiosarcoma																													1
Respiratory System																													
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Histiocytic sarcoma																													1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Special Senses System																													
Eye													+				+												5
Harderian gland					+																								1
Zymbal's gland																													2
Carcinoma																													2
Urinary System																													
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Systemic Lesions																													
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Histiocytic sarcoma																													1
Leukemia mononuclear									X				X														X		8

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Tricresyl Phosphate: 150 ppm

Number of Days on Study	3 7 2	5 9 2	6 1 1	6 1 9	6 2 4	6 3 7	6 4 2	6 5 3	6 6 6	6 7 0	6 7 0	6 9 7	7 0 4	7 0 5	7 0 5	7 0 5	7 0 5	7 1 2	7 2 2	7 2 4	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	8 7 1	8 7 4	8 4 7	8 4 6	8 7 0	8 5 4	8 3 8	8 5 7	8 4 4	8 3 4	8 4 0	8 7 3	8 7 9	8 4 5	8 5 0	8 5 1	8 6 7	8 3 9	8 6 2	8 6 3	8 3 1	8 3 2	8 3 3	8 3 5	8 3 6
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery								+					+											
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rhabdomyoma																								
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																								
Bilateral, pheochromocytoma benign																								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																				X				
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X						X	X	X	X		X	X				X	X	X	X		X	X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma													X											
Follicle, adenoma																								
General Body System																								
None																								
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma														X										
Bilateral, adenoma																								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor benign																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																								
Polyp stromal				X										X							X			

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Tricresyl Phosphate: 150 ppm
(continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	8 3 7	8 4 1	8 4 2	8 4 3	8 4 8	8 4 9	8 5 2	8 5 3	8 5 5	8 5 6	8 5 8	8 5 9	8 6 0	8 6 1	8 6 4	8 6 5	8 6 6	8 6 8	8 6 9	8 7 2	8 7 5	8 7 6	8 7 7	8 7 8	8 8 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery															+						+					4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Rhabdomyoma																								X		1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign					X						X															2
Bilateral, pheochromocytoma benign				X																						1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X				X		X	X		X	X		X	X							X	X	X	X		25
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma									X																	2
Follicle, adenoma								X																		1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Adenoma							X																	X		3
Bilateral, adenoma				X																						1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa-theca tumor benign			X																							1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																			X							1
Polyp stromal		X		X	X												X		X							8

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Tricresyl Phosphate: 150 ppm
(continued)

Number of Days on Study	3 7 2	5 9 2	6 1 1	6 1 9	6 2 4	6 3 7	6 4 2	6 5 3	6 6 6	6 7 0	6 7 0	6 9 7	7 0 4	7 0 5	7 0 5	7 0 5	7 0 5	7 1 2	7 2 2	7 2 4	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	8 7 1	8 7 4	8 4 7	8 4 6	8 7 0	8 5 4	8 3 8	8 5 7	8 4 4	8 3 4	8 4 0	8 7 3	8 7 9	8 4 5	8 5 0	8 5 1	8 6 7	8 3 9	8 6 2	8 6 3	8 3 1	8 3 2	8 3 3	8 3 5	8 3 6
Hematopoietic System																								
Blood			+																					
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node									+										+					
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma		X						X						X	X	X	X	X		X	X			
Fibroadenoma, multiple												X							X					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma	X																							
Subcutaneous tissue, fibrous histiocytoma																		X						
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma							X																	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
None																								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X		X	X	X			X	X	X	X	X						X					

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Tricresyl Phosphate: 150 ppm
(continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	8 3 7	8 4 1	8 4 2	8 4 3	8 4 8	8 4 9	8 5 2	8 5 3	8 5 5	8 5 6	8 5 8	8 5 9	8 6 0	8 6 1	8 6 4	8 6 5	8 6 6	8 6 8	8 6 9	8 7 2	8 7 5	8 7 6	8 7 7	8 7 8	8 8 0	Total Tissues/ Tumors
Hematopoietic System																									
Blood																									1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																									2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	47
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma	X	X		X						X	X		X				X			X		X			18
Fibroadenoma, multiple								X																	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																									1
Subcutaneous tissue, fibrous histiocytoma																									1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X										X		X										13

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Tricresyl Phosphate: 300 ppm

Number of Days on Study	0 2 4	0 2 9	3 5 3	5 4 6	5 5 0	5 5 8	5 6 4	5 9 2	6 2 0	6 2 5	6 5 3	6 5 9	6 6 7	6 7 0	6 8 7	6 8 7	6 9 1	6 9 8	6 9 9	7 0 3	7 0 4	7 1 2	7 2 2	7 2 2
Carcass ID Number	9 0 7	9 0 2	9 2 5	9 1 9	9 1 2	8 8 7	8 9 5	9 0 9	8 8 6	8 0 3	8 8 3	9 1 4	8 8 1	8 8 2	8 8 9	8 9 4	9 1 3	9 1 6	8 8 8	8 9 0	8 8 4	9 1 7	9 2 9	9 3 0
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	M	M	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	A	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery					+				+		+						+							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant										X														
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X			X	X		X	X		X		X	X	X		X	X	X				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenocarcinoma																								
C-cell, adenoma														X			X			X		X		X
General Body System																								
None																								
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Adenoma																								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal					X								X											
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, skin																							X	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Tricresyl Phosphate: 300 ppm
(continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	8 8 5	8 9 1	8 9 2	8 9 3	8 9 6	8 9 7	8 9 8	8 9 9	9 0 0	9 0 1	9 0 4	9 0 5	9 0 6	9 0 8	9 1 0	9 1 1	9 1 5	9 1 8	9 2 0	9 2 1	9 2 2	9 2 3	9 2 4	9 2 6	9 2 7	9 2 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery																										4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																		X								1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X		X		X				X			X		X			X			X	X			23
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenocarcinoma																	X									1
C-cell, adenoma	X							X					X			X							X	X		11
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma				X						X										X						3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign						X																				1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal		X		X		X		X			X				X				X							9
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node					+																		+			2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, skin																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Tricresyl Phosphate: 300 ppm
(continued)

Number of Days on Study	0 2 4	0 2 9	3 5 3	5 4 6	5 5 0	5 5 8	5 6 4	5 9 2	6 2 0	6 2 5	6 5 3	6 5 9	6 6 7	6 7 0	6 8 7	6 8 7	6 9 1	6 9 8	6 9 9	7 0 3	7 0 4	7 1 2	7 2 2	7 2 2
Carcass ID Number	9 0 7	9 0 2	9 2 5	9 1 9	9 1 2	8 8 7	8 9 5	9 0 9	8 8 6	9 0 3	8 8 3	9 1 4	8 8 1	8 8 2	8 8 9	8 9 4	9 1 3	9 1 6	8 8 8	8 9 0	8 8 4	9 1 7	9 2 9	9 3 0
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Fibroadenoma							X	X			X			X	X	X								X
Fibroadenoma, multiple																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																							X	
Subcutaneous tissue, fibroma																	X							
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma															X									
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								
Alveolar/bronchiolar carcinoma																								
Pheochromocytoma malignant, metastatic, adrenal medulla										X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Ear																								
Pinna, fibrosarcoma																								
Eye																						+		
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X	X						X	X	X	X					X	X	X			X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Tricresyl Phosphate: 300 ppm
(continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	8 8 5	8 9 1	8 9 2	8 9 3	8 9 6	8 9 7	8 9 8	8 9 9	9 0 0	9 0 1	9 0 4	9 0 5	9 0 6	9 0 8	9 1 0	9 1 1	9 1 5	9 1 8	9 2 0	9 2 1	9 2 2	9 2 3	9 2 4	9 2 6	9 2 7	9 2 8	Total Tissues/ Tumors
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	X	+	+	+	+	49
Adenoma																						X					1
Fibroadenoma				X			X		X					X			X		X		X						14
Fibroadenoma, multiple	X																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																											1
Subcutaneous tissue, fibroma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma														X													1
Alveolar/bronchiolar carcinoma																X											1
Pheochromocytoma malignant, metastatic, adrenal medulla																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Ear																										+	1
Pinna, fibrosarcoma																										X	1
Eye										+																	2
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X														X			X	X			X	15

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Tricresyl Phosphate

	0 ppm	75 ppm	150 ppm	300 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	1/51 (2%)	2/53 (4%)	3/50 (6%)	0/50 (0%)
Adjusted rate[b]	2.9%	4.7%	10.0%	0.0%
Terminal rate[c]	1/34 (3%)	1/38 (3%)	3/30 (10%)	0/26 (0%)
First incidence (days)	729 (T)	620	729 (T)	–[e]
Life table test[d]	P=0.425N	P=0.544	P=0.261	P=0.554N
Logistic regression test[d]	P=0.355N	P=0.517	P=0.261	P=0.554N
Cochran-Armitage test[d]	P=0.349N			
Fisher exact test[d]		P=0.515	P=0.301	P=0.505N
Clitoral Gland: Adenoma				
Overall rate	1/51 (2%)	4/53 (8%)	4/49 (8%)	3/49 (6%)
Adjusted rate	2.9%	10.5%	12.8%	11.5%
Terminal rate	1/34 (3%)	4/38 (11%)	3/29 (10%)	3/26 (12%)
First incidence (days)	729 (T)	729 (T)	705	729 (T)
Life table test	P=0.195	P=0.214	P=0.146	P=0.214
Logistic regression test	P=0.234	P=0.214	P=0.175	P=0.214
Cochran-Armitage test	P=0.315			
Fisher exact test		P=0.194	P=0.169	P=0.294
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	2/51 (4%)	5/53 (9%)	4/49 (8%)	3/49 (6%)
Adjusted rate	5.9%	13.2%	12.8%	11.5%
Terminal rate	2/34 (6%)	5/38 (13%)	3/29 (10%)	3/26 (12%)
First incidence (days)	729 (T)	729 (T)	705	729 (T)
Life table test	P=0.352	P=0.262	P=0.280	P=0.378
Logistic regression test	P=0.404	P=0.262	P=0.328	P=0.378
Cochran-Armitage test	P=0.504			
Fisher exact test		P=0.235	P=0.320	P=0.481
Mammary Gland: Adenoma				
Overall rate	3/51 (6%)	0/53 (0%)	0/50 (0%)	1/50 (2%)
Adjusted rate	8.8%	0.0%	0.0%	3.8%
Terminal rate	3/34 (9%)	0/38 (0%)	0/30 (0%)	1/26 (4%)
First incidence (days)	729 (T)	–	–	729 (T)
Life table test	P=0.319N	P=0.102N	P=0.143N	P=0.405N
Logistic regression test	P=0.319N	P=0.102N	P=0.143N	P=0.405N
Cochran-Armitage test	P=0.255N			
Fisher exact test		P=0.114N	P=0.125N	P=0.316N
Mammary Gland: Fibroadenoma				
Overall rate	15/51 (29%)	16/53 (30%)	21/50 (42%)	15/50 (30%)
Adjusted rate	36.0%	37.9%	52.1%	42.9%
Terminal rate	8/34 (24%)	12/38 (32%)	11/30 (37%)	8/26 (31%)
First incidence (days)	557	653	592	564
Life table test	P=0.210	P=0.522N	P=0.141	P=0.391
Logistic regression test	P=0.436	P=0.577	P=0.167	P=0.547
Cochran-Armitage test	P=0.457			
Fisher exact test		P=0.551	P=0.133	P=0.561

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	75 ppm	150 ppm	300 ppm
Mammary Gland: Adenoma or Fibroadenoma				
Overall rate	18/51 (35%)	16/53 (30%)	21/50 (42%)	16/50 (32%)
Adjusted rate	43.4%	37.9%	52.1%	46.1%
Terminal rate	11/34 (32%)	12/38 (32%)	11/30 (37%)	9/26 (35%)
First incidence (days)	557	653	592	564
Life table test	P=0.281	P=0.288N	P=0.290	P=0.505
Logistic regression test	P=0.528N	P=0.332N	P=0.384	P=0.462N
Cochran-Armitage test	P=0.506N			
Fisher exact test		P=0.365N	P=0.313	P=0.445N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	30/51 (59%)	25/53 (47%)	25/50 (50%)	23/50 (46%)
Adjusted rate	66.7%	55.4%	61.7%	58.2%
Terminal rate	19/34 (56%)	18/38 (47%)	15/30 (50%)	11/26 (42%)
First incidence (days)	553	558	592	353
Life table test	P=0.524N	P=0.118N	P=0.344N	P=0.394N
Logistic regression test	P=0.175N	P=0.135N	P=0.166N	P=0.148N
Cochran-Armitage test	P=0.165N			
Fisher exact test		P=0.160N	P=0.245N	P=0.138N
Thyroid Gland (C-cell): Adenoma				
Overall rate	9/51 (18%)	7/53 (13%)	2/50 (4%)	11/50 (22%)
Adjusted rate	22.4%	18.4%	5.9%	34.5%
Terminal rate	5/34 (15%)	7/38 (18%)	1/30 (3%)	6/26 (23%)
First incidence (days)	502	729 (T)	704	670
Life table test	P=0.163	P=0.314N	P=0.037N	P=0.255
Logistic regression test	P=0.288	P=0.354N	P=0.033N	P=0.370
Cochran-Armitage test	P=0.302			
Fisher exact test		P=0.361N	P=0.028N	P=0.383
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	9/51 (18%)	7/53 (13%)	2/50 (4%)	12/50 (24%)
Adjusted rate	22.4%	18.4%	5.9%	37.8%
Terminal rate	5/34 (15%)	7/38 (18%)	1/30 (3%)	7/26 (27%)
First incidence (days)	502	729 (T)	704	670
Life table test	P=0.098	P=0.314N	P=0.037N	P=0.181
Logistic regression test	P=0.194	P=0.354N	P=0.033N	P=0.282
Cochran-Armitage test	P=0.207			
Fisher exact test		P=0.361N	P=0.028N	P=0.294
Uterus: Stromal Polyp				
Overall rate	6/51 (12%)	1/53 (2%)	8/50 (16%)	9/50 (18%)
Adjusted rate	17.0%	2.6%	23.8%	30.4%
Terminal rate	5/34 (15%)	1/38 (3%)	6/30 (20%)	7/26 (27%)
First incidence (days)	667	729 (T)	619	550
Life table test	P=0.020	P=0.043N	P=0.327	P=0.155
Logistic regression test	P=0.052	P=0.041N	P=0.429	P=0.259
Cochran-Armitage test	P=0.061			
Fisher exact test		P=0.050N	P=0.372	P=0.274

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	75 ppm	150 ppm	300 ppm
All Organs: Mononuclear Cell Leukemia				
Overall rate	8/51 (16%)	8/53 (15%)	13/50 (26%)	15/50 (30%)
Adjusted rate	22.7%	18.9%	29.6%	39.2%
Terminal rate	7/34 (21%)	5/38 (13%)	3/30 (10%)	5/26 (19%)
First incidence (days)	675	464	592	546
Life table test	P=0.012	P=0.512N	P=0.174	P=0.041
Logistic regression test	P=0.024	P=0.557N	P=0.162	P=0.064
Cochran-Armitage test	P=0.026			
Fisher exact test		P=0.574N	P=0.151	P=0.069
All Organs: Benign Neoplasms				
Overall rate	46/51 (90%)	34/53 (64%)	38/50 (76%)	42/50 (84%)
Adjusted rate	93.9%	70.6%	84.4%	93.1%
Terminal rate	31/34 (91%)	24/38 (63%)	23/30 (77%)	23/26 (88%)
First incidence (days)	412	204	592	353
Life table test	P=0.086	P=0.007N	P=0.238N	P=0.328
Logistic regression test	P=0.456	P=0.002N	P=0.016N	P=0.316N
Cochran-Armitage test	P=0.494			
Fisher exact test		P=0.001N	P=0.050N	P=0.264N
All Organs: Malignant Neoplasms				
Overall rate	13/51 (25%)	15/53 (28%)	17/50 (34%)	20/50 (40%)
Adjusted rate	34.1%	31.9%	37.0%	49.7%
Terminal rate	10/34 (29%)	7/38 (18%)	4/30 (13%)	7/26 (27%)
First incidence (days)	412	222	372	546
Life table test	P=0.028	P=0.533	P=0.258	P=0.050
Logistic regression test	P=0.060	P=0.456	P=0.181	P=0.084
Cochran-Armitage test	P=0.057			
Fisher exact test		P=0.460	P=0.237	P=0.090
All Organs: Benign or Malignant Neoplasms				
Overall rate	47/51 (92%)	40/53 (75%)	43/50 (86%)	46/50 (92%)
Adjusted rate	95.9%	78.4%	87.7%	95.8%
Terminal rate	32/34 (94%)	27/38 (71%)	24/30 (80%)	24/26 (92%)
First incidence (days)	412	204	372	353
Life table test	P=0.042	P=0.044N	P=0.471N	P=0.163
Logistic regression test	P=0.238	P=0.020N	P=0.166N	P=0.550
Cochran-Armitage test	P=0.269			
Fisher exact test		P=0.020N	P=0.251N	P=0.631N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, clitoral gland, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE B4
Historical Incidence of Leukemias in Untreated Female F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at Battelle Columbus	
2,4-Dichlorophenol	11/50
4,4'- Thiobis(6-*t*-Butyl-*m*-Cresol)	18/50
5,5-Diphenylhydantoin	13/50
Ethylene Thiourea	18/50
Polybrominated Biphenyls (Firemaster FF-1®)	14/50
Manganese (II) Sulfate Monohydrate	19/50
Triamterene	8/50
Tricresyl Phosphate	8/51
Overall Historical Incidence	
Total	324/1,251 (25.8%)
Standard deviation	8.6%
Range	14%-52%

[a] Data as of 20 August 1992; includes data for lymphocytic, monocytic, mononuclear cell, and undifferentiated leukemias

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Tricresyl Phosphate[a]

	0 ppm	75 ppm	150 ppm	300 ppm
Disposition Summary				
Animals initially in study	95	95	95	95
3-Month interim evaluation[b]	15	15	15	14
9-Month interim evaluation[b]	15	14	15	15
15-Month interim evaluation[b]	14	13	15	15
Early deaths				
Accidental deaths				1
Moribund	14	12	15	18
Natural deaths	3	3	5	5
Survivors				
Died last week of study		1		
Terminal sacrifice	34	37	30	26
Missing				1
Animals examined microscopically	95	95	95	94
3-Month Interim Evaluation				
Alimentary System				
Intestine large, rectum	(10)	(10)	(10)	(10)
Parasite metazoan	1 (10%)		1 (10%)	
Intestine small, jejunum	(10)	(10)	(10)	(10)
Peyer's patch, mineralization		1 (10%)		
Liver	(10)	(10)	(10)	(10)
Hepatodiaphragmatic nodule		2 (20%)		
Cardiovascular System				
Heart	(10)	(10)	(10)	(10)
Myocardium, degeneration				1 (10%)
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Vacuolization cytoplasmic			1 (10%)	10 (100%)
Genital System				
Clitoral gland	(10)	(10)	(10)	(10)
Inflammation, chronic		1 (10%)	2 (20%)	
Ovary	(10)	(10)	(10)	(10)
Cyst	1 (10%)			1 (10%)
Interstitium, hyperplasia			6 (60%)	10 (100%)
Uterus	(10)	(10)	(10)	(10)
Dilatation	1 (10%)			1 (10%)
Hematopoeitic System				
Lymph node, mandibular	(10)	(10)	(10)	(10)
Hyperplasia, lymphoid			1 (10%)	

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] Includes up to five animals per dose group subjected to total body perfusion for special neuropathology

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Tricresyl Phosphate
(continued)

	0 ppm	75 ppm	150 ppm	300 ppm
3-Month Interim Evaluation (continued)				
Nervous System				
Spinal cord	(15)	(14)	(15)	(14)
Cyst	2 (13%)			
Special Senses System				
Harderian gland	(1)	(2)		
Inflammation, chronic active	1 (100%)	2 (100%)		
Systems Examined With No Lesions Observed				
General Body System				
Integumentary System				
Musculoskeletal System				
Respiratory System				
Urinary System				
9-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)	(10)	(10)	(10)
Parasite metazoan			2 (20%)	1 (10%)
Intestine large, rectum	(10)	(10)	(10)	(10)
Parasite metazoan			1 (10%)	
Liver	(10)	(10)	(10)	(10)
Basophilic focus				1 (10%)
Cyst	1 (10%)			
Hepatodiaphragmatic nodule	1 (10%)	1 (10%)	1 (10%)	1 (10%)
Inflammation, granulomatous	1 (10%)	4 (40%)	1 (10%)	2 (20%)
Mesentery	(1)			
Fat, necrosis	1 (100%)			
Pancreas	(10)	(10)	(10)	(10)
Inflammation, chronic	3 (30%)			1 (10%)
Cardiovascular System				
Heart	(10)	(10)	(10)	(10)
Degeneration	1 (10%)		1 (10%)	3 (30%)
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Hyperplasia			1 (10%)	
Mineralization			1 (10%)	
Vacuolization cytoplasmic	1 (10%)		3 (30%)	10 (100%)
Pituitary gland	(10)	(10)	(10)	(10)
Pars distalis, hyperplasia			1 (10%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	75 ppm	150 ppm	300 ppm
9-Month Interim Evaluation (continued)				
Genital System				
Ovary	(10)	(10)	(10)	(10)
Cyst	1 (10%)	1 (10%)		1 (10%)
Interstitium, hyperplasia			1 (10%)	10 (100%)
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Nephropathy	5 (50%)	3 (30%)	4 (40%)	6 (60%)
Systems Examined With No Lesions Observed				
General Body System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
15-Month Interim Evaluation				
Alimentary System				
Liver	(9)	(8)	(10)	(10)
Basophilic focus	1 (11%)	2 (25%)	3 (30%)	1 (10%)
Hepatodiaphragmatic nodule	1 (11%)		1 (10%)	
Mixed cell focus				1 (10%)
Pancreas	(9)	(8)	(10)	(10)
Acinus, atrophy	4 (44%)	1 (13%)	2 (20%)	
Salivary glands	(9)	(8)	(10)	(10)
Inflammation, chronic	1 (11%)			
Cardiovascular System				
Heart	(9)	(8)	(10)	(10)
Myocardium, degeneration	3 (33%)	3 (38%)	2 (20%)	4 (40%)
Endocrine System				
Adrenal cortex	(9)	(8)	(10)	(10)
Hyperplasia	1 (11%)	1 (13%)		1 (10%)
Vacuolization cytoplasmic				10 (100%)
Adrenal medulla	(9)	(8)	(10)	(10)
Hyperplasia	1 (11%)			
Pituitary gland	(9)	(8)	(10)	(10)
Pigmentation, hemosiderin			1 (10%)	
Pars distalis, cyst		1 (13%)	2 (20%)	1 (10%)
Pars distalis, hyperplasia				1 (10%)
Thyroid gland	(9)	(8)	(10)	(10)
C-cell, hyperplasia	8 (89%)	7 (88%)	7 (70%)	8 (80%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	75 ppm	150 ppm	300 ppm
15-Month Interim Evaluation (continued)				
Genital System				
Clitoral gland	(9)	(8)	(10)	(10)
Inflammation, chronic active	1 (11%)	2 (25%)	1 (10%)	4 (40%)
Ovary	(9)	(8)	(10)	(10)
Cyst	1 (11%)	1 (13%)		
Follicle, cyst				1 (10%)
Interstitium, hyperplasia			3 (30%)	9 (90%)
Uterus	(9)	(8)	(10)	(10)
Dilatation				2 (20%)
Cervix, cyst				1 (10%)
Nervous System				
Spinal cord	(14)	(13)	(15)	(15)
Cyst			2 (13%)	
Respiratory System				
Nose	(9)	(8)	(10)	(10)
Inflammation, suppurative				1 (10%)
Urinary System				
Kidney	(9)	(8)	(10)	(10)
Nephropathy	3 (33%)	4 (50%)	6 (60%)	6 (60%)
Systems Examined With No Lesions Observed				
General Body System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Special Senses System				
2-Year Study				
Alimentary System				
Intestine large, colon	(51)	(53)	(49)	(50)
Parasite metazoan			1 (2%)	
Ulcer	1 (2%)			
Intestine large, rectum	(51)	(53)	(48)	(50)
Fibrosis				1 (2%)
Inflammation, necrotizing		1 (2%)		
Parasite metazoan	1 (2%)	1 (2%)	4 (8%)	
Intestine large, cecum	(51)	(53)	(50)	(50)
Ulcer	1 (2%)			

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	75 ppm	150 ppm	300 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Intestine large, cecum	(51)	(53)	(50)	(50)
Ulcer	1 (2%)			
Intestine small, jejunum	(50)	(52)	(48)	(47)
Ulcer	1 (2%)			
Intestine small, ileum	(51)	(53)	(48)	(48)
Ulcer	1 (2%)			
Liver	(51)	(53)	(50)	(50)
Basophilic focus	20 (39%)	19 (36%)	22 (44%)	21 (42%)
Clear cell focus	1 (2%)		1 (2%)	
Cyst	1 (2%)			
Degeneration, cystic	1 (2%)		1 (2%)	1 (2%)
Degeneration, fatty				1 (2%)
Eosinophilic focus	3 (6%)	3 (6%)	3 (6%)	7 (14%)
Fatty change		2 (4%)	2 (4%)	2 (4%)
Hepatodiaphragmatic nodule	5 (10%)	8 (15%)	2 (4%)	6 (12%)
Hyperplasia				1 (2%)
Inflammation, granulomatous	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Mixed cell focus	5 (10%)	4 (8%)	5 (10%)	3 (6%)
Pigmentation, hemosiderin			1 (2%)	
Serosa, inflammation, chronic	1 (2%)			
Mesentery	(3)	(7)	(4)	(4)
Hemorrhage				1 (25%)
Fat, necrosis	3 (100%)	5 (71%)	4 (100%)	3 (75%)
Pancreas	(51)	(53)	(50)	(50)
Acinus, atrophy	13 (25%)	11 (21%)	20 (40%)	14 (28%)
Stomach, forestomach	(51)	(53)	(49)	(50)
Cyst epithelial inclusion				1 (2%)
Ulcer			1 (2%)	1 (2%)
Epithelium, hyperplasia		1 (2%)	2 (4%)	4 (8%)
Stomach, glandular	(51)	(53)	(50)	(50)
Ulcer	1 (2%)		2 (4%)	1 (2%)
Mucosa, mineralization		2 (4%)	1 (2%)	
Tongue		(1)		
Mucosa, epithelium, hyperplasia		1 (100%)		
Tooth	(1)	(1)		
Peridontal tissue, inflammation, chronic active		1 (100%)		
Cardiovascular System				
Heart	(51)	(53)	(50)	(50)
Artery, inflammation, chronic		1 (2%)		
Myocardium, degeneration	34 (67%)	33 (62%)	35 (70%)	28 (56%)
Endocrine System				
Adrenal cortex	(51)	(53)	(50)	(50)
Hyperplasia	17 (33%)	13 (25%)	17 (34%)	21 (42%)
Vacuolization cytoplasmic	14 (27%)	12 (23%)	16 (32%)	36 (72%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Tricresyl Phosphate
(continued)

	0 ppm	75 ppm	150 ppm	300 ppm
2-Year Study (continued)				
Endocrine System (continued)				
Adrenal medulla	(51)	(53)	(50)	(50)
Hyperplasia	5 (10%)		1 (2%)	2 (4%)
Infarct		1 (2%)		
Pituitary gland	(51)	(53)	(50)	(50)
Cyst	1 (2%)	5 (9%)	5 (10%)	5 (10%)
Inflammation, chronic				1 (2%)
Pars distalis, hyperplasia	3 (6%)	6 (11%)	6 (12%)	3 (6%)
Thyroid gland	(51)	(53)	(50)	(50)
C-cell, hyperplasia	29 (57%)	37 (70%)	45 (90%)	31 (62%)
General Body System				
None				
Genital System				
Clitoral gland	(51)	(53)	(49)	(49)
Abscess	1 (2%)			
Hyperplasia	5 (10%)	2 (4%)		
Inflammation, chronic	5 (10%)	4 (8%)	3 (6%)	3 (6%)
Ovary	(51)	(53)	(50)	(50)
Cyst		4 (8%)	1 (2%)	3 (6%)
Interstitium, hyperplasia				15 (30%)
Uterus	(51)	(53)	(50)	(50)
Dilatation	1 (2%)		1 (2%)	2 (4%)
Prolapse	2 (4%)			
Cervix, cyst		2 (4%)		
Endometrium, hyperplasia	7 (14%)	6 (11%)	1 (2%)	1 (2%)
Wall, hyperplasia			1 (2%)	1 (2%)
Hematopoietic System				
Blood	(1)	(1)	(1)	
Anisocytosis			1 (100%)	
Polychromasia			1 (100%)	
Bone marrow	(51)	(53)	(50)	(50)
Atrophy			1 (2%)	
Spleen	(51)	(53)	(50)	(50)
Congestion			1 (2%)	
Depletion lymphoid				1 (2%)
Erythrophagocytosis			1 (2%)	
Fibrosis	1 (2%)	2 (4%)		
Inflammation, granulomatous	1 (2%)	3 (6%)		1 (2%)
Pigmentation, hemosiderin			1 (2%)	
Integumentary System				
Mammary gland	(49)	(53)	(50)	(49)
Hyperplasia, cystic	1 (2%)	3 (6%)	1 (2%)	1 (2%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	75 ppm	150 ppm	300 ppm
2-Year Study (continued)				
Integumentary System (continued)				
Skin	(51)	(53)	(50)	(50)
Abscess			1 (2%)	1 (2%)
Inflammation, chronic		1 (2%)	2 (4%)	
Subcutaneous tissue, edema				1 (2%)
Musculoskeletal System				
Bone	(51)	(53)	(50)	(50)
Osteopetrosis	1 (2%)		2 (4%)	
Nervous System				
Brain	(51)	(53)	(50)	(50)
Gliosis				1 (2%)
Hypothalamus, compression	13 (25%)	5 (9%)	6 (12%)	12 (24%)
Spinal cord	(51)	(52)	(50)	(50)
Axon, degeneration		1 (2%)		
Respiratory System				
Lung	(51)	(53)	(50)	(50)
Inflammation, chronic	5 (10%)	6 (11%)	2 (4%)	1 (2%)
Fat, mediastinum, necrosis			1 (2%)	
Nose	(51)	(53)	(50)	(50)
Hemorrhage				1 (2%)
Inflammation, necrotizing				1 (2%)
Inflammation, suppurative		2 (4%)		1 (2%)
Special Senses System				
Eye	(1)	(5)		(2)
Hemorrhage		1 (20%)		
Synechia				1 (50%)
Cornea, inflammation, chronic		1 (20%)		
Lens, cataract	1 (100%)	3 (60%)		1 (50%)
Urinary System				
Kidney	(51)	(53)	(50)	(50)
Infarct	1 (2%)			1 (2%)
Nephropathy	38 (75%)	34 (64%)	29 (58%)	22 (44%)

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR FEED STUDY OF TRICRESYL PHOSPHATE

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TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Tricresyl Phosphate[a]

	0 ppm	60 ppm	125 ppm	250 ppm
Disposition Summary				
Animals initially in study	95	95	95	95
3-Month interim evaluation[b]	13	15	15	15
9-Month interim evaluation[b]	15	15	15	15
15-Month interim evaluation[b]	15	15	15	15
Early deaths				
Accidental deaths	1			
Moribund	4	1	1	2
Natural deaths	4	5	4	6
Survivors				
Terminal sacrifice	43	43	44	42
Missing		1	1	
Animals examined microscopically	95	94	94	95
Systems Examined at 3 Months With No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				
9-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Hepatocellular adenoma	1 (10%)	1 (10%)		
Hepatocellular adenoma, multiple	1 (10%)			
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	60 ppm	125 ppm	250 ppm
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Hemangiosarcoma, multiple			1 (10%)	
Hepatocellular carcinoma		1 (10%)		
Hepatocellular adenoma	2 (20%)		2 (20%)	2 (20%)
Hepatocellular adenoma, multiple	1 (10%)			
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Adenoma			1 (10%)	1 (10%)
Subcapsular, adenoma	1 (10%)			
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Alveolar/bronchiolar adenoma	1 (10%)		1 (10%)	1 (10%)
Hepatocellular carcinoma, metastatic, liver		1 (10%)		
Special Senses System				
Harderian gland	(10)	(5)	(9)	(6)
Adenoma		1 (20%)		
Systems Examined at With No Neoplasms Observed				
Cardiovascular System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Urinary System				
2-Year Study				
Alimentary System				
Gallbladder	(51)	(47)	(47)	(48)
Adenoma	1 (2%)			
Intestine large, colon	(52)	(48)	(49)	(50)
Intestine small, jejunum	(51)	(49)	(49)	(50)
Adenocarcinoma				2 (4%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	60 ppm	125 ppm	250 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Liver	(52)	(49)	(49)	(50)
Hemangioma	1 (2%)			
Hemangiosarcoma			2 (4%)	
Hemangiosarcoma, metastatic, spleen		1 (2%)		
Hepatocellular carcinoma	12 (23%)	10 (20%)	8 (16%)	12 (24%)
Hepatocellular carcinoma, multiple	3 (6%)	2 (4%)	2 (4%)	3 (6%)
Hepatocellular adenoma	12 (23%)	12 (24%)	9 (18%)	11 (22%)
Hepatocellular adenoma, multiple	6 (12%)	6 (12%)	8 (16%)	7 (14%)
Histiocytic sarcoma		2 (4%)		2 (4%)
Ito cell tumor benign				1 (2%)
Schwannoma malignant, metastatic, nose			1 (2%)	
Stomach, forestomach	(52)	(49)	(49)	(50)
Squamous cell carcinoma	1 (2%)			
Squamous cell papilloma			2 (4%)	
Tooth	(3)	(3)	(2)	(1)
Odontoma	2 (67%)	2 (67%)	2 (100%)	1 (100%)
Cardiovascular System				
Heart	(52)	(49)	(49)	(50)
Hemangiosarcoma		1 (2%)		
Hemangiosarcoma, metastatic, bone marrow				1 (2%)
Histiocytic sarcoma		1 (2%)		1 (2%)
Endocrine System				
Adrenal cortex	(52)	(49)	(49)	(50)
Adenoma	1 (2%)			
Bilateral, subcapsular, adenoma	1 (2%)	1 (2%)		
Subcapsular, adenoma		2 (4%)	1 (2%)	2 (4%)
Adrenal medulla	(52)	(49)	(49)	(49)
Pheochromocytoma benign	2 (4%)			
Islets, pancreatic	(52)	(49)	(49)	(50)
Adenoma	1 (2%)		3 (6%)	2 (4%)
Pituitary gland	(50)	(49)	(45)	(46)
Schwannoma malignant, metastatic, nose			1 (2%)	
Thyroid gland	(52)	(49)	(49)	(50)
Follicular cell, adenoma			2 (4%)	1 (2%)
General Body System				
Peritoneum		(1)		
Histiocytic sarcoma		1 (100%)		
Genital System				
Epididymis	(52)	(49)	(49)	(50)
Histiocytic sarcoma		1 (2%)		1 (2%)
Testes	(52)	(49)	(49)	(50)
Interstitial cell, adenoma				1 (2%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	60 ppm	125 ppm	250 ppm
2-Year Study (continued)				
Hematopoietic System				
Bone marrow	(52)	(49)	(49)	(50)
Hemangiosarcoma				1 (2%)
Histiocytic sarcoma		1 (2%)		
Mast cell tumor malignant				1 (2%)
Sarcoma, metastatic, bone				1 (2%)
Lymph node	(1)	(2)	(1)	
Lymph node, mandibular	(51)	(46)	(43)	(46)
Adenocarcinoma, metastatic, harderian gland		1 (2%)		
Histiocytic sarcoma		1 (2%)		
Lymph node, mesenteric	(50)	(47)	(46)	(47)
Histiocytic sarcoma		1 (2%)		1 (2%)
Spleen	(52)	(49)	(49)	(49)
Hemangiosarcoma	4 (8%)	1 (2%)	1 (2%)	1 (2%)
Histiocytic sarcoma		1 (2%)		2 (4%)
Mast cell tumor malignant, metastatic, bone marrow				1 (2%)
Thymus	(45)	(42)	(45)	(45)
Histiocytic sarcoma		1 (2%)		
Integumentary System				
Skin	(52)	(49)	(49)	(50)
Fibrosarcoma		1 (2%)		
Hemangiosarcoma	1 (2%)			
Musculoskeletal System				
Bone	(52)	(49)	(49)	(50)
Hemangiosarcoma, metastatic, bone marrow				1 (2%)
Femur, sarcoma				1 (2%)
Skeletal muscle	(1)			(1)
Hemangiosarcoma, metastatic, bone marrow				1 (100%)
Nervous System				
Brain	(52)	(49)	(49)	(50)
Schwannoma malignant, metastatic, nose			1 (2%)	
Meninges, histiocytic sarcoma		1 (2%)		
Respiratory System				
Lung	(52)	(49)	(49)	(50)
Adenocarcinoma, metastatic, harderian gland	1 (2%)	1 (2%)		
Alveolar/bronchiolar adenoma	6 (12%)	7 (14%)	9 (18%)	9 (18%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)		2 (4%)	2 (4%)
Alveolar/bronchiolar carcinoma	1 (2%)	4 (8%)	2 (4%)	2 (4%)
Hepatocellular carcinoma, metastatic, liver	6 (12%)	5 (10%)	4 (8%)	2 (4%)
Histiocytic sarcoma		1 (2%)		1 (2%)
Nose	(52)	(49)	(49)	(50)
Mast cell tumor malignant, metastatic, bone marrow				1 (2%)
Schwannoma malignant			1 (2%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	60 ppm	125 ppm	250 ppm
2-Year Study (continued)				
Special Senses System				
Ear		(1)		(1)
Pinna, fibrosarcoma		1 (100%)		1 (100%)
Harderian gland	(43)	(40)	(37)	(37)
Adenocarcinoma	1 (2%)	1 (3%)	2 (5%)	
Adenoma		1 (3%)	2 (5%)	5 (14%)
Urinary System				
Kidney	(52)	(49)	(49)	(50)
Adenocarcinoma		1 (2%)		
Histiocytic sarcoma		1 (2%)		1 (2%)
Systemic Lesions				
Multiple organs[c]	(52)	(49)	(49)	(50)
Histiocytic sarcoma		2 (4%)		2 (4%)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)	
Lymphoma malignant mixed	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Lymphoma malignant undifferentiated cell		1 (2%)		1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[d]				
9-Month interim evaluation	2	1		
15-Month interim evaluation	5	2	3	3
2-Year study	37	35	39	39
Total primary neoplasms				
9-Month interim evaluation	2	1		
15-Month interim evaluation	5	2	5	4
2-Year study	60	58	60	70
Total animals with benign neoplasms				
9-Month interim evaluation	2	1		
15-Month interim evaluation	5	1	3	3
2-Year study	26	22	32	32
Total benign neoplasms				
9-Month interim evaluation	2	1		
15-Month interim evaluation	5	1	4	4
2-Year study	34	31	40	42
Total animals with malignant neoplasms				
15-Month interim evaluation		1	1	
2-Year study	22	22	16	21
Total malignant neoplasms				
15-Month interim evaluation		1	1	
2-Year study	26	27	20	28
Total animals with metastatic neoplasms				
15-Month interim evaluation		1		
2-Year study	6	7	5	5
Total metastatic neoplasms				
15-Month interim evaluation		1		
2-Year study	7	8	7	8

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Tricresyl Phosphate (continued)

[a] Number of animals examined microscopically at site and number of animals with neoplasm
[b] Includes up to five animals per dose group subjected to total body perfusion for special neuropathology
[c] Number of animals with any tissue examined microscopically
[d] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Tricresyl Phosphate: 0 ppm

Number of Days on Study	0 4 0	0 6 8	0 9 1	5 5 3	5 8 1	6 0 3	6 2 5	6 2 7	6 9 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0
Carcass ID Number	0 3 1	4 0 7	0 3 2	4 2 2	4 1 6	3 9 9	4 0 8	4 1 9	4 3 8	3 9 1	3 9 2	3 9 3	3 9 4	3 9 5	3 9 6	3 9 7	3 9 8	4 0 0	4 0 1	4 0 2	4 0 3	4 0 4	4 0 5	4 0 6	4 0 9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hepatocellular carcinoma				X		X					X		X									X	X		
Hepatocellular carcinoma, multiple									X																
Hepatocellular adenoma				X				X		X										X		X	X		
Hepatocellular adenoma, multiple																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma													X												
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Odontoma																									
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Bilateral, subcapsular, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis	+																								
Preputial gland				+	+		+	+	+	+	+		+	+	+	+	+	+	+	+	+			+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Tricresyl Phosphate: 0 ppm (continued)

Number of Days on Study	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	
Carcass ID Number	4 1 0	4 1 1	4 1 2	4 1 3	4 1 4	4 1 5	4 1 7	4 1 8	4 2 0	4 2 1	4 2 3	4 2 4	4 2 5	4 2 6	4 2 7	4 2 8	4 2 9	4 3 0	4 3 1	4 3 2	4 3 3	4 3 4	4 3 5	4 3 6	4 3 7	4 3 9	4 4 0	Total Tissues/ Tumors
Alimentary System																												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Gallbladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma	X																											1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, jejunum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	51
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Hemangioma																											X	1
Hepatocellular carcinoma		X			X		X	X											X				X					12
Hepatocellular carcinoma, multiple												X													X			3
Hepatocellular adenoma				X			X						X	X						X		X						12
Hepatocellular adenoma, multiple			X						X							X	X		X								X	6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Squamous cell carcinoma																												1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Tooth			+																			+					+	3
Odontoma			X																								X	2
Cardiovascular System																												
Blood vessel		+																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Endocrine System																												
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenoma										X																		1
Bilateral, subcapsular, adenoma							X																					1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pheochromocytoma benign		X						X																				2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenoma							X																					1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
General Body System																												
None																												
Genital System																												
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Penis																												1
Preputial gland	+	+	+		+	+		+	+		+	+		+		+	+	+	+	+	+	+	+	+	+	+	+	40
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Tricresyl Phosphate: 0 ppm (continued)

Number of Days on Study	0 4 0	0 6 8	0 9 1	5 5 3	5 8 1	6 0 3	6 2 5	6 2 7	6 9 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0
Carcass ID Number	0 3 1	4 0 7	0 3 2	4 2 2	4 1 6	3 9 9	4 0 8	4 1 9	4 3 8	3 9 1	3 9 2	3 9 3	3 9 4	3 9 5	3 9 6	3 9 7	3 9 8	4 0 0	4 0 1	4 0 2	4 0 3	4 0 4	4 0 5	4 0 6	4 0 9
Hematopoietic System																									
Blood															+										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma															X			X					X		
Thymus	+	+	+	+	+	+	M	M	M	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	+	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle															+										
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, harderian gland																									
Alveolar/bronchiolar adenoma							X														X				X
Alveolar/bronchiolar adenoma, multiple				X																					
Alveolar/bronchiolar carcinoma																									
Hepatocellular carcinoma, metastatic, liver									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Harderian gland	+	+	+	+	+	M	M	M	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	M	+
Adenocarcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed						X																			

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Tricresyl Phosphate: 0 ppm (continued)

Number of Days on Study	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	
Carcass ID Number	4 1 0	4 1 1	4 1 2	4 1 3	4 1 4	4 1 5	4 1 7	4 1 8	4 2 0	4 2 1	4 2 2	4 2 3	4 2 4	4 2 5	4 2 6	4 2 7	4 2 8	4 3 9	4 3 0	4 3 1	4 3 2	4 3 3	4 3 4	4 3 5	4 3 6	4 3 7	4 3 9	4 4 0	Total Tissues/ Tumors
Hematopoietic System																												
Blood																												1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph node														+														1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Hemangiosarcoma																X												4
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	45
Integumentary System																												
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Hemangiosarcoma														X														1
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Skeletal muscle																												1
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenocarcinoma, metastatic, harderian gland																								X				1
Alveolar/bronchiolar adenoma								X						X		X												6
Alveolar/bronchiolar adenoma, multiple																												1
Alveolar/bronchiolar carcinoma									X																			1
Hepatocellular carcinoma, metastatic, liver					X			X				X											X	X				6
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Special Senses System																												
Eye																								+				1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	M	+	43
Adenocarcinoma																								X				1
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymphoma malignant lymphocytic																									X			1
Lymphoma malignant mixed			X																									2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Tricresyl Phosphate: 60 ppm

Number of Days on Study	3 9 7	4 8 1	6 8 7	7 0 3	7 0 3	7 0 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9
Carcass ID Number	4 5 8	4 7 3	4 7 2	4 4 7	4 7 8	4 8 6	4 4 1	4 4 2	4 4 3	4 4 4	4 4 5	4 4 6	4 4 8	4 4 9	4 5 0	4 5 1	4 5 2	4 5 3	4 5 4	4 5 5	4 5 6	4 5 7	4 5 9	4 6 0
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen																								
Hepatocellular carcinoma		X	X		X							X			X			X						
Hepatocellular carcinoma, multiple																								
Hepatocellular adenoma													X				X		X	X			X	X
Hepatocellular adenoma, multiple								X				X		X				X						
Histiocytic sarcoma	X					X																		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth				+													+							
Odontoma																	X							
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Histiocytic sarcoma	X																							
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, subcapsular, adenoma																				X				
Subcapsular, adenoma																								
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																								
Peritoneum	+																							
Histiocytic sarcoma	X																							
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																							
Preputial gland		+		+	+			+				+	+		+	+	+	+			+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Tricresyl Phosphate: 60 ppm (continued)

Number of Days on Study	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	4 6 1	4 6 2	4 6 3	4 6 4	4 6 6	4 6 7	4 6 8	4 6 9	4 7 0	4 7 1	4 7 4	4 7 5	4 7 6	4 7 7	4 7 9	4 8 0	4 8 1	4 8 2	4 8 3	4 8 4	4 8 5	4 8 7	4 8 8	4 8 9	4 9 0	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma, metastatic, spleen																					X				1
Hepatocellular carcinoma				X				X			X													X	10
Hepatocellular carcinoma, multiple												X				X									2
Hepatocellular adenoma	X					X		X	X														X	X	12
Hepatocellular adenoma, multiple																X	X								6
Histiocytic sarcoma																									2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth																								+	3
Odontoma																								X	2
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma		X																							1
Histiocytic sarcoma																									1
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, subcapsular, adenoma																									1
Subcapsular, adenoma																X						X			2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
General Body System																									
Peritoneum																									1
Histiocytic sarcoma																									1
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																									1
Preputial gland		+	+	+	+	+		+		+	+	+	+	+				+		+	+		+	+	30
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Tricresyl Phosphate: 60 ppm (continued)

Number of Days on Study	3 9 7	4 8 1	6 8 7	7 0 3	7 0 3	7 0 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9
Carcass ID Number	4 5 8	4 7 3	4 7 2	4 4 7	4 7 8	4 8 6	4 4 1	4 4 2	4 4 3	4 4 4	4 4 5	4 4 6	4 4 8	4 4 9	4 5 0	5 5 1	5 5 2	5 5 3	5 5 4	5 5 5	5 5 6	5 5 7	5 5 9	6 6 0
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																							
Lymph node																								+
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, harderian gland																	X							
Histiocytic sarcoma	X																							
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Histiocytic sarcoma	X																							
Thymus	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	M
Histiocytic sarcoma	X																							
Integumentary System																								
Mammary gland	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	+	M	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma												X												
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meninges, histiocytic sarcoma	X																							
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, harderian gland																	X							
Alveolar/bronchiolar adenoma									X											X				
Alveolar/bronchiolar carcinoma													X					X				X	X	
Hepatocellular carcinoma, metastatic, liver		X			X													X						
Histiocytic sarcoma	X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Ear																								
Pinna, fibrosarcoma																								
Eye																	+							
Harderian gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Adenocarcinoma																	X							
Adenoma														X										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Tricresyl Phosphate: 60 ppm (continued)

Number of Days on Study	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	4 6 1	4 6 2	4 6 3	4 6 4	4 6 6	4 6 7	4 6 8	4 6 9	4 7 0	4 7 1	4 7 4	4 7 5	4 7 6	4 7 7	4 7 9	4 8 0	4 8 1	4 8 2	4 8 3	4 8 4	4 8 5	4 8 7	4 8 8	4 8 9	4 9 0	Total Tissues/ Tumors
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																									1
Lymph node																+									2
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Adenocarcinoma, metastatic, harderian gland																									1
Histiocytic sarcoma																									1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																									1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																					X				1
Histiocytic sarcoma																									1
Thymus	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Histiocytic sarcoma																									1
Integumentary System																									
Mammary gland	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	+	M	7
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma																									1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Meninges, histiocytic sarcoma																									1
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, metastatic, harderian gland																									1
Alveolar/bronchiolar adenoma														X			X	X					X	X	7
Alveolar/bronchiolar carcinoma																									4
Hepatocellular carcinoma, metastatic, liver																X								X	5
Histiocytic sarcoma																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																									
Ear		+																							1
Pinna, fibrosarcoma		X																							1
Eye																									1
Harderian gland	+	+	+	+	+	+	M	+	+	M	+	M	+	+	M	+	M	+	+	+	M	+	+	M	+	40
Adenocarcinoma																									1
Adenoma																									1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Tricresyl Phosphate: 60 ppm (continued)

Number of Days on Study	3 9 7	4 8 1	6 8 7	7 0 3	7 0 3	7 0 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9
Carcass ID Number	4 5 8	4 7 3	4 7 2	4 4 7	4 7 8	4 8 6	4 4 1	4 4 2	4 4 3	4 4 4	4 4 5	4 4 6	4 4 8	4 4 9	4 5 0	4 5 1	4 5 2	4 5 3	4 5 4	4 5 5	4 5 6	4 5 7	4 5 9	4 6 0
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma															X									
Histiocytic sarcoma	X																							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X					X																		
Lymphoma malignant mixed																								
Lymphoma malignant undifferentiated cell type																								X

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Tricresyl Phosphate: 60 ppm (continued)

Number of Days on Study	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	4 6 1	4 6 2	4 6 3	4 6 4	4 6 6	4 6 7	4 6 8	4 6 9	4 7 0	4 7 1	4 7 4	4 7 5	4 7 6	4 7 7	4 7 9	4 8 0	4 8 1	4 8 2	4 8 3	4 8 4	4 8 5	4 8 7	4 8 8	4 8 9	4 9 0	Total Tissues/ Tumors
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma																									1
Histiocytic sarcoma																									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																									2
Lymphoma malignant mixed																X		X							2
Lymphoma malignant undifferentiated cell type																									1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Tricresyl Phosphate: 125 ppm

Number of Days on Study	5 7 2	5 8 3	6 6 7	6 9 8	7 1 8	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7
Carcass ID Number	5 2 8	5 1 1	4 9 5	4 9 6	4 9 8	4 9 1	4 9 2	4 9 3	4 9 4	4 9 7	4 9 9	5 0 0	5 0 1	5 0 2	5 0 3	5 0 4	5 0 5	5 0 6	5 0 7	5 0 8	5 0 9	5 1 0	5 1 2	5 1 3
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X										
Hepatocellular carcinoma			X	X	X	X																		
Hepatocellular carcinoma, multiple								X														X		
Hepatocellular adenoma										X	X													
Hepatocellular adenoma, multiple								X	X							X		X		X				
Schwannoma malignant, metastatic, nose			X																					
Mesentery																								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																								
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth													+											
Odontoma													X											
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma																								
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma		X				X																		
Parathyroid gland	+	+	+	+	+	+	M	+	+	M	M	+	+	+	+	+	+	M	+	+	+	+	+	+
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M
Schwannoma malignant, metastatic, nose			X																					
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																					X			
General Body System																								
None																								
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+		+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Tricresyl Phosphate: 125 ppm (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	5 1 4	5 1 5	5 1 6	5 1 7	5 1 8	5 1 9	5 2 0	5 2 1	5 2 2	5 2 3	5 2 4	5 2 6	5 2 7	5 2 9	5 3 0	5 3 1	5 3 2	5 3 3	5 3 4	5 3 5	5 3 6	5 3 7	5 3 8	5 3 9	5 4 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma									X																	2
Hepatocellular carcinoma		X						X	X															X		8
Hepatocellular carcinoma, multiple																										2
Hepatocellular adenoma		X			X	X							X	X				X	X							9
Hepatocellular adenoma, multiple									X		X									X						8
Schwannoma malignant, metastatic, nose																										1
Mesentery							+											+								2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma									X							X										2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth																			+							2
Odontoma																			X							2
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcapsular, adenoma																		X								1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma															X											3
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Schwannoma malignant, metastatic, nose																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma				X																						2
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland		+	+		+	+	+	+	+			+	+	+	+	+	+	+		+	+	+	+	+	+	41
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Tricresyl Phosphate: 125 ppm (continued)

Number of Days on Study	5 7 2	5 8 3	6 6 7	6 9 8	7 1 8	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7
Carcass ID Number	5 2 8	5 1 1	4 9 5	4 9 6	4 9 8	4 9 1	4 9 2	4 9 3	4 9 4	4 9 7	4 9 9	5 0 0	5 0 1	5 0 2	5 0 3	5 0 4	5 0 5	5 0 6	5 0 7	5 0 8	5 0 9	5 1 0	5 1 2	5 1 3
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																				+				
Lymph node, mandibular	M	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								X
Thymus	M	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+
Integumentary System																								
Mammary gland	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, nose			X																					
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X			X								X		X		X					
Alveolar/bronchiolar adenoma, multiple																								
Alveolar/bronchiolar carcinoma					X							X												
Hepatocellular carcinoma, metastatic, liver				X		X																X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant			X																					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Harderian gland	+	M	+	+	M	M	+	+	M	M	+	M	+	M	+	+	+	M	M	+	+	+	+	+
Adenocarcinoma																								X
Adenoma																								X
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																				X				
Lymphoma malignant mixed																								

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Tricresyl Phosphate: 125 ppm (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	5 1 4	5 1 5	5 1 6	5 1 7	5 1 8	5 1 9	5 2 0	5 2 1	5 2 2	5 2 3	5 2 4	5 2 6	5 2 7	5 2 9	5 3 0	5 3 1	5 3 2	5 3 3	5 3 4	5 3 5	5 3 6	5 3 7	5 3 8	5 3 9	5 4 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node																										1
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	43
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Integumentary System																										
Mammary gland	+	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	+	M	M	M	M	M	M	5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Schwannoma malignant, metastatic, nose																										1
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma					X						X					X			X							9
Alveolar/bronchiolar adenoma, multiple														X							X					2
Alveolar/bronchiolar carcinoma																										2
Hepatocellular carcinoma, metastatic, liver								X																		4
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Schwannoma malignant																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Harderian gland	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	37
Adenocarcinoma													X													2
Adenoma																						X				2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed															X											1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Tricresyl Phosphate: 250 ppm

Number of Days on Study	0 9	5 8	5 3	5 6	6 6	6 2	7 7	7 1	7 3	7 3	7 3	7 3	7 3	7 6	7 6	7 6	7 6	7 6	7 6	7 6	7 6	7 6	7 6	7 6	7 6
Carcass ID Number	5 5 0	5 7 3	5 6 6	5 7 1	5 6 7	5 8 3	5 7 5	5 6 0	5 4 1	5 4 2	5 4 3	5 4 4	5 4 5	5 4 6	5 4 7	5 4 8	5 4 9	5 5 1	5 5 2	5 5 3	5 5 4	5 5 5	5 5 6	5 5 7	5 5 8
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma													X												
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma				X		X		X				X				X	X				X	X		X	X
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma		X			X								X					X	X	X			X		X
Hepatocellular adenoma, multiple														X										X	
Histiocytic sarcoma						X	X																		
Ito cell tumor benign				X																					
Mesentery																				+					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Odontoma																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, bone marrow								X																	
Histiocytic sarcoma							X																		
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma									X																
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X													
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Tricresyl Phosphate: 250 ppm (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	5 5 9	5 6 1	5 6 2	5 6 3	5 6 4	5 6 5	5 6 8	5 6 9	5 7 0	5 7 2	5 7 4	5 7 6	5 7 7	5 7 8	5 7 9	5 8 0	5 8 1	5 8 2	5 8 4	5 8 5	5 8 6	5 8 7	5 8 8	5 8 9	5 9 0	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma					X																				2
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																				X			X		12
Hepatocellular carcinoma, multiple					X			X											X						3
Hepatocellular adenoma						X										X							X		11
Hepatocellular adenoma, multiple					X							X						X				X	X		7
Histiocytic sarcoma																									2
Ito cell tumor benign																									1
Mesentery																			+						2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth										+															1
Odontoma										X															1
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, bone marrow																									1
Histiocytic sarcoma																									1
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcapsular, adenoma										X															2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X																				2
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	M	+	+	+	M	+	+	+	44
Pituitary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	46
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																					X				1
General Body System																									
None																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Tricresyl Phosphate: 250 ppm (continued)

Number of Days on Study	0 9	5 0	5 3	5 7	6 6	6 8	7 1	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3
Carcass ID Number	5 5 0	5 7 3	5 6 6	5 7 1	5 6 7	5 8 3	5 7 5	5 6 0	5 4 1	5 4 2	5 4 3	5 4 4	5 4 5	5 4 6	5 4 7	5 4 8	5 4 9	5 5 1	5 5 2	5 5 3	5 5 4	5 5 5	5 5 6	5 5 7	5 5 8
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Preputial gland		+	+	+	+		+	+	+	+		+		+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma												X													
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma								X																	
Mast cell tumor malignant																	X								
Sarcoma, metastatic, bone																									X
Lymph node, mandibular	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Spleen	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X											
Histiocytic sarcoma						X	X																		
Mast cell tumor malignant, metastatic, bone marrow																	X								
Thymus	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	+	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, bone marrow								X																	
Femur, sarcoma																									X
Skeletal muscle								+																	
Hemangiosarcoma, metastatic, bone marrow								X																	
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma									X						X	X	X		X						
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma																			X				X		
Hepatocellular carcinoma, metastatic, liver																									
Histiocytic sarcoma							X																		

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Tricresyl Phosphate: 250 ppm (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	5 5 9	5 6 1	5 6 2	5 6 3	5 6 4	5 6 5	5 6 8	5 6 9	5 7 0	5 7 2	5 7 4	5 7 6	5 7 7	5 7 8	5 7 9	5 8 0	5 8 1	5 8 2	5 8 4	5 8 5	5 8 6	5 8 7	5 8 8	5 8 9	5 9 0	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Preputial gland	+	+	+		+	+			+	+	+	+	+	+	+	+	+		+	+	+		+	+	+	41
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Mast cell tumor malignant																										1
Sarcoma, metastatic, bone																										1
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Histiocytic sarcoma																										2
Mast cell tumor malignant, metastatic, bone marrow																										1
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	45
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	+	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, bone marrow																										1
Femur, sarcoma																										1
Skeletal muscle																										1
Hemangiosarcoma, metastatic, bone marrow																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X		X	X												X	9
Alveolar/bronchiolar adenoma, multiple								X	X																	2
Alveolar/bronchiolar carcinoma																										2
Hepatocellular carcinoma, metastatic, liver																			X	X						2
Histiocytic sarcoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Tricresyl Phosphate: 250 ppm (continued)

Number of Days on Study	0	5	5	5	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	1	3	7	7	8	1	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	9	8	3	6	6	2	7	1	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Carcass ID Number	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	5	7	6	7	6	8	7	6	4	4	4	4	4	4	4	4	4	5	5	5	5	5	5	5	5
	0	3	6	1	7	3	5	0	1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8
Respiratory System (continued)																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, bone marrow																	X								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Pinna, fibrosarcoma																									
Eye																									
Harderian gland	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Adenoma											X								X						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X	X																		
Lymphoma malignant mixed																								X	
Lymphoma malignant undifferentiated cell type																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Tricresyl Phosphate: 250 ppm (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	5 5 9	5 6 1	5 6 2	5 6 3	5 6 4	5 6 5	5 6 8	5 6 9	5 7 0	5 7 2	5 7 4	5 7 6	5 7 7	5 7 8	5 7 9	5 8 0	5 8 1	5 8 2	5 8 4	5 8 5	5 8 6	5 8 7	5 8 8	5 8 9	5 9 0	Total Tissues/ Tumors
Respiratory System (continued)																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant, metastatic, bone marrow																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																								+		1
Pinna, fibrosarcoma																								X		1
Eye																				+						1
Harderian gland	+	+	+	+	+	M	+	M	+	M	+	+	+	+	M	+	+	M	+	+	M	M	+	M	M	37
Adenoma													X			X				X						5
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymphoma malignant mixed																										1
Lymphoma malignant undifferentiated cell type														X												1

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Tricresyl Phosphate

	0 ppm	60 ppm	125 ppm	250 ppm
Adrenal Cortex: Adenoma				
Overall rate[a]	2/52 (4%)	3/49 (6%)	1/49 (2%)	2/50 (4%)
Adjusted rate[b]	4.7%	7.0%	2.3%	4.8%
Terminal rate[c]	2/43 (5%)	3/43 (7%)	1/44 (2%)	2/42 (5%)
First incidence (days)	736 (T)	736 (T)	736 (T)	736 (T)
Life table test[d]	P=0.505N	P=0.500	P=0.492N	P=0.686
Logistic regression test[d]	P=0.505N	P=0.500	P=0.492N	P=0.686
Cochran-Armitage test[d]	P=0.508N			
Fisher exact test[d]		P=0.472	P=0.522N	P=0.676
Harderian Gland: Adenoma				
Overall rate	0/52 (0%)	1/49 (2%)	2/49 (4%)	5/50 (10%)
Adjusted rate	0.0%	2.3%	4.5%	11.9%
Terminal rate	0/43 (0%)	1/43 (2%)	2/44 (5%)	5/42 (12%)
First incidence (days)	-[e]	736 (T)	736 (T)	736 (T)
Life table test	P=0.007	P=0.500	P=0.244	P=0.031
Logistic regression test	P=0.007	P=0.500	P=0.244	P=0.031
Cochran-Armitage test	P=0.007			
Fisher exact test		P=0.485	P=0.233	P=0.025
Harderian Gland: Adenoma or Carcinoma				
Overall rate	1/52 (2%)	2/49 (4%)	3/49 (6%)	5/50 (10%)
Adjusted rate	2.3%	4.7%	6.8%	11.9%
Terminal rate	1/43 (2%)	2/43 (5%)	3/44 (7%)	5/42 (12%)
First incidence (days)	736 (T)	736 (T)	736 (T)	736 (T)
Life table test	P=0.048	P=0.500	P=0.314	P=0.098
Logistic regression test	P=0.048	P=0.500	P=0.314	P=0.098
Cochran-Armitage test	P=0.049			
Fisher exact test		P=0.478	P=0.287	P=0.094
Liver: Hepatocellular Adenoma				
Overall rate	18/52 (35%)	18/49 (37%)	17/49 (35%)	18/50 (36%)
Adjusted rate	39.9%	41.9%	38.6%	40.7%
Terminal rate	16/43 (37%)	18/43 (42%)	17/44 (39%)	16/42 (38%)
First incidence (days)	553	736 (T)	736 (T)	518
Life table test	P=0.520	P=0.583N	P=0.466N	P=0.551
Logistic regression test	P=0.529N	P=0.577N	P=0.478N	P=0.572
Cochran-Armitage test	P=0.508			
Fisher exact test		P=0.494	P=0.579	P=0.524
Liver: Hepatocellular Carcinoma				
Overall rate	15/52 (29%)	12/49 (24%)	10/49 (20%)	15/50 (30%)
Adjusted rate	32.5%	25.9%	21.3%	34.0%
Terminal rate	12/43 (28%)	9/43 (21%)	7/44 (16%)	13/42 (31%)
First incidence (days)	553	481	667	676
Life table test	P=0.479	P=0.331N	P=0.174N	P=0.559
Logistic regression test	P=0.483	P=0.367N	P=0.191N	P=0.580
Cochran-Armitage test	P=0.465			
Fisher exact test		P=0.394N	P=0.227N	P=0.535

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	60 ppm	125 ppm	250 ppm
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	28/52 (54%)	26/49 (53%)	24/49 (49%)	28/50 (56%)
Adjusted rate	59.5%	56.4%	51.1%	62.1%
Terminal rate	24/43 (56%)	23/43 (53%)	21/44 (48%)	25/42 (60%)
First incidence (days)	553	481	667	518
Life table test	P=0.479	P=0.420N	P=0.250N	P=0.533
Logistic regression test	P=0.511	P=0.445N	P=0.262N	P=0.571
Cochran-Armitage test	P=0.459			
Fisher exact test		P=0.548N	P=0.386N	P=0.492
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	7/52 (13%)	7/49 (14%)	11/49 (22%)	11/50 (22%)
Adjusted rate	15.3%	16.3%	24.4%	26.2%
Terminal rate	5/43 (12%)	7/43 (16%)	10/44 (23%)	11/42 (26%)
First incidence (days)	553	736 (T)	698	736 (T)
Life table test	P=0.119	P=0.610	P=0.239	P=0.205
Logistic regression test	P=0.129	P=0.594	P=0.203	P=0.211
Cochran-Armitage test	P=0.118			
Fisher exact test		P=0.566	P=0.179	P=0.192
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	1/52 (2%)	4/49 (8%)	2/49 (4%)	2/50 (4%)
Adjusted rate	2.3%	9.3%	4.4%	4.8%
Terminal rate	1/43 (2%)	4/43 (9%)	1/44 (2%)	2/42 (5%)
First incidence (days)	736 (T)	736 (T)	718	736 (T)
Life table test	P=0.567	P=0.180	P=0.511	P=0.492
Logistic regression test	P=0.578	P=0.180	P=0.508	P=0.492
Cochran-Armitage test	P=0.562			
Fisher exact test		P=0.163	P=0.478	P=0.485
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	8/52 (15%)	11/49 (22%)	13/49 (27%)	12/50 (24%)
Adjusted rate	17.5%	25.6%	28.3%	28.6%
Terminal rate	6/43 (14%)	11/43 (26%)	11/44 (25%)	12/42 (29%)
First incidence (days)	553	736 (T)	698	736 (T)
Life table test	P=0.195	P=0.307	P=0.187	P=0.212
Logistic regression test	P=0.209	P=0.293	P=0.153	P=0.222
Cochran-Armitage test	P=0.191			
Fisher exact test		P=0.257	P=0.128	P=0.199
Pancreatic Islets: Adenoma				
Overall rate	1/52 (2%)	0/49 (0%)	3/49 (6%)	2/50 (4%)
Adjusted rate	2.3%	0.0%	6.5%	4.8%
Terminal rate	1/43 (2%)	0/43 (0%)	2/44 (5%)	2/42 (5%)
First incidence (days)	736 (T)	–	583	736 (T)
Life table test	P=0.231	P=0.500N	P=0.315	P=0.492
Logistic regression test	P=0.231	P=0.500N	P=0.272	P=0.492
Cochran-Armitage test	P=0.231			
Fisher exact test		P=0.515N	P=0.287	P=0.485

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	60 ppm	125 ppm	250 ppm
Spleen: Hemangiosarcoma				
Overall rate	4/52 (8%)	1/49 (2%)	1/49 (2%)	1/49 (2%)
Adjusted rate	9.3%	2.3%	2.3%	2.4%
Terminal rate	4/43 (9%)	1/43 (2%)	1/44 (2%)	1/42 (2%)
First incidence (days)	736 (T)	736 (T)	736 (T)	736 (T)
Life table test	P=0.140N	P=0.180N	P=0.173N	P=0.187N
Logistic regression test	P=0.140N	P=0.180N	P=0.173N	P=0.187N
Cochran-Armitage test	P=0.148N			
Fisher exact test		P=0.200N	P=0.200N	P=0.200N
All Organs: Hemangiosarcoma				
Overall rate	5/52 (10%)	2/49 (4%)	3/49 (6%)	2/50 (4%)
Adjusted rate	11.6%	4.7%	6.8%	4.7%
Terminal rate	5/43 (12%)	2/43 (5%)	3/44 (7%)	1/42 (2%)
First incidence (days)	736 (T)	736 (T)	736 (T)	731
Life table test	P=0.220N	P=0.216N	P=0.344N	P=0.227N
Logistic regression test	P=0.210N	P=0.216N	P=0.344N	P=0.212N
Cochran-Armitage test	P=0.225N			
Fisher exact test		P=0.243N	P=0.392N	P=0.235N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	6/52 (12%)	2/49 (4%)	3/49 (6%)	2/50 (4%)
Adjusted rate	14.0%	4.7%	6.8%	4.7%
Terminal rate	6/43 (14%)	2/43 (5%)	3/44 (7%)	1/42 (2%)
First incidence (days)	736 (T)	736 (T)	736 (T)	731
Life table test	P=0.140N	P=0.134N	P=0.231N	P=0.143N
Logistic regression test	P=0.132N	P=0.134N	P=0.231N	P=0.130N
Cochran-Armitage test	P=0.145N			
Fisher exact test		P=0.155N	P=0.274N	P=0.148N
All Organs: Malignant Lymphoma (Lymphocytic, Mixed, or Undifferentiated Cell Type)				
Overall rate	3/52 (6%)	3/49 (6%)	2/49 (4%)	2/50 (4%)
Adjusted rate	6.7%	7.0%	4.5%	4.8%
Terminal rate	2/43 (5%)	3/43 (7%)	2/44 (5%)	2/42 (5%)
First incidence (days)	603	736 (T)	736 (T)	736 (T)
Life table test	P=0.379N	P=0.661	P=0.492N	P=0.510N
Logistic regression test	P=0.373N	P=0.651	P=0.521N	P=0.510N
Cochran-Armitage test	P=0.383N			
Fisher exact test		P=0.632	P=0.528N	P=0.519N
All Organs: Malignant Lymphoma or Histiocytic Sarcoma				
Overall rate	3/52 (6%)	5/49 (10%)	2/49 (4%)	4/50 (8%)
Adjusted rate	6.7%	10.9%	4.5%	9.0%
Terminal rate	2/43 (5%)	3/43 (7%)	2/44 (5%)	2/42 (5%)
First incidence (days)	603	397	736 (T)	682
Life table test	P=0.535	P=0.361	P=0.492N	P=0.495
Logistic regression test	P=0.514	P=0.282	P=0.521N	P=0.487
Cochran-Armitage test	P=0.526			
Fisher exact test		P=0.325	P=0.528N	P=0.478

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	60 ppm	125 ppm	250 ppm
All Organs: Benign Neoplasms				
Overall rate	27/52 (52%)	22/49 (45%)	32/49 (65%)	32/50 (64%)
Adjusted rate	57.3%	51.2%	69.5%	71.0%
Terminal rate	23/43 (53%)	22/43 (51%)	30/44 (68%)	29/42 (69%)
First incidence (days)	40	736 (T)	583	518
Life table test	P=0.055	P=0.216N	P=0.259	P=0.188
Logistic regression test	P=0.061	P=0.254N	P=0.158	P=0.175
Cochran-Armitage test	P=0.050			
Fisher exact test		P=0.306N	P=0.123	P=0.151
All Organs: Malignant Neoplasms				
Overall rate	22/52 (42%)	22/49 (45%)	16/49 (33%)	21/50 (42%)
Adjusted rate	47.7%	45.7%	34.0%	45.7%
Terminal rate	19/43 (44%)	17/43 (40%)	13/44 (30%)	17/42 (40%)
First incidence (days)	553	397	667	676
Life table test	P=0.425N	P=0.568N	P=0.144N	P=0.531N
Logistic regression test	P=0.410N	P=0.521	P=0.148N	P=0.503N
Cochran-Armitage test	P=0.438N			
Fisher exact test		P=0.475	P=0.213N	P=0.567N
All Organs: Benign or Malignant Neoplasms				
Overall rate	38/52 (73%)	35/49 (71%)	39/49 (80%)	39/50 (78%)
Adjusted rate	77.5%	72.9%	81.3%	81.2%
Terminal rate	32/43 (74%)	30/43 (70%)	35/44 (80%)	33/42 (79%)
First incidence (days)	40	397	583	518
Life table test	P=0.308	P=0.349N	P=0.568	P=0.441
Logistic regression test	P=0.290	P=0.454N	P=0.412	P=0.440
Cochran-Armitage test	P=0.251			
Fisher exact test		P=0.515N	P=0.297	P=0.365

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, lung, pancreas, and spleen; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE C4a
Historical Incidence of Hepatocellular Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls			
	Adenoma	Carcinoma	Adenoma or Carcinoma	Hepatoblastoma
Historical Incidence at Battelle Columbus				
2,4-Dichlorophenol	4/50	7/50	10/50	0/50
4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)	17/50	11/50	25/50	0/50
5,5-Diphenylhydantoin	19/50	13/50	29/50	0/50
Dowicide EC-7 Pentachlorophenol	5/35	1/35	6/35	0/35
Ethylene Thiourea	11/49	13/49	20/49	0/49
Polybrominated Biphenyls (Firemaster FF-1®)	9/50	8/50	16/50	0/50
Manganese (II) Sulfate Monohydrate	30/50	9/50	34/50	0/50
Technical Grade Pentachlorophenol	5/32	2/32	7/32	0/32
Triamterene	17/50	5/50	20/50	0/50
Triamterene	21/50	9/50	25/50	0/50
Tricresyl Phosphate	18/52	15/52	28/52	0/52
Overall Historical Incidence				
Total	312/1,366 (22.8%)	223/1,366 (16.3%)	485/1,366 (35.5%)	0/1,366 (0.0%)
Standard deviation	13.8%	7.2%	14.3%	
Range	4%-60%	3%-29%	10%-68%	

[a] Data as of 20 August 1992

TABLE C4b
Historical Incidence of Harderian Gland Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus			
2,4-Dichlorophenol	2/50	1/50	3/50
4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)	1/50	2/50	3/50
5,5-Diphenylhydantoin	5/50	1/50	6/50
Dowicide EC-7 Pentachlorophenol	2/35	0/35	2/35
Ethylene Thiourea	1/50	0/50	1/50
Polybrominated Biphenyls (Firemaster FF-1®)	2/50	0/50	2/50
Manganese (II) Sulfate Monohydrate	4/50	1/50	5/50
Technical Grade Pentachlorophenol	1/35	0/35	1/35
Triamterene	0/50	1/50	1/50
Triamterene	1/50	0/50	1/50
Tricresyl Phosphate	0/52	1/52	1/52
Overall Historical Incidence			
Total	66/1,374 (4.8%)	8/1,374 (0.6%)	74/1,374 (5.4%)
Standard deviation	4.3%	1.1%	4.5%
Range	0%-18%	0%-4%	0%-20%

[a] Data as of 20 August 1992

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Tricresyl Phosphate[a]

	0 ppm	60 ppm	125 ppm	250 ppm
Disposition Summary				
Animals initially in study	95	95	95	95
3-Month interim evaluation[b]	13	15	15	15
9-Month interim evaluation[b]	15	15	15	15
15-Month interim evaluation[b]	15	15	15	15
Early deaths				
Accidental deaths	1			
Moribund	4	1	1	2
Natural deaths	4	5	4	6
Survivors				
Terminal sacrifice	43	43	44	42
Missing		1	1	
Animals examined microscopically	95	94	94	95
3-Month Interim Evaluation				
Endocrine System				
Adrenal cortex	(8)	(10)	(10)	(10)
Accessory adrenal cortical nodule			1 (10%)	1 (10%)
Pigmentation, ceroid		3 (30%)	3 (30%)	6 (60%)
Subcapsular, hyperplasia	2 (25%)	4 (40%)	5 (50%)	3 (30%)
Adrenal medulla	(8)	(10)	(10)	(9)
Hyperplasia				1 (11%)
Pituitary gland	(8)	(10)	(9)	(9)
Pars distalis, hyperplasia	1 (13%)			
Hematopoietic System				
Thymus	(8)	(10)	(10)	(10)
Necrosis			1 (10%)	
Nervous System				
Brain	(8)	(10)	(10)	(10)
Infiltration cellular, lipocyte	1 (13%)			
Respiratory System				
Lung	(8)	(10)	(10)	(10)
Inflammation, chronic active			2 (20%)	
Urinary System				
Kidney	(8)	(10)	(10)	(10)
Nephropathy				1 (10%)

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] Includes up to five animals per dose group subjected to total body perfusion for special neuropathology

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	60 ppm	125 ppm	250 ppm
3-Month Interim Evaluation (continued)				
Systems Examined No Lesions Observed				
Alimentary System				
Cardiovascular System				
General Body System				
Genital System				
Integumentary System				
Musculoskeletal System				
Special Senses System				
9-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Clear cell focus			1 (10%)	
Necrosis				2 (20%)
Pigmentation, ceroid				1 (10%)
Pancreas	(10)	(10)	(10)	(10)
Atrophy		3 (30%)		
Cyst	1 (10%)			
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Hyperplasia			1 (10%)	
Pigmentation, ceroid	10 (100%)	10 (100%)	10 (100%)	10 (100%)
Subcapsular, hyperplasia	8 (80%)	4 (40%)	5 (50%)	7 (70%)
Integumentary System				
Skin	(10)	(10)	(10)	(10)
Inflammation, chronic active				1 (10%)
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Nephropathy	4 (40%)	5 (50%)	3 (30%)	4 (40%)
Systems Examined With No Lesions Observed				
Cardiovascular System				
General Body System				
Genital System				
Hematopoietic System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Tricresyl Phosphate
(continued)

	0 ppm	60 ppm	125 ppm	250 ppm
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Basophilic focus		1 (10%)	1 (10%)	
Clear cell focus		1 (10%)		
Eosinophilic focus	1 (10%)	1 (10%)	1 (10%)	
Fatty change	1 (10%)	3 (30%)	5 (50%)	5 (50%)
Necrosis			1 (10%)	
Pigmentation, ceroid			4 (40%)	2 (20%)
Pancreas	(10)	(10)	(10)	(10)
Atrophy		1 (10%)	1 (10%)	
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule		1 (10%)		1 (10%)
Hyperplasia			1 (10%)	1 (10%)
Pigmentation, ceroid	10 (100%)	10 (100%)	10 (100%)	10 (100%)
Subcapsular, hyperplasia	8 (80%)	10 (100%)	9 (90%)	7 (70%)
Islets, pancreatic	(10)	(10)	(10)	(10)
Hyperplasia	1 (10%)	1 (10%)		3 (30%)
Parathyroid gland	(8)	(8)	(10)	(9)
Cyst			1 (10%)	
Pituitary gland	(10)	(10)	(10)	(9)
Cyst	1 (10%)			
Genital System				
Preputial gland	(5)	(9)	(5)	(4)
Duct, dilatation	5 (100%)	9 (100%)	5 (100%)	4 (100%)
Hematopoietic System				
Thymus	(10)	(10)	(9)	(10)
Cyst	1 (10%)			
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Inflammation, chronic active			1 (10%)	
Bronchiole, hyperplasia			1 (10%)	1 (10%)
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Nephropathy	10 (100%)	10 (100%)	10 (100%)	9 (90%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	60 ppm	125 ppm	250 ppm
15-Month Interim Evaluation (continued)				
Systems Examined With No Lesions Observed				
Cardiovascular System				
General Body System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
2-Year Study				
Alimentary System				
Esophagus	(52)	(49)	(49)	(50)
Inflammation	1 (2%)			
Gallbladder	(51)	(47)	(47)	(48)
Hyperplasia	1 (2%)			
Intestine small, duodenum	(52)	(49)	(49)	(50)
Thrombosis		1 (2%)		
Intestine small, jejunum	(51)	(49)	(49)	(50)
Serosa, fibrosis				1 (2%)
Liver	(52)	(49)	(49)	(50)
Angiectasis	1 (2%)			
Basophilic focus	1 (2%)	2 (4%)	4 (8%)	
Clear cell focus	5 (10%)	8 (16%)	17 (35%)	12 (24%)
Eosinophilic focus	6 (12%)	3 (6%)	9 (18%)	5 (10%)
Erythrophagocytosis				1 (2%)
Fatty change	6 (12%)	10 (20%)	23 (47%)	22 (44%)
Hematopoietic cell proliferation		1 (2%)		
Mixed cell focus	1 (2%)		2 (4%)	
Necrosis	2 (4%)	2 (4%)	2 (4%)	2 (4%)
Pigmentation, ceroid			30 (61%)	28 (56%)
Vacuolization cytoplasmic, focal	1 (2%)			
Bile duct, cyst		1 (2%)		
Bile duct, hyperplasia	1 (2%)			
Serosa, inflammation	1 (2%)			
Mesentery			(2)	(2)
Inflammation, chronic active			1 (50%)	
Fat, necrosis			1 (50%)	2 (100%)
Pancreas	(52)	(49)	(49)	(50)
Atrophy	3 (6%)	1 (2%)	2 (4%)	1 (2%)
Duct, cyst	1 (2%)		1 (2%)	
Salivary glands	(52)	(49)	(49)	(50)
Duct, hyperplasia	1 (2%)			
Stomach, forestomach	(52)	(49)	(49)	(50)
Hyperplasia	2 (4%)	1 (2%)		1 (2%)
Stomach, glandular	(52)	(49)	(49)	(50)
Erosion	1 (2%)			1 (2%)
Hyperplasia	1 (2%)	1 (2%)		
Tooth	(3)	(3)	(2)	(1)
Inflammation, chronic active	1 (33%)	1 (33%)		

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	60 ppm	125 ppm	250 ppm
2-Year Study (continued)				
Cardiovascular System				
Blood vessel	(1)			
Polyarteritis	1 (100%)			
Heart	(52)	(49)	(49)	(50)
Inflammation, chronic active			3 (6%)	1 (2%)
Mineralization			2 (4%)	2 (4%)
Artery, inflammation, chronic active		1 (2%)		
Atrium, thrombosis	1 (2%)			
Endocrine System				
Adrenal cortex	(52)	(49)	(49)	(50)
Accessory adrenal cortical nodule	2 (4%)	1 (2%)	2 (4%)	2 (4%)
Hyperplasia	26 (50%)	23 (47%)	29 (59%)	25 (50%)
Pigmentation, ceroid	48 (92%)	47 (96%)	49 (100%)	49 (98%)
Subcapsular, hyperplasia	44 (85%)	46 (94%)	45 (92%)	44 (88%)
Adrenal medulla	(52)	(49)	(49)	(49)
Hyperplasia	3 (6%)	1 (2%)		1 (2%)
Islets, pancreatic	(52)	(49)	(49)	(50)
Hyperplasia	8 (15%)	10 (20%)	10 (20%)	12 (24%)
Pituitary gland	(50)	(49)	(45)	(46)
Cyst	3 (6%)	2 (4%)		4 (9%)
Pars distalis, hyperplasia	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Thyroid gland	(52)	(49)	(49)	(50)
Follicle, cyst		1 (2%)	1 (2%)	1 (2%)
Follicular cell, hyperplasia			1 (2%)	1 (2%)
General Body System				
None				
Genital System				
Epididymis	(52)	(49)	(49)	(50)
Atrophy	1 (2%)			
Granuloma sperm			4 (8%)	
Inflammation, chronic active	2 (4%)			
Inflammation, granulomatous				2 (4%)
Preputial gland	(40)	(30)	(41)	(41)
Atrophy				1 (2%)
Inflammation, granulomatous			1 (2%)	
Inflammation, suppurative	6 (15%)	4 (13%)	3 (7%)	3 (7%)
Duct, dilatation	39 (98%)	29 (97%)	40 (98%)	40 (98%)
Prostate	(52)	(49)	(49)	(50)
Inflammation, suppurative	1 (2%)			
Seminal vesicle	(52)	(49)	(49)	(50)
Dilatation			1 (2%)	
Hemorrhage, acute			1 (2%)	
Inflammation, chronic active	1 (2%)		2 (4%)	
Testes	(52)	(49)	(49)	(50)
Atrophy	1 (2%)		2 (4%)	3 (6%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Tricresyl Phosphate
(continued)

	0 ppm	60 ppm	125 ppm	250 ppm
2-Year Study (continued)				
Hematopoietic System				
Bone marrow	(52)	(49)	(49)	(50)
Granuloma	1 (2%)			1 (2%)
Hyperplasia	7 (13%)	10 (20%)	9 (18%)	8 (16%)
Myelofibrosis			1 (2%)	
Lymph node	(1)	(2)	(1)	
Inguinal, hyperplasia, lymphoid	1 (100%)			
Lymph node, mandibular	(51)	(46)	(43)	(46)
Depletion lymphoid	1 (2%)			
Hematopoietic cell proliferation				2 (4%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Lymph node, mesenteric	(50)	(47)	(46)	(47)
Cyst	1 (2%)			
Hematopoietic cell proliferation	1 (2%)	1 (2%)		2 (4%)
Hyperplasia, lymphoid	1 (2%)			
Spleen	(52)	(49)	(49)	(49)
Angiectasis			2 (4%)	1 (2%)
Depletion lymphoid	5 (10%)		4 (8%)	2 (4%)
Hematocyst		1 (2%)		
Hematopoietic cell proliferation	15 (29%)	19 (39%)	15 (31%)	18 (37%)
Hyperplasia, lymphoid	1 (2%)		1 (2%)	2 (4%)
Thymus	(45)	(42)	(45)	(45)
Atrophy				2 (4%)
Depletion lymphoid	4 (9%)	3 (7%)	3 (7%)	9 (20%)
Hyperplasia, lymphoid	1 (2%)			
Epithelial cell, hyperplasia				1 (2%)
Integumentary System				
Skin	(52)	(49)	(49)	(50)
Abscess	1 (2%)			
Cyst epithelial inclusion		1 (2%)		1 (2%)
Granuloma	1 (2%)			
Hemorrhage	1 (2%)			
Inflammation, chronic active		1 (2%)		
Ulcer		1 (2%)	1 (2%)	
Musculoskeletal System				
None				
Nervous System				
Brain	(52)	(49)	(49)	(50)
Necrosis	1 (2%)	1 (2%)	1 (2%)	
Peripheral nerve	(52)	(49)	(49)	(50)
Axon, degeneration	4 (8%)	2 (4%)	3 (6%)	3 (6%)
Spinal cord	(52)	(49)	(49)	(50)
Cyst				1 (2%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Tricresyl Phosphate
(continued)

	0 ppm	60 ppm	125 ppm	250 ppm
2-Year Study (continued)				
Respiratory System				
Lung	(52)	(49)	(49)	(50)
Inflammation, chronic active	1 (2%)		3 (6%)	
Thrombosis			1 (2%)	
Alveolar epithelium, hyperplasia	3 (6%)	5 (10%)	2 (4%)	2 (4%)
Alveolus, pigmentation, hemosiderin	1 (2%)			
Nose	(52)	(49)	(49)	(50)
Developmental malformation				1 (2%)
Proliferation connective tissue	1 (2%)			
Nasolacrimal duct, inflammation			1 (2%)	2 (4%)
Respiratory epithelium, inflammation	1 (2%)		1 (2%)	
Special Senses System				
Eye	(1)	(1)		(1)
Atrophy				1 (100%)
Cornea, inflammation	1 (100%)	1 (100%)		
Harderian gland	(43)	(40)	(37)	(37)
Hyperplasia	2 (5%)	1 (3%)		
Inflammation, chronic active			1 (3%)	1 (3%)
Urinary System				
Kidney	(52)	(49)	(49)	(50)
Cyst	2 (4%)	5 (10%)	3 (6%)	1 (2%)
Hydronephrosis			1 (2%)	1 (2%)
Infarct	2 (4%)		1 (2%)	1 (2%)
Inflammation, suppurative	2 (4%)			
Nephropathy	47 (90%)	47 (96%)	49 (100%)	45 (90%)
Artery, inflammation, chronic active	1 (2%)			
Renal tubule, necrosis				1 (2%)
Urinary bladder	(52)	(49)	(49)	(49)
Inflammation, suppurative	2 (4%)			

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR FEED STUDY OF TRICRESYL PHOSPHATE

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TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Tricresyl Phosphate[a]

	0 ppm	60 ppm	125 ppm	250 ppm
Disposition Summary				
Animals initially in study	95	95	95	95
3-Month interim evaluation[b]	15	15	15	15
9-Month interim evaluation[b]	15	15	15	15
15-Month interim evaluation[b]	15	15	15	14
Early deaths				
Moribund	4	5	4	3
Natural deaths	5	7	2	3
Survivors				
Died last week of study	1	1		
Terminal sacrifice	40	37	42	45
Missing			2	
Animals examined microscopically	95	95	93	95
Systems Examined at 3 and 9 Months With No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(9)
Hepatocellular adenoma	1 (10%)	2 (20%)		1 (11%)
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(9)
Subcapsular, adenoma	1 (10%)			
Respiratory System				
Lung	(10)	(10)	(10)	(9)
Alveolar/bronchiolar adenoma			1 (10%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	60 ppm	125 ppm	250 ppm
15-Month Interim Evaluation (continued)				
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Urinary System				
2-Year Study				
Alimentary System				
Gallbladder	(49)	(48)	(47)	(51)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Intestine large, rectum	(50)	(48)	(48)	(51)
Osteosarcoma, metastatic, bone				1 (2%)
Intestine small, jejunum	(49)	(50)	(48)	(51)
Liver	(50)	(50)	(48)	(51)
Hemangiosarcoma, metastatic, spleen		1 (2%)		
Hepatocellular carcinoma	9 (18%)	2 (4%)	1 (2%)	5 (10%)
Hepatocellular carcinoma, multiple	1 (2%)	1 (2%)		1 (2%)
Hepatocellular adenoma	7 (14%)	10 (20%)	10 (21%)	7 (14%)
Hepatocellular adenoma, multiple	5 (10%)	1 (2%)	3 (6%)	8 (16%)
Hepatocholangiocarcinoma		1 (2%)		
Histiocytic sarcoma		2 (4%)	1 (2%)	
Mesentery	(5)	(5)	(6)	(3)
Fibrosarcoma, metastatic, skin	1 (20%)	1 (20%)		
Pancreas	(50)	(50)	(48)	(51)
Salivary glands	(49)	(50)	(48)	(51)
Stomach, forestomach	(50)	(50)	(48)	(51)
Squamous cell papilloma		1 (2%)		
Cardiovascular System				
Heart	(50)	(50)	(48)	(51)
Hemangiosarcoma	1 (2%)			
Histiocytic sarcoma		1 (2%)		
Endocrine System				
Adrenal cortex	(50)	(49)	(48)	(51)
Adenoma	1 (2%)			1 (2%)
Subcapsular, adenoma	2 (4%)			
Adrenal medulla	(50)	(49)	(48)	(51)
Pheochromocytoma benign	2 (4%)		1 (2%)	
Islets, pancreatic	(50)	(50)	(48)	(51)
Carcinoma	1 (2%)			
Parathyroid gland	(46)	(42)	(43)	(44)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	60 ppm	125 ppm	250 ppm
2-Year Study (continued)				
Endocrine System (continued)				
Pituitary gland	(46)	(46)	(46)	(50)
Pars distalis, adenoma	6 (13%)	8 (17%)	6 (13%)	9 (18%)
Pars intermedia, adenoma		1 (2%)		2 (4%)
Thyroid gland	(49)	(50)	(48)	(51)
Follicular cell, adenoma	1 (2%)		1 (2%)	
General Body System				
Tissue NOS	(1)			
Leiomyoma	1 (100%)			
Genital System				
Ovary	(48)	(50)	(47)	(50)
Cystadenoma			1 (2%)	2 (4%)
Fibrous histiocytoma				1 (2%)
Granulosa cell tumor malignant	1 (2%)			
Hemangioma			1 (2%)	
Histiocytic sarcoma		1 (2%)		
Luteoma		1 (2%)		
Teratoma NOS	1 (2%)			
Uterus	(50)	(50)	(48)	(51)
Hemangioma			1 (2%)	
Histiocytic sarcoma	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Polyp stromal	1 (2%)	1 (2%)	3 (6%)	
Polyp stromal, multiple	1 (2%)			
Serosa, fibrosarcoma, metastatic, skin	1 (2%)			
Hematopoietic System				
Blood				(1)
Bone marrow	(50)	(50)	(48)	(51)
Osteosarcoma, metastatic, bone				1 (2%)
Sarcoma				1 (2%)
Lymph node	(3)	(4)	(3)	
Lumbar, renal, thoracic, iliac, bronchial, mediastinal, lymphoma malignant mixed		1 (33%)		
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung	1 (33%)			
Mediastinal, histiocytic sarcoma		1 (25%)		
Pancreatic, hepatocholangiocarcinoma, metastatic, liver		1 (25%)		
Renal, histiocytic sarcoma			1 (33%)	
Lymph node, mandibular	(46)	(47)	(48)	(47)
Histiocytic sarcoma		1 (2%)	1 (2%)	
Lymph node, mesenteric	(49)	(46)	(45)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma		2 (4%)	1 (2%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	60 ppm	125 ppm	250 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Spleen	(50)	(50)	(48)	(51)
Hemangioma			1 (2%)	
Hemangiosarcoma	3 (6%)	1 (2%)	1 (2%)	1 (2%)
Histiocytic sarcoma		2 (4%)	2 (4%)	
Thymus	(45)	(44)	(47)	(46)
Histiocytic sarcoma			1 (2%)	
Thymoma malignant			1 (2%)	
Integumentary System				
Mammary gland	(49)	(50)	(47)	(51)
Adenocarcinoma				1 (2%)
Skin	(50)	(50)	(48)	(51)
Fibrosarcoma	2 (4%)	1 (2%)	1 (2%)	
Hemangioma			1 (2%)	
Sarcoma				1 (2%)
Subcutaneous tissue, myxosarcoma		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(48)	(51)
Vertebra, osteosarcoma				1 (2%)
Skeletal muscle	(2)		(1)	
Fibrosarcoma, multiple, metastatic, skin	1 (50%)			
Sarcoma	1 (50%)			
Nervous System				
Brain	(50)	(50)	(48)	(51)
Meninges, myxosarcoma, metastatic, skin		1 (2%)		
Respiratory System				
Lung	(50)	(50)	(48)	(51)
Adenocarcinoma, metastatic, harderian gland	1 (2%)			
Alveolar/bronchiolar adenoma	2 (4%)	4 (8%)	2 (4%)	5 (10%)
Alveolar/bronchiolar adenoma, multiple			1 (2%)	
Alveolar/bronchiolar carcinoma	3 (6%)	1 (2%)	2 (4%)	1 (2%)
Alveolar/bronchiolar carcinoma, multiple	1 (2%)			
Fibrosarcoma, metastatic, skin	2 (4%)			
Hepatocellular carcinoma, metastatic, liver	5 (10%)	1 (2%)	1 (2%)	2 (4%)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma		2 (4%)	1 (2%)	
Osteosarcoma, multiple, metastatic, bone				1 (2%)
Special Senses System				
Ear			(2)	
Pinna, fibrosarcoma			1 (50%)	
Harderian gland	(47)	(38)	(29)	(36)
Adenocarcinoma			1 (3%)	
Adenoma	5 (11%)	3 (8%)		

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	60 ppm	125 ppm	250 ppm
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(50)	(48)	(51)
Renal tubule, adenoma	1 (2%)			
Urinary bladder	(49)	(50)	(47)	(51)
Systemic Lesions				
Multiple organs[c]	(50)	(50)	(48)	(51)
Histiocytic sarcoma	1 (2%)	3 (6%)	2 (4%)	1 (2%)
Leukemia lymphocytic				1 (2%)
Lymphoma malignant lymphocytic		3 (6%)	3 (6%)	3 (6%)
Lymphoma malignant mixed	3 (6%)		2 (4%)	3 (6%)
Lymphoma malignant undifferentiated cell	1 (2%)	3 (6%)	1 (2%)	
Neoplasm Summary				
Total animals with primary neoplasms[d]				
15-Month interim evaluation	1	2	1	1
2-Year study	40	39	32	41
Total primary neoplasms				
15-Month interim evaluation	2	2	1	1
2-Year study	64	47	48	55
Total animals with benign neoplasms				
15-Month interim evaluation	1	2	1	1
2-Year study	27	29	24	31
Total benign neoplasms				
15-Month interim evaluation	2	2	1	1
2-Year study	35	30	32	34
Total animals with malignant neoplasms				
2-Year study	22	16	15	19
Total malignant neoplasms				
2-Year study	28	17	16	21
Total animals with metastatic neoplasms				
2-Year study	9	5	1	3
Total metastatic neoplasm				
2-Year study	13	8	1	5
Total animals with neoplasms uncertain-benign or malignant				
2-Year study	1			
Total uncertain neoplasms				
2-Year study	1			

[a] Number of animals examined microscopically at site and number of animals with neoplam
[b] Includes up to five animals per dose group subjected to total body perfusion for special neuropathology
[c] Number of animals with any tissue examined microscopically
[d] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Tricresyl Phosphate: 0 ppm

Number of Days on Study	4 2 5	5 2 3	5 3 8	5 6 0	6 4 5	6 7 7	6 9 4	6 9 8	7 1 2	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0
Carcass ID Number	6 1 7	6 3 7	6 3 6	6 2 2	6 3 3	6 0 1	6 1 0	5 9 4	5 9 3	5 9 1	5 9 2	5 9 5	5 9 6	5 9 7	5 9 8	5 9 9	6 0 0	6 0 2	6 0 3	6 0 4	6 0 5	6 0 6	6 0 7	6 0 8	6 0 9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma			X									X													
Hepatocellular carcinoma, multiple					X																				
Hepatocellular adenoma				X							X		X												X
Hepatocellular adenoma, multiple										X							X		X						
Mesentery									+	+										+					
Fibrosarcoma, metastatic, skin																				X					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel									+																
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X											
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Subcapsular, adenoma																	X								
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign														X											
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Parathyroid gland	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X												X					X		
Thyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma		X																							
General Body System																									
Tissue NOS																									
Leiomyoma																									

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Tricresyl Phosphate: 0 ppm
(continued)

Number of Days on Study	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	
Carcass ID Number	6 1 1	6 1 2	6 1 3	6 1 4	6 1 5	6 1 6	6 1 8	6 1 9	6 2 0	6 2 1	6 2 3	6 2 4	6 2 5	6 2 6	6 2 7	6 2 8	6 2 9	6 3 0	6 3 1	6 3 2	6 3 4	6 3 5	6 3 8	6 3 9	6 4 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma					X					X				X		X		X			X					9
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma						X	X		X																	7
Hepatocellular adenoma, multiple													X			X										5
Mesentery													+					+								5
Fibrosarcoma, metastatic, skin																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma														X												1
Subcapsular, adenoma																	X									2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign							X																			2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma													X													1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pars distalis, adenoma		X					X		X																	6
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma																										1
General Body System																										
Tissue NOS		+																								1
Leiomyoma		X																								1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Tricresyl Phosphate: 0 ppm
(continued)

Number of Days on Study	4 2 5	5 2 3	5 3 8	5 6 0	6 4 5	6 7 7	6 9 4	6 9 8	7 1 2	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0
Carcass ID Number	6 1 7	6 3 7	6 3 6	6 2 2	6 3 3	6 0 1	6 1 0	5 9 4	5 9 3	5 9 1	5 9 2	5 9 5	5 9 6	5 9 7	5 9 8	5 9 9	6 0 0	6 0 2	6 0 3	6 0 4	6 0 5	6 0 6	6 0 7	6 0 8	6 0 9
Genital System																									
Ovary	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Granulosa cell tumor malignant																									
Teratoma NOS	X																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Polyp stromal																									
Polyp stromal, multiple																									
Serosa, fibrosarcoma, metastatic, skin																				X					
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+					+							+										
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung			X																						
Lymph node, mandibular	+	+	+	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung			X																						
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma												X													
Thymus	M	+	+	+	+	M	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma						X														X					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle							+													+					
Fibrosarcoma, multiple, metastatic, skin																				X					
Sarcoma							X																		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, harderian gland																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Tricresyl Phosphate: 0 ppm
(continued)

Number of Days on Study	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	
Carcass ID Number	6 1 1	6 1 2	6 1 3	6 1 4	6 1 5	6 1 6	6 1 8	6 1 9	6 2 0	6 2 1	6 2 3	6 2 4	6 2 5	6 2 6	6 2 7	6 2 8	6 2 9	6 3 0	6 3 1	6 3 2	6 3 4	6 3 5	6 3 8	6 3 9	6 4 0	Total Tissues/ Tumors
Genital System																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Granulosa cell tumor malignant																						X				1
Teratoma NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																				X						1
Polyp stromal														X												1
Polyp stromal, multiple	X																									1
Serosa, fibrosarcoma, metastatic, skin																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										3
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma												X										X				3
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	45
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Fibrosarcoma, multiple, metastatic, skin																										1
Sarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, harderian gland																		X								1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Tricresyl Phosphate: 0 ppm
(continued)

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Tricresyl Phosphate: 0 ppm
(continued)

Number of Days on Study	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	
Carcass ID Number	6 1 1	6 1 2	6 1 3	6 1 4	6 1 5	6 1 6	6 1 8	6 1 9	6 2 0	6 2 1	6 2 3	6 2 4	6 2 5	6 2 6	6 2 7	6 2 8	6 2 9	6 3 0	6 3 1	6 3 2	6 3 4	6 3 5	6 3 8	6 3 9	6 4 0	Total Tissues/ Tumors
Respiratory System (continued)																										
Lung (continued)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X					X																		2
Alveolar/bronchiolar carcinoma			X									X								X						3
Alveolar/bronchiolar carcinoma, multiple																										1
Fibrosarcoma, metastatic, skin																										2
Hepatocellular carcinoma, metastatic, liver					X					X						X							X			5
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye																										1
Harderian gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	47
Adenoma												X					X	X								5
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																				X						1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																				X						1
Lymphoma malignant mixed																										3
Lymphoma malignant undifferentiated cell type																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Tricresyl Phosphate: 60 ppm

Number of Days on Study	4 1 3	4 5 4	5 6 1	5 7 1	6 0 3	6 4 5	6 5 2	6 7 4	6 7 7	6 8 9	6 9 6	7 0 0	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8
Carcass ID Number	6 7 9	6 4 1	6 5 9	6 8 1	6 9 0	6 8 6	6 8 4	6 4 8	6 4 7	6 6 5	6 8 3	6 7 1	6 4 2	6 4 3	6 4 4	6 4 5	6 4 6	6 4 9	6 5 0	6 5 1	6 5 2	6 5 3	6 5 4	6 5 5	6 5 6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen							X																		
Hepatocellular carcinoma			X																X						
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma								X					X			X								X	
Hepatocellular adenoma, multiple																									
Hepatocholangiocarcinoma																									
Histiocytic sarcoma				X						X															
Mesentery				+	+				+																
Fibrosarcoma, metastatic, skin									X																
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma									X																
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																							+		
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X			X													X						X
Pars intermedia, adenoma						X																			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Tricresyl Phosphate: 60 ppm
(continued)

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	6 5 7	6 5 8	6 6 2	6 6 0	6 6 1	6 6 3	6 6 4	6 6 6	6 6 7	6 6 8	6 6 9	6 7 0	6 7 2	6 7 3	6 7 4	6 7 5	6 7 6	6 7 7	6 7 8	6 8 0	6 8 2	6 8 5	6 8 7	6 8 8	6 8 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocholangiocarcinoma, metastatic, liver															X											1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, spleen																										1
Hepatocellular carcinoma																										2
Hepatocellular carcinoma, multiple																X										1
Hepatocellular adenoma				X	X	X				X									X					X		10
Hepatocellular adenoma, multiple																					X					1
Hepatocholangiocarcinoma															X											1
Histiocytic sarcoma																										2
Mesentery	+		+																							5
Fibrosarcoma, metastatic, skin																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	M	+	+	M	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	M	+	+	+	M	+	+	+	46
Pars distalis, adenoma	X	X							X			X														8
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Tricresyl Phosphate: 60 ppm
(continued)

Number of Days on Study	4 1 3	4 5 4	5 6 1	5 7 1	6 0 3	6 4 5	6 5 2	6 7 4	6 7 7	6 8 9	6 9 6	7 0 0	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8
Carcass ID Number	6 7 9	6 4 1	6 5 9	6 8 1	6 9 0	6 8 6	6 8 4	6 4 8	6 4 7	6 6 5	6 8 3	6 7 1	6 4 2	6 4 3	6 4 4	6 4 5	6 4 6	6 4 9	6 5 0	6 5 1	6 5 2	6 5 3	6 5 4	6 5 5	6 5 6
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Luteoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X		X																			
Polyp stromal																					X				
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node										+								+							
Mediastinal, histiocytic sarcoma										X															
Pancreatic, hepatocholangiocarcinoma, metastatic, liver																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Histiocytic sarcoma				X						X															
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma							X																		
Histiocytic sarcoma				X						X															
Thymus	+	+	M	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma									X																
Subcutaneous tissue, myxosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meninges, myxosarcoma, metastatic, skin																									
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																							X		
Alveolar/bronchiolar carcinoma																									
Hepatocellular carcinoma, metastatic, liver																			X						
Hepatocholangiocarcinoma, metastatic, liver																									
Histiocytic sarcoma				X						X															

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Tricresyl Phosphate: 60 ppm
(continued)

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	6 5 7	6 5 8	6 6 2	6 6 0	6 6 1	6 6 3	6 6 4	6 6 6	6 6 7	6 6 8	6 6 9	6 7 0	6 7 2	6 7 3	6 7 4	6 7 5	6 7 6	6 7 7	6 7 8	6 8 0	6 8 2	6 8 5	6 8 7	6 8 8	6 8 9	Total Tissues/ Tumors
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																									1
Luteoma																						X			1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																									2
Polyp stromal																									1
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+														+										4
Mediastinal, histiocytic sarcoma																									1
Pancreatic, hepatocholangiocarcinoma, metastatic, liver															X										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																									1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+	46
Hepatocholangiocarcinoma, metastatic, liver															X										1
Histiocytic sarcoma																									2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																									1
Histiocytic sarcoma																									2
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	44
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																									1
Subcutaneous tissue, myxosarcoma																X									1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Meninges, myxosarcoma, metastatic, skin																X									1
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma													X		X									X	4
Alveolar/bronchiolar carcinoma			X																						1
Hepatocellular carcinoma, metastatic, liver																									1
Hepatocholangiocarcinoma, metastatic, liver															X										1
Histiocytic sarcoma																									2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Tricresyl Phosphate: 60 ppm
(continued)

Number of Days on Study	4	4	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	1	5	6	7	0	4	5	7	7	8	9	0	3	3	3	3	3	3	3	3	3	3	3	3	3	
	3	4	1	1	3	5	2	4	7	9	6	0	8	8	8	8	8	8	8	8	8	8	8	8	8	
Carcass ID Number	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	
	7	4	5	8	9	8	8	4	4	6	8	7	4	4	4	4	4	4	5	5	5	5	5	5	5	
	9	1	9	1	0	6	4	8	7	5	3	1	2	3	4	5	6	9	0	1	2	3	4	5	6	
Respiratory System (continued)																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Special Senses System																										
Harderian gland	M	+	M	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+	M	M	+	+	M	M	
Adenoma					X																	X				
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Histiocytic sarcoma				X		X				X																
Lymphoma malignant lymphocytic												X					X									
Lymphoma malignant undifferentiated cell type														X				X								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Tricresyl Phosphate: 60 ppm
(continued)

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	6 5 7	6 5 8	6 6 2	6 6 0	6 6 1	6 6 3	6 6 4	6 6 6	6 6 7	6 6 8	6 6 9	6 7 0	6 7 2	6 7 3	6 7 4	6 7 5	6 7 6	6 7 7	6 7 8	6 8 0	6 8 2	6 8 5	6 8 7	6 8 8	6 8 9	Total Tissues/ Tumors
Respiratory System (continued)																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																									
Harderian gland	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	38
Adenoma							X																		3
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																									3
Lymphoma malignant lymphocytic	X																								3
Lymphoma malignant undifferentiated cell type																X									3

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Tricresyl Phosphate: 125 ppm

Number of Days on Study	2 8 3	6 0 7	6 2 1	6 5 3	7 2 3	7 3 0	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7
Carcass ID Number	7 0 8	7 1 4	7 3 1	7 3 2	7 2 8	6 9 5	6 9 1	6 9 2	6 9 3	6 9 4	6 9 6	6 9 7	6 9 8	6 9 9	7 0 0	7 0 1	7 0 2	7 0 3	7 0 4	7 0 5	7 0 6	7 0 7	7 0 9	
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hepatocellular carcinoma			X																					
Hepatocellular adenoma								X			X								X	X		X	X	
Hepatocellular adenoma, multiple														X				X						
Histiocytic sarcoma				X																				
Mesentery					+	+												+		+	+			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Cardiovascular System																								
Blood vessel	+																							
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Pheochromocytoma benign			X																					
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Parathyroid gland	+	+	+	+	+	+	M	+	M	+	+	+	M	+	+	+	+	+	M	+	+	+	+	
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Pars distalis, adenoma											X													
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Follicular cell, adenoma																								
General Body System																								
None																								
Genital System																								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Cystadenoma												X												
Hemangioma															X									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hemangioma																								
Histiocytic sarcoma																								
Polyp stromal																								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Tricresyl Phosphate: 125 ppm
(continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	7 1 1	7 1 2	7 1 3	7 1 5	7 1 6	7 1 7	7 1 8	7 1 9	7 2 0	7 2 1	7 2 2	7 2 3	7 2 4	7 2 5	7 2 6	7 2 7	7 2 9	7 3 0	7 3 3	7 3 4	7 3 5	7 3 6	7 3 7	7 3 8	7 4 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular carcinoma																										1
Hepatocellular adenoma								X				X							X			X				10
Hepatocellular adenoma, multiple																					X					3
Histiocytic sarcoma																										1
Mesentery	+																									6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	46
Pars distalis, adenoma								X									X				X		X		X	6
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell, adenoma		X																								1
General Body System																										
None																										
Genital System																										
Ovary	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Cystadenoma																										1
Hemangioma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangioma											X															1
Histiocytic sarcoma						X																				1
Polyp stromal											X			X								X				3

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Tricresyl Phosphate: 125 ppm
(continued)

Number of Days on Study	2 8 3	6 0 7	6 2 1	6 5 3	7 2 3	7 3 0	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7
Carcass ID Number	7 0 8	7 1 4	7 3 1	7 3 2	7 2 8	6 9 5	6 9 1	6 9 2	6 9 3	6 9 4	6 9 6	6 9 7	6 9 8	6 9 9	7 0 0	7 0 1	7 0 2	7 0 3	7 0 4	7 0 5	7 0 6	7 0 7	7 0 9
Hematopoietic System																							
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+		+		+																	
Lumbar, renal, thoracic, iliac, Renal, histiocytic sarcoma				X																			
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																			
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																			
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																							
Hemangiosarcoma																							
Histiocytic sarcoma				X																			
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																			
Thymoma malignant																		X					
Integumentary System																							
Mammary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																			X				
Hemangioma																							
Musculoskeletal System																							
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																							
Nervous System																							
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																							
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																							
Alveolar/bronchiolar adenoma, multiple								X															
Alveolar/bronchiolar carcinoma					X																		
Hepatocellular carcinoma, metastatic, liver			X																				
Histiocytic sarcoma				X																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Tricresyl Phosphate: 125 ppm
(continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	7 1 1	7 1 2	7 1 3	7 1 5	7 1 6	7 1 7	7 1 8	7 1 9	7 2 0	7 2 1	7 2 2	7 2 3	7 2 4	7 2 5	7 2 6	7 2 7	7 2 9	7 3 0	7 3 3	7 3 4	7 3 5	7 3 6	7 3 7	7 3 8	7 4 0	Total Tissues/ Tumors
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node																									3
Lumbar, renal, thoracic, iliac,																									
Renal, histiocytic sarcoma																									1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																									1
Lymph node, mesenteric	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	45
Histiocytic sarcoma																									1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangioma					X																				1
Hemangiosarcoma																X									1
Histiocytic sarcoma						X																			2
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																									1
Thymoma malignant																									1
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrosarcoma																									1
Hemangioma																		X							1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Skeletal muscle		+																							1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar adenoma																					X			X	2
Alveolar/bronchiolar adenoma, multiple																									1
Alveolar/bronchiolar carcinoma																				X					2
Hepatocellular carcinoma, metastatic, liver																									1
Histiocytic sarcoma																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Tricresyl Phosphate: 125 ppm
(continued)

Number of Days on Study	26837	26071	26213	26533	27233	27300	27337	27337	27337	27337	27337	27337	27337	27337	27337	27337	27337	27337	27337	27337	27337	27337	27337	27337
Carcass ID Number	70818	70144	70413	70432	70428	69605	69911	69923	69934	69946	69967	69978	69989	70090	70001	70012	70023	70034	70045	70056	70067	70078	70089	70090
Special Senses System																								
Ear	+															+								
Pinna, fibrosarcoma																X								
Harderian gland	+	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+	M	M	M	M	M	M	M
Adenocarcinoma					X																			
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																				
Lymphoma malignant lymphocytic								X												X				
Lymphoma malignant mixed		X																						
Lymphoma malignant undifferentiated cell type																							X	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Tricresyl Phosphate: 125 ppm
(continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	7 1 1	7 1 2	7 1 3	7 1 5	7 1 6	7 1 7	7 1 8	7 1 9	7 2 0	7 2 1	7 2 2	7 2 3	7 2 4	7 2 5	7 2 6	7 2 7	7 2 9	7 3 0	7 3 3	7 3 4	7 3 5	7 3 6	7 3 7	7 3 8	7 4 0	Total Tissues/ Tumors
Special Senses System																										
Ear																										2
Pinna, fibrosarcoma																										1
Harderian gland	+	+	M	+	M	M	M	M	+	+	+	M	M	+	+	+	M	+	+	+	M	+	+	+	M	29
Adenocarcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma						X																				2
Lymphoma malignant lymphocytic		X																								3
Lymphoma malignant mixed	X																									2
Lymphoma malignant undifferentiated cell type																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Tricresyl Phosphate: 250 ppm

Number of Days on Study	0 7 9	4 7 1	5 5 1	5 5 5	5 9 3	7 0 7	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	3 3 1	7 4 2	7 8 1	7 7 1	7 5 1	7 5 9	7 4 1	7 4 3	7 4 4	7 4 5	7 4 6	7 4 7	7 4 8	7 4 9	7 5 0	7 5 2	7 5 3	7 5 4	7 5 5	7 5 6	7 5 7	7 5 8	7 6 0	7 6 1	7 6 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone		X																							
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma				X		X					X														
Hepatocellular carcinoma, multiple																									X
Hepatocellular adenoma						X		X																X	
Hepatocellular adenoma, multiple											X												X		
Mesentery																		+						+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X																					
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	M	+	+	M	M	+	+	M	
Pituitary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	
Pars distalis, adenoma										X			X			X			X	X					
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Clitoral gland		+																							
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																			X						
Fibrous histiocytoma											X														
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Tricresyl Phosphate: 250 ppm
(continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	7 6 3	7 6 4	7 6 5	7 6 6	7 6 7	7 6 8	7 6 9	7 7 0	7 7 2	7 7 3	7 7 4	7 7 5	7 7 6	7 7 7	7 7 8	7 7 9	7 8 0	7 8 2	7 8 3	7 8 4	7 8 5	7 8 6	7 8 7	7 8 8	7 8 9	7 9 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Osteosarcoma, metastatic, bone																										1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular carcinoma	X																				X					5
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma	X				X												X								X	7
Hepatocellular adenoma, multiple				X		X	X				X		X	X												8
Mesentery					+																					3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma									X	X														X	X	9
Pars intermedia, adenoma		X																			X					2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
General Body System																										
None																										
Genital System																										
Clitoral gland																										1
Ovary	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																X										2
Fibrous histiocytoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																			X							1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Tricresyl Phosphate: 250 ppm
(continued)

Number of Days on Study	0 7 9	4 7 1	5 5 1	5 5 5	5 9 3	7 0 7	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	3 3 1	7 4 2	7 8 1	7 7 1	7 5 1	7 5 9	7 4 1	7 4 3	7 4 4	7 4 5	7 4 6	7 4 7	7 4 8	7 4 9	7 5 0	7 5 2	7 5 3	7 5 4	7 5 5	7 5 6	7 5 7	7 5 8	7 6 0	7 6 1	7 6 2
Hematopoietic System																										
Blood																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone		X																								
Sarcoma																										
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																						X				
Thymus	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma										X																
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vertebra, osteosarcoma		X																								
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X			X			X													
Alveolar/bronchiolar carcinoma			X																							
Hepatocellular carcinoma, metastatic, liver				X																						X
Osteosarcoma, multiple, metastatic, bone		X																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Harderian gland	+	+	+	+	M	+	M	+	+	+	M	+	+	+	+	+	M	+	M	+	+	+	M	M	M	
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																										
Leukemia lymphocytic																										
Lymphoma malignant lymphocytic																X										
Lymphoma malignant mixed									X									X								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Tricresyl Phosphate: 250 ppm
(continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	7 6 3	7 6 4	7 6 5	7 6 6	7 6 7	7 6 8	7 6 9	7 7 0	7 7 2	7 7 3	7 7 4	7 7 5	7 7 6	7 7 7	7 7 8	7 7 9	7 8 0	7 8 2	7 8 3	7 8 4	7 8 5	7 8 6	7 8 7	7 8 8	7 8 9	7 9 0	Total Tissues/ Tumors
Hematopoietic System																											
Blood										+																	1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Osteosarcoma, metastatic, bone																											1
Sarcoma									X																		1
Lymph node, mandibular	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangiosarcoma																											1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	46
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenocarcinoma														X													1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Sarcoma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Vertebra, osteosarcoma																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma														X								X					5
Alveolar/bronchiolar carcinoma																											1
Hepatocellular carcinoma, metastatic, liver																											2
Osteosarcoma, multiple, metastatic, bone																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Special Senses System																											
Harderian gland	+	+	+	M	+	+	+	M	+	+	+	+	M	+	+	M	M	M	+	+	+	+	+	M	+	+	36
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																			X								1
Leukemia lymphocytic									X																		1
Lymphoma malignant lymphocytic																			X				X				3
Lymphoma malignant mixed															X												3

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Tricresyl Phosphate

	0 ppm	60 ppm	125 ppm	250 ppm
Adrenal Cortex: Adenoma				
Overall rate[a]	3/50 (6%)	0/50 (0%)	0/48 (0%)	1/51 (2%)
Adjusted rate[b]	7.3%	0.0%	0.0%	2.1%
Terminal rate[c]	3/41 (7%)	0/38 (0%)	0/42 (0%)	0/45 (0%)
First incidence (days)	736 (T)	–[e]	–	555
Life table test[d]	P=0.234N	P=0.135N	P=0.117N	P=0.281N
Logistic regression test[d]	P=0.243N	P=0.135N	P=0.117N	P=0.288N
Cochran-Armitage test[d]	P=0.250N			
Fisher exact test[d]		P=0.121N	P=0.129N	P=0.301N
Harderian Gland: Adenoma				
Overall rate	5/50 (10%)	3/50 (6%)	0/48 (0%)	0/51 (0%)
Adjusted rate	12.2%	7.3%	0.0%	0.0%
Terminal rate	5/41 (12%)	2/38 (5%)	0/42 (0%)	0/45 (0%)
First incidence (days)	736 (T)	603	–	–
Life table test	P=0.006N	P=0.394N	P=0.031N	P=0.026N
Logistic regression test	P=0.007N	P=0.365N	P=0.031N	P=0.026N
Cochran-Armitage test	P=0.007N			
Fisher exact test		P=0.357N	P=0.031N	P=0.027N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	5/50 (10%)	3/50 (6%)	1/48 (2%)	0/51 (0%)
Adjusted rate	12.2%	7.3%	2.3%	0.0%
Terminal rate	5/41 (12%)	2/38 (5%)	0/42 (0%)	0/45 (0%)
First incidence (days)	736 (T)	603	723	–
Life table test	P=0.010N	P=0.394N	P=0.098N	P=0.026N
Logistic regression test	P=0.012N	P=0.365N	P=0.098N	P=0.026N
Cochran-Armitage test	P=0.012N			
Fisher exact test		P=0.357N	P=0.112N	P=0.027N
Liver: Hepatocellular Adenoma				
Overall rate	12/50 (24%)	11/50 (22%)	13/48 (27%)	15/51 (29%)
Adjusted rate	28.4%	28.0%	31.0%	32.6%
Terminal rate	11/41 (27%)	10/38 (26%)	13/42 (31%)	14/45 (31%)
First incidence (days)	560	674	736 (T)	707
Life table test	P=0.358	P=0.577N	P=0.527	P=0.430
Logistic regression test	P=0.277	P=0.534N	P=0.491	P=0.355
Cochran-Armitage test	P=0.245			
Fisher exact test		P=0.500N	P=0.453	P=0.349
Liver: Hepatocellular Carcinoma				
Overall rate	10/50 (20%)	3/50 (6%)	1/48 (2%)	6/51 (12%)
Adjusted rate	22.9%	7.2%	2.2%	12.7%
Terminal rate	8/41 (20%)	2/38 (5%)	0/42 (0%)	4/45 (9%)
First incidence (days)	538	561	621	555
Life table test	P=0.179N	P=0.051N	P=0.006N	P=0.170N
Logistic regression test	P=0.202N	P=0.035N	P=0.007N	P=0.192N
Cochran-Armitage test	P=0.211N			
Fisher exact test		P=0.036N	P=0.005N	P=0.195N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	60 ppm	125 ppm	250 ppm
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	21/50 (42%)	14/50 (28%)	14/48 (29%)	18/51 (35%)
Adjusted rate	47.4%	34.6%	32.5%	38.3%
Terminal rate	18/41 (44%)	12/38 (32%)	13/42 (31%)	16/45 (36%)
First incidence (days)	538	561	621	555
Life table test	P=0.266N	P=0.160N	P=0.096N	P=0.236N
Logistic regression test	P=0.388N	P=0.110N	P=0.128N	P=0.318N
Cochran-Armitage test	P=0.392N			
Fisher exact test		P=0.104N	P=0.132N	P=0.313N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	2/50 (4%)	4/50 (8%)	3/48 (6%)	5/51 (10%)
Adjusted rate	4.9%	10.5%	7.1%	11.1%
Terminal rate	2/41 (5%)	4/38 (11%)	3/42 (7%)	5/45 (11%)
First incidence (days)	736 (T)	736 (T)	736 (T)	736 (T)
Life table test	P=0.260	P=0.302	P=0.511	P=0.256
Logistic regression test	P=0.260	P=0.302	P=0.511	P=0.256
Cochran-Armitage test	P=0.210			
Fisher exact test		P=0.339	P=0.480	P=0.226
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	4/50 (8%)	1/50 (2%)	2/48 (4%)	1/51 (2%)
Adjusted rate	9.2%	2.6%	4.6%	2.0%
Terminal rate	3/41 (7%)	1/38 (3%)	1/42 (2%)	0/45 (0%)
First incidence (days)	538	736 (T)	723	551
Life table test	P=0.148N	P=0.200N	P=0.329N	P=0.164N
Logistic regression test	P=0.155N	P=0.173N	P=0.361N	P=0.146N
Cochran-Armitage test	P=0.166N			
Fisher exact test		P=0.181N	P=0.359N	P=0.175N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	5/50 (10%)	5/50 (10%)	5/48 (10%)	6/51 (12%)
Adjusted rate	11.6%	13.2%	11.6%	12.9%
Terminal rate	4/41 (10%)	5/38 (13%)	4/42 (10%)	5/45 (11%)
First incidence (days)	538	736 (T)	723	551
Life table test	P=0.506	P=0.587	P=0.613N	P=0.556
Logistic regression test	P=0.434	P=0.624	P=0.604	P=0.520
Cochran-Armitage test	P=0.434			
Fisher exact test		P=0.630N	P=0.603	P=0.514
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	6/46 (13%)	8/46 (17%)	6/46 (13%)	9/50 (18%)
Adjusted rate	15.4%	21.2%	15.0%	20.5%
Terminal rate	5/37 (14%)	6/34 (18%)	6/40 (15%)	9/44 (20%)
First incidence (days)	677	561	736 (T)	736 (T)
Life table test	P=0.447	P=0.336	P=0.571N	P=0.413
Logistic regression test	P=0.368	P=0.378	P=0.585N	P=0.371
Cochran-Armitage test	P=0.352			
Fisher exact test		P=0.386	P=0.621N	P=0.351

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	60 ppm	125 ppm	250 ppm
Spleen: Hemangiosarcoma				
Overall rate	3/50 (6%)	1/50 (2%)	1/48 (2%)	1/51 (2%)
Adjusted rate	7.3%	2.3%	2.4%	2.2%
Terminal rate	3/41 (7%)	0/38 (0%)	1/42 (2%)	1/45 (2%)
First incidence (days)	736 (T)	652	736 (T)	736 (T)
Life table test	P=0.218N	P=0.329N	P=0.297N	P=0.273N
Logistic regression test	P=0.239N	P=0.308N	P=0.297N	P=0.273N
Cochran-Armitage test	P=0.241N			
Fisher exact test		P=0.309N	P=0.324N	P=0.301N
Uterus: Stromal Polyp				
Overall rate	2/50 (4%)	1/50 (2%)	3/48 (6%)	0/51 (0%)
Adjusted rate	4.9%	2.6%	7.1%	0.0%
Terminal rate	2/41 (5%)	1/38 (3%)	3/42 (7%)	0/45 (0%)
First incidence (days)	736 (T)	736 (T)	736 (T)	–
Life table test	P=0.213N	P=0.527N	P=0.511	P=0.218N
Logistic regression test	P=0.213N	P=0.527N	P=0.511	P=0.218N
Cochran-Armitage test	P=0.241N			
Fisher exact test		P=0.500N	P=0.480	P=0.243N
All Organs: Hemangioma				
Overall rate	0/50 (0%)	0/50 (0%)	4/48 (8%)	0/51 (0%)
Adjusted rate	0.0%	0.0%	9.5%	0.0%
Terminal rate	0/41 (0%)	0/38 (0%)	4/42 (10%)	0/45 (0%)
First incidence (days)	–	–	736 (T)	–
Life table test	P=0.532	–	P=0.066	–
Logistic regression test	P=0.532	–	P=0.066	–
Cochran-Armitage test	P=0.499			
Fisher exact test		–	P=0.054	–
All Organs: Hemangiosarcoma				
Overall rate	4/50 (8%)	1/50 (2%)	1/48 (2%)	1/51 (2%)
Adjusted rate	9.8%	2.3%	2.4%	2.2%
Terminal rate	4/41 (10%)	0/38 (0%)	1/42 (2%)	1/45 (2%)
First incidence (days)	736 (T)	652	736 (T)	736 (T)
Life table test	P=0.119N	P=0.202N	P=0.172N	P=0.153N
Logistic regression test	P=0.133N	P=0.184N	P=0.172N	P=0.153N
Cochran-Armitage test	P=0.135N			
Fisher exact test		P=0.181N	P=0.194N	P=0.175N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	4/50 (8%)	1/50 (2%)	5/48 (10%)	1/51 (2%)
Adjusted rate	9.8%	2.3%	11.9%	2.2%
Terminal rate	4/41 (10%)	0/38 (0%)	5/42 (12%)	1/45 (2%)
First incidence (days)	736 (T)	652	736 (T)	736 (T)
Life table test	P=0.212N	P=0.202N	P=0.515	P=0.153N
Logistic regression test	P=0.238N	P=0.184N	P=0.515	P=0.153N
Cochran-Armitage test	P=0.248N			
Fisher exact test		P=0.181N	P=0.474	P=0.175N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	60 ppm	125 ppm	250 ppm
All Organs: Histiocytic Sarcoma				
Overall rate	1/50 (2%)	3/50 (6%)	2/48 (4%)	1/51 (2%)
Adjusted rate	2.4%	6.6%	4.6%	2.2%
Terminal rate	1/41 (2%)	0/38 (0%)	1/42 (2%)	1/45 (2%)
First incidence (days)	736 (T)	571	653	736 (T)
Life table test	P=0.441N	P=0.296	P=0.506	P=0.741N
Logistic regression test	P=0.441N	P=0.326	P=0.483	P=0.741N
Cochran-Armitage test	P=0.463N			
Fisher exact test		P=0.309	P=0.485	P=0.748N
All Organs: Malignant Lymphoma (Lymphocytic, Mixed, or Undifferentiated Cell Type)				
Overall rate	4/50 (8%)	6/50 (12%)	6/48 (13%)	6/51 (12%)
Adjusted rate	9.5%	15.4%	13.8%	13.3%
Terminal rate	3/41 (7%)	5/38 (13%)	5/42 (12%)	6/45 (13%)
First incidence (days)	698	700	607	736 (T)
Life table test	P=0.440	P=0.324	P=0.386	P=0.428
Logistic regression test	P=0.377	P=0.343	P=0.347	P=0.395
Cochran-Armitage test	P=0.365			
Fisher exact test		P=0.370	P=0.344	P=0.383
All Organs: Malignant Lymphoma or Histiocytic Sarcoma				
Overall rate	5/50 (10%)	9/50 (18%)	8/48 (17%)	6/51 (12%)
Adjusted rate	11.9%	21.0%	18.0%	13.3%
Terminal rate	4/41 (10%)	5/38 (13%)	6/42 (14%)	6/45 (13%)
First incidence (days)	698	571	607	736 (T)
Life table test	P=0.460N	P=0.169	P=0.295	P=0.563
Logistic regression test	P=0.537N	P=0.194	P=0.250	P=0.530
Cochran-Armitage test	P=0.537N			
Fisher exact test		P=0.194	P=0.250	P=0.514
All Organs: Benign Neoplasms				
Overall rate	27/50 (54%)	29/50 (58%)	24/48 (50%)	32/51 (63%)
Adjusted rate	61.1%	67.1%	55.7%	66.6%
Terminal rate	24/41 (59%)	24/38 (63%)	23/42 (55%)	29/45 (64%)
First incidence (days)	523	561	621	79
Life table test	P=0.471	P=0.288	P=0.305N	P=0.389
Logistic regression test	P=0.249	P=0.387	P=0.387N	P=0.240
Cochran-Armitage test	P=0.252			
Fisher exact test		P=0.420	P=0.423N	P=0.245
All Organs: Malignant Neoplasms				
Overall rate	22/50 (44%)	16/50 (32%)	15/48 (31%)	20/51 (39%)
Adjusted rate	47.7%	35.1%	32.5%	39.9%
Terminal rate	17/41 (41%)	9/38 (24%)	11/42 (26%)	15/45 (33%)
First incidence (days)	538	561	607	79
Life table test	P=0.335N	P=0.244N	P=0.114N	P=0.314N
Logistic regression test	P=0.443N	P=0.148N	P=0.138N	P=0.375N
Cochran-Armitage test	P=0.449N			
Fisher exact test		P=0.151N	P=0.137N	P=0.388N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	60 ppm	125 ppm	250 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	40/50 (80%)	39/50 (78%)	32/48 (67%)	42/51 (82%)
Adjusted rate	81.6%	82.9%	69.5%	84.0%
Terminal rate	32/41 (78%)	30/38 (79%)	28/42 (67%)	37/45 (82%)
First incidence (days)	425	561	607	79
Life table test	P=0.321N	P=0.455	P=0.076N	P=0.470N
Logistic regression test	P=0.459	P=0.508N	P=0.104N	P=0.476
Cochran-Armitage test	P=0.461			
Fisher exact test		P=0.500N	P=0.103N	P=0.481

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, lung, pituitary gland, and spleen; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE D4a
Historical Incidence of Hepatocellular Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls			
	Adenoma	Carcinoma	Adenoma or Carcinoma	Hepatoblastoma
Historical Incidence at Battelle Columbus				
2,4-Dichlorophenol	0/50	2/50	2/50	0/50
4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)	17/51	4/51	20/51	0/51
5,5-Diphenylhydantoin	5/48	0/48	5/48	0/48
Dowicide EC-7 Pentachlorophenol	1/34	0/34	1/34	0/34
Ethylene Thiourea	2/50	2/50	4/50	0/50
Polybrominated Biphenyls (Firemaster FF-1®)	4/50	1/50	5/50	0/50
Manganese (II) Sulfate Monohydrate	12/51	3/51	13/51	0/51
Technical Grade Pentachlorophenol	3/33	0/33	3/33	0/33
Triamterene	10/50	4/50	13/50	0/50
Triamterene	7/50	5/50	10/50	0/50
Tricresyl Phosphate	12/50	10/50	21/50	0/50
Overall Historical Incidence				
Total	159/1,363 (11.7%)	80/1,363 (5.9%)	223/1,363 (16.4%)	1/1,363 (0.1%)
Standard deviation	8.3%	5.5%	10.7%	0.4%
Range	0%-33%	0%-20%	3%-42%	0%-2%

[a] Data as of 20 August 1992

TABLE D4b
Historical Incidence of Harderian Gland Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus			
2,4-Dichlorophenol	1/50	0/50	1/50
4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)	0/51	1/51	1/51
5,5-Diphenylhydantoin	3/50	1/50	4/50
Dowicide EC-7 Pentachlorophenol	2/35	0/35	2/35
Ethylene Thiourea	2/50	0/50	2/50
Polybrominated Biphenyls (Firemaster FF-1®)	3/50	0/50	3/50
Manganese (II) Sulfate Monohydrate	2/51	1/51	3/51
Technical Grade Pentachlorophenol	2/35	0/35	2/35
Triamterene	1/50	0/50	1/50
Triamterene	0/50	0/50	0/50
Tricresyl Phosphate	5/50	0/50	5/50
Overall Historical Incidence			
Total	47/1,371 (3.4%)	8/1,371 (0.6%)	55/1,371 (4.0%)
Standard deviation	3.1%	0.95	3.2%
Range	0%-10%	0%-2%	0%-10%

[a] Data as of 20 August 1992

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Tricresyl Phosphate[a]

	0 ppm	60 ppm	125 ppm	250 ppm
Disposition Summary				
Animals initially in study	95	95	95	95
3-Month interim evaluation[b]	15	15	15	15
9-Month interim evaluation[b]	15	15	15	15
15-Month interim evaluation[b]	15	15	15	14
Early deaths				
Moribund	4	5	4	3
Natural deaths	5	7	2	3
Survivors				
Died last week of study	1	1		
Terminal sacrifice	40	37	42	45
Missing			2	
Animals examined microscopically	95	95	93	95
3-Month Interim Evaluation				
Alimentary System				
Stomach, glandular	(10)	(10)	(10)	(10)
Cyst				1 (10%)
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule		1 (10%)		
Pigmentation, ceroid				1 (10%)
Subcapsular, hyperplasia	10 (100%)	10 (100%)	7 (70%)	10 (100%)
Parathyroid gland	(7)	(8)	(8)	(6)
Cyst		1 (13%)		
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Hydronephrosis			1 (10%)	
Systems Examined With No Lesions Observed				
Cardiovascular System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] Includes up to five animals per dose group subjected to total body perfusion for special neuropathology

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	60 ppm	125 ppm	250 ppm
9-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Basophilic focus		1 (10%)		
Inflammation, chronic active			1 (10%)	
Necrosis	1 (10%)		1 (10%)	1 (10%)
Mesentery	(1)			
Fat, necrosis	1 (100%)			
Pancreas	(10)	(10)	(10)	(10)
Atrophy			1 (10%)	
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule	2 (20%)	1 (10%)	1 (10%)	
Pigmentation, ceroid	9 (90%)	10 (100%)	10 (100%)	10 (100%)
Subcapsular, hyperplasia	10 (100%)	10 (100%)	10 (100%)	10 (100%)
Genital System				
Ovary	(10)	(10)	(10)	(10)
Cyst	2 (20%)	1 (10%)		1 (10%)
Uterus	(10)	(10)	(10)	(10)
Hyperplasia, cystic	10 (100%)	7 (70%)	8 (80%)	7 (70%)
Hematopoietic System				
Thymus	(10)	(10)	(10)	(10)
Cyst			1 (10%)	1 (10%)
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Inflammation, chronic active		1 (10%)		1 (10%)
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Nephropathy		1 (10%)	3 (30%)	2 (20%)
Systems Examined With No Lesions Observed				
Cardiovascular System				
General Body System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	60 ppm	125 ppm	250 ppm
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(9)
Basophilic focus		1 (10%)		
Clear cell focus				1 (11%)
Eosinophilic focus				1 (11%)
Inflammation, chronic active	1 (10%)			
Necrosis	1 (10%)	1 (10%)		
Pancreas	(10)	(10)	(10)	(9)
Atrophy			2 (20%)	
Salivary glands	(10)	(10)	(10)	(9)
Inflammation, chronic active	1 (10%)			
Duct, hyperplasia		1 (10%)		
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(9)
Pigmentation, ceroid	10 (100%)	10 (100%)	10 (100%)	9 (100%)
Subcapsular, hyperplasia	10 (100%)	10 (100%)	10 (100%)	9 (100%)
Pituitary gland	(10)	(10)	(10)	(9)
Pars distalis, hyperplasia		1 (10%)		1 (11%)
Genital System				
Clitoral gland	(2)	(1)	(1)	
Duct, dilatation	2 (100%)	1 (100%)	1 (100%)	
Ovary	(10)	(10)	(10)	(9)
Cyst	3 (30%)		1 (10%)	2 (22%)
Uterus	(10)	(10)	(10)	(9)
Hyperplasia, cystic	10 (100%)	10 (100%)	10 (100%)	9 (100%)
Integumentary System				
Skin	(10)	(10)	(10)	(9)
Inflammation, chronic active	1 (10%)			1 (11%)
Nervous System				
Peripheral nerve	(15)	(15)	(15)	(14)
Axon, degeneration		1 (7%)		1 (7%)
Respiratory System				
Lung	(10)	(10)	(10)	(9)
Artery, inflammation, chronic active			1 (10%)	
Special Senses System				
Harderian gland	(7)	(4)	(5)	(8)
Hyperplasia	1 (14%)			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	60 ppm	125 ppm	250 ppm
15-Month Interim Evaluation (continued)				
Urinary System				
Kidney	(10)	(10)	(10)	(9)
Nephropathy	2 (20%)	2 (20%)	3 (30%)	2 (22%)
Systems Examined With No Lesions Observed				
Cardiovascular System				
General Body System				
Hematopoietic System				
Musculoskeletal System				
2-Year Study				
Alimentary System				
Esophagus	(50)	(50)	(48)	(51)
Inflammation	1 (2%)			
Intestine small, duodenum	(50)	(50)	(48)	(50)
Ulcer, chronic active			1 (2%)	1 (2%)
Intestine small, jejunum	(49)	(50)	(48)	(51)
Lymphoid tissue, hyperplasia	1 (2%)		1 (2%)	1 (2%)
Lymphoid tissue, ulcer, chronic active				1 (2%)
Intestine small, ileum	(49)	(50)	(48)	(51)
Amyloid deposition			1 (2%)	1 (2%)
Lymphoid tissue, hyperplasia				1 (2%)
Liver	(50)	(50)	(48)	(51)
Angiectasis		1 (2%)		1 (2%)
Basophilic focus	4 (8%)	1 (2%)	1 (2%)	
Clear cell focus				3 (6%)
Eosinophilic focus	8 (16%)	4 (8%)	5 (10%)	6 (12%)
Fatty change		3 (6%)	1 (2%)	1 (2%)
Hematopoietic cell proliferation	1 (2%)	1 (2%)		
Infarct		1 (2%)		
Inflammation, chronic active		1 (2%)		
Mixed cell focus	1 (2%)		2 (4%)	2 (4%)
Necrosis	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Pigmentation, ceroid			1 (2%)	2 (4%)
Pigmentation, hemosiderin			1 (2%)	
Bile duct, cyst	1 (2%)			
Centrilobular, degeneration		1 (2%)		
Serosa, inflammation		1 (2%)		
Mesentery	(5)	(5)	(6)	(3)
Hemorrhage		1 (20%)		
Inflammation, chronic active		1 (20%)	1 (17%)	1 (33%)
Inflammation, suppurative		1 (20%)		
Fat, necrosis	3 (60%)	1 (20%)	5 (83%)	2 (67%)
Pancreas	(50)	(50)	(48)	(51)
Atrophy	4 (8%)	6 (12%)	1 (2%)	1 (2%)
Hyperplasia			1 (2%)	
Duct, cyst	1 (2%)	2 (4%)		1 (2%)
Stomach, forestomach	(50)	(50)	(48)	(51)
Hyperplasia	2 (4%)		1 (2%)	1 (2%)
Stomach, glandular	(50)	(50)	(48)	(51)
Erosion	1 (2%)	1 (2%)		

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	60 ppm	125 ppm	250 ppm
2-Year Study (continued)				
Cardiovascular System				
Blood vessel	(1)		(1)	
Mineralization	1 (100%)			
Polyarteritis			1 (100%)	
Heart	(50)	(50)	(48)	(51)
Degeneration		1 (2%)		
Infarct	1 (2%)			
Inflammation, chronic active		1 (2%)	1 (2%)	1 (2%)
Mineralization	1 (2%)			
Artery, inflammation, chronic active			1 (2%)	
Atrium, thrombosis		1 (2%)		
Pericardium, inflammation, chronic active		2 (4%)		
Endocrine System				
Adrenal cortex	(50)	(49)	(48)	(51)
Accessory adrenal cortical nodule	3 (6%)	4 (8%)	3 (6%)	1 (2%)
Hematopoietic cell proliferation	1 (2%)			
Hyperplasia	4 (8%)	1 (2%)	7 (15%)	2 (4%)
Pigmentation, ceroid	49 (98%)	49 (100%)	47 (98%)	51 (100%)
Subcapsular, hyperplasia	50 (100%)	49 (100%)	47 (98%)	51 (100%)
Adrenal medulla	(50)	(49)	(48)	(51)
Hyperplasia	1 (2%)	3 (6%)	1 (2%)	4 (8%)
Islets, pancreatic	(50)	(50)	(48)	(51)
Hyperplasia	2 (4%)	5 (10%)	2 (4%)	
Parathyroid gland	(46)	(42)	(43)	(44)
Cyst				1 (2%)
Hyperplasia	1 (2%)			
Pituitary gland	(46)	(46)	(46)	(50)
Angiectasis				2 (4%)
Cyst	2 (4%)	1 (2%)		
Pars distalis, hyperplasia	21 (46%)	22 (48%)	21 (46%)	18 (36%)
Pars intermedia, hyperplasia			1 (2%)	1 (2%)
Thyroid gland	(49)	(50)	(48)	(51)
Inflammation	1 (2%)		1 (2%)	3 (6%)
Follicle, cyst	3 (6%)		2 (4%)	4 (8%)
Follicular cell, hyperplasia	7 (14%)	9 (18%)	13 (27%)	15 (29%)
General Body System				
None				
Genital System				
Clitoral gland				(1)
Duct, dilatation				1 (100%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	60 ppm	125 ppm	250 ppm
2-Year Study (continued)				
Genital System (continued)				
Ovary	(48)	(50)	(47)	(50)
Angiectasis	1 (2%)		1 (2%)	1 (2%)
Atrophy	5 (10%)	1 (2%)	2 (4%)	1 (2%)
Cyst	11 (23%)	12 (24%)	15 (32%)	19 (38%)
Hyperplasia, cystic			1 (2%)	
Inflammation, suppurative		1 (2%)		
Thrombosis		1 (2%)		
Corpus luteum, hyperplasia	1 (2%)	1 (2%)		
Periovarian tissue, inflammation, granulomatous				1 (2%)
Rete ovarii, hyperplasia				2 (4%)
Uterus	(50)	(50)	(48)	(51)
Angiectasis	1 (2%)		2 (4%)	2 (4%)
Hemorrhage		1 (2%)		
Hyperplasia, cystic	41 (82%)	36 (72%)	35 (73%)	41 (80%)
Inflammation, suppurative		1 (2%)		
Thrombosis				2 (4%)
Lymphatic, angiectasis			1 (2%)	
Hematopoietic System				
Bone marrow	(50)	(50)	(48)	(51)
Hyperplasia	10 (20%)	6 (12%)	5 (10%)	6 (12%)
Infarct	1 (2%)			
Myelofibrosis	18 (36%)	23 (46%)	27 (56%)	26 (51%)
Lymph node	(3)	(4)	(3)	
Mediastinal, pigmentation, hemosiderin			1 (33%)	
Lymph node, mandibular	(46)	(47)	(48)	(47)
Hyperplasia, lymphoid	1 (2%)		3 (6%)	2 (4%)
Hyperplasia, plasma cell	1 (2%)			
Lymph node, mesenteric	(49)	(46)	(45)	(50)
Cyst				1 (2%)
Hematopoietic cell proliferation	1 (2%)			
Hyperplasia, lymphoid	1 (2%)		3 (7%)	6 (12%)
Spleen	(50)	(50)	(48)	(51)
Depletion lymphoid	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Fibrosis	1 (2%)			
Hematopoietic cell proliferation	23 (46%)	20 (40%)	18 (38%)	26 (51%)
Hyperplasia, lymphoid	5 (10%)	7 (14%)	4 (8%)	8 (16%)
Thymus	(45)	(44)	(47)	(46)
Depletion lymphoid	3 (7%)	9 (20%)	1 (2%)	4 (9%)
Hyperplasia, lymphoid	2 (4%)	2 (5%)	1 (2%)	3 (7%)
Artery, inflammation, chronic active	1 (2%)			
Capsule, inflammation, chronic		1 (2%)		
Epithelial cell, hyperplasia		1 (2%)		

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	60 ppm	125 ppm	250 ppm
2-Year Study (continued)				
Integumentary System				
Mammary gland	(49)	(50)	(47)	(51)
Hyperplasia, cystic	1 (2%)		1 (2%)	2 (4%)
Skin	(50)	(50)	(48)	(51)
Ulcer	1 (2%)			
Subcutaneous tissue, inflammation, chronic active				1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(48)	(51)
Joint, inflammation, chronic active	2 (4%)			
Nervous System				
Brain	(50)	(50)	(48)	(51)
Necrosis		3 (6%)	1 (2%)	3 (6%)
Peripheral nerve	(50)	(50)	(48)	(51)
Axon, degeneration	5 (10%)	5 (10%)	4 (8%)	11 (22%)
Spinal cord	(50)	(50)	(48)	(51)
Degeneration				1 (2%)
Respiratory System				
Lung	(50)	(50)	(48)	(51)
Hyperplasia, lymphoid	1 (2%)			
Inflammation, chronic active		2 (4%)		1 (2%)
Thrombosis	1 (2%)			
Alveolar epithelium, hyperplasia	3 (6%)	1 (2%)	2 (4%)	1 (2%)
Artery, inflammation, chronic active			1 (2%)	
Pleura, inflammation, chronic		1 (2%)		
Nose	(50)	(50)	(48)	(51)
Nasolacrimal duct, inflammation	1 (2%)			
Respiratory epithelium, inflammation	2 (4%)			3 (6%)
Special Senses System				
Eye	(1)			
Cornea, inflammation	1 (100%)			
Harderian gland	(47)	(38)	(29)	(36)
Hemorrhage		1 (3%)		
Hyperplasia	2 (4%)	1 (3%)	1 (3%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	60 ppm	125 ppm	250 ppm
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(50)	(48)	(51)
Hydronephrosis	1 (2%)	1 (2%)		1 (2%)
Infarct	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Mineralization				1 (2%)
Nephropathy	29 (58%)	28 (56%)	36 (75%)	34 (67%)
Pigmentation, hemosiderin			1 (2%)	
Artery, inflammation, chronic active			1 (2%)	
Renal tubule, dilatation		1 (2%)		
Urinary bladder	(49)	(50)	(47)	(51)
Artery, inflammation, chronic active	1 (2%)			2 (4%)
Serosa, inflammation, chronic		1 (2%)		

APPENDIX E
GENETIC TOXICOLOGY

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GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Haworth *et al.* (1983). Tricresyl phosphate was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, and TA1537) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with *l*-histidine and *d*-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and at least five doses of tricresyl phosphate. The high dose was limited to 10,000 μg/plate. All trials were repeated.

In this test, a positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants that is not dose related, not reproducible, or is not of sufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment. No minimum percentage or fold increase is required for a chemical to be judged positive or weakly positive.

CHINESE HAMSTER OVARY CELL CYTOGENETICS TEST PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1987). Tricresyl phosphate was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least four doses of tricresyl phosphate; the high dose was 5,000 μg/mL. A single flask per dose was used.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 26 hours with tricresyl phosphate in McCoy's 5A medium supplemented with fetal bovine serum, *l*-glutamine, and antibiotics. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing tricresyl phosphate was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 hours. Cells were harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with tricresyl phosphate, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no tricresyl phosphate, and incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.*, 1987). An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. An increase of 20% or greater at any single dose was considered weak evidence

of activity; increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend ($P \leq 0.05$) in the absence of any responses reaching 20% above background led to a call of equivocal.

Chromosomal Aberrations Test: In the Abs test without S9, cells were incubated in McCoy's 5A medium with tricresyl phosphate for 12 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with tricresyl phosphate and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 12 hours in fresh medium, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9.

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

Chromosomal aberration data are presented as percentage of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted on both the dose response curve and individual dose points. For a single trial, a statistically significant ($P \leq 0.05$) difference for one dose point and a significant trend ($P \leq 0.015$) are considered weak evidence for a positive response; significant differences for two or more doses indicate the trial is positive. A positive trend test in the absence of a statistically significant increase at any one dose results in an equivocal call (Galloway *et al.*, 1987). Ultimately, the trial calls were based on consideration of the statistical analyses as well as the biological information available to the reviewers.

RESULTS

Tricresyl phosphate (100 to 10,000 μg/plate) was tested in two laboratories for induction of gene mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 (Table E1; Haworth *et al.*, 1983). No induction of gene mutations was observed in either laboratory in any of the four tester strains. Precipitation of tricresyl phosphate was noted at concentrations of 3,333 μg/plate and above in the study conducted at SRI, International. In cytogenetic tests with cultured Chinese hamster ovary cells, tricresyl phosphate did not induce sister chromatid exchanges (Table E2) or chromosomal aberrations (Table E3), with or without Aroclor 1254-induced male Sprague-Dawley rat liver S9. No tricresyl phosphate-induced cell cycle delay was observed in either of these two assays.

TABLE E1
Mutagenicity of Tricresyl Phosphate in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
Study conducted at Case Western Reserve University							
TA100	0	129 ± 12.5	178 ± 17.5	167 ± 13.8	192 ± 12.7	194 ± 5.0	197 ± 2.8
	100	175 ± 42.0	180 ± 5.4	135 ± 7.3	183 ± 14.5	165 ± 3.8	209 ± 21.1
	333	148 ± 8.8	210 ± 16.1	147 ± 5.3	192 ± 13.9	184 ± 4.9	208 ± 11.6
	1,000	121 ± 8.4	223 ± 10.1	148 ± 1.0	190 ± 10.2	267 ± 48.0	227 ± 22.3
	3,333	107 ± 5.5	181 ± 16.7	150 ± 14.9	210 ± 24.2	285 ± 51.5	209 ± 9.5
	10,000	129 ± 7.4	198 ± 10.3	155 ± 12.5	215 ± 19.1	228 ± 11.2	213 ± 11.0
Trial summary		Negative	Equivocal	Negative	Negative	Negative	Negative
Positive control[c]		591 ± 84.5	519 ± 61.2	621 ± 29.1	622 ± 60.0	633 ± 128.5	510 ± 45.5
TA1535	0	7 ± 0.3	9 ± 2.0	10 ± 0.7	8 ± 1.2	13 ± 3.5	12 ± 2.6
	100	8 ± 0.9	11 ± 1.0	13 ± 4.1	5 ± 2.8	14 ± 2.3	9 ± 1.9
	333	6 ± 1.3	8 ± 0.6	14 ± 1.7	11 ± 0.9	11 ± 2.0	8 ± 1.2
	1,000	10 ± 1.2	9 ± 1.3	14 ± 0.7	6 ± 2.6	13 ± 0.9	9 ± 1.8
	3,333	9 ± 1.8	11 ± 0.6	12 ± 1.5	8 ± 1.3	11 ± 1.8	8 ± 2.2
	10,000	11 ± 0.3	12 ± 1.2	19 ± 2.1	8 ± 3.5	11 ± 0.7	8 ± 1.2
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		199 ± 40.5	270 ± 30.1	72 ± 7.2	79 ± 13.9	69 ± 8.6	62 ± 10.1
TA1537	0	7 ± 0.9	5 ± 1.0	8 ± 0.6	5 ± 1.5	6 ± 2.0	4 ± 1.2
	100	7 ± 1.7	4 ± 0.7	14 ± 0.7	10 ± 2.1	10 ± 3.8	6 ± 1.0
	333	6 ± 0.9	6 ± 1.0	16 ± 0.0	10 ± 0.3	12 ± 1.0	7 ± 1.0
	1,000	7 ± 0.3	5 ± 0.3	14 ± 2.3	9 ± 1.7	14 ± 0.9	9 ± 2.1
	3,333	8 ± 1.2	4 ± 1.0	16 ± 0.9	10 ± 2.3	10 ± 1.5	9 ± 2.7
	10,000	5 ± 0.9	6 ± 2.3	11 ± 2.2	6 ± 0.7	12 ± 1.2	7 ± 0.7
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		155 ± 14.2	150 ± 14.8	87 ± 15.0	45 ± 11.2	199 ± 17.6	154 ± 32.0
TA98	0	19 ± 2.9	11 ± 4.4	22 ± 3.4	19 ± 1.8	24 ± 1.2	15 ± 2.3
	100	18 ± 2.1	9 ± 0.6	31 ± 3.8	21 ± 2.8	23 ± 1.3	21 ± 1.9
	333	16 ± 0.7	8 ± 0.9	28 ± 0.9	18 ± 3.0	23 ± 1.3	18 ± 5.0
	1,000	11 ± 1.5	12 ± 1.3	22 ± 4.9	17 ± 2.8	26 ± 5.2	19 ± 3.4
	3,333	18 ± 1.9	15 ± 1.7	26 ± 3.5	19 ± 1.8	19 ± 2.5	18 ± 0.7
	10,000	22 ± 1.5	12 ± 1.2	28 ± 2.5	14 ± 3.0	18 ± 4.7	10 ± 0.7
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		296 ± 15.5	356 ± 28.4	594 ± 56.9	651 ± 53.1	586 ± 42.4	560 ± 34.8

TABLE E1
Mutagenicity of Tricresyl Phosphate in *Salmonella typhimurium* (continued)

Strain	Dose (μg/plate)	Revertants/plate -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
Study conducted at SRI, International							
TA100	0.0	95 ± 4.2	112 ± 5.9	110 ± 9.9	112 ± 12.9	120 ± 5.0	124 ± 4.3
	100.0	127 ± 2.0	108 ± 7.9	129 ± 3.2	115 ± 4.2	129 ± 6.2	120 ± 3.6
	333.3	140 ± 2.0	102 ± 6.3	131 ± 4.1	126 ± 11.1	105 ± 3.5	126 ± 8.7
	1,000.0	126 ± 12.1	116 ± 9.0	128 ± 7.8	135 ± 4.1	119 ± 7.8	118 ± 3.8
	3,333.3	112 ± 4.4	107 ± 3.8[d]	123 ± 4.1[d]	132 ± 2.3[d]	128 ± 3.4[d]	127 ± 7.5[d]
	10,000.0	121 ± 9.6[d]	126 ± 2.1[d]	130 ± 8.3[d]	123 ± 7.5[d]	125 ± 11.1[d]	127 ± 4.4[d]
Trial summary		Equivocal	Negative	Negative	Negative	Negative	Negative
Positive control		286 ± 9.0	190 ± 7.4	203 ± 9.0	1,646 ± 98.9	195 ± 11.0	904 ± 24.8
TA1535	0.0	20 ± 2.8	26 ± 4.2	10 ± 0.7	13 ± 0.3	12 ± 1.5	12 ± 0.9
	100.0	21 ± 2.0	19 ± 1.0	16 ± 1.2	12 ± 1.9	16 ± 1.9	7 ± 0.6
	333.3	24 ± 3.5	21 ± 5.5	16 ± 0.9	9 ± 0.3	10 ± 1.5	9 ± 1.9
	1,000.0	25 ± 0.7	14 ± 2.0	13 ± 2.3	11 ± 1.2	14 ± 0.3	12 ± 1.5
	3,333.3	28 ± 2.1	11 ± 1.8[d]	18 ± 1.3[d]	11 ± 1.9[d]	8 ± 1.9[d]	13 ± 3.5[d]
	10,000.0	17 ± 1.7[d]	20 ± 0.3[d]	14 ± 3.2[d]	10 ± 0.9[d]	12 ± 1.7[d]	11 ± 2.2[d]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		287 ± 11.6	191 ± 9.0	127 ± 1.0	538 ± 8.4	94 ± 11.4	490 ± 12.3
TA1537	0.0	9 ± 3.4	7 ± 1.0	12 ± 2.0	17 ± 0.7	18 ± 0.7	16 ± 2.0
	100.0	16 ± 1.8	10 ± 2.5	31 ± 3.5	16 ± 0.3	18 ± 3.5	17 ± 2.3
	333.3	12 ± 2.0	8 ± 3.0	15 ± 2.0	13 ± 3.0	20 ± 4.0	18 ± 3.4
	1,000.0	14 ± 1.2	6 ± 1.8	23 ± 1.9	17 ± 2.1	24 ± 0.9	16 ± 1.8
	3,333.3	15 ± 3.2	8 ± 0.9[d]	24 ± 2.3[d]	14 ± 2.1[d]	12 ± 5.5[d]	15 ± 2.7[d]
	10,000.0	16 ± 2.2[d]	9 ± 1.5[d]	21 ± 1.8[d]	16 ± 2.2[d]	16 ± 1.7[d]	14 ± 1.7[d]
Trial summary		Negative	Negative	Equivocal	Negative	Negative	Negative
Positive control		413 ± 39.1	248 ± 75.8	50 ± 0.9	554 ± 29.2	39 ± 7.4	532 ± 21.7
TA98	0.0	33 ± 1.5	23 ± 2.2	49 ± 2.1	38 ± 3.8	35 ± 2.8	24 ± 3.2
	100.0	30 ± 0.3	34 ± 7.9	43 ± 2.7	35 ± 5.0	43 ± 3.8	32 ± 5.8
	333.3	20 ± 3.0	29 ± 3.7	31 ± 4.7	34 ± 2.5	36 ± 3.5	28 ± 2.4
	1,000.0	28 ± 7.0	34 ± 4.8	40 ± 6.6	33 ± 4.3	37 ± 1.9	28 ± 0.6
	3,333.3	35 ± 2.5	23 ± 2.8[d]	37 ± 4.4	38 ± 3.6[d]	41 ± 2.7[d]	30 ± 5.2[d]
	10,000.0	28 ± 1.5[d]	27 ± 6.4[d]	40 ± 1.5	42 ± 2.6[d]	41 ± 2.2[d]	28 ± 2.2[d]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		626 ± 11.2	883 ± 13.5	158 ± 7.3	1,361 ± 21.7	114 ± 6.5	666 ± 158.7

[a] The detailed protocol is presented in Haworth *et al.* (1983).
[b] Revertants are presented as mean ± standard error from three plates.
[c] 2-Aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was tested on TA98, sodium azide was tested on TA100 and TA1535, and 9-aminoacridine was tested on TA1537.
[d] Precipitate on plate

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Tricresyl Phosphate[a]

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative SCEs/ Chromosome (%)[b]
-S9								
Trial 1								
Summary: Negative								
Dimethylsulfoxide		50	1,038	434	0.41	8.7	26.0	
Mitomycin-C	.01	50	1,039	1,865	1.79	37.3	26.0	329.31
Tricresyl phosphate	.05	50	1,038	475	0.45	9.5	26.0	9.45
	.16	50	1,032	444	0.43	8.9	26.0	2.90
	.50	50	1,048	435	0.41	8.7	26.0	-0.73
	1.60	50	1,043	394	0.37	7.9	26.0	-9.65
	5.00	50	1,018	428	0.42	8.6	26.0	0.55
	16.00	0						
								P=0.927[c]
+S9								
Trial 2								
Summary: Negative								
Dimethylsulfoxide		50	1,043	488	0.46	9.8	26.0	
Cyclophosphamide	1.5	50	1,036	2,341	2.25	46.8	26.0	382.96
Tricresyl phosphate	16	50	1,041	447	0.42	8.9	26.0	-8.23
	50	50	1,045	446	0.42	8.9	26.0	-8.78
	160	50	1,041	468	0.44	9.4	26.0	-3.92
	500	50	1,046	458	0.43	9.2	26.0	-6.42
	1,600	50	1,045	418	0.40	8.4	26.0	-14.51
	5,000	50	1,036	501	0.48	10.0	29.0	3.36
								P=0.507

[a] Study performed at Environmental Health Research & Testing. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway *et al.* (1987).
[b] SCEs/chromosome of culture exposed to tricresyl phosphate relative to those of culture exposed to solvent
[c] Significance of relative SCEs/chromosome tested by the linear regression trend test vs. log of the dose.

TABLE E3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Tricresyl Phosphate[a]

-S9					+S9				
Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells w/Abs	Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells w/Abs
Trial 1 - Harvest time: 14.0 hours Summary: Negative					**Trial 1** - Harvest time: 14.0 hours Summary: Negative				
Dimethylsulfoxide					Dimethylsulfoxide				
	100	0	0.00	0.0		100	1	0.01	1.0
Cyclophosphamide					Cyclophosphamide				
25	100	21	0.21	18.0	25	100	74	0.74	51.0
Tricresyl phosphate					Tricresyl phosphate				
50	100	0	0.00	0.0	160	100	0	0.00	0.0
160	100	1	0.00	0.0	500	100	0	0.00	0.0
500	100	1	0.01	1.0	1,600	100	1	0.01	1.0
1,600	100	0	0.00	0.0	5,000	100	0	0.00	0.0
5,000	100	1	0.01	1.0					
				P=0.199[b]					P=0.690

[a] Study performed at Environmental Health Research & Testing. Abs = aberrations. A detailed presentation of the protocol is found in Galloway *et al.* (1987).
[b] Significance of percent cells with aberrations tested by the linear regression trend test vs. log of the dose.

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

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TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 16-Day Gavage Study of Tricresyl Phosphate[a]

	Vehicle Control	360 mg/kg	730 mg/kg	1,450 mg/kg	2,900 mg/kg	5,800 mg/kg
Male						
n	9	10	9	10	5	10
Necropsy body wt	214 ± 6	209 ± 4	199 ± 4	178 ± 5**	164 ± 16**	168 ± 9**
Brain						
Absolute	1.780 ± 0.012	1.761 ± 0.020	1.740 ± 0.018	1.729 ± 0.023	1.747 ± 0.039	1.717 ± 0.021*
Relative	8.36 ± 0.23	8.45 ± 0.18	8.78 ± 0.18	9.78 ± 0.25**	11.04 ± 0.92**	10.44 ± 0.45**
Heart						
Absolute	0.823 ± 0.042	0.766 ± 0.027	0.704 ± 0.011**	0.677 ± 0.030**	0.673 ± 0.038**	0.635 ± 0.021**
Relative	3.84 ± 0.14	3.66 ± 0.09	3.55 ± 0.06	3.80 ± 0.10	4.20 ± 0.24	3.83 ± 0.11
R. Kidney						
Absolute	0.999 ± 0.034	1.017 ± 0.028	0.955 ± 0.026	0.947 ± 0.025	0.935 ± 0.040	0.907 ± 0.041
Relative	4.66 ± 0.11	4.86 ± 0.07	4.81 ± 0.10	5.34 ± 0.11**	5.86 ± 0.37**	5.44 ± 0.15**
Liver						
Absolute	12.321 ± 0.816	14.038 ± 0.559	13.407 ± 0.428	13.264 ± 0.515	13.420 ± 1.093	13.254 ± 0.891
Relative	57.15 ± 2.75	66.99 ± 1.84**	67.45 ± 1.50**	74.46 ± 1.71**	82.64 ± 2.59**	78.60 ± 1.51**
Lungs						
Absolute	1.400 ± 0.076[b]	1.367 ± 0.072	1.306 ± 0.067	1.245 ± 0.068[c]	1.238 ± 0.076	1.115 ± 0.042**[c]
Relative	6.61 ± 0.30[b]	6.54 ± 0.32	6.57 ± 0.31	7.05 ± 0.28[c]	7.71 ± 0.45	6.74 ± 0.49[c]
R. Testis						
Absolute	1.257 ± 0.034	1.288 ± 0.023	1.178 ± 0.034	0.980 ± 0.082**[c]	0.839 ± 0.065**	0.930 ± 0.051**
Relative	5.87 ± 0.10	6.17 ± 0.08	5.93 ± 0.12	5.41 ± 0.33[c]	5.19 ± 0.24	5.62 ± 0.34
Thymus						
Absolute	0.444 ± 0.020	0.376 ± 0.020	0.365 ± 0.011	0.332 ± 0.013**[c]	0.257 ± 0.067**	0.277 ± 0.039**
Relative	2.07 ± 0.08	1.80 ± 0.09	1.85 ± 0.08	1.82 ± 0.06[c]	1.47 ± 0.28*	1.59 ± 0.16**

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 16-Day Gavage Study of Tricresyl Phosphate
(continued)

	Vehicle Control	360 mg/kg	730 mg/kg	1,450 mg/kg	2,900 mg/kg	5,800 mg/kg
Female						
n	9	10	10	9	2	10
Necropsy body wt	148 ± 2	154 ± 2	153 ± 4	136 ± 4*	122 ± 7**	125 ± 5**
Brain						
Absolute	1.699 ± 0.023	1.654 ± 0.015	1.687 ± 0.016	1.649 ± 0.014	1.602 ± 0.019	1.641 ± 0.019*
Relative	11.49 ± 0.18	10.76 ± 0.13	11.07 ± 0.21	12.18 ± 0.32	13.14 ± 0.85*	13.30 ± 0.46**
Heart						
Absolute	0.560 ± 0.014	0.575 ± 0.012	0.581 ± 0.017	0.531 ± 0.017	0.488 ± 0.054	0.508 ± 0.013*
Relative	3.78 ± 0.06	3.74 ± 0.07	3.79 ± 0.05	3.90 ± 0.07	3.97 ± 0.22	4.10 ± 0.12**
R. Kidney						
Absolute	0.689 ± 0.022	0.733 ± 0.010	0.727 ± 0.019	0.743 ± 0.020	0.702 ± 0.043	0.671 ± 0.014
Relative	4.65 ± 0.10	4.77 ± 0.09	4.75 ± 0.08	5.51 ± 0.29**	5.73 ± 0.04*	5.41 ± 0.13**
Liver						
Absolute	6.840 ± 0.201	8.994 ± 0.215**	9.648 ± 0.208**	10.149 ± 0.351**	8.697 ± 0.263**	9.520 ± 0.313**
Relative	46.14 ± 0.82	58.42 ± 0.99**	63.19 ± 1.18**	74.45 ± 0.87**	71.17 ± 1.66**	76.53 ± 1.41**
Lungs						
Absolute	1.132 ± 0.075	1.230 ± 0.043[c]	1.138 ± 0.057	1.020 ± 0.032	0.851 ± 0.076	0.935 ± 0.029**
Relative	7.63 ± 0.45	8.04 ± 0.32[c]	7.45 ± 0.36	7.52 ± 0.26	6.94 ± 0.25	7.55 ± 0.26
Thymus						
Absolute	0.363 ± 0.014	0.377 ± 0.012	0.329 ± 0.008	0.219 ± 0.028**	0.192 ± 0.044**	0.181 ± 0.028**
Relative	2.45 ± 0.09	2.45 ± 0.07	2.16 ± 0.06	1.57 ± 0.17**	1.55 ± 0.27**	1.40 ± 0.18**

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)
[b] n=8
[c] n=9

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Gavage Study of Tricresyl Phosphate[a]

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg	800 mg/kg
Male						
n	10	10	10	10	10	10
Necropsy body wt	373 ± 8	361 ± 4	360 ± 7	348 ± 7**	338 ± 5**	321 ± 6**
Brain						
Absolute	1.941 ± 0.023	1.918 ± 0.010	1.934 ± 0.023	1.919 ± 0.015	1.909 ± 0.022	1.890 ± 0.023
Relative	5.22 ± 0.09	5.32 ± 0.07	5.39 ± 0.11	5.53 ± 0.09**	5.64 ± 0.06**	5.90 ± 0.06**
Heart						
Absolute	0.999 ± 0.015	0.955 ± 0.014	1.024 ± 0.031	0.992 ± 0.032	0.963 ± 0.013	0.950 ± 0.027
Relative	2.69 ± 0.05	2.65 ± 0.04	2.84 ± 0.05	2.85 ± 0.07*	2.85 ± 0.04*	2.96 ± 0.07**
R. Kidney						
Absolute	1.195 ± 0.039	1.123 ± 0.023	1.165 ± 0.039	1.132 ± 0.033	1.136 ± 0.015	1.095 ± 0.022
Relative	3.20 ± 0.05	3.11 ± 0.06	3.23 ± 0.05	[illegible] ± 0.06	3.36 ± 0.06	3.42 ± 0.07*
Liver						
Absolute	14.416 ± 0.686	13.866 ± 0.370	14.331 ± 0.551	[illegible]75 ± 0.522	15.556 ± 0.392	15.939 ± 0.344*
Relative	38.53 ± 1.16	38.45 ± 1.08	39.76 ± 1.06	41.26 ± 1.06	46.04 ± 1.27**	49.71 ± 0.94**
Lungs						
Absolute	1.938 ± 0.068	2.025 ± 0.056	1.839 ± 0.036	1.800 ± 0.027*	1.754 ± 0.034**	1.710 ± 0.047**
Relative	5.19 ± 0.12	5.62 ± 0.17*	5.12 ± 0.10	5.18 ± 0.05	5.19 ± 0.08	5.33 ± 0.09
L. Testis						
Absolute	1.564 ± 0.026	1.724 ± 0.147	1.528 ± 0.042[b]	1.542 ± 0.029	1.405 ± 0.027	0.857 ± 0.095**
Relative	4.20 ± 0.06	4.77 ± 0.40	4.17 ± 0.11[b]	4.44 ± 0.04	4.15 ± 0.07	2.66 ± 0.29**
Thymus						
Absolute	0.286 ± 0.011	0.277 ± 0.012	0.237 ± 0.010**	0.234 ± 0.013**[b]	0.196 ± 0.012**	0.169 ± 0.009**
Relative	0.77 ± 0.03	0.77 ± 0.03	0.66 ± 0.03*	0.67 ± 0.03*[b]	0.58 ± 0.03**	0.53 ± 0.03**

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Gavage Study of Tricresyl Phosphate (continued)

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg	800 mg/kg
Female						
n	10	10	10	10	10	10
Necropsy body wt	206 ± 5	207 ± 3	210 ± 3	211 ± 3	205 ± 3	212 ± 3
Brain						
Absolute	1.791 ± 0.023	1.779 ± 0.016	1.770 ± 0.014	1.792 ± 0.016	1.793 ± 0.016	1.801 ± 0.016
Relative	8.72 ± 0.18	8.58 ± 0.08	8.46 ± 0.12	8.53 ± 0.12	8.77 ± 0.14	8.51 ± 0.09
Heart						
Absolute	0.626 ± 0.013	0.637 ± 0.017	0.636 ± 0.013	0.633 ± 0.018	0.632 ± 0.026	0.650 ± 0.017
Relative	3.04 ± 0.03	3.07 ± 0.07	3.03 ± 0.03	3.00 ± 0.07	3.08 ± 0.10	3.06 ± 0.06
R. Kidney						
Absolute	0.691 ± 0.015	0.677 ± 0.020	0.662 ± 0.014	0.708 ± 0.009	0.727 ± 0.015	0.761 ± 0.016**
Relative	3.36 ± 0.04	3.26 ± 0.07	3.16 ± 0.07	3.37 ± 0.06	3.55 ± 0.06*	3.59 ± 0.04**
Liver						
Absolute	7.382 ± 0.172	7.593 ± 0.210	7.649 ± 0.145	7.909 ± 0.136	8.644 ± 0.295**	9.552 ± 0.248**
Relative	35.87 ± 0.62	36.60 ± 0.80	36.52 ± 0.63	37.57 ± 0.39	42.12 ± 1.01**	45.07 ± 0.86**
Lungs						
Absolute	1.426 ± 0.039	1.268 ± 0.040	1.378 ± 0.038	1.426 ± 0.056	1.366 ± 0.062	1.338 ± 0.051
Relative	6.95 ± 0.24	6.11 ± 0.16*	6.58 ± 0.18	6.78 ± 0.27	6.65 ± 0.23	6.31 ± 0.21
Thymus						
Absolute	0.226 ± 0.011	0.225 ± 0.011	0.225 ± 0.008	0.218 ± 0.012	0.192 ± 0.007*	0.199 ± 0.007*
Relative	1.10 ± 0.05	1.08 ± 0.05	1.07 ± 0.04	1.03 ± 0.06	0.93 ± 0.02*	0.94 ± 0.03*

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)
[b] n=9

TABLE F3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Study of Tricresyl Phosphate[a]

	0 ppm	900 ppm	1,700 ppm	3,300 ppm	6,600 ppm	13,000 ppm
Male						
n	10	10	10	10	10	10
Necropsy body wt	369 ± 7	364 ± 9	372 ± 6	338 ± 5**	337 ± 8**	240 ± 9**
Brain						
Absolute	1.952 ± 0.034	1.985 ± 0.023	1.965 ± 0.022	1.973 ± 0.018	1.953 ± 0.025	1.886 ± 0.043
Relative	5.29 ± 0.06	5.48 ± 0.11	5.29 ± 0.05	5.85 ± 0.03**	5.82 ± 0.11**	7.95 ± 0.29**
Heart						
Absolute	1.132 ± 0.044	1.121 ± 0.035	1.110 ± 0.031	1.087 ± 0.081	1.070 ± 0.036	0.782 ± 0.027**
Relative	3.07 ± 0.11	3.08 ± 0.05	2.98 ± 0.06	3.21 ± 0.21	3.17 ± 0.05	3.27 ± 0.06
R. Kidney						
Absolute	2.653 ± 0.049	2.529 ± 0.054	2.604 ± 0.077	2.541 ± 0.053	2.462 ± 0.077*	2.060 ± 0.068**
Relative	7.20 ± 0.08	6.97 ± 0.16	7.00 ± 0.13	7.52 ± 0.08	7.31 ± 0.12	8.62 ± 0.15**
Liver						
Absolute	14.819 ± 0.264	14.584 ± 0.385	16.303 ± 0.375	15.795 ± 0.580	17.723 ± 0.611**	14.013 ± 0.707
Relative	40.21 ± 0.44	40.11 ± 0.72	43.85 ± 0.53**	46.68 ± 1.21**	52.60 ± 0.95**	58.32 ± 1.21**
Lungs						
Absolute	1.780 ± 0.058	1.945 ± 0.050	1.924 ± 0.075	1.849 ± 0.073	1.766 ± 0.053	1.443 ± 0.062**
Relative	4.82 ± 0.10	5.36 ± 0.12	5.17 ± 0.15	5.48 ± 0.21*	5.26 ± 0.18*	6.06 ± 0.26**
R. Testis						
Absolute	1.494 ± 0.019	1.531 ± 0.037	1.587 ± 0.034	1.532 ± 0.021	0.965 ± 0.085**	0.488 ± 0.025**
Relative	4.06 ± 0.06	4.21 ± 0.09	4.27 ± 0.07	4.54 ± 0.08	2.87 ± 0.24**	2.04 ± 0.07**
Thymus						
Absolute	0.343 ± 0.016	0.319 ± 0.009	0.321 ± 0.007	0.272 ± 0.012**	0.301 ± 0.015**	0.205 ± 0.012**
Relative	0.93 ± 0.05	0.88 ± 0.02	0.86 ± 0.02	0.81 ± 0.03	0.90 ± 0.05	0.86 ± 0.05

TABLE F3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Study of Tricresyl Phosphate
(continued)

	0 ppm	900 ppm	1,700 ppm	3,300 ppm	6,600 ppm	13,000 ppm
Female						
n	10	10	10	10	10	10
Necropsy body wt	202 ± 3	195 ± 4	195 ± 3	188 ± 3**	180 ± 3**	176 ± 2**
Brain						
Absolute	1.821 ± 0.013	1.773 ± 0.015	1.788 ± 0.021	1.796 ± 0.014	1.807 ± 0.025	1.833 ± 0.019
Relative	9.05 ± 0.12	9.14 ± 0.19	9.17 ± 0.08	9.56 ± 0.13*	10.08 ± 0.20**	10.44 ± 0.18**
Heart						
Absolute	0.694 ± 0.014	0.676 ± 0.018	0.657 ± 0.016	0.676 ± 0.022	0.605 ± 0.013**	0.611 ± 0.017**
Relative	3.45 ± 0.07	3.48 ± 0.09	3.37 ± 0.07	3.59 ± 0.10	3.37 ± 0.05	3.47 ± 0.07
R. Kidney						
Absolute	1.492 ± 0.027	1.523 ± 0.033	1.480 ± 0.030	1.478 ± 0.041	1.440 ± 0.031	1.537 ± 0.023
Relative	7.40 ± 0.09	7.83 ± 0.08	7.59 ± 0.10	7.86 ± 0.18**	8.01 ± 0.09**	8.74 ± 0.07**
Liver						
Absolute	6.631 ± 0.131[b]	6.794 ± 0.231	6.903 ± 0.175	6.920 ± 0.114	7.576 ± 0.176**	9.399 ± 0.185**
Relative	33.15 ± 0.57[b]	34.82 ± 0.57	35.37 ± 0.67*	36.81 ± 0.43**	42.17 ± 0.82**	53.45 ± 0.91**
Lungs						
Absolute	1.291 ± 0.028	1.319 ± 0.038	1.286 ± 0.048	1.283 ± 0.045	1.248 ± 0.040	1.255 ± 0.059
Relative	6.41 ± 0.11	6.81 ± 0.27	6.59 ± 0.23	6.83 ± 0.26	6.96 ± 0.24	7.13 ± 0.31
Thymus						
Absolute	0.257 ± 0.012	0.246 ± 0.007	0.243 ± 0.013	0.237 ± 0.010	0.238 ± 0.008	0.214 ± 0.009**
Relative	1.28 ± 0.06	1.27 ± 0.03	1.24 ± 0.05	1.26 ± 0.05	1.32 ± 0.05	1.22 ± 0.05

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)
[b] n=9

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 3-Month Interim Evaluation in the 2-Year Feed Study of Tricresyl Phosphate[a]

	0 ppm	75 ppm	150 ppm	300 ppm	600 ppm
Male					
n	10	10	10	10	10
Necropsy body wt	342 ± 11	337 ± 5	349 ± 6	332 ± 4	340 ± 11
L. Adrenal Gland					
Absolute	0.024 ± 0.002	0.024 ± 0.001	0.021 ± 0.001	0.023 ± 0.001	0.025 ± 0.001[b]
Relative	0.07 ± 0.00	0.07 ± 0.00	0.06 ± 0.00	0.07 ± 0.00	0.07 ± 0.00[b]
R. Adrenal Gland					
Absolute	0.021 ± 0.001	0.022 ± 0.001	0.023 ± 0.001	0.024 ± 0.001	0.023 ± 0.001
Relative	0.06 ± 0.00	0.06 ± 0.00	0.06 ± 0.00	0.07 ± 0.00	0.07 ± 0.00
Brain					
Absolute	1.939 ± 0.042	1.943 ± 0.021	1.968 ± 0.013	1.986 ± 0.017	1.945 ± 0.019
Relative	5.69 ± 0.12	5.77 ± 0.07	5.66 ± 0.11	5.99 ± 0.06	5.76 ± 0.13
L. Kidney					
Absolute	1.269 ± 0.047	1.219 ± 0.031	1.231 ± 0.028	1.192 ± 0.022	1.239 ± 0.039
Relative	3.71 ± 0.06	3.62 ± 0.08	3.53 ± 0.05	3.59 ± 0.04	3.65 ± 0.04
R. Kidney					
Absolute	1.267 ± 0.048	1.179 ± 0.026	1.207 ± 0.026	1.188 ± 0.018	1.219 ± 0.041
Relative	3.69 ± 0.05	3.50 ± 0.07	3.46 ± 0.06*	3.58 ± 0.05	3.59 ± 0.05
Liver					
Absolute	14.055 ± 0.670	13.611 ± 0.375	14.530 ± 0.514	13.714 ± 0.339	15.149 ± 0.522
Relative	40.91 ± 1.09	40.36 ± 0.85	41.72 ± 1.52	41.30 ± 0.95	44.61 ± 1.01*
L. Testis					
Absolute	1.423 ± 0.043	1.395 ± 0.033	1.429 ± 0.027[b]	1.368 ± 0.016	1.436 ± 0.027
Relative	4.16 ± 0.05	4.14 ± 0.06	4.08 ± 0.06[b]	4.12 ± 0.04	4.24 ± 0.07
R. Testis					
Absolute	1.345 ± 0.049	1.354 ± 0.028	1.360 ± 0.043	1.374 ± 0.011	1.396 ± 0.034
Relative	3.94 ± 0.11	4.02 ± 0.06	3.90 ± 0.11	4.14 ± 0.05	4.12 ± 0.06

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 3-Month Interim Evaluation in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	75 ppm	150 ppm	300 ppm	600 ppm
Female					
n	10	10	10	10	10
Necropsy body wt	189 ± 1	194 ± 3	191 ± 2	188 ± 3	186 ± 4
L. Adrenal Gland					
Absolute	0.024 ± 0.001	0.026 ± 0.001	0.027 ± 0.001	0.030 ± 0.002*	0.033 ± 0.001**
Relative	0.13 ± 0.01	0.13 ± 0.01	0.14 ± 0.01	0.16 ± 0.01**	0.18 ± 0.00**
R. Adrenal Gland					
Absolute	0.024 ± 0.002	0.023 ± 0.002	0.025 ± 0.002	0.029 ± 0.001	0.033 ± 0.002**
Relative	0.13 ± 0.01	0.12 ± 0.01	0.13 ± 0.01	0.16 ± 0.01	0.18 ± 0.01**
Brain					
Absolute	1.795 ± 0.021	1.800 ± 0.020	1.807 ± 0.019	1.789 ± 0.020	1.763 ± 0.025
Relative	9.51 ± 0.11	9.29 ± 0.13	9.46 ± 0.10	9.56 ± 0.16	9.51 ± 0.11
L. Kidney					
Absolute	0.705 ± 0.015	0.722 ± 0.027	0.721 ± 0.017	0.686 ± 0.017	0.682 ± 0.022
Relative	3.74 ± 0.07	3.71 ± 0.10	3.78 ± 0.08	3.66 ± 0.06	3.67 ± 0.05
R. Kidney					
Absolute	0.698 ± 0.016	0.701 ± 0.025	0.719 ± 0.015	0.692 ± 0.019	0.688 ± 0.022
Relative	3.70 ± 0.08	3.61 ± 0.10	3.77 ± 0.07	3.69 ± 0.07	3.70 ± 0.05
Liver					
Absolute	6.650 ± 0.138	6.968 ± 0.242	6.907 ± 0.146	6.559 ± 0.191	6.716 ± 0.146
Relative	35.23 ± 0.69	35.87 ± 0.97	36.17 ± 0.68	35.01 ± 0.96	36.18 ± 0.34

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=9

TABLE F5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 9-Month Interim Evaluation in the 2-Year Feed Study of Tricresyl Phosphate[a]

	0 ppm	75 ppm	150 ppm	300 ppm	600 ppm
Male					
n	9	9	10	10	10
Necropsy body wt	441 ± 12	420 ± 8	443 ± 10	419 ± 10	432 ± 11
L. Adrenal Gland					
Absolute	0.028 ± 0.002	0.027 ± 0.002	0.026 ± 0.001	0.032 ± 0.002	0.027 ± 0.001
Relative	0.06 ± 0.00	0.06 ± 0.00	0.06 ± 0.00	0.08 ± 0.01	0.06 ± 0.00
R. Adrenal Gland					
Absolute	0.027 ± 0.002	0.024 ± 0.001	0.026 ± 0.001	0.028 ± 0.001	0.027 ± 0.001
Relative	0.06 ± 0.00	0.06 ± 0.00	0.06 ± 0.00	0.07 ± 0.00	0.06 ± 0.00
Brain					
Absolute	2.040 ± 0.022	2.008 ± 0.025	2.013 ± 0.029	2.070 ± 0.024	2.063 ± 0.024
Relative	4.65 ± 0.13	4.78 ± 0.07	4.56 ± 0.10	4.97 ± 0.15	4.80 ± 0.09
L. Kidney					
Absolute	1.622 ± 0.059	1.477 ± 0.032	1.512 ± 0.044	1.542 ± 0.037	1.597 ± 0.044
Relative	3.68 ± 0.08	3.51 ± 0.05	3.41 ± 0.06	3.71 ± 0.14	3.70 ± 0.06
R. Kidney					
Absolute	1.580 ± 0.050	1.433 ± 0.017*	1.508 ± 0.042	1.483 ± 0.027	1.540 ± 0.045
Relative	3.58 ± 0.07	3.41 ± 0.06	3.40 ± 0.07	3.56 ± 0.09	3.57 ± 0.06
Liver					
Absolute	17.200 ± 0.580	14.900 ± 0.351*	16.362 ± 0.523	16.083 ± 0.522	15.703 ± 0.562
Relative	39.08 ± 1.08	35.51 ± 0.93	36.90 ± 0.80	38.52 ± 1.38	36.37 ± 0.85
L. Testis					
Absolute	1.573 ± 0.027	1.500 ± 0.023	1.557 ± 0.024	1.579 ± 0.037[b]	1.587 ± 0.026[b]
Relative	3.58 ± 0.07	3.57 ± 0.07	3.52 ± 0.06	3.73 ± 0.12[b]	3.63 ± 0.07[b]
R. Testis					
Absolute	1.495 ± 0.034	1.471 ± 0.016	1.569 ± 0.030	1.538 ± 0.032[b]	1.594 ± 0.033*[b]
Relative	3.40 ± 0.08	3.51 ± 0.08	3.55 ± 0.05	3.64 ± 0.12[b]	3.64 ± 0.07*[b]

TABLE F5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 9-Month Interim Evaluation in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	75 ppm	150 ppm	300 ppm	600 ppm
Female					
n	10	10	10	10	10
Necropsy body wt	236 ± 4	239 ± 6	235 ± 6	229 ± 4	243 ± 4
L. Adrenal Gland					
Absolute	0.032 ± 0.002	0.030 ± 0.001	0.034 ± 0.002	0.033 ± 0.001	0.032 ± 0.001
Relative	0.14 ± 0.01	0.13 ± 0.00	0.14 ± 0.01	0.14 ± 0.00	0.13 ± 0.00
R. Adrenal Gland					
Absolute	0.031 ± 0.002	0.031 ± 0.001	0.030 ± 0.001	0.030 ± 0.001	0.029 ± 0.002
Relative	0.13 ± 0.01	0.13 ± 0.00	0.13 ± 0.01	0.13 ± 0.01	0.12 ± 0.01
Brain					
Absolute	1.895 ± 0.019	1.846 ± 0.023	1.858 ± 0.027	1.840 ± 0.023	1.852 ± 0.013
Relative	8.06 ± 0.16	7.78 ± 0.19	7.95 ± 0.15	8.04 ± 0.14	7.64 ± 0.13
L. Kidney					
Absolute	0.937 ± 0.027	0.891 ± 0.026	0.898 ± 0.034	0.905 ± 0.024	0.914 ± 0.018
Relative	3.98 ± 0.10	3.74 ± 0.06	3.82 ± 0.08	3.95 ± 0.08	3.76 ± 0.07
R. Kidney					
Absolute	0.904 ± 0.025	0.871 ± 0.029	0.861 ± 0.034	0.893 ± 0.028	0.898 ± 0.026
Relative	3.84 ± 0.09	3.65 ± 0.06	3.66 ± 0.08	3.89 ± 0.07	3.69 ± 0.08
Liver					
Absolute	8.373 ± 0.232	8.249 ± 0.249	8.653 ± 0.319	8.119 ± 0.258	8.385 ± 0.262
Relative	35.60 ± 1.05	34.60 ± 0.61	36.90 ± 0.98	35.39 ± 0.82	34.43 ± 0.65

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=9

TABLE F6
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of Tricresyl Phosphate[a]

	0 ppm	75 ppm	150 ppm	300 ppm	600 ppm
Male					
n	10	10	10	10	10
Necropsy body wt	472 ± 8	470 ± 15	464 ± 9	466 ± 11	467 ± 10
L. Adrenal Gland					
Absolute	0.026 ± 0.001	0.028 ± 0.001	0.026 ± 0.001	0.025 ± 0.002	0.026 ± 0.001
Relative	0.06 ± 0.00	0.06 ± 0.00	0.06 ± 0.00	0.05 ± 0.00	0.06 ± 0.00
R. Adrenal Gland					
Absolute	0.027 ± 0.001	0.027 ± 0.001	0.024 ± 0.000	0.025 ± 0.001	0.026 ± 0.001
Relative	0.06 ± 0.00	0.06 ± 0.00	0.05 ± 0.00	0.05 ± 0.00	0.06 ± 0.00
Brain					
Absolute	2.142 ± 0.024	2.113 ± 0.027	2.087 ± 0.015	2.122 ± 0.028	2.126 ± 0.018
Relative	4.55 ± 0.10	4.53 ± 0.14	4.51 ± 0.07	4.57 ± 0.09	4.57 ± 0.08
L. Kidney					
Absolute	1.882 ± 0.032	1.848 ± 0.062	1.745 ± 0.047	1.771 ± 0.069	1.778 ± 0.045
Relative	4.00 ± 0.10	3.94 ± 0.10	3.76 ± 0.06	3.80 ± 0.12	3.82 ± 0.10
R. Kidney					
Absolute	1.839 ± 0.034	1.790 ± 0.052	1.736 ± 0.053	1.754 ± 0.061	1.795 ± 0.034
Relative	3.91 ± 0.11	3.82 ± 0.10	3.74 ± 0.06	3.77 ± 0.10	3.85 ± 0.07
Liver					
Absolute	19.466 ± 0.355	18.654 ± 0.516	18.019 ± 0.814	18.564 ± 0.619	18.963 ± 0.916
Relative	41.28 ± 0.64	39.82 ± 1.05	38.76 ± 1.37	39.95 ± 1.31	40.74 ± 2.07
L. Testis					
Absolute	1.647 ± 0.056	1.761 ± 0.146	1.688 ± 0.090	1.835 ± 0.114	1.717 ± 0.092
Relative	3.51 ± 0.16	3.76 ± 0.30	3.63 ± 0.17	3.97 ± 0.29	3.67 ± 0.17
R. Testis					
Absolute	1.583 ± 0.033[b]	1.547 ± 0.039[b]	1.512 ± 0.051	1.568 ± 0.067	1.547 ± 0.040
Relative	3.36 ± 0.08[b]	3.32 ± 0.12[b]	3.26 ± 0.08	3.36 ± 0.10	3.32 ± 0.09

TABLE F6
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	75 ppm	150 ppm	300 ppm	600 ppm
Female					
n	9	8	10	10	9
Necropsy body wt	274 ± 8	314 ± 9*	295 ± 11	304 ± 8	292 ± 7
L. Adrenal Gland					
Absolute	0.030 ± 0.002	0.035 ± 0.002	0.030 ± 0.003	0.034 ± 0.002	0.030 ± 0.001
Relative	0.11 ± 0.01	0.11 ± 0.00	0.10 ± 0.01	0.11 ± 0.01	0.10 ± 0.00
R. Adrenal Gland					
Absolute	0.029 ± 0.002	0.032 ± 0.002	0.033 ± 0.001*	0.032 ± 0.001	0.029 ± 0.001
Relative	0.10 ± 0.01	0.10 ± 0.00	0.11 ± 0.01	0.11 ± 0.00	0.10 ± 0.00
Brain					
Absolute	1.892 ± 0.030	1.924 ± 0.014	1.873 ± 0.015	1.910 ± 0.017	1.932 ± 0.029
Relative	6.96 ± 0.22	6.16 ± 0.18*	6.42 ± 0.24	6.31 ± 0.14	6.64 ± 0.13
L. Kidney					
Absolute	1.016 ± 0.025	1.132 ± 0.023*	1.040 ± 0.031	1.098 ± 0.031	1.040 ± 0.025
Relative	3.72 ± 0.07	3.63 ± 0.15	3.54 ± 0.09	3.61 ± 0.05	3.57 ± 0.08
R. Kidney					
Absolute	1.010 ± 0.024	1.104 ± 0.021	1.022 ± 0.035	1.073 ± 0.032	1.056 ± 0.024
Relative	3.70 ± 0.04	3.53 ± 0.11	3.48 ± 0.11	3.53 ± 0.05	3.62 ± 0.06
Liver					
Absolute	9.024 ± 0.465	11.022 ± 0.445*	11.084 ± 0.568*	10.741 ± 0.483*	10.426 ± 0.304
Relative	32.88 ± 1.12	35.27 ± 1.65	37.40 ± 0.85*	35.28 ± 1.01	35.85 ± 1.12

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=9

TABLE F7
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 16-Day Gavage Study of Tricresyl Phosphate[a]

	Vehicle Control	360 mg/kg	730 mg/kg	1,450 mg/kg	5,800 mg/kg
Male					
n	10	10	10	5	6
Necropsy body wt	27.4 ± 0.3	27.9 ± 0.3	27.8 ± 0.6	24.5 ± 0.6*	26.3 ± 1.0*
Brain					
Absolute	0.436 ± 0.005	0.448 ± 0.017	0.457 ± 0.008	0.447 ± 0.006	0.451 ± 0.015
Relative	15.93 ± 0.22	16.08 ± 0.62	16.49 ± 0.30	18.32 ± 0.60*	17.28 ± 0.92*
Heart					
Absolute	0.139 ± 0.009	0.156 ± 0.007	0.165 ± 0.010	0.126 ± 0.007	0.132 ± 0.014
Relative	5.07 ± 0.29	5.60 ± 0.25	5.89 ± 0.24	5.17 ± 0.27	4.98 ± 0.41
R. Kidney					
Absolute	0.258 ± 0.010	0.265 ± 0.008	0.274 ± 0.013	0.230 ± 0.008	0.241 ± 0.014
Relative	9.40 ± 0.31	9.48 ± 0.26	9.81 ± 0.29	9.42 ± 0.27	9.14 ± 0.31
Liver					
Absolute	1.703 ± 0.069	2.030 ± 0.033**	2.266 ± 0.088**	1.696 ± 0.100	1.758 ± 0.120
Relative	62.06 ± 2.02	72.87 ± 1.25**	81.42 ± 2.06**	69.25 ± 3.38**	66.72 ± 3.16**
Lungs					
Absolute	0.221 ± 0.008	0.259 ± 0.011*	0.244 ± 0.010	0.217 ± 0.014[b]	0.218 ± 0.016
Relative	8.08 ± 0.28	9.30 ± 0.38	8.77 ± 0.31	8.94 ± 0.57[b]	8.36 ± 0.73
R. Testis					
Absolute	0.090 ± 0.006	0.103 ± 0.006	0.102 ± 0.004	0.094 ± 0.004	0.098 ± 0.009
Relative	3.29 ± 0.21	3.70 ± 0.21	3.65 ± 0.13	3.86 ± 0.20	3.76 ± 0.35
Thymus					
Absolute	0.044 ± 0.003	0.043 ± 0.004	0.046 ± 0.003	0.030 ± 0.003*	0.032 ± 0.002*
Relative	1.60 ± 0.08	1.52 ± 0.16	1.68 ± 0.11	1.22 ± 0.14	1.20 ± 0.04*

TABLE F7
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 16-Day Gavage Study of Tricresyl Phosphate (continued)

	Vehicle Control	360 mg/kg	730 mg/kg	5,800 mg/kg
Female				
n	10	10	10	9
Necropsy body wt	20.8 ± 0.3	22.6 ± 0.3**	24.3 ± 0.4**	23.3 ± 0.4**
Brain				
Absolute	0.452 ± 0.008	0.466 ± 0.009	0.450 ± 0.006	0.465 ± 0.011
Relative	21.81 ± 0.41	20.66 ± 0.23*	18.59 ± 0.31**	20.03 ± 0.57**
Heart				
Absolute	0.130 ± 0.009	0.129 ± 0.008	0.119 ± 0.005	0.117 ± 0.005
Relative	6.23 ± 0.38	5.72 ± 0.32	4.90 ± 0.19**	5.00 ± 0.20**
R. Kidney				
Absolute	0.186 ± 0.008	0.187 ± 0.007	0.183 ± 0.006	0.190 ± 0.009
Relative	8.96 ± 0.29	8.30 ± 0.28	7.56 ± 0.23**	8.16 ± 0.28**
Liver				
Absolute	1.297 ± 0.055	1.580 ± 0.041**	1.936 ± 0.054**	1.926 ± 0.069**
Relative	62.30 ± 1.88	70.02 ± 1.26**	79.78 ± 1.89**	82.64 ± 1.89**
Lungs				
Absolute	0.202 ± 0.009	0.228 ± 0.010	0.220 ± 0.007	0.211 ± 0.009
Relative	9.73 ± 0.41	10.09 ± 0.42	9.06 ± 0.26	9.10 ± 0.47
Thymus				
Absolute	0.061 ± 0.003	0.060 ± 0.003	0.057 ± 0.004	0.049 ± 0.005*
Relative	2.94 ± 0.15	2.66 ± 0.11	2.36 ± 0.16*	2.12 ± 0.21**

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error). No measurements taken for females receiving 1,450 mg/kg and males and females receiving 2,900 mg/kg due to 100% mortality.
[b] n=4

TABLE F8
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Gavage Study of Tricresyl Phosphate[a]

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg	800 mg/kg
Male						
n	10	10	10	10	10	10
Necropsy body wt	35.8 ± 0.5	36.7 ± 0.7	36.8 ± 1.1	32.1 ± 1.0**	32.4 ± 0.4**	28.0 ± 0.5**
Brain						
Absolute	0.457 ± 0.003	0.457 ± 0.006	0.459 ± 0.006	0.447 ± 0.005	0.452 ± 0.005	0.449 ± 0.007
Relative	12.77 ± 0.18	12.50 ± 0.25	12.56 ± 0.32	14.03 ± 0.41**	13.99 ± 0.19**	16.04 ± 0.21**
Heart						
Absolute	0.196 ± 0.006	0.185 ± 0.006	0.180 ± 0.005	0.167 ± 0.006**	0.163 ± 0.004**	0.148 ± 0.010**
Relative	5.50 ± 0.20	5.05 ± 0.19	4.93 ± 0.21	5.23 ± 0.24	5.03 ± 0.12	5.25 ± 0.27
R. Kidney						
Absolute	0.305 ± 0.005	0.312 ± 0.009	0.318 ± 0.005	0.278 ± 0.006**	0.275 ± 0.007**	0.262 ± 0.008**
Relative	8.51 ± 0.16	8.51 ± 0.22	8.71 ± 0.24	8.70 ± 0.25	8.51 ± 0.22	9.35 ± 0.20**
Liver						
Absolute	1.929 ± 0.056	1.826 ± 0.051	2.105 ± 0.067	1.666 ± 0.046**	2.013 ± 0.034	1.752 ± 0.046
Relative	53.92 ± 1.62	49.78 ± 1.10	57.68 ± 2.36	52.09 ± 1.50	62.27 ± 0.96**	62.49 ± 0.76**
Lungs						
Absolute	0.242 ± 0.005	0.234 ± 0.009	0.258 ± 0.011	0.223 ± 0.008	0.232 ± 0.009	0.198 ± 0.006**
Relative	6.77 ± 0.16	6.39 ± 0.22	7.04 ± 0.30	6.98 ± 0.29	7.18 ± 0.34	7.09 ± 0.24
L. Testis						
Absolute	0.119 ± 0.002	0.123 ± 0.002	0.120 ± 0.002	0.115 ± 0.002	0.111 ± 0.002*	0.104 ± 0.003**
Relative	3.33 ± 0.07	3.36 ± 0.06	3.30 ± 0.12	3.62 ± 0.11	3.45 ± 0.08	3.72 ± 0.09**
Thymus						
Absolute	0.029 ± 0.003	0.037 ± 0.002	0.040 ± 0.002*	0.030 ± 0.003	0.035 ± 0.002	0.030 ± 0.002
Relative	0.81 ± 0.08	1.00 ± 0.06	1.10 ± 0.06	0.95 ± 0.11	1.09 ± 0.06*	1.06 ± 0.07*

TABLE F8
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Gavage Study of Tricresyl Phosphate (continued)

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg	800 mg/kg
Female						
n	10	9	10	10	10	10
Necropsy body wt	26.7 ± 0.7	26.4 ± 1.0	27.5 ± 0.7	25.6 ± 0.4	23.8 ± 0.4**	22.4 ± 0.3**
Brain						
Absolute	0.478 ± 0.006	0.464 ± 0.005	0.465 ± 0.006	0.471 ± 0.004	0.469 ± 0.006	0.468 ± 0.006
Relative	17.97 ± 0.48	17.03 ± 0.30	16.94 ± 0.35	18.40 ± 0.25	19.73 ± 0.33**	20.95 ± 0.26**
Heart						
Absolute	0.124 ± 0.003	0.128 ± 0.004	0.127 ± 0.005	0.123 ± 0.003	0.115 ± 0.004	0.120 ± 0.006
Relative	4.66 ± 0.10	4.68 ± 0.08	4.65 ± 0.21	4.80 ± 0.13	4.81 ± 0.10	5.36 ± 0.24**
R. Kidney						
Absolute	0.189 ± 0.006	0.192 ± 0.003	0.182 ± 0.004	0.177 ± 0.006	0.174 ± 0.006	0.183 ± 0.005
Relative	7.08 ± 0.15	7.03 ± 0.11	6.63 ± 0.13	6.89 ± 0.17	7.28 ± 0.20	8.19 ± 0.16**
Liver						
Absolute	1.376 ± 0.035	1.491 ± 0.036	1.465 ± 0.039	1.565 ± 0.057**	1.583 ± 0.034**	1.531 ± 0.049**
Relative	51.58 ± 0.91	54.61 ± 1.24	53.24 ± 0.95	61.00 ± 1.48**	66.43 ± 0.68**	68.39 ± 1.46**
Lungs						
Absolute	0.215 ± 0.007	0.216 ± 0.012	0.209 ± 0.006[b]	0.206 ± 0.007[b]	0.208 ± 0.006	0.194 ± 0.008
Relative	8.07 ± 0.23	7.94 ± 0.46	7.64 ± 0.25[b]	8.05 ± 0.24[b]	8.74 ± 0.26	8.67 ± 0.30
Thymus						
Absolute	0.046 ± 0.003	0.044 ± 0.003	0.042 ± 0.001	0.039 ± 0.004	0.043 ± 0.002	0.034 ± 0.002**
Relative	1.71 ± 0.10	1.62 ± 0.10	1.53 ± 0.07	1.52 ± 0.15	1.83 ± 0.10	1.52 ± 0.09

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)
[b] n=9

TABLE F9
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Feed Study of Tricresyl Phosphate[a]

	0 ppm	250 ppm	500 ppm	1,000 ppm	2,100 ppm	4,200 ppm
Male						
n	10	10	10	10	10	10
Necropsy body wt	31.2 ± 1.0	32.3 ± 0.9	31.2 ± 0.8	31.6 ± 1.0	29.7 ± 0.6	25.6 ± 0.3**
Brain						
Absolute	0.463 ± 0.006	0.467 ± 0.007	0.471 ± 0.009	0.462 ± 0.007	0.459 ± 0.006	0.474 ± 0.007
Relative	15.00 ± 0.51	14.57 ± 0.48	15.15 ± 0.33	14.74 ± 0.40	15.50 ± 0.34	18.52 ± 0.29**
Heart						
Absolute	0.170 ± 0.005	0.165 ± 0.008	0.170 ± 0.011	0.165 ± 0.006	0.150 ± 0.005	0.134 ± 0.006**
Relative	5.50 ± 0.24	5.13 ± 0.27	5.43 ± 0.30	5.23 ± 0.18	5.04 ± 0.15	5.22 ± 0.21
R. Kidney						
Absolute	0.529 ± 0.017	0.529 ± 0.011	0.523 ± 0.018	0.518 ± 0.015	0.518 ± 0.013	0.454 ± 0.012**
Relative	17.03 ± 0.45	16.47 ± 0.52	16.77 ± 0.41	16.44 ± 0.34	17.47 ± 0.49	17.72 ± 0.40
Liver						
Absolute	1.389 ± 0.037	1.453 ± 0.046	1.423 ± 0.045	1.474 ± 0.056	1.447 ± 0.056	1.306 ± 0.026
Relative	44.68 ± 0.61	44.99 ± 0.89	45.63 ± 0.92	46.76 ± 1.26	48.68 ± 1.67*	51.04 ± 0.80**
Lungs						
Absolute	0.231 ± 0.010	0.239 ± 0.010	0.226 ± 0.008	0.223 ± 0.008	0.218 ± 0.010	0.216 ± 0.013
Relative	7.47 ± 0.42	7.42 ± 0.33	7.25 ± 0.16	7.08 ± 0.26	7.33 ± 0.23	8.41 ± 0.45
R. Testis						
Absolute	0.119 ± 0.002	0.123 ± 0.004	0.114 ± 0.002	0.114 ± 0.003	0.110 ± 0.002	0.105 ± 0.004**
Relative	3.83 ± 0.09	3.81 ± 0.12	3.66 ± 0.08	3.62 ± 0.09	3.72 ± 0.05	4.09 ± 0.15
Thymus						
Absolute	0.042 ± 0.003	0.041 ± 0.004	0.044 ± 0.003	0.042 ± 0.002	0.039 ± 0.003	0.037 ± 0.002
Relative	1.34 ± 0.08	1.28 ± 0.10	1.40 ± 0.10	1.35 ± 0.07	1.33 ± 0.12	1.43 ± 0.06

TABLE F9
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Feed Study of Tricresyl Phosphate
(continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm	2,100 ppm	4,200 ppm
Female						
n	10	10	10	10	10	10
Necropsy body wt	28.3 ± 0.1	27.5 ± 0.7	27.4 ± 0.7	26.9 ± 0.8	24.2 ± 0.5**	22.6 ± 0.3**
Brain						
Absolute	0.483 ± 0.006	0.463 ± 0.006	0.473 ± 0.008	0.469 ± 0.005	0.484 ± 0.010	0.498 ± 0.014
Relative	17.24 ± 0.59	16.94 ± 0.52	17.40 ± 0.57	17.53 ± 0.42	20.07 ± 0.49**	22.07 ± 0.78**
Heart						
Absolute	0.169 ± 0.005	0.141 ± 0.007	0.165 ± 0.009	0.145 ± 0.005*	0.145 ± 0.006*	0.133 ± 0.008**
Relative	6.06 ± 0.28	5.16 ± 0.33	6.04 ± 0.36	5.41 ± 0.18	6.03 ± 0.29	5.87 ± 0.35
R. Kidney						
Absolute	0.358 ± 0.006	0.355 ± 0.006	0.353 ± 0.006	0.365 ± 0.010	0.342 ± 0.007	0.330 ± 0.008*
Relative	12.75 ± 0.38	12.95 ± 0.26	12.96 ± 0.31	13.56 ± 0.25	14.17 ± 0.25**	14.61 ± 0.33**
Liver						
Absolute	1.334 ± 0.041	1.328 ± 0.034	1.366 ± 0.039	1.338 ± 0.042	1.351 ± 0.037	1.309 ± 0.028
Relative	47.34 ± 1.07	48.48 ± 1.44	50.07 ± 1.47	49.73 ± 0.89	55.91 ± 1.34**	57.90 ± 0.98**
Lungs						
Absolute	0.269 ± 0.012	0.228 ± 0.013	0.267 ± 0.021	0.250 ± 0.013	0.265 ± 0.015	0.238 ± 0.019[b]
Relative	9.53 ± 0.36	8.34 ± 0.57	9.75 ± 0.70	9.32 ± 0.47	11.00 ± 0.66	10.45 ± 0.85[b]
Thymus						
Absolute	0.054 ± 0.003	0.051 ± 0.002	0.050 ± 0.003	0.052 ± 0.002	0.052 ± 0.003	0.051 ± 0.004
Relative	1.90 ± 0.08	1.86 ± 0.12	1.86 ± 0.15	1.94 ± 0.07	2.16 ± 0.14	2.25 ± 0.16

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=9

TABLE F10
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 3-Month Interim Evaluation in the 2-Year Feed Study of Tricresyl Phosphate[a]

	0 ppm	60 ppm	125 ppm	250 ppm
Male				
n	8	10	10	10
Necropsy body wt	31.9 ± 0.7	30.5 ± 0.5	30.7 ± 0.9	31.5 ± 1.5
L. Adrenal Gland				
Absolute	0.004 ± 0.000	0.003 ± 0.000[b]	0.005 ± 0.001	0.004 ± 0.000
Relative	0.12 ± 0.01	0.11 ± 0.01[b]	0.16 ± 0.02	0.14 ± 0.01
R. Adrenal Gland				
Absolute	0.003 ± 0.001	0.003 ± 0.000	0.004 ± 0.000	0.004 ± 0.001
Relative	0.10 ± 0.02	0.10 ± 0.01	0.13 ± 0.01	0.14 ± 0.02
Brain				
Absolute	0.462 ± 0.004	0.448 ± 0.004	0.444 ± 0.004	0.452 ± 0.007
Relative	14.53 ± 0.27	14.76 ± 0.32	14.57 ± 0.36	14.61 ± 0.61
L. Kidney				
Absolute	0.274 ± 0.009	0.268 ± 0.004	0.266 ± 0.010	0.264 ± 0.007
Relative	8.61 ± 0.32	8.82 ± 0.14	8.68 ± 0.24	8.49 ± 0.27
R. Kidney				
Absolute	0.290 ± 0.010	0.279 ± 0.005	0.282 ± 0.010	0.284 ± 0.010
Relative	9.13 ± 0.38	9.18 ± 0.21	9.19 ± 0.18	9.11 ± 0.25
Liver				
Absolute	1.360 ± 0.042	1.417 ± 0.033	1.427 ± 0.057	1.431 ± 0.080
Relative	42.73 ± 1.22	46.50 ± 0.55*	46.50 ± 0.91*	45.35 ± 0.99
L. Testis				
Absolute	0.112 ± 0.003	0.109 ± 0.001	0.108 ± 0.003	0.108 ± 0.004
Relative	3.54 ± 0.11	3.61 ± 0.09	3.51 ± 0.06	3.47 ± 0.15
R. Testis				
Absolute	0.114 ± 0.002	0.113 ± 0.003	0.108 ± 0.003	0.109 ± 0.004
Relative	3.60 ± 0.10	3.73 ± 0.10	3.55 ± 0.09	3.50 ± 0.16

TABLE F10
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 3-Month Interim Evaluation in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	60 ppm	125 ppm	250 ppm
Female				
n	10	10	10	10
Necropsy body wt	29.1 ± 1.1	29.8 ± 1.0	29.7 ± 0.8	28.0 ± 0.9
L. Adrenal Gland				
Absolute	0.007 ± 0.001	0.007 ± 0.000	0.006 ± 0.000	0.007 ± 0.000
Relative	0.24 ± 0.02	0.22 ± 0.02	0.22 ± 0.02	0.24 ± 0.02
R. Adrenal Gland				
Absolute	0.005 ± 0.000	0.006 ± 0.001	0.006 ± 0.000	0.006 ± 0.000
Relative	0.18 ± 0.01	0.21 ± 0.02	0.22 ± 0.02	0.21 ± 0.01
Brain				
Absolute	0.470 ± 0.006	0.472 ± 0.005	0.469 ± 0.004	0.462 ± 0.005
Relative	16.36 ± 0.62	15.94 ± 0.40	15.90 ± 0.48	16.65 ± 0.50
L. Kidney				
Absolute	0.189 ± 0.005	0.184 ± 0.003	0.199 ± 0.007	0.184 ± 0.004
Relative	6.56 ± 0.20	6.21 ± 0.17	6.75 ± 0.31	6.59 ± 0.17
R. Kidney				
Absolute	0.200 ± 0.006	0.201 ± 0.003	0.203 ± 0.004	0.199 ± 0.006
Relative	6.93 ± 0.19	6.79 ± 0.22	6.88 ± 0.23	7.12 ± 0.17
Liver				
Absolute	1.313 ± 0.037	1.380 ± 0.029	1.396 ± 0.047	1.307 ± 0.047
Relative	45.49 ± 1.35	46.58 ± 1.30	47.04 ± 1.24	46.83 ± 1.39

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=9

TABLE F11
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 9-Month Interim Evaluation in the 2-Year Feed Study of Tricresyl Phosphate[a]

	0 ppm	60 ppm	125 ppm	250 ppm
Male				
n	10	10	10	10
Necropsy body wt	41.4 ± 1.2	38.2 ± 1.3	41.3 ± 1.2	42.0 ± 1.3
L. Adrenal Gland				
Absolute	0.003 ± 0.000	0.003 ± 0.000	0.003 ± 0.000	0.003 ± 0.000
Relative	0.06 ± 0.01	0.08 ± 0.01	0.06 ± 0.01	0.06 ± 0.01
R. Adrenal Gland				
Absolute	0.002 ± 0.000	0.002 ± 0.000	0.002 ± 0.000	0.003 ± 0.000
Relative	0.05 ± 0.00	0.07 ± 0.01	0.05 ± 0.01	0.07 ± 0.01
Brain				
Absolute	0.445 ± 0.005	0.454 ± 0.008	0.461 ± 0.009	0.466 ± 0.009
Relative	10.84 ± 0.29	12.00 ± 0.42	11.25 ± 0.41	11.22 ± 0.49
L. Kidney				
Absolute	0.313 ± 0.010	0.308 ± 0.012	0.331 ± 0.011	0.326 ± 0.010
Relative	7.60 ± 0.23	8.08 ± 0.25	8.06 ± 0.31	7.80 ± 0.25
R. Kidney				
Absolute	0.331 ± 0.007	0.324 ± 0.012	0.352 ± 0.011	0.340 ± 0.009
Relative	8.03 ± 0.20	8.51 ± 0.25	8.55 ± 0.28	8.14 ± 0.27
Liver				
Absolute	1.712 ± 0.091	1.660 ± 0.098	1.793 ± 0.040	1.779 ± 0.085
Relative	41.24 ± 1.25	43.25 ± 1.51	43.60 ± 1.10	42.24 ± 1.03
L. Testis				
Absolute	0.108 ± 0.003	0.106 ± 0.007	0.115 ± 0.005	0.113 ± 0.004
Relative	2.63 ± 0.06	2.76 ± 0.16	2.79 ± 0.11	2.72 ± 0.12
R. Testis				
Absolute	0.111 ± 0.003	0.107 ± 0.007	0.119 ± 0.004	0.118 ± 0.004
Relative	2.69 ± 0.07	2.81 ± 0.17	2.88 ± 0.10	2.83 ± 0.15

TABLE F11
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 9-Month Interim Evaluation in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	60 ppm	125 ppm	250 ppm
Female				
n	10	10	10	10
Necropsy body wt	40.1 ± 1.1	43.9 ± 1.6	41.3 ± 1.1	40.8 ± 1.0
L. Adrenal Gland				
Absolute	0.005 ± 0.000	0.006 ± 0.000	0.005 ± 0.000	0.006 ± 0.000
Relative	0.12 ± 0.01	0.13 ± 0.01	0.12 ± 0.01	0.14 ± 0.01
R. Adrenal Gland				
Absolute	0.005 ± 0.000	0.005 ± 0.000	0.004 ± 0.000	0.006 ± 0.000
Relative	0.11 ± 0.01	0.12 ± 0.01	0.10 ± 0.01	0.14 ± 0.01
Brain				
Absolute	0.483 ± 0.006	0.488 ± 0.009	0.469 ± 0.009	0.465 ± 0.005
Relative	12.11 ± 0.27	11.20 ± 0.35	11.43 ± 0.37	11.47 ± 0.31
L. Kidney				
Absolute	0.233 ± 0.009	0.237 ± 0.009	0.232 ± 0.006	0.223 ± 0.003
Relative	5.81 ± 0.20	5.40 ± 0.16	5.66 ± 0.22	5.51 ± 0.14
R. Kidney				
Absolute	0.242 ± 0.008	0.247 ± 0.008	0.252 ± 0.006	0.250 ± 0.006
Relative	6.06 ± 0.17	5.64 ± 0.14	6.13 ± 0.22	6.16 ± 0.21
Liver				
Absolute	1.561 ± 0.049	1.787 ± 0.054**	1.709 ± 0.055	1.619 ± 0.033
Relative	39.06 ± 1.15	40.82 ± 0.81	41.44 ± 0.88	39.95 ± 1.31

** Significantly different ($P \leq 0.01$) from the control group by Dunnett's test
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

TABLE F12
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of Tricresyl Phosphate[a]

	0 ppm	60 ppm	125 ppm	250 ppm
Male				
n	10	10	10	10
Necropsy body wt	46.7 ± 0.9	46.6 ± 1.3	45.7 ± 1.4	49.2 ± 1.2
L. Adrenal Gland				
Absolute	0.003 ± 0.000	0.003 ± 0.000	0.003 ± 0.000	0.002 ± 0.000*
Relative	0.07 ± 0.01	0.06 ± 0.01	0.07 ± 0.01	0.05 ± 0.00*
R. Adrenal Gland				
Absolute	0.003 ± 0.000	0.003 ± 0.000	0.003 ± 0.000	0.002 ± 0.000
Relative	0.06 ± 0.01	0.06 ± 0.01	0.07 ± 0.00	0.05 ± 0.01
Brain				
Absolute	0.436 ± 0.006	0.453 ± 0.004	0.443 ± 0.005	0.466 ± 0.003**
Relative	9.37 ± 0.17	9.78 ± 0.31	9.76 ± 0.24	9.51 ± 0.24
L. Kidney				
Absolute	0.356 ± 0.013	0.365 ± 0.011	0.359 ± 0.010	0.353 ± 0.011
Relative	7.61 ± 0.16	7.86 ± 0.25	7.87 ± 0.14	7.18 ± 0.14
R. Kidney				
Absolute	0.384 ± 0.014	0.379 ± 0.010	0.382 ± 0.011	0.379 ± 0.013
Relative	8.20 ± 0.17	8.15 ± 0.17	8.37 ± 0.12	7.69 ± 0.14*
Liver				
Absolute	2.029 ± 0.085	2.085 ± 0.179	2.179 ± 0.193	2.141 ± 0.118
Relative	43.44 ± 1.44	44.32 ± 2.84	47.40 ± 3.55	43.25 ± 1.59
L. Testis				
Absolute	0.102 ± 0.004	0.112 ± 0.003	0.109 ± 0.003	0.112 ± 0.002
Relative	2.18 ± 0.08	2.41 ± 0.09	2.39 ± 0.06	2.28 ± 0.03
R. Testis				
Absolute	0.106 ± 0.004	0.110 ± 0.003	0.108 ± 0.003	0.113 ± 0.002
Relative	2.26 ± 0.07	2.36 ± 0.09	2.37 ± 0.08	2.30 ± 0.04

TABLE F12
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of Tricresyl Phosphate (continued)

	0 ppm	60 ppm	125 ppm	250 ppm
Female				
n	10	10	10	9
Necropsy body wt	48.7 ± 1.9	49.2 ± 1.8	49.3 ± 1.9	49.6 ± 2.4
L. Adrenal Gland				
Absolute	0.005 ± 0.000	0.005 ± 0.000	0.005 ± 0.000	0.007 ± 0.000**
Relative	0.10 ± 0.01	0.11 ± 0.01	0.11 ± 0.01	0.14 ± 0.01*
R. Adrenal Gland				
Absolute	0.004 ± 0.000	0.006 ± 0.000	0.005 ± 0.000	0.006 ± 0.001**
Relative	0.09 ± 0.01	0.12 ± 0.01	0.11 ± 0.01	0.13 ± 0.02*
Brain				
Absolute	0.465 ± 0.006	0.459 ± 0.005	0.476 ± 0.008	0.469 ± 0.008
Relative	9.67 ± 0.34	9.43 ± 0.33	9.77 ± 0.34	9.62 ± 0.40
L. Kidney				
Absolute	0.275 ± 0.006	0.252 ± 0.006*	0.263 ± 0.004	0.257 ± 0.009
Relative	5.72 ± 0.24	5.16 ± 0.16	5.41 ± 0.23	5.23 ± 0.16
R. Kidney				
Absolute	0.282 ± 0.008	0.265 ± 0.006	0.279 ± 0.005	0.279 ± 0.009
Relative	5.86 ± 0.25	5.43 ± 0.17	5.73 ± 0.26	5.70 ± 0.24
Liver				
Absolute	1.743 ± 0.038	1.794 ± 0.054	1.775 ± 0.048	1.801 ± 0.077
Relative	36.27 ± 1.62	36.64 ± 0.98	36.27 ± 1.14	36.80 ± 2.01

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

APPENDIX G
HEMATOLOGY AND CLINICAL CHEMISTRY RESULTS

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TABLE G1
Hematology and Clinical Chemistry Data for Rats in the 13-Week Gavage Study of Tricresyl Phosphate[a]

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg	800 mg/kg
Male						
n	10	10	10	10	10	10
Hematology						
Hematocrit (%)	46.7 ± 0.6	47.9 ± 0.5	46.3 ± 0.9	46.3 ± 0.3	44.8 ± 0.5*	44.1 ± 0.7*
Hemoglobin (g/dL)	16.1 ± 0.2	16.2 ± 0.2	15.7 ± 0.3	16.1 ± 0.1	15.2 ± 0.2**	15.0 ± 0.3**
Erythrocytes (10^6/μL)	9.84 ± 0.09	9.95 ± 0.09	9.64 ± 0.19	9.74 ± 0.05	9.32 ± 0.09**	9.25 ± 0.20**
Mean cell volume (fL)	47.3 ± 0.3	47.8 ± 0.3	48.2 ± 0.2	47.5 ± 0.3	48.1 ± 0.2	48.0 ± 0.4
Mean cell hemoglobin (pg)	16.3 ± 0.1	16.3 ± 0.1	16.3 ± 0.1	16.5 ± 0.1	16.3 ± 0.1	16.2 ± 0.1
Mean cell hemoglobin concentration (g/dL)	34.4 ± 0.3	33.8 ± 0.3	33.9 ± 0.2	34.7 ± 0.3	33.9 ± 0.3	34.0 ± 0.2
Platelets (10^3/μL)	468.3 ± 37.1	468.1 ± 32.5	473.4 ± 14.2	500.8 ± 21.1	529.8 ± 10.7	542.6 ± 40.9
Leukocytes (10^3/μL)	9.12 ± 0.28	9.16 ± 0.81	8.04 ± 0.36	10.01 ± 0.35	8.12 ± 0.24	8.36 ± 0.32
Segmented neutrophils (10^3/μL)	1.13 ± 0.16	1.26 ± 0.27	1.05 ± 0.08	1.36 ± 0.15	1.14 ± 0.09	1.37 ± 0.13
Lymphocytes (10^3/μL)	7.62 ± 0.21	7.66 ± 0.58	6.72 ± 0.30*	8.38 ± 0.34	6.76 ± 0.20*	6.71 ± 0.28*
Monocytes (10^3/μL)	0.21 ± 0.04	0.11 ± 0.03	0.15 ± 0.03	0.10 ± 0.03	0.16 ± 0.04	0.18 ± 0.06
Eosinophils (10^3/μL)	0.14 ± 0.04	0.13 ± 0.04	0.12 ± 0.03	0.16 ± 0.06	0.06 ± 0.02	0.09 ± 0.03
Nucleated erythrocytes (10^3/μL)	0.05 ± 0.02	0.06 ± 0.02	0.02 ± 0.01	0.07 ± 0.04	0.07 ± 0.02	0.09 ± 0.03
Clinical Chemistry						
Cholinesterase (IU/L)	593.5 ± 21.0	349.0 ± 8.2**	304.3 ± 5.5**	261.6 ± 6.9**	237.0 ± 10.4**	188.9 ± 7.2**
Female						
n	10	10	10	10	10	10
Hematology						
Hematocrit (%)	46.2 ± 0.8	46.3 ± 0.6	46.7 ± 0.7	44.5 ± 0.6	45.7 ± 0.6	44.6 ± 0.5
Hemoglobin (g/dL)	15.5 ± 0.2	15.4 ± 0.2	15.4 ± 0.1	14.8 ± 0.2**	15.0 ± 0.2*	14.7 ± 0.2**
Erythrocytes (10^6/μL)	8.71 ± 0.10	8.79 ± 0.10	8.82 ± 0.07	8.43 ± 0.07*	8.61 ± 0.07	8.58 ± 0.06
Mean cell volume (fL)	53.1 ± 0.5	52.9 ± 0.6	53.0 ± 0.5	53.0 ± 0.5	53.1 ± 0.4	52.1 ± 0.5
Mean cell hemoglobin (pg)	17.8 ± 0.1	17.5 ± 0.1	17.5 ± 0.1	17.6 ± 0.1	17.4 ± 0.1*	17.2 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	33.6 ± 0.4	33.2 ± 0.4	33.1 ± 0.4	33.3 ± 0.4	32.8 ± 0.3	33.0 ± 0.3
Platelets (10^3/μL)	486.1 ± 13.3	438.6 ± 20.6	447.8 ± 24.4	370.8 ± 21.5**	432.8 ± 35.5	425.6 ± 36.0
Leukocytes (10^3/μL)	9.01 ± 0.44	8.09 ± 0.43	8.74 ± 0.34	8.58 ± 0.33	8.83 ± 0.66	9.46 ± 0.28
Segmented neutrophils (10^3/μL)	1.65 ± 0.20	1.19 ± 0.17	1.37 ± 0.18	1.22 ± 0.19	1.37 ± 0.14	1.55 ± 0.23
Lymphocytes (10^3/μL)	7.02 ± 0.31	6.76 ± 0.41	7.22 ± 0.19	7.09 ± 0.37	7.13 ± 0.49	7.63 ± 0.25
Monocytes (10^3/μL)	0.16 ± 0.03	0.07 ± 0.03	0.09 ± 0.04	0.10 ± 0.04	0.13 ± 0.03	0.14 ± 0.02
Eosinophils (10^3/μL)	0.17 ± 0.04	0.07 ± 0.03	0.07 ± 0.02	0.09 ± 0.03	0.07 ± 0.02	0.13 ± 0.03
Nucleated erythrocytes (10^3/μL)	0.16 ± 0.04	0.05 ± 0.02	0.10 ± 0.04	0.10 ± 0.03	0.08 ± 0.04	0.06 ± 0.02
Clinical Chemistry						
Cholinesterase (IU/L)	2,785 ± 128	882 ± 45**	594 ± 18**	287 ± 7**	243 ± 11**	166 ± 6**

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error

TABLE G2
Hematology and Clinical Chemistry Data for Rats in the 13-Week Feed Study of Tricresyl Phosphate[a]

	0 ppm	900 ppm	1,700 ppm	3,300 ppm	6,600 ppm	13,000 ppm
Male						
n	10	10	10	10	10	10
Hematology						
Hematocrit (%)	48.0 ± 1.2	48.9 ± 1.1	48.4 ± 0.8	49.9 ± 1.4	46.3 ± 1.0	45.2 ± 1.3
Hemoglobin (g/dL)	15.2 ± 0.3	15.6 ± 0.1	15.1 ± 0.2	15.5 ± 0.2	14.8 ± 0.2	14.3 ± 0.3*
Erythrocytes (10^6/μL)	9.21 ± 0.19	9.35 ± 0.09	9.09 ± 0.13	9.29 ± 0.14	8.89 ± 0.10	9.14 ± 0.18
Mean cell volume (fL)	52.0 ± 1.0	52.2 ± 1.1	53.0 ± 0.3	53.5 ± 0.5	52.2 ± 0.9	49.3 ± 1.0**
Mean cell hemoglobin (pg)	16.5 ± 0.1	16.6 ± 0.1	16.6 ± 0.1	16.7 ± 0.1	16.6 ± 0.1	15.7 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	31.8 ± 0.6	32.0 ± 0.8	31.3 ± 0.2	31.3 ± 0.3	31.9 ± 0.6	31.8 ± 0.7
Platelets (10^3/μL)	767.2 ± 23.4	767.6 ± 13.5	831.1 ± 25.3*	837.8 ± 22.4*	841.6 ± 19.9*	959.3 ± 27.1**
Reticulocytes (10^6/μL)	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Leukocytes (10^3/μL)	10.18 ± 0.61	10.09 ± 0.59	9.97 ± 0.58	10.72 ± 0.48	9.90 ± 0.21	10.07 ± 0.54
Segmented neutrophils (10^3/μL)	1.35 ± 0.16	1.46 ± 0.16	1.20 ± 0.14[b]	1.37 ± 0.09	1.02 ± 0.09	1.81 ± 0.21
Lymphocytes (10^3/μL)	8.72 ± 0.51	8.38 ± 0.43	8.66 ± 0.54	9.17 ± 0.45	8.57 ± 0.20	8.11 ± 0.39
Monocytes (10^3/μL)	0.08 ± 0.03	0.20 ± 0.12	0.10 ± 0.04	0.12 ± 0.04	0.22 ± 0.09	0.14 ± 0.06
Eosinophils (10^3/μL)	0.03 ± 0.02	0.04 ± 0.02	0.04 ± 0.02	0.05 ± 0.02	0.09 ± 0.03	0.00 ± 0.00
Clinical Chemistry						
Cholinesterase (IU/L)	1,033.0 ± 23.5[c]	573.4 ± 14.4**	534.9 ± 17.5**	416.6 ± 16.4**	295.4 ± 7.2**	225.4 ± 12.9**
Female						
n	10	10	10	10	10	10
Hematology						
Hematocrit (%)	50.1 ± 1.0	48.9 ± 1.3	49.3 ± 1.1	47.7 ± 0.9*	43.7 ± 1.1**	43.5 ± 0.6**
Hemoglobin (g/dL)	15.5 ± 0.2	15.4 ± 0.2	15.5 ± 0.2	14.7 ± 0.2**	13.6 ± 0.2**	13.3 ± 0.2**
Erythrocytes (10^6/μL)	8.83 ± 0.16	8.73 ± 0.15	8.77 ± 0.09	8.30 ± 0.16**	7.95 ± 0.15**	8.20 ± 0.12**
Mean cell volume (fL)	56.7 ± 0.5	56.1 ± 1.3	55.8 ± 0.9	57.2 ± 0.3	54.8 ± 0.4**	52.9 ± 0.4**
Mean cell hemoglobin (pg)	17.6 ± 0.1	17.7 ± 0.2	17.6 ± 0.1	17.7 ± 0.3	17.1 ± 0.1	16.2 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	31.1 ± 0.3	31.6 ± 0.8	31.6 ± 0.6	31.0 ± 0.5	31.2 ± 0.4	30.6 ± 0.2
Platelets (10^3/μL)	745.1 ± 25.2	712.4 ± 39.6	746.9 ± 21.6[b]	802.5 ± 37.6	909.2 ± 59.0*	985.0 ± 49.3**[b]
Reticulocytes (10^6/μL)	0.12 ± 0.01	0.14 ± 0.01[b]	0.12 ± 0.01	0.18 ± 0.02*	0.17 ± 0.02	0.18 ± 0.01**
Leukocytes (10^3/μL)	7.26 ± 0.51	8.65 ± 0.80	8.69 ± 0.31	10.12 ± 0.59**	9.59 ± 0.39**	11.42 ± 0.60**
Segmented neutrophils (10^3/μL)	1.08 ± 0.09	1.29 ± 0.25[c]	1.43 ± 0.19	1.53 ± 0.19	1.62 ± 0.18	1.29 ± 0.19
Lymphocytes (10^3/μL)	6.10 ± 0.44	7.17 ± 0.74[b]	7.14 ± 0.31	8.41 ± 0.50**	7.90 ± 0.40**	9.95 ± 0.41**
Monocytes (10^3/μL)	0.05 ± 0.03	0.13 ± 0.09[b]	0.07 ± 0.03	0.16 ± 0.06	0.03 ± 0.02	0.15 ± 0.06
Eosinophils (10^3/μL)	0.03 ± 0.02	0.04 ± 0.02[b]	0.06 ± 0.03	0.03 ± 0.02	0.05 ± 0.02	0.02 ± 0.02
Clinical Chemistry						
Cholinesterase (IU/L)	4,793.8 ±188.0[d]	1,337.1 ± 78.8**	1,025.9 ± 57.4**	636.7 ± 26.7**	372.1 ± 28.8**	208.9 ± 6.6**

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error
[b] n=9
[c] n=8
[d] n=5

TABLE G3
Hematology and Clinical Chemistry Data for Rats at the 3-Month Interim Evaluation in the 2-Year Feed Study of Tricresyl Phosphate[a]

	0 ppm	75 ppm	150 ppm	300 ppm	600 ppm
Male					
n	10	9	10	9	10
Hematology					
Hematocrit (%)	50.6 ± 0.5	49.9 ± 0.8	47.5 ± 1.4	49.2 ± 0.3	48.4 ± 0.8*
Hemoglobin (g/dL)	15.5 ± 0.2	15.3 ± 0.2	14.9 ± 0.4	15.4 ± 0.2	15.1 ± 0.3
Erythrocytes (10^6/μL)	9.51 ± 0.11	9.40 ± 0.15	9.01 ± 0.26	9.40 ± 0.05	9.23 ± 0.11
Mean cell volume (fL)	53.2 ± 0.1	53.2 ± 0.2	52.6 ± 0.3	52.3 ± 0.2**	52.3 ± 0.3*
Mean cell hemoglobin (pg)	16.3 ± 0.1	16.3 ± 0.1	16.5 ± 0.1	16.4 ± 0.1	16.3 ± 0.2
Mean cell hemoglobin concentration (g/dL)	30.7 ± 0.2	30.7 ± 0.1	31.4 ± 0.3	31.3 ± 0.2	31.1 ± 0.4
Platelets (10^3/μL)	500.8 ± 34.7	533.9 ± 9.0	477.4 ± 60.1	543.8 ± 11.8	467.7 ± 39.2
Reticulocytes (10^6/μL)	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Leukocytes (10^3/μL)	7.94 ± 0.51	9.44 ± 0.37	8.95 ± 0.86	9.27 ± 0.50	8.37 ± 0.74
Segmented neutrophils (10^3/μL)	1.08 ± 0.17	1.58 ± 0.14	1.63 ± 0.46	1.57 ± 0.20	1.26 ± 0.22
Lymphocytes (10^3/μL)	6.76 ± 0.44	7.78 ± 0.40	7.25 ± 0.70	7.59 ± 0.35	7.02 ± 0.54
Monocytes (10^3/μL)	0.02 ± 0.01	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00
Eosinophils (10^3/μL)	0.07 ± 0.02	0.07 ± 0.02	0.07 ± 0.04	0.10 ± 0.03	0.09 ± 0.03
Nucleated erythrocytes (10^3/μL)	0.00 ± 0.00	0.03 ± 0.02	0.01 ± 0.01	0.01 ± 0.01	0.00 ± 0.00
Clinical Chemistry					
Cholinesterase (IU/L)	814.4 ± 29.1	773.2 ± 35.4[b]	748.6 ± 47.3	664.4 ± 16.2**[b]	592.3 ± 14.8**
Female					
n	10	10	9	8	10
Hematology					
Hematocrit (%)	49.6 ± 0.7	50.3 ± 0.7	48.7 ± 0.4	49.9 ± 0.7	49.3 ± 0.8
Hemoglobin (g/dL)	15.3 ± 0.2	15.7 ± 0.2	15.0 ± 0.1	15.6 ± 0.2	15.6 ± 0.2
Erythrocytes (10^6/μL)	8.71 ± 0.14	8.87 ± 0.13	8.52 ± 0.08	8.79 ± 0.10	8.76 ± 0.11
Mean cell volume (fL)	57.1 ± 0.3	56.6 ± 0.3	57.0 ± 0.2	57.0 ± 0.3	56.3 ± 0.3
Mean cell hemoglobin (pg)	17.6 ± 0.1	17.7 ± 0.1	17.6 ± 0.1	17.8 ± 0.1	17.8 ± 0.1
Mean cell hemoglobin concentration (g/dL)	30.9 ± 0.2	31.2 ± 0.2	30.9 ± 0.2	31.2 ± 0.3	31.6 ± 0.2*
Platelets (10^3/μL)	517.1 ± 23.8	491.6 ± 38.1	526.8 ± 15.2	554.1 ± 14.2[c]	537.8 ± 19.8[d]
Reticulocytes (10^6/μL)	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Leukocytes (10^3/μL)	7.73 ± 0.52	6.90 ± 0.50	7.39 ± 0.70	7.99 ± 0.77	6.41 ± 0.49
Segmented neutrophils (10^3/μL)	1.14 ± 0.11	1.03 ± 0.10	1.18 ± 0.20	1.48 ± 0.23	1.16 ± 0.18
Lymphocytes (10^3/μL)	6.50 ± 0.48	5.80 ± 0.43	6.13 ± 0.58	6.46 ± 0.66	5.21 ± 0.34
Monocytes (10^3/μL)	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00
Eosinophils (10^3/μL)	0.08 ± 0.03	0.06 ± 0.02	0.07 ± 0.02	0.05 ± 0.01	0.04 ± 0.02
Nucleated erythrocytes (10^3/μL)	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01
Clinical Chemistry					
Cholinesterase (IU/L)	3,860 ± 222	4,059 ± 122	2,970 ± 157**[b]	2,521 ± 140**[b]	1,983 ± 118**

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error
[b] n=10
[c] n=7
[d] n=9

TABLE G4
Hematology and Clinical Chemistry Data for Rats at the 9-Month Interim Evaluation in the 2-Year Feed Study of Tricresyl Phosphate[a]

	0 ppm	75 ppm	150 ppm	300 ppm	600 ppm
Male					
n	9	9	10	10	10
Hematology					
Hematocrit (%)	49.0 ± 0.6	48.3 ± 0.5	49.7 ± 1.0	49.4 ± 0.9	49.4 ± 0.6
Hemoglobin (g/dL)	14.8 ± 0.2	14.7 ± 0.2	15.1 ± 0.2	15.0 ± 0.2	14.9 ± 0.1
Erythrocytes (10^6/μL)	9.21 ± 0.11	8.98 ± 0.11	9.29 ± 0.15	9.24 ± 0.13	9.20 ± 0.09
Mean cell volume (fL)	53.2 ± 0.4	53.7 ± 0.5	53.4 ± 0.3	53.5 ± 0.3	53.6 ± 0.4
Mean cell hemoglobin (pg)	16.0 ± 0.1	16.3 ± 0.1	16.2 ± 0.1	16.3 ± 0.1	16.2 ± 0.1
Mean cell hemoglobin concentration (g/dL)	30.2 ± 0.2	30.3 ± 0.3	30.4 ± 0.2	30.5 ± 0.3	30.3 ± 0.2
Platelets (10^3/μL)	542.2 ± 19.6	525.2 ± 7.9	509.1 ± 11.5	535.9 ± 13.6	516.5 ± 6.2
Reticulocytes (10^6/μL)	0.2 ± 0.0	0.2 ± 0.0	0.1 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Leukocytes (10^3/μL)	8.61 ± 0.42	8.12 ± 0.44	7.79 ± 0.52	8.08 ± 0.35	7.25 ± 0.53
Segmented neutrophils (10^3/μL)	2.54 ± 0.11	1.99 ± 0.20	2.03 ± 0.20	2.33 ± 0.33	1.71 ± 0.18**
Lymphocytes (10^3/μL)	5.96 ± 0.40	5.97 ± 0.34	5.60 ± 0.35	5.53 ± 0.29	5.39 ± 0.47
Monocytes (10^3/μL)	0.01 ± 0.01	0.04 ± 0.03	0.03 ± 0.02	0.06 ± 0.04	0.02 ± 0.01
Eosinophils (10^3/μL)	0.11 ± 0.05	0.13 ± 0.03	0.13 ± 0.02	0.16 ± 0.03	0.14 ± 0.03
Nucleated erythrocytes (10^3/μL)	0.06 ± 0.03	0.01 ± 0.01	0.03 ± 0.02	0.01 ± 0.01	0.01 ± 0.01
Clinical Chemistry					
Cholinesterase (IU/L)	899.3 ± 45.5	875.3 ± 40.3	910.4 ± 32.0	728.9 ± 36.4*	915.5 ± 35.8
Female					
n	10	10	10	10	10
Hematology					
Hematocrit (%)	47.7 ± 0.6	48.7 ± 0.4	48.2 ± 0.4	48.6 ± 0.5	48.3 ± 0.5
Hemoglobin (g/dL)	14.6 ± 0.1	15.0 ± 0.1	14.8 ± 0.2	14.9 ± 0.1	14.9 ± 0.2
Erythrocytes (10^6/μL)	8.11 ± 0.09	8.29 ± 0.06	8.32 ± 0.06	8.32 ± 0.10	8.31 ± 0.09
Mean cell volume (fL)	58.9 ± 0.2	58.8 ± 0.1	57.9 ± 0.4*	58.4 ± 0.2*	58.3 ± 0.3
Mean cell hemoglobin (pg)	18.0 ± 0.1	18.0 ± 0.1	17.8 ± 0.2	17.9 ± 0.1	18.0 ± 0.1
Mean cell hemoglobin concentration (g/dL)	30.6 ± 0.1	30.7 ± 0.1	30.8 ± 0.2	30.6 ± 0.2	30.9 ± 0.2
Platelets (10^3/μL)	511.9 ± 16.8	500.2 ± 9.9	515.7 ± 12.3	487.3 ± 12.7	526.0 ± 14.3
Reticulocytes (10^6/μL)	0.1 ± 0.0	0.2 ± 0.0	0.2 ± 0.0*	0.2 ± 0.0	0.1 ± 0.0
Leukocytes (10^3/μL)	5.10 ± 0.30	5.54 ± 0.38	6.09 ± 0.39	5.13 ± 0.30	5.51 ± 0.37
Segmented neutrophils (10^3/μL)	1.33 ± 0.12	1.16 ± 0.14	1.38 ± 0.11	0.96 ± 0.09	1.30 ± 0.21
Lymphocytes (10^3/μL)	3.70 ± 0.26	4.32 ± 0.37	4.64 ± 0.32	4.11 ± 0.24	4.13 ± 0.29
Monocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01
Eosinophils (10^3/μL)	0.07 ± 0.02	0.06 ± 0.02	0.06 ± 0.02	0.07 ± 0.02	0.07 ± 0.04
Nucleated erythrocytes (10^3/μL)	0.02 ± 0.01	0.00 ± 0.00	0.06 ± 0.02	0.02 ± 0.02	0.00 ± 0.00
Clinical Chemistry					
Cholinesterase (IU/L)	4,348 ± 196	3,890 ± 159	2,803 ± 249**	2,661 ± 129**	4,376 ± 269

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error. Animals in the 600 ppm group received dosed feed for 13 weeks, after which they received control diet.

TABLE G5
Hematology and Clinical Chemistry Data for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of Tricresyl Phosphate[a]

	0 ppm	75 ppm	150 ppm	300 ppm	600 ppm
Male					
n	10	10	10	10	10
Hematology					
Hematocrit (%)	47.7 ± 1.0	48.5 ± 0.9	48.5 ± 0.7	49.4 ± 0.6	47.3 ± 0.7
Hemoglobin (g/dL)	14.5 ± 0.3	14.7 ± 0.3	14.6 ± 0.2	15.0 ± 0.2	14.3 ± 0.3
Erythrocytes (10^6/μL)	8.76 ± 0.11	8.84 ± 0.16	8.80 ± 0.13	8.87 ± 0.11	8.57 ± 0.18
Mean cell volume (fL)	54.2 ± 0.6	54.9 ± 0.6	54.9 ± 0.5	55.8 ± 0.4	55.3 ± 0.8
Mean cell hemoglobin (pg)	16.5 ± 0.2	16.6 ± 0.2	16.6 ± 0.1	16.9 ± 0.1	16.7 ± 0.3
Mean cell hemoglobin concentration (g/dL)	30.3 ± 0.2	30.3 ± 0.3	30.2 ± 0.3	30.3 ± 0.3	30.2 ± 0.3
Platelets (10^3/μL)	656.2 ± 53.2	653.6 ± 31.2	641.6 ± 19.5	594.6 ± 24.7	584.3 ± 27.9
Reticulocytes (10^6/μL)	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0[b]
Leukocytes (10^3/μL)	7.02 ± 0.31	7.00 ± 0.62	6.85 ± 0.42	7.11 ± 0.63	7.33 ± 0.55
Segmented neutrophils (10^3/μL)	2.59 ± 0.29	2.69 ± 0.32	2.19 ± 0.24	2.64 ± 0.34	2.26 ± 0.27
Lymphocytes (10^3/μL)	4.35 ± 0.28	4.20 ± 0.40	4.59 ± 0.32	4.35 ± 0.38	5.01 ± 0.46
Monocytes (10^3/μL)	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils (10^3/μL)	0.08 ± 0.02	0.10 ± 0.03	0.07 ± 0.02	0.12 ± 0.04	0.06 ± 0.02
Nucleated erythrocytes (10^3/μL)	0.01 ± 0.01	0.02 ± 0.01	0.01 ± 0.01	0.02 ± 0.01	0.02 ± 0.01
Clinical Chemistry					
Cholinesterase (IU/L)	1,038.7 ± 59.6	1,036.2 ± 71.7	1,004.8 ± 27.0	847.2 ± 32.0**	1,083.2 ± 84.6
Female					
n	9	8	10	10	9
Hematology					
Hematocrit (%)	49.5 ± 0.7	47.4 ± 0.6*	46.9 ± 0.3**	47.0 ± 0.5**	47.6 ± 0.6*
Hemoglobin (g/dL)	15.6 ± 0.2	14.9 ± 0.1	14.9 ± 0.1*	14.9 ± 0.2	15.0 ± 0.1
Erythrocytes (10^6/μL)	8.48 ± 0.11	8.04 ± 0.08**	8.22 ± 0.04	8.24 ± 0.07	8.13 ± 0.08
Mean cell volume (fL)	58.4 ± 0.4	58.9 ± 0.4	57.0 ± 0.5	57.0 ± 0.6	58.7 ± 0.3
Mean cell hemoglobin (pg)	18.3 ± 0.1	18.5 ± 0.1	18.1 ± 0.1	18.1 ± 0.2	18.5 ± 0.1
Mean cell hemoglobin concentration (g/dL)	31.4 ± 0.2	31.5 ± 0.3	31.7 ± 0.2	31.7 ± 0.2	31.5 ± 0.3
Platelets (10^3/μL)	505.7 ± 12.6	531.6 ± 14.6	516.4 ± 9.7	489.1 ± 22.0	519.1 ± 23.6
Reticulocytes (10^6/μL)	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Leukocytes (10^3/μL)	4.31 ± 0.38	3.84 ± 0.26	5.29 ± 0.56	4.31 ± 0.47	4.31 ± 0.53
Segmented neutrophils (10^3/μL)	1.23 ± 0.17	0.99 ± 0.08	1.28 ± 0.12	1.14 ± 0.16	1.00 ± 0.12
Lymphocytes (10^3/μL)	2.99 ± 0.36	2.81 ± 0.19	3.96 ± 0.47	3.13 ± 0.36	3.25 ± 0.50
Monocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils (10^3/μL)	0.09 ± 0.02	0.04 ± 0.01	0.05 ± 0.02	0.05 ± 0.01	0.06 ± 0.02
Nucleated erythrocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00
Clinical Chemistry					
Cholinesterase (IU/L)	4,176 ± 144	3,245 ± 168**	2,365 ± 260**[b]	2,150 ± 124**	3,716 ± 236**

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error. Animals in the 600 ppm group received dosed feed for 13 weeks, after which they received control diet.
[b] n=9

TABLE G6
Hematology and Clinical Chemistry Data for Mice in the 13-Week Gavage Study of Tricresyl Phosphate[a]

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg	800 mg/kg
Male						
n	10	10	10	10	10	10
Hematology						
Hematocrit (%)	42.2 ± 1.0	44.1 ± 0.8	43.0 ± 0.7	42.3 ± 1.2	42.6 ± 0.5	42.0 ± 0.9
Hemoglobin (g/dL)	15.0 ± 0.3	15.4 ± 0.2	14.9 ± 0.3	14.4 ± 0.4	14.6 ± 0.2	14.6 ± 0.3
Erythrocytes (10^6/μL)	9.87 ± 0.21	10.09 ± 0.16	9.87 ± 0.17	9.63 ± 0.28	9.89 ± 0.11	9.83 ± 0.30
Mean cell volume (fL)	42.7 ± 0.2	43.6 ± 0.3	43.5 ± 0.3	43.9 ± 0.5	43.0 ± 0.4	42.9 ± 0.6
Mean cell hemoglobin (pg)	15.2 ± 0.1	15.3 ± 0.2	15.1 ± 0.1	14.9 ± 0.1	14.8 ± 0.1*	14.9 ± 0.3*
Mean cell hemoglobin concentration (g/dL)	35.5 ± 0.3	35.0 ± 0.4	34.7 ± 0.2	34.0 ± 0.2**	34.2 ± 0.2**	34.8 ± 0.4*
Platelets (10^3/μL)	977.6 ± 29.3	795.4 ± 34.1	877.2 ± 45.9	938.4 ± 48.1	1,028.0 ± 38.7	960.2 ± 31.4
Reticulocytes (10^6/μL)	0.3 ± 0.0	0.2 ± 0.0	0.3 ± 0.0	0.3 ± 0.0	0.4 ± 0.0**	0.4 ± 0.0**
Leukocytes (10^3/μL)	7.46 ± 0.59	6.64 ± 0.49[b]	8.30 ± 0.76	9.64 ± 1.16	12.04 ± 1.88*	8.22 ± 1.01
Segmented neutrophils (10^3/μL)	2.59 ± 0.32	1.96 ± 0.32[b]	4.87 ± 0.91	6.23 ± 1.20**	7.83 ± 1.86*	3.08 ± 0.83
Lymphocytes (10^3/μL)	4.68 ± 0.50	4.58 ± 0.42[b]	3.32 ± 0.42	3.33 ± 0.36	4.07 ± 0.31	5.02 ± 0.37
Monocytes (10^3/μL)	0.04 ± 0.03	0.01 ± 0.01[b]	0.02 ± 0.02	0.02 ± 0.02	0.03 ± 0.02	0.02 ± 0.02
Eosinophils (10^3/μL)	0.14 ± 0.02	0.09 ± 0.03	0.09 ± 0.02	0.06 ± 0.03	0.11 ± 0.04	0.10 ± 0.03
Nucleated erythrocytes (10^3/μL)	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Clinical Chemistry						
Cholinesterase (IU/L)	3,255 ± 280	1,184 ± 44**[b]	1,011 ± 145**	862 ± 39**	603 ± 79**	453 ± 18**[b]
Female						
n	10	9	10	10	10	10
Hematology						
Hematocrit (%)	45.6 ± 0.4	45.3 ± 1.2	45.7 ± 0.6	43.2 ± 0.7*	45.1 ± 0.6	41.9 ± 0.5**
Hemoglobin (g/dL)	16.2 ± 0.2	15.8 ± 0.3	15.8 ± 0.2	14.9 ± 0.2**	15.5 ± 0.2**	15.1 ± 0.2**
Erythrocytes (10^6/μL)	10.53 ± 0.11	10.30 ± 0.18	10.24 ± 0.10	9.84 ± 0.14**	10.35 ± 0.09*	10.12 ± 0.14*
Mean cell volume (fL)	43.2 ± 0.3	44.0 ± 0.5	44.7 ± 0.3	44.0 ± 0.3	43.3 ± 0.3	41.5 ± 0.2*
Mean cell hemoglobin (pg)	15.4 ± 0.1	15.3 ± 0.1	15.4 ± 0.1	15.1 ± 0.1	15.0 ± 0.1**	14.9 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	35.5 ± 0.3	34.8 ± 0.3	34.5 ± 0.3	34.5 ± 0.3	34.4 ± 0.2*	36.0 ± 0.1
Platelets (10^3/μL)	696.6 ± 37.8	711.1 ± 59.7	734.4 ± 23.8	732.6 ± 30.5	698.6 ± 20.9	721.6 ± 34.4
Reticulocytes (10^6/μL)	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.3 ± 0.0	0.3 ± 0.0	0.3 ± 0.0
Leukocytes (10^3/μL)	5.88 ± 0.37	5.38 ± 0.34	5.28 ± 0.38	6.26 ± 0.37	6.89 ± 0.43	6.90 ± 0.51
Segmented neutrophils (10^3/μL)	0.99 ± 0.14	0.99 ± 0.21	0.87 ± 0.15	1.15 ± 0.16[b]	1.18 ± 0.15	1.63 ± 0.30
Lymphocytes (10^3/μL)	4.82 ± 0.25	4.26 ± 0.30	4.26 ± 0.32	4.74 ± 0.39	5.64 ± 0.38	5.05 ± 0.35
Monocytes (10^3/μL)	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01
Eosinophils (10^3/μL)	0.06 ± 0.03	0.12 ± 0.06	0.08 ± 0.03	0.06 ± 0.02	0.07 ± 0.03	0.13 ± 0.04
Nucleated erythrocytes (10^3/μL)	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01
Clinical Chemistry						
Cholinesterase (IU/L)	4,344 ± 728	1,278 ± 158**	780 ± 64**	691 ± 43**	474 ± 30**	380 ± 16**

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error
[b] n=9

TABLE G7
Hematology and Clinical Chemistry Data for Mice in the 13-Week Feed Study of Tricresyl Phosphate[a]

	0 ppm	250 ppm	500 ppm	1,000 ppm	2,100 ppm	4,200 ppm
Male						
n	10	10	10	10	9	10
Hematology						
Hematocrit (%)	47.1 ± 1.2	46.8 ± 0.5	47.0 ± 0.4	47.3 ± 0.4	47.7 ± 0.7	46.5 ± 0.6
Hemoglobin (g/dL)	16.1 ± 0.3	15.9 ± 0.2	15.7 ± 0.2	15.7 ± 0.2	15.9 ± 0.1	15.4 ± 0.2*
Erythrocytes (10^6/μL)	10.31 ± 0.17	10.15 ± 0.08	10.18 ± 0.11	10.05 ± 0.09	10.08 ± 0.09	10.28 ± 0.17
Mean cell volume (fL)	45.5 ± 0.7	46.2 ± 0.3	46.1 ± 0.4	47.1 ± 0.2	47.3 ± 0.3*	45.2 ± 0.5
Mean cell hemoglobin (pg)	15.6 ± 0.1	15.7 ± 0.1	15.5 ± 0.1	15.7 ± 0.1	15.8 ± 0.1	15.0 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	34.4 ± 0.5	34.0 ± 0.2	33.5 ± 0.3	33.3 ± 0.2*	33.4 ± 0.3	33.2 ± 0.3*
Platelets (10^3/μL)	964.2 ± 31.1	963.8 ± 33.9	952.2 ± 35.0	970.8 ± 45.2	1,014.0 ± 24.4	951.8 ± 27.8
Reticulocytes (10^6/μL)	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.2 ± 0.0	0.1 ± 0.0	0.2 ± 0.0
Leukocytes (10^3/μL)	3.44 ± 0.41	4.74 ± 0.40	3.46 ± 0.48	3.94 ± 0.53	4.91 ± 0.71	4.24 ± 0.40
Segmented neutrophils (10^3/μL)	0.50 ± 0.09	0.69 ± 0.18	0.65 ± 0.13	0.86 ± 0.16	1.61 ± 0.48*	1.11 ± 0.12**
Lymphocytes (10^3/μL)	2.94 ± 0.34	4.00 ± 0.25	2.81 ± 0.41	3.05 ± 0.42	3.28 ± 0.62	3.07 ± 0.32
Monocytes (10^3/μL)	0.02 ± 0.01	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.04 ± 0.02	0.03 ± 0.02
Eosinophils (10^3/μL)	0.01 ± 0.01	0.02 ± 0.02	0.00 ± 0.00	0.01 ± 0.01	0.04 ± 0.02	0.03 ± 0.02
Clinical Chemistry						
Cholinesterase (IU/L)	6,988.4 ± 249.0	1,691.2 ± 76.7**	1,143.8 ± 36.4**	931.8 ± 41.3**	843.0 ± 34.1**[b]	634.7 ± 22.7**
Female						
n	10	10	10	10	10	10
Hematology						
Hematocrit (%)	50.0 ± 0.9	47.9 ± 0.8	48.0 ± 1.1	48.4 ± 0.8	47.9 ± 1.2	48.0 ± 1.0
Hemoglobin (g/dL)	16.9 ± 0.3	16.1 ± 0.2	16.4 ± 0.2	16.1 ± 0.2	16.3 ± 0.3	16.0 ± 0.3*
Erythrocytes (10^6/μL)	10.79 ± 0.21	10.21 ± 0.11	10.28 ± 0.17	10.19 ± 0.17	10.20 ± 0.21	10.51 ± 0.19
Mean cell volume (fL)	46.5 ± 0.5	47.0 ± 0.5	46.8 ± 1.0	47.4 ± 0.3	47.0 ± 0.3	45.8 ± 0.5
Mean cell hemoglobin (pg)	15.7 ± 0.2	15.8 ± 0.1	16.0 ± 0.2	15.8 ± 0.1	15.9 ± 0.1	15.3 ± 0.2
Mean cell hemoglobin concentration (g/dL)	33.7 ± 0.2	33.7 ± 0.3	34.3 ± 0.6	33.2 ± 0.3[c]	34.0 ± 0.4	33.3 ± 0.3
Platelets (10^3/μL)	761.2 ± 58.8	817.0 ± 46.5	753.0 ± 24.8	883.4 ± 37.8	837.6 ± 42.6	784.8 ± 43.3
Reticulocytes (10^6/μL)	0.1 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.1 ± 0.0	0.2 ± 0.0
Leukocytes (10^3/μL)	3.66 ± 0.33	4.36 ± 0.44	4.94 ± 0.48	4.02 ± 0.23	3.76 ± 0.27	3.58 ± 0.39
Segmented neutrophils (10^3/μL)	0.36 ± 0.06	0.50 ± 0.12	0.58 ± 0.09	0.48 ± 0.09	0.41 ± 0.07	0.62 ± 0.07
Lymphocytes (10^3/μL)	3.28 ± 0.29	3.81 ± 0.33	4.28 ± 0.41	3.51 ± 0.19	3.33 ± 0.23	2.92 ± 0.33
Monocytes (10^3/μL)	0.00 ± 0.00	0.03 ± 0.02	0.03 ± 0.02	0.00 ± 0.00	0.01 ± 0.01	0.02 ± 0.01
Eosinophils (10^3/μL)	0.02 ± 0.01	0.00 ± 0.00	0.03 ± 0.02	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00
Clinical Chemistry						
Cholinesterase (IU/L)	10,443.0 ± 347.0	1,963.7 ± 109.0**	1,052.4 ± 78.0**[c]	812.0 ± 44.5**	661.6 ± 27.5**	536.6 ± 27.4**

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error
[b] n=10
[c] n=9

TABLE G8
Hematology and Clinical Chemistry Data for Mice at the 3-Month Interim Evaluation in the 2-Year Feed Study of Tricresyl Phosphate[a]

	0 ppm	60 ppm	125 ppm	250 ppm
Male				
n	9	10	10	10
Hematology				
Hematocrit (%)	52.4 ± 1.2	52.1 ± 1.4	52.2 ± 0.9	52.7 ± 0.5
Hemoglobin (g/dL)	17.8 ± 0.4	17.8 ± 0.4	17.6 ± 0.3	18.0 ± 0.2
Erythrocytes ($10^6/\mu L$)	11.24 ± 0.27	11.13 ± 0.29	11.18 ± 0.21	11.36 ± 0.15
Mean cell volume (fL)	46.7 ± 0.2	46.7 ± 0.2	46.6 ± 0.3	46.4 ± 0.3
Mean cell hemoglobin (pg)	15.8 ± 0.1	16.0 ± 0.1	15.8 ± 0.1	15.9 ± 0.1
Mean cell hemoglobin concentration (g/dL)	33.9 ± 0.2	34.2 ± 0.2	33.8 ± 0.2	34.2 ± 0.2
Platelets ($10^3/\mu L$)	616.8 ± 32.7	598.5 ± 42.1	565.6 ± 35.0	609.3 ± 28.1
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0	0.2 ± 0.0	0.1 ± 0.0	0.2 ± 0.0
Leukocytes ($10^3/\mu L$)	4.41 ± 0.48	4.59 ± 0.35	5.20 ± 0.82	4.37 ± 0.43
Segmented neutrophils ($10^3/\mu L$)	0.63 ± 0.10	0.45 ± 0.13	0.62 ± 0.14	0.45 ± 0.07
Lymphocytes ($10^3/\mu L$)	3.69 ± 0.38	4.01 ± 0.25	4.47 ± 0.77	3.78 ± 0.40
Monocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils ($10^3/\mu L$)	0.09 ± 0.03	0.13 ± 0.03	0.12 ± 0.02	0.14 ± 0.03
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Clinical Chemistry				
Cholinesterase (IU/L)	7,433 ± 425	5,118 ± 174**	3,502 ± 187**	2,090 ± 108**
Female				
n	10	10	10	10
Hematology				
Hematocrit (%)	51.9 ± 0.8	51.9 ± 1.0	50.9 ± 0.9	51.7 ± 1.0
Hemoglobin (g/dL)	17.7 ± 0.3	17.4 ± 0.3	17.2 ± 0.3	17.4 ± 0.3
Erythrocytes ($10^6/\mu L$)	10.99 ± 0.15	10.92 ± 0.20	10.80 ± 0.18	10.89 ± 0.24
Mean cell volume (fL)	47.2 ± 0.1	47.7 ± 0.2	47.0 ± 0.3	47.3 ± 0.2
Mean cell hemoglobin (pg)	16.1 ± 0.1	16.0 ± 0.1	16.0 ± 0.1	16.0 ± 0.1
Mean cell hemoglobin concentration (g/dL)	34.0 ± 0.2	33.6 ± 0.1	33.9 ± 0.2	33.7 ± 0.1
Platelets ($10^3/\mu L$)	501.8 ± 40.5	544.0 ± 40.7	568.8 ± 39.8	545.3 ± 39.5
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0	0.1 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Leukocytes ($10^3/\mu L$)	4.48 ± 0.44	4.31 ± 0.32	4.21 ± 0.35	3.77 ± 0.26
Segmented neutrophils ($10^3/\mu L$)	0.52 ± 0.07	0.42 ± 0.07	0.50 ± 0.08	0.38 ± 0.06
Lymphocytes ($10^3/\mu L$)	3.87 ± 0.39	3.81 ± 0.28	3.62 ± 0.29	3.36 ± 0.23
Monocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils ($10^3/\mu L$)	0.10 ± 0.02	0.07 ± 0.02	0.10 ± 0.03	0.04 ± 0.01*
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Clinical Chemistry				
Cholinesterase (IU/L)	8,840 ± 160	6,386 ± 105**	3,882 ± 60**	2,076 ± 187**

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error

TABLE G9
Hematology and Clinical Chemistry Data for Mice at the 9-Month Interim Evaluation in the 2-Year Feed Study of Tricresyl Phosphate[a]

	0 ppm	60 ppm	125 ppm	250 ppm
Male				
n	10	10	10	10
Hematology				
Hematocrit (%)	56.2 ± 1.2	55.6 ± 0.9	55.4 ± 0.7	56.1 ± 1.0
Hemoglobin (g/dL)	16.2 ± 0.3	16.0 ± 0.3	16.0 ± 0.2	16.2 ± 0.3
Erythrocytes (10^6/μL)	10.77 ± 0.22	10.49 ± 0.19	10.51 ± 0.14	10.71 ± 0.17
Mean cell volume (fL)	52.2 ± 0.3	53.2 ± 0.3	52.7 ± 0.2	52.3 ± 0.3
Mean cell hemoglobin (pg)	15.0 ± 0.1	15.2 ± 0.1	15.2 ± 0.1	15.1 ± 0.1
Mean cell hemoglobin concentration (g/dL)	28.9 ± 0.2	28.7 ± 0.2	28.8 ± 0.1	28.8 ± 0.1
Platelets (10^3/μL)	794.4 ± 34.9	769.5 ± 37.5	779.9 ± 49.4	724.8 ± 33.6
Reticulocytes (10^6/μL)	0.2 ± 0.0	0.1 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Leukocytes (10^3/μL)	4.99 ± 0.43	4.93 ± 0.21	4.97 ± 0.31	5.04 ± 0.40
Segmented neutrophils (10^3/μL)	1.07 ± 0.22	0.88 ± 0.10	1.04 ± 0.24	0.96 ± 0.12
Lymphocytes (10^3/μL)	3.77 ± 0.36	3.87 ± 0.21	3.77 ± 0.17	3.91 ± 0.34
Monocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00
Eosinophils (10^3/μL)	0.15 ± 0.02	0.18 ± 0.03	0.16 ± 0.03	0.17 ± 0.04
Nucleated erythrocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Clinical Chemistry				
Cholinesterase (IU/L)	8,457 ± 244	6,278 ± 191**	4,338 ± 222**[b]	2,210 ± 66**
Female				
n	10	10	10	10
Hematology				
Hematocrit (%)	54.4 ± 0.7	56.8 ± 0.7*	56.1 ± 0.6*	56.9 ± 0.7*
Hemoglobin (g/dL)	15.5 ± 0.2	15.9 ± 0.2	15.8 ± 0.2	15.9 ± 0.2
Erythrocytes (10^6/μL)	10.17 ± 0.12	10.66 ± 0.12*	10.62 ± 0.12*	10.61 ± 0.14*
Mean cell volume (fL)	53.4 ± 0.4	53.3 ± 0.3	52.8 ± 0.4	53.5 ± 0.2
Mean cell hemoglobin (pg)	15.2 ± 0.1	15.0 ± 0.1	14.9 ± 0.1	15.0 ± 0.1
Mean cell hemoglobin concentration (g/dL)	28.5 ± 0.2	28.1 ± 0.1	28.2 ± 0.1	28.0 ± 0.1
Platelets (10^3/μL)	692.4 ± 32.0	627.1 ± 40.0	649.2 ± 39.8	640.6 ± 28.0
Reticulocytes (10^6/μL)	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Leukocytes (10^3/μL)	4.08 ± 0.22	4.24 ± 0.42	3.40 ± 0.19	4.72 ± 0.27
Segmented neutrophils (10^3/μL)	0.79 ± 0.12	0.79 ± 0.10	0.64 ± 0.06	0.83 ± 0.12
Lymphocytes (10^3/μL)	3.22 ± 0.20	3.39 ± 0.32	2.71 ± 0.21	3.81 ± 0.22
Monocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils (10^3/μL)	0.07 ± 0.02	0.06 ± 0.02	0.05 ± 0.01	0.07 ± 0.03
Nucleated erythrocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Clinical Chemistry				
Cholinesterase (IU/L)	10,568 ± 261[b]	7,199 ± 104**	3,877 ± 205**	2,223 ± 151**

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error
[b] n=9

TABLE G10
Hematology and Clinical Chemistry Data for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of Tricresyl Phosphate[a]

	0 ppm	60 ppm	125 ppm	250 ppm
Male				
n	10	10	10	10
Hematology				
Hematocrit (%)	54.2 ± 0.7	56.9 ± 1.4	55.6 ± 0.9	55.4 ± 0.6
Hemoglobin (g/dL)	15.2 ± 0.2	15.7 ± 0.4	15.5 ± 0.3	15.6 ± 0.2
Erythrocytes (10^6/μL)	9.79 ± 0.13	10.32 ± 0.31	10.16 ± 0.26	9.97 ± 0.11
Mean cell volume (fL)	55.4 ± 0.4	55.3 ± 0.5	54.8 ± 0.6	55.6 ± 0.3
Mean cell hemoglobin (pg)	15.5 ± 0.2	15.3 ± 0.1	15.3 ± 0.2	15.6 ± 0.1
Mean cell hemoglobin concentration (g/dL)	28.0 ± 0.3	27.6 ± 0.2	27.8 ± 0.1	28.1 ± 0.2
Platelets (10^3/μL)	894.0 ± 25.3	908.7 ± 49.3	898.3 ± 36.8	819.9 ± 30.0
Reticulocytes (10^6/μL)	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Leukocytes (10^3/μL)	3.40 ± 0.20	3.21 ± 0.31	3.80 ± 0.23	3.08 ± 0.26
Segmented neutrophils (10^3/μL)	0.93 ± 0.08	0.67 ± 0.12*	0.91 ± 0.09	0.59 ± 0.06**
Lymphocytes (10^3/μL)	2.39 ± 0.14	2.46 ± 0.22	2.76 ± 0.16	2.44 ± 0.24
Monocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils (10^3/μL)	0.08 ± 0.02	0.08 ± 0.02	0.13 ± 0.02	0.05 ± 0.01
Nucleated erythrocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Clinical Chemistry				
Cholinesterase (IU/L)	8,777 ± 184	6,965 ± 371**	5,026 ± 402**	2,134 ± 198**
Female				
n	10	10	10	9
Hematology				
Hematocrit (%)	52.6 ± 1.1	53.9 ± 0.8	54.6 ± 0.7	54.3 ± 0.9
Hemoglobin (g/dL)	14.6 ± 0.3	14.9 ± 0.2	15.3 ± 0.2	15.2 ± 0.2
Erythrocytes (10^6/μL)	9.39 ± 0.17	9.72 ± 0.15	9.87 ± 0.12	9.70 ± 0.16
Mean cell volume (fL)	56.1 ± 0.3	55.6 ± 0.6	55.3 ± 0.5	56.1 ± 0.3
Mean cell hemoglobin (pg)	15.5 ± 0.1	15.3 ± 0.1	15.5 ± 0.1	15.6 ± 0.1
Mean cell hemoglobin concentration (g/dL)	27.8 ± 0.3	27.7 ± 0.3	28.0 ± 0.2	27.9 ± 0.1
Platelets (10^3/μL)	792.3 ± 42.2	739.8 ± 30.0	721.0 ± 35.4	703.3 ± 27.2
Reticulocytes (10^6/μL)	0.2 ± 0.0	0.3 ± 0.0	0.3 ± 0.0	0.3 ± 0.0
Leukocytes (10^3/μL)	2.52 ± 0.24	2.52 ± 0.19	2.07 ± 0.17	2.43 ± 0.29
Segmented neutrophils (10^3/μL)	0.77 ± 0.16	0.59 ± 0.05	0.53 ± 0.05	0.64 ± 0.11
Lymphocytes (10^3/μL)	1.70 ± 0.13	1.87 ± 0.16	1.48 ± 0.15	1.74 ± 0.19
Monocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils (10^3/μL)	0.06 ± 0.01	0.06 ± 0.02	0.06 ± 0.01	0.06 ± 0.01
Nucleated erythrocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Clinical Chemistry				
Cholinesterase (IU/L)	10,775 ± 454	6,479 ± 114**	3,497 ± 133**[b]	1,525 ± 77**

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error
[b] n=9

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NEUROBEHAVIORAL STUDIES

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NEUROBEHAVIORAL STUDIES

METHODS

16-Day Studies

Approximately one week before dosing began and again on the day before necropsy, all rats and mice were tested for spontaneous motor activity, forelimb and hindlimb grip strength, startle response, and paw-lick latency.

Spontaneous motor activity was measured using a photocell movement detection procedure. Darkened sound-insulating chambers were used to house individual plexiglass test cages. Each cubicle had a ventilation fan with a baffled intake and exhaust system and a 4-inch speaker for the delivery of 75 dB white noise. Photo beam detector units were inserted so that infrared photo beams 6 cm apart passed through the test cages just above the cage floors. Animal movement inside the cages was translated into activity counts by means of Coulbourn Instruments modular signal processing equipment. Measurements were recorded for three consecutive 5 minute periods. Test groups consisted of one male from each dose group or one female from each dose group to eliminate bias among groups due to order, time of day, or other environmental variables.

Grip strength was measured using a device and procedure similar to that described by Meyer *et al.* (1979). Each animal was allowed to grip a triangular ring with its forepaws and was pulled back along a platform until its grip was broken. As the backward motion continued, its hindpaws reached a T-shaped rear-limb grip bar which it was allowed to grasp and then was forced to release by continued pulling. Push-pull strain gauges (Chatillon, Kew Gardens, NY) were used to record the maximum strain required to break the animal's grip in each case. The average of three valid measurements was taken as the animal's score for either forelimb or hindlimb grip strength.

Startle responses were measured using a Responder IV Startle Response Monitor (Columbus Instruments, Columbus, OH) within an Industrial Acoustics sound-isolation cubicle equipped with light, ventilation fan, and one-way viewing window. The cubicle contained four independent startle platforms (transducers) equipped for the delivery of a 4.5 kHz, 200 msec, 120 dB acoustic stimulus at pre-programmed intervals. The startle monitor measures and prints the amplitude and latency of startle responses for each platform separately. A 4.5 kHz, 50 msec, 102 dB pre-pulse was delivered 1.8 seconds prior to each startle stimulus. The effect of the pre-pulse was to produce a brief hesitation in the spontaneous movement of the animal, during which the main stimulus was presented. In the absence of these signals, the speakers presented 80 dB white noise. The amplitude data were transformed to equivalent load values using conversion factors obtained during calibration. Startle measurement sessions consisted of ten startle stimuli presented 60 seconds apart. The sensitivity settings used were pre-adjusted to detect both increases and decreases in startle reactivity.

Paw-lick latency was measured by placing four animals on individual, heated (55° C) plates (Technilab Instruments Model 475 Analgesia Meter) for a period of up to 60 seconds. This test procedure allowed the animals to move about freely and did not require any restraint devices. In general, each animal in the test came from a different dose group and individuals from one dose group were not always placed on the same plate.

13-Week Studies

During the 13-week studies, each rat and mouse was tested for forelimb and hindlimb grip strength the day before the beginning of the studies, and again on the day prior to scheduled necropsy. Measurements were made following the same procedure described in the 16-day studies and at the end of the testing, the body weight of each animal was recorded. Grip strengths and body weight data were analyzed for overall treatment responses using one-way analysis of variance followed by Bonferroni's test (Miller, 1981) for pairwise comparisons between groups. Analysis of covariance, with body weight as a covariate, was also conducted on post-exposure grip strength data.

2-Year Studies

During the 2-year studies, each rat and mouse was tested for forelimb and hindlimb grip strength during the week before the beginning of the studies, and again prior to scheduled necropsy at the 3-, 9-, and 15-month interim evaluations. Measurements were made following the same procedure described in the 16-day studies, except that five trials were conducted with less than 1 minute between trials so that the degree of habituation or fatigue could be measured. The body weight of each animal was also recorded at the end of the grip strength evaluations.

TABLE H1
Neurobehavioral Data for Rats in the 16-Day Gavage Study of Tricresyl Phosphate[a]

Parameter/Day	Vehicle Control	360 mg/kg	730 mg/kg	1,450 mg/kg	2,900 mg/kg	5,800 mg/kg
Male						
n	9	10	9	10	6	10
Body weight (g)						
14	208 ± 5	204 ± 3	190 ± 4**	170 ± 5**	146 ± 16**	156 ± 9**
Body temperature (° C)						
14	35.16 ± 0.19	35.41 ± 0.38	35.51 ± 0.34	35.79 ± 0.32	35.25 ± 0.56	35.27 ± 0.36
Total activity (15 min)						
0	309.6 ± 45.8[b]	288.7 ± 23.8	274.5 ± 25.0[b]	294.3 ± 25.5[c]	259.3 ± 34.0[b]	281.4 ± 39.4
14	332.4 ± 74.0	216.4 ± 27.3	240.1 ± 40.1	226.8 ± 24.4	162.3 ± 43.9	171.0 ± 36.8
Startle response latency (ms)						
0	21.60 ± 0.85[b]	20.30 ± 0.60	25.20 ± 3.57[b]	19.50 ± 0.40	22.30 ± 1.39[b]	20.20 ± 0.65
14	19.56 ± 0.90	18.20 ± 0.39	19.00 ± 0.76	18.00 ± 0.47	17.67 ± 0.61	16.60 ± 0.43**
Startle response amplitude						
0	460.8 ± 42.0[b]	617.7 ± 61.4	594.6 ± 95.4[b]	685.4 ± 64.0	556.2 ± 80.2[b]	537.9 ± 45.4
14	804.1 ± 133	778.3 ± 83.8	841.2 ± 87.8	1,034.3 ± 121	1,224 ± 123*	1,218.5 ± 125*
Forelimb grip strength (g)						
0	537.0 ± 14.3[b]	520.0 ± 25.3	506.0 ± 17.3[b]	506.0 ± 16.4	513.0 ± 15.1[b]	495.0 ± 18.9
14	547.8 ± 24.4	486.0 ± 21.9	537.8 ± 18.2	490.0 ± 18.6	400.0 ± 36.7**[d]	406.0 ± 15.2**
Hindlimb grip strength (g)						
0	142.0 ± 9.3[b]	163.0 ± 8.6	145.0 ± 8.6[b]	147.0 ± 10.4	158.0 ± 4.9[b]	157.0 ± 7.3
14	223.3 ± 11.4	227.0 ± 9.2	197.8 ± 10.4	187.0 ± 17.8	168.0 ± 12.4**[d]	172.0 ± 12.3**
Paw-lick latency (s)						
0	16.84 ± 1.86[b]	17.88 ± 2.01	14.54 ± 1.28[b]	16.31 ± 0.85	16.19 ± 1.83[b]	17.50 ± 0.76
14	23.38 ± 2.59	19.16 ± 2.30	25.97 ± 2.76	30.12 ± 3.54	30.65 ± 4.79	26.44 ± 2.60
Change in total activity (15 min)						
14	20.111 ± 29.858	-72.30 ± 36.371	-32.22 ± 27.088	-59.89 ± 19.675[c]	-75.00 ± 42.611	-110.4 ± 15.527**
Change in startle response latency (ms)						
14	-1.778 ± 1.128	-2.100 ± 0.690	-6.667 ± 3.536	-1.500 ± 0.401	-3.833 ± 1.579	-3.600 ± 0.792
Change in startle response amplitude						
14	341.0 ± 109	160.6 ± 110	307.2 ± 94.8	348.9 ± 130	690.8 ± 160	680.6 ± 135
Change in forelimb grip strength (g)						
14	18.89 ± 31.11	-34.00 ± 27.41	31.11 ± 28.45	-16.00 ± 23.81	-102.0 ± 42.36*[d]	-89.00 ± 24.74*
Change in hindlimb grip strength (g)						
14	80.0 ± 13.8	64.0 ± 11.5	55.6 ± 8.7	40.0 ± 19.6	14.0 ± 13.6**[d]	15.0 ± 12.3**
Change in paw-lick latency (s)						
14	6.57 ± 3.96	1.28 ± 3.23	11.71 ± 2.29	13.81 ± 3.56	15.77 ± 6.27	8.94 ± 2.43

TABLE H1
Neurobehavioral Data for Rats in the 16-Day Gavage Study of Tricresyl Phosphate (continued)

Parameter/Day	Vehicle Control	360 mg/kg	730 mg/kg	1,450 mg/kg	2,900 mg/kg	5,800 mg/kg
Female						
n	9	10	10	9	2	10
Body weight (g)						
14	144 ± 2	149 ± 1	147 ± 3	128 ± 4*	118 ± 5*	119 ± 4**
Body temperature (° C)						
14	36.74 ± 0.24	36.23 ± 0.34	36.32 ± 0.25	36.83 ± 0.19	36.90 ± 0.20	36.32 ± 0.18
Total activity (15 min)						
0	318.7 ± 28.8[b]	283.3 ± 28.0	355.3 ± 45.0	236.1 ± 20.0[b]	320.9 ± 36.3[b]	331.8 ± 38.9
14	375.67 ± 45.12	343.40 ± 34.45	300.40 ± 42.46	146.25 ± 35.37**[e]	77.50 ± 10.50*	199.80 ± 45.37**
Startle response latency (ms)						
0	26.67 ± 2.73	22.22 ± 1.92[c]	21.40 ± 0.87	21.33 ± 0.75	25.80 ± 3.18[b]	24.90 ± 3.14
14	19.56 ± 0.69	20.20 ± 0.63	18.80 ± 0.59	16.67 ± 0.47**	16.50 ± 0.50	17.10 ± 0.48**
Startle response amplitude						
0	468.9 ± 84.5[b]	485.6 ± 82.1	461.5 ± 29.9	461.6 ± 68.1[b]	370.1 ± 35.4[b]	431.0 ± 47.8
14	674.0 ± 81.0	668.0 ± 69.7	927.3 ± 121	1,373.2 ± 141**	1653.0 ± 87.0*	1,366.8 ± 97.2**
Forelimb grip strength (g)						
0	433.0 ± 12.8[b]	429.0 ± 20.9	479.0 ± 17.3	437.0 ± 13.2[b]	443.0 ± 11.8[b]	452.0 ± 13.9
14	537.8 ± 31.2	458.0 ± 8.4*	494.0 ± 22.5	442.2 ± 21.4*	375.0 ± 25.0**	357.0 ± 14.9**
Hindlimb grip strength (g)						
0	129.0 ± 7.2[b]	128.0 ± 8.3	136.0 ± 8.3	132.0 ± 9.4[b]	141.0 ± 6.9[b]	131.0 ± 6.0
14	192.2 ± 14.2	192.0 ± 6.8	182.0 ± 14.2	156.7 ± 11.4	140.0 ± 10.0	144.0 ± 9.3**
Paw-lick latency (s)						
0	30.08 ± 1.85[b]	34.38 ± 1.20	26.62 ± 2.89	29.32 ± 2.52[b]	34.92 ± 2.18[b]	28.65 ± 1.53
14	28.26 ± 2.26	32.54 ± 2.78	24.85 ± 2.71	48.59 ± 5.45*	60.00 ± 0.00*	42.63 ± 4.78*
Change in total activity (15 min)						
14	59.333 ± 56.631	60.100 ± 29.747	-54.90 ± 38.262	-77.25 ± 36.626*[e]	-209.5 ± 117.50*	-132.0 ± 31.803**
Change in startle response latency (ms)						
14	-7.875 ± 3.165[e]	-2.111 ± 1.982[c]	-2.600 ± 0.897	-4.667 ± 0.726	-21.00 ± 14.000	-7.800 ± 2.820
Change in startle response amplitude						
14	198.4 ± 115	182.4 ± 70.5	465.8 ± 112	891.8 ± 122**	1,315.0 ± 21.0**	935.8 ± 87.1**
Change in forelimb grip strength (g)						
14	103.33 ± 38.80	29.00 ± 21.88	15.00 ± 26.04	11.11 ± 30.07	-10.00 ± 40.00	-95.00 ± 23.58**
Change in hindlimb grip strength (g)						
14	63.3 ± 19.1	64.0 ± 8.5	46.0 ± 11.9	30.0 ± 14.1	30.0 ± 10.0	13.0 ± 12.0*
Change in paw-lick latency (s)						
14	-1.778 ± 2.794	-1.840 ± 2.780	-1.770 ± 4.386	20.044 ± 6.157*	31.350 ± 2.650*	13.980 ± 4.546*

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error
[b] n=10
[c] n=9
[d] n=5
[e] n=8

TABLE H2
Neurobehavioral Data for Rats in the 13-Week Gavage Study of Tricresyl Phosphate[a]

Parameter/Week	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg	800 mg/kg
Male						
n	10	10	10	10	10	10
Body weight (g)						
0	185 ± 5	177 ± 4	182 ± 5	181 ± 4	177 ± 5	181 ± 5
13	368 ± 6	359 ± 4	357 ± 7	345 ± 7**	336 ± 5**	315 ± 5**
Total activity (1 hour)						
0	249.1 ± 35.7	274.3 ± 37.4	256.4 ± 31.9	262.7 ± 31.2	199.1 ± 23.2	261.4 ± 20.6
13	154.8 ± 16.7	163.1 ± 14.8	177.2 ± 35.3	156.0 ± 29.0	150.5 ± 28.0	175.7 ± 15.5
Startle response latency (ms)						
0	21.00 ± 0.49	26.60 ± 4.24	24.10 ± 2.46	22.80 ± 1.11	23.40 ± 1.76	22.00 ± 1.61
13	18.20 ± 0.59	18.60 ± 0.52	19.50 ± 1.10	35.50 ± 16.62	20.10 ± 0.69	20.00 ± 0.80
Startle response amplitude						
0	204.3 ± 33.0	157.6 ± 27.3	217.4 ± 21.1	168.9 ± 24.6	169.6 ± 22.4	203.2 ± 23.4
13	335.3 ± 33.2	307.6 ± 27.5	306.6 ± 31.4	250.0 ± 24.9	269.8 ± 31.0	298.8 ± 32.9
Forelimb grip strength (g)						
0	70.10 ± 0.92	71.30 ± 1.65	70.40 ± 1.71	70.90 ± 1.82	71.50 ± 2.07	71.90 ± 1.93
13	90.20 ± 1.19	88.00 ± 1.75	89.10 ± 1.82	87.80 ± 1.24	86.40 ± 2.15	85.90 ± 1.67
Hindlimb grip strength (g)						
0	23.00 ± 0.52	23.00 ± 0.75	22.50 ± 0.64	20.90 ± 1.04	22.20 ± 0.80	21.70 ± 0.68
13	43.70 ± 1.61	41.90 ± 1.39	43.10 ± 1.61	43.20 ± 1.57	39.80 ± 1.49	40.00 ± 1.45
Paw-lick latency (s)						
0	32.69 ± 3.89	38.01 ± 3.67	35.22 ± 3.43	38.15 ± 2.52	40.27 ± 3.10	37.44 ± 1.89
13	17.71 ± 2.05	23.34 ± 2.33	18.12 ± 3.01	14.86 ± 1.63	14.74 ± 1.47	18.48 ± 2.28
Change in total activity (1 hour)						
13	-94.30 ± 29.77	-111.2 ± 32.06	-79.20 ± 40.25	-106.7 ± 10.51	-48.60 ± 23.84	-85.70 ± 28.00
Change in startle response latency (ms)						
13	-2.800 ± 0.593	-8.000 ± 4.271	-4.600 ± 2.868	12.70 ± 15.95	-3.300 ± 1.856	-2.000 ± 1.926
Change in startle response amplitude						
13	130.96 ± 40.99	150.00 ± 34.52	89.21 ± 33.54	81.17 ± 27.09	100.19 ± 38.28	95.59 ± 38.89
Change in forelimb grip strength (g)						
13	20.10 ± 1.29	16.70 ± 2.68	18.70 ± 2.80	16.90 ± 1.73	14.90 ± 2.62	14.00 ± 1.88*
Change in hindlimb grip strength (g)						
13	20.70 ± 1.69	18.90 ± 1.39	20.60 ± 1.72	22.30 ± 1.59	17.60 ± 1.36	18.30 ± 1.48
Change in paw-lick latency (s)						
13	-14.98 ± 4.184	-14.67 ± 4.073	-17.10 ± 4.229	-23.29 ± 2.981	-25.53 ± 2.721*	-18.96 ± 2.769

TABLE H2
Neurobehavioral Data for Rats in the 13-Week Gavage Study of Tricresyl Phosphate (continued)

Parameter/Week	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg	800 mg/kg
Female						
n	10	10	10	10	10	10
Body weight (g)						
0	140 ± 2	141 ± 2	140 ± 2	141 ± 2	137 ± 3	139 ± 2
13	204 ± 5	206 ± 2	207 ± 2	208 ± 3	201 ± 3	208 ± 3
Total activity (1 hour)						
0	320.2 ± 47.2	287.4 ± 42.4	322.5 ± 42.5	333.9 ± 59.3	241.7 ± 26.9	301.6 ± 30.2
13	214.8 ± 24.3	198.7 ± 20.2	221.5 ± 24.1	220.2 ± 33.9	201.2 ± 21.1	251.2 ± 21.6
Startle response latency (ms)						
0	21.20 ± 0.51	23.90 ± 2.74	23.10 ± 0.66	21.90 ± 0.66	45.00 ± 19.41	81.50 ± 60.50
13	20.50 ± 1.19	22.30 ± 1.26	21.40 ± 0.93	18.40 ± 0.52	21.60 ± 0.64	21.40 ± 0.91
Startle response amplitude						
0	177.5 ± 14.3	184.4 ± 27.2	163.2 ± 13.7	169.1 ± 20.3	137.6 ± 23.8	163.1 ± 22.1
13	230.1 ± 28.0	201.3 ± 22.7	201.8 ± 22.6	276.1 ± 22.4	196.2 ± 13.5	259.8 ± 33.2
Forelimb grip strength (g)						
0	70.70 ± 1.56	69.10 ± 0.97	73.00 ± 2.35	70.10 ± 1.89	66.50 ± 2.05	69.00 ± 1.25
13	74.60 ± 2.05	76.40 ± 1.73	84.20 ± 2.30*	78.30 ± 1.17	76.80 ± 1.32	75.40 ± 2.04
Hindlimb grip strength (g)						
0	22.90 ± 0.72	21.20 ± 0.33	22.40 ± 1.03	21.50 ± 0.93	20.60 ± 0.88	20.60 ± 0.65*
13	33.90 ± 1.33	31.90 ± 1.00	32.10 ± 0.97	33.00 ± 0.83	30.00 ± 0.65*	29.00 ± 0.91**
Paw-lick latency (s)						
0	26.94 ± 2.29	30.95 ± 2.79	33.44 ± 2.75	33.72 ± 2.66	30.18 ± 3.08	25.62 ± 2.22
13	22.81 ± 2.19	18.17 ± 2.78	20.32 ± 2.22	26.89 ± 3.02	25.07 ± 3.76	21.53 ± 2.74
Change in total activity (1 hour)						
13	-105.4 ± 32.33	-88.70 ± 27.00	-101.0 ± 33.95	-113.7 ± 54.44	-40.50 ± 33.33	-50.40 ± 26.65
Change in startle response latency (ms)						
13	-0.700 ± 1.212	-1.600 ± 2.334	-1.700 ± 1.001	-3.500 ± 0.872	-23.40 ± 19.02	-60.10 ± 60.44
Change in startle response amplitude						
13	52.55 ± 31.84	16.96 ± 38.07	38.53 ± 18.88	106.99 ± 34.09	58.60 ± 32.88	96.67 ± 22.12
Change in forelimb grip strength (g)						
13	3.90 ± 2.07	7.30 ± 2.10	11.20 ± 2.12	8.20 ± 2.22	10.30 ± 2.54	6.40 ± 2.00
Change in hindlimb grip strength (g)						
13	11.00 ± 1.37	10.70 ± 1.04	9.70 ± 0.79	11.50 ± 0.90	9.40 ± 1.08	8.40 ± 1.02
Change in paw-lick latency (s)						
13	-4.130 ± 3.187	-12.78 ± 3.620	-13.12 ± 2.333	-6.830 ± 4.633	-5.110 ± 4.713	-4.090 ± 2.720

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error

TABLE H3
Neurobehavioral Data for Rats in the 13-Week Feed Study of Tricresyl Phosphate[a]

	0 ppm	900 ppm	1,700 ppm	3,300 ppm	6,600 ppm	13,000 ppm
Male						
n	10	10	10	10	10	10
Body weight (g)	364 ± 7	361 ± 8	366 ± 6	336 ± 4**	329 ± 8**	241 ± 8**
Forelimb grip strength (kg)	0.769 ± 0.046	0.811 ± 0.038	0.850 ± 0.019	0.796 ± 0.039	0.796 ± 0.034	0.688 ± 0.043
Hindlimb grip strength (kg)	0.805 ± 0.029	0.824 ± 0.029	0.790 ± 0.031	0.737 ± 0.015	0.721 ± 0.029	0.655 ± 0.042**
Change in forelimb grip strength (kg)	0.120 ± 0.036	0.123 ± 0.038	0.144 ± 0.019	0.107 ± 0.040	0.144 ± 0.036	0.055 ± 0.043
Change in hindlimb grip strength (kg)	0.457 ± 0.027	0.474 ± 0.030	0.454 ± 0.030	0.415 ± 0.019	0.385 ± 0.025	0.342 ± 0.038*
Female						
n	10	10	10	10	10	10
Body weight (g)	198 ± 3	194 ± 3	194 ± 3	187 ± 3	180 ± 4**	174 ± 3**
Forelimb grip strength (kg)	0.642 ± 0.029	0.667 ± 0.031	0.626 ± 0.037	0.650 ± 0.031	0.661 ± 0.033	0.708 ± 0.025
Hindlimb grip strength (kg)	0.692 ± 0.018	0.668 ± 0.032	0.675 ± 0.014	0.714 ± 0.016	0.687 ± 0.019	0.648 ± 0.015
Change in forelimb grip strength (kg)	0.018 ± 0.037	0.049 ± 0.030	-0.010 ± 0.040	0.006 ± 0.029	-0.002 ± 0.032	0.075 ± 0.033
Change in hindlimb grip strength (kg)	0.396 ± 0.020	0.377 ± 0.031	0.387 ± 0.020	0.423 ± 0.018	0.387 ± 0.020	0.351 ± 0.012

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error

TABLE H4
Neurobehavioral Data for Rats at the 3-Month Interim Evaluation in the 2-Year Feed Study of Tricresyl Phosphate[a]

	0 ppm	75 ppm	150 ppm	300 ppm	600 ppm
Male					
n	15	15	15	15	15
Forelimb grip strength (kg)	0.950 ± 0.004	0.954 ± 0.005	0.957 ± 0.006	0.947 ± 0.003	0.949 ± 0.003
Hindlimb grip strength (kg)	0.802 ± 0.008	0.770 ± 0.020	0.759 ± 0.017	0.715 ± 0.013**	0.712 ± 0.013**
Change in forelimb grip strength (kg)	0.571 ± 0.021	0.593 ± 0.021	0.576 ± 0.020	0.588 ± 0.017	0.591 ± 0.019
Change in hindlimb grip strength (kg)	0.518 ± 0.017	0.513 ± 0.022	0.481 ± 0.022	0.446 ± 0.018*	0.447 ± 0.021
Female					
n	15	15	15	14	15
Forelimb grip strength (kg)	0.921 ± 0.016	0.907 ± 0.011	0.925 ± 0.009	0.932 ± 0.008	0.917 ± 0.011
Hindlimb grip strength (kg)	0.709 ± 0.019	0.678 ± 0.018	0.687 ± 0.013	0.676 ± 0.011	0.658 ± 0.015*
Change in forelimb grip strength (kg)	0.565 ± 0.023	0.552 ± 0.017	0.570 ± 0.012	0.574 ± 0.016	0.569 ± 0.015
Change in hindlimb grip strength (kg)	0.445 ± 0.019	0.410 ± 0.022	0.413 ± 0.014	0.408 ± 0.018	0.394 ± 0.016

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error

TABLE H5
Neurobehavioral Data for Rats at the 9-Month Interim Evaluation in the 2-Year Feed Study of Tricresyl Phosphate[a]

	0 ppm	75 ppm	150 ppm	300 ppm	600 ppm
Male					
n	14	15	15	15	15
Forelimb grip strength (kg)	1.58 ± 0.04	1.54 ± 0.03	1.57 ± 0.03	1.56 ± 0.03	1.55 ± 0.04
Hindlimb grip strength (kg)	1.15 ± 0.02	1.13 ± 0.02	1.17 ± 0.02	1.12 ± 0.02	1.15 ± 0.03
Change in forelimb grip strength (kg)	1.22 ± 0.05	1.18 ± 0.03	1.21 ± 0.04	1.21 ± 0.04	1.19 ± 0.05
Change in hindlimb grip strength (kg)	0.889 ± 0.032	0.870 ± 0.019	0.908 ± 0.028	0.870 ± 0.025	0.887 ± 0.029
Female					
n	15	14	15	15	15
Forelimb grip strength (kg)	1.21 ± 0.02	1.21 ± 0.03	1.21 ± 0.02	1.25 ± 0.02	1.25 ± 0.02
Hindlimb grip strength (kg)	0.899 ± 0.017	0.908 ± 0.022	0.905 ± 0.017	0.919 ± 0.017	0.929 ± 0.024
Change in forelimb grip strength (kg)	0.857 ± 0.023	0.863 ± 0.025	0.850 ± 0.024	0.905 ± 0.029	0.883 ± 0.016
Change in hindlimb grip strength (kg)	0.637 ± 0.016	0.654 ± 0.020	0.631 ± 0.026	0.663 ± 0.024	0.655 ± 0.024

[a] Mean ± standard error

TABLE H6
Neurobehavioral Data for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of Tricresyl Phosphate[a]

	0 ppm	75 ppm	150 ppm	300 ppm	600 ppm
Male					
n	15	15	15	15	15
Forelimb grip strength (kg)	1.58 ± 0.04	1.63 ± 0.04	1.60 ± 0.04	1.62 ± 0.02	1.64 ± 0.03
Hindlimb grip strength (kg)	1.06 ± 0.02	1.11 ± 0.02	1.08 ± 0.03	1.07 ± 0.02	1.09 ± 0.02
Change in forelimb grip strength (kg)	1.22 ± 0.03	1.27 ± 0.05	1.26 ± 0.03	1.24 ± 0.03	1.27 ± 0.04
Change in hindlimb grip strength (kg)	0.793 ± 0.019	0.840 ± 0.022	0.827 ± 0.027	0.787 ± 0.017	0.819 ± 0.020
Female					
n	14	13	15	15	14
Forelimb grip strength (kg)	1.35 ± 0.02	1.38 ± 0.02	1.35 ± 0.03	1.36 ± 0.02	1.34 ± 0.03
Hindlimb grip strength (kg)	0.881 ± 0.021	0.875 ± 0.019	0.883 ± 0.021	0.905 ± 0.022	0.896 ± 0.021
Change in forelimb grip strength (kg)	0.986 ± 0.022	1.018 ± 0.032	1.009 ± 0.026	0.970 ± 0.027	0.974 ± 0.028
Change in hindlimb grip strength (kg)	0.612 ± 0.021	0.609 ± 0.021	0.629 ± 0.021	0.625 ± 0.017	0.630 ± 0.016

[a] Mean ± standard error

TABLE H7
Neurobehavioral Data for Mice in the 16-Day Gavage Study of Tricresyl Phosphate[a]

Parameter/Day	Vehicle Control	363 mg/kg	726 mg/kg	1,452 mg/kg	2,905 mg/kg	5,810 mg/kg
Male						
n	10	10	10	6	0[b]	6
Body weight (g)						
14	26.0 ± 0.3	25.8 ± 0.2	25.1 ± 0.5	22.2 ± 0.7**	–	23.7 ± 0.8**[c]
Body temperature (° C)						
14	37.41 ± 0.35	37.65 ± 0.22	37.78 ± 0.32	35.35 ± 1.04*	–	35.66 ± 1.37[c]
Total activity (15 min)						
0	302.2 ± 26.5	303.5 ± 18.3	279.3 ± 20.9	254.8 ± 17.5[d]	293.9 ± 16.5[e]	331.6 ± 17.8[e]
14	282.80 ± 16.36	284.80 ± 14.18	246.40 ± 16.34	87.86 ± 24.89**[c]	–	212.83 ± 5.05**
Startle response latency (ms)						
0	16.40 ± 0.43	16.40 ± 0.48	16.80 ± 0.42	15.40 ± 0.34[d]	16.00 ± 0.42[d]	16.10 ± 0.50[d]
14	15.20 ± 0.39	16.13 ± 0.35[f]	21.78 ± 2.87**[e]	18.33 ± 1.41**	–	17.50 ± 1.12*
Startle response amplitude						
0	490.1 ± 44.3	550.8 ± 63.5	515.5 ± 30.0	536.5 ± 49.9[d]	489.4 ± 48.6[d]	583.6 ± 80.8[d]
14	628.3 ± 57.5	532.8 ± 85.3[e]	378.4 ± 32.8*[e]	570.0 ± 117	–	532.0 ± 67.4
Forelimb grip strength (g)						
0	130.8 ± 5.7	123.6 ± 4.3	130.5 ± 6.0	128.3 ± 4.8[d]	127.4 ± 4.1[d]	125.9 ± 4.1[d]
14	142.30 ± 2.81	133.40 ± 5.25	140.80 ± 4.93	55.71 ± 14.98**[c]	–	82.43 ± 19.14**[c]
Hindlimb grip strength (g)						
0	37.80 ± 2.33	35.70 ± 2.02	35.80 ± 2.41	36.70 ± 1.94[d]	34.30 ± 1.84[d]	35.70 ± 2.03[d]
14	52.50 ± 2.28	43.90 ± 2.60*	42.50 ± 2.26**	21.71 ± 6.26**[c]	–	26.71 ± 5.96**[c]
Paw-lick latency (s)						
0	25.25 ± 2.31	21.51 ± 2.40	25.29 ± 2.26	25.00 ± 3.03[d]	21.87 ± 1.37[d]	20.59 ± 1.62[d]
14	23.83 ± 2.01	23.59 ± 2.59	24.34 ± 3.14	33.00 ± 7.66	–	21.53 ± 1.82
Change in total activity (15 min)						
14	-19.40 ± 25.359	-18.70 ± 17.915	-32.90 ± 13.321	-165.7 ± 35.290**[c]	–	-130.8 ± 27.942**[g]
Change in startle response latency (ms)						
14	-1.200 ± 0.467	0.125 ± 0.398[b]	4.889 ± 2.685**[e]	3.167 ± 1.327**	–	1.333 ± 0.615**
Change in startle response amplitude						
14	138.20 ± 45.092	-37.22 ± 67.329*[e]	-124.8 ± 42.532**[e]	-9.667 ± 134.12*	–	-103.0 ± 112.08*
Change in forelimb grip strength (g)						
14	11.500 ± 5.596	9.800 ± 3.255	10.300 ± 6.043	-71.86 ± 17.678**[c]	–	-43.57 ± 19.638**[c]
Change in hindlimb grip strength (g)						
14	14.700 ± 2.390	8.200 ± 3.144	6.700 ± 2.608*	-16.71 ± 6.693**[c]	–	-8.857 ± 6.544**[c]
Change in paw-lick latency (s)						
14	-1.420 ± 2.175	2.080 ± 2.976	-0.950 ± 3.576	10.167 ± 9.619	–	0.533 ± 2.420

TABLE H7
Neurobehavioral Data for Mice in the 16-Day Gavage Study of Tricresyl Phosphate (continued)

Parameter/Day	Vehicle Control	363 mg/kg	726 mg/kg	1,452 mg/kg	2,905 mg/kg	5,810 mg/kg
Female						
n	10	10	10	0[b]	0[b]	9
Body weight (g)						
14	20.0 ± 0.3	21.8 ± 0.3**	22.4 ± 0.3**	–	–	21.7 ± 0.4**
Body temperature (° C)						
14	38.38 ± 0.12	37.86 ± 0.22	38.32 ± 0.06	–	–	37.98 ± 0.18
Total activity (15 min)						
0	324.1 ± 15.7	311.4 ± 24.9	272.8 ± 18.5	297.2 ± 19.2[d]	283.4 ± 19.0[d]	313.5 ± 15.5[d]
14	291.3 ± 16.8	273.4 ± 14.5	272.2 ± 14.2	–	–	240.0 ± 17.2
Startle response latency (ms)						
0	17.90 ± 0.55	15.10 ± 0.18**	17.30 ± 0.79	16.50 ± 0.54[d]	18.40 ± 1.71[d]	15.80 ± 0.39*[d]
14	15.78 ± 0.15[e]	17.00 ± 1.89[e]	17.90 ± 1.72	–	–	16.56 ± 0.75
Startle response amplitude						
0	386.7 ± 26.5	553.4 ± 45.0*	508.4 ± 48.3	435.7 ± 45.8[d]	443.2 ± 45.2[d]	478.6 ± 25.2[d]
14	478.4 ± 32.4[e]	474.9 ± 59.3	538.1 ± 40.0	–	–	552.2 ± 60.2
Forelimb grip strength (g)						
0	107.6 ± 3.5	102.3 ± 2.1	105.3 ± 4.1	107.4 ± 3.0[d]	103.9 ± 3.7[d]	109.1 ± 3.7[d]
14	126.00 ± 3.92	123.20 ± 2.58	121.70 ± 4.07	–	–	86.22 ± 6.78**
Hindlimb grip strength (g)						
0	27.20 ± 2.82	26.60 ± 1.73	25.70 ± 1.07	25.90 ± 1.12[d]	26.30 ± 2.15[d]	25.40 ± 1.87[d]
14	39.90 ± 2.11	38.30 ± 2.70	33.90 ± 1.83*	–	–	23.67 ± 2.40**
Paw-lick latency (s)						
0	17.88 ± 1.53	22.29 ± 2.24	18.72 ± 1.80	16.32 ± 1.21[d]	21.64 ± 1.51[d]	17.63 ± 1.41[d]
14	18.65 ± 1.76	20.95 ± 2.37	21.25 ± 3.11	–	–	25.58 ± 2.53
Change in total activity (15 min)						
14	-32.80 ± 25.800	-38.00 ± 26.484	-0.600 ± 18.343	–	–	-77.56 ± 19.395
Change in startle response latency (ms)						
14	-1.667 ± 0.333[e]	2.000 ± 1.900**[e]	0.600 ± 1.536*	–	–	0.778 ± 0.909*
Change in startle response amplitude						
14	81.667 ± 38.804[e]	-78.50 ± 68.653	29.700 ± 47.529	–	–	71.333 ± 51.762
Change in forelimb grip strength (g)						
14	18.400 ± 2.945	20.900 ± 2.850	16.400 ± 4.626	–	–	-23.67 ± 7.906**
Change in hindlimb grip strength (g)						
14	12.700 ± 2.879	11.700 ± 3.253	8.200 ± 1.323	–	–	-1.778 ± 2.344**
Change in paw-lick latency (s)						
14	0.770 ± 1.543	-1.340 ± 3.280	2.530 ± 2.781	–	–	7.456 ± 2.694

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error
[b] n=0; no data calculated for groups with 100% mortality
[c] n=7
[d] n=10
[e] n=9
[f] n=8
[g] n=5

TABLE H8
Neurobehavioral Data for Mice in the 13-Week Gavage Study of Tricresyl Phosphate[a]

Parameter/Week	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg	800 mg/kg
Male						
n	10	10	10	10	10	10
Body weight (g)						
0	24.3 ± 0.5	24.4 ± 0.6	24.6 ± 0.4	24.6 ± 0.4	23.8 ± 0.5	24.1 ± 0.5
13	35.0 ± 0.7	37.2 ± 0.8	38.0 ± 0.8	32.7 ± 0.9	31.7 ± 0.5*	28.1 ± 0.5**
Total activity (1 hour)						
0	259.0 ± 21.3	271.4 ± 16.5	262.2 ± 15.2	251.9 ± 15.0	248.6 ± 14.0	245.6 ± 24.2
13	183.80 ± 30.76	232.90 ± 18.57	207.80 ± 20.59	172.00 ± 18.55	139.50 ± 13.20	90.70 ± 13.53*
Startle response latency (ms)						
0	15.90 ± 0.41	19.60 ± 2.38	17.40 ± 2.08	15.80 ± 0.49	15.78 ± 0.32[b]	16.50 ± 0.48
13	17.80 ± 2.06	16.80 ± 1.63	18.70 ± 1.62	21.44 ± 2.87*[b]	35.63 ± 9.41**[c]	26.57 ± 2.26**[d]
Startle response amplitude						
0	157.4 ± 11.9	171.2 ± 22.1	190.0 ± 17.8	192.0 ± 14.5	197.5 ± 17.3[b]	176.1 ± 18.5
13	152.09 ± 22.58	188.81 ± 19.46	141.26 ± 17.43	131.50 ± 15.24[b]	88.84 ± 6.54*[c]	121.67 ± 12.85[d]
Forelimb grip strength (g)						
0	147.0 ± 3.7	147.9 ± 3.4	145.8 ± 3.7	143.6 ± 5.3	146.1 ± 5.0	143.4 ± 3.2
13	184.8 ± 4.1	184.3 ± 4.2	188.0 ± 3.5	174.1 ± 3.7	158.2 ± 4.2**	143.5 ± 3.2**
Hindlimb grip strength (g)						
0	50.50 ± 1.24	52.30 ± 1.78	46.60 ± 1.78	52.60 ± 2.51	50.80 ± 2.97	43.70 ± 1.60*
13	82.10 ± 1.792	83.80 ± 3.711	81.20 ± 3.952	73.40 ± 4.053*	35.10 ± 6.095**	0.000 ± 0.000**
Paw-lick latency (s)						
0	24.42 ± 2.74	24.38 ± 1.95	22.41 ± 1.44	19.71 ± 2.06	19.60 ± 1.49	18.01 ± 1.14*
13	12.69 ± 0.67	14.24 ± 0.82	13.83 ± 1.32	12.20 ± 0.77	13.56 ± 1.21	18.63 ± 1.36**
Change in total activity (1 hour)						
13	-75.20 ± 23.84	-38.50 ± 23.32	-54.40 ± 14.74	-79.90 ± 19.89	-109.1 ± 22.80	-154.9 ± 30.58
Change in startle response latency (ms)						
13	1.900 ± 2.025	-2.800 ± 2.590	1.300 ± 2.883	5.778 ± 3.031[b]	22.143 ± 10.439**[d]	10.571 ± 2.318**[d]
Change in startle response amplitude						
13	-5.334 ± 21.01	17.627 ± 23.93	-48.74 ± 22.27	-62.56 ± 20.97[b]	-106.8 ± 17.99**[d]	-70.30 ± 23.52*[d]
Change in forelimb grip strength (g)						
13	37.80 ± 6.026	36.40 ± 3.936	42.20 ± 4.044	30.50 ± 4.225	12.10 ± 5.322**	0.100 ± 5.104**
Change in hindlimb grip strength (g)						
13	31.60 ± 2.146	31.50 ± 3.933	34.60 ± 3.792	20.80 ± 3.586*	-15.70 ± 5.976**	-43.70 ± 1.599**
Change in paw-lick latency (s)						
13	-11.73 ± 2.524	-10.14 ± 1.718	-8.580 ± 1.252	-7.510 ± 2.106	-6.040 ± 1.793	0.620 ± 1.851**

TABLE H8
Neurobehavioral Data for Mice in the 13-Week Gavage Study of Tricresyl Phosphate (continued)

Parameter/Week	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg	800 mg/kg
Female						
n	10	9	10	10	10	10
Body weight (g)						
0	19.0 ± 0.4	18.6 ± 0.5[e]	19.1 ± 0.3	18.4 ± 0.3	18.9 ± 0.5	19.5 ± 0.3
13	26.8 ± 0.8	27.2 ± 0.7	27.4 ± 0.8	24.3 ± 0.3*	23.6 ± 0.4**	22.4 ± 0.3**
Total activity (1 hour)						
0	260.0 ± 11.9	284.7 ± 24.0[e]	277.3 ± 22.5	274.6 ± 28.5	272.8 ± 22.8	293.9 ± 19.4
13	226.0 ± 18.4	268.0 ± 40.7	224.2 ± 23.9	202.8 ± 18.4	173.1 ± 18.5	130.1 ± 9.1**
Startle response latency (ms)						
0	20.88 ± 2.70[c]	22.71 ± 2.52[d]	22.14 ± 2.42[d]	20.43 ± 3.08[d]	20.33 ± 3.19[f]	29.75 ± 9.25[c]
13	20.88 ± 2.84[c]	24.33 ± 2.96	21.70 ± 2.24	26.50 ± 1.79	38.00 ± 6.40**[c]	36.25 ± 3.22**[c]
Startle response amplitude						
0	132.21 ± 14.49[c]	115.62 ± 10.46[d]	119.22 ± 15.87[d]	136.70 ± 17.21[d]	120.15 ± 20.11[f]	99.26 ± 6.22[c]
13	131.50 ± 20.46[c]	143.62 ± 18.87	103.05 ± 9.40	74.76 ± 14.21*	76.49 ± 7.75*[c]	86.58 ± 5.16[c]
Forelimb grip strength (g)						
0	120.4 ± 3.1	112.2 ± 4.0[e]	119.7 ± 4.3	126.0 ± 3.6	112.4 ± 3.2	124.2 ± 4.0
13	161.10 ± 3.21	150.67 ± 3.80	158.40 ± 5.14	142.60 ± 2.51**	133.30 ± 4.91**	99.50 ± 3.95**
Hindlimb grip strength (g)						
0	36.00 ± 1.96	36.90 ± 2.54[e]	35.20 ± 0.70	36.80 ± 2.13	33.70 ± 1.72	35.00 ± 2.30
13	67.30 ± 2.642	61.44 ± 2.804	63.30 ± 3.044	51.40 ± 2.192**	0.200 ± 0.200**	0.200 ± 0.200**
Paw-lick latency (s)						
0	19.43 ± 1.66	18.41 ± 1.32[e]	22.67 ± 2.41	24.81 ± 2.23	17.74 ± 1.54	25.04 ± 1.94*
13	15.26 ± 1.75	15.82 ± 0.74	15.44 ± 1.17	17.70 ± 1.36	22.53 ± 3.18*	27.41 ± 3.23**
Change in total activity (1 hour)						
13	-34.00 ± 19.39	-24.67 ± 21.76	-53.10 ± 22.82	-71.80 ± 27.80	-99.70 ± 29.65	-163.8 ± 17.78**
Change in startle response latency (ms)						
13	5.833 ± 3.371[f]	-1.167 ± 4.102[f]	1.429 ± 2.034[d]	6.571 ± 3.046[d]	22.00 ± 12.087[g]	17.00 ± 3.625[d]
Change in startle response amplitude						
13	-38.86 ± 25.374[f]	31.94 ± 21.963[f]	-8.95 ± 13.477[d]	-60.72 ± 24.895[d]	-44.89 ± 18.531[g]	-16.88 ± 6.225[d]
Change in forelimb grip strength (g)						
13	40.70 ± 4.719	36.78 ± 6.346	38.70 ± 6.384	16.60 ± 5.679*	20.90 ± 5.063*	-24.70 ± 5.300**
Change in hindlimb grip strength (g)						
13	31.30 ± 3.030	23.22 ± 2.639	28.10 ± 3.485	14.60 ± 2.774**	-33.50 ± 1.621**	-34.80 ± 2.289**
Change in paw-lick latency (s)						
13	-4.170 ± 2.617	-2.400 ± 1.816	-7.230 ± 1.949	-7.110 ± 2.646	4.790 ± 2.882	2.370 ± 4.194

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error
[b] n=9
[c] n=8
[d] n=7
[e] n=10
[f] n=6
[g] n=5

TABLE H9
Neurobehavioral Data for Mice in the 13-Week Feed Study of Tricresyl Phosphate[a]

	0 ppm	250 ppm	500 ppm	1,000 ppm	2,100 ppm	4,200 ppm
Male						
n	10	10	10	10	10	10
Body weight (g)	31.5 ± 1.0	32.2 ± 0.9	31.5 ± 0.8	30.7 ± 0.9	28.9 ± 0.6*	25.0 ± 0.4**
Forelimb grip strength (g)	137.00 ± 4.36	136.30 ± 3.59	133.30 ± 2.91	131.30 ± 6.45	114.90 ± 3.54**	95.50 ± 2.40**
Hindlimb grip strength (g)	123.80 ± 4.40	124.60 ± 4.25	127.20 ± 2.16	114.60 ± 3.04	116.30 ± 2.43	58.60 ± 6.98**
Change in forelimb grip strength (g)	23.76 ± 5.49	21.15 ± 4.06	13.99 ± 5.97	13.44 ± 7.64	0.25 ± 6.64*	-15.66 ± 4.79**
Change in hindlimb grip strength (g)	57.39 ± 4.05	55.71 ± 4.25	59.63 ± 2.98	48.47 ± 1.90	48.73 ± 4.11	-5.61 ± 7.54**
Female						
n	10	10	10	10	10	10
Body weight (g)	27.9 ± 1.1	27.6 ± 0.6	26.9 ± 0.8	25.7 ± 0.8	23.0 ± 0.4**	21.0 ± 0.2**
Forelimb grip strength (g)	116.20 ± 3.22	116.00 ± 2.61	124.10 ± 2.70	103.20 ± 4.26	89.80 ± 2.84**	75.80 ± 2.78**
Hindlimb grip strength (g)	110.67 ± 3.09	117.90 ± 3.40	107.80 ± 3.11	110.30 ± 3.53	76.10 ± 6.66**	13.50 ± 2.86**
Change in forelimb grip strength (g)	22.07 ± 3.68	22.01 ± 3.80	36.92 ± 3.02	16.50 ± 5.49	0.64 ± 5.29*	-10.11 ± 3.28**
Change in hindlimb grip strength (g)	56.58 ± 3.45	63.23 ± 3.60	52.47 ± 3.54	54.44 ± 3.84	17.80 ± 7.37**	-44.03 ± 2.93**

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error

TABLE H10
Neurobehavioral Data for Mice at the 3-Month Interim Evaluation in the 2-Year Feed Study of Tricresyl Phosphate[a]

	0 ppm	60 ppm	125 ppm	250 ppm
Male				
n	14	15	15	15
Forelimb grip strength (g)	127.4 ± 3.6	127.3 ± 2.0	130.2 ± 2.4	123.7 ± 2.3
Hindlimb grip strength (g)	105.14 ± 2.97	101.60 ± 1.68	100.67 ± 1.90	99.60 ± 1.66
Change in forelimb grip strength (g)	54.71 ± 2.67	53.53 ± 2.37	57.73 ± 2.66	49.87 ± 2.95
Change in hindlimb grip strength (g)	51.21 ± 1.99	42.73 ± 1.78*	45.00 ± 1.93	42.13 ± 1.99**
Female				
n	15	15	15	15
Forelimb grip strength (g)	126.0 ± 2.6	124.5 ± 1.9	123.1 ± 2.4	122.7 ± 2.7
Hindlimb grip strength (g)	104.67 ± 2.19	104.40 ± 1.29	98.33 ± 1.95	97.13 ± 1.76*
Change in forelimb grip strength (g)	51.47 ± 2.92	50.00 ± 2.54	50.27 ± 3.19	51.47 ± 3.05
Change in hindlimb grip strength (g)	49.40 ± 3.20	46.53 ± 2.05	41.40 ± 1.71	40.87 ± 2.81

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error

TABLE H11
Neurobehavioral Data for Mice at the 9-Month Interim Evaluation in the 2-Year Feed Study of Tricresyl Phosphate[a]

	0 ppm	60 ppm	125 ppm	250 ppm
Male				
n	15	15	15	15
Forelimb grip strength (g)	125.2 ± 3.3	122.5 ± 3.3	127.1 ± 4.0	121.5 ± 4.4
Hindlimb grip strength (g)	98.13 ± 2.74	98.73 ± 2.18	97.00 ± 2.24	91.87 ± 3.38
Change in forelimb grip strength (g)	52.27 ± 4.14	50.07 ± 3.41	52.47 ± 4.40	48.40 ± 4.40
Change in hindlimb grip strength (g)	41.53 ± 2.87	43.93 ± 2.89	39.93 ± 3.68	35.13 ± 3.88
Female				
n	15	15	15	15
Forelimb grip strength (g)	117.7 ± 3.4	121.8 ± 3.2	117.5 ± 3.1	123.6 ± 2.9
Hindlimb grip strength (g)	92.80 ± 2.54	98.67 ± 2.81	88.93 ± 2.34	96.87 ± 2.35
Change in forelimb grip strength (g)	46.20 ± 3.97	49.60 ± 3.74	42.67 ± 3.23	51.60 ± 2.84
Change in hindlimb grip strength (g)	39.80 ± 3.52	42.67 ± 3.51	31.00 ± 3.36	42.93 ± 2.57

[a] Mean ± standard error

TABLE H12
Neurobehavioral Data for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of Tricresyl Phosphate[a]

	0 ppm	60 ppm	125 ppm	250 ppm
Male				
n	15	15	15	15
Forelimb grip strength (g)	134.7 ± 5.0	135.5 ± 4.9	137.2 ± 3.1	141.3 ± 4.2
Hindlimb grip strength (g)	95.40 ± 3.08	100.07 ± 3.08	97.73 ± 1.86	99.40 ± 2.04
Change in forelimb grip strength (g)	55.80 ± 4.97	59.13 ± 5.36	60.27 ± 3.83	62.33 ± 4.86
Change in hindlimb grip strength (g)	36.53 ± 3.54	42.67 ± 4.08	42.13 ± 2.20	43.07 ± 2.27
Female				
n	15	15	15	14
Forelimb grip strength (g)	139.6 ± 6.4	138.7 ± 3.7	135.9 ± 2.8	138.4 ± 6.6
Hindlimb grip strength (g)	93.87 ± 3.72	96.67 ± 3.13	96.93 ± 1.63	95.93 ± 3.55
Change in forelimb grip strength (g)	66.27 ± 6.72	68.13 ± 5.02	64.73 ± 2.70	68.86 ± 5.80
Change in hindlimb grip strength (g)	36.40 ± 3.22	41.67 ± 3.82	42.40 ± 1.95	41.21 ± 3.36

[a] Mean ± standard error

APPENDIX I
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

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CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF TRICRESYL PHOSPHATE

Tricresyl phosphate was obtained as a clear, colorless liquid from Stauffer Chemical Company (Westport, CT) in one lot (1202A-2-7), which was used throughout the 16-day, 13-week, and 2-year studies in rats and mice. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Confirmatory analyses were conducted by Radian Corporation (Austin, TX). The reports on analyses performed in support of the tricresyl phosphate studies are on file at the National Institute of Environmental Health Sciences.

The chemical was characterized by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The ultraviolet/visible spectrum was consistent with the literature spectrum of tricresyl phosphate (*Sadtler Standard Spectra*). The infrared and nuclear magnetic resonance spectra were consistent with those of a mixture of isomers of tricresyl phosphate (Figures I1 and I2).

The purity of tricresyl phosphate was determined by elemental analyses, Karl Fischer water analysis, thin-layer chromatography (TLC), and gas chromatography. Thin-layer chromatography was performed on Silica Gel 60 F-254 plates using two solvent systems: 1) diethyl ether:hexanes (80:20) and 2) ethyl acetate: iso-octane (30:70). Plates were examined under ultraviolet light (254 nm) and a spray of diazotized (acid) 4-nitroaniline. Gas chromatography was performed using a chromatograph with a flame ionization detector. Two systems were used:

A) 3% Dexsil 400 on 100/120 Supelcoport column and a nitrogen carrier gas at a flow rate of 70 mL/minute, with an oven temperature program of 50° C for 5 minutes, then 50° to 270° C at 10° C per minute

B) SP-2100 coated capillary column and a helium carrier gas at a linear velocity of 20 cm/second, with an isothermal oven temperature of 250° C.

Elemental analyses for carbon, hydrogen, and phosphorus were in agreement with the theoretical values for tricresyl phosphate. Karl Fischer water analysis indicated 0.072% ± 0.003% water. Thin-layer chromatography indicated only one major spot in each system. Gas chromatography using system A indicated 13 components. Gas chromatography using system B indicated 28 components, with nine of these components having peak areas greater than 2% of the total chromatographic peak area. From the second gas chromatography system, the concentrations of tri-*m*-cresyl phosphate and tri-*p*-cresyl phosphate were estimated at 21% and 4% of the total. The concentration of tri-*o*-cresyl phosphate was estimated at less than 0.1%.

Special analyses were performed to identify the other seven components of tricresyl phosphate which represent greater than 2% of the chromatographic peak area using a mass spectrometer and a gas chromatograph equipped with a helium gas carrier at a linear velocity of 20 cm/second and an oven temperature program of 40° C for 2 minutes, then 40° to 250° C at 10° C per minute.

Two peaks representing 24% and 30% of the total chromatographic peak area were identified as tricresyl phosphate esters whose isomeric composition could not be confirmed. The remaining five peaks (2%, 3%, 3%, 4%, and 5%) were identified as dicresyl phosphate esters, but again the isomeric composition could not be confirmed.

To summarize, the test chemical is a complex mixture consisting of 18% dicresyl phosphate esters and 79% tricresyl phosphate esters. Two of the tricresyl phosphate esters were identified as tri-*m*-cresyl phosphate (21%) and tri-*p*-cresyl phosphate (4%), with no detectable tri-*o*-cresyl phosphate (<0.1%).

Stability studies were performed by the analytical chemistry laboratory. Gas chromatography was performed using system A described above, except with a flow rate of 15 mL/minute; an oven temperature program of 230° C for 5 minutes, then 230° to 270° C at 2° C per minute; and *n*-hexacosane added as an internal standard. These studies were based on the four major peaks and indicated that tricresyl phosphate was stable as a bulk chemical for at least 2 weeks when stored protected from light at temperatures up to 60° C. The stability of the bulk chemical was monitored periodically at the study laboratory with ultraviolet spectroscopy and gas chromatography methods similar to those described above. No degradation of the bulk chemical was observed.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

In the 16-day gavage studies, the 5,800 mg/kg dose consisted of undiluted bulk chemical. The remaining gavage formulations for the 16-day and 13-week studies were derived by serial dilution of the bulk chemical with USP grade corn oil. Dose formulations for the 13-week and 2-year feed studies were prepared by mixing tricresyl phosphate with feed in a blender (Patterson-Kelley Twin Shell with intensifier bar) for 15 minutes (Table I1). Dose formulations were prepared once (mice) or twice (rats) for the 16-day studies and weekly for the 13-week and 2-year studies.

For the gavage studies, dose formulation stability analyses at the 40 mg/mL concentration were performed by the analytical chemistry laboratory. Aliquots were extracted with methanol, then 1,3,5-triphenylbenzene (1.0 mg/mL in acetone) was added as an internal standard. Gas chromatography was performed using system A described above, except with a carrier gas rate of 15 mL/minute and an oven temperature program of 230° C for 5 minutes, then 230° to 270° C at 2° C per minute. The stability of the dose formulations based on the four largest peaks was confirmed for at least 2 weeks at room temperature when stored in the dark, and for 3 hours when exposed to air and light.

Studies to determine the homogeneity and stability of the dosed feed preparations were conducted by the analytical chemistry laboratory. For homogeneity and stability analyses, tricresyl phosphate at a concentration of 60 ppm in feed was extracted with 100 mL isooctane; tricresyl phosphate at a concentration of 500 ppm in feed was extracted with 100 mL hexane. The samples were then evaporated under a stream of nitrogen and 4 mL of water:methanol (10:90) was added. Aliquots from the 60 ppm sample were mixed with 2 mL di(2-ethyl-hexyl)phthalate (75 μg/mL in methanol) as an internal standard, while aliquots of supernatant from the 500 ppm sample were mixed with 2 mL squalane (0.5 μL/mL in methanol) as an internal standard. Gas chromatography was performed as described earlier for system A, except with a carrier gas flow rate of 20 mL/minute and an oven temperature program of 230° C, then 230° with a 10 minute delay to 280° C at 2° C per minute. Homogeneity was confirmed and the stability of the dose formulations was established based on the major tricresyl phosphate peak for at least 2 weeks when stored in the dark at room temperature.

Periodic analyses of the dose formulations of tricresyl phosphate were conducted at the study laboratory using ultraviolet spectroscopy (16-day and 13-week gavage studies), high performance liquid chromatography (13-week feed studies), and gas chromatography (13-week and 2-year feed studies). For ultraviolet spectroscopy, samples were extracted with methanol; then after centrifugation the extracts were diluted with methanol and the absorbance determined at 265 nm. For high performance liquid chromatography, samples were extracted with acetonitrile; then after centrifugation the extracts were diluted with acetonitrile or deionized water and injected onto a Waters μBondapak C_{18} column with the detector wavelength set at 254 nm. For gas chromatography, the system described above for the determination of homogeneity and stability of dose formulations was used (except with a 100/120 Chromosorb W-HP column). During

the 16-day studies, all formulations were analyzed (Table I2). During the 13-week studies, the dose formulations were analyzed at the beginning, midpoint, and end of the studies (Tables I3 and I4). During the 2-year studies, the dose formulations were analyzed every 6 to 10 weeks (Table I5). In the 2-year studies all dose formulations (89/89) were within 10% of the target concentrations. Results of the periodic referee analyses performed by the analytical chemistry laboratory were in agreement with the results obtained by the study laboratory (Tables I6 and I7).

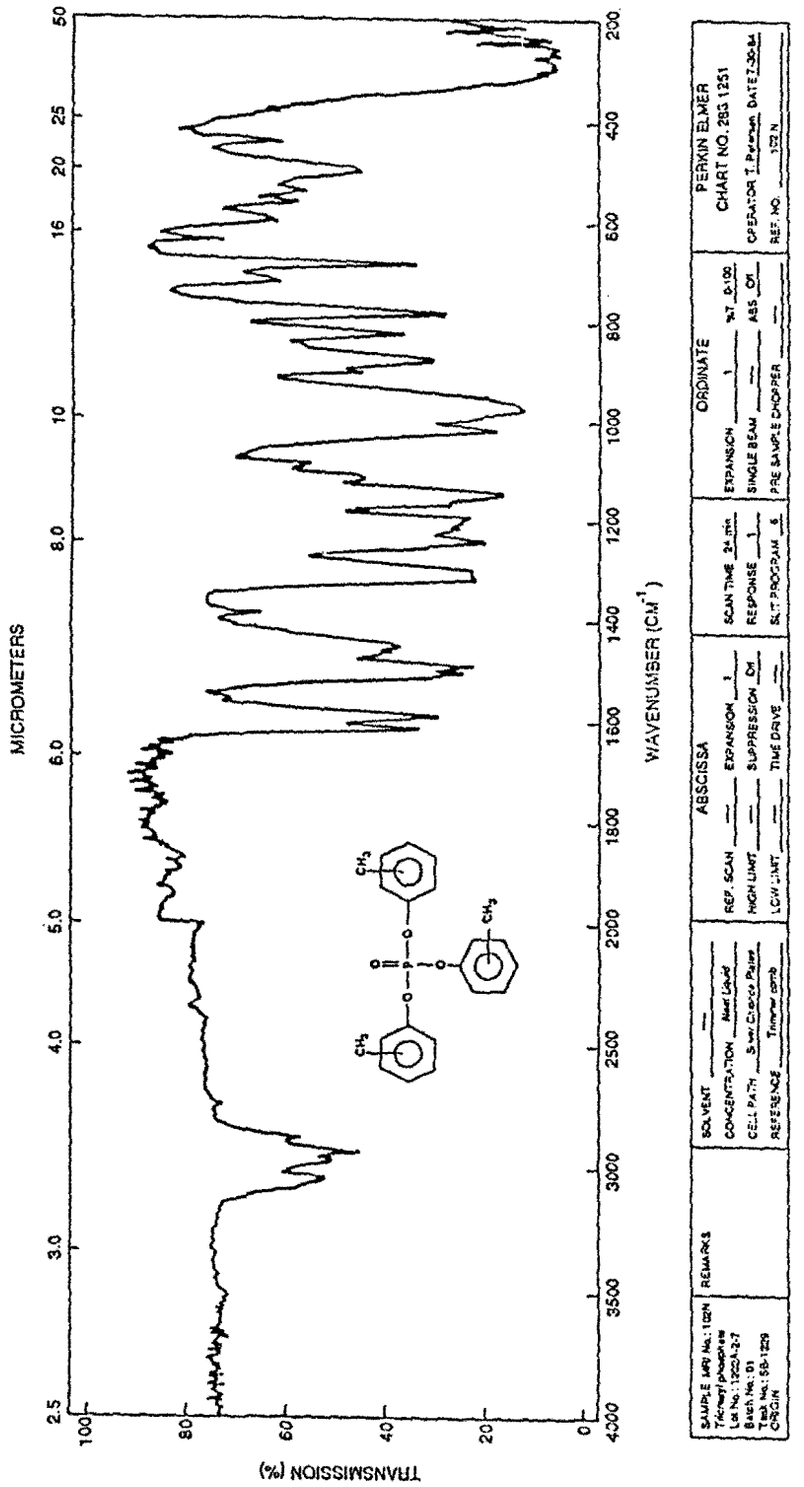

FIGURE 11
Infrared Absorption Spectrum of Tricresyl Phosphate

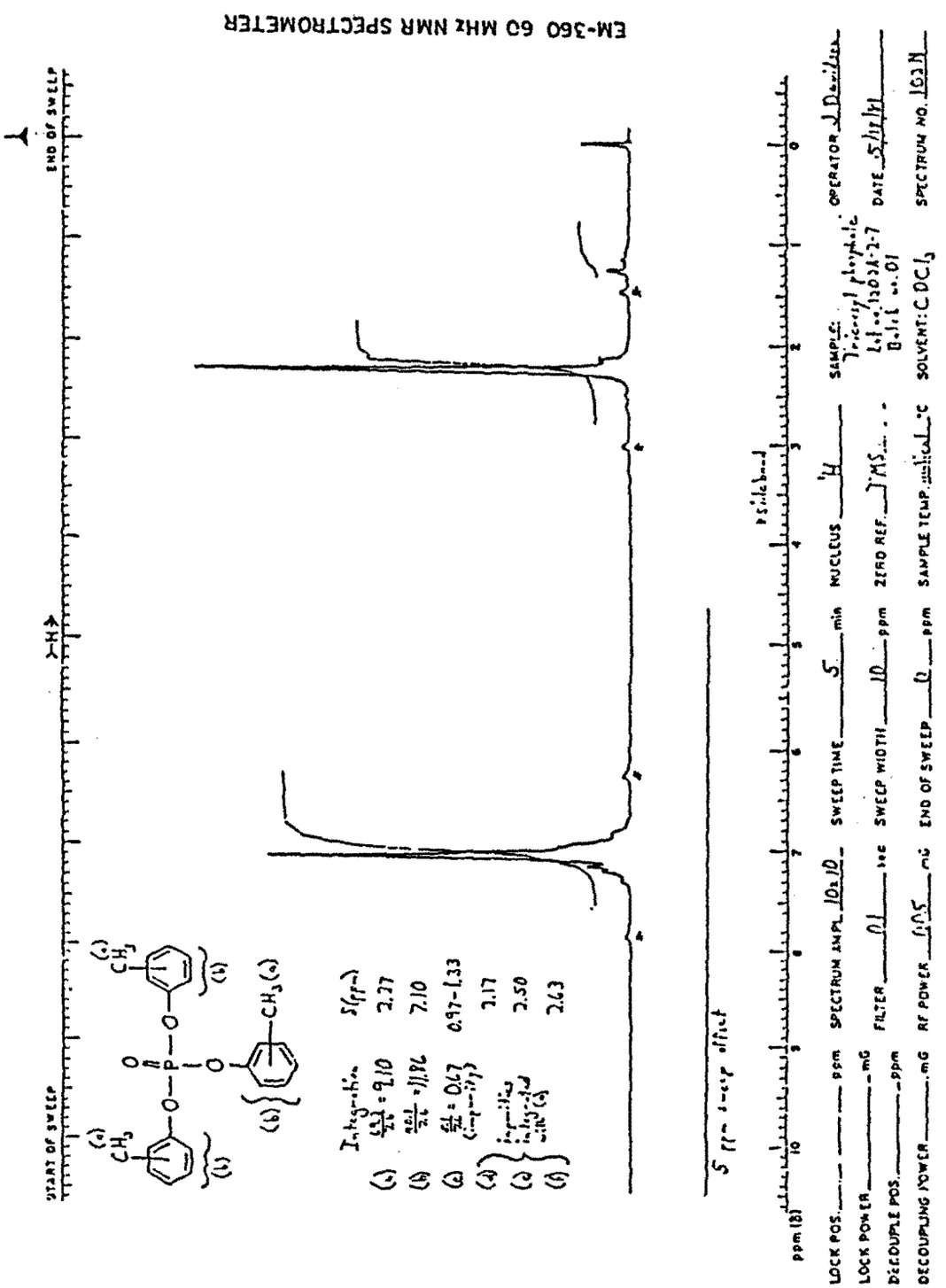

FIGURE I2
Nuclear Magnetic Resonance Spectrum of Tricresyl Phosphate

TABLE I1
Preparation and Storage of Dose Formulations in the Gavage and Feed Studies of Tricresyl Phosphate

16-Day Gavage Studies	13-Week Gavage Studies	13-Week Feed Studies	2-Year Studies
Preparation			
Except high dose, tricresyl phosphate was mixed with USP grade corn oil in amber glass containers. High dose (5,800 mg/kg) given neat.	Tricresyl phosphate was mixed with USP grade corn oil in a beaker. Contents of the beaker were transferred to a graduated cylinder which was stoppered and manually inverted 21 times for mixing.	Premix was prepared by mixing tricresyl phosphate and feed with a spatula; premix and remaining feed were layered in a blender with an intensifier bar and mixed for 15 minutes. The intensifier bar was turned on for 5 minutes and turned off for the next 10 minutes.	Same as 13-week feed studies
Chemical Lot Number			
1202A-2-7	1202A-2-7	1202A-2-7	1202A-2-7
Maximum Storage Time			
2 weeks	2 weeks	3 weeks	2 weeks
Storage Conditions			
Stored in amber glass bottles at room temperature.	Stored in 4-ounce (rats) or 1-ounce (mice) amber glass bottles at room temperature.	Stored in plastic containers at 4° C in the dark.	Stored in plastic buckets at 4° C in the dark.
Study Laboratory			
Battelle Columbus Laboratories, Columbus, OH	Same as 16-day gavage studies	Same as 16-day gavage studies	Same as 16-day gavage studies
Referee Laboratory			
Midwest Research Institute, Kansas City, MO	Same as 16-day gavage studies	Same as 16-day gavage studies	Same as 16-day gavage studies

TABLE I2
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 16-Day Gavage Studies of Tricresyl Phosphate

Date Prepared	Date Analyzed	Target Concentration (mg/mL)[a]	Determined Concentration[b] (mg/mL)	% Difference from Target
Rats[c]				
8 April 1982	15 April 1982	73	72	−1
		145	152	+5
		290	315	+9
		581	615	+6
		1,162	1,240	+7
Rats and Mice				
15 April 1982	26 April 1982	73	78	+7
		145	148	+2
		290	304	+5
		581	578	−1
		1,162	1,200	+3
Mice[c]				
15 April 1982	26 April 1982	73	76	+4
		145	158	+9
		290	294	+1
		581	580	0
		1,162	1,150	−1

[a] Target concentrations expressed as mg/kg body weight: 73 mg/mL = 360 mg/kg, 145 mg/mL = 730 mg/kg, 290 mg/mL = 1,450 mg/kg, 581 mg/mL = 2,900 mg/kg, Dose volume = 5 mL/kg; 1,162 mg/mL = 5,800 mg/kg (neat).
[b] Results of duplicate analyses
[c] Animal room samples

TABLE I3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week Gavage Studies of Tricresyl Phosphate

Date Prepared	Date Analyzed	Target Concentration[a] (mg/mL)	Determined Concentration[b] (mg/mL)	% Difference from Target
Rats				
17 December 1982	21 December 1982	10.0	10.0	0
		20.0	19.7	–2
		40.0	40.4	+1
		80.0	85.0	+6
		160	159	–1
14 January 1983	17 January 1983	10.0	9.59	–4
		20.0	21.0	+5
		40.0	42.5	+6
		80.0	83.9	+5
		160	162	+1
14 January 1983	24 January 1983[c]	10.0	9.72	–3
		20.0	20.9	+5
		40.0	39.8	–1
		80.0	85.2	+7
		160	169	+6
4 March 1983	7 March 1983	10.0	9.81	–2
		20.0	20.4	+2
		40.0	40.7	+2
		80.0	80.1	0
		160	158	–1
Mice				
12 October 1982	14 October 1982	10.0	9.00	–10
		20.0	18.4	–8
		40.0	38.6	–4
		80.0	76.3	–5
		160	168	+5
12 October 1982	25 October 1982[c]	10.0	9.00	–10
		20.0	18.1	–10
		40.0	37.7	–6
		80.0	72.1	–10
		160	154	–4
24 November 1982	29 November 1982	10.0	10.6	+6
		20.0	21.5	+8
		40.0	38.6	–4
		80.0	79.9	0
		160	157	–2
24 November 1982	10 December 1982[c]	10.0	9.72	–3
		20.0	19.6	–2
		40.0	41.8	+4
		80.0	86.0	+8
		160	163	+2

TABLE I3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week Gavage Studies of Tricresyl Phosphate (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	% Difference from Target
Mice (continued)				
17 December 1982	21 December 1982	10.0	10.0	0
		20.0	19.7	–2
		40.0	40.4	+1
		80.0	85.0	+6
		160	159	–1
14 January 1983	17 January 1983	10.0	9.59	–4
		20.0	21.0	+5
		40.0	42.5	+6
		80.0	83.9	+5
		160	162	+1
14 January 1983	24 January 1983[c]	10.0	10.1	+1
		20.0	19.7	–2
		40.0	40.4	+1
		80.0	79.5	–1
		160	162	+1

[a] Target concentrations expressed as mg/kg body weight: 10 mg/mL = 100 mg/kg; 20 mg/mL = 200 mg/kg; 40 mg/mL = 400 mg/kg; 80 mg/mL = 800 mg/kg; 160 mg/mL = 1,600 mg/kg. Dose volume = 10 mL/kg.
[b] Results of duplicate analyses
[c] Animal room samples

TABLE I4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week Feed Studies of Tricresyl Phosphate

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	% Difference from Target
Rats				
16 November 1984	23 November 1984	900	713	-21
		1,700	1,620	-5
		3,300	3,510	+6
		6,600	6,640	+1
		13,000	12,600[b]	-3
3 January 1985	4 January 1985	900	881	-2
		1,700	1,690	-1
		3,300	3,260	-1
		6,600	6,400	-3
		13,000	12,500	-4
13 February 1985	16 February 1985	900	927	+3
		1,700	1,730	+2
		3,300	3,350	+2
		6,600	6,630	0
		13,000	13,200	+2
Mice				
28 November 1984	11 December 1984	250	282[c]	+13
		500	491[c]	-2
		1,000	1,020[c]	+2
5 December 1984	11 December 1984	2,100	2,010[c]	-4
		4,200	4,280[c]	+2
6 January 1985	17 January 1985	250	229	-8
		500	465	-7
		1,000	967	-3
17 January 1985	17 January 1985	2,100	2,060	-2
		4,200	4,100	-2
20 February 1985	22 February 1985	250	253	+1
		500	509	+2
		1,000	985	-2
		2,100	2,040	-3
		4,200	4,270	+2

[a] Results of duplicate analyses
[b] Result pooled from duplicate analyses from top left, top right, and bottom of blender
[c] Results of triplicate analyses

TABLE I5
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Tricresyl Phosphate

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	% Difference from Target
Rats				
9 September 1986	12 September 1986	150	152	+1
		300	307	+2
	13 September 1986	75	70.5[b,c]	-6
		75	72.9[c,d]	-3
		75	70.8[c,e]	-6
		600	649[b,c]	+8
		600	659[c,d]	+10
		600	612[e]	+2
13 November 1986	14 November 1986	75	74.2	-1
		150	150	0
		300	308	+3
18 November 1986	18 November 1986	600	603	+1
8 January 1987	9 January 1987	75	71.4	-5
		150	149	-1
		300	297	-1
		600	594	-1
5 March 1987	6 March 1987	75	74.6	-1
		150	154	+3
		300	301	0
30 April 1987	1 May 1987	75	77.1	+3
		150	156	+4
		300	310	+3
25 June 1987	28 June 1987	75	67.7	-10
		300	289	-4
	28-29 June 1987	150	148[f]	-1
20 August 1987	22 August 1987	75	81.8	+9
		150	155	+3
		300	326	+9
23 October 1987	27 October 1987	75	80.1	+7
		150	159	+6
		300	326	+9
17 December 1987	23 December 1987	75	81.6	+9
		150	148	-1
		300	308	+3
25 February 1988	3 March 1988	75	78.7	+5
		150	151	+1
		300	289	-4

TABLE I5
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Tricresyl Phosphate (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	% Difference from Target
Rats (continued)				
7 April 1988	12 April 1988	75	72.7	–3
		150	143	–5
		300	286	–5
2 June 1988	7-8 June 1988	75	73.7	–2
		150	153	+2
		300	299	0
28 July 1988	29 July 1988	75	75.1	0
		150	147	–2
		300	292	–3
Mice				
9 September 1986	13 September 1986	75	70.5[b,c]	–6
		75	72.9[c,d]	–3
		75	70.8[c,e]	–6
		600	649[b,c]	+8
		600	659[c,d]	+10
		600	612[e]	+2
30 September 1986	2 October 1986	125	122	–2
		250	249	0
	2-6 October 1986	60	59.7[c]	–1
13 November 1986	14 November 1986	60	58.4	–3
		125	129	+3
		250	249	0
8 January 1987	9 January 1987	125	117	–6
		250	249	0
13 January 1987	13 January 1987	60	59.4	–1
5 March 1987	6 March 1987	60	59.1	–2
		125	124	–1
		250	249	0
30 April 1987	1 May 1987	60	61.5	+3
		125	129	+3
		250	251	0
25 June 1987	28-29 June 1987	60	57.2[f]	–5
		125	130	+4
		250	245[f]	–2
20 August 1987	22 August 1987	60	63.0	+5
		125	125	0
		250	245	–2

TABLE I5
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Tricresyl Phosphate (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	% Difference from Target
Mice (continued)				
23 October 1987	27 October 1987	60	59.0	–2
		125	133	+6
		250	259	+4
17 December 1987	23 December 1987	250	233	–7
	23-28 December 1987	125	127[f]	+2
	23 December 1987	60	64.6	+8
25 February 1988	3 March 1988	60	61.7	+3
		125	128	+2
		250	226	–10
3 March 1988	4 March 1988	250	225	–10
7 April 1988	12 April 1988	60	60.2	0
		125	128	+2
		250	247	–1
2 June 1988	7-8 June 1988	60	55.5	–8
		125	124	–1
		250	248	–1
28 July 1988	29 July 1988	60	59.5	–1
		125	122	–2
		250	245	–2
21 September 1988	23 September 1988	60	63.7	+6
		125	120	–4
		250	260	+4

[a] Results of duplicate analyses
[b] Sample taken from top left of blender
[c] Results of triplicate analyses
[d] Sample taken from top right of blender
[e] Sample taken from bottom of blender
[f] Results of quadruplicate analyses

TABLE I6
Results of Referee Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week Gavage Studies of Tricresyl Phosphate

Date Prepared	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	
		Study Laboratory[a]	Referee Laboratory[b]
Rats			
17 December 1982	80.0	85.0	81.7 ± 0.9
Mice			
12 October 1982	80.0	76.3	80.1 ± 3.0

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

TABLE I7
Results of Referee Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week and 2-Year Feed Studies of Tricresyl Phosphate

Date Prepared	Target Concentration (ppm)	Determined Concentration (ppm)	
		Study Laboratory[a]	Referee Laboratory[b]
13-Weeks			
Rats			
16 November 1984	900	731	901 ± 8
2-Years			
Rats			
9 September 1986	150	152	147 ± 3
25 February 1988	300	289	289 ± 3
Mice			
5 March 1987	250	249	231 ± 4
20 August 1987	60	63.0	60.0 ± 6.9
28 July 1988	125	122	126 ± 2

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

APPENDIX J
FEED AND COMPOUND CONSUMPTION IN THE 2-YEAR FEED STUDIES OF TRICRESYL PHOSPHATE

TABLE J1 Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of Tricresyl Phosphate 310

TABLE J2 Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of Tricresyl Phosphate 311

TABLE J3 Feed and Compound Consumption by Male Mice in the 2-Year Feed Study of Tricresyl Phosphate 312

TABLE J4 Feed and Compound Consumption by Female Mice in the 2-Year Feed Study of Tricresyl Phosphate 313

TABLE J1
Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of Tricresyl Phosphate

Week	0 ppm		75 ppm			150 ppm			300 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
3	15.3	175	15.7	170	7	16.5	174	14	16.4	173	29
4	16.6	205	16.4	202	6	16.4	204	12	16.9	203	25
7	16.6	264	16.3	264	5	17.1	266	10	17.3	263	20
8	15.9	274	17.1	278	5	16.3	279	9	15.9	276	17
10	16.3	299	17.7	302	4	17.3	301	9	17.4	299	18
11	16.6	309	16.6	311	4	16.9	314	8	16.9	310	16
12	15.6	315	15.5	318	4	15.5	320	7	15.7	315	15
17	17.0	354	16.2	352	3	16.6	353	7	16.5	352	14
20	16.6	377	16.6	378	3	16.9	380	7	16.9	374	14
21	17.6	373	16.1	373	3	17.3	366	7	17.5	365	14
24	16.0	394	16.5	399	3	16.2	401	6	16.2	392	12
25	17.6	385	17.3	393	3	17.9	381	7	18.2	380	14
28	16.6	411	16.1	411	3	16.5	412	6	17.1	403	13
29	17.5	404	17.7	400	3	17.7	398	7	18.1	396	14
32	15.2	423	15.5	420	3	15.7	429	6	15.2	418	11
33	16.7	408	17.1	410	3	16.6	404	6	17.2	401	13
36	15.5	429	15.7	426	3	15.1	434	5	14.6	420	11
37	16.8	415	16.1	417	3	17.1	408	6	17.6	406	13
40	16.7	431	16.2	442	3	16.8	436	6	16.5	432	11
41	17.2	423	17.3	427	3	17.7	415	6	17.3	414	13
44	15.3	441	16.2	440	3	15.9	449	5	16.2	446	11
45	19.6	429	19.1	430	3	18.1	418	7	19.0	419	14
48	17.1	455	16.7	452	3	17.2	454	6	16.8	455	11
49	18.2	438	18.6	441	3	19.1	429	7	19.8	426	14
52	14.1	455	15.4	453	3	15.6	458	5	15.0	456	10
53	18.0	429	19.0	446	3	16.8	428	6	17.9	422	13
56	14.8	453	14.7	456	2	14.9	455	5	14.6	454	10
57	14.4	438	18.6	443	3	18.1	432	6	17.2	426	12
60	16.1	457	16.9	460	3	16.8	458	6	16.4	460	11
61	18.5	442	17.9	444	3	18.4	435	6	18.1	429	13
64	15.3	467	15.8	464	3	15.2	462	5	14.4	466	9
65	18.5	441	17.9	450	3	18.4	436	6	18.1	431	13
69	16.0	442	16.7	450	3	15.6	434	5	16.5	433	11
73	14.2	445	15.1	453	3	15.2	441	5	16.0	437	11
77	15.7	445	15.8	450	3	16.8	444	6	16.1	436	11
81	15.7	443	15.6	450	3	15.6	441	5	15.7	436	11
85	15.1	444	14.8	444	3	14.9	439	5	13.8	427	10
89	14.0	445	14.4	443	2	14.0	436	5	13.5	421	10
93	15.0	432	15.7	435	3	16.3	434	6	15.4	428	11
97	12.9	437	16.0	440	3	15.6	433	5	14.7	430	10
101	12.7	421	14.6	426	3	14.1	428	5	14.6	417	11
104	12.7	412	14.6	421	3	14.1	424	5	14.6	419	11
Mean for weeks											
1-13	16.1	263	16.5	264	4.9	16.6	265	9.8	16.6	263	19.9
14-52	16.7	414	16.7	415	3.0	16.9	413	6.2	17.0	409	12.5
53-104	15.3	441	16.1	446	2.7	15.9	439	5.4	15.7	434	10.9

[a] Grams of feed consumed per animal per day
[b] Milligrams of tricresyl phosphate consumed per day per kilogram body weight

TABLE J2
Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of Tricresyl Phosphate

Week	0 ppm		75 ppm			150 ppm			300 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
3	11.4	126	11.6	125	7	11.6	128	14	11.7	126	28
4	11.9	140	11.8	139	6	12.2	141	13	11.9	140	26
7	11.8	164	11.8	168	5	11.7	168	11	11.5	166	21
8	11.2	170	11.1	173	5	11.6	173	10	11.9	171	21
11	11.2	182	11.4	181	5	10.8	183	9	11.6	183	19
12	10.5	182	10.0	184	4	10.3	186	8	9.9	183	16
13	10.7	185	10.9	186	4	10.7	188	9	10.9	186	18
17	12.0	196	11.4	195	4	10.8	199	8	11.2	197	17
20	11.0	208	11.4	211	4	11.5	204	9	10.7	206	16
21	11.7	204	11.6	203	4	11.3	207	8	11.6	201	17
24	10.5	215	10.3	219	4	10.6	210	8	10.9	213	15
25	11.4	210	11.7	209	4	11.5	214	8	11.4	210	16
28	10.6	220	10.4	226	3	11.0	218	8	10.5	218	15
29	11.4	216	11.3	213	4	11.3	222	8	11.3	214	16
32	10.4	225	10.0	230	3	10.4	226	7	10.2	226	14
33	11.2	220	10.9	219	4	10.8	224	7	11.2	221	15
36	10.4	231	10.2	229	3	10.2	228	7	10.3	229	14
37	11.0	228	11.4	224	4	11.4	232	7	11.7	226	16
40	11.7	236	11.4	241	4	11.9	235	8	11.5	237	15
41	11.8	234	12.1	232	4	11.8	239	7	11.8	234	15
44	11.3	241	11.1	246	3	11.4	244	7	11.8	242	15
45	13.1	242	13.7	237	4	13.6	248	8	13.6	241	17
48	12.2	256	11.9	262	3	12.1	260	7	12.0	255	14
49	13.7	252	14.9	249	5	14.1	259	8	14.8	249	18
52	10.8	261	10.9	274	3	11.1	270	6	10.6	264	12
53	12.0	262	14.2	256	4	13.2	258	8	13.1	257	15
56	10.9	264	10.7	281	3	11.5	275	6	10.8	268	12
57	12.1	268	14.8	263	4	12.7	274	7	14.0	264	16
60	12.9	275	12.3	288	3	13.0	283	7	12.8	282	14
61	14.1	279	14.9	273	4	13.9	285	7	15.2	270	17
64	12.0	286	11.6	301	3	11.9	297	6	11.5	298	12
65	14.1	289	14.9	285	4	13.9	297	7	15.2	286	16
69	12.5	299	12.8	294	3	12.0	303	6	12.8	292	13
73	11.1	310	12.1	304	3	12.1	312	6	12.3	304	12
77	12.3	312	12.5	308	3	12.8	317	6	12.2	307	12
81	12.7	319	12.7	315	3	12.3	324	6	12.3	312	12
85	12.3	325	12.5	322	3	12.5	332	6	12.7	318	12
89	11.3	323	11.2	323	3	11.1	328	5	11.3	317	11
93	13.2	326	12.9	330	3	13.0	335	6	12.4	324	12
97	11.3	328	12.6	331	3	12.4	336	6	12.0	319	11
101	10.4	319	11.6	327	3	10.6	332	5	10.5	312	10
104	10.4	315	11.6	320	3	10.6	332	5	10.5	313	10
Mean for weeks											
1-13	11.2	164	11.2	165	5.2	11.3	167	10.4	11.3	165	21.1
14-52	11.4	228	11.5	229	3.8	11.5	230	7.5	11.5	227	15.3
53-104	12.1	300	12.7	301	3.2	12.3	307	6.1	12.4	297	12.7

[a] Grams of feed consumed per animal per day
[b] Milligrams of tricresyl phosphate consumed per day per kilogram body weight

TABLE J3
Feed and Compound Consumption by Male Mice in the 2-Year Feed Study of Tricresyl Phosphate

Week	0 ppm		60 ppm			125 ppm			250 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
4	4.2	25.6	4.2	25.5	10	4.0	25.4	20	4.4	25.5	44
5	4.8	26.3	4.8	26.1	11	5.0	26.4	24	4.7	26.3	45
8	4.7	28.6	4.4	28.5	9	4.4	28.6	19	4.5	28.8	39
9	4.8	29.4	5.0	29.4	10	5.1	29.3	22	5.2	29.4	44
12	4.6	31.8	4.9	31.7	9	4.9	31.4	20	5.0	31.8	39
13	5.7	32.0	5.5	32.0	10	5.2	31.9	21	5.6	32.3	43
17	4.6	34.6	4.9	34.6	8	4.7	35.0	17	4.8	35.5	34
21	4.7	36.5	4.5	36.4	8	4.4	36.8	15	4.7	37.2	31
25	4.5	38.3	4.9	38.5	8	4.4	38.9	14	4.5	39.7	28
29	4.7	39.6	4.7	39.5	7	4.5	39.8	14	4.6	40.8	28
33	4.6	41.0	4.4	40.9	7	4.2	41.4	13	4.3	41.9	26
37	4.4	42.9	4.4	43.1	6	4.2	43.5	12	4.4	44.1	25
41	4.3	42.9	4.0	42.4	6	4.0	42.8	12	4.1	44.1	23
45	4.2	43.6	4.2	43.9	6	4.0	44.3	11	4.4	45.7	24
49	4.9	45.3	4.9	45.5	7	4.7	45.7	13	5.0	47.3	27
53	4.0	45.2	4.3	45.8	6	4.2	46.3	11	4.3	47.4	23
57	3.9	46.2	4.5	46.4	6	4.3	46.3	12	4.4	47.9	23
61	4.2	46.4	4.6	47.0	6	4.3	47.7	11	4.5	48.3	24
65	4.4	47.2	4.7	47.8	6	4.4	48.4	11	4.7	48.6	24
69	4.3	48.0	4.2	47.7	5	4.2	49.1	11	4.5	48.7	23
73	3.9	46.5	4.0	47.6	5	4.1	49.0	11	4.1	48.1	21
77	4.2	48.0	4.2	48.8	5	4.2	50.2	10	4.1	49.6	21
81	4.2	47.3	4.1	48.5	5	4.3	50.1	11	4.3	49.2	22
85	4.9	46.3	4.2	47.7	5	4.2	49.0	11	4.3	47.7	22
89	4.5	47.3	4.3	48.7	5	4.5	50.1	11	4.6	49.2	23
93	4.4	46.6	4.2	46.9	5	4.3	49.1	11	4.4	48.3	23
97	4.4	47.2	4.2	47.4	5	4.1	48.7	11	4.5	48.5	23
101	3.7	46.1	3.7	45.8	5	3.9	48.6	10	4.1	46.9	22
105	4.0	44.7	3.9	43.7	5	3.9	47.0	10	4.0	44.3	23
Mean for weeks											
1-13	4.8	29.0	4.8	28.9	10	4.8	28.8	21	4.9	29.0	42
14-52	4.5	40.5	4.6	40.5	7	4.4	40.9	13	4.5	41.8	27
53-105	4.2	46.6	4.2	47.1	5	4.2	48.5	11	4.3	48.1	23

[a] Grams of feed consumed per animal per day
[b] Milligrams of tricresyl phosphate consumed per day per kilogram body weight

TABLE J4
Feed and Compound Consumption by Female Mice in the 2-Year Feed Study of Tricresyl Phosphate

Week	0 ppm		60 ppm			125 ppm			250 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
4	4.7	22.2	4.7	22.2	13	4.6	22.1	26	4.7	21.8	54
5	5.7	22.8	5.2	23.1	14	5.8	23.1	31	5.8	23.0	64
8	5.7	25.5	5.5	26.1	13	5.5	25.9	27	5.6	25.9	54
9	6.6	26.3	6.5	26.7	15	6.3	26.9	29	6.7	26.3	64
12	6.6	28.4	7.1	29.3	15	6.4	29.1	27	7.3	28.6	64
13	7.9	29.1	7.9	29.7	16	7.1	29.9	30	8.0	29.2	69
17	5.5	31.9	5.9	33.3	11	5.7	33.2	21	5.9	32.9	45
21	5.7	34.8	6.0	35.7	10	6.3	35.5	22	6.3	35.2	45
25	6.5	37.1	6.5	38.3	10	6.1	38.3	20	6.5	37.5	44
29	7.1	38.6	6.8	39.3	10	6.4	39.2	20	7.2	39.0	46
33	6.5	40.0	6.3	41.0	9	6.3	40.9	19	6.9	40.5	42
37	6.2	41.6	6.2	42.9	9	6.2	42.4	18	6.6	42.3	39
41	6.1	42.1	6.0	41.7	9	6.8	41.7	21	6.6	41.6	40
45	6.6	43.0	6.2	43.9	9	6.7	43.8	19	6.9	43.8	39
49	7.2	44.9	6.7	45.0	9	6.3	45.7	17	6.5	45.5	36
53	6.3	45.2	5.8	45.8	8	5.7	45.5	16	6.4	46.3	35
57	6.4	45.6	5.9	46.4	8	5.6	45.9	15	6.1	46.5	33
61	6.3	47.0	5.8	47.9	7	5.6	47.8	15	5.6	47.9	29
65	5.7	47.8	5.6	49.1	7	5.5	49.1	14	5.9	49.0	30
69	5.1	49.0	5.1	50.3	6	5.1	50.2	13	5.8	49.7	29
73	4.7	48.8	4.9	50.0	6	5.0	50.1	12	5.2	49.6	26
77	5.0	50.9	5.1	51.6	6	5.1	51.1	13	5.1	50.9	25
81	4.9	50.8	4.8	51.6	6	5.0	51.3	12	5.0	51.6	24
85	5.5	49.7	4.9	50.9	6	4.9	50.4	12	5.0	50.1	25
89	5.2	50.8	4.9	51.7	6	5.2	51.1	13	5.5	51.3	27
93	4.6	50.3	4.6	51.1	5	4.7	50.6	12	5.0	50.5	25
97	4.9	50.2	4.8	50.6	6	4.9	49.7	12	5.1	50.8	25
101	4.4	49.1	4.3	50.4	5	4.5	49.0	11	4.8	48.9	24
105	4.8	46.7	4.7	47.0	6	4.5	47.1	12	4.8	46.0	26
Mean for weeks											
1-13	6.2	25.7	6.2	26.2	14	5.9	26.2	28	6.4	25.8	61
14-52	6.4	38.4	6.3	40.1	9	6.3	40.1	20	6.6	39.8	42
53-105	5.3	48.7	5.1	49.6	6	5.1	49.2	13	5.4	49.2	27

[a] Grams of feed consumed per animal per day
[b] Milligrams of tricresyl phosphate consumed per day per kilogram body weight

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

TABLE K1	Ingredients of NIH-07 Rat and Mouse Ration	316
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TABLE K1
Ingredients of NIH-07 Rat and Mouse Ration[a]

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

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

TABLE K2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

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

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

TABLE K3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.48 ± 0.84	21.30 – 24.00	18
Crude Fat (% by weight)	5.45 ± 0.32	4.80 – 5.90	18
Crude Fiber (% by weight)	3.49 ± 0.31	3.00 – 4.10	18
Ash (% by weight)	6.82 ± 0.33	6.01 – 7.27	18
Amino Acids (% of total diet)			
Arginine	1.287 ± 0.084	1.100 – 1.390	10
Cystine	0.306 ± 0.075	0.181 – 0.400	10
Glycine	1.160 ± 0.050	1.060 – 1.220	10
Histidine	0.580 ± 0.024	0.531 – 0.608	10
Isoleucine	0.917 ± 0.034	0.867 – 0.965	10
Leucine	1.972 ± 0.052	1.850 – 2.040	10
Lysine	1.273 ± 0.051	1.200 – 1.370	10
Methionine	0.437 ± 0.115	0.306 – 0.699	10
Phenylalanine	0.994 ± 0.125	0.665 – 1.110	10
Threonine	0.896 ± 0.055	0.824 – 0.985	10
Tryptophan	0.223 ± 0.160	0.107 – 0.671	10
Tyrosine	0.677 ± 0.105	0.564 – 0.794	10
Valine	1.089 ± 0.057	0.962 – 1.170	10
Essential Fatty Acids (% of total diet)			
Linoleic	2.389 ± 0.233	1.830 – 2.570	9
Linolenic	0.277 ± 0.036	0.210 – 0.320	9
Vitamins			
Vitamin A (IU/kg)	6,316 ± 1,143	4,500 – 8,240	18
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 – 6,300	4
α-Tocopherol (ppm)	36.92 ± 9.32	22.5 – 48.9	9
Thiamine (ppm)	19.89 ± 2.76	15.0 – 25.0	18
Riboflavin (ppm)	7.92 ± 0.93	6.10 – 9.00	10
Niacin (ppm)	100.95 ± 25.92	65.0 – 150.0	9
Pantothenic Acid (ppm)	30.30 ± 3.60	23.0 – 34.6	10
Pyridoxine (ppm)	9.25 ± 2.62	5.60 – 14.0	10
Folic Acid (ppm)	2.51 ± 0.64	1.80 – 3.70	10
Biotin (ppm)	0.267 ± 0.049	0.19 – 0.35	10
Vitamin B_{12} (ppb)	40.14 ± 20.04	10.6 – 65.0	10
Choline (ppm)	3,608 ± 314	2,400 – 3,430	9
Minerals			
Calcium (%)	1.25 ± 0.12	0.96 – 1.45	18
Phosphorus (%)	0.97 ± 0.06	0.85 – 1.10	18
Potassium (%)	0.887 ± 0.067	0.772 – 0.971	8
Chloride (%)	0.526 ± 0.092	0.380 – 0.635	8
Sodium (%)	0.315 ± 0.344	0.258 – 0.370	10
Magnesium (%)	0.168 ± 0.008	0.151 – 0.180	10
Sulfur (%)	0.274 ± 0.063	0.208 – 0.420	10
Iron (ppm)	356.2 ± 90.0	255.0 – 523.0	10
Manganese (ppm)	92.24 ± 5.35	81.70 – 99.40	10
Zinc (ppm)	58.14 ± 9.91	46.10 – 81.60	10
Copper (ppm)	11.50 ± 2.40	8.090 – 15.39	10
Iodine (ppm)	3.70 ± 1.14	1.52 – 5.83	10
Chromium (ppm)	1.71 ± 0.45	0.85 – 2.09	9
Cobalt (ppm)	0.797 ± 0.23	0.490 – 1.150	6

TABLE K4
Contaminant Levels in NIII-07 Rat and Mouse Ration

	Mean ± Standard Deviation[a]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.32 ± 0.21	0.05 – 0.77	18
Cadmium (ppm)	<0.10		18
Lead (ppm)	0.26 ± 0.15	0.05 – 0.60	18
Mercury (ppm)[b]	0.05 ± 0.01	0.05 – 0.80	18
Selenium (ppm)	0.35 ± 0.10	0.20 – 0.55	18
Aflatoxins (ppb)	<5.0		18
Nitrate nitrogen (ppm)[c]	21.79 ± 9.46	0.30 – 34.0	18
Nitrite nitrogen (ppm)[c]	0.13 ± 0.06	<0.10 – 0.30	18
BHA (ppm)[d]	4.44 ± 6.45	<2.00 – 3.00	18
BHT (ppm)[d]	1.00		18
Aerobic plate count (CFU/g)[e]	302,444 ± 326,586	38,000 – 1,200,000	18
Coliform (MPN/g)[f]	200.1 ± 268.9	<3.00 – 1,100	18
E. coli (MPN/g)[g]	3.11 ±0.32	<3.00 – 4.00	18
Total Nitrosoamines (ppb)[h]	10.10 ± 3.91	5.00 – 19.40	18
N-Nitrosodimethylamine (ppb)[h]	7.86 ± 3.38	3.20 – 14.00	18
N-Nitrosopyrrolidine (ppb)[h]	2.24 ± 1.26	1.00 – 5.40	18
Pesticides (ppm)			
α-BHC[i]	<0.01		18
β-BHC	<0.02		18
γ-BHC	<0.01		18
δ-BHC	<0.01		18
Heptachlor	<0.01		18
Aldrin	<0.01		18
Heptachlor epoxide	<0.01		18
DDE	<0.01		18
DDD	<0.01		18
DDT	<0.01		18
HCB	<0.01		18
Mirex	<0.01		18
Methoxychlor	<0.05		18
Dieldrin	<0.01		18
Endrin	<0.01		18
Telodrin	<0.01		18
Chlordane	<0.05		18
Toxaphene	<0.1		18
Estimated PCBs	<0.2		18
Ronnel	<0.01		18
Ethion	<0.02		18
Trithion	<0.05		18
Diazinon	<0.1		18
Methyl parathion	<0.02		18
Ethyl parathion	<0.02		18
Malathion	0.17± 0.20	0.05 – 0.85	18
Endosulfan I	<0.01		18
Endosulfan II	<0.01		18
Endosulfan sulfate	<0.03		18

TABLE K4
Contaminant Levels in NIH-07 Rat and Mouse Ration (continued)

[a] For values less than the limit of detection, the detection limit is given as the mean.
[b] One lot milled 3 September 1986 contained 0.08 ppm, all other lots were less than or equal to the detection limit.
[c] Sources of contamination: alfalfa, grains, and fish meal
[d] Sources of contamination: soy oil and fish meal
[e] CFU - colony forming units
[f] MPN - most probable number
[g] Two lots milled 6 May 1987 and 4 April 1988 contained 4 MPN; all other lots contained 3 MPN or less.
[h] All values were corrected for % recovery
[i] BHC is hexachlorocyclohexane or benzene hexachloride

APPENDIX L
SENTINEL ANIMAL PROGRAM

METHODS 322
TABLE L1 Murine Virus Antibody Determinations for Rats and Mice in the 13-Week and 2-Year Studies of Tricresyl Phosphate 325

SENTINEL ANIMAL PROGRAM

METHODS

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via serology on sera from extra (sentinel) animals in the study rooms. These animals and the study animals are 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.

Rats

During the 13-week gavage study, samples for viral screening were collected from five male and five female control animals. These samples were processed appropriately and were submitted to Microbiological Associates, Inc. (Bethesda, MD), for determination of antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
Complement Fixation	
RCV (rat coronavirus)	Study termination
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	Study termination
KRV (Kilham rat virus)	Study termination
PVM (pneumonia virus of mice)	Study termination
Sendai	Study termination

During the 13-week feed study, samples for viral screening were collected from five male and five female control animals. These samples were processed appropriately and were submitted to Microbiological Associates, Inc., for determination of antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
ELISA	
Mycoplasma pulmonis	Study termination
PVM	Study termination
RCV/SDA (rat coronavirus/sialodacryoadenitis virus)	Study termination
Sendai	Study termination
Hemagglutination Inhibition	
H-1	Study termination
KRV	Study termination

During the 2-year feed study, 15 male and 15 female F344/N rats were maintained with the study animals to serve as sentinel animals. Blood samples were taken from five males and five females at 6, 12, and 18 months. Samples for viral screening at 24 months were collected from high-dose male and female rats. In addition, at 6, 12, and 15 months, blood samples were taken from five male and female rats designated for interim evaluations. Blood collected from each animal was allowed to clot and the sera were separated, cooled on ice, and shipped to Microbiological Associates, Inc., for determination of antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
ELISA	
CARB (cilia-associated respiratory virus)	12 months
Mycoplasma arthritidis	24 months
M. pulmonis	24 months
PVM	6, 12, 15, 18, and 24 months
RCV/SDA	6, 12, 15, 18, and 24 months
Sendai	6, 12, 15, 18, and 24 months
Hemagglutination Inhibition	
H-1	6, 12, 15, 18, and 24 months
KRV	6, 12, 15, 18, and 24 months
Immunofluorescence Assay	
CARB	12 months (core group only)
LCM (lymphocytic choriomeningitis virus)	24 months

Mice

During the 13-week feed study, samples for viral screening were collected from five male and five female control animals. These samples were processed appropriately and were submitted to Microbiological Associates, Inc., for determination of antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
Complement Fixation	
LCM	Study termination
ELISA	
Ectromelia virus	Study termination
GDVII (mouse encephalomyelitis virus)	Study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
MHV (mouse hepatitis virus)	Study termination
Mouse adenoma virus	Study termination
PVM	Study termination
Reovirus 3	Study termination
Sendai	Study termination
Hemagglutination Inhibition	
K (papovavirus)	Study termination
MVM (minute virus of mice)	Study termination
Polyoma virus	Study termination

During the 2-year study, 15 male and 15 female B6C3F$_1$ mice were maintained with the study animals to serve as sentinel animals. Blood samples were taken from five males and five females at 6, 12, and 18 months. Samples for viral screening at 24 months were collected from untreated control male and female mice. In addition, at 6, 12, and 15 months, blood samples were taken from five male and female mice designated for interim evaluations. Blood collected from each animal was allowed to clot and the sera were separated, cooled on ice, and shipped to Microbiological Associates, Inc., for determination of antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
ELISA	
Ectromelia virus	6, 12, 15, 18, and 24 months
GDVII	6, 12, 15, 18, and 24 months
LCM	6, 12, 15, and 18 months
M. arthritidis	24 months
M. pulmonis	24 months
MHV	6, 12, 15, 18, and 24 months
Mouse adenoma virus	6, 12, 15, 18, and 24 months
MVM	6, 12, 15, 18, and 24 months
PVM	6, 12, 15, 18, and 24 months
Reovirus 3	6, 12, 15, 18, and 24 months
Sendai	6, 12, 15, 18, and 24 months
Hemagglutination Inhibition	
K	6, 12, 15, 18, and 24 months
Polyoma virus	6, 12, 15, 18, and 24 months
Immunofluorescence Assay	
EDIM (epizootic diarrhea of infant mice)	6, 12, 15, 18, and 24 months
LCM	24 months

Results are presented in Table L1.

TABLE L1
Murine Virus Antibody Determinations for Rats and Mice in the 13-Week and 2-Year Studies of Tricresyl Phosphate

	Interval	Incidences of Antibody in Sentinel Animals	Positive Serologic Reaction for
13-Week Gavage Study			
Rats	13 weeks	1/10	Sendai
		4/10	RCV
13-Week Feed Studies			
Rats	13 weeks	0/10	None positive
Mice	13 weeks	0/9	None positive
2-Year Studies			
Rats	6 months (core)	0/10	None positive
	6 months (interim)	0/10	None positive
	12 months (core)	1/10[a]	CARB
	12 months (interim)	0/10	None positive
	15 months	0/10	None positive
	18 months	0/10	None positive
	24 months	0/10	None positive
Mice	6 months (core)	0/10	None positive
	6 months (interim)	0/10	None positive
	12 months (core)	0/10	None positive
	12 months (interim)	0/10	None positive
	15 months	0/10	None positive
	18 months	0/10	None positive
	24 months	0/10	None positive

[a] Serum from this animal was positive for CARB using ELISA and IFA.

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TR No.	CHEMICAL
201	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Dermal)
206	1,2-Dibromo-3-chloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butyl Benzyl Phthalate
214	Caprolactam
215	Bisphenol A
216	11-Aminoundecanoic Acid
217	Di(2-ethylhexyl)phthalate
219	2,6-Dichloro-p-phenylenediamine
220	C.I. Acid Red 14
221	Locust Bean Gum
222	C.I. Disperse Yellow 3
223	Eugenol
224	Tara Gum
225	D & C Red No. 9
226	C.I. Solvent Yellow 14
227	Gum Arabic
228	Vinylidene Chloride
229	Guar Gum
230	Agar
231	Stannous Chloride
232	Pentachloroethane
233	2-Biphenylamine Hydrochloride
234	Allyl Isothiocyanate
235	Zearalenone
236	*D*-Mannitol
237	1,1,1,2-Tetrachloroethane
238	Ziram
239	Bis(2-chloro-1-methylethyl)ether
240	Propyl Gallate
242	Diallyl Phthalate (Mice)
243	Trichlorethylene (Rats and Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
246	Chrysotile Asbestos (Hamsters)
247	L-Ascorbic Acid
248	4,4'-Methylenedianiline Dihydrochloride
249	Amosite Asbestos (Hamsters)
250	Benzyl Acetate
251	2,4- & 2,6-Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
254	Dichloromethane (Methylene Chloride)
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
266	Monuron
267	1,2-Propylene Oxide
269	Telone II® (1,3-Dichloropropene)
271	HC Blue No. 1
272	Propylene
273	Trichloroethylene (Four Rat Strains)
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
277	Tremolite
278	2,6-Xylidine
279	Amosite Asbestos
280	Crocidolite Asbestos
281	HC Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No. 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethyl)phosphonium Sulfate & Tetrakis(hydroxymethyl)phosphonium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	*o*-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane (Methylene Chloride)
307	Ephedrine Sulfate
308	Chlorinated Paraffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	*n*-Butyl Chloride
313	Mirex
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
320	Rotenone
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
323	Dimethyl Methylphosphonate
324	Boric Acid
325	Pentachloronitrobenzene
326	Ethylene Oxide
327	Xylenes (Mixed)
328	Methyl Carbamate
329	1,2-Epoxybutane
330	4-Hexylresorcinol
331	Malonaldehyde, Sodium Salt
332	2-Mercaptobenzothiazole
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol
335	C.I. Acid Orange 3

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TR No.	CHEMICAL
336	Penicillin VK
337	Nitrofurazone
338	Erythromycin Stearate
339	2-Amino-4-nitrophenol
340	Iodinated Glycerol
341	Nitrofurantoin
342	Dichlorvos
343	Benzyl Alcohol
344	Tetracycline Hydrochloride
345	Roxarsone
346	Chloroethane
347	D-Limonene
348	α-Methyldopa Sesquihydrate
349	Pentachlorophenol
350	Tribromomethane
351	*p*-Chloroaniline Hydrochloride
352	N-Methylolacrylamide
353	2,4-Dichlorophenol
354	Dimethoxane
355	Diphenhydramine Hydrochloride
356	Furosemide
357	Hydrochlorothiazide
358	Ochratoxin A
359	8-Methoxypsoralen
360	N,N-Dimethylaniline
361	Hexachloroethane
362	4-Vinyl-1-cyclohexene Diepoxide
363	Bromoethane (Ethyl Bromide)
364	Rhodamine 6G (C.I. Basic Red 1)
365	Pentaerythritol Tetranitrate
366	Hydroquinone
367	Phenylbutazone
368	Nalidixic Acid
369	α-Methylbenzyl Alcohol
370	Benzofuran
371	Toluene
372	3,3-Dimethoxybenzidine Dihydrochloride
373	Succinic Anhydride
374	Glycidol
375	Vinyl Toluene
376	Allyl Glycidyl Ether
377	*o*-Chlorobenzalmalononitrile
378	Benzaldehyde
379	2-Chloroacetophenone
380	Epinephrine Hydrochloride
381	*d*-Carvone
382	Furfural
384	1,2,3-Trichloropropane
385	Methyl Bromide
386	Tetranitromethane
387	Amphetamine Sulfate
388	Ethylene Thiourea
389	Sodium Azide
390	3,3'-Dimethylbenzidine Dihydrochloride
391	Tris(2-chloroethyl) Phosphate
392	Chlorinated Water and Chloraminated Water
393	Sodium Fluoride
394	Acetaminophen
395	Probenecid
396	Monochloroacetic Acid
397	C.I. Direct Blue 15
398	Polybrominated Biphenyls
399	Titanocene Dichloride
400	2,3-Dibromo-1-propanol
401	2,4-Diaminophenol Dihydrochloride
402	Furan
403	Resorcinol
404	5,5-Diphenylhydantoin
405	C.I. Acid Red 114
406	γ-Butyrolactone
407	C.I. Pigment Red 3
408	Mercuric Chloride
409	Quercetin
410	Naphthalene
411	C.I. Pigment Red 23
412	4,4-Diamino-2,2-stilbenedisulfonic Acid
413	Ethylene Glycol
414	Pentachloroanisole
415	Polysorbate 80
416	*o*-Nitroanisole
417	*p*-Nitrophenol
418	*p*-Nitroaniline
419	HC Yellow 4
420	Triamterene
421	Talc
422	Coumarin
423	Dihydrocoumarin
424	*o*-Benzyl-*p*-chlorophenol
425	Promethazine Hydrochloride
426	Corn Oil, Safflower Oil, and Tricaprylin
427	Turmeric Oleoresin
428	Manganese (II) Sulfate Monohydrate
430	C.I. Direct Blue 218
431	Benzyl Acetate
432	Barium Chloride Dihydrate
434	1,3-Butadiene
437	Hexachlorocyclopentadiene
443	Oxazepam

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