NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 435

TOXICOLOGY AND CARCINOGENESIS STUDIES OF 4,4′-THIOBIS(6-*t*-BUTYL-*m*-CRESOL)

(CAS NO. 96-69-5)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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

FOREWORD

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

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

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP 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.

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Technical Report are available without charge while supplies last from NTP Central Data Management, NIEHS, P.O. Box 12233, MD A0-01, Research Triangle Park, NC 27709 (919-541-1371).

NTP TECHNICAL REPORT

ON THE

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P.O. Box 12233
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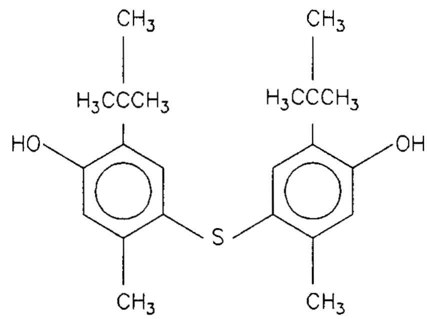
ABSTRACT



4,4′-THIOBIS(6-*t*-BUTYL-*m*-CRESOL)

CAS No. 96-69-5

Chemical Formula: $C_{22}H_{30}SO_2$ Molecular Weight: 358.52

Synonyms: 4,4′-Thiobis(6-*t*-butyl-3-cresol); bis(3-*t*-butyl-4-hydroxy-6-methylphenyl)sulfide
Trade names: Santonox; Santowhite Crystals; Sumilizer; Thioalkofen; Yoshinox

4,4′-Thiobis(6-*t*-butyl-*m*-cresol) (TBBC) is used in the rubber and plastics industries as an antioxidant. TBBC is also used as a stabilizer in polyethylene and polyolefin packaging materials for foodstuffs. Toxicology and carcinogenesis studies were conducted by administering TBBC (99% pure) in feed to groups of male and female F344/N rats and B6C3F_1 mice for 15 days, 13 weeks, and 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium* and cultured Chinese hamster ovary cells.

15-Day Study in Rats

Groups of 10 male and 10 female F344/N rats were fed diets containing 0, 1,000, 2,500, 5,000, 10,000 or 25,000 ppm TBBC for 15 days. Rats given to 1,000, 2,500, 5,000, or 10,000 ppm received approximate doses of 95, 235, 335, or 365 mg TBBC per kilogram body weight per day (males) or 85, 220, 325, or 270 mg/kg per day (females). Approximate doses for rats receiving 25,000 ppm could not be calculated due to early deaths. All 25,000 ppm rats and three male and four female 10,000 ppm rats died. Surviving rats in the 10,000 ppm groups had a significant weight loss and the final mean body weights of 5,000 and 10,000 ppm male and female rats were significantly lower than those of the controls. Male and female rats exposed to 5,000, 10,000, or 25,000 ppm TBBC consumed markedly less feed than the controls.

Diarrhea occurred in 5,000, 10,000, and 25,000 ppm males and females. The principal lesions attributed to the administration of TBBC were renal papillary and tubule necroses which occurred in 10,000 ppm rats. Focal necrosis or erosions of the glandular stomach also occurred in some 10,000 ppm rats. Changes observed in the thymus and spleen were attributed to debilitation or stress; bone marrow depletion was attributed to nutrient deficiency accompanying weight loss.

15-Day Study in Mice

Groups of 10 male and 10 female B6C3F_1 mice were fed diets containing 0, 1,000, 2,500, 5,000, 10,000, or 25,000 ppm TBBC for 15 days. Mice given 1,000, 2,500, or 5,000 ppm received approximate doses of 285, 585, or 475 mg TBBC per kilogram body weight per day (males) or 360, 950, or 1,030 mg/kg per day (females). Approximate doses for mice given 10,000 or 25,000 ppm could not be calculated due to early deaths. All 10,000 and 25,000 ppm mice died, as did eight males and eight females given 5,000 ppm. A

significant weight loss occurred in surviving 5,000 ppm males and females and the final mean body weights of 2,500 ppm females and 5,000 ppm males and females were significantly lower than those of the controls. Feed consumption by mice given 5,000, 10,000, or 25,000 ppm was markedly reduced. Diarrhea occurred in all 25,000 ppm mice and in most male and female mice given 5,000 or 10,000 ppm. Renal tubule necrosis occurred in eight males and three females in the 5,000 ppm groups. Lymphocytic depletion of lymphoid tissues in many 5,000 ppm males and females was attributed to debilitation and stress or to nutrient deficiency accompanying weight loss.

13-Week Study in Rats

Groups of 10 male and 10 female F344/N rats were fed diets containing 0, 250, 500, 1,000, 2,500, or 5,000 ppm TBBC for 13 weeks. These exposure levels delivered approximate doses of 15, 30, 60, 165, or 315 mg TBBC per kilogram body weight per day (males) or 15, 35, 70, 170, or 325 mg/kg per day (females). All rats survived to the end of the study. The final mean body weight of 5,000 ppm males was 40% lower than that of the controls; the final mean body weight of 5,000 ppm females was 27% lower than that of the controls. Feed consumption by male and female rats exposed to 5,000 ppm TBBC was markedly lower than that by the controls throughout the study. The absolute and relative liver weights of 5,000 ppm females were significantly greater than those of the controls.

Serum alkaline phosphatase (ALP) levels were significantly higher in 2,500 and 5,000 ppm males and slightly higher in 5,000 ppm females. Serum alanine aminotransferase levels were significantly higher in 2,500 and 5,000 ppm males and females. Hematocrit and hemoglobin concentrations and mean erythrocyte volume (MCV) values were significantly lower in 1,000, 2,500, and 5,000 ppm males than in controls; MCV values were also significantly lower in 5,000 ppm females. A dose-related significant increase in forelimb and hindlimb grip strength was observed in exposed male and female rats.

Histopathologic findings in the liver of 2,500 and 5,000 ppm males and females included hypertrophy of Kupffer cells, bile duct hyperplasia, and individual cell necrosis of hepatocytes; centrilobular hepatocyte hypertrophy also occurred in males and females exposed to 5,000 ppm TBBC. Macrophages were increased in size and number in the mesenteric lymph nodes of males and females exposed to 5,000 ppm, and to a lesser extent in 2,500 ppm male and female rats. Pigmentation and degeneration of the renal cortical tubule epithelial cells was also present in males and females in the 2,500 and 5,000 ppm groups; cortical tubule necrosis occurred in 5,000 ppm males and females.

13-Week Study in Mice

Groups of up to 10 male and 10 female B6C3F$_1$ mice were fed diets containing 0, 100, 250, 500, 1,000, or 2,500 ppm TBBC for 13 weeks. These exposure levels delivered approximate doses of 15, 30, 65, 145, or 345 mg TBBC per kilogram body weight per day (males) or 10, 35, 60, 165, or 340 mg/kg per day (females). All mice survived to the end of the study. The final mean body weights of 2,500 ppm males and of 500, 1,000, or 2,500 ppm females were significantly lower than those of the controls. Feed consumption by 2,500 ppm males averaged 24% lower than that by controls through week 3 and was similar to that by controls for the remainder of the study. Feed consumption by females receiving 2,500 ppm averaged 27% less than that by the controls during most of the study. The absolute and relative liver weights of males and females exposed to 2,500 ppm TBBC were slightly but significantly greater than those of the controls. Males exposed to 500, 1,000, or 2,500 ppm and females exposed to 2,500 ppm had significantly increased absolute and relative spleen weights. No clinical findings in mice were considered chemical related.

Hematocrit concentrations and erythrocyte counts of males receiving 1,000 or 2,500 ppm were significantly less than those of the controls; hemoglobin concentration in males receiving 2,500 ppm was significantly less and mean erythrocyte volume was significantly less in males receiving 2,500 ppm. Females in the 1,000 and 2,500 ppm groups had significantly decreased hematocrit concentrations and erythrocyte counts; 2,500 ppm females also had significantly decreased hemoglobin concentrations and mean erythrocyte volumes.

Kupffer cell hypertrophy, bile duct hyperplasia, and an increase in size and number of macrophages in mesenteric lymph nodes were present in 2,500 ppm male and female mice.

2-Year Study in Rats

Doses selected for the 2-year study of TBBC were based on the lower body weights and liver and kidney toxicity observed at 5,000 ppm in the 13-week study.

Groups of 115 male and 75 female F344/N rats were fed diets containing 0, 500, 1,000, or 2,500 ppm TBBC for 2 years. Based on average daily feed consumption, these exposure levels resulted in a daily ingestion of TBBC of approximately 20, 40, or 100 mg/kg body weight for males and 20, 45, or 120 mg/kg body weight for females. Hematology, clinical chemistry, and urinalysis evaluations were performed on 15 male and 15 female rats from each group at 3, 9, and 15 months. Also at 15 months, an additional 10 male and 10 female rats from each group were evaluated for histopathology, hematology, and clinical chemistry. Forty male rats per group were evaluated for neurotoxic effects.

Survival, Body Weights, Feed Consumption, and Clinical Findings

Two-year survival rates and mean body weights of exposed male and female rats were generally similar to those of the controls. The mean body weights of 2,500 ppm male rats were slightly lower than those of the controls throughout the study. At week 65, the mean body weight of 2,500 ppm females was 14% lower than that of the controls, but the final mean body weight of this group was 6% lower than that of the control group. Feed consumption, behavior, and general health and appearance of exposed male and female rats were similar to those of the controls.

Hematology and Clinical Chemistry

Results of the hematology evaluation were not uniformly consistent at 3, 9, and 15 months in one set of rats, nor were they consistent between the two sets of rats evaluated at 15 months. Slight but significant decreases in hematocrit levels, hemoglobin concentrations, and erythrocyte counts were observed in the 1,000 and 2,500 ppm groups in one set of males at 15 months. Similar significant decreases in hematocrit level and hemoglobin concentration occurred in 2,500 ppm females at 9 months. Mean erythrocyte hemoglobin and mean erythrocyte hemoglobin concentration of 2,500 ppm females were also significantly lower than those of controls at 9 months and in both sets of female rats evaluated at 15 months. Platelet counts of 2,500 ppm male and female rats were slightly but significantly higher than those of controls at 3 and 9 months. Platelet counts were also slightly but significantly increased in 2,500 ppm males of one set evaluated at 15 months, and in 2,500 ppm females of the second set evaluated at 15 months.

Serum activities of alkaline phosphatase, alanine aminotransferase, and sorbitol dehydrogenase in 2,500 ppm males were significantly greater than those in the controls at 3, 9, and 15 months. Alkaline phosphatase activities in both sets of 1,000 ppm males evaluated at 15 months were also significantly greater than those of controls. Serum activities of alanine aminotransferase and sorbitol dehydrogenase in 2,500 ppm females were also significantly greater than those in controls at 3, 9, and 15 months.

Neurotoxicity Findings

There were no significant inhibitory effects of TBBC on motor nerve excitability or conduction, neuromuscular transmission, or muscle contractility. There were no microscopic lesions in the sciatic nerve, quadriceps muscle, or teased nerve preparations of sciatic nerve that could be attributed to TBBC administration.

Pathology Findings

At the 15-month interim evaluation, the absolute and relative liver weights of 2,500 ppm female rats were significantly greater than those of controls; at 15 months and at the end of the study, the incidences of Kupffer cell hypertrophy, hepatocyte cytoplasmic vacuolization, and mixed cell foci were also significantly increased. At the end of the study, the incidence of hepatocellular fatty change was significantly increased in 2,500 ppm females. The incidence of Kupffer cell hypertrophy was significantly increased in 2,500 ppm males at 15 months and at 2 years; the incidence of cytoplasmic vacuolization was significantly increased in all exposed males at 15 months but only moderately increased in 1,000 and 2,500 ppm males at 2 years; the incidence of basophilic foci was significantly increased in 2,500 ppm males at 15 months and the incidence of mixed cell foci was significantly increased in 1,000 and 2,500 ppm male rats at 2 years. The incidences of hepatocellular adenoma or carcinoma (combined) in exposed male rats were not significantly greater than that in the controls (0 ppm, 1/50; 500 ppm, 3/50; 1,000 ppm, 3/50; 2,500 ppm, 5/49), were within the historical control range, and were not considered chemical related. The severity of nephropathy was significantly increased in 2,500 ppm female rats.

There was a significant negative trend in the incidence of mammary gland fibroadenoma, adenoma, or carcinoma (combined) in female rats (32/50, 24/50, 11/50, 16/50), and the incidences of fibroadenoma in 1,000 and 2,500 ppm females were significantly less than that of the controls.

2-Year Study in Mice

Because of the reduction in body weights, the increase in liver and spleen weights, and the accompanying histopathologic changes in the liver of 2,500 ppm male and female mice in the 13-week study, the doses selected for the 2-year study were 250, 500, and 1,000 ppm.

Groups of 80 male and 80 female mice were fed diets containing 0, 250, 500, or 1,000 ppm TBBC for 2 years. Based on average daily feed consumption, these exposure levels resulted in the daily ingestion of approximately 30, 60, or 145 mg TBBC/kg body weight for males and 45, 110, or 255 mg TBBC/kg body weight for females. Nine or 10 animals from each exposure group were evaluated at 3, 9, and 15 months.

Survival, Body Weights, Feed Consumption, and Clinical Findings

Two-year survival rates of exposed male and female mice were similar to those of the controls. The final mean body weights of male and female mice exposed to 1,000 ppm were 8% and 18% lower than those of the controls, respectively. The final mean body weights of females exposed to 250 or 500 ppm were 8% to 9% lower than that of the controls. Feed consumption by exposed males was similar to that by controls, and there were no clinical findings attributed to TBBC administration.

Hematology and Clinical Chemistry

Hematocrit level, hemoglobin concentration, and erythrocyte count in 1,000 ppm male mice were significantly lower than those in controls at the 15-month interim evaluation. Serum alkaline phosphatase activities in 1,000 ppm males were slightly but significantly greater than those in controls at 3 and 9 months, as was the serum alkaline phosphatase activity in 1,000 ppm females at 9 months. Serum levels of total bilirubin in all exposed groups of males were significantly greater than those in controls at 9 and 15 months.

Pathology Findings

In the liver of male mice, negative trends in the incidences of fatty change, clear cell foci, and adenoma or carcinoma combined occurred at the end of the 2-year study. There were no compound-related increased incidences of neoplasms or non-neoplastic lesions in mice receiving TBBC for 2 years. A negative trend in the incidence of fatty change in the liver of male mice also occurred at 15 months.

Genetic Toxicology

4,4'-Thiobis(6-*t*-butyl-*m*-cresol) was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 with or without exogenous metabolic activation (S9). Sister chromatid exchanges were induced in cultured Chinese hamster ovary cells treated with TBBC, with and without S9, but no increases in chromosomal aberrations were noted in cultured Chinese hamster ovary cells after treatment with TBBC.

Conclusions

Under the conditions of these 2-year feed studies, there was *no evidence of carcinogenic activity** of 4,4'-thiobis(6-*t*-butyl-*m*-cresol) in male or female F344/N rats administered 500, 1,000, or 2,500 ppm or in male or female B6C3F$_1$ mice administered 250, 500, or 1,000 ppm.

Nonneoplastic lesions associated with exposure to TBBC included: Kupffer cell hypertrophy, cytoplasmic vacuolization, and mixed cell foci in the liver of male and female rats, fatty change in the liver of female rats, and an increase in the severity of nephropathy in the kidney of female rats. In addition, decreased incidences of fibroadenoma, adenoma, or carcinoma (combined) were observed in the mammary gland of female rats. Decreases also occurred in the incidences of fatty change, clear cell foci, and adenoma or carcinoma (combined) in the liver of male mice.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 13.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)

	Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Doses	0, 500, 1,000, or 2,500 ppm in feed (approximately 20, 40, or 100 mg/kg/day)	0, 500, 1,000, or 2,500 ppm in feed (approximately 20, 45, or 120 mg/kg/day)	0, 250, 500, or 1,000 ppm in feed (approximately 30, 60, or 145 mg/kg/day)	0, 250, 500, or 1,000 ppm in feed (approximately 45, 110, or 255 mg/kg/day)
Body weights	Exposed groups lower than controls	2,500 ppm group lower than controls	1,000 ppm group lower than controls	Exposed groups lower than controls
2-Year survival rates	18/50, 28/50, 22/50, 18/50	34/50, 31/50, 32/50, 28/50	42/50, 42/50, 49/50, 45/50	40/51, 38/50, 36/50, 35/50
Nonneoplastic effects	Liver: Kupffer cell hypertrophy: 2/50, 3/50, 2/50, 31/49; cytoplasmic vacuolization: 13/50, 11/50, 19/50, 18/49; mixed cell foci: 6/50, 14/50, 18/50, 15/49	Liver: Kupffer cell hypertrophy: 11/50, 10/50, 9/50, 42/50; cytoplasmic vacuolization: 12/50, 10/50, 20/50, 34/50; fatty change: 9/50, 8/50, 15/50, 19/50; mixed cell foci: 5/50, 4/50, 14/50, 34/50 Kidney: nephropathy severity (1.4, 1.4, 1.6, 2.3)	None	None
Neoplastic effects	None	None	None	None
Other findings	None	Mammary gland: fibroadenoma, adenoma, or carcinoma (combined): 32/50, 24/50, 11/50, 16/50	Liver: fatty change: 19/50, 17/50, 5/50, 6/50; clear cell foci: 6/50, 5/50, 2/50, 0/50; adenoma or carcinoma (combined): 25/50, 30/50, 27/50, 16/50	None
Level of evidence of carcinogenic activity	No evidence	No evidence	No evidence	No evidence

Genetic toxicology

Salmonella typhimurium gene mutation: Negative in strains TA98, TA100, TA1535, and TA1537 with and without S9

Chinese hamster ovary cells *in vitro*

Sister chromatid exchanges: Positive with and without S9

Chromosomal aberrations: Negative with and without S9

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a 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 4,4′-thiobis(6-*t*-butyl-*m*-cresol) 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 4,4′-thiobis(6-*t*-butyl-*m*-cresol) (TBBC) 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.

Mr. J.D. Cirvello, NIEHS, introduced the toxicology and carcinogenesis studies of TBBC by discussing the uses of the chemical 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 4,4′-thiobis(6-*t*-butyl-*m*-cresol) in male or female F344/N rats or male or female B6C3F$_1$ mice.

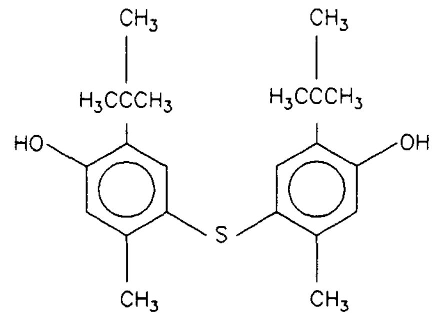
Mr. Beliczky, a principal reviewer, agreed with the proposed conclusions. He asked if the literature had been reviewed as most of the references were from the 1950's. Mr. Cirvello said a literature search had been done in 1992. Mr. Beliczky questioned the reference to the NIOSH Permissible Exposure Limit because the levels that were mentioned as either total dust or respirable dust are generally referred to as nuisance dust, those dusts which are physiologically inactive or inert. He did not think one could call TBBC inert or physiologically inactive. He commented that the nomination for review by the NTP was referenced to a 1978 study at Harvard and wanted to note that this epidemiological study had been funded by the United Rubber Worker's Joint Occupational Health Program.

Dr. Zeise, the second principal reviewer, agreed in principle with the proposed conclusions. She pointed out that, while the liver in male rats is clearly a target organ for toxicity, the data are unclear as to whether or not the liver is a target organ for carcinogenicity. She said the incidence of hepatocellular adenoma would be statistically significant if the historical control incidence at the study laboratory were used instead of the concurrent controls. She said there should be consideration given to changing the conclusion in male rats to "equivocal evidence of carcinogenic activity." Mr. Cirvello commented that if one looks at the overall historical control database, there were three studies from other laboratories with control values as high as those recorded in male rats in the high-dose group in the present study.

Dr. Ward, the third principal reviewer, agreed in principle with the proposed conclusions. He said it should be noted that the degree of nephropathy was increased in female rats and there should be a statement that male rats may have been able to tolerate a slightly higher dose. Mr. Cirvello said a statement about the nephropathy should have been included. He said that toxicity and reduction in body weight gain in the prechronic and 2-year studies indicated that the high dose was correct in male rats. Dr. Ward agreed with Dr. Zeise as to the uncertain significance of the liver neoplasms in male rats. Since mixed cell foci were increased more in exposed animals, Dr. Ward said it would be useful to have a morphologic description and an assessment as to whether they are preneoplastic lesions. Dr. S.L. Eustis, NIEHS, said a description would be added to the report, but it was difficult to say whether the foci were preneoplastic. There was no atypia reported, a finding often found in foci induced by hepatocarcinogens.

Mr. Beliczky moved that the Technical Report on 4,4′-thiobis(6-*t*-butyl-*m*-cresol) be accepted with the revisions 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 ten votes.

INTRODUCTION



4,4′-THIOBIS(6-*t*-BUTYL-*m*-CRESOL)

CAS No. 96-69-5

Chemical Formula: $C_{22}H_{30}SO_2$ Molecular Weight: 358.52

Synonyms: 4,4′-Thiobis(6-*t*-butyl-3-cresol); bis(3-*t*-butyl-4-hydroxy-6-methylphenyl)sulfide
Trade names: Santonox; Santowhite Crystals; Sumilizer; Thioalkofen; Yoshinox

Chemical and Physical Properties

4,4′-Thiobis(6-*t*-butyl-*m*-cresol) (TBBC) is a fine, white crystalline powder with a melting point of 161° C and specific gravity of 1.10. This chemical is very soluble in methanol (79 g/mL), soluble in acetone (20 g/mL), less soluble in benzene (5.0 g/mL), and slightly soluble in water (0.08 g/mL) (Lefaux, 1968).

Use and Human Exposure

TBBC is widely used in the rubber and plastics industries as an antioxidant for polyolefins, polyethylenes, polypropylenes, natural rubber, and latex. TBBC is approved by the U.S. Food and Drug Administration as a constituent of high-pressure polyethylene packaging for foodstuffs, excluding fats, and as a component of polyolefin film packaging in contact with meat or meat food products (Lefaux, 1968). Although the potential exists for the general population to be exposed through contact with polymer products or leaching of TBBC from such products into food, two studies investigating the migration of TBBC from plastic packaging materials indicated no significant exposure from this source (Udhe and Woggon, 1971; Ruedt and Herbolzheimer, 1976). Exposure is also possible via surface water contamination resulting from releases through manufacturing or use operations. No data were found on the environmental occurrence of TBBC.

TBBC reportedly has potential uses as a fungicide against such molds as *Aspergillus niger*, *Penicillium citrinum*, and *Rhizopus nigricans*, and as a preservative for paints, paper, fiber, and leather (Umekawa *et al.*, 1972). However, Hejtmankova *et al.* (1979) found that TBBC did not inhibit *A. niger* or *A. fumigatus*, and only weakly to moderately inhibited seven other strains of fungi.

No recent annual TBBC production or use data were found. Based on a survey conducted by NIOSH from 1981 to 1983, an estimated 12,349 workers are potentially exposed to TBBC in the workplace (NIOSH, 1991). The current Permissible Exposure Limits established by NIOSH for TBBC (as an 8-hour time-weighted average) are 15 mg/m^3 for total dust and 5 mg/m^3 for the respirable fraction.

Absorption, Distribution, Metabolism, and Excretion

Experimental Animals

The disposition of [^{14}C]-labeled TBBC was studied in male F344/N rats (Birnbaum *et al.*, 1983). TBBC was administered by single oral gavage doses of 5, 50, or

500 mg TBBC/kg body weight in corn oil or in Emulphor:ethanol and by intravenous injection of 5 mg/kg in Emulphor:ethanol:water. Following oral exposure, TBBC was incompletely absorbed (the percentage absorbed was not determined) and there was a dose-related decrease in the rate of absorption. When administered *in situ* via luminal perfusion of 4, 49, or 500 mg/kg body weight, TBBC absorption in the small intestine was directly proportional to dose, suggesting that retention of the compound in the stomach was responsible for the apparent dose-related decline in absorption. Following intravenous administration of 5 mg/kg, very low percentages of total dose administered were detected rapidly in liver, adipose tissue, skin, muscle, and blood. The highest percentage of total dose was found in the liver, which had 2% after 15 minutes, 0.5% after 2 hours, and 0.4% after 1 day. The initial rate of clearance from liver and skin was very rapid, followed by a slower terminal decay phase. A slow rate of clearance was also observed in adipose tissue. Twenty-four hours after treatment, the parent compound accounted for most of the residual radioactivity in liver and adipose tissue; chronic exposure to TBBC could result in some accumulation of unmetabolized compound at these sites. More than half of the administered compound was excreted the first day, primarily through the bile into the feces; less than 2% was excreted into the urine. All radioactivity in the bile was in the form of metabolites of TBBC, the major metabolite being a glucuronide conjugate. A later study (Smith *et al.*, 1985) identified the major metabolite of TBBC in bile as the monoglucuronic acid conjugate.

To evaluate the effects of age on the glucuronidation of TBBC, male F344 rats 2.5, 16, and 26 months old were administered 5 mg [^{14}C]-labeled TBBC/kg intravenously. Urine and feces were collected for 3 days (Borghoff *et al.*, 1988). Bile was also collected for 6 hours after intravenous doses of 5 or 25 mg/kg. The 26-month-old animals excreted significantly less TBBC-derived radioactivity in bile, feces, and urine than both of the younger groups. The percentage of the dose eliminated in bile as a glucuronide also decreased with age. After 30 minutes of bile collection following a 5 mg/kg dose, 8% had been eliminated as a glucuronide by the 2.5-month-old group, 5.6% by the 16-month-old group, and 4.4% by the 26-month-old group. When the 26-month-old animals were given 25 mg/kg, elimination as glucuronide was only 2% of the dose. *In vitro* studies using TBBC as a substrate demonstrated that hepatic uridine diphosphate glucuronyl transferase activity decreased in aging animals. Further, the hepatic concentration of uridine diphosphate glucuronyl acid (UDPGA) also decreased in animals from 2.5 to 28 months of age. Thus, the decrease in the ability of the aging rats to conjugate and excrete TBBC may be caused by a decrease in both the activity of the conjugating enzyme and the availability of UDPGA.

Humans

No information on the absorption, distribution, metabolism, or excretion of TBBC in humans was found in the literature.

TOXICITY

Experimental Animals

Few published studies on the toxicity of TBBC exist. In acute oral toxicity studies in rats, the LD_{50} varies from 5,000 to 7,000 mg/kg depending on the purity of the test material (personal communication cited in Birnbaum *et al.*, 1983). Details are not given except that rats exhibited severe diarrhea preceding death. In the previously discussed disposition studies (Birnbaum *et al.*, 1983), TBBC administered by gavage in either Emulphor:ethanol or corn oil (5, 50, or 500 mg/kg) caused mild inflammation, congestion, hemorrhage, and mucosal erosion of the stomach in rats. These findings were dose related and detectable as early as 1 hour after administration of 500 mg/kg. Studies in which rats ingested TBBC in feed for 30 or 90 days were performed by E.I. du Pont de Nemours & Co. and the results are summarized briefly by Lefaux (1968). In the 30-day study, groups of six male and six female rats were fed diets containing 500 or 2,500 ppm TBBC. The 500 ppm group displayed no signs of toxicity, whereas at 2,500 ppm, rats exhibited growth retardation and increased liver weights. In the 90-day study, rats were fed diets containing 50 or 500 ppm TBBC, and the only effects noted were decreased feed consumption and slight growth retardation in 500 ppm males. Monsanto Chemical Company conducted 3-month feed studies using the same doses of TBBC (50 or 500 ppm) and obtained similar results; the only sign of toxicity was growth retardation in animals receiving 500 ppm (McCormick, 1972).

TBBC toxicity was also studied in adult female $B6C3F_1$ mice by administering 10, 100, or 200 mg/kg daily in corn oil by gavage for 14 consecutive days (Munson *et al.*, 1988). No overt toxicity was observed and no marked effects on serum enzymes occurred. The highest exposure group had a 41% increase in total leukocytes with a 31% increase in lymphocytes and a 177% increase in neutrophils. Bone marrow studies revealed a significant (30%) increase in the number of cells/femur in 200 mg/kg mice; macrophage progenitors were significantly increased by 28% and granulocyte-monocyte progenitors were increased by 20%. A dose-related increase occurred in absolute weights of both the spleen and liver, although the histopathology of the spleens of TBBC-treated mice was not different from that of the controls. The livers of mice in the high-dose group had changes described as mild focal hydropic degeneration, mild hepatitis, and a slight increase in the number of Kupffer cells. Hepatic cytochrome P-450 and microsomal protein levels exhibited a dose-related increase, as did enzyme activities of aminopyrine demethylase and aniline hydroxylase.

Immunotoxicologic studies were conducted after administering TBBC in corn oil by gavage at doses of 10, 100, or 200 mg/kg to $B6C3F_1$ mice daily for 14 consecutive days (Holsapple *et al.*, 1988). A 200 mg/kg dose produced a decrease in the peak IgM (44%) and peak IgG (48%) antibody response to *in vivo* challenge with sheep erythrocytes, but had no effect on the delayed hypersensitivity response to challenge with keyhole limpet hemocyanin. At 10 and 200 mg/kg, a significant decrease in the mixed lymphocyte response (MLR) occurred, but doses of 10, 100, or 200 mg/kg produced no effects on the *in vitro* lymphoproliferative responses of spleen cells to optimal concentrations of concanavalin A, phytohemagglutinin, or lipopolysaccharide. A dose-related increase in the basal (unstimulated) DNA synthesis of the spleen cells occurred in both the MLR and the mitogen assays. A significant increase in natural killer cell and serum complement activity was also observed. The increase in natural killer cell activity was significant in mice administered 100 and 200 mg/kg, with the greatest increase at the 100 mg/kg dose; 10 mg/kg TBBC produced a significant (35%) increase in CH50 and at 100 mg/kg a significant (54%) increase occurred. Effects on macrophage function were complex; either an increase or no effect was observed, depending on the parameter measured. Exposure to 10, 100, or 200 mg/kg caused a dose-related increased resistance to challenge with *Streptococcus pneumoniae* and B16F10 melanoma, a decreased resistance to challenge with PYB_6 neoplasms, and no effect on the resistance to HSV-2, *Listeria*, or *Plasmodium*. Thus, several parameters reflecting immune function were altered following 14-day gavage exposure to TBBC.

Humans

Two patients with allergic contact dermatitis were found to be patch-test positive to latex gloves made by the same manufacturer. TBBC was the antioxidant used in making the gloves and both patients had a positive patch test reaction to the TBBC itself (Rich *et al.*, 1991). No other information on the toxicity of TBBC in humans was found in the literature.

Reproductive and Developmental Toxicity

Experimental Animals

In a study to evaluate the effects of TBBC on reproduction in female Swiss mice, 485 mg/kg was administered daily by gavage to 50 pregnant mice on days 6 through 15 of gestation (EHRT, 1989). TBBC caused maternal mortality and a decreased rate of survival of pups, but had no effect on the number of viable litters, litter size, pup birth weight, or pup weight gain.

Humans

No information on the reproductive and developmental toxicity of TBBC in humans was found in the literature.

Carcinogenicity

Experimental Animals

A report by Draganov *et al.* (1974) suggests that TBBC may be a neoplasm promoter. When Yoshida sarcomas were transplanted to rats, neoplasm development was enhanced if TBBC was administered orally for 10 days at a dose of 80 mg/kg daily, beginning 5 days after transplantation. No other data were provided in the report.

Humans

No information on the potential carcinogenicity of TBBC in humans was found in the literature.

Genetic Toxicity

TBBC was tested for mutagenicity in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 with a preincubation protocol in the presence and absence of S9; no mutagenic activity was observed in any of these four strains (Zeiger *et al.*, 1987). There are no other published data on the genotoxicity of this compound.

Study Rationale

The National Cancer Institute nominated TBBC for study as a representative of the sulfur-containing class of antioxidants used in rubber processing. A study that was recent at the time of nomination demonstrated an excess of several types of cancer among a cohort of 13,570 rubber workers (Monson and Fine, 1978). In addition, the presence of TBBC in plastic food wraps and containers was viewed as a possible hazard to the general population.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF 4,4'-THIOBIS(6-*T*-BUTYL-*M*-CRESOL)

4,4'-Thiobis(6-*t*-butyl-*m*-cresol) was obtained in one lot (12) from Monsanto Industrial Chemical Company (Akron, OH). Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO), (Appendix I).

The chemical, a white powdered solid, was identified as 4,4'-thiobis(6-*t*-butyl-*m*-cresol) (TBBC) by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. Purity was determined by elemental analyses, Karl Fischer water analysis, functional group titration, thin-layer chromatography, and gas chromatography. Analyses of the chemical for carbon, hydrogen and sulfur were in agreement with theoretical values for TBBC. Functional group titration indicated a purity of 100% ± 3%. Thin-layer chromatography using two systems indicated a major spot and two trace impurities. Gas chromatography using one system indicated two impurities with a total area of 0.7% relative to the major peak area that eluted before the major peak. A second system indicated one impurity that eluted before the major peak and had an area of 0.39% relative to the major peak. The overall purity was determined to be approximately 99%. Subsequent analysis by the analytical chemistry laboratory indicated a purity of approximately 99%.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared weekly by mixing 4,4'-thiobis(6-*t*-butyl-*m*-cresol) with feed (Table I1). Homogeneity and stability studies of the 250 and 25,000 ppm dose formulations were performed by the analytical chemistry laboratory. For the homogeneity and stability studies, dose formulations were analyzed by high performance liquid chromatography. Homogeneity was confirmed at the 100 and 10,000 ppm concentrations, and stability was established at these concentrations for at least 3 weeks at –20° C when stored in the dark and for 3 days when exposed to air and light.

Periodic analyses of the dose formulations of TBBC were conducted at the study laboratory and analytical chemistry laboratory using high-performance liquid chromatography. During the 15-day studies, only the initial formulation was analyzed (Table I2). During the 13-week and the 2-year studies, the dose formulations were analyzed every 6 to 10 weeks (Tables I3 and I4). In the 2-year studies, 93% (86/92) of the formulations were within 10% of the target concentrations. Results of the periodic referee analyses performed by the analytical chemistry laboratory were in good agreement with the results obtained by the study laboratory (Table I5).

15-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Frederick Cancer Research Center (Frederick, MD). At receipt, the rats and mice were 6 weeks old. Animals were quarantined for 13 to 15 days before exposure began. At 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 were fed diets containing 0, 1,000, 2,500, 5,000, 10,000, or 25,000 ppm TBBC. Feed and water were available *ad libitum*. Rats and mice were housed five per cage. Clinical findings were recorded daily for rats and mice. Feed consumption was recorded daily by cage. The animals were weighed initially, weekly, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 1.

At the end of the 15-day studies, blood was collected from all animals by cardiac puncture for hematology analyses. The parameters measured are listed in Table 1. A necropsy was performed on all rats and mice. The brain, gastrointestinal tract, heart, right kidney, liver, lung, spleen, right testis, and thymus 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 performed on 0, 2,500, 5,000, and 10,000 ppm rats and 0, 2,500, and 5,000 ppm mice. Table 1 lists the tissues and organs examined microscopically.

13-Week Studies

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

Male and female F344/N rats and B6C3F$_1$ mice were obtained from the Frederick Cancer Research Center (Frederick, MD). On receipt, the rats and mice were 29 days old. The rats were quarantined for 15 days and the mice for 22 days before exposure began. Before initiation of the studies, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. At the end of the studies, serologic analyses were performed on five male and five female control rats and mice using the protocols of the NTP Sentinel Animal Program (Appendix L).

Groups of 10 male and 10 female rats were fed diets containing 0, 250, 500, 1,000 2,500, or 5,000 ppm TBBC. Groups of 10 male and 10 female mice were fed diets containing 0, 100, 250, 500, 1,000, or 2,500 ppm TBBC. Feed and water were available *ad libitum*. Rats were housed five per cage and mice were housed individually. Clinical findings were recorded weekly. Feed consumption was recorded daily by cage for rats and daily by animal for mice. The animals were weighed initially, weekly, and at the end of the studies. Further details of study design and animal maintenance are summarized in Table 1.

During the final eight days of the 13-week study in rats, males and females receiving 0, 1,000, and 2,500 ppm were tested for forelimb and hindlimb grip strength, startle response, tail flick, and foot splay. See Appendix H for detailed methods.

Two days before the end of the 13-week studies, blood was collected from the orbital sinus of all rats and mice for hematology analyses. At the end of the 13-week studies, blood was collected from all rats by cardiac puncture for clinical chemistry analyses. The hematology and clinical chemistry parameters measured are listed in Table 1. A necropsy was performed on all animals. The brain, heart, right kidney, liver, lung, spleen, right testicle, and thymus were weighed. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 μm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on 0, 1,000, 2,500, and 5,000 ppm rats and 0, 1,000, and 2,500 ppm mice. Table 1 lists the tissues and organs routinely examined.

2-Year Studies

Study Design

Groups of 115 male and 75 female rats were fed diets containing 0, 500, 1,000, or 2,500 ppm TBBC (Table 1). Fifteen male and 15 female rats from each group were evaluated at 3, 9, and 15 months for alterations in hematology, clinical chemistry, and urinalysis parameters and then discarded. An additional 10 male and 10 female rats from each group were also evaluated at 15 months for alterations in hematology and clinical chemistry parameters; these animals received complete necropsy and histopathology examinations.

Forty of the 115 male rats in each exposure group were designated for neurotoxicity evaluation at 3 and 6 months (Appendix H). At 3 months, startle reflex and fore- and hindlimb grip strength were measured in all 40 animals. Ten males per group received electrophysiologic evaluations, including measurements of sciatic nerve conduction time following various frequencies of electrical stimulation and contractile tension of the gastrocnemius muscle following various frequencies of electrical stimulation or following graded electrical stimulation. An additional 10 males per group received whole body perfusion for histopathologic examination of the left quadriceps muscle and left sciatic nerve and of teased nerve preparations of the sciatic nerve. The remaining 20 male rats in each group were fed the control diet for 13 additional weeks to determine the reversibility of TBBC-induced changes. At 6 months, grip strength tests were repeated in all 20 rats per group. These 20 rats were then split into two groups of 10 and given electrophysiologic and neuropathologic evaluations as described above.

Groups of 80 male and 80 female mice were fed diets containing 0, 250, 500, or 1,000 ppm TBBC. At 3, 9, and 15 months, groups of 10 male and 10 female mice per group were killed and evaluated for alterations in hematology and clinical chemistry parameters. The 10 male and 10 female mice per group killed at 15 months also received a complete necropsy and histopathologic evaluation.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Farms (Germantown, NY) for use in the 2-year studies. Rats and mice were quarantined for 11 days before the beginning of the studies. Five male and five female rats and mice were selected for parasite evaluation and gross observation of disease. Serology samples were collected for viral screening. Rats were approximately 43 days old and mice approximately 39 days old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix L).

Animal Maintenance

Rats were housed five per cage and mice were housed individually. Feed and water were available *ad libitum*. Feed consumption was measured twice weekly by cage. Cages and racks were rotated biweekly. Further details of animal maintenance are given in Table 1. 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 at the beginning of the studies, weekly for 13 weeks, and monthly thereafter. A complete necropsy and microscopic examination were performed on all rats and mice except: the 15 male and 15 female rats per group designated for hematology, clinical chemistry, and urinalysis evaluations at 3, 9, and 15 months; the 10 male and 10 female mice per group designated for hematology and clinical chemistry at 3 and 9 months; and the 40 male rats per group designated for neurotoxicity and neuropathologic evaluations. At the 15-month interim evaluation, the brain, gastrointestinal tract, right kidney, liver, and spleen of rats and mice were weighed. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 μm, and stained with hematoxylin and eosin for microscopic examination. Tissues examined microscopically are listed in Table 1.

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 the histotechnique was evaluated. For the 2-year studies, a quality assessment pathologist reviewed the liver of male and female rats, neoplasms of the thyroid gland, mammary gland, and uterus of female rats, neoplasms of the skin, bone, and nose of male rats, the liver of female mice, and neoplasms of the ovary of female mice.

The quality assessment report and slides were submitted to the NTP Pathology Working Group (PWG) chair, who reviewed the selected tissues and any other tissues for which a disagreement in diagnosis between the laboratory and quality assessment pathologists existed. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologist, or lesions of general interest were presented by the chair to the PWG for review. Tissues examined included the skin, bone, and nose of male rats, the liver of male and female rats, the mammary gland, thyroid gland, and uterus of female rats, and the liver and ovary of female mice. 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 exposure groups or previously rendered diagnoses. When the PWG consensus differed from the opinion 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 the 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 found dead of other than natural causes or missing were censored from the survival analyses; 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, A5, B1, B5, C1, C5, D1, and D4 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 numbers of animals affected at each 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 the fit of the model was not significantly enhanced. The neoplasm incidences of 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 methods 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 exposed group with controls and a test for an overall dose-related 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 this study 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 nonneoplastic 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.

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between exposed 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 and hematology data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related 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-related trend (Dunnett's or Dunn's test). Average severity values were analyzed for significance using the Mann-Whitney U test (Hollander and Wolfe, 1973).

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, historical control data can be helpful in the overall assessment of neoplasm incidence in certain instances. 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.

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, these studies were audited retrospectively by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and preliminary 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 all comments had been resolved or were otherwise addressed during the preparation of this Technical Report.

Genetic Toxicology

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

The genetic toxicity studies of TBBC 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 and responses of the chemical 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 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 complementarity 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 1
Experimental Design and Materials and Methods in the Feed Studies of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)

15-Day Studies	13-Week Studies	2-Year Studies
Study Laboratory		
American Biogenics Corporation (Woburn, MA)	American Biogenics Corporation (Woburn, MA)	Battelle Columbus Laboratories (Columbus, OH)
Strain and Species		
Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$
Animal Source		
Frederick Cancer Research Center (Frederick, MD)	Frederick Cancer Research Center (Frederick, MD)	Taconic Farms (Germantown, NY)
Time Held Before Studies		
Rats: 14 days (males) or 15 days (females) Mice: 13 days (males) or 14 days (females)	Rats: 15 days Mice: 22 days	11 days
Average Age When Studies Began		
Rats: 44 days Mice: 43 days	Rats: 43 days Mice: 50 days	Rats: 43 days Mice: 39 days
Date of First Dose		
Rats: 29 December (males) or 30 December (females) 1983 Mice: 3 January (males) or 4 January (females) 1984	Rats: 1 August 1984 Mice: 15 August 1984	Rats: 29 December 1986 (special studies and 15-month interim) or 22 December 1986 (2-year study) Mice: 19 January 1987
Duration of Dosing		
15 days	92-94 days	104 weeks
Date of Last Dose		
Rats: 12 January (males) or 13 January (females) 1984 Mice: 17 January (males) or 18 January (females) 1984	Rats: 2 November 1984 Mice: November 1984	Rats: 12 December 1988 Mice: 9 January 1989
Necropsy Dates		
Rats: 12 January (males) or 13 January (females) 1984 Mice: 17 January (males) or 18 January (females) 1984	Rats: 31 October to 2 November 1984 Mice: 14 to 16 November 1984	Rats: 15-Month interim evaluation and clinical pathology - 21-22 March 1988 Terminal - 19-21 December 1988 Mice: 15-Month interim - 18-19 April 1988 Terminal - 16-20 January 1989

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

15-Day Studies	13-Week Studies	2-Year Studies
Average Age at Necropsy		
Rats: 59 days Mice: 57 days	Rats: 135 days Mice: 141 days	15-Month interim evaluation and clinical pathology - 71 weeks Terminal - 111 weeks
Size of Study Groups		
10 males and 10 females	Same as 15-day studies	Rats: 115 males and 75 females Mice 80 males and 80 females
Method of Distribution		
Animals randomized from weight classes into cage groups using a computer-generated list of random numbers; cages randomized into test groups from another computer-generated list of random numbers	Same as 15-day studies	Animals randomized from weight classes into cage groups and dose groups using a partitioning algorithm
Animals per Cage		
5	Rats: 5 Mice: 1	Rats: 5 Mice: 1
Method of Animal Identification		
Ear punch	Same as 15-day studies	Rats: Neurological - ear tag Clinical pathology - toe clip Terminal - toe clip Mice: Toe clip
Diet		
NIH-07 open formula meal diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*, changed daily	Same as 15-day studies	Same as 15-day studies, changed twice weekly
Maximum Storage Time for Feed		
108 days post-milling	120 days post-milling	Same as 13-week studies
Water Distribution		
Tap water (Woburn municipal supply) via automatic watering system (Hardco, Cincinnati, OH), available *ad libitum*	Same as 15-day studies	Tap water (Columbus municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

15-Day Studies	13-Week Studies	2-Year Studies
Cages		
Polycarbonate, (Suburban Surgical Co., Inc., Wheeling, IL), changed twice weekly	Same as 15-day studies except cages were changed twice weekly for rats.	Polycarbonate (Lab Products, Inc., Garfield, NJ), changed twice weekly (rats) or weekly (mice)
Bedding		
SaniChip® hardwood chips (P.J. Murphy Forest Products Corp., Rochelle Park, NJ), changed twice weekly	Same as 15-day studies	BetaChip® hardwood chips (Northeastern Products, Inc., Warrensburg, NY) until 22 May 1988; SaniChip® (P.J. Murphy Forest Products Corp., Montville, NJ) thereafter; changed twice weekly (rats) or weekly (mice)
Cage Filters		
Nonwoven filter sheets, DuPont (Snow Filtration Co., Cincinnati, OH), changed biweekly	Same as 15-day studies	Spun-bonded polyester, DuPont 2024 (Snow Filtration Co., Cincinnati, OH), changed biweekly
Racks		
Stainless steel, changed biweekly	Stainless steel, changed biweekly	Stainless steel (Lab Products, Inc., Maywood, NJ), changed biweekly
Animal Room Environment		
Average temperature: 18.6° C (male rats), 18.5° C (female rats), 18.4° C (mice) Relative humidity: 35% to 51% Fluorescent light: 12 hours/day Room air: 12 to 16 changes/hour	Average temperature: 21.7° C (rats), 17.8° C (mice) Relative humidity: 41% to 60% Fluorescent light: 12 hours/day Room air: 12 changes/hour	Average temperature: 22.5° C (rats), 22.2° C (mice) Relative humidity: 40% to 56% (rats), 45% to 58% (mice) Fluorescent light: 12 hours/day Room air: minimum of 10 changes/hour
Doses		
0, 1,000, 2,500, 5,000, 10,000, or 25,000 ppm in feed, available *ad libitum*	Rats: 0, 250, 500, 1,000, 2,500, or 5,000 ppm in feed, available *ad libitum* Mice: 0, 100, 250, 500, 1,000, or 2,500 ppm in feed, available *ad libitum*	Rats: 0, 500, 1,000, or 2,500 ppm in feed, available *ad libitum* Mice: 0, 250, 500, or 1,000 ppm in feed, available *ad libitum*

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

15-Day Studies	13-Week Studies	2-Year Studies
Type and Frequency of Observation		
Observed twice daily; animals were weighed initially, weekly, and at the end of the studies; and clinical observations were recorded daily. Feed consumption was recorded daily by cage.	Observed twice daily; animals were weighed initially, weekly, and at the end of the studies; clinical observations were recorded weekly. Feed consumption was recorded daily by cage (rats) and daily by animal (mice).	Observed twice daily; animals were weighed and clinical observations were recorded initially, weekly for 13 weeks, monthly thereafter, and at the end of the studies. Feed consumption was recorded monthly by cage (rats) or by animal (mice).
Method of Sacrifice		
Anesthesia with methoxyflurane followed by exsanguination by cardiac puncture	Same as 15-day studies	Carbon dioxide asphyxiation or pentobarbital anesthesia with exsanguination and transcardial perfusion (neurotoxicity evaluation rats)
Necropsy		
Necropsy performed on all animals. Organs weighed were brain, gastrointestinal tract, heart, right kidney, liver, lung, spleen, right testis, and thymus.	Necropsy performed on all animals. Organs weighed were brain, heart, right kidney, liver, lung, spleen, right testis, and thymus.	Necropsy performed on all animals. Organs weighed were brain, gastrointestinal tract, right kidney, liver, and spleen.
Clinical Pathology		
Blood was collected from all animals surviving to the end of the studies by cardiac puncture for hematology. *Hematology:* hematocrit, hemoglobin, erythrocytes, mean erythrocyte volume, mean erythrocyte hemoglobin, mean erythrocyte hemoglobin concentration, reticulocytes, leukocyte counts, and nucleated erythrocytes	Blood was collected from all animals from the orbital sinus for hematology and by cardiac puncture from rats for clinical chemistry. *Hematology:* hematocrit, hemoglobin, erythrocytes, mean erythrocyte volume, reticulocytes, leukocyte differentials, and nucleated erythrocytes *Clinical chemistry:* (rats) urea nitrogen, creatinine, alkaline phosphatase, alanine aminotransferase, and γ-glutamyltranspeptidase	Blood was collected from the orbital sinus and urine was collected from up to 15 male and female rats per group (slated only for clinical pathology evaluation). Blood was also collected from the orbital sinus of 10 male and female rats and mice at 3, 9, and 15 months into the 2-year study. *Hematology:* hematocrit, hemoglobin, erythrocytes, mean erythrocyte volume, mean erythrocyte hemoglobin, mean erythrocyte hemoglobin concentration, platelets, reticulocytes, leukocyte differentials, and nucleated erythrocytes *Clinical chemistry:* urea nitrogen, creatinine, sodium, potassium, chloride, calcium, direct bilirubin (15-month rats and mice), total bilirubin, alkaline phosphatase, alanine aminotransferase, sorbitol dehydrogenase, and bile salts (rats and 15-month mice) *Urinalysis:* creatinine, alkaline phosphatase, lactate dehydrogenase, *N*-acetyl-β-*D*-glucosaminidase, volume, and β-galactosidase

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

15-Day Studies	13-Week Studies	2-Year Studies
Histopathology		
Histopathology was performed on 0, 2,500, 5,000, and 10,000 ppm rats and 0, 2,500, and 5,000 ppm mice. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, bone and marrow, large intestine (cecum, colon, rectum), mandibular or mesenteric lymph node, small intestine (duodenum, jejunum, ileum), spleen, stomach (forestomach and glandular), and thymus. The following tissues were examined only from the 10,000 ppm rats and 5,000 ppm mice: brain, clitoral gland (rats), esophagus, gallbladder (mice), heart, kidney, liver, lung, mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland (rats), prostate gland, salivary gland, skin, testis with epididymis and seminal vesicle, thyroid gland, trachea, urinary bladder, and uterus.	Complete histopathology was performed on 0, 1,000, 2,500, and 5,000 ppm rats and 0, 1,000 and 2,500 ppm mice. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, brain, clitoral gland (rats), esophagus, gallbladder (mice), heart, kidney, large intestine (cecum, colon, rectum), liver, lung, mammary gland, mandibular or mesenteric lymph node, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland (rats), prostate gland, salivary gland, skin, small intestine (duodenum, jejunum, ileum), spleen, sternum and vertebra (including marrow), stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thyroid gland, thymus, trachea, urinary bladder, and uterus. Only the following tissues were examined from the 1,000 and 2,500 ppm rats and 1,000 ppm mice: liver and mandibular or mesenteric lymph node. The kidney from the 2,500 ppm rats was also examined.	Complete histopathology was performed on all rats and mice. No histopathology was performed on the clinical pathology group rats or mice or the neurotoxicity group male rats. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, bone (including marrow), brain, clitoral gland (rats), esophagus, gallbladder (mice), heart, kidney, large intestine (cecum, colon, rectum), liver, lung, mammary gland with surface skin, mandibular or mesenteric lymph node, nose, ovary, pancreas, parathyroid gland, pharynx, pituitary gland, preputial gland (rats), prostate gland, salivary gland, skeletal muscle, skin, small intestine (duodenum, jejunum, and ileum), spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thyroid gland, thymus, trachea, urinary bladder, and uterus.
Neurotoxicity Evaluations		
None	Male and female 0, 1,000, and 2,500 ppm rats were tested for forelimb and hindlimb grip strength, tail flick, startle response, and foot splay.	Forty male rats per group were designated for neurotoxicity studies. After 3 months of exposure, startle reflex and forelimb and hindlimb grip strength were measured in all 40 animals. Ten males per group were killed and given electrophysiological evaluations; another ten males per group were killed and given whole body perfusion for histopathologic examination. The remaining 20 males per group were fed the control diet for an additional 14-16 weeks to determine the reversibility of TBBC-induced changes. At 6 months, grip strength tests were repeated in all 20 rats per group; these 20 were then split into two groups of ten and given electrophysiologic and neuropathologic evaluations.

RESULTS

Rats

15-Day Study

All male and female rats receiving diets containing 25,000 ppm 4,4′-thiobis(6-*t*-butyl-*m*-cresol) (TBBC), and three males and four females receiving 10,000 ppm died before the end of the study (Table 2). The majority of these deaths occurred during the second week of the study. The seven surviving 10,000 ppm males had a mean body weight loss of 29% and a final mean body weight 51% lower than those of the controls. The mean body weight gain of the 5,000 ppm males was 71% lower than that of the controls, and the final mean body weight was 22% lower than that of the controls. Surviving females in the 10,000 ppm group had a 27% mean body weight loss and a final mean body weight 43% lower than those of the controls. The 5,000 ppm females had a mean body weight gain 77% lower than that of the controls and a final mean body weight 18% lower than that of the controls. Mean body weight gains, final mean body weights, and feed consumption by males and females receiving 1,000 and 2,500 ppm were generally similar to those of the controls. All rats exposed to 5,000, 10,000, or

Table 2
Survival, Body Weights, and Feed Consumption of Rats in the 15-Day Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol)

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)	Feed Consumption[c] Week 1	Week 2
Male							
0	10/10	145 ± 2	212 ± 4	67 ± 4		15.8	16.2
1,000	10/10	149 ± 3	224 ± 3	75 ± 2	106	16.0	18.8
2,500	10/10	147 ± 4	222 ± 5	74 ± 2	105	15.2	19.6
5,000	10/10	146 ± 2	165 ± 3**	19 ± 5**	78	8.8	11.9
10,000	7/10[d]	145 ± 3	103 ± 4**	–44 ± 3**	49	3.1	6.0
25,000	0/10[e]	149 ± 2	–	–	–	3.4	5.4
Female							
0	10/10	118 ± 3	154 ± 3	36 ± 1		11.9	12.1
1,000	10/10	120 ± 2	156 ± 2	36 ± 2	101	12.3	10.9
2,500	10/10	118 ± 2	157 ± 2	39 ± 1	102	11.9	12.3
5,000	10/10	118 ± 2	127 ± 1**	8 ± 2**	82	7.8	8.1
10,000	6/10[f]	121 ± 2	88 ± 4**	–35 ± 4**	57	2.2	3.4
25,000	0/10[g]	117 ± 2	–	–	–	1.1	4.8

** Significantly different ($P \leq 0.01$) from the control group by Williams' or Dunnett's test
[a] Number of animals surviving at 15 days/number initially in group
[b] Weights are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study. No final mean body weights were calculated for groups with 100% mortality.
[c] Feed consumption is expressed as grams per animal per day.
[d] Day of death: 11, 14, 14
[e] Day of death: 9, 9, 9, 10, 11, 11, 11, 12, 12, 13
[f] Day of death: 12, 13, 15, 15
[g] Day of death: 7, 8, 8, 9, 10, 11, 11, 11, 15, 15

25,000 ppm TBBC consumed markedly less feed than did the control groups. Rats exposed to 1,000, 2,500, 5,000, or 10,000 ppm received approximate doses of 95, 235, 335, or 365 mg TBBC per kilogram body weight per day (males) and 85, 220, 325, or 270 mg per kg per day (females). Approximate doses for rats exposed to 25,000 ppm cannot be calculated due to early deaths. Since the reduction in feed consumption was evident from the beginning of the study when no signs of toxicity were apparent, reduced feed consumption appeared to be due to poor feed palatability.

Diarrhea was observed in two 25,000 ppm males on day 3 of the study and in the eight remaining 25,000 ppm males on days 6, 7, or 8. Diarrhea occurred in three 25,000 ppm females on day 2 and was observed in other females exposed to 25,000 ppm from day 6 onward. Male and female rats exposed to 5,000 or 10,000 ppm TBBC began to experience diarrhea midway or late into the study. No clinical signs were observed in male or female rats receiving 1,000 or 2,500 ppm TBBC. Statistically significant changes in absolute or relative organ weights reflected decreased final mean body weights or stress and were not considered to be directly related to chemical administration (Table F1).

Since no 25,000 ppm rats survived, hematology parameters were measured only in rats receiving 10,000 ppm or less (Table G1). Leukocyte counts in all exposed females were slightly but significantly greater than those of the controls. Segmented neutrophil counts were significantly higher in the 10,000 and 25,000 ppm male and female groups. This increase was not accompanied by an increase in immature forms, suggesting that this was not an inflammatory response but rather to a shift in the total blood pool distribution without an absolute increase.

Significantly lower reticulocyte counts occurred in male rats receiving 10,000 and 5,000 ppm TBBC and in females receiving 10,000 ppm. In males, this decrease was accompanied by a decrease in nucleated erythrocytes. The slightly lower reticulocyte counts in rats receiving TBBC were probably related to the debilitation rather than to a primary effect on the bone marrow. Females receiving 5,000 or 10,000 ppm also had a very slight decrease in erythrocyte size compared to controls as indicated by decreased mean erythrocyte volume values. This also was probably related to debilitation.

Microscopic examination was not performed on tissues from 25,000 ppm rats since they died before the end of the study. The principal lesions associated with the ingestion of TBBC occurred in the kidney and glandular stomach of 10,000 ppm rats (Table 3). There was partial to complete necrosis of the tip of the renal papilla in one male and two females and minimal focal or multifocal necrosis of tubule epithelium in the cortex or outer medulla of four males and seven females receiving 10,000 ppm (Plates 1 and 2). Erosion and/or focal necrosis of the mucosal epithelium was also observed in the glandular stomach of several male and female rats in the 10,000 ppm groups. Lymphocyte depletion in the thymus and spleen were also observed in rats receiving 10,000 ppm, but these changes were attributed to severe debilitation and stress. Depletion of hematopoietic cells from the bone marrow was attributed to nutrient deficiency accompanying weight loss.

Because of decreased survival in 10,000 and 25,000 ppm rats in the 15-day study, the high exposure selected for the 13-week study was 5,000 ppm.

TABLE 3
Incidences of Selected Nonneoplastic Lesions in Rats in the 15-Day Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

Dose (ppm)	0	1,000	2,500	5,000	10,000
Male					
Kidney[b]	10	–[d]	–	10	10
Renal Papillary Necrosis[c]	0	–	–	0	1 (4.0)[e]
Renal Tubule Necrosis	0	–	–	0	4* (1.3)
Glandular Stomach	10	–	–	10	10
Erosion	0	–	–	0	1 (3.0)
Necrosis	0	–	–	0	2 (2.0)
Hemorrhage	0	–	–	0	4* (1.8)
Congestion	0	–	–	0	4* (1.8)
Female					
Kidney	10	–	–	10	9
Renal Papillary Necrosis	0	–	–	0	2 (3.5)
Renal Tubule Necrosis	0	–	–	0	7**(1.0)
Glandular Stomach	10	–	–	10	9
Erosion	0	–	–	0	1 (3.0)
Necrosis	0	–	–	0	3 (2.3)
Hemorrhage	0	–	–	0	2 (2.5)
Congestion	0	–	–	0	5* (2.4)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
a No histopathology performed on animals receiving 25,000 ppm due to 100% mortality in this group.
b Number of animals with organ examined microscopically
c Number of animals with lesion
d Animals in these groups not examined microscopically
e Average severity grade of lesions in affected animals (1=minimal; 2=mild; 3=moderate; 4=marked)

13-WEEK STUDY

All animals survived to the end of the study (Table 4). The final mean body weights of 5,000 ppm males and females were markedly lower than those of the controls; the mean body weight of males receiving 2,500 ppm was slightly but consistently lower than that of the controls throughout the study. Feed consumption by 5,000 ppm rats was markedly lower than that by controls throughout the study. Feed consumption by 2,500 ppm males was somewhat reduced initially, but was similar to or greater than that by the controls after week 4. Rats exposed to 250, 500, 1,000, 2,500, or 5,000 ppm received approximate doses of 15, 30, 60, 165, or 315 mg TBBC per kilogram body weight per day (males) or 15, 35, 70, 170, or 325 mg/kg per day (females). Since reduction in feed consumption was apparent from the beginning of the study, the reduction would seem more likely to have been caused by decreased feed palatability than by anorexia resulting from toxicity. This conclusion is supported by the fact that diarrhea, the major clinical finding in 5,000 ppm rats, did not appear in the males until day 64 (with the exception of one male in which diarrhea was observed on day 29) or in the females until day 57.

TABLE 4
Survival, Body Weights, and Feed Consumption of Rats in the 13-Week Feed Study of 4,4'-Thiobis(6-t-Butyl-m-Cresol)

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)	Feed Consumption[c] Week 1	Week 13
Male							
0	10/10	142 ± 4	359 ± 7	220 ± 7		16.3	14.9
250	10/10	140 ± 4	382 ± 6	243 ± 7	107	16.5	15.8
500	10/10	138 ± 5	378 ± 6	240 ± 7	105	16.1	16.1
1,000	10/10	139 ± 3	368 ± 5	230 ± 6	103	15.8	14.1
2,500	10/10	138 ± 4	351 ± 7	213 ± 7	98	15.2	16.7
5,000	10/10	134 ± 5	217 ± 3**	82 ± 3**	60	10.0	12.1
Female							
0	10/10	109 ± 3	209 ± 8	99 ± 7		11.2	9.9
250	10/10	108 ± 3	204 ± 5	96 ± 6	98	11.4	9.0
500	10/10	108 ± 3	200 ± 2	93 ± 3	96	11.5	9.8
1,000	10/10	107 ± 3	201 ± 3	94 ± 4	96	11.8	9.5
2,500	10/10	109 ± 3	200 ± 3	91 ± 3	96	11.9	9.3
5,000	10/10	106 ± 3	153 ± 5**	48 ± 3**	73	8.5	8.3

** Significantly different ($P \leq 0.01$) from the control group by Williams' or Dunnett's test
[a] Number of animals surviving/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.

A significant increase in absolute and relative liver weights occurred in females that received 5,000 ppm TBBC (Table F2). The relative, but not absolute, liver weight of 2,500 ppm males was significantly increased. As in the 15-day study, other significant differences in absolute or relative organ weights were considered due to much lower final mean body weights and not to organ-specific toxicity.

Serum alkaline phosphatase levels were significantly higher in 2,500 and 5,000 ppm males and were slightly higher in the females exposed to 5,000 ppm (Table G2). Males and females exposed to 2,500 or 5,000 ppm TBBC had significantly higher serum alanine aminotransferase levels. The increased activity of γ-glutamyl transpeptidase in rats exposed to 5,000 ppm was not considered to be biologically significant.

Hematocrit and hemoglobin concentrations in male rats exposed to 1,000, 2,500, and 5,000 ppm were significantly lower than those of the controls; these results suggest a mild anemia. However, considering the diarrhea and unthriftiness that occurred in these animals, possible dehydration could be masking larger decreases, including decreases in erythrocyte counts, or could account for the absence of changes in hematocrit or hemoglobin values in females. Since reticulocyte counts in male rats were not higher than those of the controls, the anemia in the male rats was considered nonresponsive. Mean erythrocyte volume was significantly lower in males that received 1,000 or 2,500 ppm TBBC and in males and females that received 5,000 ppm; this effect is usually associated with a disturbance in hemoglobin production and has commonly been observed with anemias of chronic inflammation or iron deficiency.

Total leukocyte counts were significantly higher in 5,000 ppm females and slightly increased in 5,000 ppm males. Male and female rats that received 5,000 ppm also exhibited significantly higher segmented neutrophil counts. Band neutrophil counts were significantly higher in all exposed female groups than in controls; the largest increase occurred in 5,000 ppm rats. These changes in leukocyte parameters are consistent with an inflammatory response.

Results of three neurotoxicity trials in 0, 1,000, and 2,500 ppm rats demonstrated a significant dose-related increase in forelimb and hindlimb grip strength (Table H1). Foot splay, tail flick, and startle response reflexes were unaffected by exposure to TBBC.

The principal lesions associated with the administration of TBBC for 13 weeks occurred in the liver and kidney, primarily in 2,500 and 5,000 ppm males and females (Table 5). The lesions in the liver consisted of scattered individual cell necrosis, individual or aggregates of enlarged Kupffer cells with abundant yellow-tan pigmented cytoplasm (Kupffer cell hypertrophy), focal accumulations of similar macrophages in or adjacent to the portal areas, and a slight increase in small bile ductules in the portal areas (Plate 3). By electron microscopy, the pigmented material in the cytoplasm of Kupffer cells was amorphous to finely granular and light to moderately electron dense with a scattering of irregular, highly electron-dense bodies. While the more abundant amorphous substance was not membrane bound, many of the smaller electron-dense bodies were partially surrounded by a plasma membrane. The cytoplasm of the Kupffer cells stained strongly positive with PAS, weakly to strongly by the Ziehl-Neelsen method for acid-fast material, and inconsistently weakly positive by Perl's iron method. While not observed by the study pathologist, enlargement of centrilobular hepatocytes, relative to the periportal hepatocytes, in the 5,000 ppm group was also observed by the Pathology Working Group. This finding is consistent with hepatocellular hypertrophy and with the higher activities of serum enzymes in the 2,500 and 5,000 ppm groups.

The kidney lesions consisted of focal, segmental degeneration and necrosis of the proximal tubule epithelium, primarily in the outer stripe of the outer medulla, and extensive pigmentation of the proximal convoluted tubule epithelium (Plate 4). The degeneration and necrosis were characterized by faintly stained, pale cells with little cytoplasmic or nuclear detail, suggestive of cytolysis and karyolysis. The pigmentation was characterized by pale, yellow-red discoloration of the epithelial cytoplasm.

Both the size and number of macrophages were increased in the mesenteric lymph nodes of male and female rats exposed to 2,500 or 5,000 ppm TBBC (Table 5).

Dose selection rationale: The exposure levels selected for the 2-year rat study were 500, 1,000, and 2,500 ppm. A high dose of 5,000 ppm was not included because of reduced body weights and the degree of liver and kidney toxicity observed in 5,000 ppm males and females in the 13-week study.

TABLE 5
Incidences of Selected Nonneoplastic Lesions in Rats in the 13-Week Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol)

Dose (ppm)	0	250	500	1,000	2,500	5,000
Male						
Liver[a]	10	–[c]	–	10	10	10
Bile Duct Hyperplasia[b]	0	–	–	1 (1.0)[d]	2 (1.5)	10** (2.0)
Kupffer Cell Hypertrophy	0	–	–	0	6** (1.0)	10** (3.7)
Necrosis	0	–	–	1 (1.0)	3 (1.0)	10** (1.0)
Lymph Node, Mesenteric	10	–	–	10	10	10
Macrophage Hyperplasia	0	–	–	1 (2.0)	2 (1.0)	10** (3.2)
Kidney	10	–	–	10	10	10
Necrosis	0	–	–	0	0	9** (1.3)
Pigmentation	0	–	–	0	2 (1.0)	10** (1.1)
Female						
Liver	10	–	–	10	10	10
Bile Duct Hyperplasia	0	–	–	0	1 (1.0)	10** (1.7)
Kupffer Cell Hypertrophy	0	–	–	0	10** (1.6)	10** (3.6)
Necrosis	0	–	–	0	1 (1.0)	10** (1.1)
Lymph Node, Mesenteric	10	–	–	10	10	10
Macrophage, Hyperplasia	0	–	–	0	3 (1.7)	10** (2.9)
Kidney	10	–	–	10	10	10
Necrosis	0	–	–	0	0	9** (1.8)
Pigmentation	0	–	–	0	3 (1.0)	10** (1.0)

** 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] Animals in these groups not examined microscopically
[d] Average severity grade of lesions in affected animals (1=minimal; 2=mild; 3=moderate; 4=marked)

2-YEAR STUDY

Survival

Estimates of survival probabilities for male and female rats receiving TBBC in feed for 2 years are presented in Table 6 and in Kaplan-Meier survival curves (Figure 1). Survival rates of exposed rats were similar to those of the controls.

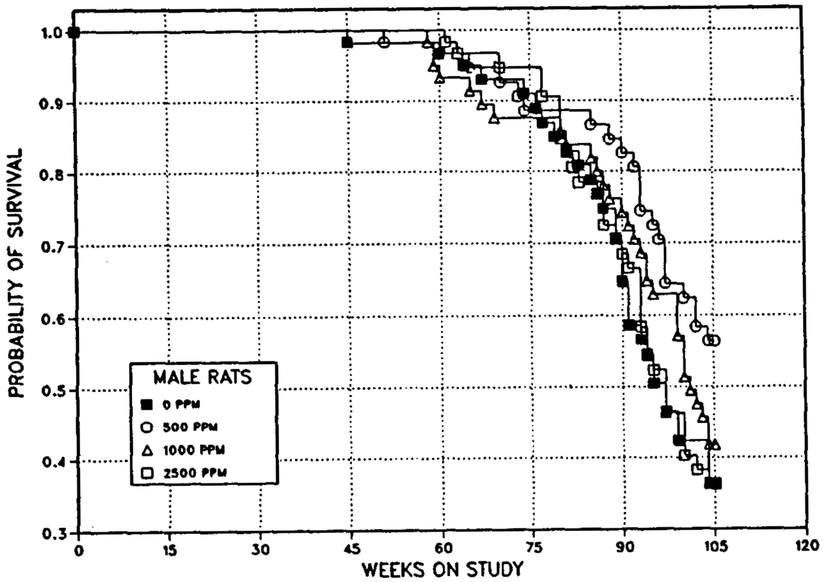
Body Weights, Feed Consumption, and Clinical Findings

Throughout most of the study, the mean body weights of 2,500 ppm male rats were approximately 3% lower than those of the controls and the final mean body weight was 5% lower than that of the controls. Mean body weights of 500 and 1,000 ppm males were similar to those of the controls during the study, but the final mean body weights of these groups were 5% and 6% lower than that of the controls, respectively. The mean body weights of 2,500 ppm females began to decrease 12 weeks into the study and at week 65 was 14% lower than that of the controls. The final mean body weight, however, was 6% lower than that of the controls (Figure 2 and Tables 7 and 8). Exposure levels of 500, 1,000, or 2,500 ppm TBBC resulted in a daily ingestion of 20, 40, or 100 mg/kg body weight for males or 20, 45, or 120 mg/kg body weight for females. Feed consumption by male and female rats was similar to that by controls (Tables J1 and J2). The behavior and general health and appearance of exposed male and female rats were similar to those of controls.

TABLE 6
Survival of Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
Male				
Animals initially in study	60	60	60	60
15-month interim evaluation[a]	10	10	10[e]	10
Natural deaths	9	8	6	9
Moribund	23	14	22	23
Animals surviving to study termination	18	28	22	18
Percent probability of survival at end of study[b]	36	56	42	36
Mean survival (days)[c]	614	637	633	620
Survival analysis[d]	P=0.506	P=0.049N	P=0.540N	P=1.000N
Female				
Animals initially in study	60	60	60	60
15-month interim evaluation[a]	10	10	10	10
Natural deaths	5	5	2	6
Moribund	11	14	16	16
Animals surviving to study termination	34	31[f]	32	28
Percent probability of survival at end of study	68	62	64	56
Mean survival (days)	663	651	645	644
Survival analysis	P=0.202	P=0.559	P=0.711	P=0.195

[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 exposed columns. A lower mortality in an exposure group is indicated by N.
[e] Three male rats exposed to 1,000 ppm were killed moribund prior to the 15-month interim evaluation.
[f] Includes one animal that died the last week of the study



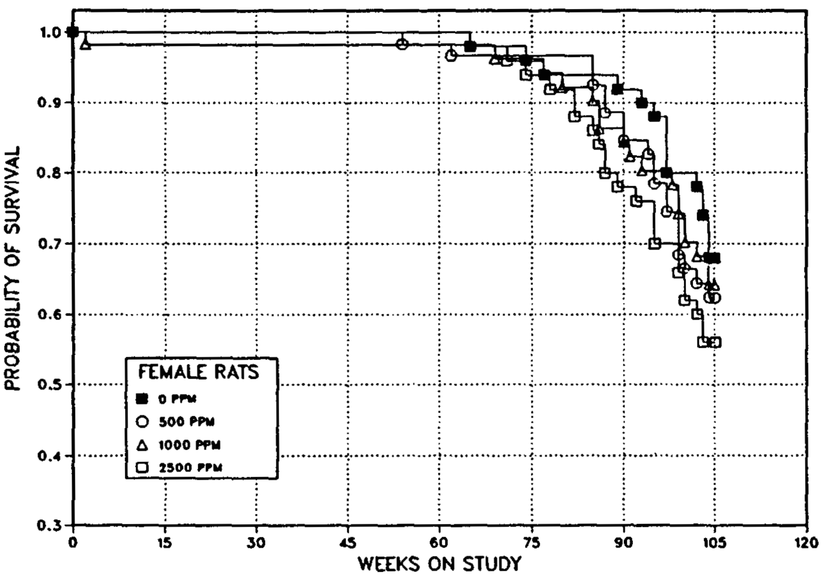
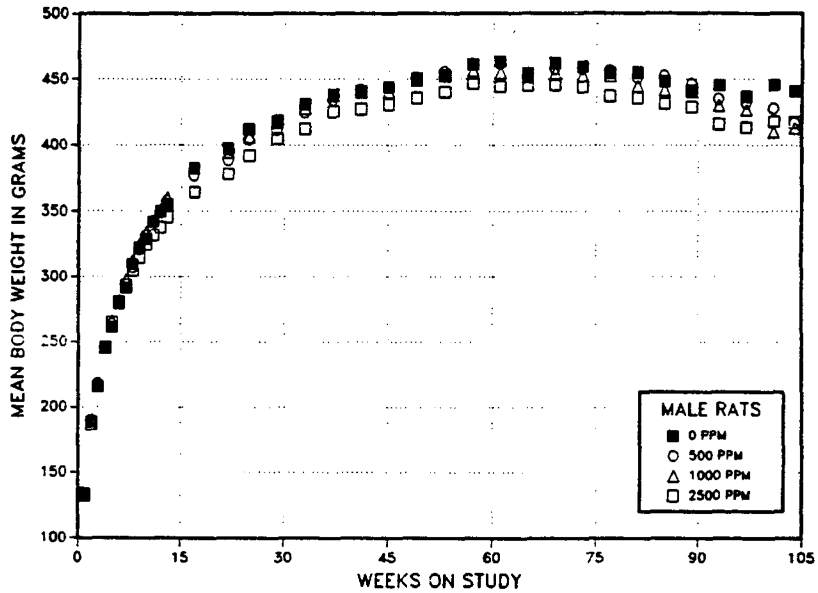


FIGURE 1
Kaplan-Meier Survival Curves for Male and Female Rats Administered 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) in Feed for 2 Years



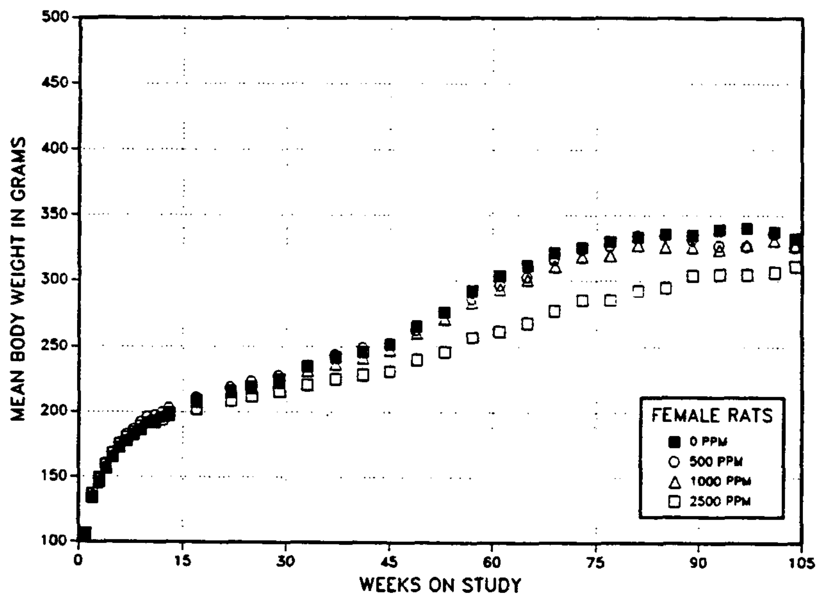


FIGURE 2
Growth Curves for Male and Female Rats
Administered 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol) in Feed for 2 Years

TABLE 7
Mean Body Weights and Survival of Male Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)

Weeks on Study	0 ppm		500 ppm			1,000 ppm			2,500 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	134	60	135	100	60	134	100	60	132	99	60
2	188	60	190	101	60	189	100	60	186	99	60
3	215	60	218	101	60	218	101	60	216	100	60
4	245	60	246	100	60	246	100	60	246	100	60
5	261	60	264	101	60	266	102	60	265	102	60
6	281	60	280	100	60	282	100	60	280	100	60
7	292	60	295	101	60	298	102	60	294	101	60
8	310	60	307	99	60	312	101	60	305	98	60
9	323	60	321	100	60	325	101	60	315	98	60
10	329	60	332	101	60	335	102	60	325	99	60
11	342	60	341	100	60	343	100	60	332	97	60
12	350	60	349	100	60	351	100	60	338	97	60
13	355	60	358	101	60	360	102	60	346	97	60
17	383	60	377	99	60	383	100	60	365	95	60
22	397	60	389	98	60	395	99	60	382	95	60
25	412	60	405	98	60	406	99	60	392	95	60
29	419	60	412	98	60	417	100	60	405	97	60
33	431	60	425	99	60	428	99	60	413	96	60
37	438	60	434	99	60	437	100	60	425	97	60
41	441	60	442	100	60	440	100	60	428	97	60
45	444	59	444	100	60	440	99	60	431	97	60
49	451	59	451	100	60	449	100	60	436	97	60
53	453	59	455	101	59	453	100	60	440	97	60
57	461	59	462	100	59	456	99	60	447	97	60
61	464	58	462	100	58	455	98	56	445	96	59
65[a]	454	47	453	100	47	452	100	48	445	98	48
69	462	46	458	99	47	455	98	46	446	96	48
73	459	46	458	100	44	453	99	46	444	97	48
77	455	43	457	100	44	453	100	46	437	96	46
81	455	41	451	99	44	445	98	44	436	96	42
85	448	39	453	101	43	442	99	43	431	96	39
89	442	35	447	101	42	441	100	40	429	97	35
93	445	28	435	98	40	430	97	37	416	94	32
97	437	24	432	99	33	427	98	33	413	95	25
101	446	21	428	96	31	410	92	27	418	94	20
104	441	20	417	95	29	413	94	23	417	95	18
Mean for weeks											
1-13	279		280	100		281	101		275	99	
14-52	427		424	99		422	100		409	96	
53-104	451		452	99		442	98		433	96	

[a] Interim evaluation occurred.

TABLE 8
Mean Body Weights and Survival of Female Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	500 ppm Av. Wt. (g)	500 ppm Wt. (% of controls)	500 ppm No. of Survivors	1,000 ppm Av. Wt. (g)	1,000 ppm Wt. (% of controls)	1,000 ppm No. of Survivors	2,500 ppm Av. Wt. (g)	2,500 ppm Wt. (% of controls)	2,500 ppm No. of Survivors
1	107	60	107	100	60	107	100	60	107	100	60
2	134	60	137	102	60	136	101	60	137	102	60
3	146	60	148	102	60	147	101	59	149	102	60
4	156	60	159	102	60	158	101	59	160	102	60
5	165	60	169	102	60	166	101	59	168	102	60
6	173	60	176	102	60	174	101	59	175	101	60
7	178	60	182	103	60	178	101	59	180	101	60
8	182	60	186	102	60	184	101	59	184	101	60
9	186	60	192	103	60	188	101	59	189	102	60
10	192	60	196	103	60	192	100	59	191	100	60
11	192	60	197	103	59	194	101	59	193	101	60
12	196	60	200	102	60	196	100	59	193	99	60
13	199	60	203	102	60	198	100	59	197	99	60
17	209	60	211	101	60	208	99	59	202	97	60
22	216	60	219	101	60[b]	215	100	59	209	97	60
25	219	60	223	102	60	218	100	59	212	97	60
29	225	60	228	101	60	223	99	59	216	96	60
33	235	60	236	100	60	232	99	59	221	94	60
41	246	60	249	101	60	241	98	59	228	93	60
45	252	60	253	100	60	248	98	59	231	92	60
49	266	60	263	100	60	261	98	59	240	90	60
53	277	60	277	100	60	272	98	59	246	89	60
57	293	60	287	98	59	284	97	59	257	88	60
61	304	60	297	98	59	294	97	59	262	86	60
65[a]	312	49	303	97	48	301	97	49	268	86	49
69	322	49	316	98	48	312	97	48	278	86	49
73	326	49	324	100	48	319	98	48	286	88	48
77	330	47	327	99	48	320	97	48	286	87	47
81	334	47	335	100	48	328	98	46	293	88	46
85	336	47	335	100	46	326	97	45	295	88	43
89	335	47	331	99	44	327	98	43	304	91	39
93	339	46	327	96	42	324	96	41	305	90	38
97	341	40	327	96	38	328	96	40	305	90	35
101	338	40	336	100	33	331	98	35	307	91	31
104	333	37	326	98	32	327	98	32	311	94	28
Mean for weeks											
1-13	170		173	102		171	101		171	101	
14-52	234		236	101		231	99		220	94	
53-104	323		318	98		314	97		286	89	

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

Hematology, Clinical Chemistry, and Urinalysis

Results of hematology evaluations at 3, 9, and 15 months are presented in Tables G3 through G6. Slight but significant decreases in hematocrit levels, hemoglobin concentrations, and erythrocyte counts were observed in one set of 1,000 and 2,500 ppm males at 15 months, but not in the other set. These differences were not observed in males at 3 or 9 months. Similar significant decreases in hematocrit level and hemoglobin concentration occurred in 2,500 ppm females at 9 months; hemoglobin concentrations of 2,500 ppm females were significantly decreased in both sets evaluated at 15 months, but hematocrit levels were similar to those of the controls. Mean erythrocyte hemoglobin counts and concentration in the 2,500 female group were significantly lower than those of the controls at 9 months and in both sets of animals evaluated at 15 months. Platelet counts in 2,500 ppm males and females were slightly but significantly higher than those of the controls at 3 and 9 months, as were the platelet counts of 2,500 ppm males in one set of animals evaluated at 15 months and of 2,500 ppm females in the other set. While the results of the hematology evaluations were somewhat variable, they do suggest a slight chemical-related effect. It is not clear, however, if these differences indicate a direct effect on stem cells in the bone marrow or on circulating erythrocytes, or if they are secondary to other physiological alterations caused by TBBC.

Clinical chemistry results for rats evaluated at 3 and 9 months and for the two sets of rats evaluated at 15 months were generally similar (Tables G3, G4, G5, and G6). Serum activities of alkaline phosphatase, alanine aminotransferase, and sorbitol dehydrogenase in 2,500 ppm males were significantly greater that those of the controls at each evaluation. Alkaline phosphatase activities in both sets of 1,000 ppm males evaluated at 15 months were also significantly greater than those of controls. Serum activities of alanine aminotransferase and sorbitol dehydrogenase in 2,500 ppm females were also significantly greater than those in the controls at each evaluation. These results are consistent with hepatocellular damage caused by TBBC.

Urine volumes of all exposed groups of males and females were significantly lower than those of the controls at 3 months, but not at later evaluations. This is consistent with decreased water or feed intake in the exposed groups, but it is not considered a direct chemical effect. Elevated urine creatinine concentrations at the 3-month evaluation, particularly in exposed groups of male rats, indicate that the urine constituents were more highly concentrated in these groups and are consistent with the volume measurements. Urine specific gravity was not measured, however. The urinary activity of *N*-acetyl-ß-D-glucosaminidase was mildly increased at all evaluations in 2,500 ppm females in comparison to controls. Differences in other urine enzyme activities between exposed and control rats were variable and not considered chemical related.

Neurotoxicity Evaluation

At 3 months, there was no difference in startle reflex between exposed and control male groups and, in contrast to the findings in the 13-week study, there were no differences in forelimb or hindlimb grip strength between exposed and control groups in the first three trials (Table H2). The standard methodology for measuring grip strength consists of three trials. However, eight trials were used in the chronic study, and the grip strength of control groups decreased with subsequent trials, apparently due to fatigue or habituation. Although the grip strength of exposed groups also decreased with repeated trials, the decrement was less than that of the controls. Thus, grip strength in later trials (particularly that of the forelimbs) of each exposed group was significantly greater than controls. The electrophysiologic evaluation revealed no significant inhibitory effects of TBBC on motor nerve excitability or conduction, neuromuscular transmission, or muscle contractility (Tables H4, H5, and H6). Further, there were no microscopic lesions that could be attributed to TBBC observed in the sciatic nerve, quadriceps muscle, or teased nerve preparations of the sciatic nerve.

In the reversibility study, the effects on grip strength observed at 3 months were no longer evident at the 6 month evaluation (Table H3). The results of the remaining neurotoxicity studies at 6 months were similar to those at 3 months (Tables H4, H5, and H6), and there were no significant effects of TBBC on motor nerve excitability or conduction, neuromuscular transmission, muscle contractility, or pathology.

Pathology and Statistical Evaluation

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions in the liver, kidney, thyroid gland, uterus, and mammary 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 the neoplasms mentioned in this section are presented in Appendix A for male rats and Appendix B for female rats.

Liver: At the 15-month interim evaluation, both the absolute and relative liver weights of 2,500 ppm females were significantly greater than those of the controls (Table F3). Relative liver weights of 2,500 ppm males and 1,000 ppm females were also significantly greater than those of the controls.

The incidence of Kuppfer cell hypertrophy was significantly increased in 2,500 ppm males and females at the 15-month interim evaluation and at the end of the 2-year study (Tables 9, A5, and B5). At 15 months, the incidence of cytoplasmic vacuolization was significantly increased in all exposed groups of males and in 2,500 ppm females. At 2 years, the incidence of cytoplasmic vacuolization was slightly increased in 1,000 and 2,500 ppm males and significantly increased in 1,000 and 2,500 ppm females. Also at 2 years, the incidence of fatty change was significantly increased in 2,500 ppm females. Cytoplasmic vacuolization was characterized by the presence of multiple, small vacuoles, whereas fatty change was indicated by the presence of single, large cytoplasmic vacuoles. In both instances, these changes are presumably the result of lipid accumulation.

At 15 months, the incidence of basophilic foci was significantly increased in 2,500 ppm males and these foci were present in all females; the incidences in exposed males and females at terminal sacrifice were similar to those in the controls. Incidences of mixed cell foci were significantly increased in 2,500 ppm males and females at 15 months and in 1,000 and 2,500 ppm males and females at the end of the study; at each time point, the incidence of mixed cell foci in 2,500 ppm females was twice that in 2,500 ppm males. Hepatocyte foci were characterized as basophilic, eosinophilic, clear, or mixed based on cytoplasmic staining properties. These differences in staining properties are generally attributed to variations in the amounts of rough or smooth endoplasmic reticulum, glycogen, or fat. Thus, basophilic foci consist predominantly of cells with greater amounts of rough endoplasmic reticulum, while eosinophilic foci consist of cells with more smooth endoplasmic reticulum. Clear cell foci consist of cells with vacuolated cytoplasm caused by the accumulation of lipid or with clear cytoplasm caused by the accumulation of glycogen. The mixed cell foci consist of cells with either basophilic or eosinophilic cytoplasm and cells with vacuolated or clear cytoplasm.

The incidences of hepatocellular adenoma or carcinoma (combined) in exposed male rats were not significantly greater than that in the control group (Tables 9 and A3).

TABLE 9
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)

Dose (ppm)	0	500	1,000	2,500
Male				
15-Month Interim Evaluation				
Liver[a]	10	10	7	10
Kupffer Cell Hypertrophy[b]	0	0	0	10** (1.2)[c]
Cytoplasmic Vacuolization	1 (1.0)	10** (1.1)	7** (1.0)	10** (1.7)
Basophilic Focus	5	2	7	10*
Mixed Cell Focus	1	1	1	5
2-Year Study				
Liver	50	50	50	49
Kupffer Cell Hypertrophy	2 (1.5)	3 (1.0)	2 (1.0)	31** (2.1)
Cytoplasmic Vacuolization	13 (1.2)	11 (1.5)	19 (1.4)	18 (2.0)
Basophilic Focus	18	22	23	22
Mixed Cell Focus	6	14	18*	15*
Clear Cell Focus	2	0	1	1
Eosinophilic Focus	3	7	2	1
Hepatocellular Adenoma				
Overall rates[d]	1/50 (2%)	2/50 (4%)	3/50 (6%)	4/49 (8%)
Adjusted rates[e]	5.6%	7.1%	13.6%	17.0%
Terminal rates[f]	1/18 (6%)	2/28 (7%)	3/22 (14%)	2/18 (11%)
First incidence (days)	729 (T)	729 (T)	729 (T)	625
Logistic regression test[g]	P=0.091	P=0.653	P=0.377	P=0.177
Hepatocellular Carcinoma	0/50 (0%)	1/50 (2%)	0/50 (0%)	1/49 (2%)
Hepatocellular Adenoma or Carcinoma[h]				
Overall rates	1/50 (2%)	3/50 (6%)	3/50 (6%)	5/49 (10%)
Adjusted rates	5.6%	10.7%	13.6%	21.0%
Terminal rates	1/18 (6%)	3/28 (11%)	3/22 (14%)	2/18 (11%)
First incidence (days)	729 (T)	729 (T)	729 (T)	625
Logistic regression test	P=0.056	P=0.472	P=0.377	P=0.100

(continued)

TABLE 9
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

Dose (ppm)	0		500		1,000		2,500	
Female								
15-Month Interim Evaluation								
Liver	10		10		10		10	
Kupffer Cell Hypertrophy	1	(1.0)	0		5	(1.0)	10**	(2.7)
Cytoplasmic Vacuolization	0		1	(1.0)	1	(1.0)	8**	(1.0)
Basophilic Focus	10		10		10		10	
Eosinophilic Focus	0		0		1		0	
Mixed Cell Focus	0		1		0		10**	
2-Year study								
Liver	50		50		50		50	
Kupffer Cell Hypertrophy	11	(1.2)	10	(1.5)	9	(1.0)	42**	(2.7)
Cytoplasmic Vacuolization	12	(1.3)	10	(1.4)	20*	(1.3)	34**	(2.7)
Fatty Change	9	(1.4)	8	(1.5)	15	(1.3)	19*	(1.5)
Basophilic Focus	37		34		38		36	
Mixed Cell Focus	5		4		14*		34**	
Eosinophilic Focus	5		7		8		4	
Clear Cell Focus	0		1		1		1	
Adenoma	0		0		0		1	

* Significantly different (P≤0.05) by the Fisher exact test (15-month interim evaluation) or the logistic regression test (terminal sacrifice)
** (P≤0.01)
(T) Terminal sacrifice
[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)
[d] Number of animals with neoplasm per number of animals with liver examined microscopically
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[f] Observed incidence at terminal kill
[g] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The logistic regression test regards these neoplasms as nonfatal.
[h] Historical incidence for 2-year feed studies with untreated control groups (mean ± standard deviation): 41/1,251 (3.3% ± 3.6%); range 0%-10%

Kidney: Nephropathy is a common occurrence in aging F344/N rats and was observed in nearly all males and the majority of females in this study. In comparison to the control group, the severity of nephropathy was significantly increased in 2,500 ppm females both at 15 months and 2 years (Table 10). The number of females with a moderate severity of nephropathy was much higher in the 2,500 ppm group than in the control group, whereas the reverse was true for minimal nephropathy. The severity of nephropathy was similar among all groups of male rats.

TABLE 10
Incidences and Severity of Nephropathy in Female Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol)

Dose (ppm)	0	500	1,000	2,500
15-Month Interim Evaluation				
Kidney[a]	10	10	10	10
Nephropathy[b]	9	10	10	10
Absent (Grade 0)	1	0	0	0
Minimal (Grade 1)	6	8	9	0
Mild (Grade 2)	3	2	1	8
Moderate (Grade 3)	0	0	0	2
Marked (Grade 4)	0	0	0	0
Group average severity grade	1.2	1.2	1.1	2.2**
2-Year Study				
Kidney	50	50	50	50
Nephropathy	44	41	46	48
Absent (Grade 0)	6	9	4	2
Minimal (Grade 1)	17	14	19	1
Mild (Grade 2)	26	25	22	29
Moderate (Grade 3)	1	2	5	18
Marked (Grade 4)	0	0	0	0
Group average severity grade	1.4	1.4	1.6	2.3**

** Significantly different ($P \leq 0.01$) from the control group by the Mann-Whitney U test
[a] Number of animals with kidney examined microscopically
[b] Number of animals with lesion

Thyroid gland: The incidence of C-cell adenoma or carcinoma (combined) occurred with a significant positive trend in female rats and was slightly, but not significantly, increased in the 1,000 and 2,500 ppm groups at the end of the 2-year study (0 ppm, 3/49; 500 ppm, 4/49; 1,000 ppm, 8/50; 2,500 ppm, 9/50; Table B3). This positive trend was not considered chemical related because the incidence in 2,500 ppm females was only slightly above the historical average of 15% and well within the range of 6% to 31% for historical controls (Table B4b). Further, C-cell hyperplasia was decreased in females (28/49, 24/49, 27/50, 18/50; Table B5), although the decrease in 2,500 ppm females was not statistically significant by pairwise comparison.

Uterus: Stromal polyps occurred with a significant positive trend (0 ppm, 2/50; 500 ppm, 5/50; 1,000 ppm, 9/50; 2,500 ppm, 9/50; Table B3) in the uteri of female rats exposed to TBBC. Increased incidences of stromal polyps in females exposed to 1,000 or 2,500 ppm were significant; however, the incidences are only slightly above the historical control average of 16% and are well within the historical control range of 2% to 30% (Table B4c). The incidence in controls is unusually low compared to that in historical controls. Stromal sarcoma was also present in one 500 ppm and one 2,500 ppm female.

Mammary gland: The incidence of fibroadenoma occurred with a statistically significant negative trend in female rats (29/50, 24/50, 11/50, 16/50; Table B3), and the decreases were significant in the 1,000 and 2,500 ppm groups. There was also a significant negative trend in the incidence of mammary gland fibroadenoma, adenoma, or carcinoma (combined) in females (32/50, 24/50, 11/50, 16/50; Table B3).

MICE

15-DAY STUDY

All 10,000 and 25,000 ppm male and female mice and eight males and eight females receiving 5,000 ppm TBBC died (Table 11). The two surviving 5,000 ppm males had a mean body weight loss of 25% and a final mean body weight 35% lower than that of the controls; the final mean body weight of 2,500 ppm males was similar to that of the controls. The two surviving 5,000 ppm females had a mean body weight loss of 10% and a final mean body weight 27% lower than that of the controls; the final mean body weight of 2,500 ppm females was 13% lower than that of the controls. Male and female mice receiving 1,000 ppm TBBC had final mean body weights similar to those of the controls. Feed consumption by 5,000, 10,000, and 25,000 ppm males and females was markedly lower than that by controls. Mice exposed to 1,000, 2,500, or 5,000 ppm received approximate doses of 285, 585, or 475 mg TBBC per kilogram body weight per day (males) or 360, 950, or 1,030 mg/kg per day (females). Approximate doses for mice exposed to 10,000 or

TABLE 11
Survival, Body Weights, and Feed Consumption of Mice in the 15-Day Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol)

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)	Feed Consumption[c] Week 1	Week 2
Male							
0	10/10	21.3 ± 0.4	24.2 ± 0.7	3.0 ± 0.6		6.7	9.1
1,000	10/10	21.6 ± 0.5	26.1 ± 0.5	4.5 ± 0.2	108	5.9	7.7
2,500	10/10	21.9 ± 0.2	23.8 ± 0.4	2.0 ± 0.5	98	4.0	6.7
5,000	2/10[d]	21.0 ± 0.6	15.9 ± 0.4**	−5.3 ± 0.3**	65	1.2	2.3
10,000	0/10[e]	21.7 ± 0.5	–	–	–	1.0	1.4
25,000	0/10[f]	22.0 ± 0.4	–	–	–	1.7	–[g]
Female							
0	10/10	15.7 ± 0.3	18.9 ± 0.4	3.1 ± 0.3	–	6.1	13.1
1,000	10/10	15.5 ± 0.3	19.3 ± 0.2	3.8 ± 0.4	103	4.8	7.8
2,500	10/10	16.2 ± 0.4	16.5 ± 0.5**	0.3 ± 0.4**	87	4.2	8.2
5,000	2/10[h]	15.3 ± 0.2	13.8 ± 0.1**	−1.2 ± 0.7**	73	2.2	3.8
10,000	0/10[i]	16.4 ± 0.3	–	–	–	1.3	–[g]
25,000	0/10[j]	16.8 ± 0.2*	–	–	–	0.9	–[g]

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** (P≤0.01)
a Number of animals surviving at 15 days/number initially in group
b Weights are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies. No final mean body weights or body weight changes were calculated for groups with 100% mortality.
c Feed consumption is expressed as grams per animal per day.
d Day of death: 10, 12, 12, 12, 13, 14, 15, 15
e Day of death: 8, 8, 9, 10, 10, 10, 11, 11, 12, 12
f Day of death: 4, 4, 4, 5, 5, 5, 6, 6, 6, 6
g All animals in these exposure groups died prior to the second week of the study
h Day of death: 9, 10, 10, 10, 11, 11, 11, 15
i Day of death: 6, 7, 7, 7, 7, 8, 8, 8, 8, 8
j Day of death: 4, 4, 4, 4, 5, 5, 5, 5, 5, 5

to 10,000 or 25,000 ppm cannot be calculated due to early deaths. Reduced feed consumption by exposed groups was seen as early as the first day of the study. The reduction in feed consumption was attributed to poor feed palatability.

Diarrhea was observed in 25,000 ppm mice beginning on either day 2 or day 3 of the study. Diarrhea was also present in most 10,000 ppm males (beginning on day 8) and females (beginning on day 2). Five 5,000 ppm males exhibited diarrhea (beginning on day 9), as did nine 5,000 ppm females (beginning on day 2).

Significantly different absolute or relative organ weights in exposed groups of mice were associated with lower mean body weights or were attributed to severe debilitation and stress (thymus, spleen) and were not considered to be the result of organ-specific toxicity (Table F4).

Because all 10,000 and 25,000 ppm male and female mice died and because of morbidity in surviving 5,000 ppm males, hematology parameters were measured only in males and females receiving 1,000 or 2,500 ppm and in 5,000 ppm females (Table G7). Segmented neutrophil counts were significantly higher in 2,500 and 5,000 ppm females. The increases were modest and were not accompanied by an increase in the number of immature cells, suggesting that these increases were not an inflammatory response. The increased numbers of circulating mature neutrophils may have been related to a shift in the total blood pool distribution without an absolute increase.

Significant increases in mean erythrocyte hemoglobin concentration values occurred in all surviving exposed male and female mice. Increased mean erythrocyte hemoglobin concentration is not a physiologic possibility and is usually an artifact caused by sample handling or analytical error. However, any condition that would cause increased erythrocyte fragility leading to increased post-sampling hemolysis could cause an increase in mean erythrocyte hemoglobin concentration values.

Microscopic examination was not performed on tissues from mice in the 10,000 or 25,000 ppm groups because they died before the end of the study. Kidneys were examined microscopically in the 2,500 and 5,000 ppm groups. The principal lesion caused by the ingestion of TBBC was minimal focal renal tubule necrosis in eight males and three females that received 5,000 ppm. Most of the affected mice also had a few protein casts within tubule lumens. Depletion of cells from the bone marrow and lymphoid organs was observed in many mice in the 5,000 ppm group. Bone marrow depletion was attributed to nutrient deficiency accompanying weight loss; depletion of lymphoid organs is commonly associated with low body weight, debilitation, and stress.

13-Week Study

All animals survived to the end of the study (Table 12). The final mean body weight of 2,500 ppm males was 15% lower than that of the controls. Female mice receiving 500, 1,000, or 2,500 ppm TBBC had final mean body weights 11%, 15%, and 22% lower than that of the controls, respectively. Final mean body weights of mice in other exposure groups were similar to those of the controls. Due to spillage and scattering, there were limitations in measuring feed consumption by mice and the data were difficult to interpret. Feed consumption by 2,500 ppm males averaged 24% less than that by the controls through week 3 of the study and was similar to that by the controls throughout the remainder of the study. No conclusions can be drawn from the slight variations in feed consumption observed in the male control group in the latter part of the study. Feed consumption by 2,500 ppm females averaged 27% less than that by the controls during most of the study. Mice exposed to 100, 250, 500, 1,000, or 2,500 ppm received approximate doses of 15, 30, 65, 145, or 345 mg TBBC per kilogram body weight per day (males) or 10, 35, 60, 165, or 340 mg/kg per day (females). Variations in feed consumption by males or females at other exposure levels did not appear to be chemical related. Since no clinical findings related to TBBC administration were observed in the present study, the reduction in feed consumption by 2,500 ppm females was probably due to poor feed palatability.

Table 12
Survival, Body Weights, and Feed Consumption of Mice in the 13-Week Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol)

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)	Feed Consumption[c] Week 1	Week 13
Male							
0	9/9	21.3 ± 0.4	30.8 ± 1.1	9.5 ± 0.8		3.3	2.8
100	10/10	21.5 ± 0.5	30.6 ± 1.0	9.0 ± 0.6	99	3.6	2.9
250	10/10	21.8 ± 0.4	31.7 ± 0.6	9.8 ± 0.6	103	3.1	3.5
500	10/10	21.6 ± 0.6	30.5 ± 0.9	8.9 ± 0.6	99	3.7	3.2
1,000	10/10	22.2 ± 0.4	30.8 ± 0.6	8.7 ± 0.6	100	–[d]	3.8
2,500	10/10	21.6 ± 0.4	26.3 ± 0.4**	4.7 ± 0.3**	85	2.6	4.0
Female							
0	10/10	17.7 ± 0.3	30.7 ± 0.8	13.0 ± 0.8		3.0	3.4
100	10/10	17.7 ± 0.3	28.1 ± 0.7	10.4 ± 0.6**	91	2.2	2.6
250	10/10	17.9 ± 0.3	29.2 ± 0.7	11.3 ± 0.6**	95	3.1	3.4
500	10/10	17.9 ± 0.4	27.3 ± 0.7**	9.4 ± 0.4**	89	2.8	3.4
1,000	10/10	17.7 ± 0.3	26.0 ± 0.4**	8.3 ± 0.3**	85	2.9	4.2
2,500	10/10	17.9 ± 0.3	23.8 ± 0.5**	5.9 ± 0.4**	78	2.0	3.7

** Significantly different ($P \leq 0.01$) from the control group by Williams' or Dunnett's test
[a] Number of animals surviving/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.
[d] Feed consumption values were invalid due to technical error.

Absolute and relative liver weights of 2,500 ppm males and females were slightly but significantly greater than those of the controls (Table F5). Males exposed to 500, 1,000, or 2,500 ppm and females exposed to 2,500 ppm had significantly increased absolute and relative spleen weights. Differences in the absolute or relative weights of other organs were related to reductions in mean body weights.

The erythrocyte counts, hematocrit and hemoglobin concentrations, and mean erythrocyte volume values of 2,500 ppm males and females were significantly less than those of the controls (Table G8). The hematocrit and erythrocyte counts of 1,000 ppm males and females were also significantly reduced. These differences were consistent with a developing mild microcytic, normochromic, nonresponsive anemia similar to differences observed in male rats in the 13-week study.

The principal lesions associated with the administration of TBBC to mice for 13 weeks occurred in the liver and were similar to those observed in rats (Table 13). The lesions were only observed in 2,500 ppm mice. The lesions in the liver consisted of individual or aggregates of enlarged Kupffer cells with abundant yellow-tan, pigmented cytoplasm (Kupffer cell hypertrophy), focal accumulations of similar macrophages in or adjacent to the portal areas, and a slight increase in small bile ductules in the portal areas (bile duct hyperplasia) (Plates 5 and 6). As in rats, the mesenteric lymph nodes of the 2,500 ppm mice contained increased numbers of enlarged macrophages.

Dose selection rationale: Because of the reduction in mean body weights, the increase in liver and spleen weights, and the accompanying histopathologic changes of the liver in 2,500 ppm males and females, the exposures selected for the 2-year study in mice were 250, 500, and 1,000 ppm.

TABLE 13
Incidences of Selected Nonneoplastic Lesions in Mice in the 13-Week Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)

Dose (ppm)	0	100	250	500	1,000	2,500
Male						
Liver[a]	9	–[c]	–	–	10	10
Bile Duct Hyperplasia[b]	0	–	–	–	0	10**(1.0)[d]
Kupffer Cell Hypertrophy	0	–	–	–	0	10**(4.0)
Lymph Node, Mesenteric	9	–	–	–	10	10
Macrophage, Hyperplasia	0	–	–	–	0	5* (1.0)
Female						
Liver	10	–	–	–	10	10
Bile Duct Hyperplasia	0	–	–	–	0	6**(1.0)
Kupffer Cell Hypertrophy	0	–	–	–	0	10**(3.4)
Lymph Node, Mesenteric	10	–	–	–	10	10
Macrophage, Hyperplasia	0	–	–	–	1 (1.0)	1 (2.0)

* Significantly different (P≤0.05) from the control group by Fisher's exact test
** P≤0.01
a Number of animals with organ examined microscopically
b Number of animals with lesion
c Organ not examined microscopically
d Average severity grade of lesions in affected animals (1=minimal; 2=mild; 3=moderate; 4=marked)

2-Year Study

Survival

Estimates of survival probabilities for male and female mice administered TBBC in feed for 2 years are presented in Table 14 and in Kaplan-Meier survival curves (Figure 3). Survival rates of exposed males and females were similar to those of the controls.

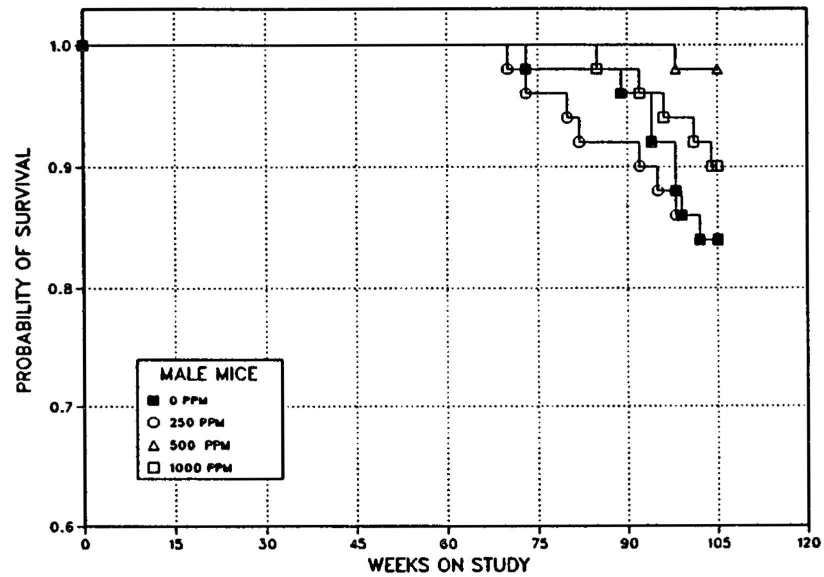
Body Weights, Feed Consumption, and Clinical Findings

The mean body weight of male mice receiving 1,000 ppm TBBC was approximately 10% lower than that of the controls from week 45 through the end of the study (Table 15). The mean body weight of males receiving 500 ppm TBBC was slightly lower than that of the controls throughout the study. The mean body weight of 250 ppm males was similar to that of the controls throughout the study. The mean body weight of 1,000 ppm females was 11% lower than that of the controls by week 45 and was 18% lower by the end of the study (Table 16 and Figure 4). Final mean body weights of 250 and 500 ppm females were approximately 9% lower than that of the controls. Exposure levels of 250, 500, or 1,000 ppm resulted in a daily ingestion of TBBC of 30, 60, or 145 mg/kg body weight for males or 45, 110, or 255 mg/kg for females. Feed consumption by exposed male mice was similar to that by the controls (Tables J3 and J4). No clinical findings were attributed to TBBC administration.

Table 14
Survival of Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)

	0 ppm	250 ppm	500 ppm	1,000 ppm
Male				
Animals initially in study	60	60	60	60
15-month interim evaluation[a]	10	10	10	10
Natural deaths	6	6	1	4
Moribund	2	2	0	1
Animals surviving to study termination	42[e]	42[e]	49	45
Percent probability of survival at end of study[b]	84	84	98	90
Mean survival (days)[c]	673	667	683	678
Survival analysis[d]	P=0.242N	P=0.859	P=0.036N	P=0.536N
Female				
Animals initially in study	60	60	60	60
15-month interim evaluation[a]	9	9	10	10
Natural deaths	7	9	11	11
Moribund	4	3	3	4
Missing[a]		1		
Animals surviving to study termination	40[e]	38	36	35
Percent probability of survival at end of study	79	76	72	71
Mean survival (days)	658	660	654	644
Survival analysis	P=0.346	P=1.000	P=0.651	P=0.468

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 exposed columns. A negative trend or lower mortality in an exposure group is indicated by N.
e Includes one animal that died the last week of the study



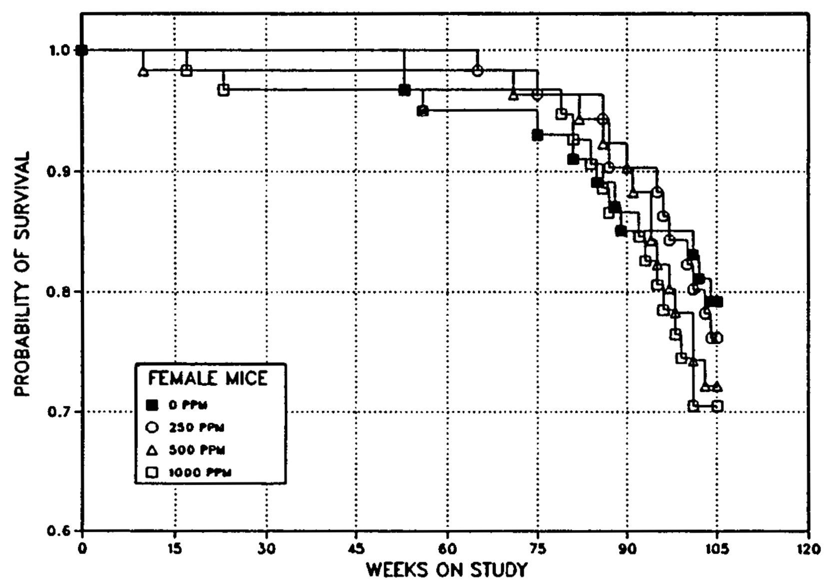


FIGURE 3
Kaplan-Meier Survival Curves for Male and Female Mice Administered 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol) in Feed for 2 Years

TABLE 15
Mean Body Weights and Survival of Male Mice in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol)

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	250 ppm Av. Wt. (g)	250 ppm Wt. (% of controls)	250 ppm No. of Survivors	500 ppm Av. Wt. (g)	500 ppm Wt. (% of controls)	500 ppm No. of Survivors	1,000 ppm Av. Wt. (g)	1,000 ppm Wt. (% of controls)	1,000 ppm No. of Survivors
1	22.1	60	22.2	101	60	22.2	101	60	22.4	101	60
2	23.5	60	23.8	101	60	23.9	102	60	24.4	104	60
3	24.7	60	24.8	100	60	25.1	102	60	25.2	102	60
4	25.4	60	25.5	100	60	25.9	102	60	25.9	102	60
5	26.5	60	26.2	99	60	26.6	100	60	26.4	100	60
6	27.3	60	27.2	100	60	27.4	100	60	27.3	100	60
7	27.8	60	27.8	100	60	27.8	100	60	28.0	101	60
8	28.8	60	28.5	99	60	28.6	99	60	28.4	99	60
9	29.2	60	29.1	100	60	28.8	99	60	28.8	99	60
10	30.2	60	30.1	100	60	29.6	98	60	29.3	97	60
11	30.6	60	30.4	99	60	30.2	99	60	29.9	98	60
12	31.6	60	31.2	99	60	31.0	98	60	30.5	97	60
13	32.0	60	31.5	98	60	31.1	97	60	30.9	97	60
17	35.1	60	34.5	98	60	33.8	96	60	33.3	95	60
21	37.0	60	36.4	98	60	35.7	97	60	34.8	94	60
25	38.0	60	37.2	98	60	36.2	95	60	35.3	93	60
29	38.9	60	37.8	97	60	36.7	94	60	35.8	92	60
33	41.1	60	40.1	98	60	39.3	96	60	37.6	92	60
37	41.5	60	42.0	101	60	40.6	98	60	37.9	91	60
41	42.3	60	42.2	100	60	41.1	97	60	38.5	91	60
45	44.2	60	43.5	98	60	42.2	96	60	39.9	90	60
49	45.6	60	44.7	98	60	43.6	96	60	41.3	91	60
53	46.8	60	46.1	99	60	44.5	95	60	42.3	90	60
57	47.5	60	46.9	99	60	45.6	96	60	43.3	91	60
61	48.0	60	46.9	98	60	45.8	95	60	43.2	90	60
65[a]	48.3	60	47.5	98	60	45.9	95	60	44.1	91	60
69	47.7	50	47.1	99	50	46.0	96	50	43.7	92	50
73	47.8	50	47.5	99	49	46.0	96	50	43.4	91	50
77	48.8	49	49.0	100	48	47.5	97	50	44.9	92	50
81	48.3	49	48.8	101	47	47.5	98	50	43.9	91	50
85	47.5	49	48.5	102	46	45.8	96	50	42.8	90	50
89	46.9	49	47.2	101	46	45.3	97	50	42.8	91	49
93	46.4	48	47.4	102	45	44.5	96	50	42.3	91	48
97	46.5	46	49.2	106	44	45.2	97	50	42.6	92	47
101	46.0	43	48.3	105	43	45.0	98	49	42.8	93	46
104	47.0	42	49.5	105	42	46.2	98	49	43.2	92	45
Mean for weeks											
1-13	27.7		27.6	96		27.6	100		27.5	99	
14-52	40.4		39.8	99		38.8	96		36.2	90	
53-104	47.4		47.9	101		45.7	96		43.2	91	

[a] Interim evaluation occurred.

TABLE 16
Mean Body Weights and Survival of Female Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	250 ppm Av. Wt. (g)	250 ppm Wt. (% of controls)	250 ppm No. of Survivors	500 ppm Av. Wt. (g)	500 ppm Wt. (% of controls)	500 ppm No. of Survivors	1,000 ppm Av. Wt. (g)	1,000 ppm Wt. (% of controls)	1,000 ppm No. of Survivors
1	18.2	60	18.2	100	60	18.5	102	60	18.6	102	60
2	20.2	60	20.5	102	60	20.5	102	60	20.7	103	60
3	21.3	60	21.7	102	60	21.8	102	60	21.9	103	60
4	22.6	60	22.6	100	60	22.5	100	60	22.7	100	60
5	23.6	60	23.6	100	60	23.5	100	60	23.6	100	60
6	24.6	60	24.5	100	60	24.3	99	60	24.5	100	60
7	25.2	60	25.3	100	60	25.1	100	60	25.3	100	60
8	26.1	60	25.8	99	60	25.8	99	60	25.8	99	60
9	27.0	60	26.6	99	60	26.5	98	60	26.4	98	60
10	28.2	60	27.8	99	60	27.2	97	60	27.2	97	60
11	28.6	60	28.3	99	60	27.8	97	59	27.8	97	60
12	29.4	60	29.0	99	60	28.4	97	59	28.4	97	60
13	30.3	60	29.8	98	60	28.7	95	59	28.9	95	60
17	33.3	60	32.8	99	60	32.1	96	59	31.3	94	59
21	35.8	60	34.9	98	60	34.2	96	59	33.5	94	59
25	36.2	60	35.3	98	59	34.4	95	59	33.6	93	58
29	37.8	60	35.9	95	59	35.2	93	59	34.3	91	58
33	40.6	60	39.1	96	59	38.5	95	59	36.8	91	58
37	41.1	60	40.6	99	59	40.0	97	59	37.3	91	58
41	41.9	60	40.8	97	59	40.0	96	59	38.0	91	58
45	43.9	60	42.7	97	59	41.7	95	59	39.2	89	58
49	45.1	60	44.1	98	59	43.0	95	59	40.3	89	58
53	46.8	60	45.8	98	59	44.6	95	59	42.1	90	58
57	49.1	57	47.0	96	59	45.8	93	59	42.7	87	58
61	49.8	57	47.5	95	59	46.8	94	59	43.0	86	58
65[a]	50.5	57	48.1	95	58	48.1	95	59	43.5	86	58
69	49.9	48	48.3	97	49	47.3	95	49	43.1	86	48
73	51.2	48	48.4	95	49	47.6	93	48	43.4	85	48
77	53.2	47	50.2	94	48	48.7	92	48	44.4	84	48
81	52.5	47	50.1	95	48	47.8	91	48	43.2	82	47
85	51.7	46	49.0	95	48	46.8	91	47	42.5	82	45
89	51.2	44	49.3	96	45	46.6	91	46	42.5	83	43
93	51.0	43	48.3	95	45	45.2	89	44	42.0	82	41
97	50.9	43	49.7	98	42	45.9	90	41	42.0	83	39
101	50.2	43	46.7	93	41	45.0	90	38	41.1	82	36
104	50.7	40	46.4	92	38	46.0	91	36	41.6	82	35
Mean for weeks											
1-13	25.0		24.9	100		24.7	99		24.8	99	
14-52	39.5		38.4	97		37.7	95		36.0	91	
53-104	50.6		48.2	95		46.6	92		42.7	84	

[a] Interim evaluation occurred.

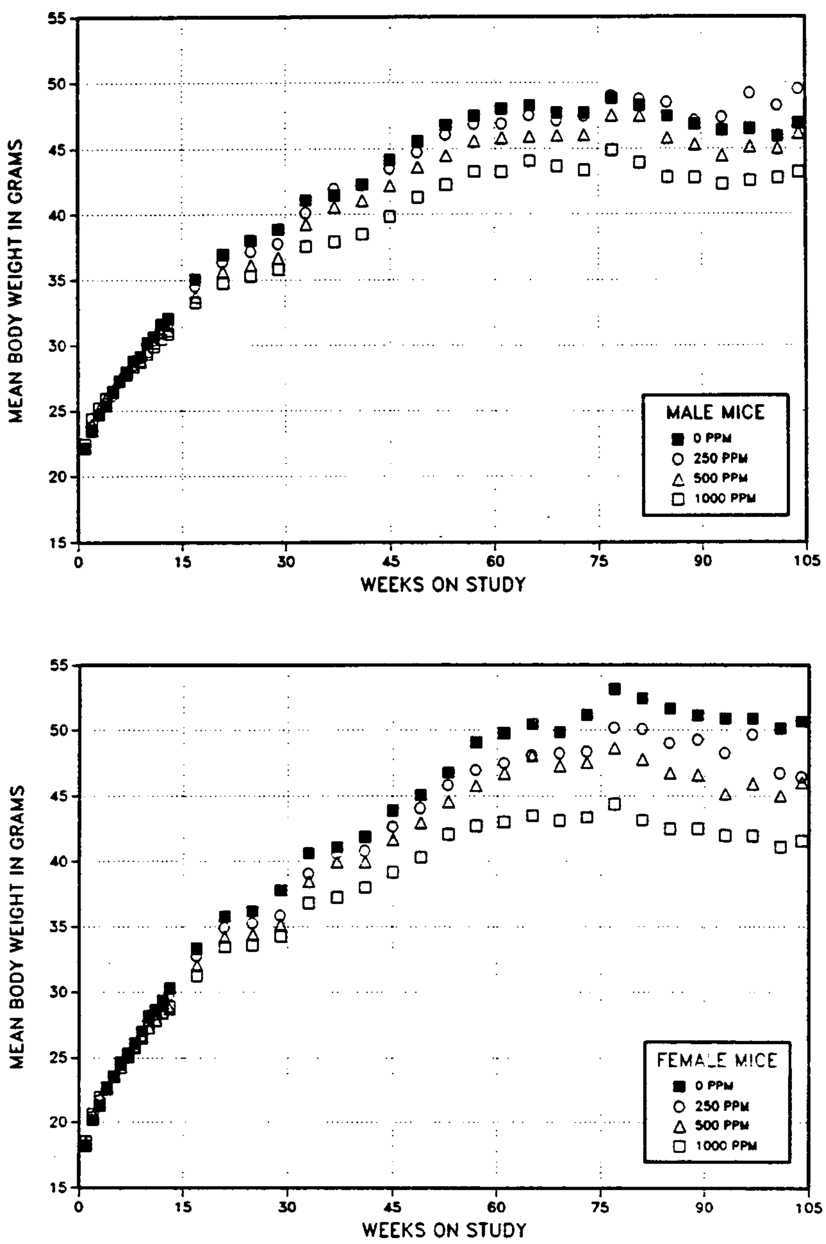


FIGURE 4
Growth Curves for Male and Female Mice Administered 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) in Feed for 2 Years

Hematology and Clinical Chemistry

Significantly lower hematocrit level, hemoglobin concentration, and erythrocyte count in 1,000 ppm males at 15 months were considered evidence of a mild normocytic normochromic nonresponsive anemia (Table G11). These decreases were similar to those that occurred in rats. Significantly decreased total leukocyte counts occurred in 500 and 1,000 ppm male mice at the 15-month interim evaluation.

Serum alkaline phosphatase (ALP) activities in 1,000 ppm males were slightly but significantly greater than those of the controls at 3 and 9 months (Tables G9 and G10). While ALP activity in 1,000 ppm males was numerically greater than that in controls at 15 months, the difference was not statistically significant. The ALP activity in 1,000 ppm females at 9 months was significantly greater than that in controls. Serum levels of total bilirubin in 250, 500, and 1,000 ppm males were significantly greater than those in controls at 9 and 15 months. At 9 months, the serum total bilirubin level in 250 ppm males was also significantly greater. These findings are consistent with hepatocellular damage.

Pathology and Statistical Evaluation

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions in the liver and bone marrow. 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 the neoplasms mentioned in this section are presented in Appendix C for male mice and Appendix D for female mice.

Liver: At the 15-month interim evaluation, the relative liver weight of 1,000 ppm females was greater than that of controls due to a decrease in mean body weight in this group (Table F6). Absolute and relative liver weights of all other exposed male and female mice were similar to those of the controls. The incidence and severity of cytoplasmic vacuolization occurred with a negative trend in male mice (lipid accumulation was characterized as cytoplasmic vacuolization at 15 months, and as fatty change at 2 years, based on criteria discussed previously on page 41 in the rat study) (Tables 17, C3, and C5). An eosinophilic focus was present in one 500 ppm male at 15 months. At the end of the study, the incidences of fatty change, clear cell and eosinophilic foci, and hepatocellular adenoma or carcinoma (combined) all occurred with negative trends in male mice. Most of the negative trends were statistically significant and most occurrences in 1,000 ppm males were significant by pairwise comparison. A basophilic focus was present in one 500 ppm male.

Bone marrow: Myelofibrosis was present in all groups of females with a significant positive trend (0 ppm, 21/51; 250 ppm, 18/50; 500 ppm, 23/50; 1,000 ppm, 34/50; Table D4) and the incidence in 1,000 ppm females was significant by pairwise comparison.

GENETIC TOXICOLOGY

TBBC (33 to 10,000 μg/plate) was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 when tested in a pre-incubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Table E1; Zeiger *et al.*, 1987). A precipitate was observed on plates treated with 333 μg or greater TBBC. In cytogenetic tests with cultured Chinese hamster ovary cells, TBBC induced sister chromatid exchanges with and without S9, at doses which induced cell cycle delay (Table E2). No induction of chromosomal aberrations was observed in these cells, with or without S9 (Table E3). Because of TBBC-induced cell cycle delay, cultures analyzed for chromosomal aberrations were incubated for 20.5 hours, rather than the usual 12 hours, to allow sufficient cells to accumulate for harvest.

TABLE 17
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Male Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)

Dose (ppm)	0	250	500	1,000
15-Month Interim Evaluation				
Liver[a]	10	10	10	10
Cytoplasmic Vacuolization[b]	6 (2.7)[c]	2 (2.0)	3 (2.3)	1* (1.0)
Eosinophilic Focus	0	0	1	0
Hepatocellular Adenoma	0	2	4	2
2-Year Study				
Liver	50	50	50	50
Fatty Change	19 (1.9)	17 (2.0)	5**(2.0)	6**(1.0)
Clear Cell Focus	6	5	2	0*
Eosinophilic Focus	2	3	2	0
Basophilic Focus	0	0	1	0
Focus, Any Type	8	8	5	0**
Hepatocellular Adenoma or Carcinoma[d]				
Overall rate[e]	25/50 (50%)	30/50 (60%)	27/50 (54%)	16/50 (32%)
Adjusted rate[f]	55.4%	62.4%	54.0%	34.7%
Terminal rate[g]	22/42 (52%)	24/42 (57%)	26/49 (53%)	15/45 (33%)
First incidence (days)	620	489	682	638
Logistic regression test[h]	P=0.018N	P=0.221	P=0.471	P=0.046N

* Significantly different (P≤0.05) from the control group by the Fisher exact test (15-month interim evaluation) or the logistic regression test (2-year study)
** P≤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)
[d] Historical incidence for 2-year feed studies with untreated control groups (mean ± standard deviation): 485/1,366 (35.5% ± 14.3%); range 10%-68%
[e] Number of animals with neoplasm per number of animals with liver examined microscopically
[f] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[g] Observed incidence at terminal kill
[h] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The logistic regression test regards these neoplasms as nonfatal. A negative trend or lower incidence in an exposed group is indicated by N.

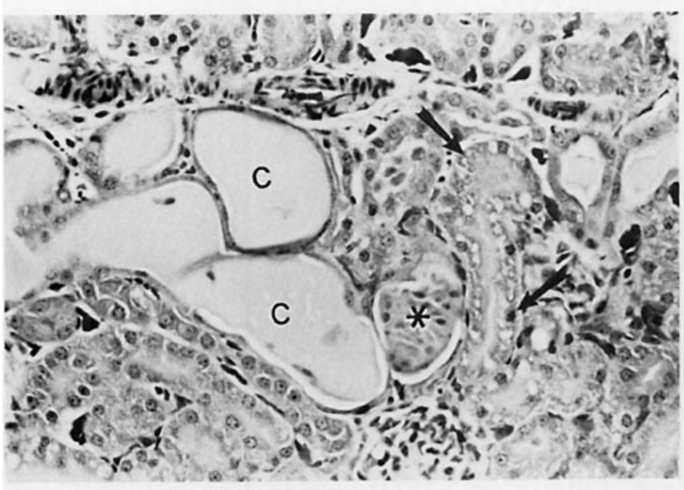


Plate 1
Kidney of a female F344/N rat receiving 10,000 ppm 4,4′-thiobis(6-*t*-butyl-*m*-cresol) in the 15-day feed study. A segment of a proximal convoluted tubule with flattened epithelium is distended by a hyaline cast (C). Note the adjacent tubule filled with exfoliated necrotic cells (*) and other tubules with vacuolated epithelial cells and pyknotic nuclei (arrows). H&E, 80×

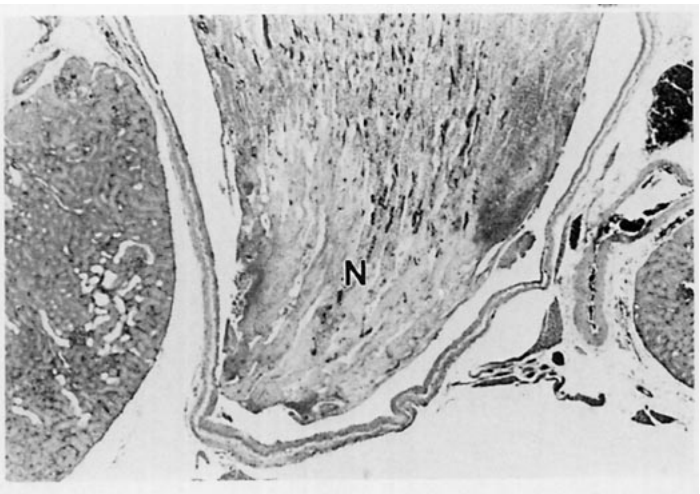


Plate 2
Kidney of another female F344/N rat receiving 10,000 ppm 4,4′-thiobis(6-*t*-butyl-*m*-cresol) in the 15-day feed study. Note the coagulation necrosis of the renal papilla (N). H&E, 10×

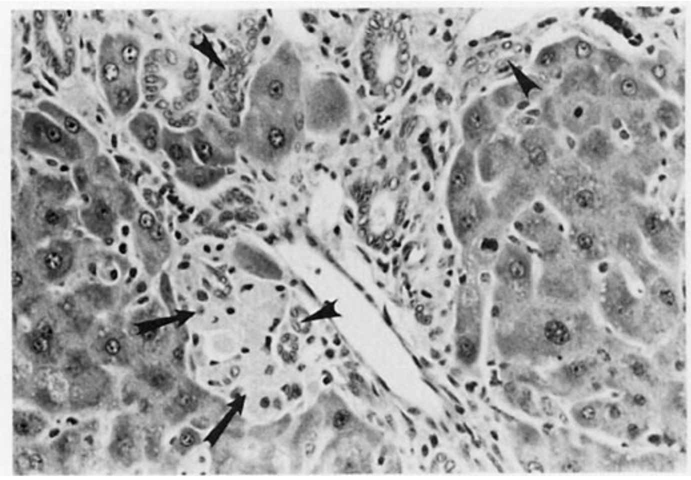


Plate 3
Liver of a male F344/N rat receiving 5,000 ppm 4,4′-thiobis(6-*t*-butyl-*m*-cresol) in the 13-week feed study. Note the accumulation of enlarged Kupffer cells in the hepatic sinusoids and portal area (arrows) and proliferation of small bile ductules (arrow heads). H&E, 80×

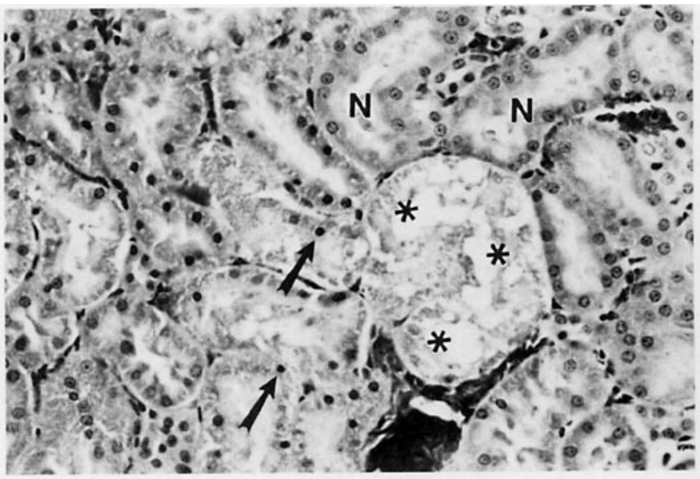


Plate 4
Kidney of a male F344/N rat receiving 5,000 ppm 4,4′-thiobis(6-*t*-butyl-*m*-cresol) in the 13-week feed study. The segment of proximal convoluted tubule in the center of the field exhibits complete necrosis of the epithelium (*). Adjacent tubules exhibit necrosis of individual cells which have pyknotic nuclei (arrows). Compare with normal tubule epithelium (N). H&E, 80×

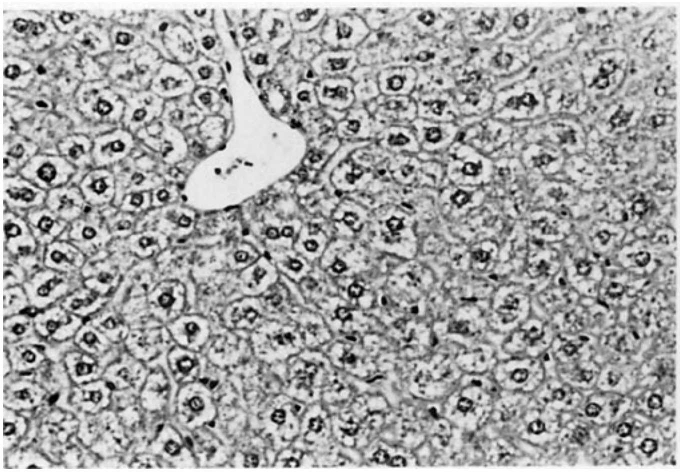


PLATE 5
Liver of a control male $B6C3F_1$ mouse in the 13-week feed study of 4,4′-thiobis(6-*t*-butyl-*m*-cresol). Compare with Plate 6. H&E, 80×

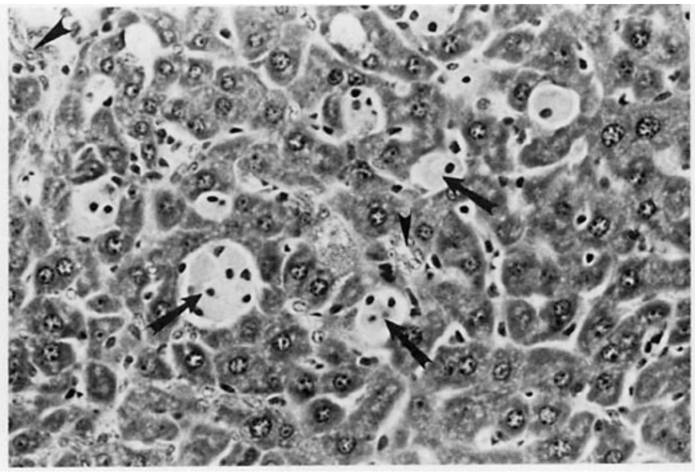


PLATE 6
Liver of a male $B6C3F_1$ mouse receiving 2,500 ppm 4,4′-thiobis(6-*t*-butyl-*m*-cresol) in the 13-week feed study. Note the scattered individual and small clusters of enlarged Kupffer cells (arrows) and the proliferation of small bile ductules (arrow heads). The hepatocyte nuclei are larger than normal and the cytoplasm contains an increased amount of basophilic material (rough endoplasmic reticulum). H&E, 80×

DISCUSSION AND CONCLUSIONS

4,4′-Thiobis(6-*t*-butyl-*m*-cresol) (TBBC) is used in the rubber and plastics industries as an antioxidant and as a stabilizer in polyethylene and polyolefin food packaging materials. Because of concern regarding the elevated cancer risk of workers in the rubber industry, the National Cancer Institute nominated TBBC for toxicology and carcinogenesis studies as a representative of the sulfur-containing class of antioxidants used in rubber processing. Because food packaging appeared to represent the most widespread potential for human exposure, the oral route of administration was chosen for the 15-day, 13-week, and 2-year studies in F344/N rats and B6C3F$_1$ mice.

The principal toxic effects associated with the administration of TBBC in the present studies occurred in the liver and kidney of rats and mice. With the exception of the renal lesions observed in the 15-day and 13-week studies, these findings are in agreement with the few studies reported in the literature. Birnbaum *et al.* (1983) reported that the liver was the major site of metabolism of TBBC in rats and that the compound was excreted primarily in the bile. In a 30-day feed study in rats, 2,500 ppm TBBC produced increased liver weight and growth retardation; rats fed diets containing 500 ppm for 90 days displayed only reduced feed consumption and slight growth retardation (Lefaux, 1968). A dose-related increase in liver weight accompanied by a slight increase in the number of Kupffer cells was reported in females exposed to 200 mg/kg in a study in which mice were administered 10, 100, or 200 mg/kg daily by gavage for 14 days (Munson *et al.*, 1988). In the NTP 15-day studies in rats or mice receiving TBBC in feed at doses ranging from 1,000 to 25,000 ppm, liver toxicity was not observed in surviving animals. However, in the NTP 13-week studies in rats, absolute and relative liver weights were significantly greater in females receiving 5,000 ppm than in controls. Males and females in the 2,500 and 5,000 ppm groups exhibited Kupffer cell hypertrophy, hepatocyte necrosis, and bile duct hyperplasia. In addition, males and females exposed to 5,000 ppm TBBC also exhibited centrilobular hepatocyte hypertrophy. Consistent with these histopathologic findings in the 13-week rat studies, there were significant elevations in serum levels of alanine aminotransferase (ALT) and alkaline phosphatase (ALP). Increased levels of ALT are usually associated with damage to hepatocytes; increases in ALP are usually associated with biliary disease. Male and female rats receiving 5,000 ppm in these studies exhibited a significant increase in size and number of macrophages in the mesenteric lymph nodes; a lesser, but similar response occurred in 2,500 ppm rats.

The 13-week NTP study in mice also elicited hepatotoxicity in 2,500 ppm males and females as exhibited by slight but significant increases in absolute and relative liver weights and the presence of Kupffer cell hypertrophy and bile duct hyperplasia. The response in rats at the same exposure level (2,500 ppm) was similar, except that liver weights in 2,500 ppm rats were unaffected and necrosis and centrilobular hypertrophy were observed in rats but not in mice. Based on average daily feed consumption, 2,500 ppm rats ingested roughly one-third as much TBBC on a body weight basis as mice. Thus, the liver of rats may be more sensitive than that of mice to the effects of this chemical. Additionally, there was a mild increase in size and number of macrophages in mesenteric lymph nodes of male and female mice administered 2,500 ppm; this response was similar to that observed in 2,500 ppm rats.

In the 2-year rat study, the highest exposure level (2,500 ppm TBBC) produced liver toxicity. At this exposure level, males and females exhibited increases in liver weights, Kupffer cell hypertrophy, cytoplasmic vacuolization, and basophilic and mixed cell foci at the 15-month interim evaluation and at the end of the 2-year study. In addition, marked significant increases in serum ALT and sorbitol dehydrogenase activities (SDH) occurred in males and females at the 15-month evaluation; these cytoplasmic enzymes are released into the blood following hepatocellular injury. The mild but significant increases in ALP which occurred in males in various exposure groups at the 3-, 9-, and 15-month evaluations are indicative of disturbances involving the hepatobiliary system. This increase did not occur in females. Although certain liver responses occurred in males and females, liver weight increase was more pronounced in females, there was a strong significant increase in the incidence of cytoplasmic vacuolization in females but not in males, and mixed cell foci occurred in twice as many 2,500 ppm females as 2,500 ppm males. Thus, the preponderance of these responses occurred in females.

The incidence of hepatocellular adenoma or carcinoma (combined) was slightly increased in male rats administered 2,500 ppm TBBC (0 ppm, 1/50; 500 ppm, 3/50; 1,000 ppm, 3/50; 2,500 ppm, 5/49), but the increased incidence was not significant and did not exceed the range of 0% to 10% in historical control male rats. Furthermore, the incidences of these neoplasms were not increased in females, despite the fact that females demonstrated a greater number of different nonneoplastic responses. Therefore, the incidence of hepatocellular adenoma or carcinoma (combined) in male rats is not considered a carcinogenic response to TBBC.

In contrast to the findings in the 13-week study at 2,500 ppm, liver weights of mice were unaffected and there were no microscopic findings of hepatotoxicity in mice exposed to 1,000 ppm TBBC in feed for 2 years. Since 1,000 ppm male and female mice actually had a greater average daily ingestion of TBBC on a mg/kg body weight basis than did rats exposed to 2,500 ppm TBBC, the lack of microscopic findings in mice may indicate (as appeared to be the case in the 13-week studies) a higher degree of liver sensitivity in rats. This conclusion is strengthened by the marked significant increase in ALT and SDH found in rats but not mice. Total bilirubin in 1,000 ppm male mice was slightly but significantly greater than that in controls at 9 and 15 months. This response did not occur in female mice or in rats. In addition, the serum activity of ALP was significantly higher in male and female mice at various exposure levels and time points; these increases were milder in degree but similar to those that occurred in the rats. Increases in serum levels of total bilirubin would be consistent with either cholestasis or a liver function disorder in which circulating bilirubin could not be removed by the liver for conjugation and excretion. Increases in both ALP activity and total bilirubin concentration would be consistent with cholestasis. However, increases in total bilirubin concentration related to cholestasis are usually accompanied by increases in direct bilirubin, which did not occur in the present studies. In males, liver lesions which occurred with a significant negative trend included fatty change, clear cell foci, and hepatocellular adenoma or carcinoma (combined). The significant negative trends were considered to be related to the administration of TBBC. In 1,000 ppm male mice, the incidence of hepatocellular adenoma or carcinoma (combined) was significantly lower than that of controls by pairwise comparison. This result may be due to the reduction in mean body weight, since a significant positive association has been found between liver neoplasm prevalence and body weight in male $B6C3F_1$ mice (Rao *et al.*, 1990).

Evidence of kidney toxicity was present in rats and mice in the NTP 15-day studies and in rats in the 13-week study. In 10,000 ppm rats in the 15-day study, necrosis of the papilla was observed in one female and two males and focal necrosis of the tubules was observed in four males and seven females. Eight male mice and three female mice receiving 5,000 ppm in the 15-day study had tubule necrosis. Following 13 weeks of exposure, pigmentation and degeneration of the renal cortical tubule epithelial cells were present in male and female rats receiving 2,500 or 5,000 ppm; mild to moderate cortical tubule necrosis was also found in 5,000 ppm males and females. These lesions appear to be related to the administration of TBBC. Kidney lesions were not reported in the feed studies summarized by Lefaux (1968) in which rats were exposed to 500 or 2,500 ppm for 30 days and 50 or 500 ppm for 90 days. In the present NTP 2-year rat study, chronic nephropathy common in aging rats was found in nearly all animals. However, the severity of nephropathy in 2,500 ppm females was significantly greater than that in the control group, and the increase was attributed to the administration of TBBC. In remaining female exposure groups and in all exposed males, the severity of nephropathy was similar to that of the controls.

In the 13-week NTP studies, TBBC again affected hematology parameters in rats and mice. Significant decreases in hemoglobin and hematocrit values occurred in male rats and male and female mice; mean erythrocyte volume values were significantly lower in rats and mice; erythrocyte counts were significantly lower in mice but not in rats; and neutrophil counts were significantly higher in rats but not in mice.

In the 2-year study, results of hematocrit and hemoglobin analyses performed on two sets of male rats evaluated at 15 months were conflicting. However, the results in each set of females indicated significant decreases; male mice also had a significant decrease in these parameters and in erythrocyte counts.

The significant increases in platelets which occurred mainly in 2,500 ppm male and female rats in the 2-year study are consistent with a reactive thrombocytosis. This condition has been observed with inflammations, trauma, surgery, hyposplenic or asplenic states, malignancies, acute blood loss, and hyperadrenocorticism.

The neurotoxicity evaluation in the 13-week study demonstrated statistically significant increases in grip strength in exposed rats, which did not occur in the 2-year study. While these evaluations were performed on animals of the same strain and age using the same methodology, they were conducted at two different laboratories. Therefore, the toxicologic significance of the positive findings in the 13-week study is uncertain. Further, no significant effects of TBBC were found on motor nerve excitability or conduction, neuromuscular transmission, muscle contractility, or neuropathology.

Although the rate of survival was less than 50% in 1,000 ppm male rats (42%) and 2,500 ppm male rats (36%), the survival rate for the control group was only 36% and reduced survival does not appear to be chemical related. Further, 50% of the 2,500 ppm males survived until week 97 and 50% of the 1,000 ppm male rats survived until week 101, allowing adequate time for the possible development of neoplasms. Some degree of chemical-related toxicity in 2,500 ppm rats was observed; mean body weights of rats in this group were slightly but consistently reduced, despite the fact that feed consumption by this group was similar to that by the controls. The final mean body weight of 2,500 ppm males was 5% less than that of the controls; the mean body weight of females exposed to 2,500 ppm TBBC dropped to 14% below that of the controls at week 65 and was 6% lower than that of the controls at the end of the study. There was also enough evidence of liver toxicity in the 2,500 ppm male and female rats in the 2-year study to indicate that a greater exposure level would have compromised the sensitivity of the study to detect neoplasia. In addition, exposure to 5,000 ppm TBBC in the 13-week study resulted in a significant increase in absolute and relative liver weight in females, marked reductions in final mean body weights and feed consumption in both males and females, and liver and kidney toxicity in males and females, as mentioned earlier. These observations indicate that rats could not have tolerated an exposure level much higher than 2,500 ppm.

Although no overt organ toxicity was observed in mice in the highest exposure group in the 2-year study (1,000 ppm), the reductions in final mean body weights were indicative of a toxic response to TBBC. The final mean body weights of 1,000 ppm male and female mice were 8% and 18% lower than that of the controls, respectively; feed consumption by the 1,000 ppm males was similar to that by the controls. In the 13-week study, 2,500 ppm males had a final mean body weight 15% lower than that of the controls and the final mean body weight of 2,500 ppm females was 22% lower than that of the controls. This exposure level also produced Kupffer cell hypertrophy and bile duct hyperplasia in males and females. At 15 months, males had a significant increase in total bilirubin at all exposure levels and 500 and 1,000 ppm females had a significant elevation in ALP. It is probable that an exposure level greater than 1,000 ppm for 2 years would have caused severe weight loss and liver toxicity in mice.

CONCLUSIONS

Under the conditions of these 2-year feed studies, there was *no evidence of carcinogenic activity** of 4,4′-thiobis(6-*t*-butyl-*m*-cresol) in male or female F344/N rats administered 500, 1,000, or 2,500 ppm or in male or female B6C3F$_1$ mice administered 250, 500, or 1,000 ppm.

Nonneoplastic lesions associated with exposure to TBBC included: Kupffer cell hypertrophy, cytoplasmic vacuolization, and mixed cell foci in the liver of male and female rats, fatty change in the liver of female rats, and an increase in the severity of nephropathy in the kidney of female rats. In addition, decreased incidences of fibroadenoma, adenoma, or carcinoma (combined) were observed in the mammary gland of female rats. Decreases also occurred in the incidences of fatty change, clear cell foci, and adenoma or carcinoma (combined) in the liver of male mice.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 13.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR FEED STUDY OF 4,4′-THIOBIS(6-*t*-BUTYL-*m*-CRESOL)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	7	10
Early deaths				
Moribund	23	14	22	23
Natural deaths	9	8	6	9
Survivors				
Terminal sacrifice	18	28	22	18
Animals examined microscopically	60	60	57[b]	59[c]
15-Month Interim Evaluation				
Alimentary System				
Pharynx		(1)		
Squamous cell papilloma		1 (100%)		
Cardiovascular System				
None				
Endocrine System				
Adrenal medulla	(10)	(10)	(7)	(10)
Pheochromocytoma benign	1 (10%)	1 (10%)		1 (10%)
Islets, pancreatic	(10)	(10)	(7)	(10)
Adenoma		1 (10%)		
Pituitary gland	(10)	(10)	(7)	(10)
Pars distalis, adenoma	1 (10%)	2 (20%)	1 (14%)	
Thyroid gland	(10)	(10)	(7)	(10)
C-cell, adenoma				1 (10%)
Follicular cell, adenoma		1 (10%)		
General Body System				
None				
Genital System				
Epididymis	(10)	(10)	(7)	(10)
Testes	(10)	(10)	(7)	(10)
Bilateral, interstitial cell, adenoma	5 (50%)	5 (50%)	2 (29%)	3 (30%)
Interstitial cell, adenoma	1 (10%)	3 (30%)	4 (57%)	3 (30%)
Hematopoietic System				
None				
Integumentary System				
None				

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
15-Month Interim Evaluation (continued)				
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
None				
Special Senses System				
None				
Urinary System				
None				
Systemic Lesions				
Multiple organs[d]	(10)	(10)	(7)	(10)
Mesothelioma benign				1 (10%)
2-Year Study				
Alimentary System				
Intestine large, colon	(50)	(50)	(50)	(48)
Polyp adenomatous		1 (2%)		
Intestine large, rectum	(50)	(50)	(50)	(48)
Adenocarcinoma		1 (2%)		
Intestine large, cecum	(50)	(50)	(50)	(49)
Intestine small, jejunum	(50)	(50)	(50)	(49)
Adenocarcinoma			1 (2%)	
Intestine small, ileum	(50)	(49)	(50)	(49)
Carcinoma, metastatic, kidney				1 (2%)
Liver	(50)	(50)	(50)	(49)
Carcinoma, metastatic, kidney				1 (2%)
Hepatocellular carcinoma		1 (2%)		1 (2%)
Hepatocellular adenoma	1 (2%)	2 (4%)	2 (4%)	4 (8%)
Hepatocellular adenoma, multiple			1 (2%)	
Histiocytic sarcoma			1 (2%)	
Mesentery	(11)	(7)	(10)	(9)
Histiocytic sarcoma			1 (10%)	
Liposarcoma		1 (14%)		
Pancreas	(50)	(50)	(50)	(49)
Carcinoma, metastatic, kidney				1 (2%)
Histiocytic sarcoma			1 (2%)	
Pharynx		(1)		
Palate, squamous cell papilloma		1 (100%)		

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-t-Butyl-m-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Salivary glands	(49)	(50)	(50)	(49)
Carcinoma, metastatic, kidney				1 (2%)
Stomach, forestomach	(50)	(50)	(50)	(49)
Leiomyosarcoma	1 (2%)			
Stomach, glandular	(50)	(50)	(50)	(49)
Tongue	(1)	(2)	(1)	(1)
Carcinoma, metastatic, kidney				1 (100%)
Squamous cell papilloma	1 (100%)	1 (50%)	1 (100%)	
Tooth	(1)			
Peridontal tissue, fibrosarcoma	1 (100%)			
Cardiovascular System				
Heart	(50)	(50)	(50)	(49)
Carcinoma, metastatic, kidney				1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(49)
Carcinoma, metastatic, kidney				1 (2%)
Adrenal medulla	(50)	(50)	(50)	(49)
Carcinoma, metastatic, kidney				1 (2%)
Pheochromocytoma malignant			1 (2%)	
Pheochromocytoma benign	11 (22%)	12 (24%)	7 (14%)	9 (18%)
Bilateral, pheochromocytoma malignant				1 (2%)
Bilateral, pheochromocytoma benign	3 (6%)	2 (4%)	3 (6%)	
Islets, pancreatic	(50)	(50)	(50)	(49)
Adenoma	2 (4%)			
Carcinoma		1 (2%)	1 (2%)	
Parathyroid gland	(47)	(45)	(47)	(46)
Adenoma	2 (4%)			1 (2%)
Pituitary gland	(50)	(49)	(50)	(49)
Histiocytic sarcoma			1 (2%)	
Pars distalis, adenoma	14 (28%)	10 (20%)	10 (20%)	9 (18%)
Pars distalis, adenoma, multiple			2 (4%)	1 (2%)
Pars intermedia, carcinoma	1 (2%)			
Thyroid gland	(50)	(50)	(50)	(49)
Carcinoma, metastatic, kidney				1 (2%)
Bilateral, C-cell, adenoma	1 (2%)			
C-cell, adenoma	4 (8%)	3 (6%)	8 (16%)	2 (4%)
C-cell, carcinoma				1 (2%)
Follicular cell, adenoma		2 (4%)	1 (2%)	
Follicular cell, carcinoma	1 (2%)		1 (2%)	1 (2%)
General Body System				
None				

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
2-Year Study (continued)				
Genital System				
Epididymis	(50)	(50)	(50)	(49)
Preputial gland	(50)	(49)	(49)	(49)
Adenoma	1 (2%)	4 (8%)	2 (4%)	4 (8%)
Carcinoma	2 (4%)	2 (4%)		
Histiocytic sarcoma			1 (2%)	
Bilateral, adenoma		1 (2%)	1 (2%)	
Prostate	(49)	(50)	(50)	(48)
Carcinoma, metastatic, kidney				1 (2%)
Seminal vesicle	(49)	(50)	(50)	(48)
Testes	(50)	(49)	(50)	(49)
Bilateral, interstitial cell, adenoma	36 (72%)	38 (78%)	42 (84%)	31 (63%)
Interstitial cell, adenoma	10 (20%)	6 (12%)	5 (10%)	13 (27%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(49)
Femoral, histiocytic sarcoma			1 (2%)	
Maxilla, histiocytic sarcoma			1 (2%)	
Lymph node	(24)	(19)	(26)	(30)
Mediastinal, carcinoma, metastatic, kidney				1 (3%)
Mediastinal, histiocytic sarcoma			1 (4%)	
Pancreatic, histiocytic sarcoma			1 (4%)	
Renal, leiomyosarcoma, metastatic, stomach, forestomach	1 (4%)			
Lymph node, mandibular	(48)	(50)	(50)	(49)
Histiocytic sarcoma			1 (2%)	
Lymph node, mesenteric	(50)	(50)	(49)	(48)
Carcinoma, metastatic, kidney				1 (2%)
Histiocytic sarcoma			1 (2%)	
Spleen	(50)	(50)	(49)	(49)
Fibrosarcoma			1 (2%)	
Histiocytic sarcoma			1 (2%)	
Thymus	(48)	(46)	(46)	(46)
Integumentary System				
Mammary gland	(47)	(47)	(46)	(49)
Adenoacanthoma	1 (2%)			
Fibroadenoma	3 (6%)	4 (9%)		2 (4%)
Skin	(50)	(50)	(50)	(48)
Basosquamous tumor benign	1 (2%)			
Histiocytic sarcoma			1 (2%)	
Keratoacanthoma	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Squamous cell papilloma	2 (4%)	1 (2%)		1 (2%)
Sebaceous gland, adenocarcinoma			1 (2%)	
Sebaceous gland, adenoma	1 (2%)			
Subcutaneous tissue, fibroma	5 (10%)	1 (2%)	4 (8%)	1 (2%)
Subcutaneous tissue, fibroma, multiple				1 (2%)
Subcutaneous tissue, fibrosarcoma		2 (4%)		

Table A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-t-Butyl-m-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
2-Year Study (continued)				
Integumentary System (continued)				
Subcutaneous tissue, hemangioma				1 (2%)
Subcutaneous tissue, neurofibroma		1 (2%)	1 (2%)	1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(49)
Cranium, chondrosarcoma		1 (2%)		
Cranium, osteosarcoma			1 (2%)	
Femur, histiocytic sarcoma			1 (2%)	
Femur, osteosarcoma			1 (2%)	
Maxilla, histiocytic sarcoma			1 (2%)	
Skeletal muscle	(50)	(50)	(50)	(49)
Histiocytic sarcoma			1 (2%)	
Osteosarcoma, metastatic, bone			1 (2%)	
Nervous System				
Brain	(50)	(50)	(50)	(49)
Astrocytoma malignant		2 (4%)		2 (4%)
Carcinoma, metastatic, pituitary gland	1 (2%)			
Histiocytic sarcoma			1 (2%)	
Oligodendroglioma malignant	1 (2%)			
Spinal cord	(2)	(2)	(3)	
Astrocytoma malignant	1 (50%)			
Respiratory System				
Lung	(49)	(50)	(50)	(49)
Adenocarcinoma, metastatic, Zymbal's gland	1 (2%)			
Alveolar/bronchiolar adenoma		2 (4%)		
Alveolar/bronchiolar carcinoma	1 (2%)	1 (2%)		
Carcinoma, metastatic, kidney				1 (2%)
Histiocytic sarcoma			1 (2%)	
Osteosarcoma, metastatic, bone			1 (2%)	
Pheochromocytoma malignant, metastatic, adrenal medulla				1 (2%)
Mediastinum, schwannoma malignant	1 (2%)			
Nose	(50)	(50)	(50)	(49)
Carcinoma, metastatic, kidney				1 (2%)
Chondrosarcoma, metastatic, bone		1 (2%)		
Squamous cell carcinoma			2 (4%)	
Special Senses System				
Ear	(1)	(1)	(2)	
Fibrosarcoma		1 (100%)		
Eye	(3)	(2)	(5)	
Lids, left, fibroma			1 (20%)	

Table A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
2-Year Study (continued)				
Special Senses System (continued)				
Harderian gland	(49)	(49)	(50)	(48)
Zymbal's gland	(1)	(1)		
Adenocarcinoma	1 (100%)	1 (100%)		
Urinary System				
Kidney	(50)	(50)	(50)	(49)
Renal tubule, carcinoma				1 (2%)
Urinary bladder	(49)	(50)	(50)	(48)
Systemic Lesions				
Multiple organs	(50)	(50)	(50)	(49)
Histiocytic sarcoma			1 (2%)	
Leukemia mononuclear	30 (60%)	36 (72%)	34 (68%)	33 (67%)
Mesothelioma malignant	2 (4%)	1 (2%)		
Neoplasm Summary				
Total animals with primary neoplasms[e]				
15-Month interim evaluation	7	9	7	7
2-Year study	49	49	50	49
Total primary neoplasms				
15-Month interim evaluation	8	14	7	9
2-Year study	143	144	137	123
Total animals with benign neoplasms				
15-Month interim evaluation	7	9	7	7
2-Year study	49	47	50	46
Total benign neoplasms				
15-Month interim evaluation	8	14	7	9
2-Year study	99	93	92	83
Total animals with malignant neoplasms				
2-Year study	37	41	39	37
Total malignant neoplasms				
2-Year study	44	51	45	40
Total animals with metastatic neoplasms				
2-Year study	3	1	1	2
Total metastatic neoplasms				
2-Year study	3	1	2	15

[a] Number of animals examined microscopically at site and number of animals with neoplasm
[b] Three male rats exposed to 1,000 ppm were killed moribund prior to the 15-month interim evaluation.
[c] One animal discarded due to autolysis.
[d] Number of animals with any tissue examined microscopically
[e] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol): 0 ppm

Number of Days on Study	312	418	443	467	517	530	533	547	564	579	589	596	605	619	621	625	625	625	632	632	633	648	656	660	663
Carcass ID Number	004	025	044	010	038	020	036	026	022	006	012	013	037	005	015	016	021	030	046	048	001	035	047	018	049
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery				+							+		+	+						+	+				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma										X															
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell papilloma																									
Tooth																									
Peridontal tissue, fibrosarcoma																									
Cardiovascular System																									
Blood vessel	+																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign										X											X				
Bilateral, pheochromocytoma benign																						X			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma														X											
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma										X		X	X			X				X	X		X		
Pars intermedia, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																				X					
C-cell, adenoma																									
Follicular cell, carcinoma																									
General Body System																									
None																									

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 0 ppm (continued)

Number of Days on Study	676	678	688	688	723	725	736	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	017	045	032	041	034	011	031	002	003	007	008	009	014	019	023	024	027	028	029	033	039	040	042	043	050	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma													X													1
Mesentery	+						+		+					+		+										11
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue				+																						1
Squamous cell papilloma				X																						1
Tooth					+																					1
Peridontal tissue, fibrosarcoma					X																					1
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign				X							X		X	X		X	X		X	X					X	11
Bilateral, pheochromocytoma benign							X		X																	3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X																						2
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma																	X					X				2
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X	X			X			X				X									X			14
Pars intermedia, carcinoma																				X						1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma																										1
C-cell, adenoma	X						X		X															X		4
Follicular cell, carcinoma																									X	1
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol): 0 ppm (continued)

Number of Days on Study	312	418	443	467	517	530	533	547	564	579	589	596	605	619	621	625	625	625	632	632	633	648	656	660	663
Carcass ID Number	004	025	044	010	038	020	036	026	022	006	012	013	037	005	015	016	021	030	046	048	001	035	047	018	049
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma		X			X		X	X		X		X		X	X		X	X	X			X		X	X
Interstitial cell, adenoma			X	X		X			X		X									X	X				
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+	+		+		+	+			+	+	+			+	+	+	+		+	
Renal, leiomyosarcoma, metastatic, stomach, forestomach										X															
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Adenoacanthoma																									
Fibroadenoma																X		X							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor benign														X											
Keratoacanthoma																									
Squamous cell papilloma							X																		
Sebaceous gland, adenoma															X										
Subcutaneous tissue, fibroma							X										X								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																									
Oligodendroglioma malignant																									
Peripheral nerve			+																						
Spinal cord			+		+																				
Astrocytoma malignant			X																						
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, Zymbal's gland									X																
Alveolar/bronchiolar carcinoma																									
Mediastinum, schwannoma malignant		X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol): 0 ppm (continued)

Number of Days on Study	676	678	688	688	723	725	726	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	017	045	032	041	034	011	031	002	003	007	008	009	014	019	023	024	027	028	029	033	039	040	042	043	050	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X										1
Carcinoma												X														2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	36
Interstitial cell, adenoma	X		X	X																						10
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+		+		+			+			+	+				+	+	+						+	24
Renal, leiomyosarcoma, metastatic, stomach, forestomach																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoacanthoma											X															1
Fibroadenoma													X													3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basosquamous tumor benign																										1
Keratoacanthoma		X																								1
Squamous cell papilloma													X													2
Sebaceous gland, adenoma																										1
Subcutaneous tissue, fibroma												X			X						X					5
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																				X						1
Oligodendroglioma malignant																				X						1
Peripheral nerve																										1
Spinal cord																										2
Astrocytoma malignant																										1
Respiratory System																										
Lung	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, metastatic, Zymbal's gland																										1
Alveolar/bronchiolar carcinoma																						X				1
Mediastinum, schwannoma malignant																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol): 0 ppm (continued)

Number of Days on Study	312	418	443	467	517	530	533	547	564	579	589	596	605	619	621	625	625	625	632	632	633	648	656	660	663
Carcass ID Number	004	025	044	010	038	020	036	026	022	006	012	013	037	005	015	016	021	030	046	048	001	035	047	018	049
Special Senses System																									
Ear																							+		
Eye																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal's gland									+																
Adenocarcinoma									X																
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X	X	X		X	X	X		X		X	X	X			X	X	X	X		X	
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol): 0 ppm (continued)

	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	7	7	8	8	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	6	8	8	8	3	5	6	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Total
Carcass ID Number	1	4	3	4	3	1	3	0	0	0	0	0	1	1	2	2	2	2	2	3	3	4	4	4	5	Tissues/
	7	5	2	1	4	1	1	2	3	7	8	9	4	9	3	4	7	8	9	3	9	0	2	3	0	Tumors
Special Senses System																										
Ear																										1
Eye					+				+		+															3
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Zymbal's gland																										1
Adenocarcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X		X		X			X	X	X	X	X		X	X	X	X	X						X	30
Mesothelioma malignant							X												X							2

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 500 ppm

Number of Days on Study	352	416	452	488	505	513	589	610	625	642	649	649	650	663	669	673	676	677	695	708	712	725	730	730	730
Carcass ID Number	089	088	087	072	080	071	069	107	082	079	101	109	067	087	099	092	084	095	091	065	075	096	061	062	063
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Hepatocellular adenoma																									
Mesentery				+			+												+	+		+			
Liposarcoma				X																					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx																									+
Palate, squamous cell papilloma																									X
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell papilloma																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign										X									X		X				X
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																				X					
Parathyroid gland	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma											X		X		X										
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																	X				X				
Follicular cell, adenoma																									
General Body System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 500 ppm (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	064	066	068	070	073	074	076	078	081	083	085	086	090	093	094	097	098	100	102	103	104	105	106	108	110	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous																									X	1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																									X	1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma				X																						1
Hepatocellular adenoma					X																X					2
Mesentery															+								+			7
Liposarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pharynx																										1
Palate, squamous cell papilloma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue		+																			+					2
Squamous cell papilloma		X																								1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign		X					X			X	X					X						X	X		X	12
Bilateral, pheochromocytoma benign												X	X													2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma					X			X		X			X							X		X			X	10
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma												X														3
Follicular cell, adenoma		X										X														2
General Body System																										
None																										

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol): 500 ppm (continued)

Number of Days on Study	352	416	452	485	505	513	589	610	625	642	649	649	650	663	669	673	676	677	695	708	712	725	730	730	730
Carcass ID Number	089	088	077	072	080	071	069	107	082	079	101	109	067	087	099	092	084	095	091	065	075	096	061	062	063
Genital System																									
Coagulating gland					+																				
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X						X										
Carcinoma																									
Bilateral, 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
Interstitial cell, adenoma		X			X	X	X				X														
Hematopoietic System																									
Blood																		+							
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+					+	+	+			+			+		+	+	+	+	+	+				
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Squamous cell papilloma																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma									X																
Subcutaneous tissue, neurofibroma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cranium, chondrosarcoma												X													
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant															X										
Peripheral nerve																+									
Spinal cord																+					+				
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chondrosarcoma, metastatic, bone												X													
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 500 ppm (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	Total
Carcass ID Number	6	6	6	7	7	7	7	7	8	8	8	8	9	9	9	9	9	0	0	0	0	0	0	0	1	Tissues/
	4	6	8	0	3	4	6	8	1	3	5	6	0	3	4	7	8	0	2	3	4	5	6	8	0	Tumors
Genital System																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma		X		X																						4
Carcinoma								X							X											2
Bilateral, adenoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, interstitial cell, adenoma	X	X	X	X		X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	38
Interstitial cell, adenoma																X										6
Hematopoietic System																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+					+										+		+			+			+	+	19
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Fibroadenoma				X		X			X				X													4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma							X																			1
Squamous cell papilloma						X																				1
Subcutaneous tissue, fibroma														X												1
Subcutaneous tissue, fibrosarcoma														X												2
Subcutaneous tissue, neurofibroma																					X					1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cranium, chondrosarcoma																										1
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																	X									2
Peripheral nerve																										1
Spinal cord																										2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma													X											X		2
Alveolar/bronchiolar carcinoma																							X			1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chondrosarcoma, metastatic, bone																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol): 500 ppm (continued)

Number of Days on Study	352	416	452	488	505	513	589	610	625	642	649	649	650	663	669	673	676	677	695	708	712	725	730	730	730
Carcass ID Number	089	088	077	072	080	071	069	107	082	079	101	119	067	087	099	092	084	095	091	065	075	096	061	062	063
Special Senses System																									
Ear																									
Fibrosarcoma																									
Eye																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Zymbal's gland																									
Adenocarcinoma																									
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	X	X	X	X	X
Mesothelioma malignant																									

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 500 ppm (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	064	066	068	070	073	074	076	078	081	083	085	086	090	093	094	097	098	100	102	103	104	105	106	108	110	Total Tissues/ Tumors
Special Senses System																										
Ear						+																				1
Fibrosarcoma						X																				1
Eye										+							+									2
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Zymbal's gland																									+	1
Adenocarcinoma																									X	1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X			X	X	X	X	X	X				X	X	X		X			X		X	X	X	36
Mesothelioma malignant																							X			1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 1,000 ppm

Number of Days on Study	416	450	466	477	555	561	592	599	604	610	627	633	639	650	652	653	660	688	688	688	695	697	698	703	709
Carcass ID Number	145	144	156	141	152	122	158	149	139	166	163	165	123	164	162	167	151	129	140	148	154	133	131	135	153
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular adenoma, multiple																									
Histiocytic sarcoma																						X			
Mesentery							+		+									+				+			
Histiocytic sarcoma																						X			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																						X			
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell papilloma																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign																									
Bilateral, pheochromocytoma benign																						X			X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																						X			
Pars distalis, adenoma	X	X																					X		
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma			X													X						X	X		
Follicular cell, adenoma																							X		
Follicular cell, carcinoma																									
General Body System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 1,000 ppm (continued)

Number of Days on Study	719	723	725	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	130	159	124	121	125	126	127	128	132	134	136	137	138	142	143	146	147	150	155	157	160	161	168	169	170	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																									X	1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma											X									X						2
Hepatocellular adenoma, multiple								X																		1
Histiocytic sarcoma																										1
Mesentery	+							+						+		+			+			+				10
Histiocytic sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue		+																								1
Squamous cell papilloma		X																								1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																					X					1
Pheochromocytoma benign					X	X	X			X		X			X						X					7
Bilateral, pheochromocytoma benign								X																		3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma															X											1
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Pars distalis, adenoma							X				X	X	X	X	X										X	10
Pars distalis, adenoma, multiple	X							X																		2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X															X		X			X				8
Follicular cell, adenoma																										1
Follicular cell, carcinoma			X																							1
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-t-Butyl-m-Cresol): 1,000 ppm (continued)

Number of Days on Study	4 1 6	4 5 0	4 6 6	4 7 7	5 5 5	5 6 1	5 9 2	5 9 9	6 0 4	6 1 0	6 2 7	6 3 3	6 3 9	6 5 0	6 5 2	6 5 3	6 6 0	6 8 8	6 8 8	6 8 8	6 9 5	6 9 7	6 9 8	7 0 3	7 0 9
Carcass ID Number	1 4 5	1 4 4	1 5 6	1 4 1	1 5 2	1 2 2	1 5 8	1 4 9	1 3 9	1 6 6	1 6 3	1 6 5	1 2 3	1 6 4	1 6 2	1 6 7	1 5 1	1 2 9	1 4 0	1 4 8	1 5 4	1 3 3	1 3 1	1 3 5	1 5 3
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							X		
Histiocytic sarcoma																						X			
Bilateral, 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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, histiocytic sarcoma																						X			
Maxilla, histiocytic sarcoma																						X			
Lymph node				+	+	+	+	+	+	+		+	+			+	+	+			+	+		+	+
Mediastinal, histiocytic sarcoma																						X			
Pancreatic, histiocytic sarcoma																						X			
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																						X			
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Histiocytic sarcoma																						X			
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Histiocytic sarcoma																						X			
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																						X			
Keratoacanthoma																					X				
Sebaceous gland, adenocarcinoma																									
Subcutaneous tissue, fibroma																			X	X	X				
Subcutaneous tissue, neurofibroma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cranium, osteosarcoma			X																						
Femur, histiocytic sarcoma																						X			
Femur, osteosarcoma														X											
Maxilla, histiocytic sarcoma																						X			
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																						X			
Osteosarcoma, metastatic, bone														X											

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol): 1,000 ppm (continued)

Number of Days on Study	719	723	725	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	130	159	124	121	125	126	127	128	132	134	136	137	138	142	143	146	147	150	155	157	160	161	168	169	170	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																	X									2
Histiocytic sarcoma																										1
Bilateral, adenoma																										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	X	X	X	42
Interstitial cell, adenoma																										5
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femoral, histiocytic sarcoma																										1
Maxilla, histiocytic sarcoma																										1
Lymph node	+		+	+			+	+		+	+	+	+							+						26
Mediastinal, histiocytic sarcoma																										1
Pancreatic, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma												X														1
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Keratoacanthoma																										1
Sebaceous gland, adenocarcinoma			X																							1
Subcutaneous tissue, fibroma			X																							4
Subcutaneous tissue, neurofibroma		X																								1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cranium, osteosarcoma																										1
Femur, histiocytic sarcoma																										1
Femur, osteosarcoma																										1
Maxilla, histiocytic sarcoma																										1
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Osteosarcoma, metastatic, bone																										1

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol): 1,000 ppm (continued)

Number of Days on Study	416	450	466	477	555	561	592	599	604	610	627	633	639	650	652	653	660	688	688	688	695	697	698	703	709
Carcass ID Number	145	144	156	141	152	122	158	149	139	166	163	165	123	164	162	167	151	129	140	148	154	133	131	135	153
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																						X			
Peripheral nerve							+						+												
Spinal cord							+						+												
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																						X			
Osteosarcoma, metastatic, bone														X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma											X												X		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear												+	+												
Eye		+												+									+		
Lids, left, fibroma																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																						X			
Leukemia mononuclear				X	X	X	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 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 1,000 ppm (continued)

Number of Days on Study	719	723	725	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	130	159	124	121	125	126	127	128	132	134	136	137	138	142	143	146	147	150	155	157	160	161	168	169	170	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Peripheral nerve	+																									3
Spinal cord	+																									3
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Osteosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										2
Eye											+			+												5
Lids, left, fibroma											X															1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear	X			X	X	X	X	X		X	X	X	X		X	X				X	X		X		X	34

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 2,500 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 2,500 ppm (continued)

Number of Days on Study	677	677	695	695	698	712	723	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	219	220	181	201	187	218	197	186	189	193	194	195	196	202	207	208	209	211	212	214	216	217	222	228	230	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, kidney			X																							1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, kidney			X																							1
Hepatocellular carcinoma					X																					1
Hepatocellular adenoma															X				X							4
Mesentery				+																						9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, kidney			X																							1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, kidney			X																							1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue			+																							1
Carcinoma, metastatic, kidney			X																							1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, kidney			X																							1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, kidney			X																							1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, kidney			X																							1
Pheochromocytoma benign				X	X	X							X						X		X			X		9
Bilateral, pheochromocytoma malignant																							X			1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma									X																	1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma				X							X	X							X							9
Pars distalis, adenoma, multiple																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, kidney			X																							1
C-cell, adenoma									X																X	2
C-cell, carcinoma																										1
Follicular cell, carcinoma																							X			1
General Body System																										
None																										

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 2,500 ppm (continued)

Number of Days on Study	4	4	4	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6
	2	4	8	3	3	5	5	5	6	7	7	0	0	0	2	2	3	4	4	4	5	5	6	7
	3	1	4	3	9	5	5	5	6	1	6	3	4	4	1	5	3	9	9	9	2	6	3	3
Carcass ID Number	1	1	2	1	1	1	2	2	2	2	2	1	2	2	2	1	1	1	2	2	2	2	1	2
	8	9	0	8	9	9	0	1	2	1	2	9	0	1	2	8	8	8	0	0	2	2	9	2
	2	8	3	4	2	0	6	3	4	0	5	9	5	5	1	8	5	3	0	4	3	6	1	7
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X		X		X																
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney																								
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma				X			X		X	X	X	X	X	X				X			X	X	X	X
Interstitial cell, adenoma		X			X	X									X		X		X	X				
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+		+		+		+			+	+	+	+	+	+		+	+	+	+	+	+
Mediastinal, carcinoma, metastatic, kidney																								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney																								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma								X																
Skin	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma					X																			
Squamous cell papilloma															X									
Subcutaneous tissue, fibroma																		X						
Subcutaneous tissue, fibroma, multiple																								
Subcutaneous tissue, hemangioma																								
Subcutaneous tissue, neurofibroma															X									
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant				X																				
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney																								
Pheochromocytoma malignant, metastatic, adrenal medulla																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney																								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 2,500 ppm (continued)

Number of Days on Study	677	677	795	795	798	712	723	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	219	220	181	201	187	218	197	186	189	193	194	195	196	202	207	208	209	211	212	214	216	217	222	228	230	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma				X																						4
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, kidney			X																							1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, interstitial cell, adenoma	X		X			X		X	X	X	X	X	X		X	X	X	X		X	X	X	X	X		31
Interstitial cell, adenoma				X	X		X							X					X						X	13
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+		+			+	+							+	+			+		+		30
Mediastinal, carcinoma, metastatic, kidney			X																							1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, kidney			X																							1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroadenoma											X															2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Keratoacanthoma	X																									2
Squamous cell papilloma																										1
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibroma, multiple																				X						1
Subcutaneous tissue, hemangioma						X																				1
Subcutaneous tissue, neurofibroma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Astrocytoma malignant									X																	2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, kidney			X																							1
Pheochromocytoma malignant, metastatic, adrenal medulla																							X			1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, kidney			X																							1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol): 2,500 ppm (continued)

	4	4	4	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6
Number of Days on Study	2	4	8	3	3	5	5	5	6	7	7	0	0	0	2	2	3	4	4	4	5	5	6	7
	3	1	4	3	9	5	5	5	6	1	6	3	4	4	1	5	3	9	9	9	2	6	3	3
	1	1	2	1	1	1	2	2	2	2	2	1	2	2	2	1	1	1	2	2	2	2	1	2
Carcass ID Number	8	9	0	8	9	9	0	1	2	1	2	9	0	1	2	8	8	8	0	0	2	2	9	2
	2	8	3	4	2	0	6	3	4	0	5	9	5	5	1	8	5	3	0	4	3	6	1	7
Special Senses System																								
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, carcinoma																								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X	X		X		X		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 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 2,500 ppm (continued)

Number of Days on Study	677	677	695	695	698	712	723	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	219	220	181	201	187	218	197	186	189	193	194	195	196	202	207	208	209	211	212	214	216	217	222	228	230	Total Tissues/ Tumors
Special Senses System																										
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	48
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Renal tubule, carcinoma			X																							1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear	X	X		X	X	X	X			X	X		X					X	X			X		X		33

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rates[a]	14/50 (28%)	14/50 (28%)	10/50 (20%)	9/49 (18%)
Adjusted rates[b]	58.7%	44.5%	40.9%	36.3%
Terminal rates[c]	9/18 (50%)	11/28 (39%)	8/22 (36%)	4/18 (22%)
First incidence (days)	579	642	697	555
Life table tests[d]	P=0.199N	P=0.144N	P=0.090N	P=0.168N
Logistic regression tests[d]	P=0.150N	P=0.289N	P=0.090N	P=0.159N
Cochran-Armitage test[d]	P=0.126N			
Fisher exact test[d]		P=0.588N	P=0.241N	P=0.185N
Liver: Hepatocellular Adenoma				
Overall rates	1/50 (2%)	2/50 (4%)	3/50 (6%)	4/49 (8%)
Adjusted rates	5.6%	7.1%	13.6%	17.0%
Terminal rates	1/18 (6%)	2/28 (7%)	3/22 (14%)	2/18 (11%)
First incidence (days)	729 (T)	729 (T)	729 (T)	625
Life table tests	P=0.079	P=0.653	P=0.377	P=0.182
Logistic regression tests	P=0.091	P=0.653	P=0.377	P=0.177
Cochran-Armitage test	P=0.123			
Fisher exact test		P=0.500	P=0.309	P=0.175
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rates	1/50 (2%)	3/50 (6%)	3/50 (6%)	5/49 (10%)
Adjusted rates	5.6%	10.7%	13.6%	21.0%
Terminal rates	1/18 (6%)	3/28 (11%)	3/22 (14%)	2/18 (11%)
First incidence (days)	729 (T)	729 (T)	729 (T)	625
Life table tests	P=0.047	P=0.472	P=0.377	P=0.107
Logistic regression tests	P=0.056	P=0.472	P=0.377	P=0.100
Cochran-Armitage test	P=0.083			
Fisher exact test		P=0.309	P=0.309	P=0.098
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rates	1/49 (2%)	3/50 (6%)	0/50 (0%)	0/49 (0%)
Adjusted rates	5.6%	10.7%	0.0%	0.0%
Terminal rates	1/18 (6%)	3/28 (11%)	0/22 (0%)	0/18 (0%)
First incidence (days)	729 (T)	729 (T)	–[e]	–
Life table tests	P=0.188N	P=0.472	P=0.460N	P=0.500N
Logistic regression tests	P=0.188N	P=0.472	P=0.460N	P=0.500N
Cochran-Armitage test	P=0.173N			
Fisher exact test		P=0.316	P=0.495N	P=0.500N
Mammary Gland: Fibroadenoma				
Overall rates	3/50 (6%)	4/50 (8%)	0/50 (0%)	2/49 (4%)
Adjusted rates	11.0%	14.3%	0.0%	7.7%
Terminal rates	1/18 (6%)	4/28 (14%)	0/22 (0%)	1/18 (6%)
First incidence (days)	625	729 (T)	–	555
Life table tests	P=0.372N	P=0.615N	P=0.097N	P=0.501N
Logistic regression tests	P=0.338N	P=0.589	P=0.118N	P=0.509N
Cochran-Armitage test	P=0.333N			
Fisher exact test		P=0.500	P=0.121N	P=0.510N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	14/50 (28%)	10/49 (20%)	12/50 (24%)	10/49 (20%)
Adjusted rates	43.9%	30.8%	43.4%	33.7%
Terminal rates	3/18 (17%)	7/28 (25%)	8/22 (36%)	3/18 (17%)
First incidence (days)	579	649	416	555
Life table tests	P=0.406N	P=0.065N	P=0.235N	P=0.259N
Logistic regression tests	P=0.300N	P=0.190N	P=0.374N	P=0.249N
Cochran-Armitage test	P=0.293N			
Fisher exact test		P=0.259N	P=0.410N	P=0.259N
Preputial Gland: Adenoma				
Overall rates	1/50 (2%)	5/49 (10%)	3/49 (6%)	4/49 (8%)
Adjusted rates	5.6%	14.9%	10.3%	10.7%
Terminal rates	1/18 (6%)	2/28 (7%)	1/22 (5%)	0/18 (0%)
First incidence (days)	729 (T)	625	627	533
Life table tests	P=0.246	P=0.213	P=0.391	P=0.199
Logistic regression tests	P=0.289	P=0.137	P=0.340	P=0.157
Cochran-Armitage test	P=0.289			
Fisher exact test		P=0.098	P=0.301	P=0.175
Preputial Gland: Adenoma or Carcinoma				
Overall rates	3/50 (6%)	7/49 (14%)	3/49 (6%)	4/49 (8%)
Adjusted rates	14.5%	21.5%	10.3%	10.7%
Terminal rates	2/18 (11%)	4/28 (14%)	1/22 (5%)	0/18 (0%)
First incidence (days)	663	625	627	533
Life table tests	P=0.567	P=0.361	P=0.554N	P=0.520
Logistic regression tests	P=0.540N	P=0.237	P=0.617N	P=0.481
Cochran-Armitage test	P=0.536N			
Fisher exact test		P=0.151	P=0.651	P=0.489
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rates	3/50 (6%)	2/50 (4%)	1/50 (2%)	3/49 (6%)
Adjusted rates	11.5%	7.1%	3.3%	8.8%
Terminal rates	1/18 (6%)	2/28 (7%)	0/22 (0%)	0/18 (0%)
First incidence (days)	533	729 (T)	695	539
Life table tests	P=0.497	P=0.357N	P=0.231N	P=0.654N
Logistic regression tests	P=0.527	P=0.470N	P=0.304N	P=0.643
Cochran-Armitage test	P=0.527			
Fisher exact test		P=0.500N	P=0.309N	P=0.651
Skin (Subcutaneous Tissue): Fibroma				
Overall rates	5/50 (10%)	1/50 (2%)	4/50 (8%)	2/49 (4%)
Adjusted rates	20.9%	3.6%	13.1%	8.5%
Terminal rates	3/18 (17%)	1/28 (4%)	0/22 (0%)	1/18 (6%)
First incidence (days)	533	729 (T)	688	649
Life table tests	P=0.339N	P=0.046N	P=0.368N	P=0.211N
Logistic regression tests	P=0.304N	P=0.087N	P=0.453N	P=0.218N
Cochran-Armitage test	P=0.298N			
Fisher exact test		P=0.102N	P=0.500N	P=0.226N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
Skin (Subcutaneous Tissue): Fibroma or Neurofibroma				
Overall rates	5/50 (10%)	2/50 (4%)	5/50 (10%)	3/49 (6%)
Adjusted rates	20.9%	7.1%	16.8%	11.1%
Terminal rates	3/18 (17%)	2/28 (7%)	0/22 (0%)	1/18 (6%)
First incidence (days)	533	729 (T)	688	621
Life table tests	P=0.489N	P=0.103N	P=0.492N	P=0.351N
Logistic regression tests	P=0.439N	P=0.177N	P=0.575N	P=0.360N
Cochran-Armitage test	P=0.427N			
Fisher exact test		P=0.218N	P=0.630N	P=0.369N
Skin (Subcutaneous Tissue): Fibroma, Neurofibroma, or Fibrosarcoma				
Overall rates	5/50 (10%)	3/50 (6%)	5/50 (10%)	3/49 (6%)
Adjusted rates	20.9%	9.4%	16.8%	11.1%
Terminal rates	3/18 (17%)	2/28 (7%)	0/22 (0%)	1/18 (6%)
First incidence (days)	533	625	688	621
Life table tests	P=0.436N	P=0.200N	P=0.492N	P=0.351N
Logistic regression tests	P=0.384N	P=0.321N	P=0.575N	P=0.360N
Cochran-Armitage test	P=0.376N			
Fisher exact test		P=0.357N	P=0.630N	P=0.369N
Testes: Adenoma				
Overall rates	46/50 (92%)	44/49 (90%)	47/50 (94%)	44/49 (90%)
Adjusted rates	100.0%	97.7%	100.0%	100.0%
Terminal rates	18/18 (100%)	26/27 (96%)	22/22 (100%)	18/18 (100%)
First incidence (days)	418	416	466	441
Life table tests	P=0.317	P=0.016N	P=0.181N	P=0.434N
Logistic regression tests	P=0.381N	P=0.345N	P=0.650N	P=0.383N
Cochran-Armitage test	P=0.464N			
Fisher exact test		P=0.487N	P=0.500	P=0.487N
Thyroid Gland (C-cell): Adenoma				
Overall rates	5/50 (10%)	3/50 (6%)	8/50 (16%)	2/49 (4%)
Adjusted rates	21.7%	9.5%	26.7%	11.1%
Terminal rates	2/18 (11%)	1/28 (4%)	3/22 (14%)	2/18 (11%)
First incidence (days)	632	676	466	729 (T)
Life table tests	P=0.306N	P=0.187N	P=0.421	P=0.220N
Logistic regression tests	P=0.254N	P=0.262N	P=0.332	P=0.214N
Cochran-Armitage test	P=0.244N			
Fisher exact test		P=0.357N	P=0.277	P=0.226N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rates	5/50 (10%)	3/50 (6%)	8/50 (16%)	3/49 (6%)
Adjusted rates	21.7%	9.5%	26.7%	13.8%
Terminal rates	2/18 (11%)	1/28 (4%)	3/22 (14%)	2/18 (11%)
First incidence (days)	632	676	466	633
Life table tests	P=0.464N	P=0.187N	P=0.421	P=0.354N
Logistic regression tests	P=0.402N	P=0.262N	P=0.332	P=0.356N
Cochran-Armitage test	P=0.387N			
Fisher exact test		P=0.357N	P=0.277	P=0.369N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
All Organs: Mononuclear Cell Leukemia				
Overall rates	30/50 (60%)	36/50 (72%)	34/50 (68%)	33/49 (67%)
Adjusted rates	78.6%	79.6%	81.5%	74.1%
Terminal rates	11/18 (61%)	19/28 (68%)	15/22 (68%)	7/18 (39%)
First incidence (days)	467	352	477	423
Life table tests	P=0.261	P=0.319N	P=0.445N	P=0.407
Logistic regression tests	P=0.388	P=0.166	P=0.313	P=0.284
Cochran-Armitage test	P=0.389			
Fisher exact test		P=0.146	P=0.266	P=0.291
All Organs: Benign Neoplasms				
Overall rates	49/50 (98%)	47/50 (94%)	50/50 (100%)	46/49 (94%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%
Terminal rates	18/18 (100%)	28/28 (100%)	22/22 (100%)	18/18 (100%)
First incidence (days)	418	416	416	441
Life table tests	P=0.352	P=0.010N	P=0.182N	P=0.388N
Logistic regression tests	P=0.114N	P=0.165N	–[f]	P=0.131N
Cochran-Armitage test	P=0.295N			
Fisher exact test		P=0.309N	P=0.500	P=0.301N
All Organs: Malignant Neoplasms				
Overall rates	37/50 (74%)	41/50 (82%)	39/50 (78%)	37/49 (76%)
Adjusted rates	87.3%	85.3%	84.3%	80.2%
Terminal rates	13/18 (72%)	21/28 (75%)	15/22 (68%)	9/18 (50%)
First incidence (days)	418	352	466	423
Life table tests	P=0.375	P=0.168N	P=0.301N	P=0.537N
Logistic regression tests	P=0.491N	P=0.239	P=0.432	P=0.514
Cochran-Armitage test	P=0.494N			
Fisher exact test		P=0.235	P=0.408	P=0.523
All Organs: Benign or Malignant Neoplasms				
Overall rates	49/50 (98%)	49/50 (98%)	50/50 (100%)	49/49 (100%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%
Terminal rates	18/18 (100%)	28/28 (100%)	22/22 (100%)	18/18 (100%)
First incidence (days)	418	352	416	423
Life table tests	P=0.228	P=0.023N	P=0.182N	P=0.540N
Logistic regression tests	P=0.577	P=0.745N	–	–
Cochran-Armitage test	P=0.288			
Fisher exact test		P=0.753N	P=0.500	P=0.505

(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, 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 tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE A4
Historical Incidence of Hepatocellular Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle-Columbus			
2,4-Dichlorophenol	4/50	3/50	5/50
4,4'-Thiobis(6-*t*-butyl-*m*-cresol)	1/50	0/50	1/50
5,5-Diphenylhydantoin	0/50	0/50	0/50
Ethylene Thiourea	0/50	0/50	0/50
Polybrominated Biphenyls (Firemaster FF-1®)	1/50	0/50	1/50
Manganese Sulfate Monohydrate	0/52	0/52	0/52
Triamterene	0/50	0/50	0/50
Tricresyl Phosphate	0/50	0/50	0/50
Overall Historical Incidence			
Total	33/1,251 (2.6%)	11/1,251 (0.9%)	41/1,251 (3.3%)
Standard deviation	3.3%	1.5%	3.6%
Range	0%-10%	0%-6%	0%-10%

[a] Data as of 20 August 1992

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	7	10
Early deaths				
Moribund	23	14	22	23
Natural deaths	9	8	6	9
Survivors				
Terminal sacrifice	18	28	22	18
Animals examined microscopically	60	60	57[b]	59[c]
15-Month Interim Evaluation				
Alimentary System				
Intestine large, rectum	(10)	(10)	(7)	(10)
Parasite metazoan	3 (30%)	1 (10%)		1 (10%)
Liver	(10)	(10)	(7)	(10)
Basophilic focus	5 (50%)	2 (20%)	7 (100%)	10 (100%)
Hepatodiaphragmatic nodule		2 (20%)	1 (14%)	
Inflammation, chronic	1 (10%)	1 (10%)		
Mixed cell focus	1 (10%)	1 (10%)	1 (14%)	5 (50%)
Bile duct, cyst		1 (10%)		
Bile duct, hyperplasia	9 (90%)	9 (90%)	7 (100%)	9 (90%)
Hepatocyte, vacuolization cytoplasmic	1 (10%)	10 (100%)	7 (100%)	10 (100%)
Periportal, kupffer cell, hypertrophy				10 (100%)
Mesentery	(2)	(1)	(1)	
Inflammation, chronic active	2 (100%)	1 (100%)	1 (100%)	
Pancreas	(10)	(10)	(7)	(10)
Inflammation, chronic active		1 (10%)		
Acinus, atrophy	5 (50%)	4 (40%)	1 (14%)	3 (30%)
Cardiovascular System				
Heart	(10)	(10)	(7)	(10)
Cardiomyopathy, chronic	10 (100%)	10 (100%)	7 (100%)	10 (100%)
Endocrine System				
Adrenal cortex	(10)	(10)	(7)	(10)
Degeneration, fatty	1 (10%)	2 (20%)	1 (14%)	
Hyperplasia	1 (10%)	1 (10%)		
Adrenal medulla	(10)	(10)	(7)	(10)
Hyperplasia	1 (10%)			
Pituitary gland	(10)	(10)	(7)	(10)
Pars distalis, cyst			1 (14%)	
Pars distalis, hyperplasia	3 (30%)	5 (50%)	5 (71%)	2 (20%)
Pars distalis, pigmentation, hemosiderin	1 (10%)			
Thyroid gland	(10)	(10)	(7)	(10)
Cyst				1 (10%)
C-cell, hyperplasia	4 (40%)	2 (20%)		

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] Three male rats exposed to 1.000 ppm were killed moribund prior to the 15-month interim evaluation.
[c] One animal discarded due to autolysis.

Table A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-t-Butyl-m-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
15-Month Interim Evaluation (continued)				
General Body System				
None				
Genital System				
Epididymis	(10)	(10)	(7)	(10)
Hypospermia	2 (20%)	1 (10%)		
Preputial gland	(10)	(10)	(7)	(10)
Inflammation, chronic active	8 (80%)	9 (90%)	5 (71%)	6 (60%)
Prostate	(10)	(10)	(7)	(10)
Inflammation, chronic active	8 (80%)	7 (70%)	7 (100%)	10 (100%)
Testes	(10)	(10)	(7)	(10)
Granuloma sperm		1 (10%)		
Mineralization		2 (20%)	2 (29%)	1 (10%)
Interstitial cell, hyperplasia	10 (100%)	10 (100%)	7 (100%)	10 (100%)
Seminiferous tubule, atrophy	1 (10%)	1 (10%)		
Hematopoietic System				
Lymph node, mandibular	(10)	(10)	(7)	(10)
Hyperplasia, plasma cell		1 (10%)		
Sinus, ectasia	1 (10%)		1 (14%)	
Spleen	(10)	(10)	(7)	(10)
Fibrosis	1 (10%)	1 (10%)		
Integumentary System				
Mammary gland	(10)	(10)	(7)	(10)
Hyperplasia, cystic	9 (90%)	10 (100%)	7 (100%)	10 (100%)
Musculoskeletal System				
Skeletal muscle	(10)	(10)	(7)	(10)
Necrosis, coagulative	2 (20%)			1 (10%)
Nervous System				
None				
Respiratory System				
Lung	(10)	(10)	(7)	(10)
Inflammation, chronic active	1 (10%)	1 (10%)	1 (14%)	2 (20%)
Metaplasia, osseous			1 (14%)	
Alveolar epithelium, hyperplasia		1 (10%)		
Nose	(10)	(10)	(7)	(10)
Fungus				1 (10%)
Inflammation, chronic active		1 (10%)	1 (14%)	1 (10%)
Nasolacrimal duct, inflammation, suppurative	2 (20%)			

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
15-Month Interim Evaluation (continued)				
Special Senses System				
None				
Urinary System				
Kidney	(10)	(10)	(7)	(10)
Cyst	1 (10%)			
Nephropathy, chronic	10 (100%)	10 (100%)	7 (100%)	10 (100%)
2-Year Study				
Alimentary System				
Intestine large, colon	(50)	(50)	(50)	(48)
Inflammation, chronic active				1 (2%)
Parasite metazoan		2 (4%)	2 (4%)	
Intestine large, rectum	(50)	(50)	(50)	(48)
Inflammation, chronic active		2 (4%)		
Parasite metazoan	5 (10%)	1 (2%)	2 (4%)	1 (2%)
Intestine large, cecum	(50)	(50)	(50)	(49)
Inflammation, chronic active				1 (2%)
Liver	(50)	(50)	(50)	(49)
Basophilic focus	18 (36%)	22 (44%)	23 (46%)	22 (45%)
Clear cell focus	2 (4%)		1 (2%)	1 (2%)
Eosinophilic focus	3 (6%)	7 (14%)	2 (4%)	1 (2%)
Fatty change	15 (30%)	14 (28%)	13 (26%)	15 (31%)
Hematopoietic cell proliferation		1 (2%)		
Hepatodiaphragmatic nodule	1 (2%)	3 (6%)	4 (8%)	4 (8%)
Inflammation, chronic	8 (16%)	2 (4%)	6 (12%)	3 (6%)
Mixed cell focus	6 (12%)	14 (28%)	18 (36%)	15 (31%)
Necrosis, coagulative	2 (4%)	1 (2%)	3 (6%)	2 (4%)
Thrombosis			1 (2%)	1 (2%)
Bile duct, hyperplasia	45 (90%)	47 (94%)	43 (86%)	46 (94%)
Hepatocyte, degeneration, cystic	10 (20%)	14 (28%)	9 (18%)	11 (22%)
Hepatocyte, vacuolization cytoplasmic	13 (26%)	11 (22%)	19 (38%)	18 (37%)
Periportal, kupffer cell, hypertrophy	2 (4%)	3 (6%)	2 (4%)	31 (63%)
Mesentery	(11)	(7)	(10)	(9)
Ectopic tissue			1 (10%)	
Hemorrhage, acute				1 (11%)
Inflammation, chronic active	2 (18%)			1 (11%)
Inflammation, necrotizing	6 (55%)	4 (57%)	7 (70%)	4 (44%)
Mineralization	2 (18%)	1 (14%)	1 (10%)	1 (11%)
Pancreas	(50)	(50)	(50)	(49)
Acinus, atrophy	27 (54%)	25 (50%)	28 (56%)	30 (61%)
Artery, inflammation, chronic active	1 (2%)		2 (4%)	
Artery, necrosis, fibrinoid			1 (2%)	
Stomach, forestomach	(50)	(50)	(50)	(49)
Acanthosis	3 (6%)	1 (2%)	3 (6%)	1 (2%)
Inflammation, chronic active	2 (4%)	1 (2%)		

Table A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Stomach, glandular	(50)	(50)	(50)	(49)
Erosion		1 (2%)	1 (2%)	
Inflammation, chronic active	4 (8%)	2 (4%)	1 (2%)	
Mineralization			1 (2%)	1 (2%)
Cardiovascular system				
Blood vessel	(1)			
Mesenteric artery, hemorrhage	1 (100%)			
Mesenteric artery, inflammation, chronic active	1 (100%)			
Heart	(50)	(50)	(50)	(49)
Bacterium	1 (2%)			
Cardiomyopathy, chronic	47 (94%)	45 (90%)	40 (80%)	39 (80%)
Metaplasia, cartilagenous		1 (2%)		1 (2%)
Mineralization	1 (2%)			1 (2%)
Thrombosis		6 (12%)	4 (8%)	3 (6%)
Valve, inflammation, chronic active	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(49)
Accessory adrenal cortical nodule	2 (4%)			3 (6%)
Degeneration, fatty	19 (38%)	15 (30%)	15 (30%)	16 (33%)
Hematopoietic cell proliferation		1 (2%)		
Hyperplasia	10 (20%)	9 (18%)	9 (18%)	13 (27%)
Hypertrophy	1 (2%)	1 (2%)		
Inflammation, necrotizing	1 (2%)			
Necrosis, coagulative	2 (4%)	1 (2%)		4 (8%)
Adrenal medulla	(50)	(50)	(50)	(49)
Hyperplasia	15 (30%)	21 (42%)	21 (42%)	18 (37%)
Necrosis	1 (2%)	1 (2%)		
Islets, pancreatic	(50)	(50)	(50)	(49)
Hyperplasia		1 (2%)		1 (2%)
Parathyroid gland	(47)	(45)	(47)	(46)
Hyperplasia	1 (2%)			2 (4%)
Pituitary gland	(50)	(49)	(50)	(49)
Pigmentation, hemosiderin		1 (2%)	1 (2%)	
Craniopharyngeal duct, pars intermedia, cyst multilocular			1 (2%)	
Pars distalis, cyst	3 (6%)	7 (14%)	4 (8%)	3 (6%)
Pars distalis, degeneration, cystic	1 (2%)			
Pars distalis, hyperplasia	19 (38%)	10 (20%)	14 (28%)	20 (41%)
Pars intermedia, cyst	1 (2%)		1 (2%)	1 (2%)
Pars intermedia, ectasia	1 (2%)			

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-t-Butyl-m-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
2-Year Study (continued)				
Endocrine System (continued)				
Thyroid gland	(50)	(50)	(50)	(49)
Cyst	1 (2%)			
Inflammation, chronic active	2 (4%)			1 (2%)
C-cell, hyperplasia	9 (18%)	12 (24%)	14 (28%)	8 (16%)
Follicle, cyst			1 (2%)	1 (2%)
Follicular cell, hyperplasia	1 (2%)		1 (2%)	1 (2%)
General Body System				
None				
Genital System				
Coagulating gland		(1)		
Inflammation, chronic active		1 (100%)		
Epididymis	(50)	(50)	(50)	(49)
Granuloma sperm	1 (2%)	5 (10%)	4 (8%)	9 (18%)
Preputial gland	(50)	(49)	(49)	(49)
Hyperplasia	3 (6%)	6 (12%)	6 (12%)	5 (10%)
Inflammation, chronic active	48 (96%)	43 (88%)	39 (80%)	44 (90%)
Metaplasia, osseous	1 (2%)			
Duct, dilatation		1 (2%)	3 (6%)	1 (2%)
Prostate	(49)	(50)	(50)	(48)
Inflammation, chronic active	33 (67%)	32 (64%)	28 (56%)	40 (83%)
Seminal vesicle	(49)	(50)	(50)	(48)
Atrophy		1 (2%)		
Inflammation, chronic active	1 (2%)	1 (2%)		
Testes	(50)	(49)	(50)	(49)
Cyst				1 (2%)
Inflammation, chronic	1 (2%)			
Mineralization	35 (70%)	37 (76%)	44 (88%)	29 (59%)
Spermatocele		1 (2%)		
Arteriole, inflammation, chronic active	1 (2%)			
Interstitial cell, hyperplasia	23 (46%)	29 (59%)	28 (56%)	34 (69%)
Seminiferous tubule, atrophy	5 (10%)	1 (2%)	1 (2%)	5 (10%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(49)
Femoral, myelofibrosis	1 (2%)	1 (2%)		
Lymph node	(24)	(19)	(26)	(30)
Mediastinal, edema	1 (4%)			
Mediastinal, hyperplasia, plasma cell			1 (4%)	
Lymph node, mandibular	(48)	(50)	(50)	(49)
Cyst		1 (2%)		2 (4%)
Hyperplasia, plasma cell		1 (2%)	2 (4%)	
Necrosis, coagulative		1 (2%)		
Lymph node, mesenteric	(50)	(50)	(49)	(48)
Sinus, ectasia	1 (2%)			

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Spleen	(50)	(50)	(49)	(49)
Depletion lymphoid	1 (2%)			
Ectopic tissue				2 (4%)
Fibrosis	4 (8%)	9 (18%)	3 (6%)	4 (8%)
Hematopoietic cell proliferation		1 (2%)	1 (2%)	1 (2%)
Necrosis, coagulative	1 (2%)		2 (4%)	2 (4%)
Thrombosis			1 (2%)	
Red pulp, atrophy	2 (4%)	1 (2%)		2 (4%)
Thymus	(48)	(46)	(46)	(46)
Ectopic parathyroid gland	1 (2%)	1 (2%)		
Ectopic thyroid	1 (2%)	1 (2%)		
Integumentary System				
Mammary gland	(47)	(47)	(46)	(49)
Hyperplasia, cystic	28 (60%)	37 (79%)	34 (74%)	33 (67%)
Skin	(50)	(50)	(50)	(48)
Acanthosis		1 (2%)		
Hyperplasia, squamous		1 (2%)		
Inflammation, chronic active		1 (2%)		
Musculoskeletal system				
Bone	(50)	(50)	(50)	(49)
Cranium, fibrous osteodystrophy	1 (2%)			1 (2%)
Femur, fibrous osteodystrophy	1 (2%)			1 (2%)
Skeletal muscle	(50)	(50)	(50)	(49)
Fibrosis	1 (2%)			
Mineralization			1 (2%)	
Necrosis, coagulative	7 (14%)	7 (14%)	5 (10%)	7 (14%)
Nervous System				
Brain	(50)	(50)	(50)	(49)
Compression	4 (8%)	1 (2%)	2 (4%)	
Cyst	1 (2%)			
Hemorrhage, acute	2 (4%)		2 (4%)	2 (4%)
Hydrocephalus	4 (8%)	1 (2%)	2 (4%)	
Inflammation, suppurative	1 (2%)			1 (2%)
Necrosis			1 (2%)	1 (2%)
Spinal cord	(2)	(2)	(3)	
Hemorrhage, acute	1 (50%)		1 (33%)	
White matter, degeneration	1 (50%)		2 (67%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
2-Year Study (continued)				
Respiratory System				
Lung	(49)	(50)	(50)	(49)
Hemorrhage, acute				3 (6%)
Inflammation, chronic active	10 (20%)	6 (12%)	8 (16%)	7 (14%)
Leukocytosis		1 (2%)		
Metaplasia, osseous	2 (4%)			1 (2%)
Alveolar epithelium, hyperplasia	4 (8%)	1 (2%)	3 (6%)	4 (8%)
Alveolus, infiltration cellular, histiocyte	10 (20%)	10 (20%)	13 (26%)	9 (18%)
Nose	(50)	(50)	(50)	(49)
Fungus				1 (2%)
Inflammation, chronic active	3 (6%)	3 (6%)	4 (8%)	7 (14%)
Thrombosis		1 (2%)		
Nasolacrimal duct, inflammation, suppurative	15 (30%)	13 (26%)	4 (8%)	10 (20%)
Special Senses System				
Ear	(1)	(1)	(2)	
Inflammation, chronic active	1 (100%)			
Eye	(3)	(2)	(5)	
Anterior chamber, hemorrhage, acute			1 (20%)	
Cornea, inflammation, chronic active	1 (33%)		1 (20%)	
Lens, cataract	1 (33%)	1 (50%)	4 (80%)	
Retina, atrophy	1 (33%)	2 (100%)	3 (60%)	
Urinary System				
Kidney	(50)	(50)	(50)	(49)
Bacterium	1 (2%)			
Cyst	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Inflammation, chronic active			1 (2%)	
Inflammation, suppurative	1 (2%)			
Necrosis, coagulative	2 (4%)	2 (4%)		2 (4%)
Nephropathy, chronic	47 (94%)	48 (96%)	47 (94%)	47 (96%)
Urinary bladder	(49)	(50)	(50)	(48)
Inflammation, chronic active		1 (2%)		
Transitional epithelium, hyperplasia		1 (2%)		

APPENDIX B SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR FEED STUDY OF 4,4′-THIOBIS(6-*t*-BUTYL-*m*-CRESOL)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	11	14	16	16
Natural deaths	5	5	2	6
Survivors				
Died last week of study		1		
Terminal sacrifice	34	30	32	28
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
None				
Cardiovascular System				
None				
Endocrine System				
Pituitary gland	(10)	(10)	(10)	(10)
Pars distalis, adenoma	3 (30%)	1 (10%)		1 (10%)
General Body System				
None				
Genital System				
Uterus	(10)	(10)	(10)	(10)
Polyp stromal			1 (10%)	
Hematopoietic System				
None				
Integumentary System				
Mammary gland	(10)	(10)	(10)	(10)
Fibroadenoma		1 (10%)		
Musculoskeletal System				
None				
Nervous System				
None				

Table B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-t-Butyl-m-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
15-Month Interim Evaluation (continued)				
Respiratory System				
None				
Special Senses System				
None				
Urinary System				
None				
2-Year Study				
Alimentary System				
Intestine large, colon	(50)	(50)	(50)	(49)
Intestine large, cecum	(50)	(50)	(50)	(49)
Intestine small, duodenum	(50)	(50)	(50)	(49)
Intestine small, jejunum	(50)	(50)	(50)	(49)
Adenocarcinoma				1 (2%)
Intestine small, ileum	(50)	(50)	(50)	(49)
Liver	(50)	(50)	(50)	(50)
Hepatocellular adenoma				1 (2%)
Mesentery	(9)	(7)	(8)	(4)
Schwannoma malignant		1 (14%)		
Pancreas	(50)	(50)	(50)	(49)
Pharynx	(1)		(2)	
Palate, squamous cell papilloma	1 (100%)		2 (100%)	
Salivary glands	(49)	(49)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(49)
Stomach, glandular	(50)	(50)	(50)	(49)
Tongue	(1)			(1)
Squamous cell papilloma	1 (100%)			
Tooth	(2)		(1)	
Gingiva, squamous cell carcinoma	1 (50%)			
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Schwannoma malignant, moderately well differentiated			1 (2%)	
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma	1 (2%)	1 (2%)		
Adrenal medulla	(50)	(50)	(49)	(50)
Pheochromocytoma malignant				1 (2%)
Pheochromocytoma benign	1 (2%)	1 (2%)	3 (6%)	1 (2%)
Bilateral, pheochromocytoma benign		1 (2%)		

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
2-Year Study (continued)				
Endocrine System (continued)				
Islets, pancreatic	(50)	(50)	(50)	(49)
Carcinoma	1 (2%)			
Pituitary gland	(49)	(50)	(50)	(49)
Pars distalis, adenoma	27 (55%)	15 (30%)	17 (34%)	16 (33%)
Pars distalis, adenoma, multiple				1 (2%)
Pars distalis, carcinoma				1 (2%)
Thyroid gland	(49)	(49)	(50)	(50)
Bilateral, C-cell, adenoma			1 (2%)	
C-cell, adenoma	3 (6%)	2 (4%)	7 (14%)	8 (16%)
C-cell, carcinoma		2 (4%)		2 (4%)
General Body System				
None				
Genital System				
Clitoral gland	(49)	(48)	(50)	(49)
Adenoma	4 (8%)	1 (2%)		1 (2%)
Carcinoma	1 (2%)	1 (2%)		2 (4%)
Ovary	(50)	(50)	(50)	(50)
Uterus	(50)	(50)	(50)	(50)
Polyp stromal	2 (4%)	5 (10%)	9 (18%)	9 (18%)
Sarcoma stromal		1 (2%)		1 (2%)
Vagina			(2)	(3)
Fibrosarcoma			1 (50%)	
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(50)
Lymph node	(14)	(10)	(10)	(10)
Lymph node, mandibular	(49)	(49)	(50)	(50)
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Spleen	(50)	(50)	(50)	(50)
Thymus	(47)	(49)	(47)	(48)
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Adenocarcinoma	1 (2%)			
Adenoma	2 (4%)	1 (2%)		
Fibroadenoma	18 (36%)	14 (28%)	9 (18%)	14 (28%)
Fibroadenoma, multiple	11 (22%)	10 (20%)	2 (4%)	2 (4%)
Skin	(50)	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)			
Subcutaneous tissue, fibroma	1 (2%)	1 (2%)		1 (2%)
Subcutaneous tissue, lipoma	1 (2%)		1 (2%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
2-Year Study (continued)				
Musculoskeletal System				
Bone	(49)	(50)	(50)	(50)
Cervical, vertebra, hemangiosarcoma			1 (2%)	
Femur, osteosarcoma	1 (2%)			
Skeletal muscle	(50)	(50)	(50)	(50)
Osteosarcoma, metastatic, bone	1 (2%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Spinal cord			(1)	(1)
Respiratory System				
Lung	(50)	(49)	(49)	(50)
Alveolar/bronchiolar adenoma	1 (2%)		1 (2%)	1 (2%)
Carcinoma, metastatic, thyroid gland		1 (2%)		1 (2%)
Fibrosarcoma			1 (2%)	
Osteosarcoma, metastatic, bone	1 (2%)			
Nose	(50)	(50)	(50)	(50)
Squamous cell carcinoma, metastatic, tooth	1 (2%)			
Trachea	(50)	(50)	(50)	(50)
Special Senses System				
Ear		(1)		
Fibrosarcoma		1 (100%)		
Harderian gland	(49)	(50)	(50)	(50)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Urinary bladder	(50)	(49)	(50)	(50)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Leukemia mononuclear	18 (36%)	18 (36%)	22 (44%)	20 (40%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	3	2	1	1
2-Year study	47	45	43	47
Total primary neoplasms				
15-Month interim evaluation	3	2	1	1
2-Year study	98	76	78	83
Total animals with benign neoplasms				
15-Month interim evaluation	3	2	1	1
2-Year study	42	35	36	38
Total benign neoplasms				
15-Month interim evaluation	3	2	1	1
2-Year study	75	52	52	55
Total animals with malignant neoplasms				
2-Year study	22	23	24	25
Total malignant neoplasms				
2-Year study	23	24	26	28
Total animals with metastatic neoplasms				
2-Year study	2	1		1
Total metastatic neoplasms				
2-Year study	3	1		1

[a] Number of animals examined microscopically at site and number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 0 ppm

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

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 0 ppm (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Carcass ID Number	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	Total
	5	5	5	5	5	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	8	8	8	8	Tissues/
	4	5	6	8	9	0	1	2	4	5	6	7	8	9	1	2	3	4	7	8	9	0	2	5	9	Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery	+								+											+					+	9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pharynx																										1
Palate, squamous cell papilloma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue							+																			1
Squamous cell papilloma							X																			1
Tooth						+																				2
Gingiva, squamous cell carcinoma																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X																		1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																					X					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X		X	X		X		X		X		X	X			X	X	X	X	X			X	X		27
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma														X								X				3
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Adenoma																						X	X			4
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal			X																							2

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-t-Butyl-m-Cresol): 0 ppm (continued)

Number of Days on Study	453	518	536	623	653	661	673	673	673	676	709	715	721	725	725	728	731	731	731	731	731	731	731	731	731
Carcass ID Number	284	276	252	257	263	270	281	283	290	288	241	275	244	286	287	249	242	243	245	246	247	248	250	251	253
Hematopoietic System																									
Blood									+																
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+					+				+	+	+	+	+											
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Adenoma														X								X			
Fibroadenoma								X			X		X		X					X	X			X	
Fibroadenoma, multiple							X		X								X						X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma					X																				
Subcutaneous tissue, fibroma																							X		
Subcutaneous tissue, lipoma																					X				
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femur, osteosarcoma																									
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																	X								
Osteosarcoma, metastatic, bone																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, tooth				X																					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Harderian gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X			X				X	X	X	X	X											

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 0 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	2 5 4	2 5 5	2 5 6	2 5 8	2 5 9	2 6 0	2 6 1	2 6 2	2 6 4	2 6 5	2 6 6	2 6 7	2 6 8	2 6 9	2 7 1	2 7 2	2 7 3	2 7 4	2 7 7	2 7 8	2 7 9	2 8 0	2 8 2	2 8 5	2 8 9	Total Tissues/ Tumors
Hematopoietic System																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Lymph node					+						+	+			+	+		+		+						14
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																			X							1
Adenoma																										2
Fibroadenoma		X	X		X			X			X	X		X							X	X	X	X		18
Fibroadenoma, multiple	X			X					X	X			X			X		X								11
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, lipoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Femur, osteosarcoma			X																							1
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone			X																							1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Osteosarcoma, metastatic, bone			X																							1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, tooth																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye									+															+		2
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X			X			X	X			X	X		X	X	X		X				18

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 500 ppm

Number of Days on Study	372	428	590	591	604	605	624	626	652	663	665	677	677	688	688	688	697	712	725	729	730	730	730	730	730
Carcass ID Number	329	332	310	333	314	319	306	309	322	307	324	347	349	303	305	339	330	311	344	320	301	302	304	308	312
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery		+	+														+	+	+						
Schwannoma malignant		X																							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X														
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																		X							
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X			X		X	X	X						X				X		X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma									X																
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal								X																	
Sarcoma stromal			X																						
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+		+			+			+	+	+	+	+	+							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 500 ppm (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	313	315	316	317	318	321	323	325	326	327	328	331	334	335	336	337	338	340	341	342	343	345	346	348	350	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery			+															+								7
Schwannoma malignant																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										1
Bilateral, pheochromocytoma benign																								X		1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X				X				X									X				X	X	X	15
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma						X												X								2
C-cell, carcinoma				X												X										2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma	X																									1
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal				X	X										X			X								5
Sarcoma stromal																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																				+						10
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 500 ppm (continued)

Number of Days on Study	372	428	590	591	604	605	624	626	652	663	665	677	677	688	688	688	697	712	725	729	730	730	730	730	730
Carcass ID Number	329	332	310	333	314	319	306	309	322	307	324	347	349	303	305	339	330	311	344	320	301	302	304	308	312
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X							
Fibroadenoma	X			X			X	X				X				X							X		
Fibroadenoma, multiple										X								X	X			X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																+									
Fibrosarcoma																X									
Eye																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X		X			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 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 500 ppm (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	313	315	316	317	318	321	323	325	326	327	328	331	334	335	336	337	338	340	341	342	343	345	346	348	350	Total Tissues/ Tumors
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Fibroadenoma			X								X	X		X							X		X		X	14
Fibroadenoma, multiple	X	X				X			X	X						X										10
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma															X											1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, thyroid gland																X										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Fibrosarcoma																										1
Eye						+															+			+		3
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X							X								X		X	X	X					18

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 1,000 ppm

Number of Days on Study	014	481	539	555	592	598	598	626	633	649	680	688	688	695	695	712	723	723	729	729	729	730	730	730	730
Carcass ID Number	405	361	391	382	395	362	394	381	378	371	387	396	400	386	399	366	367	375	363	364	365	368	369	370	372
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery		+								+			+								+				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx																									
Palate, squamous cell papilloma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, moderately well differentiated							X																		
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																				X					
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	M	+	M	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X		X	X						X	X				X	X	X				X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma							X									X					X			X	
General Body System																									
Tissue NOS																				+					
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal		X			X											X				X					
Vagina						+										+									
Fibrosarcoma																X									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+				+	+		+			+	+					+							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 1,000 ppm (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	4	4	4	4	4	4	4	4	4	Total
Carcass ID Number	7	7	7	7	7	8	8	8	8	8	8	9	9	9	9	9	0	0	0	0	0	0	0	0	1	Tissues/
	3	4	6	7	9	0	3	4	5	8	9	0	2	3	7	8	1	2	3	4	6	7	8	9	0	Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery	+		+						+													+				8
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pharynx				+													+									2
Palate, squamous cell papilloma				X													X									2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth												+														1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, moderately well differentiated																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign											X											X				3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma					X						X				X		X	X		X			X	X		17
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma															X											1
C-cell, adenoma														X						X		X				7
General Body System																										
Tissue NOS																										1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal										X									X		X			X	X	9
Vagina																										2
Fibrosarcoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node					+						+			+												10
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	47

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 1,000 ppm (continued)

	0	4	5	5	5	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	1	8	3	5	9	9	9	2	3	4	8	8	8	9	9	1	2	2	2	2	2	3	3	3	3
	4	1	9	5	2	8	8	6	3	9	0	8	8	5	5	2	3	3	9	9	9	0	0	0	0
	4	3	3	3	3	3	3	3	3	3	3	3	4	3	3	3	3	3	3	3	3	3	3	3	3
Carcass ID Number	0	6	9	8	9	6	9	8	7	7	8	9	0	8	9	6	6	7	6	6	6	6	6	7	7
	5	1	1	2	5	2	4	1	8	1	7	6	0	6	9	6	7	5	3	4	5	8	9	0	2
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma								X		X		X			X							X			
Fibroadenoma, multiple														X											
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cervical, vertebra, hemangiosarcoma			X																						
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve			+																						
Spinal cord			+																						
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Fibrosarcoma									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X				X	X		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 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 1,000 ppm (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	373	374	376	377	379	380	383	384	385	388	389	390	392	393	397	398	401	402	403	404	406	407	408	409	410	Total Tissues/ Tumors
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma			X		X		X															X				9
Fibroadenoma, multiple																		X								2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, lipoma		X																								1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cervical, vertebra, hemangiosarcoma																										1
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma												X														1
Fibrosarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																		+								1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X	X	X				X		X	X					X			X		X		22

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 2,500 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol): 2,500 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	
Carcass ID Number	425	429	430	432	433	434	435	436	437	440	441	442	443	444	447	449	450	455	457	464	465	466	467	469	470	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma																X										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																	X									1
Mesentery						+																				4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma			X			X	X	X			X			X						X	X				X	16
Pars distalis, adenoma, multiple																			X							1
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X		X		X											X				X					8
C-cell, carcinoma						X																				2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Adenoma																										1
Carcinoma																										2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal												X											X			9
Sarcoma stromal		X																								1
Vagina																									+	3

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 2,500 ppm (continued)

Number of Days on Study	452	491	518	541	572	572	591	597	604	605	620	641	660	663	663	688	688	697	698	711	715	719	729	729	729
Carcass ID Number	458	452	468	446	424	463	453	431	427	428	461	439	456	448	459	451	462	425	426	454	438	460	421	422	423
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+								+					+		+			+	+		+			
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma					X		X			X									X		X				
Fibroadenoma, multiple															X		X								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord																+									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								X	
Carcinoma, metastatic, thyroid gland											X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																								+	
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X						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 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 2,500 ppm (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	
	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	Total
Carcass ID Number	2	2	3	3	3	3	3	3	3	4	4	4	4	4	4	4	5	5	5	6	6	6	6	6	7	Tissues/
	5	9	0	2	3	4	5	6	7	0	1	2	3	4	7	9	0	5	7	4	5	6	7	9	0	Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node									+					+			+									10
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma	X					X			X		X				X			X	X		X	X				14
Fibroadenoma, multiple																										2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma													X													1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Carcinoma, metastatic, thyroid gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye								+								+						+				4
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear									X	X				X	X	X	X					X		X		20

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rates[a]	1/50 (2%)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted rates[b]	2.9%	6.2%	9.4%	3.6%
Terminal rates[c]	1/34 (3%)	1/31 (3%)	3/32 (9%)	1/28 (4%)
First incidence (days)	729 (T)	712	729 (T)	729 (T)
Life table tests[d]	P=0.614N	P=0.459	P=0.283	P=0.718
Logistic regression tests[d]	P=0.619N	P=0.460	P=0.283	P=0.718
Cochran-Armitage test[d]	P=0.541N			
Fisher exact test[d]		P=0.500	P=0.309	P=0.753N
Clitoral Gland: Adenoma				
Overall rates	4/49 (8%)	1/48 (2%)	0/50 (0%)	1/49 (2%)
Adjusted rates	12.1%	3.3%	0.0%	2.7%
Terminal rates	4/33 (12%)	1/30 (3%)	0/32 (0%)	0/27 (0%)
First incidence (days)	729 (T)	729 (T)	–[e]	663
Life table tests	P=0.196N	P=0.207N	P=0.066N	P=0.245N
Logistic regression tests	P=0.186N	P=0.207N	P=0.066N	P=0.221N
Cochran-Armitage test	P=0.157N			
Fisher exact test		P=0.187N	P=0.056N	P=0.181N
Clitoral: Adenoma or Carcinoma				
Overall rates	5/49 (10%)	2/48 (4%)	0/50 (0%)	3/49 (6%)
Adjusted rates	14.1%	5.6%	0.0%	7.3%
Terminal rates	4/33 (12%)	1/30 (3%)	0/32 (0%)	0/27 (0%)
First incidence (days)	673	652	–	597
Life table tests	P=0.475N	P=0.259N	P=0.038N	P=0.460N
Logistic regression tests	P=0.384N	P=0.238N	P=0.036N	P=0.323N
Cochran-Armitage test	P=0.394N			
Fisher exact test		P=0.226N	P=0.027N	P=0.357N
Mammary Gland: Adenoma or Carcinoma				
Overall rates	3/50 (6%)	1/50 (2%)	0/50 (0%)	0/50 (0%)
Adjusted rates	8.4%	3.0%	0.0%	0.0%
Terminal rates	2/34 (6%)	0/31 (0%)	0/32 (0%)	0/28 (0%)
First incidence (days)	725	712	–	–
Life table tests	P=0.088N	P=0.353N	P=0.139N	P=0.165N
Logistic regression tests	P=0.083N	P=0.347N	P=0.138N	P=0.164N
Cochran-Armitage test	P=0.069N			
Fisher exact test		P=0.309N	P=0.121N	P=0.121N
Mammary Gland: Fibroadenoma				
Overall rates	29/50 (58%)	24/50 (48%)	11/50 (22%)	16/50 (32%)
Adjusted rates	72.2%	58.9%	28.6%	44.0%
Terminal rates	23/34 (68%)	15/31 (48%)	6/32 (19%)	9/28 (32%)
First incidence (days)	673	372	626	572
Life table tests	P=0.048N	P=0.393N	P=0.001N	P=0.076N
Logistic regression tests	P=0.010N	P=0.261N	P<0.001N	P=0.021N
Cochran-Armitage test	P=0.006N			
Fisher exact test		P=0.212N	P<0.001N	P=0.008N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
Mammary Gland: Fibroadenoma or Adenoma				
Overall rates	31/50 (62%)	24/50 (48%)	11/50 (22%)	16/50 (32%)
Adjusted rates	75.4%	58.9%	28.6%	44.0%
Terminal rates	24/34 (71%)	15/31 (48%)	6/32 (19%)	9/28 (32%)
First incidence (days)	673	372	626	572
Life table tests	P=0.028N	P=0.274N	P<0.001N	P=0.041N
Logistic regression tests	P=0.004N	P=0.150N	P<0.001N	P=0.008N
Cochran-Armitage test	P=0.003N			
Fisher exact test		P=0.114N	P<0.001N	P=0.002N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rates	32/50 (64%)	24/50 (48%)	11/50 (22%)	16/50 (32%)
Adjusted rates	77.8%	58.9%	28.6%	44.0%
Terminal rates	25/34 (74%)	15/31 (48%)	6/32 (19%)	9/28 (32%)
First incidence (days)	673	372	626	572
Life table tests	P=0.020N	P=0.219N	P<0.001N	P=0.028N
Logistic regression tests	P=0.003N	P=0.108N	P<0.001N	P=0.004N
Cochran-Armitage test	P=0.002N			
Fisher exact test		P=0.079N	P<0.001N	P=0.001N
Oral Cavity (Tongue, Pharynx, or Tooth): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rates	3/50 (6%)	0/50 (0%)	2/50 (4%)	0/50 (0%)
Adjusted rates	7.9%	0.0%	6.3%	0.0%
Terminal rates	2/34 (6%)	0/31 (0%)	2/32 (6%)	0/28 (0%)
First incidence (days)	623	–	729 (T)	–
Life table tests	P=0.168N	P=0.138N	P=0.530N	P=0.159N
Logistic regression tests	P=0.149N	P=0.117N	P=0.516N	P=0.117N
Cochran-Armitage test	P=0.138N			
Fisher exact test		P=0.121N	P=0.500N	P=0.121N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	27/49 (55%)	15/50 (30%)	17/50 (34%)	17/49 (35%)
Adjusted rates	68.4%	39.3%	41.4%	48.4%
Terminal rates	21/33 (64%)	9/31 (29%)	9/32 (28%)	11/28 (39%)
First incidence (days)	518	605	481	572
Life table tests	P=0.263N	P=0.035N	P=0.071N	P=0.147N
Logistic regression tests	P=0.128N	P=0.013N	P=0.032N	P=0.053N
Cochran-Armitage test	P=0.103N			
Fisher exact test		P=0.010N	P=0.028N	P=0.034N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rates	27/49 (55%)	15/50 (30%)	17/50 (34%)	18/49 (37%)
Adjusted rates	68.4%	39.3%	41.4%	50.1%
Terminal rates	21/33 (64%)	9/31 (29%)	9/32 (28%)	11/28 (39%)
First incidence (days)	518	605	481	572
Life table tests	P=0.345N	P=0.035N	P=0.071N	P=0.207N
Logistic regression tests	P=0.187N	P=0.013N	P=0.032N	P=0.082N
Cochran-Armitage test	P=0.152N			
Fisher exact test		P=0.010N	P=0.028N	P=0.052N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
Thyroid Gland (C-cell): Adenoma				
Overall rates	3/49 (6%)	2/49 (4%)	8/50 (16%)	8/50 (16%)
Adjusted rates	8.0%	6.7%	22.8%	24.3%
Terminal rates	2/34 (6%)	2/30 (7%)	6/32 (19%)	5/28 (18%)
First incidence (days)	663	729 (T)	598	591
Life table tests	P=0.019	P=0.554N	P=0.084	P=0.061
Logistic regression tests	P=0.028	P=0.532N	P=0.094	P=0.088
Cochran-Armitage test	P=0.040			
Fisher exact test		P=0.500N	P=0.106	P=0.106
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rates	3/49 (6%)	4/49 (8%)	8/50 (16%)	9/50 (18%)
Adjusted rates	8.0%	13.3%	22.8%	26.2%
Terminal rates	2/34 (6%)	4/30 (13%)	6/32 (19%)	5/28 (18%)
First incidence (days)	663	729 (T)	598	591
Life table tests	P=0.017	P=0.434	P=0.084	P=0.036
Logistic regression tests	P=0.029	P=0.450	P=0.094	P=0.061
Cochran-Armitage test	P=0.039			
Fisher exact test		P=0.500	P=0.106	P=0.065
Uterus: Stromal Polyp				
Overall rates	2/50 (4%)	5/50 (10%)	9/50 (18%)	9/50 (18%)
Adjusted rates	5.9%	14.9%	24.4%	24.5%
Terminal rates	2/34 (6%)	4/31 (13%)	6/32 (19%)	2/28 (7%)
First incidence (days)	729 (T)	626	481	591
Life table tests	P=0.015	P=0.183	P=0.024	P=0.015
Logistic regression tests	P=0.028	P=0.192	P=0.027	P=0.025
Cochran-Armitage test	P=0.030			
Fisher exact test		P=0.218	P=0.026	P=0.026
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rates	2/50 (4%)	6/50 (12%)	9/50 (18%)	10/50 (20%)
Adjusted rates	5.9%	16.7%	24.4%	27.4%
Terminal rates	2/34 (6%)	4/31 (13%)	6/32 (19%)	3/28 (11%)
First incidence (days)	729 (T)	590	481	591
Life table tests	P=0.010	P=0.114	P=0.024	P=0.008
Logistic regression tests	P=0.020	P=0.133	P=0.027	P=0.013
Cochran-Armitage test	P=0.020			
Fisher exact test		P=0.134	P=0.026	P=0.014
All Organs: Mononuclear Cell Leukemia				
Overall rates	18/50 (36%)	18/50 (36%)	22/50 (44%)	20/50 (40%)
Adjusted rates	41.8%	43.5%	51.6%	48.5%
Terminal rates	10/34 (29%)	8/31 (26%)	12/32 (38%)	8/28 (29%)
First incidence (days)	453	604	481	452
Life table tests	P=0.192	P=0.448	P=0.226	P=0.222
Logistic regression tests	P=0.370	P=0.577N	P=0.275	P=0.506
Cochran-Armitage test	P=0.364			
Fisher exact test		P=0.582N	P=0.270	P=0.418

Table B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
All Organs: Benign Neoplasms				
Overall rates	42/50 (84%)	35/50 (70%)	36/50 (72%)	38/50 (76%)
Adjusted rates	93.2%	79.1%	79.8%	88.3%
Terminal rates	31/34 (91%)	22/31 (71%)	23/32 (72%)	23/28 (82%)
First incidence (days)	518	372	481	572
Life table tests	P=0.246	P=0.332N	P=0.336N	P=0.328
Logistic regression tests	P=0.503N	P=0.097N	P=0.163N	P=0.440N
Cochran-Armitage test	P=0.379N			
Fisher exact test		P=0.077N	P=0.114N	P=0.227N
All Organs: Malignant Neoplasms				
Overall rates	22/50 (44%)	23/50 (46%)	24/50 (48%)	25/50 (50%)
Adjusted rates	49.0%	51.7%	54.0%	56.9%
Terminal rates	12/34 (35%)	10/31 (32%)	12/32 (38%)	10/28 (36%)
First incidence (days)	453	428	481	452
Life table tests	P=0.155	P=0.370	P=0.341	P=0.164
Logistic regression tests	P=0.359	P=0.557	P=0.444	P=0.487
Cochran-Armitage test	P=0.311			
Fisher exact test		P=0.500	P=0.421	P=0.344
All Organs: Benign or Malignant Neoplasms				
Overall rates	47/50 (94%)	45/50 (90%)	43/50 (86%)	47/50 (94%)
Adjusted rates	95.9%	90.0%	87.8%	95.9%
Terminal rates	32/34 (94%)	26/31 (84%)	26/32 (81%)	26/28 (93%)
First incidence (days)	453	372	481	452
Life table tests	P=0.115	P=0.433	P=0.491N	P=0.118
Logistic regression tests	P=0.453	P=0.307N	P=0.195N	P=0.665N
Cochran-Armitage test	P=0.474			
Fisher exact test		P=0.357N	P=0.159N	P=0.661N

(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 tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE B4a
Historical Incidence of Hepatocellular Neoplasms in Untreated Female F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus			
2,4-Dichlorophenol	0/50	0/50	0/50
4,4′-Thiobis(6-*t*-butyl-*m*-cresol)	0/50	0/50	0/50
5,5-Diphenylhydantoin	0/50	0/50	0/50
Ethylene Thiourea	0/50	0/50	0/50
Polybrominated Biphenyls (Firemaster FF-1®)	0/50	0/50	0/50
Manganese Sulfate Monohydrate	0/50	0/50	0/50
Triamterene	0/50	0/50	0/50
Tricresyl Phosphate	0/51	0/51	0/51
Overall Historical Incidence			
Total	6/1,251 (0.5%)	1/1,251 (0.1%)	7/1,251 (0.6%)
Standard deviation	1.3%	0.4%	1.4%
Range	0%-6%	0%-2%	0%-6%

[a] Data as of 20 August 1992

TABLE B4b
Historical Incidence of Thyroid Gland C-Cell Neoplasms in Untreated Female F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus			
2,4-Dichlorophenol	9/50	3/50	12/50
4,4′-Thiobis(6-*t*-butyl-*m*-cresol)	3/49	0/49	3/49
5,5-Diphenylhydantoin	13/48	2/48	15/48
Ethylene Thiourea	11/50	1/50	12/50
Polybrominated Biphenyls (Firemaster FF-1®)	11/50	0/50	11/50
Manganese Sulfate Monohydrate	8/50	1/50	9/50
Triamterene	5/50	0/50	5/50
Tricresyl Phosphate	9/51	0/51	9/51
Overall Historical Incidence			
Total	161/1,246 (12.9%)	29/1,246 (2.3%)	188/1,246 (15.1%)
Standard deviation	5.8%	2.1%	6.3%
Range	4%-27%	0%-8%	6%-31%

[a] Data as of 20 August 1992

TABLE B4c
Historical Incidence of Uterine Neoplasms in Untreated Female F344/N Rats[a]

Study	Incidence in Controls		
	Stromal Polyp	Stromal Sarcoma	Stromal Polyp or Stromal Sarcoma
Historical Incidence at Battelle-Columbus			
2,4-Dichlorophenol	12/50	1/50	13/50
4,4′-Thiobis(6-*t*-butyl-*m*-cresol)	2/50	0/50	2/50
5,5-Diphenylhydantoin	6/50	0/50	6/50
Ethylene Thiourea	9/50	0/50	9/50
Polybrominated Biphenyls (Firemaster FF-1®)	7/50	0/50	7/50
Manganese Sulfate Monohydrate	13/50	0/50	13/50
Triamterene	4/50	0/50	4/50
Tricresyl Phosphate	6/51	0/51	6/51
Overall Historical Incidence			
Total	205/1,251 (16.4%)	9/1,251 (0.7%)	213/1,251 (17.0%)
Standard deviation	6.6%	1.5%	6.9%
Range	2%-30%	0%-6%	2%-30%

[a] Data as of 20 August 1992

Table B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	11	14	16	16
Natural deaths	5	5	2	6
Survivors				
Died last week of study		1		
Terminal sacrifice	34	30	32	28
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Intestine large, rectum	(10)	(10)	(10)	(10)
Parasite metazoan		3 (30%)	2 (20%)	
Liver	(10)	(10)	(10)	(10)
Basophilic focus	10 (100%)	10 (100%)	10 (100%)	10 (100%)
Eosinophilic focus			1 (10%)	
Hepatodiaphragmatic nodule	2 (20%)	1 (10%)	6 (60%)	
Inflammation, chronic	2 (20%)	6 (60%)	2 (20%)	4 (40%)
Mixed cell focus		1 (10%)		10 (100%)
Bile duct, hyperplasia	1 (10%)	3 (30%)	1 (10%)	3 (30%)
Hepatocyte, vacuolization cytoplasmic		1 (10%)	1 (10%)	8 (80%)
Periportal, kupffer cell, hypertrophy	1 (10%)		5 (50%)	10 (100%)
Sinusoid, ectasia			1 (10%)	
Mesentery	(1)	(2)		
Inflammation, chronic active	1 (100%)	2 (100%)		
Pancreas	(10)	(10)	(10)	(10)
Acinus, atrophy	4 (40%)	5 (50%)	4 (40%)	3 (30%)
Cardiovascular System				
Heart	(10)	(10)	(10)	(10)
Cardiomyopathy, chronic	7 (70%)	9 (90%)	5 (50%)	6 (60%)
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Degeneration, fatty	1 (10%)			1 (10%)
Hyperplasia	1 (10%)			1 (10%)
Pituitary gland	(10)	(10)	(10)	(10)
Pars distalis, cyst	8 (80%)	9 (90%)	6 (60%)	5 (50%)
Pars distalis, hyperplasia	7 (70%)	5 (50%)	6 (60%)	3 (30%)
Rathke's cleft, inflammation, chronic active	1 (10%)			
Rathke's cleft, pigmentation, hemosiderin	1 (10%)			
Thyroid gland	(10)	(10)	(10)	(10)
C-cell, hyperplasia	4 (40%)	1 (10%)	1 (10%)	1 (10%)

[a] Number of animals examined microscopically at site and number of animals with lesion

Table B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
15-Month Interim Evaluation (continued)				
General Body System				
None				
Genital System				
Clitoral gland	(10)	(10)	(10)	(10)
Inflammation, chronic active	2 (20%)	5 (50%)	1 (10%)	2 (20%)
Ovary	(10)	(10)	(10)	(10)
Cyst	2 (20%)	3 (30%)	4 (40%)	2 (20%)
Uterus	(10)	(10)	(10)	(10)
Inflammation, suppurative				1 (10%)
Hematopoietic System				
Lymph node, mandibular	(10)	(10)	(10)	(10)
Sinus, ectasia	1 (10%)			2 (20%)
Integumentary System				
Mammary gland	(10)	(10)	(10)	(10)
Hyperplasia, cystic	10 (100%)	10 (100%)	10 (100%)	10 (100%)
Musculoskeletal System				
Skeletal muscle	(10)	(10)	(10)	(10)
Necrosis, coagulative	3 (30%)	1 (10%)	3 (30%)	
Nervous System				
None				
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Inflammation, chronic active	7 (70%)	6 (60%)	3 (30%)	5 (50%)
Alveolar epithelium, hyperplasia	1 (10%)			1 (10%)
Nose	(10)	(10)	(10)	(10)
Fungus				1 (10%)
Inflammation, chronic active	1 (10%)			1 (10%)
Nasolacrimal duct, cyst				1 (10%)
Nasolacrimal duct, inflammation, suppurative	3 (30%)		2 (20%)	
Special Senses System				
Eye	(2)		(1)	(1)
Lens, cataract	2 (100%)		1 (100%)	
Retina, atrophy	2 (100%)		1 (100%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-t-Butyl-m-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
15-Month Interim Evaluation (continued)				
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Mineralization	10 (100%)	10 (100%)	10 (100%)	8 (80%)
Nephropathy, chronic	9 (90%)	10 (100%)	10 (100%)	10 (100%)
2-Year Study				
Alimentary System				
Intestine large, colon	(50)	(50)	(50)	(49)
Parasite metazoan	4 (8%)	4 (8%)	2 (4%)	
Intestine large, rectum	(50)	(50)	(50)	(50)
Parasite metazoan	5 (10%)	4 (8%)	3 (6%)	1 (2%)
Intestine large, cecum	(50)	(50)	(50)	(49)
Inflammation, chronic active		1 (2%)		
Intestine small, jejunum	(50)	(50)	(50)	(49)
Inflammation, chronic active	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)			
Basophilic focus	37 (74%)	34 (68%)	38 (76%)	36 (72%)
Clear cell focus		1 (2%)	1 (2%)	1 (2%)
Eosinophilic focus	5 (10%)	7 (14%)	8 (16%)	4 (8%)
Fatty change	9 (18%)	8 (16%)	15 (30%)	19 (38%)
Fibrosis		1 (2%)		
Hepatodiaphragmatic nodule	10 (20%)	4 (8%)	7 (14%)	8 (16%)
Inflammation, chronic	22 (44%)	21 (42%)	18 (36%)	21 (42%)
Mixed cell focus	5 (10%)	4 (8%)	14 (28%)	34 (68%)
Necrosis, coagulative		1 (2%)		
Bile duct, hyperplasia	18 (36%)	18 (36%)	21 (42%)	20 (40%)
Hepatocyte, degeneration, cystic				4 (8%)
Hepatocyte, vacuolization cytoplasmic	12 (24%)	10 (20%)	20 (40%)	34 (68%)
Periportal, kupffer cell, hypertrophy	11 (22%)	10 (20%)	9 (18%)	42 (84%)
Sinusoid, dilatation		1 (2%)		1 (2%)
Mesentery	(9)	(7)	(8)	(4)
Ectopic tissue			1 (13%)	
Inflammation, chronic active		2 (29%)		
Inflammation, necrotizing	9 (100%)	4 (57%)	6 (75%)	2 (50%)
Mineralization	5 (56%)		1 (13%)	1 (25%)
Pancreas	(50)	(50)	(50)	(49)
Acinus, atrophy	22 (44%)	18 (36%)	17 (34%)	23 (47%)
Salivary glands	(49)	(49)	(50)	(50)
Atrophy				1 (2%)
Stomach, forestomach	(50)	(50)	(50)	(49)
Acanthosis	1 (2%)	3 (6%)	4 (8%)	1 (2%)
Diverticulum				1 (2%)
Hyperkeratosis	1 (2%)	1 (2%)	1 (2%)	
Inflammation, chronic active	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Stomach, glandular	(50)	(50)	(50)	(49)
Diverticulum				2 (4%)
Erosion	3 (6%)	2 (4%)	1 (2%)	
Inflammation, chronic active	1 (2%)			1 (2%)
Mineralization			1 (2%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Tongue	(1)			(1)
Epithelium, acanthosis				1 (100%)
Tooth	(2)		(1)	
Gingiva, inflammation, chronic active	1 (50%)		1 (100%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy, chronic	41 (82%)	37 (74%)	41 (82%)	39 (78%)
Mineralization			1 (2%)	
Thrombosis	1 (2%)			
Coronary artery, necrosis, fibrinoid			1 (2%)	
Coronary artery, perivascular, inflammation, chronic active			1 (2%)	
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Degeneration, fatty	20 (40%)	20 (40%)	14 (28%)	15 (30%)
Hematocyst			1 (2%)	
Hyperplasia	11 (22%)	16 (32%)	12 (24%)	10 (20%)
Hypertrophy	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Necrosis, coagulative		1 (2%)		1 (2%)
Adrenal medulla	(50)	(50)	(49)	(50)
Hyperplasia	10 (20%)	7 (14%)	2 (4%)	7 (14%)
Islets, pancreatic	(50)	(50)	(50)	(49)
Hyperplasia	1 (2%)			
Parathyroid gland	(48)	(48)	(46)	(50)
Hyperplasia	1 (2%)		1 (2%)	1 (2%)
Pituitary gland	(49)	(50)	(50)	(49)
Craniopharyngeal duct, cyst				1 (2%)
Pars distalis, cyst	24 (49%)	29 (58%)	22 (44%)	22 (45%)
Pars distalis, hyperplasia	17 (35%)	19 (38%)	18 (36%)	22 (45%)
Pars intermedia, cyst	3 (6%)	1 (2%)		
Thyroid gland	(49)	(49)	(50)	(50)
Infiltration cellular, lymphocyte	1 (2%)			
C-cell, hyperplasia	28 (57%)	24 (49%)	27 (54%)	18 (36%)
Follicular cell, hyperplasia	2 (4%)	1 (2%)	1 (2%)	1 (2%)
General Body System				
None				
Genital System				
Clitoral gland	(49)	(48)	(50)	(49)
Hyperplasia	5 (10%)	6 (13%)	11 (22%)	5 (10%)
Inflammation, chronic active	7 (14%)	8 (17%)	7 (14%)	2 (4%)
Duct, dilatation	5 (10%)	1 (2%)		2 (4%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-t-Butyl-m-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
2-Year Study (continued)				
Genital System (continued)				
Ovary	(50)	(50)	(50)	(50)
Atrophy			1 (2%)	1 (2%)
Cyst	14 (28%)	10 (20%)	12 (24%)	16 (32%)
Necrosis, coagulative		1 (2%)		
Uterus	(50)	(50)	(50)	(50)
Dilatation	3 (6%)	3 (6%)	2 (4%)	2 (4%)
Diverticulum		1 (2%)	1 (2%)	2 (4%)
Hemorrhage	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, cystic, glandular	3 (6%)	5 (10%)	5 (10%)	1 (2%)
Inflammation, chronic active		3 (6%)	2 (4%)	2 (4%)
Vagina			(2)	(3)
Estrus				1 (33%)
Exudate			1 (50%)	1 (33%)
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(50)
Femoral, myelofibrosis	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Lymph node	(14)	(10)	(10)	(10)
Mediastinal, cyst	1 (7%)			
Lymph node, mandibular	(49)	(49)	(50)	(50)
Cyst			1 (2%)	
Hyperplasia, plasma cell			1 (2%)	
Spleen	(50)	(50)	(50)	(50)
Fibrosis		2 (4%)	2 (4%)	1 (2%)
Hematopoietic cell proliferation	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Necrosis, coagulative	1 (2%)			
Red pulp, atrophy	2 (4%)			
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Hyperplasia, cystic	41 (82%)	48 (96%)	47 (94%)	45 (90%)
Inflammation, chronic active	1 (2%)		1 (2%)	
Skin	(50)	(50)	(50)	(50)
Acanthosis		1 (2%)		2 (4%)
Cyst epithelial inclusion	3 (6%)			
Hyperkeratosis		1 (2%)		
Inflammation, chronic active	1 (2%)	1 (2%)		2 (4%)
Ulcer, multiple				2 (4%)
Musculoskeletal System				
Bone	(49)	(50)	(50)	(50)
Cranium, hyperostosis			1 (2%)	
Femur, osteopetrosis			1 (2%)	
Skeletal muscle	(50)	(50)	(50)	(50)
Inflammation, chronic active			1 (2%)	1 (2%)
Necrosis, coagulative	2 (4%)	3 (6%)	3 (6%)	3 (6%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
2-Year Study (continued)				
Nervous System				
Brain	(50)	(50)	(50)	(50)
Compression	5 (10%)	4 (8%)	2 (4%)	1 (2%)
Hemorrhage, acute	2 (4%)	2 (4%)		2 (4%)
Hydrocephalus	4 (8%)	4 (8%)	2 (4%)	1 (2%)
Perivascular, infiltration cellular, lymphocyte	1 (2%)			
Spinal cord			(1)	(1)
Compression			1 (100%)	
Respiratory System				
Lung	(50)	(49)	(49)	(50)
Hemorrhage, acute				1 (2%)
Inflammation, chronic active	12 (24%)	12 (24%)	12 (24%)	19 (38%)
Leukocytosis				1 (2%)
Metaplasia, osseous	1 (2%)			1 (2%)
Alveolar epithelium, hyperplasia	5 (10%)	4 (8%)	3 (6%)	2 (4%)
Alveolus, infiltration cellular, histiocyte	33 (66%)	20 (41%)	26 (53%)	34 (68%)
Artery, mediastinum, necrosis, fibrinoid			1 (2%)	
Artery, mediastinum, perivascular, inflammation, chronic active			1 (2%)	
Nose	(50)	(50)	(50)	(50)
Fungus			1 (2%)	
Inflammation, chronic active	1 (2%)	1 (2%)	5 (10%)	4 (8%)
Nasolacrimal duct, inflammation, suppurative	12 (24%)	11 (22%)	15 (30%)	9 (18%)
Trachea	(50)	(50)	(50)	(50)
Cyst		1 (2%)		
Special Senses System				
Eye	(2)	(3)	(1)	(4)
Cornea, inflammation, chronic active				1 (25%)
Lens, cataract	2 (100%)	3 (100%)	1 (100%)	3 (75%)
Retina, atrophy	2 (100%)	3 (100%)	1 (100%)	3 (75%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cyst			2 (4%)	2 (4%)
Hydronephrosis		1 (2%)		
Infarct, chronic		1 (2%)		
Mineralization	1 (2%)	2 (4%)	1 (2%)	
Necrosis, coagulative				1 (2%)
Nephropathy, chronic	44 (88%)	41 (82%)	46 (92%)	48 (96%)
Renal tubule, epithelium, hypertrophy	1 (2%)			
Urinary bladder	(50)	(49)	(50)	(50)
Transitional epithelium, hyperplasia	1 (2%)			

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR FEED STUDY OF 4,4′-THIOBIS(6-*t*-BUTYL-*m*-CRESOL)

Table C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

	0 ppm	250 ppm	500 ppm	1,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	2	2		1
Natural deaths	6	6	1	4
Survivors				
Died last week of study	1	1		
Terminal sacrifice	41	41	49	45
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Intestine small, duodenum	(10)	(10)	(10)	(10)
Liver	(10)	(10)	(10)	(10)
Hepatocellular carcinoma			1 (10%)	
Hepatocellular adenoma		2 (20%)	4 (40%)	1 (10%)
Hepatocellular adenoma, multiple				1 (10%)
Cardiovascular System				
None				
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Capsule, spindle cell, adenoma			1 (10%)	
General Body System				
None				
Genital System				
None				
Hematopoietic System				
Lymph node, mandibular	(9)	(10)	(10)	(10)
Lymph node, mesenteric	(9)	(9)	(10)	(8)
Integumentary System				
None				
Musculoskeletal System				
None				

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm
***15-Month Interim Evaluation* (continued)**				
Nervous System				
None				
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Alveolar/bronchiolar adenoma	1 (10%)	1 (10%)	1 (10%)	
Special Senses System				
None				
Urinary System				
None				
Systemic Lesions				
Multiple organs[b]	(10)	(10)	(10)	(10)
Lymphoma malignant mixed			1 (10%)	
2-Year Study				
Alimentary System				
Gallbladder	(50)	(49)	(50)	(49)
Intestine small, duodenum	(50)	(49)	(49)	(50)
Polyp adenomatous		1 (2%)		
Intestine small, jejunum	(50)	(50)	(50)	(50)
Adenocarcinoma			1 (2%)	
Liver	(50)	(50)	(50)	(50)
Hemangiosarcoma				1 (2%)
Hepatocellular carcinoma	8 (16%)	9 (18%)	6 (12%)	3 (6%)
Hepatocellular carcinoma, multiple	3 (6%)	2 (4%)	3 (6%)	1 (2%)
Hepatocellular adenoma	11 (22%)	11 (22%)	16 (32%)	9 (18%)
Hepatocellular adenoma, multiple	6 (12%)	11 (22%)	6 (12%)	3 (6%)
Mesentery	(1)	(1)		(1)
Pancreas	(50)	(50)	(50)	(50)
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)		1 (2%)	
Cardiovascular System				
None				

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm
2-Year Study (continued)				
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Bilateral, spindle cell, subcapsular, adenoma		1 (2%)	1 (2%)	
Spindle cell, subcapsular, adenoma	11 (22%)	6 (12%)	6 (12%)	6 (12%)
Adrenal medulla	(50)	(50)	(50)	(50)
Pheochromocytoma malignant			1 (2%)	
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma		1 (2%)		
Carcinoma	1 (2%)			
Pituitary gland	(47)	(46)	(49)	(47)
Pars distalis, adenoma			1 (2%)	
Thyroid gland	(50)	(50)	(50)	(50)
Adenocarcinoma			1 (2%)	
C-cell, adenoma	1 (2%)			
Follicular cell, adenoma			1 (2%)	
General Body System				
None				
Genital System				
Testes	(50)	(50)	(50)	(50)
Interstitial cell, adenoma	1 (2%)			
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(48)
Femoral, hemangiosarcoma	1 (2%)			1 (2%)
Lymph node		(1)	(1)	(2)
Inguinal, hemangioma		1 (100%)		
Lymph node, mandibular	(50)	(47)	(47)	(48)
Lymph node, mesenteric	(49)	(46)	(48)	(47)
Fibrosarcoma, metastatic, uncertain primary site		1 (2%)		
Spleen	(50)	(50)	(50)	(50)
Hemangioma	1 (2%)			
Hemangiosarcoma	1 (2%)	1 (2%)		1 (2%)
Thymus	(47)	(46)	(46)	(45)
Integumentary System				
None				
Musculoskeletal System				
None				

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm
2-Year Study (continued)				
Nervous System				
None				
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Adenocarcinoma, metastatic, harderian gland	2 (4%)			
Alveolar/bronchiolar adenoma	4 (8%)	6 (12%)	8 (16%)	3 (6%)
Alveolar/bronchiolar adenoma, multiple	2 (4%)	1 (2%)		
Alveolar/bronchiolar carcinoma	3 (6%)	2 (4%)	1 (2%)	
Fibrosarcoma, metastatic, uncertain primary site		1 (2%)		
Hepatocellular carcinoma, metastatic, liver	3 (6%)	4 (8%)	4 (8%)	1 (2%)
Nose	(50)	(50)	(50)	(48)
Adenocarcinoma, metastatic, harderian gland	1 (2%)			
Special Senses System				
Ear	(1)		(1)	
Pinna, fibroma	1 (100%)			
Pinna, trichoepithelioma			1 (100%)	
Eye	(2)	(2)	(1)	
Adenocarcinoma, metastatic, harderian gland	1 (50%)			
Harderian gland	(3)	(3)	(3)	
Adenocarcinoma	2 (67%)		1 (33%)	
Adenoma	1 (33%)	3 (100%)	2 (67%)	
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Artery, fibrosarcoma, metastatic, uncertain primary site		1 (2%)		
Systemic Lesions				
Multiple organs	(50)	(50)	(50)	(50)
Lymphoma malignant histiocytic	1 (2%)			1 (2%)
Lymphoma malignant lymphocytic	1 (2%)			1 (2%)
Lymphoma malignant mixed		2 (4%)	2 (4%)	3 (6%)
Lymphoma malignant undifferentiated cell				1 (2%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	1	3	6	2
2-Year study	38	38	39	25
Total primary neoplasms				
15-Month interim evaluation	1	3	8	2
2-Year study	61	58	59	34
Total animals with benign neoplasms				
15-Month interim evaluation	1	3	5	2
2-Year study	30	29	33	18
Total benign neoplasms				
15-Month interim evaluation	1	3	6	2
2-Year study	40	42	43	21
Total animals with malignant neoplasms				
15-Month interim evaluation			2	
2-Year study	17	15	14	11
Total malignant neoplasms				
15-Month interim evaluation			2	
2-Year study	21	16	16	13
Total animals with metastatic neoplasms				
2-Year study	5	5	4	1
Total metastatic neoplasms				
2-Year study	7	7	4	1
Total Animals with malignant neoplasms of uncertain primary site				
2-Year study		1		

[a] Number of animals examined microscopically at site and number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol): 0 ppm

Number of Days on Study	508	620	625	655	683	683	690	712	731	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733
Carcass ID Number	049	035	050	037	001	045	008	036	021	002	004	005	006	007	009	011	012	014	015	016	017	018	019	022	023
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma				X			X		X	X	X														
Hepatocellular carcinoma, multiple		X																							
Hepatocellular adenoma							X									X	X							X	
Hepatocellular adenoma, multiple												X						X			X				
Mesentery																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma							X																		
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spindle cell, subcapsular, adenoma	X										X			X		X	X	X						X	
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Pituitary gland	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma										X															
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma															X										

+: 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 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 0 ppm (continued)

Number of Days on Study	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	025	026	027	028	030	031	032	033	034	039	040	041	042	043	044	046	047	051	052	053	054	055	056	058	060	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma											X	X			X											8
Hepatocellular carcinoma, multiple								X													X					3
Hepatocellular adenoma			X				X			X	X		X		X		X									11
Hepatocellular adenoma, multiple		X							X										X							6
Mesentery											+															1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spindle cell, subcapsular, adenoma				X										X							X	X				11
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma							X																			1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																										1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																										1

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol): 0 ppm (continued)

Number of Days on Study	508	620	652	655	683	683	690	712	731	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733
Carcass ID Number	049	035	050	037	001	045	008	036	021	002	004	005	006	007	009	011	012	014	015	016	017	018	019	022	023
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, hemangiosarcoma																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																								X	
Hemangiosarcoma																									
Thymus	+	+	+	+	+	+	+	+	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	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, harderian gland						X																			
Alveolar/bronchiolar adenoma								X				X								X					
Alveolar/bronchiolar adenoma, multiple							X																		
Alveolar/bronchiolar carcinoma								X	X				X												
Hepatocellular carcinoma, metastatic, liver		X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, harderian gland						X																			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear												+													
Pinna, fibroma												X													
Eye						+																			
Adenocarcinoma, metastatic, harderian gland						X																			
Harderian gland						+																			
Adenocarcinoma						X																			
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic										X															

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 0 ppm (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Total
Carcass ID Number	2	2	2	2	3	3	3	3	3	3	4	4	4	4	4	4	4	5	5	5	5	5	5	5	6	Tissues/
	5	6	7	8	0	1	2	3	4	9	0	1	2	3	4	6	7	1	2	3	4	5	6	8	0	Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femoral, hemangiosarcoma															X											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Hemangiosarcoma															X											1
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	47
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	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, harderian gland	X																									2
Alveolar/bronchiolar adenoma																								X		4
Alveolar/bronchiolar adenoma, multiple													X													2
Alveolar/bronchiolar carcinoma																										3
Hepatocellular carcinoma, metastatic, liver								X				X														3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, harderian gland																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Pinna, fibroma																										1
Eye	+																									2
Adenocarcinoma, metastatic, harderian gland																										1
Harderian gland	+															+										3
Adenocarcinoma	X																									2
Adenoma																X										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																			X							1
Lymphoma malignant lymphocytic																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 250 ppm

Number of Days on Study	489	507	557	573	638	661	680	709	729	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	732
Carcass ID Number	069	118	078	116	096	093	067	100	077	062	063	064	065	066	068	070	071	072	073	074	076	079	080	081	083
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma	X	X	X		X		X								X	X				X					
Hepatocellular carcinoma, multiple								X	X																
Hepatocellular adenoma					X					X														X	
Hepatocellular adenoma, multiple												X			X			X					X		X
Mesentery																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, spindle cell, subcapsular, adenoma																									
Spindle cell, subcapsular, adenoma															X		X								X
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	I	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol): 250 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	0 8 5	0 8 6	0 8 8	0 8 9	0 9 0	0 9 1	0 9 4	0 9 8	0 9 9	1 0 1	1 0 2	1 0 4	1 0 5	1 0 6	1 0 7	1 0 8	1 0 9	1 1 0	1 1 2	1 1 3	1 1 4	1 1 5	1 1 7	1 1 9	1 2 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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp adenomatous												X														1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																					X					9
Hepatocellular carcinoma, multiple																										2
Hepatocellular adenoma		X										X					X			X		X	X	X	X	11
Hepatocellular adenoma, multiple	X					X		X					X					X			X					11
Mesentery																				+						1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, spindle cell, subcapsular, adenoma																				X						1
Spindle cell, subcapsular, adenoma	X								X								X									6
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X																					1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 250 ppm (continued)

	4	5	5	5	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	8	0	5	7	3	6	8	0	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	9	7	7	3	8	1	0	9	9	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2
	0	1	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Carcass ID Number	6	1	7	1	9	9	6	0	7	6	6	6	6	6	6	7	7	7	7	7	7	7	8	8	8
	9	8	8	6	6	3	7	0	7	2	3	4	5	6	8	0	1	2	3	4	6	9	0	1	3
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node						+																			
Inguinal, hemangioma						X																			
Lymph node, mandibular	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	+	+	+	+	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, uncertain primary site					X																				
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	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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		X																	
Fibrosarcoma, metastatic, uncertain primary site					X																				
Hepatocellular carcinoma, metastatic, liver		X					X									X				X					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye										+															
Harderian gland										+															
Adenoma										X															
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Artery, fibrosarcoma, metastatic, uncertain primary site					X																				
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 250 ppm (continued)

Number of Days on Study	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	085	086	088	089	090	091	094	098	099	101	102	104	105	106	107	108	109	110	112	113	114	115	117	119	120	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										1
Inguinal, hemangioma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Fibrosarcoma, metastatic, uncertain primary site																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
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	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X		X	X				X					X	X											6
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma																										2
Fibrosarcoma, metastatic, uncertain primary site																										1
Hepatocellular carcinoma, metastatic, liver																										4
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye				+																						2
Harderian gland				+														+								3
Adenoma				X														X								3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Artery, fibrosarcoma, metastatic, uncertain primary site																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																		X	X							2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol): 500 ppm

Number of Days on Study	682	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730
Carcass ID Number	153	121	122	123	124	125	126	127	128	130	131	132	133	135	136	138	140	141	142	143	144	147	148	149	150
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma												X													
Intestine small, ileum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma	X	X											X												
Hepatocellular carcinoma, multiple						X						X												X	
Hepatocellular adenoma		X															X	X		X			X	X	X
Hepatocellular adenoma, multiple				X			X															X			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, spindle cell, subcapsular, adenoma																									
Spindle cell, subcapsular, adenoma							X		X											X					
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant		X																							
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Follicular cell, adenoma																									
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 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 500 ppm (continued)

Number of Days on Study	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	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	1 5 1	1 5 2	1 5 4	1 5 5	1 5 6	1 5 7	1 5 8	1 5 9	1 6 0	1 6 1	1 6 2	1 6 3	1 6 4	1 6 5	1 6 6	1 6 8	1 6 9	1 7 2	1 7 3	1 7 4	1 7 5	1 7 6	1 7 7	1 7 9	1 8 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma										X			X							X						6
Hepatocellular carcinoma, multiple																										3
Hepatocellular adenoma	X	X	X					X					X			X				X		X	X			16
Hepatocellular adenoma, multiple							X		X									X								6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma	X																									1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, spindle cell, subcapsular, adenoma																							X			1
Spindle cell, subcapsular, adenoma									X			X									X					6
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma									X																	1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma									X																	1
Follicular cell, adenoma															X											1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol): 500 ppm (continued)

Number of Days on Study	682	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730
Carcass ID Number	153	121	122	123	124	125	126	127	128	130	131	132	133	135	136	138	140	141	142	143	144	147	148	149	150
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																									
Lymph node, mandibular	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma		X	X					X			X					X					X				
Alveolar/bronchiolar carcinoma																		X							
Hepatocellular carcinoma, metastatic, liver						X						X												X	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Pinna, trichoepithelioma																									
Eye																									
Harderian gland																									
Adenocarcinoma																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																	X								

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol): 500 ppm (continued)

Number of Days on Study	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	151	152	154	155	156	157	158	159	160	161	162	163	164	165	166	168	169	172	173	174	175	176	177	179	180	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																							+			1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
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	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																	X				X					8
Alveolar/bronchiolar carcinoma																										1
Hepatocellular carcinoma, metastatic, liver													X													4
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																				+						1
Pinna, trichoepithelioma																				X						1
Eye																						+				1
Harderian gland					+																	+			+	3
Adenocarcinoma																									X	1
Adenoma					X																	X				2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																							X			2

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol): 1,000 ppm

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

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 1,000 ppm (continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	
Carcass ID Number	209	210	211	212	213	214	215	216	217	218	219	220	221	222	223	224	225	228	229	233	234	235	236	237	240	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma			X																							1
Hepatocellular carcinoma										X																3
Hepatocellular carcinoma, multiple													X													1
Hepatocellular adenoma			X				X		X							X						X			X	9
Hepatocellular adenoma, multiple						X											X									3
Mesentery																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spindle cell, subcapsular, adenoma		X															X				X				X	6
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 1,000 ppm (continued)

Number of Days on Study	595	638	670	701	724	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	226	239	232	201	190	181	182	183	184	185	186	187	188	191	192	193	195	196	198	200	202	203	204	207	208
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, hemangiosarcoma				X																					
Lymph node			+										+												
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																									+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X												
Hepatocellular carcinoma, metastatic, liver																			X						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic			X																						
Lymphoma malignant lymphocytic													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 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 1,000 ppm (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	
	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	0	0	0	0	0	0	0	0	
Carcass ID Number	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	Total
	0	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	3	3	3	3	3	4	Tissues/
	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	8	9	3	4	5	6	7	0	Tumors
Hematopoietic System																										
Bone marrow	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Femoral, hemangiosarcoma																										1
Lymph node																										2
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	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	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X				X																3
Hepatocellular carcinoma, metastatic, liver																										1
Nose	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed			X					X																		3
Lymphoma malignant undifferentiated cell type												X														1

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol)

	0 ppm	250 ppm	500 ppm	1,000 ppm
Adrenal Cortex: Adenoma				
Overall rates[a]	11/50 (22%)	7/50 (14%)	7/50 (14%)	6/50 (12%)
Adjusted rates[b]	25.3%	16.7%	14.3%	13.0%
Terminal rates[c]	10/42 (24%)	7/42 (17%)	7/49 (14%)	5/45 (11%)
First incidence (days)	508	729 (T)	729 (T)	724
Life table tests[d]	P=0.099N	P=0.219N	P=0.132N	P=0.116N
Logistic regression tests[d]	P=0.127N	P=0.226N	P=0.270N	P=0.154N
Cochran-Armitage test[d]	P=0.138N			
Fisher exact test[d]		P=0.218N	P=0.218N	P=0.143N
Harderian Gland: Adenoma				
Overall rates	1/50 (2%)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted rates	2.4%	7.1%	4.1%	0.0%
Terminal rates	1/42 (2%)	3/42 (7%)	2/49 (4%)	0/45 (0%)
First incidence (days)	729 (T)	729 (T)	729 (T)	–[e]
Life table tests	P=0.216N	P=0.305	P=0.554	P=0.486N
Logistic regression tests	P=0.216N	P=0.305	P=0.554	P=0.486N
Cochran-Armitage test	P=0.242N			
Fisher exact test		P=0.309	P=0.500	P=0.500N
Harderian Gland: Adenoma or Carcinoma				
Overall rates	3/50 (6%)	3/50 (6%)	3/50 (6%)	0/50 (0%)
Adjusted rates	6.8%	7.1%	6.1%	0.0%
Terminal rates	2/42 (5%)	3/42 (7%)	3/49 (6%)	0/45 (0%)
First incidence (days)	683	729 (T)	729 (T)	–
Life table tests	P=0.077N	P=0.656	P=0.596N	P=0.114N
Logistic regression tests	P=0.085N	P=0.652	P=0.661	P=0.125N
Cochran-Armitage test	P=0.092N			
Fisher exact test		P=0.661N	P=0.661N	P=0.121N
Liver: Hepatocellular Adenoma				
Overall rates	17/50 (34%)	22/50 (44%)	22/50 (44%)	12/50 (24%)
Adjusted rates	39.5%	51.1%	44.9%	26.7%
Terminal rates	16/42 (38%)	21/42 (50%)	22/49 (45%)	12/45 (27%)
First incidence (days)	690	638	729 (T)	729 (T)
Life table tests	P=0.050N	P=0.200	P=0.416	P=0.133N
Logistic regression tests	P=0.058N	P=0.168	P=0.354	P=0.137N
Cochran-Armitage test	P=0.103N			
Fisher exact test		P=0.206	P=0.206	P=0.189N
Liver: Hepatocellular Carcinoma				
Overall rates	11/50 (22%)	11/50 (22%)	9/50 (18%)	4/50 (8%)
Adjusted rates	24.2%	22.7%	18.0%	8.6%
Terminal rates	8/42 (19%)	5/42 (12%)	8/49 (16%)	3/45 (7%)
First incidence (days)	620	489	682	638
Life table tests	P=0.022N	P=0.577	P=0.284N	P=0.041N
Logistic regression tests	P=0.058N	P=0.480N	P=0.498N	P=0.059N
Cochran-Armitage test	P=0.028N			
Fisher exact test		P=0.595N	P=0.402N	P=0.045N

Table C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rates	25/50 (50%)	30/50 (60%)	27/50 (54%)	16/50 (32%)
Adjusted rates	55.4%	62.4%	54.0%	34.7%
Terminal rates	22/42 (52%)	24/42 (57%)	26/49 (53%)	15/45 (33%)
First incidence (days)	620	489	682	638
Life table tests	P=0.007N	P=0.226	P=0.436N	P=0.032N
Logistic regression tests	P=0.018N	P=0.221	P=0.471	P=0.046N
Cochran-Armitage test	P=0.016N			
Fisher exact test		P=0.211	P=0.421	P=0.052N
Lung: Alveolar/bronchiolar Adenoma				
Overall rates	6/50 (12%)	7/50 (14%)	8/50 (16%)	3/50 (6%)
Adjusted rates	13.6%	16.7%	16.3%	6.7%
Terminal rates	4/42 (10%)	7/42 (17%)	8/49 (16%)	3/45 (7%)
First incidence (days)	690	729 (T)	729 (T)	729 (T)
Life table tests	P=0.146N	P=0.497	P=0.505	P=0.214N
Logistic regression tests	P=0.155N	P=0.478	P=0.421	P=0.232N
Cochran-Armitage test	P=0.189N			
Fisher exact test		P=0.500	P=0.387	P=0.243N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rates	3/50 (6%)	2/50 (4%)	1/50 (2%)	0/50 (0%)
Adjusted rates	7.0%	4.5%	2.0%	0.0%
Terminal rates	2/42 (5%)	0/42 (0%)	1/49 (2%)	0/45 (0%)
First incidence (days)	712	661	729 (T)	–
Life table tests	P=0.054N	P=0.504N	P=0.256N	P=0.111N
Logistic regression tests	P=0.066N	P=0.493N	P=0.287N	P=0.116N
Cochran-Armitage test	P=0.062N			
Fisher exact test		P=0.500N	P=0.309N	P=0.121N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rates	8/50 (16%)	9/50 (18%)	9/50 (18%)	3/50 (6%)
Adjusted rates	18.2%	20.4%	18.4%	6.7%
Terminal rates	6/42 (14%)	7/42 (17%)	9/49 (18%)	3/45 (7%)
First incidence (days)	690	661	729 (T)	729 (T)
Life table tests	P=0.051N	P=0.496	P=0.576N	P=0.085N
Logistic regression tests	P=0.060N	P=0.479	P=0.554	P=0.091N
Cochran-Armitage test	P=0.072N			
Fisher exact test		P=0.500	P=0.500	P=0.100N
All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, Mixed, or Undifferentiated Cell Type)				
Overall rates	2/50 (4%)	2/50 (4%)	2/50 (4%)	6/50 (12%)
Adjusted rates	4.8%	4.8%	4.1%	12.7%
Terminal rates	2/42 (5%)	2/42 (5%)	2/49 (4%)	4/45 (9%)
First incidence (days)	729 (T)	729 (T)	729 (T)	670
Life table tests	P=0.068	P=0.695	P=0.638N	P=0.162
Logistic regression tests	P=0.059	P=0.695	P=0.638N	P=0.136
Cochran-Armitage test	P=0.054			
Fisher exact test		P=0.691N	P=0.691N	P=0.134

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)
(continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm
All Organs: Benign Neoplasms				
Overall rates	31/50 (62%)	30/50 (60%)	34/50 (68%)	18/50 (36%)
Adjusted rates	68.8%	68.1%	69.4%	39.1%
Terminal rates	28/42 (67%)	28/42 (67%)	34/49 (69%)	17/45 (38%)
First incidence (days)	508	638	729 (T)	724
Life table tests	P<0.001N	P=0.506N	P=0.426N	P=0.004N
Logistic regression tests	P=0.002N	P=0.577N	P=0.437	P=0.006N
Cochran-Armitage test	P=0.005N			
Fisher exact test		P=0.500N	P=0.338	P=0.008N
All Organs: Malignant Neoplasms				
Overall rates	17/50 (34%)	15/50 (30%)	15/50 (30%)	11/50 (22%)
Adjusted rates	36.1%	30.5%	30.0%	22.4%
Terminal rates	12/42 (29%)	8/42 (19%)	14/49 (29%)	7/45 (16%)
First incidence (days)	620	489	682	638
Life table tests	P=0.087N	P=0.438N	P=0.257N	P=0.116N
Logistic regression tests	P=0.187N	P=0.324N	P=0.489N	P=0.161N
Cochran-Armitage test	P=0.113N			
Fisher exact test		P=0.415N	P=0.415N	P=0.133N
All Organs: Benign or Malignant Neoplasms				
Overall rates	39/50 (78%)	39/50 (78%)	40/50 (80%)	25/50 (50%)
Adjusted rates	81.2%	79.6%	80.0%	51.0%
Terminal rates	33/42 (79%)	32/42 (76%)	39/49 (80%)	21/45 (47%)
First incidence (days)	508	489	682	638
Life table tests	P<0.001N	P=0.560	P=0.211N	P=0.003N
Logistic regression tests	P<0.001N	P=0.583N	P=0.485	P=0.004N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.595N	P=0.500	P=0.003N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, and lung; 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 tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE C4
Historical Incidence of Hepatocellular 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	4/50	7/50	10/50
4,4′-Thiobis(6-*t*-butyl-*m*-cresol)	17/50	11/50	25/50
5,5-Diphenylhydantoin	19/50	13/50	29/50
Dowicide EC-7 Pentachlorophenol	5/35	1/35	6/35
Ethylene Thiourea	11/49	13/49	20/49
Polybrominated Biphenyls (Firemaster FF-1®)	9/50	8/50	16/50
Manganese Sulfate Monohydrate	30/50	9/50	34/50
Technical Grade Pentachlorophenol	5/32	2/32	7/32
Triamterene	17/50	5/50	20/50
Triamterene	21/50	9/50	25/50
Tricresyl Phosphate	18/52	15/52	28/52
Overall Historical Incidence			
Total	312/1,366 (22.8%)	223/1,366 (16.3%)	485/1,366 (35.5%)
Standard deviation	13.8%	7.2%	14.3%
Range	4%-60%	3%-29%	10%-68%

[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 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

	0 ppm	250 ppm	500 ppm	1,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	2	2		1
Natural deaths	6	6	1	4
Survivors				
Died last week of study	1	1		
Terminal sacrifice	41	41	49	45
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Eosinophilic focus			1 (10%)	
Vacuolization cytoplasmic	6 (60%)	2 (20%)	3 (30%)	1 (10%)
Serosa, fibrosis		1 (10%)		
Vein, dilatation	1 (10%)			
Mesentery		(1)		
Fat, inflammation, chronic active		1 (100%)		
Pancreas	(10)	(10)	(10)	(10)
Acinus, atrophy		1 (10%)		
Cardiovascular System				
None				
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule		1 (10%)		
Vacuolization cytoplasmic				1 (10%)
Pituitary gland	(8)	(10)	(9)	(10)
Pars distalis, cyst			1 (11%)	
Thyroid gland	(10)	(10)	(10)	(10)
Follicle, cyst		1 (10%)		
General Body System				
None				
Genital System				
Preputial gland	(5)		(4)	(4)
Inflammation, chronic active	1 (20%)		1 (25%)	
Duct, dilatation	5 (100%)		4 (100%)	4 (100%)

[a] Number of animals examined microscopically at site and number of animals with lesion

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm
15-Month Interim Evaluation (continued)				
Hematopoietic System				
Lymph node, mandibular	(9)	(10)	(10)	(10)
Infiltration cellular, histiocyte	1 (11%)	1 (10%)	1 (10%)	1 (10%)
Lymph node, mesenteric	(9)	(9)	(10)	(8)
Infiltration cellular, histiocyte	3 (33%)	6 (67%)	9 (90%)	8 (100%)
Integumentary System				
Skin	(10)	(10)	(10)	(10)
Subcutaneous tissue, inflammation, chronic active	1 (10%)			
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Alveolar epithelium, hyperplasia	2 (20%)		1 (10%)	1 (10%)
Special Senses System				
Harderian gland		(1)		
Hyperplasia		1 (100%)		
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Nephropathy, chronic	8 (80%)	8 (80%)	10 (100%)	10 (100%)
2-Year Study				
Alimentary System				
Intestine small, jejunum	(50)	(50)	(50)	(50)
Mucosa, hyperplasia		1 (2%)		
Peyer's patch, hyperplasia, lymphoid	1 (2%)			
Peyer's patch, ulcer, chronic active	1 (2%)			
Intestine small, ileum	(50)	(50)	(49)	(50)
Peyer's patch, inflammation, acute		1 (2%)		

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of 4,4′-Thiobis(6-t-Butyl-m-Cresol) (continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Liver	(50)	(50)	(50)	(50)
Basophilic focus			1 (2%)	
Clear cell focus	6 (12%)	2 (4%)	2 (4%)	
Clear cell focus, multiple		3 (6%)		
Congestion				1 (2%)
Eosinophilic focus	2 (4%)	3 (6%)	2 (4%)	
Hematopoietic cell proliferation	1 (2%)			
Infarct	1 (2%)			
Necrosis	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Thrombosis		1 (2%)		1 (2%)
Bile duct, cyst			1 (2%)	
Bile duct, hyperplasia				1 (2%)
Hepatocyte, fatty change	19 (38%)	17 (34%)	5 (10%)	6 (12%)
Mesentery	(1)	(1)		(1)
Fat, inflammation, chronic active	1 (100%)	1 (100%)		
Pancreas	(50)	(50)	(50)	(50)
Acinus, atrophy	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Acinus, karyomegaly		1 (2%)		
Duct, cyst		1 (2%)		1 (2%)
Salivary glands	(50)	(50)	(50)	(50)
Acinus, atrophy				1 (2%)
Stomach, forestomach	(50)	(50)	(50)	(50)
Acanthosis	1 (2%)			1 (2%)
Acanthosis, multifocal			1 (2%)	
Stomach, glandular	(50)	(50)	(50)	(50)
Submucosa, developmental malformation	2 (4%)			
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Aortic valve, thrombosis		1 (2%)		
Atrium, thrombosis	1 (2%)			
Ventricle right, thrombosis				1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Ectopic tissue		1 (2%)		
Hyperplasia	1 (2%)		4 (8%)	
Hypertrophy	30 (60%)	30 (60%)	26 (52%)	25 (50%)
Capsule, accessory adrenal cortical nodule	1 (2%)			1 (2%)
Adrenal medulla	(50)	(50)	(50)	(50)
Hyperplasia	1 (2%)		1 (2%)	
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia	3 (6%)	2 (4%)	1 (2%)	
Parathyroid gland	(49)	(48)	(46)	(47)
Cyst	2 (4%)	1 (2%)		

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-t-Butyl-m-Cresol) (continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm
2-Year Study (continued)				
Endocrine System (continued)				
Pituitary gland	(47)	(46)	(49)	(47)
Craniopharyngeal duct, cyst				1 (2%)
Pars distalis, cyst		1 (2%)	2 (4%)	2 (4%)
Pars distalis, hyperplasia		1 (2%)		
Thyroid gland	(50)	(50)	(50)	(50)
Follicle, cyst		2 (4%)	1 (2%)	1 (2%)
Follicular cell, hyperplasia	1 (2%)			
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Developmental malformation			1 (2%)	
Inflammation, chronic active		1 (2%)	2 (4%)	2 (4%)
Preputial gland	(50)	(49)	(50)	(47)
Inflammation, chronic active	2 (4%)	2 (4%)	3 (6%)	2 (4%)
Duct, dilatation	22 (44%)	14 (29%)	12 (24%)	15 (32%)
Seminal vesicle	(50)	(50)	(50)	(50)
Inflammation, chronic active				1 (2%)
Testes	(50)	(50)	(50)	(50)
Developmental malformation			1 (2%)	
Mineralization		1 (2%)		
Spermatocele	1 (2%)			
Interstitial cell, hyperplasia			2 (4%)	
Seminiferous tubule, atrophy	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Seminiferous tubule, mineralization				2 (4%)
Tunic, inflammation, chronic	1 (2%)			
Hematopoietic System				
Lymph node, mandibular	(50)	(47)	(47)	(48)
Depletion lymphoid	1 (2%)			
Infiltration cellular, plasma cell				1 (2%)
Lymph node, mesenteric	(49)	(46)	(48)	(47)
Congestion	1 (2%)	1 (2%)		
Depletion lymphoid	2 (4%)			3 (6%)
Hematopoietic cell proliferation		1 (2%)		
Hyperplasia, histiocytic, macrophage	48 (98%)	37 (80%)	44 (92%)	45 (96%)
Spleen	(50)	(50)	(50)	(50)
Angiectasis			1 (2%)	
Depletion lymphoid	1 (2%)	1 (2%)		1 (2%)
Hematopoietic cell proliferation	5 (10%)	3 (6%)	4 (8%)	5 (10%)
Hemorrhage				1 (2%)
Thymus	(47)	(46)	(46)	(45)
Angiectasis	1 (2%)			
Cyst	1 (2%)			1 (2%)
Depletion lymphoid	12 (26%)	6 (13%)	2 (4%)	3 (7%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-t-Butyl-m-Cresol) (continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm
2-Year Study (continued)				
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Subcutaneous tissue, inflammation, chronic active				1 (2%)
Thoracic, ulcer				1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(48)
Maxilla, inflammation, chronic active, necrotizing			1 (2%)	
Skeletal muscle	(50)	(50)	(50)	(50)
Diaphragm, degeneration, chronic	1 (2%)			
Nervous System				
Peripheral nerve		(1)		(1)
Sciatic, axon, degeneration		1 (100%)		
Spinal cord		(1)		
Axon, degeneration		1 (100%)		
Lumbar, axon, nerve, degeneration		1 (100%)		
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Inflammation, chronic active			1 (2%)	
Alveolar epithelium, hyperplasia		4 (8%)	1 (2%)	2 (4%)
Alveolar epithelium, hyperplasia, macrophage			1 (2%)	
Alveolus, hyperplasia, macrophage	1 (2%)			
Perivascular, infiltration cellular, lymphocyte	4 (8%)	5 (10%)	7 (14%)	10 (20%)
Subpleura, infiltration cellular, lymphocyte				1 (2%)
Special Senses System				
Eye	(2)	(2)	(1)	
Atrophy			1 (100%)	
Cornea, hyperplasia, squamous	1 (50%)	2 (100%)		
Cornea, inflammation, chronic active	1 (50%)	2 (100%)		
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Hydronephrosis		1 (2%)	1 (2%)	
Infiltration cellular, mast cell		1 (2%)		
Nephropathy, chronic	48 (96%)	47 (94%)	50 (100%)	46 (92%)
Cortex, cyst		1 (2%)		

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR FEED STUDY OF 4,4′-THIOBIS(6-*t*-BUTYL-*m*-CRESOL)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-t-Butyl-m-Cresol)[a]

	0 ppm	250 ppm	500 ppm	1,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	9	9	10	10
Early deaths				
Moribund	4	3	3	4
Natural deaths	7	9	11	11
Survivors				
Died last week of study	1			
Terminal sacrifice	39	38	36	35
Missing		1		
Animals examined microscopically	60	59	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(9)	(9)	(10)	(10)
Hepatocellular adenoma	3 (33%)	1 (11%)	1 (10%)	1 (10%)
Cardiovascular System				
None				
Endocrine System				
Adrenal cortex	(9)	(9)	(10)	(10)
Capsule, spindle cell, adenoma				1 (10%)
General Body System				
None				
Genital System				
Ovary	(9)	(9)	(10)	(10)
Sarcoma				1 (10%)
Uterus	(9)	(9)	(10)	(10)
Histiocytic sarcoma			1 (10%)	
Hematopoietic System				
None				
Integumentary System				
None				
Musculoskeletal System				
None				

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm
***15-Month Interim Evaluation* (continued)**				
Nervous System				
None				
Respiratory System				
None				
Special Senses System				
None				
Urinary System				
None				
Systemic Lesions				
Multiple organs[b]	(9)	(9)	(10)	(10)
Histiocytic sarcoma			1 (10%)	
2-Year Study				
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Gallbladder	(50)	(48)	(48)	(47)
Intestine large, colon	(50)	(50)	(50)	(50)
Leiomyosarcoma	1 (2%)			
Intestine large, rectum	(50)	(50)	(50)	(50)
Intestine large, cecum	(50)	(50)	(50)	(50)
Intestine small, duodenum	(50)	(50)	(50)	(50)
Intestine small, jejunum	(50)	(50)	(50)	(50)
Serosa, fibrosarcoma, metastatic, skin		1 (2%)		
Liver	(51)	(50)	(50)	(50)
Fibrosarcoma, metastatic, skin		1 (2%)		
Fibrous histiocytoma, multiple, metastatic, mesentery		1 (2%)		
Hepatocellular carcinoma	3 (6%)	7 (14%)	7 (14%)	4 (8%)
Hepatocellular carcinoma, multiple	1 (2%)	1 (2%)		1 (2%)
Hepatocellular adenoma	11 (22%)	10 (20%)	10 (20%)	9 (18%)
Hepatocellular adenoma, multiple	6 (12%)	7 (14%)	7 (14%)	1 (2%)
Histiocytic sarcoma	1 (2%)		1 (2%)	
Histiocytic sarcoma, metastatic, uterus			1 (2%)	
Mesentery	(4)	(6)	(4)	
Fibrous histiocytoma		1 (17%)		
Fat, fibrosarcoma, metastatic, skin		1 (17%)		
Fat, granulosa-theca tumor malignant, metastatic, ovary	1 (25%)			
Fat, histiocytic sarcoma, metastatic, uterus			1 (25%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-t-Butyl-m-Cresol) (continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Pancreas	(50)	(50)	(49)	(50)
Fibrous histiocytoma, metastatic, mesentery		1 (2%)		
Histiocytic sarcoma, metastatic, uterus			1 (2%)	
Serosa, fibrosarcoma, metastatic, skin		1 (2%)		
Salivary glands	(51)	(50)	(47)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Histiocytic sarcoma, metastatic, uterus			1 (2%)	
Squamous cell papilloma	2 (4%)			
Stomach, glandular	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, uncertain primary site			1 (2%)	
Histiocytic sarcoma, metastatic, uterus			1 (2%)	
Cardiovascular System				
Heart	(51)	(50)	(50)	(50)
Endocrine System				
Adrenal cortex	(51)	(50)	(50)	(50)
Sarcoma, metastatic, kidney				1 (2%)
Capsule, fibrosarcoma, metastatic, skin		1 (2%)		
Spindle cell, subcapsular, adenoma	1 (2%)			1 (2%)
Adrenal medulla	(49)	(50)	(50)	(50)
Pheochromocytoma benign		2 (4%)	2 (4%)	2 (4%)
Bilateral, pheochromocytoma malignant		1 (2%)		
Pituitary gland	(48)	(49)	(49)	(48)
Pars distalis, adenoma	5 (10%)	6 (12%)	9 (18%)	4 (8%)
Pars distalis, adenoma, multiple	1 (2%)			
Pars intermedia, adenoma		1 (2%)		1 (2%)
Pars intermedia, carcinoma	1 (2%)			
Thyroid gland	(51)	(50)	(49)	(50)
Follicular cell, adenoma		1 (2%)	2 (4%)	1 (2%)
General Body System				
Tissue NOS	(1)			(1)
Fibrosarcoma				1 (100%)
Genital System				
Ovary	(50)	(50)	(49)	(50)
Cystadenoma		3 (6%)	3 (6%)	2 (4%)
Granulosa-theca tumor malignant	1 (2%)			1 (2%)
Histiocytic sarcoma	1 (2%)			
Histiocytic sarcoma, metastatic, uterus			1 (2%)	
Luteoma		2 (4%)		
Teratoma benign				2 (4%)
Thecoma benign	1 (2%)			
Periovarian tissue, histiocytic sarcoma			1 (2%)	

Table D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm
2-Year Study (continued)				
Genital System (continued)				
Uterus	(51)	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)		
Histiocytic sarcoma	1 (2%)		2 (4%)	
Leiomyosarcoma		1 (2%)		
Polyp stromal	2 (4%)		1 (2%)	
Sarcoma stromal			1 (2%)	
Hematopoietic System				
Bone marrow	(51)	(50)	(50)	(50)
Femoral, hemangiosarcoma	1 (2%)	1 (2%)		
Lymph node	(9)	(7)	(4)	(7)
Lumbar, fibrous histiocytoma, metastatic, uncertain primary site			1 (25%)	
Mediastinal, fibrous histiocytoma, metastatic, mesentery		1 (14%)		
Mediastinal, fibrous histiocytoma, metastatic, uncertain primary site			1 (25%)	
Mediastinal, histiocytic sarcoma	1 (11%)			
Pancreatic, histiocytic sarcoma	1 (11%)			
Pancreatic, histiocytic sarcoma, metastatic, uterus			1 (25%)	
Renal, fibrous histiocytoma, metastatic, uncertain primary site			1 (25%)	
Renal, granulosa-theca tumor malignant, metastatic, ovary	1 (11%)			1 (14%)
Renal, sarcoma, metastatic, kidney				1 (14%)
Lymph node, mandibular	(50)	(50)	(47)	(50)
Granulosa-theca tumor malignant, metastatic, ovary				1 (2%)
Lymph node, mesenteric	(46)	(43)	(41)	(44)
Fibrosarcoma, metastatic, skin		1 (2%)		
Fibrous histiocytoma, metastatic, uncertain primary site			1 (2%)	
Granulosa-theca tumor malignant, metastatic, ovary				1 (2%)
Histiocytic sarcoma	1 (2%)			
Histiocytic sarcoma, metastatic, uterus			1 (2%)	
Spleen	(51)	(50)	(50)	(49)
Hemangiosarcoma	2 (4%)	1 (2%)	1 (2%)	
Thymus	(46)	(43)	(44)	(48)

Table D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-t-Butyl-m-Cresol) (continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm
2-Year Study (continued)				
Integumentary System				
Mammary gland	(50)	(50)	(48)	(49)
Adenocarcinoma, multiple		1 (2%)		
Skin	(51)	(50)	(50)	(50)
Sebaceous gland, adenoma	1 (2%)			
Subcutaneous tissue, fibrosarcoma	2 (4%)	2 (4%)	3 (6%)	1 (2%)
Subcutaneous tissue, fibrosarcoma, metastatic, skin		1 (2%)		
Subcutaneous tissue, fibrous histiocytoma, metastatic, uncertain primary site			1 (2%)	
Subcutaneous tissue, hemangioma	2 (4%)			
Subcutaneous tissue, hemangiosarcoma		1 (2%)		
Musculoskeletal System				
Skeletal muscle	(51)	(50)	(50)	(50)
Diaphragm, fibrous histiocytoma, metastatic, mesentery		1 (2%)		
Diaphragm, granulosa-theca tumor malignant, metastatic, ovary	1 (2%)			
Thigh, fibrosarcoma, metastatic, skin	1 (2%)	1 (2%)		
Thigh, histiocytic sarcoma, metastatic, uterus			1 (2%)	
Nervous System				
Brain	(51)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			
Meninges, cerebrum, lipoma		1 (2%)		
Respiratory System				
Lung	(51)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	2 (4%)	3 (6%)	1 (2%)	3 (6%)
Alveolar/bronchiolar carcinoma, multiple				1 (2%)
Fibrosarcoma, metastatic, skin	1 (2%)		1 (2%)	
Fibrous histiocytoma, metastatic, mesentery		1 (2%)		
Fibrous histiocytoma, metastatic, uncertain primary site			1 (2%)	
Granulosa-theca tumor malignant, metastatic, ovary	1 (2%)			
Hepatocellular carcinoma, metastatic, liver	1 (2%)	3 (6%)	3 (6%)	
Histiocytic sarcoma	1 (2%)			
Special Senses System				
Ear			(2)	(1)
Adenoma			1 (50%)	
Pinna, fibroma			1 (50%)	
Eye	(1)	(1)		(1)
Adenocarcinoma, metastatic, harderian gland	1 (100%)			

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm
2-Year Study (continued)				
Special Senses System (continued)				
Harderian gland	(1)	(3)	(1)	(1)
Adenocarcinoma	1 (100%)	2 (67%)		
Adenoma		1 (33%)	1 (100%)	1 (100%)
Urinary System				
Kidney	(51)	(50)	(50)	(50)
Histiocytic sarcoma, metastatic, uterus			1 (2%)	
Sarcoma				1 (2%)
Urinary bladder	(50)	(50)	(50)	(50)
Systemic Lesions				
Multiple organs	(51)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)		3 (6%)	
Lymphoma malignant histiocytic	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Lymphoma malignant lymphocytic	3 (6%)	2 (4%)	5 (10%)	5 (10%)
Lymphoma malignant mixed	7 (14%)	4 (8%)	4 (8%)	1 (2%)
Lymphoma malignant undifferentiated cell	2 (4%)		1 (2%)	
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	3	1	2	3
2-Year study	38	37	37	38
Total primary neoplasms				
15-Month interim evaluation	3	1	2	3
2-Year study	61	64	64	45
Total animals with benign neoplasms				
15-Month interim evaluation	3	1	1	2
2-Year study	27	30	24	23
Total benign neoplasms				
15-Month interim evaluation	3	1	1	2
2-Year study	34	37	38	27
Total animals with malignant neoplasms				
15-Month interim evaluation			1	1
2-Year study	23	22	22	17
Total malignant neoplasms				
15-Month interim evaluation			1	1
2-Year study	27	27	26	18
Total animals with metastatic neoplasms				
2-Year study	5	6	6	2
Total metastatic neoplasm				
2-Year study	8	16	21	5
Total animals with malignant neoplasms of uncertain primary site				
2-Year study			1	

[a] Number of animals examined microscopically and number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol): 0 ppm

Number of Days on Study	369	369	386	524	564	593	612	622	705	712	724	732	732	732	732	732	732	732	732	733	733	733	733	733	733
Carcass ID Number	274	292	259	276	267	260	241	290	253	299	285	242	243	244	246	247	248	249	250	251	252	254	256	257	258
Alimentary System																									
Esophagus	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																X									
Intestine large, rectum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma											X														
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma														X					X					X	
Hepatocellular adenoma, multiple															X										
Histiocytic sarcoma									X																
Mesentery	+						+								+										
Fat, granulosa-theca tumor malignant, metastatic, ovary							X																		
Pancreas	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																					X				
Stomach, glandular	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spindle cell, subcapsular, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma												X											X		
Pars distalis, adenoma, multiple							X																		
Pars intermedia, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
Tissue NOS						+																			

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 0 ppm (continued)

Number of Days on Study	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	261	264	265	268	269	270	271	272	275	277	278	279	280	281	283	284	287	288	289	291	293	294	296	297	298	300	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																											1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular carcinoma																				X			X				3
Hepatocellular carcinoma, multiple													X														1
Hepatocellular adenoma					X	X					X	X	X	X				X						X			11
Hepatocellular adenoma, multiple				X											X	X					X	X					6
Histiocytic sarcoma																											1
Mesentery																						+					4
Fat, granulosa-theca tumor malignant, metastatic, ovary																											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma															X												2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spindle cell, subcapsular, adenoma						X																					1
Adrenal medulla	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma	X														X									X			5
Pars distalis, adenoma, multiple																											1
Pars intermedia, carcinoma												X															1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
General Body System																											
Tissue NOS																											1

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol): 0 ppm (continued)

Number of Days on Study	369	369	386	522	564	593	612	622	705	712	724	732	732	732	732	732	732	732	732	733	733	733	733	733	733	
Carcass ID Number	274	292	259	276	267	260	241	290	253	299	285	242	243	244	246	247	248	249	250	251	252	254	256	257	258	
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Granulosa-theca tumor malignant							X																			
Histiocytic sarcoma									X																	
Thecoma benign																	X									
Uterus	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																	
Polyp stromal												X								X						
Hematopoietic System																										
Blood						+																				
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Femoral, hemangiosarcoma																										
Lymph node							+		+	+		+	+												+	
Mediastinal, histiocytic sarcoma									X																	
Pancreatic, histiocytic sarcoma									X																	
Renal, granulosa-theca tumor malignant, metastatic, ovary							X																			
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	
Lymph node, mesenteric	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Histiocytic sarcoma									X																	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hemangiosarcoma																										
Thymus	M	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Integumentary System																										
Mammary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Sebaceous gland, adenoma								X																		
Subcutaneous tissue, fibrosarcoma		X																								
Subcutaneous tissue, hemangioma								X																		
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Diaphragm, granulosa-theca tumor malignant, metastatic, ovary							X																			
Thigh, fibrosarcoma, metastatic, skin																										
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Histiocytic sarcoma									X																	
Peripheral nerve						+			+																	
Spinal cord						+			+																	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol): 0 ppm (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
Carcass ID Number	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	Total
	6	6	6	6	6	7	7	7	7	7	7	7	8	8	8	8	8	8	8	9	9	9	9	9	9	0	Tissues/
	1	4	5	8	9	0	1	2	5	7	8	9	0	1	3	4	7	8	9	1	3	4	6	7	8	0	Tumors
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	50
Granulosa-theca tumor malignant																											1
Histiocytic sarcoma																											1
Thecoma benign																											1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																											1
Polyp stromal																											2
Hematopoietic System																											
Blood																											1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Femoral, hemangiosarcoma																										X	1
Lymph node		+																			+					+	9
Mediastinal, histiocytic sarcoma																											1
Pancreatic, histiocytic sarcoma																											1
Renal, granulosa-theca tumor malignant, metastatic, ovary																											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	46
Histiocytic sarcoma																											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangiosarcoma														X												X	2
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Sebaceous gland, adenoma																											1
Subcutaneous tissue, fibrosarcoma																						X					2
Subcutaneous tissue, hemangioma																X											2
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Diaphragm, granulosa-theca tumor malignant, metastatic, ovary																											1
Thigh, fibrosarcoma, metastatic, skin																						X					1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																											1
Peripheral nerve																											2
Spinal cord																											2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol): 0 ppm (continued)

	3	3	3	5	5	5	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	6	6	8	2	6	9	1	2	0	1	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	9	9	6	2	4	3	2	2	5	2	4	2	2	2	2	2	2	2	2	3	3	3	3	3	3
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Carcass ID Number	7	9	5	7	6	6	4	9	5	9	8	4	4	4	4	4	4	4	5	5	5	5	5	5	5
	4	2	9	6	7	0	1	0	3	9	5	2	3	4	6	7	8	9	0	1	2	4	6	7	8
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Fibrosarcoma, metastatic, skin		X																							
Granulosa-theca tumor malignant, metastatic, ovary							X																		
Hepatocellular carcinoma, metastatic, liver											X														
Histiocytic sarcoma									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Adenocarcinoma, metastatic, harderian gland																									
Harderian gland																									
Adenocarcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Lymphoma malignant histiocytic													X												
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed												X			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 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol): 0 ppm (continued)

Number of Days on Study	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	261	264	265	268	269	270	271	272	275	277	278	279	280	281	283	284	287	288	289	291	293	294	296	297	298	300	Total Tissues/ Tumors
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma		X																					X				2
Fibrosarcoma, metastatic, skin																											1
Granulosa-theca tumor malignant, metastatic, ovary																											1
Hepatocellular carcinoma, metastatic, liver																											1
Histiocytic sarcoma																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Eye																				+							1
Adenocarcinoma, metastatic, harderian gland																				X							1
Harderian gland																				+							1
Adenocarcinoma																				X							1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																											1
Lymphoma malignant histiocytic																										X	1
Lymphoma malignant lymphocytic								X																X			3
Lymphoma malignant mixed										X	X										X	X					7
Lymphoma malignant undifferentiated cell type																											2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 250 ppm

Number of Days on Study	165	450	521	599	603	605	665	666	674	697	705	718	723	731	731	731	731	731	731	731	731	731	731	731	731
Carcass ID Number	325	312	332	330	322	340	327	304	338	324	334	305	335	301	302	303	306	307	309	311	313	314	316	318	320
Alimentary System																									
Esophagus		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, fibrosarcoma, metastatic, skin												X													
Intestine small, ileum		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin												X													
Fibrous histiocytoma, multiple, metastatic, mesentery						X																			
Hepatocellular carcinoma			X												X					X					
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma														X	X	X						X	X		
Hepatocellular adenoma, multiple																	X								
Mesentery					+	+			+			+	+												
Fibrous histiocytoma						X																			
Fat, fibrosarcoma, metastatic, skin												X													
Pancreas		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, mesentery						X																			
Serosa, fibrosarcoma, metastatic, skin												X													
Salivary glands		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, fibrosarcoma, metastatic, skin												X													
Adrenal medulla		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Bilateral, pheochromocytoma malignant		X																							
Islets, pancreatic		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland		+	+	M	+	+	+	+	M	+	+	+	M	M	+	+	+	M	+	+	+	+	+	+	+
Pituitary gland		+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma										X	X												X	X	
Pars intermedia, adenoma																									X
Thyroid gland		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 250 ppm (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	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	3 2 1	3 2 3	3 2 8	3 2 9	3 3 1	3 3 3	3 3 6	3 3 7	3 3 9	3 4 1	3 4 2	3 4 3	3 4 4	3 4 5	3 4 6	3 4 7	3 4 9	3 5 0	3 5 1	3 5 3	3 5 4	3 5 5	3 5 6	3 5 7	3 5 9	3 6 0	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Serosa, fibrosarcoma, metastatic, skin																											1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																											1
Fibrous histiocytoma, multiple, metastatic, mesentery																											1
Hepatocellular carcinoma	X	X																		X		X					7
Hepatocellular carcinoma, multiple																X											1
Hepatocellular adenoma			X								X	X			X								X				10
Hepatocellular adenoma, multiple						X			X					X		X	X								X		7
Mesentery														+													6
Fibrous histiocytoma																											1
Fat, fibrosarcoma, metastatic, skin																											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, mesentery																											1
Serosa, fibrosarcoma, metastatic, skin																											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, fibrosarcoma, metastatic, skin																											1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																				X		X					2
Bilateral, pheochromocytoma malignant																											1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma						X													X								6
Pars intermedia, adenoma																											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma										X																	1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 250 ppm (continued)

	1	4	5	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	6	5	2	9	0	0	6	6	7	9	0	1	2	3	3	3	3	3	3	3	3	3	3	3	3
	5	0	1	9	3	5	5	6	4	7	5	8	3	1	1	1	1	1	1	1	1	1	1	1	1
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Carcass ID Number	2	1	3	3	2	4	2	0	3	2	3	0	3	0	0	0	0	0	0	1	1	1	1	1	2
	5	2	2	0	2	0	7	4	8	4	4	5	5	1	2	3	6	7	9	1	3	4	6	8	0
General Body System																									
None																									
Genital System																									
Clitoral gland		M	M	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																								X	
Luteoma		X																							
Uterus		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Leiomyosarcoma																									
Hematopoietic System																									
Bone marrow		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, hemangiosarcoma																									
Lymph node		+				+			+	+			+												
Mediastinal, fibrous histiocytoma, metastatic, mesentery						X																			
Lymph node, mandibular		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric		+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Fibrosarcoma, metastatic, skin												X													
Spleen		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus		+	M	+	+	M	+	M	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, multiple		X																							
Skin		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma												X													
Subcutaneous tissue, fibrosarcoma, metastatic, skin												X													
Subcutaneous tissue, hemangiosarcoma																					X				
Musculoskeletal System																									
Bone		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Diaphragm, fibrous histiocytoma, metastatic, mesentery						X																			
Thigh, fibrosarcoma, metastatic, skin																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol): 250 ppm (continued)

Number of Days on Study	731	731	731	731	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	321	323	328	329	331	333	336	337	339	341	342	343	344	345	346	347	349	350	351	353	354	355	356	357	359	360	Total Tissues/ Tumors
General Body System																											
None																											
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma														X								X					3
Luteoma	X																										2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																X											1
Leiomyosarcoma			X																								1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femoral, hemangiosarcoma																X											1
Lymph node														+					+								7
Mediastinal, fibrous histiocytoma, metastatic, mesentery																											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	M	M	+	+	43
Fibrosarcoma, metastatic, skin																											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																X											1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	43
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, multiple																											1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma										X																	2
Subcutaneous tissue, fibrosarcoma, metastatic, skin																											1
Subcutaneous tissue, hemangiosarcoma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Diaphragm, fibrous histiocytoma, metastatic, mesentery																											1
Thigh, fibrosarcoma, metastatic, skin										X																	1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 250 ppm (continued)

Number of Days on Study	1	4	5	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	6	5	2	9	0	0	6	6	7	9	0	1	2	3	3	3	3	3	3	3	3	3	3	3	3
	5	0	1	9	3	5	5	6	4	7	5	8	3	1	1	1	1	1	1	1	1	1	1	1	1
Carcass ID Number	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	2	1	3	3	2	4	2	0	3	2	3	0	3	0	0	0	0	0	0	1	1	1	1	1	2
	5	2	2	0	2	0	7	4	8	4	4	5	5	1	2	3	6	7	9	1	3	4	6	8	0
Nervous System																									
Brain		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meninges, cerebrum, lipoma														X											
Peripheral nerve				+																					
Spinal cord				+																					
Respiratory System																									
Lung		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X				X									
Fibrous histiocytoma, metastatic, mesentery						X																			
Hepatocellular carcinoma, metastatic, liver			X												X										
Nose		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Harderian gland													+				+								
Adenocarcinoma																	X								
Adenoma													X												
Urinary System																									
Kidney		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic				X																					
Lymphoma malignant lymphocytic													X					X							
Lymphoma malignant mixed										X															

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 250 ppm (continued)

Number of Days on Study	731	731	731	731	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	321	323	328	329	331	333	336	337	339	341	342	343	344	345	346	347	349	350	351	353	354	355	356	357	359	360	Total Tissues/ Tumors
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Meninges, cerebrum, lipoma																											1
Peripheral nerve																											1
Spinal cord																											
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																		X									3
Fibrous histiocytoma, metastatic, mesentery																											1
Hepatocellular carcinoma, metastatic, liver																				X							3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Eye																				+							1
Harderian gland																				+							3
Adenocarcinoma																				X							2
Adenoma																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																											1
Lymphoma malignant lymphocytic																											2
Lymphoma malignant mixed											X			X					X								4

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol): 500 ppm

	0	4	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	6	9	6	9	2	3	5	5	6	7	8	0	0	1	3	3	3	3	3	3	3	3	3	3	3
	8	7	8	9	6	2	5	5	1	7	5	1	4	7	0	0	0	0	0	0	0	0	0	0	0
	4	3	4	3	3	3	3	4	3	4	3	4	3	3	3	3	3	3	3	3	3	3	3	3	3
Carcass ID Number	0	8	0	6	6	8	9	0	7	2	7	1	7	6	6	6	6	6	6	7	7	7	7	8	8
	9	2	4	6	2	0	3	1	0	0	1	7	8	1	3	4	5	7	8	2	3	5	6	1	3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma									X					X			X	X							X
Hepatocellular adenoma																									
Hepatocellular adenoma, multiple															X						X	X			
Histiocytic sarcoma																									
Histiocytic sarcoma, metastatic, uterus						X																			
Mesentery		+				+						+													
Fat, histiocytic sarcoma, metastatic, uterus						X																			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, uterus						X																			
Pharynx																				+					
Salivary glands	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, uterus						X																			
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, uncertain primary site											X														
Histiocytic sarcoma, metastatic, uterus						X																			
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X				X										X								
Thyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 500 ppm (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	384	387	388	389	390	391	392	394	395	396	398	399	400	402	403	405	406	407	410	412	413	414	415	416	419	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma												X				X										7
Hepatocellular adenoma		X	X		X		X		X	X			X	X									X	X		10
Hepatocellular adenoma, multiple																		X	X		X	X				7
Histiocytic sarcoma							X																			1
Histiocytic sarcoma, metastatic, uterus																										1
Mesentery																			+							4
Fat, histiocytic sarcoma, metastatic, uterus																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma, metastatic, uterus																										1
Pharynx																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic, uterus																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, uncertain primary site																										1
Histiocytic sarcoma, metastatic, uterus																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign						X		X																		2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X			X	X													X		X		X			9
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma					X					X																2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol): 500 ppm (continued)

	0	4	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	6	9	6	9	2	3	5	5	6	7	8	0	0	1	3	3	3	3	3	3	3	3	3	3	3
	8	7	8	9	6	2	5	5	1	7	5	1	4	7	0	0	0	0	0	0	0	0	0	0	0
	4	3	4	3	3	3	3	4	3	4	3	4	3	3	3	3	3	3	3	3	3	3	3	3	3
Carcass ID Number	0	8	0	6	6	8	9	0	7	2	7	1	7	6	6	6	6	6	6	7	7	7	7	8	8
	9	2	4	6	2	0	3	1	0	0	1	7	8	1	3	4	5	7	8	2	3	5	6	1	3
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																						X			
Histiocytic sarcoma, metastatic, uterus						X																			
Periovarian tissue, histiocytic sarcoma													X												
Periovarian tissue, lymphoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X							X												
Polyp stromal																	X								
Sarcoma stromal												X													
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+				+					+														
Lumbar, fibrous histiocytoma, metastatic, uncertain primary site											X														
Mediastinal, fibrous histiocytoma, metastatic, uncertain primary site											X														
Pancreatic, histiocytic sarcoma, metastatic, uterus						X																			
Renal, fibrous histiocytoma, metastatic, uncertain primary site											X														
Lymph node, mandibular	+	+	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	+	+	M	M	+	M	+	+	M	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, uncertain primary site											X														
Histiocytic sarcoma, metastatic, uterus						X																			
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	M	+	+	+	M	+	M	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma								X																	
Subcutaneous tissue, fibrous histiocytoma, metastatic, uncertain primary site											X														

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 500 ppm (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	384	387	388	389	390	391	392	394	395	396	398	399	400	402	403	405	406	407	410	412	413	414	415	416	419	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Ovary	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma					X			X																		3
Histiocytic sarcoma, metastatic, uterus																										1
Periovarian tissue, histiocytic sarcoma																										1
Periovarian tissue, lymphoma																										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Polyp stromal																										1
Sarcoma stromal																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+																								4
Lumbar, fibrous histiocytoma, metastatic, uncertain primary site																										1
Mediastinal, fibrous histiocytoma, metastatic, uncertain primary site																										1
Pancreatic, histiocytic sarcoma, metastatic, uterus																										1
Renal, fibrous histiocytoma, metastatic, uncertain primary site																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	41
Fibrous histiocytoma, metastatic, uncertain primary site																										1
Histiocytic sarcoma, metastatic, uterus																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																X										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma														X					X							3
Subcutaneous tissue, fibrous histiocytoma, metastatic, uncertain primary site																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 500 ppm (continued)

	0	4	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	6	9	6	9	2	3	5	5	6	7	8	0	0	1	3	3	3	3	3	3	3	3	3	3	3
	8	7	8	9	6	2	5	5	1	7	5	1	4	7	0	0	0	0	0	0	0	0	0	0	0
	4	3	4	3	3	3	3	4	3	4	3	4	3	3	3	3	3	3	3	3	3	3	3	3	3
Carcass ID Number	0	8	0	6	6	8	9	0	7	2	7	1	7	6	6	6	6	6	6	7	7	7	7	8	8
	9	2	4	6	2	0	3	1	0	0	1	7	8	1	3	4	5	7	8	2	3	5	6	1	3
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thigh, histiocytic sarcoma, metastatic, uterus						X																			
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve			+																						
Spinal cord			+																						
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																					X				
Fibrosarcoma, metastatic, skin								X																	
Fibrous histiocytoma, metastatic, uncertain primary site											X														
Hepatocellular carcinoma, metastatic, liver									X					X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Adenoma																									
Pinna, fibroma																									
Harderian gland												+													
Adenoma												X													
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, uterus						X																			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X							X												
Lymphoma malignant histiocytic				X																					
Lymphoma malignant lymphocytic										X		X													
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 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 500 ppm (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	384	387	388	389	390	391	392	394	395	396	398	399	400	402	403	405	406	407	410	412	413	414	415	416	419	Total Tissues/ Tumors
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thigh, histiocytic sarcoma, metastatic, uterus																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Fibrosarcoma, metastatic, skin																										1
Fibrous histiocytoma, metastatic, uncertain primary site																										1
Hepatocellular carcinoma, metastatic, liver																X										3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear							+								+											2
Adenoma															X											1
Pinna, fibroma							X																			1
Harderian gland																										1
Adenoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic, uterus																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma							X																			3
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic										X				X								X				5
Lymphoma malignant mixed		X																								4
Lymphoma malignant undifferentiated cell type																										1

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 1,000 ppm

	1	1	5	5	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	1	5	5	6	8	9	0	4	4	6	7	8	9	0	0	2	2	2	2	2	2	2	2	2	2
	3	6	1	5	2	7	6	1	6	1	1	0	2	1	4	9	9	9	9	9	9	9	9	9	9
	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Carcass ID Number	7	2	5	3	4	4	8	7	5	2	5	3	7	6	5	2	2	2	2	2	3	3	3	3	3
	4	3	3	9	5	0	0	0	1	1	8	7	9	9	7	2	4	5	6	8	0	2	5	6	8
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma			X														X								
Hepatocellular carcinoma, multiple														X											
Hepatocellular adenoma																	X		X					X	X
Hepatocellular adenoma, multiple																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, kidney																									
Spindle cell, subcapsular, adenoma																X									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma													X								X	X			
Pars intermedia, adenoma																			X						
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
Tissue NOS										+															
Fibrosarcoma										X															
Genital System																									
Clitoral gland	+	+	+	+	M	M	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma													X												
Granulosa-theca tumor malignant											X														
Teratoma benign	X	X																							
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 1,000 ppm (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	
	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	0	0	0	0	0	0	0	
	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	Total
Carcass ID Number	4	4	4	4	4	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	7	7	7	7	7	Tissues/
	1	2	3	4	6	0	2	4	5	6	9	0	1	2	3	4	5	6	7	8	1	2	5	6	7	Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma			X				X																			4
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma					X			X									X		X		X					9
Hepatocellular adenoma, multiple						X																				1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, kidney											X															1
Spindle cell, subcapsular, adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign														X				X								2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma	X																									4
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma		X																								1
General Body System																										
Tissue NOS																										1
Fibrosarcoma																										1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	44
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																X										2
Granulosa-theca tumor malignant																										1
Teratoma benign																										2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 1,000 ppm (continued)

Number of Days on Study	113	156	551	565	582	597	606	641	646	661	671	680	692	701	704	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	474	423	453	439	445	440	480	470	451	421	458	437	479	469	457	422	424	425	426	428	430	432	435	436	438
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+	+			+		+														
Renal, granulosa-theca tumor malignant, metastatic, ovary											X														
Renal, sarcoma, metastatic, kidney																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor malignant, metastatic, ovary											X														
Lymph node, mesenteric	M	M	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	M	+	+	+	+	+
Granulosa-theca tumor malignant, metastatic, ovary											X														
Spleen	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma														X											
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve				+							+			+	+										
Spinal cord				+							+			+	+										
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X											X		X						
Alveolar/bronchiolar carcinoma, multiple												X													
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Eye				+																					
Harderian gland				+																					
Adenoma				X																					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic					X				X																
Lymphoma malignant lymphocytic								X										X							
Lymphoma malignant mixed															X										

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol): 1,000 ppm (continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	
Carcass ID Number	441	442	443	444	446	450	452	454	455	456	459	460	461	462	463	464	465	466	467	468	471	472	475	476	477	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node				+							+						+									7
Renal, granulosa-theca tumor malignant, metastatic, ovary																										1
Renal, sarcoma, metastatic, kidney											X															1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa-theca tumor malignant, metastatic, ovary																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Granulosa-theca tumor malignant, metastatic, ovary																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										4
Spinal cord																										4
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										3
Alveolar/bronchiolar carcinoma, multiple																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																					+					1
Eye																										1
Harderian gland																										1
Adenoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma											X															1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										2
Lymphoma malignant lymphocytic				X									X				X									5
Lymphoma malignant mixed																										1

Table D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)

	0 ppm	250 ppm	500 ppm	1,000 ppm
Harderian Gland: Adenoma or Carcinoma				
Overall rates[a]	1/51 (2%)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted rates[b]	2.5%	7.7%	2.6%	2.1%
Terminal rates[c]	1/40 (3%)	2/38 (5%)	0/36 (0%)	0/35 (0%)
First incidence (days)	729 (T)	723	701	565
Life table tests[d]	P=0.487N	P=0.289	P=0.738	P=0.748
Logistic regression tests[d]	P=0.451N	P=0.296	P=0.759	P=0.757N
Cochran-Armitage test[d]	P=0.450N			
Fisher exact test[d]		P=0.301	P=0.748	P=0.748
Liver: Hepatocellular Adenoma				
Overall rates	17/51 (33%)	17/50 (34%)	17/50 (34%)	10/50 (20%)
Adjusted rates	42.5%	44.7%	47.2%	28.6%
Terminal rates	17/40 (43%)	17/38 (45%)	17/36 (47%)	10/35 (29%)
First incidence (days)	729 (T)	729 (T)	729 (T)	729 (T)
Life table tests	P=0.121N	P=0.512	P=0.428	P=0.157N
Logistic regression tests	P=0.121N	P=0.512	P=0.428	P=0.157N
Cochran-Armitage test	P=0.070N			
Fisher exact test		P=0.555	P=0.555	P=0.098N
Liver: Hepatocellular Carcinoma				
Overall rates	4/51 (8%)	8/50 (16%)	7/50 (14%)	5/50 (10%)
Adjusted rates	9.8%	20.1%	18.2%	12.9%
Terminal rates	3/40 (8%)	7/38 (18%)	5/36 (14%)	3/35 (9%)
First incidence (days)	724	521	661	551
Life table tests	P=0.466	P=0.159	P=0.213	P=0.426
Logistic regression tests	P=0.529	P=0.179	P=0.243	P=0.478
Cochran-Armitage test	P=0.546			
Fisher exact test		P=0.169	P=0.251	P=0.487
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rates	20/51 (39%)	23/50 (46%)	24/50 (48%)	14/50 (28%)
Adjusted rates	48.8%	58.8%	63.1%	37.4%
Terminal rates	19/40 (48%)	22/38 (58%)	22/36 (61%)	12/35 (34%)
First incidence (days)	724	521	661	551
Life table tests	P=0.203N	P=0.254	P=0.130	P=0.273N
Logistic regression tests	P=0.148N	P=0.345	P=0.148	P=0.204N
Cochran-Armitage test	P=0.103N			
Fisher exact test		P=0.313	P=0.245	P=0.163N
Lung: Alveolar/bronchiolar Adenoma				
Overall rates	2/51 (4%)	3/50 (6%)	1/50 (2%)	3/50 (6%)
Adjusted rates	5.0%	7.6%	2.8%	7.8%
Terminal rates	2/40 (5%)	2/38 (5%)	1/36 (3%)	2/35 (6%)
First incidence (days)	729 (T)	718	729 (T)	597
Life table tests	P=0.422	P=0.479	P=0.537N	P=0.452
Logistic regression tests	P=0.455	P=0.493	P=0.537N	P=0.485
Cochran-Armitage test	P=0.470			
Fisher exact test		P=0.491	P=0.508N	P=0.491

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rates	2/51 (4%)	3/50 (6%)	1/50 (2%)	4/50 (8%)
Adjusted rates	5.0%	7.6%	2.8%	10.2%
Terminal rates	2/40 (5%)	2/38 (5%)	1/36 (3%)	2/35 (6%)
First incidence (days)	729 (T)	718	729 (T)	597
Life table tests	P=0.245	P=0.479	P=0.537N	P=0.293
Logistic regression tests	P=0.274	P=0.493	P=0.537N	P=0.323
Cochran-Armitage test	P=0.285			
Fisher exact test		P=0.491	P=0.508N	P=0.329
Ovary: Cystadenoma				
Overall rates	0/50 (0%)	3/50 (6%)	3/49 (6%)	2/50 (4%)
Adjusted rates	0.0%	7.9%	8.6%	5.4%
Terminal rates	0/39 (0%)	3/38 (8%)	3/35 (9%)	1/35 (3%)
First incidence (days)	–[e]	729 (T)	729 (T)	692
Life table tests	P=0.270	P=0.116	P=0.102	P=0.215
Logistic regression tests	P=0.279	P=0.116	P=0.102	P=0.233
Cochran-Armitage test	P=0.312			
Fisher exact test		P=0.121	P=0.117	P=0.247
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	6/48 (13%)	6/49 (12%)	9/49 (18%)	4/48 (8%)
Adjusted rates	14.4%	14.8%	22.9%	11.0%
Terminal rates	5/40 (13%)	4/38 (11%)	7/36 (19%)	3/35 (9%)
First incidence (days)	612	697	568	692
Life table tests	P=0.441N	P=0.587	P=0.238	P=0.450N
Logistic regression tests	P=0.377N	P=0.609N	P=0.295	P=0.397N
Cochran-Armitage test	P=0.348N			
Fisher exact test		P=0.606N	P=0.303	P=0.370N
Skin (Subcutaneous Tissue): Fibrosarcoma				
Overall rates	2/51 (4%)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted rates	4.4%	5.1%	7.7%	2.7%
Terminal rates	1/40 (3%)	1/38 (3%)	2/36 (6%)	0/35 (0%)
First incidence (days)	369	718	655	701
Life table tests	P=0.455N	P=0.679	P=0.470	P=0.540N
Logistic regression tests	P=0.391N	P=0.615	P=0.500	P=0.460N
Cochran-Armitage test	P=0.410N			
Fisher exact test		P=0.684	P=0.491	P=0.508N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rates	4/51 (8%)	2/50 (4%)	1/50 (2%)	0/50 (0%)
Adjusted rates	9.6%	5.3%	2.8%	0.0%
Terminal rates	3/40 (8%)	2/38 (5%)	1/36 (3%)	0/35 (0%)
First incidence (days)	622	729 (T)	729 (T)	–
Life table tests	P=0.038N	P=0.356N	P=0.205N	P=0.079N
Logistic regression tests	P=0.032N	P=0.336N	P=0.184N	P=0.067N
Cochran-Armitage test	P=0.031N			
Fisher exact test		P=0.348N	P=0.187N	P=0.061N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm
All Organs: Histiocytic Sarcoma				
Overall rates	1/51 (2%)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted rates	2.3%	0.0%	7.4%	0.0%
Terminal rates	0/40 (0%)	0/38 (0%)	1/36 (3%)	0/35 (0%)
First incidence (days)	705	–	632	–
Life table tests	P=0.540N	P=0.509N	P=0.280	P=0.541N
Logistic regression tests	P=0.504N	P=0.502N	P=0.298	P=0.507N
Cochran-Armitage test	P=0.505N			
Fisher exact test		P=0.505N	P=0.301	P=0.505N
All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, Mixed, or Undifferentiated Cell Type)				
Overall rates	13/51 (25%)	7/50 (14%)	11/50 (22%)	8/50 (16%)
Adjusted rates	31.7%	16.7%	26.6%	19.7%
Terminal rates	12/40 (30%)	4/38 (11%)	7/36 (19%)	4/35 (11%)
First incidence (days)	712	599	497	582
Life table tests	P=0.333N	P=0.133N	P=0.509N	P=0.257N
Logistic regression tests	P=0.251N	P=0.100N	P=0.424N	P=0.189N
Cochran-Armitage test	P=0.238N			
Fisher exact test		P=0.115N	P=0.430N	P=0.176N
All Organs: Benign Neoplasms				
Overall rates	28/51 (55%)	31/50 (62%)	25/50 (50%)	24/50 (48%)
Adjusted rates	66.6%	72.0%	62.2%	59.1%
Terminal rates	26/40 (65%)	26/38 (68%)	21/36 (58%)	19/35 (54%)
First incidence (days)	612	450	568	113
Life table tests	P=0.366N	P=0.248	P=0.542N	P=0.509N
Logistic regression tests	P=0.195N	P=0.369	P=0.366N	P=0.324N
Cochran-Armitage test	P=0.168N			
Fisher exact test		P=0.301	P=0.384N	P=0.310N
All Organs: Malignant Neoplasms				
Overall rates	23/51 (45%)	22/50 (44%)	24/50 (48%)	18/50 (36%)
Adjusted rates	51.0%	48.4%	52.0%	39.5%
Terminal rates	18/40 (45%)	15/38 (39%)	14/36 (39%)	8/35 (23%)
First incidence (days)	369	450	497	113
Life table tests	P=0.377N	P=0.565N	P=0.361	P=0.385N
Logistic regression tests	P=0.198N	P=0.535N	P=0.466	P=0.228N
Cochran-Armitage test	P=0.207N			
Fisher exact test		P=0.536N	P=0.463	P=0.233N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rates	39/51 (76%)	37/50 (74%)	39/50 (78%)	39/50 (78%)
Adjusted rates	84.7%	80.3%	81.2%	79.5%
Terminal rates	33/40 (83%)	29/38 (76%)	27/36 (75%)	25/35 (71%)
First incidence (days)	369	450	497	113
Life table tests	P=0.191	P=0.552N	P=0.327	P=0.268
Logistic regression tests	P=0.385	P=0.384N	P=0.554	P=0.503
Cochran-Armitage test	P=0.418			
Fisher exact test		P=0.477N	P=0.522	P=0.522

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, ovary and pituitary 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 tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-t-Butyl-m-Cresol)[a]

	0 ppm	250 ppm	500 ppm	1,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	9	9	10	10
Early deaths				
Moribund	4	3	3	4
Natural deaths	7	9	11	11
Survivors				
Died last week of study	1			
Terminal sacrifice	39	38	36	35
Missing		1		
Animals examined microscopically	60	59	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(9)	(9)	(10)	(10)
Basophilic focus		1 (11%)	1 (10%)	
Hematopoietic cell proliferation		3 (33%)	1 (10%)	
Vacuolization cytoplasmic			1 (10%)	
Hepatocyte, hypertrophy	2 (22%)			
Mesentery	(1)			(1)
Fat, inflammation, chronic active	1 (100%)			1 (100%)
Pancreas	(9)	(9)	(10)	(10)
Acinus, atrophy			2 (20%)	1 (10%)
Cardiovascular System				
Heart	(9)	(9)	(10)	(10)
Degeneration, chronic		1 (11%)		
Endocrine System				
Pituitary gland	(9)	(9)	(10)	(10)
Pars distalis, hyperplasia		2 (22%)	3 (30%)	
Pars distalis, hypertrophy				1 (10%)
Thyroid gland	(9)	(9)	(10)	(10)
Cyst				1 (10%)
General Body System				
None				
Genital System				
Ovary	(9)	(9)	(10)	(10)
Mineralization			1 (10%)	
Bilateral, follicle, cyst		1 (11%)		
Follicle, cyst	2 (22%)	1 (11%)	2 (20%)	5 (50%)
Periovarian tissue, cyst		2 (22%)		3 (30%)

[a] Number of animals examined microscopically at site and number of animals with lesion

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm
15-Month Interim Evaluation (continued)				
Genital System (continued)				
Uterus	(9)	(9)	(10)	(10)
Endometrium, hyperplasia, cystic, glandular	9 (100%)	9 (100%)	9 (90%)	10 (100%)
Hematopoietic System				
Bone marrow	(9)	(9)	(10)	(10)
Femoral, myelofibrosis		1 (11%)		1 (10%)
Lymph node, mandibular	(9)	(9)	(10)	(10)
Infiltration cellular, histiocyte				5 (50%)
Lymph node, mesenteric	(6)	(8)	(10)	(8)
Cyst	1 (17%)			
Infiltration cellular, histiocyte	5 (83%)	3 (38%)	9 (90%)	8 (100%)
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
None				
Special Senses System				
None				
Urinary System				
Kidney	(9)	(9)	(10)	(10)
Nephropathy, chronic	2 (22%)	1 (11%)	1 (10%)	4 (40%)
2-Year Study				
Alimentary System				
Intestine small, jejunum	(50)	(50)	(50)	(50)
Necrosis, focal	1 (2%)			

Table D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Liver	(51)	(50)	(50)	(50)
Angiectasis	2 (4%)		1 (2%)	
Basophilic focus	2 (4%)	3 (6%)	2 (4%)	
Clear cell focus		2 (4%)	3 (6%)	
Eosinophilic focus	10 (20%)	8 (16%)	10 (20%)	7 (14%)
Hematopoietic cell proliferation	2 (4%)	1 (2%)		
Inflammation, chronic active	1 (2%)			
Necrosis	1 (2%)	1 (2%)		
Bile duct, cyst			2 (4%)	
Bile duct, dilatation		1 (2%)		
Hepatocyte, fatty change	7 (14%)	6 (12%)	5 (10%)	6 (12%)
Periportal, inflammation, chronic active		1 (2%)		
Serosa, inflammation, chronic	1 (2%)			
Mesentery	(4)	(6)	(4)	
Fat, inflammation, chronic active	3 (75%)	3 (50%)	1 (25%)	
Pancreas	(50)	(50)	(49)	(50)
Inflammation, chronic active		1 (2%)		
Acinus, atrophy		1 (2%)	1 (2%)	1 (2%)
Duct, cyst			1 (2%)	
Pharynx			(1)	
Submucosa, palate, infiltration cellular, mast cell			1 (100%)	
Stomach, forestomach	(50)	(50)	(50)	(50)
Acanthosis, multifocal			1 (2%)	
Ulcer	1 (2%)			
Stomach, glandular	(50)	(50)	(50)	(50)
Necrosis	1 (2%)			1 (2%)
Mucosa, hyperplasia				1 (2%)
Submucosa, inflammation, chronic active	1 (2%)			
Cardiovascular System				
Heart	(51)	(50)	(50)	(50)
Degeneration, chronic	2 (4%)			1 (2%)
Endocrine System				
Adrenal cortex	(51)	(50)	(50)	(50)
Cyst	2 (4%)	1 (2%)		1 (2%)
Hematopoietic cell proliferation	1 (2%)			
Hyperplasia		2 (4%)	1 (2%)	1 (2%)
Hypertrophy	3 (6%)	6 (12%)	5 (10%)	3 (6%)
Capsule, accessory adrenal cortical nodule	1 (2%)	2 (4%)		1 (2%)
Adrenal medulla	(49)	(50)	(50)	(50)
Hyperplasia		2 (4%)	1 (2%)	3 (6%)
Parathyroid gland	(46)	(45)	(48)	(47)
Cyst				1 (2%)

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm
2-Year Study (continued)				
Endocrine System (continued)				
Pituitary gland	(48)	(49)	(49)	(48)
Pars distalis, angiectasis		2 (4%)		
Pars distalis, cyst	4 (8%)			3 (6%)
Pars distalis, hyperplasia	9 (19%)	12 (24%)	10 (20%)	11 (23%)
Pars intermedia, cyst		1 (2%)		
Pars intermedia, hyperplasia		1 (2%)		
Thyroid gland	(51)	(50)	(49)	(50)
Inflammation, chronic active		1 (2%)		
Ultimobranchial cyst		1 (2%)		
Follicle, cyst	2 (4%)	1 (2%)		
Follicle, cyst, multiple				1 (2%)
Follicular cell, hyperplasia	4 (8%)	2 (4%)	1 (2%)	
General Body System				
None				
Genital System				
Clitoral gland	(51)	(45)	(48)	(44)
Duct, dilatation		1 (2%)	1 (2%)	
Ovary	(50)	(50)	(49)	(50)
Angiectasis		1 (2%)		
Inflammation, granulomatous	1 (2%)			1 (2%)
Mineralization			1 (2%)	1 (2%)
Thrombosis	1 (2%)			
Bilateral, inflammation, granulomatous		2 (4%)		1 (2%)
Bilateral, periovarian tissue, cyst			1 (2%)	
Bilateral, follicle, cyst		2 (4%)	2 (4%)	4 (8%)
Follicle, cyst	24 (48%)	21 (42%)	21 (43%)	16 (32%)
Periovarian tissue, cyst	1 (2%)	1 (2%)		5 (10%)
Periovarian tissue, inflammation, granulomatous	1 (2%)			
Rete ovarii, hyperplasia	2 (4%)			1 (2%)
Uterus	(51)	(50)	(50)	(50)
Endometrium, hyperplasia, cystic, glandular	48 (94%)	48 (96%)	43 (86%)	47 (94%)
Endometrium, vein, thrombosis		2 (4%)		
Hematopoietic System				
Bone marrow	(51)	(50)	(50)	(50)
Myelofibrosis	21 (41%)	18 (36%)	23 (46%)	34 (68%)
Lymph node	(9)	(7)	(4)	(7)
Inguinal, inflammation, chronic active		1 (14%)		
Mediastinal, hyperplasia, lymphoid		1 (14%)		
Mediastinal, infiltration cellular, histiocyte	1 (11%)			
Mediastinal, inflammation, acute				1 (14%)

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mandibular	(50)	(50)	(47)	(50)
Congestion		2 (4%)		
Hematopoietic cell proliferation		1 (2%)		
Hyperplasia, lymphoid		1 (2%)		
Infiltration cellular, histiocyte				1 (2%)
Inflammation, chronic active		1 (2%)		
Lymphocyte, necrosis	1 (2%)			
Lymph node, mesenteric	(46)	(43)	(41)	(44)
Hematopoietic cell proliferation	1 (2%)			
Hyperplasia, histiocytic, macrophage	40 (87%)	33 (77%)	31 (76%)	42 (95%)
Infiltration cellular, histiocyte				1 (2%)
Inflammation, chronic active		1 (2%)		1 (2%)
Lymphatic, cyst			1 (2%)	
Lymphocyte, necrosis	1 (2%)			
Spleen	(51)	(50)	(50)	(49)
Depletion lymphoid			2 (4%)	
Fibrosis	1 (2%)			
Hematopoietic cell proliferation	8 (16%)	12 (24%)	7 (14%)	4 (8%)
Inflammation, chronic				1 (2%)
Lymphocyte, necrosis	1 (2%)			
Thymus	(46)	(43)	(44)	(48)
Concretion		1 (2%)		
Depletion lymphoid	6 (13%)	2 (5%)	8 (18%)	4 (8%)
Necrosis	1 (2%)			
Integumentary System				
Mammary gland	(50)	(50)	(48)	(49)
Hyperplasia, cystic		2 (4%)	2 (4%)	2 (4%)
Skin	(51)	(50)	(50)	(50)
Inguinal, ulcer			1 (2%)	
Subcutaneous tissue, hemorrhage		1 (2%)		
Subcutaneous tissue, inflammation, acute		1 (2%)		
Tail, ulcer			1 (2%)	
Musculoskeletal System				
Skeletal muscle	(51)	(50)	(50)	(50)
Hemorrhage	1 (2%)			
Nervous System				
Brain	(51)	(50)	(50)	(50)
Compression	1 (2%)	3 (6%)	3 (6%)	
Necrosis	1 (2%)			
Neuron, degeneration			1 (2%)	
Peripheral nerve	(2)	(1)	(1)	(4)
Sciatic, axon, degeneration	2 (100%)	1 (100%)	1 (100%)	4 (100%)
Spinal cord	(2)	(1)	(1)	(4)
Axon, degeneration	1 (50%)			2 (50%)
Lumbar, axon, nerve, degeneration	1 (50%)		1 (100%)	4 (100%)

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm
2-Year Study (continued)				
Respiratory System				
Lung	(51)	(50)	(50)	(50)
Congestion				1 (2%)
Hemorrhage, focal	1 (2%)			
Inflammation, acute		1 (2%)		
Alveolar epithelium, hyperplasia		2 (4%)		
Alveolar epithelium, hyperplasia, macrophage			1 (2%)	
Mediastinum, inflammation, chronic active	1 (2%)	1 (2%)		
Perivascular, infiltration cellular, lymphocyte	4 (8%)	5 (10%)	3 (6%)	7 (14%)
Perivascular, inflammation, chronic active		1 (2%)		
Special Senses System				
Eye	(1)	(1)		(1)
Atrophy		1 (100%)		
Urinary System				
Kidney	(51)	(50)	(50)	(50)
Amyloid deposition	1 (2%)		1 (2%)	
Metaplasia, focal, osseous				1 (2%)
Nephropathy, chronic	20 (39%)	26 (52%)	15 (30%)	14 (28%)
Cortex, cyst			1 (2%)	
Cortex, infarct		1 (2%)	2 (4%)	

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Zeiger *et al.* (1987). 4,4'-Thiobis(6-*t*-butyl-*m*-cresol) was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). 4,4'-Thiobis(6-*t*-butyl-*m*-cresol) 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 4,4'-thiobis(6-*t*-butyl-*m*-cresol). The high dose was limited to 10,000 μg/plate. All trials were repeated.

In this assay, 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 PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1987). 4,4'-Thiobis(6-*t*-butyl-*m*-cresol) was sent to the laboratory as a coded aliquot by Radian Corporation. 4,4'-Thiobis(6-*t*-butyl-*m*-cresol) 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 three doses of 4,4'-thiobis(6-*t*-butyl-*m*-cresol); the high dose was limited by toxicity. A single flask per dose was used, and tests yielding equivocal or positive results were repeated.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 26 hours with 4,4'-thiobis(6-*t*-butyl-*m*-cresol) 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 4,4'-thiobis(6-*t*-butyl-*m*-cresol) was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with 4,4'-thiobis(6-*t*-butyl-*m*-cresol), serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no 4,4'-thiobis(6-*t*-butyl-*m*-cresol), 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. Because significant chemical-induced cell cycle delay was seen at the higher doses tested with and without S9, incubation time was lengthened to ensure a sufficient number of scorable (second-division metaphase) cells.

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 4,4'-thiobis(6-*t*-butyl-*m*-cresol) for 18.5 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 4,4'-thiobis(6-*t*-butyl-*m*-cresol) and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 18.5 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9. The harvest time for the Abs test was based on the cell cycle information obtained in the SCE test; because cell cycle delay was anticipated, the incubation period was extended beyond the usual time period of approximately 12 hours.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind and those from a single test were read by the same person. 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 ($P \leq 0.015$) were considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive. A positive trend test in the absence of a statistically significant increase at any one dose resulted in an equivocal call (Galloway *et al.*, 1987). Ultimately the trial cells were based on a consideration of the statistical analyses as well as the biological information available to the reviewers.

RESULTS

4,4'-Thiobis(6-*t*-butyl-*m*-cresol) (33 to 10,000 μg/plate) was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537, with or without induced hamster or rat liver S9 (Table E1; Zeiger *et al.*, 1987). A precipitate was observed on plates treated with 333 μg 4,4'-thiobis(6-*t*-butyl-*m*-cresol) and all higher concentrations. In cytogenetic tests with CHO cells, 4,4'-thiobis(6-*t*-butyl-*m*-cresol) induced SCEs, with and without S9, at doses that induced cell cycle delay (Table E2). No induction of chromosomal aberrations was observed in these cells, with or without S9 (Table E3). Because 4,4'-thiobis(6-*t*-butyl-*m*-cresol) induced cell cycle delay, cultures analyzed for chromosomal aberrations were incubated for 20.5 hours, rather than the usual 12 hours, to allow sufficient cells to accumulate for harvest.

TABLE E1
Mutagenicity of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol) in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA100	0	97 ± 2.3	115 ± 4.4	101 ± 5.9	190 ± 8.8	108 ± 15.1	179 ± 14.2
	100	78 ± 1.9	111 ± 8.5	131 ± 10.7	175 ± 2.1	145 ± 6.5	192 ± 7.0
	333	79 ± 4.3[c]	109 ± 4.9[c]	122 ± 2.2[c]	197 ± 6.8[c]	169 ± 12.1[c]	190 ± 4.4[c]
	1,000	103 ± 8.1[c]	120 ± 6.6[c]	126 ± 5.9[c]	150 ± 18.8[c]	137 ± 9.8[c]	164 ± 6.9[c]
	3,333	68 ± 19.9[c]	118 ± 1.7[c]	75 ± 7.9[c]	174 ± 23.7[c]	68 ± 5.2[c]	159 ± 11.0[c]
	10,000	78 ± 15.7[c]	143 ± 10.1[c]	76 ± 10.1[c]	131 ± 7.1[c]	72 ± 9.9[c]	121 ± 10.4[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[d]		439 ± 41.8	1,499 ± 34.9	1,678 ± 99.2	1,987 ± 17.7	1,642 ± 41.2	1,329 ± 27.2
TA1535	0	3 ± 0.9	13 ± 0.9	4 ± 0.6	17 ± 1.5	9 ± 1.8	25 ± 1.3
	33		15 ± 1.2				
	100	3 ± 0.9	16 ± 1.2	7 ± 2.3	21 ± 0.7	6 ± 1.2	28 ± 1.5
	333	3 ± 0.6[c]	14 ± 1.3[c]	8 ± 1.5[c]	19 ± 1.8[c]	5 ± 0.7[c]	22 ± 2.6[c]
	1,000	1 ± 0.7[c]	9 ± 1.5[c]	5 ± 0.9[c]	12 ± 2.0[c]	3 ± 0.3[c]	20 ± 2.5[c]
	3,333	1 ± 0.7[c]	7 ± 0.9[c]	6 ± 1.9[c]	14 ± 2.0[c]	7 ± 1.7[c]	11 ± 2.5[c]
	10,000	0 ± 0.0[c]		1 ± 0.7[c]	Toxic	1 ± 0.3[c]	Toxic
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		126 ± 11.1	972 ± 63.7	197 ± 38.9	260 ± 42.3	102 ± 16.2	346 ± 20.3
TA1537	0	8 ± 1.2	9 ± 1.8	4 ± 1.2	14 ± 0.6	6 ± 1.5	17 ± 2.8
	33		7 ± 0.9				
	100	4 ± 1.2	5 ± 1.8	7 ± 0.9	16 ± 1.8	8 ± 0.6	19 ± 3.1
	333	4 ± 0.0[c]	8 ± 0.9[c]	10 ± 1.8[c]	10 ± 2.5[c]	7 ± 1.2[c]	17 ± 4.1[c]
	1,000	1 ± 0.7[c]	3 ± 1.0[c]	10 ± 1.0[c]	7 ± 1.9[c]	4 ± 1.2[c]	9 ± 3.7[c]
	3,333	1 ± 0.6[c]	3 ± 1.2[c]	11 ± 2.3[c]	5 ± 1.2[c]	4 ± 0.6[c]	7 ± 1.7[c]
	10,000	0 ± 0.0[c]		3 ± 0.9[c]	Toxic	2 ± 0.9[c]	Toxic
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		116 ± 13.4	328 ± 35.7	120 ± 8.0	346 ± 7.9	204 ± 29.4	739 ± 45.4
TA98	0	20 ± 0.6	17 ± 1.5	22 ± 3.8	27 ± 4.2	29 ± 0.9	39 ± 1.8
	100	9 ± 0.9	20 ± 3.0	18 ± 4.3	32 ± 0.7	23 ± 2.0	38 ± 2.7
	333	9 ± 0.5[c]	12 ± 1.8[c]	13 ± 1.7[c]	23 ± 8.5[c]	29 ± 2.6[c]	43 ± 1.5[c]
	1,000	13 ± 4.2[c]	15 ± 1.2[c]	12 ± 0.3[c]	13 ± 2.8[c]	25 ± 2.7[c]	15 ± 2.8[c]
	3,333	9 ± 3.2[c]	9 ± 0.9[c]	8 ± 1.2[c]	14 ± 2.0[c]	17 ± 2.3[c]	13 ± 2.1[c]
	10,000	6 ± 1.8[c]	9 ± 2.4[c]	14 ± 1.2[c]	Toxic	17 ± 3.5[c]	Toxic
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		170 ± 15.4	199 ± 13.0	2,076 ± 87.7	1,302 ± 51.3	942 ± 83.8	583 ± 2.2

[a] Study performed at Case Western Reserve University. The detailed protocol and these data are presented in Zeiger *et al.* (1987).
[b] Revertants are presented as mean ± the standard error from three plates.
[c] Precipitate on plate
[d] 2-Aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was tested on TA98, sodium azide was tested on TA100 and TA1535, and 9-aminoacridine was tested on TA1537.

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome[b] (%)
-S9								
Trial 1								
Summary: Equivocal								
Dimethylsulfoxide		50	1,043	512	0.49	10.2	26.0	
Mitomycin-C	0.0015	50	1,049	805	0.76	16.1	26.0	56.33
	0.0100	5	105	280	2.66	56.0	26.0	443.23
4,4'-Thiobis(6-*t*-butyl-*m*-cresol)								
	1.75	50	1,039	527	0.50	10.5	26.0	3.32
	2.00	50	1,036	526	0.50	10.5	26.0	3.43
	2.50	50	1,048	602	0.57	12.0	31.5[c]	17.02
					P=0.004[d]			
Trial 2								
Summary: Weakly positive								
Dimethylsulfoxide		50	1,051	477	0.45	9.5	26.0	
Mictomycin-C	0.0015	50	1,046	815	0.77	16.3	26.0	71.68
	0.0100	5	105	237	2.25	47.4	26.0	397.33
4,4'-Thiobis(6-*t*-butyl-*m*-cresol)								
	1.5	50	1,047	551	0.52	11.0	26.0	15.95
	2.0	50	1,050	492	0.46	9.8	26.0	3.24
	2.5	50	1,050	578	0.55	11.6	33.5[c]	21.29*
					P=0.012			

Table E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by 4,4′-Thiobis(6-t-Butyl-m-Cresol) (continued)

Compound	Dose µg/mL	Total Cells	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-some	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome[b] (%)
+S9								
Trial 1								
Summary: Positive								
Dimethylsulfoxide		50	1,042	583	0.55	11.7	26.0	
Cyclophosphamide	0.4	50	1,043	866	0.83	17.3	26.0	48.40
	2.0	5	105	249	2.37	49.8	26.0	323.85
4,4′-Thiobis(6-t-butyl-m-cresol)								
	7.5	50	1,044	741	0.70	14.8	31.5[c]	26.86*
	10.0	50	1,045	741	0.70	14.8	31.5[c]	26.74*
	12.5	50	1,044	820	0.78	16.4	34.3[c]	40.38*
						P<0.001		
Trial 2								
Summary: Positive								
Dimethylsulfoxide		50	1,044	471	0.45	9.4	26.0	
Cyclophosphamide	0.4	50	1,049	750	0.71	15.0	26.0	58.48
	2.0	5	105	199	1.89	39.8	26.0	320.10
4,4′-Thiobis(6-t-butyl-m-cresol)								
	7.5	50	1,047	519	0.49	10.4	26.0	9.88
	10.0	50	1,050	574	0.54	11.5	33.5[c]	21.17*
	12.5	50	1,050	625	0.59	12.5	33.5[c]	31.94*
						P<0.001		

* Positive (> 20% increase over solvent control)
[a] Study performed at Litton Bionetics, Inc. 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 4,4′-thiobis(6-t-butyl-m-cresol) relative to those of culture exposed to solvent
[c] Because 4,4′-thiobis(6-t-butyl-m-cresol) induced a delay in the cell division cycle, harvest time was extended to maximize the proportion of second-division cells available for analysis.
[d] 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 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)[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: 20.5 hours[b]					**Trial 1** - Harvest time: 20.5 hours[b]				
Summary: Negative					Summary: Negative				
Dimethylsulfoxide					Dimethylsulfoxide				
	100	5	0.05	5.0		100	2	0.02	2.0
Mitomycin-C					Cyclophosphamide				
0.0350	100	16	0.16	14.0	2.5	100	19	0.19	10.0
0.0625	25	13	0.52	40.0	12.5	25	18	0.72	40.0
4,4'-Thiobis(6-*t*-butyl-*m*-cresol)					4,4'-Thiobis(6-*t*-butyl-*m*-cresol)				
3	100	5	0.05	5.0	7.5	100	2	0.02	2.0
4	100	3	0.03	3.0	10.0	100	3	0.03	3.0
5	100	2	0.02	2.0	12.5	100	4	0.04	4.0
				P=0.903[c]					P=0.170

[a] Study performed at Litton Bionetics, Inc. Abs=aberrations. A detailed description of the chromosomal aberrations protocol is presented by Galloway *et al.* (1987).
[b] Because of significant chemical-induced cell cycle delay, incubation time prior to addition of Colcemid was lengthened to provide sufficient metaphase cells at harvest.
[c] 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

Table F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 15-Day Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

	0 ppm	1,000 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Male					
n	10	10	10	10	7
Necropsy body wt	212 ± 4	224 ± 3	222 ± 5	165 ± 3**	103 ± 4**
Brain					
Absolute	1.832 ± 0.029	1.861 ± 0.016	1.839 ± 0.018	1.745 ± 0.015**	1.641 ± 0.019**
Relative	8.68 ± 0.22	8.31 ± 0.10	8.34 ± 0.20	10.61 ± 0.17**	16.01 ± 0.56**
Heart					
Absolute	0.850 ± 0.044	0.778 ± 0.022	0.785 ± 0.022	0.565 ± 0.027**	0.350 ± 0.014**
Relative	4.03 ± 0.23	3.47 ± 0.09*	3.55 ± 0.09*	3.42 ± 0.14**	3.39 ± 0.09**
R. Kidney					
Absolute	0.859 ± 0.018	0.885 ± 0.024	0.869 ± 0.024	0.652 ± 0.014**	0.503 ± 0.014**
Relative	4.06 ± 0.03	3.94 ± 0.08	3.92 ± 0.04	3.95 ± 0.05	4.90 ± 0.21**
Liver					
Absolute	9.792 ± 0.420	10.622 ± 0.201	11.146 ± 0.310	8.689 ± 0.190*	6.420 ± 0.371**
Relative	46.13 ± 1.36	47.37 ± 0.62	50.30 ± 0.50*	52.72 ± 0.60**	62.22 ± 2.83**
Lungs					
Absolute	1.131 ± 0.077	1.278 ± 0.127	1.257 ± 0.123	0.876 ± 0.048	0.678 ± 0.030**
Relative	5.33 ± 0.32	5.71 ± 0.57	5.66 ± 0.51	5.30 ± 0.23	6.64 ± 0.43
Spleen					
Absolute	0.600 ± 0.039	0.588 ± 0.015	0.619 ± 0.014	0.481 ± 0.013**	0.196 ± 0.021**
Relative	2.83 ± 0.17	2.62 ± 0.04	2.81 ± 0.07	2.92 ± 0.05	1.88 ± 0.13**
R. Testis					
Absolute	1.120 ± 0.020	1.185 ± 0.017	1.157 ± 0.028	1.127 ± 0.019	0.813 ± 0.044**
Relative	5.30 ± 0.09	5.29 ± 0.06	5.23 ± 0.08	6.85 ± 0.15**	7.89 ± 0.35**
Thymus					
Absolute	0.514 ± 0.038	0.496 ± 0.028	0.520 ± 0.021	0.312 ± 0.035**	0.034 ± 0.007**
Relative	2.44 ± 0.20	2.21 ± 0.11	2.35 ± 0.10	1.88 ± 0.19*	0.33 ± 0.07**

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 15-Day Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	1,000 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Female					
n	10	10	10	10	6
Necropsy body wt	154 ± 3	156 ± 2	157 ± 2	126 ± 1**	88 ± 4**
Brain					
Absolute	1.733 ± 0.022	1.716 ± 0.020	1.744 ± 0.020	1.762 ± 0.088	1.627 ± 0.034
Relative	11.27 ± 0.21	10.99 ± 0.16	11.12 ± 0.17	13.93 ± 0.66**	18.59 ± 0.80**
Heart					
Absolute	0.568 ± 0.016	0.567 ± 0.015	0.594 ± 0.022	0.497 ± 0.026*	0.344 ± 0.013**
Relative	3.68 ± 0.07	3.63 ± 0.08	3.79 ± 0.13	3.94 ± 0.22	3.91 ± 0.13
R. Kidney					
Absolute	0.646 ± 0.020	0.620 ± 0.012	0.653 ± 0.010	0.507 ± 0.010**	0.519 ± 0.049**
Relative	4.18 ± 0.08	3.96 ± 0.05	4.17 ± 0.09	4.01 ± 0.08	5.94 ± 0.62**
Liver					
Absolute	6.793 ± 0.239	6.625 ± 0.165	7.367 ± 0.132	6.696 ± 0.149	5.217 ± 0.581**
Relative	43.98 ± 1.08	42.37 ± 0.83	46.91 ± 0.68	52.98 ± 1.29**	58.51 ± 4.72**
Lungs					
Absolute	0.950 ± 0.032	0.997 ± 0.055	0.939 ± 0.034	0.748 ± 0.015**	0.593 ± 0.024**
Relative	6.17 ± 0.22	6.36 ± 0.31	5.98 ± 0.20	5.91 ± 0.12	6.75 ± 0.28
Spleen					
Absolute	0.432 ± 0.017	0.441 ± 0.013	0.483 ± 0.013	0.387 ± 0.012*	0.199 ± 0.026**
Relative	2.80 ± 0.08	2.82 ± 0.08	3.08 ± 0.09	3.06 ± 0.09	2.22 ± 0.22**
Thymus					
Absolute	0.430 ± 0.029	0.405 ± 0.025	0.496 ± 0.049	0.328 ± 0.023*	0.026 ± 0.005**
Relative	2.78 ± 0.17	2.60 ± 0.18	3.19 ± 0.35	2.59 ± 0.17	0.30 ± 0.07**

* 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 males or females receiving 25,000 ppm due to 100% mortality in these groups.

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

	0 ppm	250 ppm	500 ppm	1,000 ppm	2,500 ppm	5,000 ppm
Male						
n	10	10	9	10	10	10
Necropsy body wt	359 ± 7	382 ± 6	378 ± 6	368 ± 5	351 ± 7	217 ± 3**
Brain						
Absolute	2.002 ± 0.049	2.022 ± 0.027	2.035 ± 0.022	2.021 ± 0.012	1.997 ± 0.024	1.793 ± 0.013**
Relative	5.59 ± 0.12	5.30 ± 0.08	5.37 ± 0.05	5.50 ± 0.07	5.70 ± 0.09	8.29 ± 0.08**
Heart						
Absolute	1.013 ± 0.050[b]	1.024 ± 0.024	1.002 ± 0.020[c]	0.984 ± 0.028	0.955 ± 0.027	0.581 ± 0.011**
Relative	2.82 ± 0.10[b]	2.68 ± 0.05	2.65 ± 0.03[c]	2.67 ± 0.05	2.72 ± 0.05	2.68 ± 0.04
R. Kidney						
Absolute	1.300 ± 0.046[d]	1.282 ± 0.044[d]	1.267 ± 0.040[c]	1.306 ± 0.027	1.328 ± 0.035	0.870 ± 0.018**
Relative	3.59 ± 0.10[d]	3.36 ± 0.07[d]	3.34 ± 0.08[c]	3.55 ± 0.05	3.79 ± 0.11	4.02 ± 0.06**
Liver						
Absolute	13.263 ± 0.345	13.566 ± 0.424	13.813 ± 0.361	13.168 ± 0.252	14.078 ± 0.309	11.520 ± 0.218**
Relative	36.96 ± 0.52	35.44 ± 0.68	36.23 ± 0.81	35.74 ± 0.28	40.14 ± 0.60**	53.21 ± 0.72**
Lungs						
Absolute	1.697 ± 0.089[d]	1.824 ± 0.086	1.865 ± 0.058[c]	1.781 ± 0.082	1.680 ± 0.083	1.065 ± 0.022**
Relative	4.78 ± 0.25[d]	4.78 ± 0.23	4.94 ± 0.16[c]	4.84 ± 0.21	4.78 ± 0.22	4.92 ± 0.07
Spleen						
Absolute	0.852 ± 0.060	0.823 ± 0.018	0.803 ± 0.016[c]	0.801 ± 0.020	0.744 ± 0.014*	0.620 ± 0.009**
Relative	2.38 ± 0.17	2.15 ± 0.04	2.13 ± 0.05[c]	2.17 ± 0.03	2.12 ± 0.03	2.87 ± 0.04**
R. Testis						
Absolute	1.492 ± 0.042	1.601 ± 0.044	1.600 ± 0.032	1.512 ± 0.027	1.669 ± 0.114	1.427 ± 0.024
Relative	4.16 ± 0.09	4.20 ± 0.14	4.24 ± 0.03	4.11 ± 0.05	4.75 ± 0.29**	6.59 ± 0.08**
Thymus						
Absolute	0.472 ± 0.032	0.448 ± 0.065	0.367 ± 0.031	0.380 ± 0.029	0.329 ± 0.020*[b]	0.190 ± 0.014**[e]
Relative	1.32 ± 0.09	1.16 ± 0.16	0.97 ± 0.08*	1.03 ± 0.08*	0.95 ± 0.06*[b]	0.87 ± 0.07**[e]

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm	2,500 ppm	5,000 ppm
Female						
n	10	10	10	10	10	10
Necropsy body wt	209 ± 8	204 ± 5	200 ± 2	201 ± 3	200 ± 3	153 ± 5**
Brain						
Absolute	1.865 ± 0.018	1.815 ± 0.030	1.836 ± 0.011	1.877 ± 0.023	1.896 ± 0.056	1.720 ± 0.026**
Relative	9.02 ± 0.25	8.94 ± 0.19	9.19 ± 0.11	9.37 ± 0.19	9.51 ± 0.37	11.31 ± 0.32**
Heart						
Absolute	0.648 ± 0.013	0.631 ± 0.018	0.627 ± 0.014	0.625 ± 0.014	0.569 ± 0.011**[d]	0.465 ± 0.021**
Relative	3.14 ± 0.11	3.10 ± 0.08	3.14 ± 0.07	3.13 ± 0.11	2.84 ± 0.04[d]	3.04 ± 0.09
R. Kidney						
Absolute	0.743 ± 0.020	0.708 ± 0.020	0.714 ± 0.013	0.725 ± 0.015	0.717 ± 0.015[d]	0.615 ± 0.015**
Relative	3.59 ± 0.11	3.49 ± 0.12	3.57 ± 0.06	3.62 ± 0.10	3.61 ± 0.06[d]	4.03 ± 0.07**
Liver						
Absolute	6.480 ± 0.142	6.086 ± 0.253	6.222 ± 0.129	6.113 ± 0.143	6.871 ± 0.139	8.088 ± 0.226**
Relative	31.36 ± 1.11	29.95 ± 1.30	31.11 ± 0.62	30.59 ± 1.07	34.35 ± 0.48	53.05 ± 1.49**
Lungs						
Absolute	1.200 ± 0.049[d]	1.251 ± 0.027	1.254 ± 0.057	1.182 ± 0.031	1.212 ± 0.043	0.934 ± 0.038**
Relative	5.74 ± 0.26[d]	6.16 ± 0.17	6.26 ± 0.25	5.90 ± 0.19	6.05 ± 0.18	6.09 ± 0.13
Spleen						
Absolute	0.515 ± 0.012	0.514 ± 0.014	0.538 ± 0.018	0.521 ± 0.017	0.553 ± 0.009[d]	0.484 ± 0.014
Relative	2.48 ± 0.06	2.53 ± 0.07	2.69 ± 0.09	2.61 ± 0.10	2.77 ± 0.03*[d]	3.17 ± 0.06**
Thymus						
Absolute	0.301 ± 0.013[d]	0.250 ± 0.018[b]	0.266 ± 0.009	0.278 ± 0.015[d]	0.287 ± 0.022	0.175 ± 0.014**[f]
Relative	1.45 ± 0.07[d]	1.23 ± 0.11[b]	1.33 ± 0.04	1.40 ± 0.08[d]	1.43 ± 0.11	1.15 ± 0.09[f]

* 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=10
[d] n=9
[e] n=7
[f] n=6

TABLE F3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
Male				
n	10	10	7	10
Necropsy body wt	488 ± 11	495 ± 11	482 ± 8	453 ± 9*
Brain				
Absolute	2.121 ± 0.024	2.111 ± 0.023	2.093 ± 0.017	2.092 ± 0.015
Relative	4.36 ± 0.09	4.28 ± 0.08	4.35 ± 0.08	4.63 ± 0.07*
R. Kidney				
Absolute	1.782 ± 0.064	1.870 ± 0.078	1.756 ± 0.056	1.757 ± 0.042
Relative	3.65 ± 0.11	3.77 ± 0.10	3.64 ± 0.08	3.88 ± 0.07
Liver				
Absolute	16.695 ± 0.667	18.204 ± 0.760	17.442 ± 0.781	17.859 ± 0.568
Relative	34.19 ± 0.93	36.69 ± 0.99	36.12 ± 1.29	39.40 ± 0.86**
Spleen				
Absolute	1.122 ± 0.061	1.088 ± 0.051	1.008 ± 0.048	0.997 ± 0.076
Relative	2.30 ± 0.11	2.20 ± 0.09	2.09 ± 0.09	2.20 ± 0.15
Female				
n	10	10	10	10
Necropsy body wt	312 ± 8	309 ± 8	293 ± 7	280 ± 5**
Brain				
Absolute	1.910 ± 0.023	1.910 ± 0.015	1.854 ± 0.033	1.889 ± 0.017
Relative	6.14 ± 0.14	6.22 ± 0.16	6.35 ± 0.10	6.77 ± 0.17**
R. Kidney				
Absolute	1.072 ± 0.019	1.076 ± 0.028	1.033 ± 0.023	1.086 ± 0.028
Relative	3.44 ± 0.04	3.49 ± 0.07	3.53 ± 0.04	3.88 ± 0.09**
Liver				
Absolute	9.897 ± 0.260	10.267 ± 0.293	10.078 ± 0.309	11.115 ± 0.324**
Relative	31.73 ± 0.59	33.28 ± 0.56	34.41 ± 0.45**	39.69 ± 0.87**
Spleen				
Absolute	0.587 ± 0.021	0.578 ± 0.018	0.562 ± 0.021	0.634 ± 0.028
Relative	1.88 ± 0.05	1.88 ± 0.05	1.93 ± 0.09	2.27 ± 0.11**

* 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).

Table F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 15-Day Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

	0 ppm	1,000 ppm	2,500 ppm	5,000 ppm
Male				
n	10	10	10	2
Necropsy body wt	24.2 ± 0.7	26.1 ± 0.5	23.8 ± 0.4	15.9 ± 0.4**
Brain				
Absolute	0.486 ± 0.011	0.480 ± 0.008	0.466 ± 0.005	0.422 ± 0.013**
Relative	20.17 ± 0.62	18.44 ± 0.41*	19.62 ± 0.41	26.63 ± 0.22**
Heart				
Absolute	0.141 ± 0.006	0.132 ± 0.007	0.114 ± 0.002**	0.090 ± 0.006**
Relative	5.85 ± 0.28	5.05 ± 0.21*	4.79 ± 0.07**	5.67 ± 0.27
R. Kidney				
Absolute	0.230 ± 0.009	0.220 ± 0.009	0.175 ± 0.007**	0.119 ± 0.003**
Relative	9.49 ± 0.28	8.43 ± 0.28**	7.33 ± 0.22**	7.49 ± 0.36**
Liver				
Absolute	1.292 ± 0.069	1.322 ± 0.037	1.365 ± 0.045	1.223 ± 0.048
Relative	53.15 ± 1.89	50.66 ± 1.19	57.28 ± 1.28	77.25 ± 4.74**
Lungs				
Absolute	0.187 ± 0.013	0.181 ± 0.006	0.154 ± 0.007*[b]	0.134 ± 0.005*
Relative	7.69 ± 0.46	6.92 ± 0.19	6.40 ± 0.26*[b]	8.49 ± 0.51
Spleen				
Absolute	0.089 ± 0.009	0.096 ± 0.008	0.088 ± 0.003	0.030 ± 0.002**
Relative	3.64 ± 0.28	3.67 ± 0.28	3.71 ± 0.08	1.90 ± 0.19**
R. Testis				
Absolute	0.105 ± 0.003	0.100 ± 0.003	0.108 ± 0.003	0.084 ± 0.001**
Relative	4.35 ± 0.09	3.84 ± 0.10	4.54 ± 0.11	5.33 ± 0.16**
Thymus				
Absolute	0.060 ± 0.009	0.053 ± 0.005	0.054 ± 0.004	0.008 ± 0.007**
Relative	2.51 ± 0.37	2.05 ± 0.18	2.26 ± 0.18	0.49 ± 0.46**

Table F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 15-Day Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	1,000 ppm	2,500 ppm	5,000 ppm
Female				
n	10	10	10	2
Necropsy body wt	18.9 ± 0.4	19.3 ± 0.2	16.5 ± 0.5**	13.8 ± 0.1**
Brain				
Absolute	0.463 ± 0.004	0.447 ± 0.005*	0.435 ± 0.005**	0.432 ± 0.021*
Relative	24.62 ± 0.48	23.14 ± 0.30	26.57 ± 0.75*	31.32 ± 1.73**
Heart				
Absolute	0.100 ± 0.003	0.103 ± 0.003	0.088 ± 0.003**	0.080 ± 0.003**
Relative	5.31 ± 0.12	5.34 ± 0.13	5.36 ± 0.14	5.83 ± 0.21
R. Kidney				
Absolute	0.143 ± 0.004	0.135 ± 0.004	0.112 ± 0.004**	0.107 ± 0.000**
Relative	7.58 ± 0.21	6.98 ± 0.19	6.82 ± 0.17*	7.79 ± 0.03
Liver				
Absolute	0.933 ± 0.027	0.993 ± 0.032	0.971 ± 0.030	1.069 ± 0.143
Relative	49.46 ± 1.08	51.34 ± 1.56	58.98 ± 1.23**	77.40 ± 9.82**
Lungs				
Absolute	0.154 ± 0.005	0.140 ± 0.007	0.127 ± 0.006**	0.119 ± 0.001*
Relative	8.15 ± 0.24	7.24 ± 0.34	7.70 ± 0.29	8.63 ± 0.10
Spleen				
Absolute	0.070 ± 0.002	0.080 ± 0.004	0.070 ± 0.004	0.034 ± 0.008**
Relative	3.75 ± 0.13	4.12 ± 0.18	4.25 ± 0.18	2.49 ± 0.59**
Thymus				
Absolute	0.070 ± 0.003	0.068 ± 0.003	0.050 ± 0.006**	0.011 ± 0.007**
Relative	3.74 ± 0.18	3.52 ± 0.17	3.03 ± 0.36	0.81 ± 0.49**

* 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 measurement taken for male or female mice receiving 10,000 or 25,000 ppm due to 100% mortality in these groups.
[b] n=9

TABLE F5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

	0 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm	2,500 ppm
Male						
n	9	10	10	10	10	10
Necropsy body wt	30.8 ± 1.1	30.6 ± 1.0	31.7 ± 0.6	30.5 ± 0.9	30.8 ± 0.6	26.3 ± 0.4**
Brain						
Absolute	0.484 ± 0.006	0.483 ± 0.003	0.481 ± 0.005	0.473 ± 0.008	0.499 ± 0.007	0.491 ± 0.005
Relative	15.85 ± 0.57	15.95 ± 0.50	15.24 ± 0.29	15.59 ± 0.32	16.25 ± 0.39	18.73 ± 0.31**
Heart						
Absolute	0.153 ± 0.007	0.145 ± 0.004	0.153 ± 0.004	0.142 ± 0.005	0.152 ± 0.003	0.131 ± 0.003**
Relative	4.96 ± 0.09	4.78 ± 0.13	4.85 ± 0.12	4.69 ± 0.17	4.96 ± 0.13	4.99 ± 0.11
R. Kidney						
Absolute	0.306 ± 0.009	0.294 ± 0.013	0.315 ± 0.012	0.302 ± 0.013	0.315 ± 0.011	0.243 ± 0.006**
Relative	9.98 ± 0.22	9.63 ± 0.25	9.95 ± 0.28	9.88 ± 0.25	10.24 ± 0.31	9.25 ± 0.20
Liver						
Absolute	1.483 ± 0.039	1.321 ± 0.057	1.516 ± 0.046	1.502 ± 0.064	1.570 ± 0.048	1.744 ± 0.021**
Relative	48.32 ± 0.96	43.36 ± 1.50	47.81 ± 0.72	49.21 ± 1.40	51.00 ± 1.43	66.54 ± 1.00**
Lungs						
Absolute	0.223 ± 0.007	0.244 ± 0.014	0.234 ± 0.011	0.224 ± 0.009	0.235 ± 0.007	0.219 ± 0.007
Relative	7.30 ± 0.31	8.03 ± 0.42	7.36 ± 0.29	7.36 ± 0.27	7.64 ± 0.18	8.36 ± 0.29*
Spleen						
Absolute	0.083 ± 0.002	0.087 ± 0.003	0.093 ± 0.004	0.099 ± 0.005*	0.098 ± 0.002*	0.137 ± 0.005**
Relative	2.73 ± 0.13	2.85 ± 0.11	2.92 ± 0.11	3.28 ± 0.23*	3.19 ± 0.06*	5.21 ± 0.17**
R. Testis						
Absolute	0.145 ± 0.015	0.132 ± 0.003	0.137 ± 0.008[b]	0.126 ± 0.005	0.131 ± 0.003	0.126 ± 0.003
Relative	4.68 ± 0.39	4.35 ± 0.13	4.32 ± 0.21[b]	4.13 ± 0.11	4.26 ± 0.11	4.80 ± 0.11
Thymus						
Absolute	0.060 ± 0.009	0.045 ± 0.003	0.053 ± 0.004	0.044 ± 0.005	0.048 ± 0.005	0.050 ± 0.003
Relative	1.91 ± 0.24	1.47 ± 0.09	1.66 ± 0.11	1.44 ± 0.13	1.55 ± 0.14	1.91 ± 0.15

Table F5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm	2,500 ppm
Female						
n	10	10	10	10	10	10
Necropsy body wt	30.7 ± 0.8	28.1 ± 0.7*	29.2 ± 0.7*	27.3 ± 0.7**	26.0 ± 0.4**	23.8 ± 0.5**
Brain						
Absolute	0.494 ± 0.006	0.504 ± 0.005	0.492 ± 0.006	0.508 ± 0.006	0.504 ± 0.007	0.477 ± 0.005
Relative	16.19 ± 0.40	18.03 ± 0.43*	16.90 ± 0.42*	18.69 ± 0.39**	19.39 ± 0.24**	20.08 ± 0.49**
Heart						
Absolute	0.135 ± 0.002	0.132 ± 0.005	0.141 ± 0.005	0.132 ± 0.003	0.130 ± 0.002	0.123 ± 0.004*
Relative	4.41 ± 0.13	4.73 ± 0.15	4.81 ± 0.13*	4.87 ± 0.13*	4.99 ± 0.06**	5.18 ± 0.18**
R. Kidney						
Absolute	0.222 ± 0.006	0.211 ± 0.005	0.220 ± 0.006	0.217 ± 0.004	0.215 ± 0.006	0.184 ± 0.006**
Relative	7.27 ± 0.17	7.55 ± 0.17	7.52 ± 0.17	8.00 ± 0.19**	8.28 ± 0.17**	7.72 ± 0.20**
Liver						
Absolute	1.450 ± 0.046	1.245 ± 0.039	1.314 ± 0.034	1.325 ± 0.050	1.354 ± 0.043	1.614 ± 0.044*
Relative	47.25 ± 0.89	44.37 ± 1.09	45.03 ± 0.89	48.62 ± 1.59	52.11 ± 1.46*	67.77 ± 1.65**
Lungs						
Absolute	0.230 ± 0.014	0.237 ± 0.007	0.252 ± 0.009	0.238 ± 0.005	0.234 ± 0.008	0.218 ± 0.009
Relative	7.50 ± 0.39	8.47 ± 0.28*	8.65 ± 0.36**	8.73 ± 0.10**	9.03 ± 0.29**	9.12 ± 0.27**
Spleen						
Absolute	0.132 ± 0.004	0.128 ± 0.006	0.143 ± 0.007	0.132 ± 0.004	0.137 ± 0.004	0.161 ± 0.007**
Relative	4.31 ± 0.16	4.57 ± 0.25	4.90 ± 0.22	4.85 ± 0.17	5.29 ± 0.18**	6.76 ± 0.24**
Thymus						
Absolute	0.063 ± 0.005	0.057 ± 0.002	0.059 ± 0.003	0.062 ± 0.002	0.051 ± 0.002*	0.060 ± 0.002
Relative	2.05 ± 0.17	2.03 ± 0.11	2.00 ± 0.09	2.29 ± 0.07	1.94 ± 0.08	2.51 ± 0.10**

* 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 F6
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

	0 ppm	250 ppm	500 ppm	1,000 ppm
Male				
n	10	10	10	10
Necropsy body wt	48.4 ± 0.7	45.9 ± 1.6	45.5 ± 1.7	44.2 ± 1.5
Brain				
Absolute	0.464 ± 0.005	0.459 ± 0.005	0.460 ± 0.009	0.464 ± 0.004
Relative	9.60 ± 0.20	10.12 ± 0.40	10.23 ± 0.34	10.60 ± 0.36*
R. Kidney				
Absolute	0.386 ± 0.012	0.374 ± 0.008	0.386 ± 0.013	0.410 ± 0.018
Relative	7.99 ± 0.24	8.20 ± 0.24	8.54 ± 0.27	9.27 ± 0.25**
Liver				
Absolute	1.991 ± 0.053	1.942 ± 0.123	2.128 ± 0.151	1.887 ± 0.063
Relative	41.12 ± 0.76	42.01 ± 1.33	47.12 ± 3.62	42.78 ± 0.94
Spleen				
Absolute	0.077 ± 0.006	0.073 ± 0.003	0.082 ± 0.004	0.083 ± 0.002
Relative	1.58 ± 0.10	1.58 ± 0.05	1.81 ± 0.10	1.89 ± 0.04*
Female				
n	9	9	10	10
Necropsy body wt	52.0 ± 1.8	46.2 ± 1.4*	47.6 ± 1.7	43.1 ± 1.9**
Brain				
Absolute	0.472 ± 0.005	0.460 ± 0.005	0.469 ± 0.004	0.470 ± 0.007
Relative	9.16 ± 0.35	10.05 ± 0.35	9.97 ± 0.38	11.11 ± 0.54**
R. Kidney				
Absolute	0.273 ± 0.008	0.262 ± 0.004	0.274 ± 0.011	0.259 ± 0.009
Relative	5.26 ± 0.09	5.73 ± 0.20	5.80 ± 0.22	6.08 ± 0.23**
Liver				
Absolute	1.865 ± 0.100[b]	1.724 ± 0.045	1.794 ± 0.045	1.777 ± 0.059
Relative	35.70 ± 0.80[b]	37.41 ± 0.53	37.93 ± 0.97	41.94 ± 2.33**
Spleen				
Absolute	0.099 ± 0.005	0.098 ± 0.003[b]	0.107 ± 0.003	0.106 ± 0.004
Relative	1.93 ± 0.12	2.13 ± 0.13[b]	2.27 ± 0.08	2.50 ± 0.15**

* 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=8

APPENDIX G
HEMATOLOGY, CLINICAL CHEMISTRY, AND URINALYSIS RESULTS

TABLE G1
Hematology Data for Rats in the 15-Day Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

	0 ppm	1,000 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Male					
n	10	10	10	10	7
Hematocrit (%)	44.5 ± 0.5	43.0 ± 0.4	43.2 ± 0.5	42.2 ± 0.3*	45.0 ± 1.8
Hemoglobin (g/dL)	15.1 ± 0.2	14.9 ± 0.2	15.2 ± 0.2	14.8 ± 0.1	15.6 ± 0.6
Erythrocytes (10^6/µL)	7.74 ± 0.08	7.53 ± 0.08	7.47 ± 0.09	7.49 ± 0.06	7.88 ± 0.32
Mean cell volume (fL)	57.5 ± 0.2	57.2 ± 0.2	57.6 ± 0.2	56.3 ± 0.5*	57.1 ± 0.3
Mean cell hemoglobin (pg)	19.5 ± 0.1	19.7 ± 0.1	20.3 ± 0.1**	19.7 ± 0.1**	19.8 ± 0.2*
Mean cell hemoglobin concentration (g/dL)	34.0 ± 0.2	34.6 ± 0.3*	35.1 ± 0.1**	35.0 ± 0.4**	34.7 ± 0.3**
Reticulocytes (10^6/µL)	0.3 ± 0.0	0.3 ± 0.0	0.3 ± 0.0	0.1 ± 0.0**	0.0 ± 0.0**
Leukocytes (10^3/µL)	5.76 ± 0.24	5.74 ± 0.39	6.08 ± 0.11	6.13 ± 0.32	6.40 ± 0.63
Segmented neutrophils (10^3/µL)	0.49 ± 0.09	0.35 ± 0.03	0.46 ± 0.05	0.89 ± 0.09**	2.31 ± 0.21**
Lymphocytes (10^3/µL)	4.95 ± 0.15	5.04 ± 0.38	5.31 ± 0.14	4.81 ± 0.24	3.80 ± 0.60
Atypical lymphocytes (10^3/µL)	0.08 ± 0.03	0.07 ± 0.03	0.05 ± 0.02	0.13 ± 0.05	0.10 ± 0.03
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)	0.01 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.05 ± 0.01	0.01 ± 0.01
Nucleated erythrocytes (10^3/µL)	0.03 ± 0.01	0.05 ± 0.02	0.04 ± 0.02	0.01 ± 0.01	0.00 ± 0.00
Female					
n	10	10	10	10	6
Hematocrit (%)	41.9 ± 0.6	42.8 ± 0.5	42.3 ± 0.6	41.7 ± 0.7	39.3 ± 2.8
Hemoglobin (g/dL)	14.6 ± 0.2	15.1 ± 0.2	14.7 ± 0.2	14.5 ± 0.1	14.2 ± 1.0
Erythrocytes (10^6/µL)	7.28 ± 0.11	7.44 ± 0.10	7.29 ± 0.08	7.37 ± 0.11	7.01 ± 0.47
Mean cell volume (fL)	58.5 ± 0.4	58.2 ± 0.3	58.6 ± 0.3	57.5 ± 0.2*	56.7 ± 0.6**
Mean cell hemoglobin (pg)	20.1 ± 0.2	20.3 ± 0.1	20.2 ± 0.3	19.7 ± 0.2	20.2 ± 0.1
Mean cell hemoglobin concentration (g/dL)	34.9 ± 0.4	35.3 ± 0.2	34.8 ± 0.5	34.9 ± 0.5	36.1 ± 0.2
Reticulocytes (10^6/µL)	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.0 ± 0.0**
Leukocytes (10^3/µL)	4.56 ± 0.33	5.43 ± 0.24*	5.89 ± 0.34**	5.90 ± 0.34**	6.08 ± 0.93*
Segmented neutrophils (10^3/µL)	0.25 ± 0.04	0.24 ± 0.06	0.36 ± 0.07	0.92 ± 0.10**	2.71 ± 0.66**
Lymphocytes (10^3/µL)	3.96 ± 0.32	4.88 ± 0.22	5.12 ± 0.30*	4.33 ± 0.21	2.98 ± 0.54
Atypical lymphocytes (10^3/µL)	0.17 ± 0.03	0.08 ± 0.03	0.12 ± 0.03	0.13 ± 0.04	0.13 ± 0.09
Monocytes (10^3/µL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.04 ± 0.03**
Eosinophils (10^3/µL)	0.04 ± 0.01	0.04 ± 0.01	0.06 ± 0.02	0.08 ± 0.02	0.00 ± 0.00
Nucleated erythrocytes (10^3/µL)	0.00 ± 0.00	0.03 ± 0.02	0.02 ± 0.01	0.00 ± 0.00	0.00 ± 0.00

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error; no measurements taken for males or females receiving 25,000 ppm due to 100% mortality in these groups.

TABLE G2
Hematology and Clinical Chemistry Data for Rats in the 13-Week Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

	0 ppm	250 ppm	500 ppm	1,000 ppm	2,500 ppm	5,000 ppm
Male						
n	10	10	10	10	10	10
Hematology						
Hematocrit (%)	43.1 ± 0.6	41.4 ± 0.7	42.4 ± 0.7	41.2 ± 0.3**	41.4 ± 0.7*	39.5 ± 0.5**
Hemoglobin (g/dL)	16.3 ± 0.3	16.1 ± 0.1	16.1 ± 0.1	15.9 ± 0.1*	15.9 ± 0.1**	15.5 ± 0.2**
Erythrocytes ($10^6/\mu L$)	8.67 ± 0.12	8.57 ± 0.09	8.59 ± 0.07	8.54 ± 0.05	8.57 ± 0.08	8.67 ± 0.14
Mean cell volume (fL)	50.2 ± 0.5	48.5 ± 0.7	49.7 ± 0.7	48.6 ± 0.4*	48.7 ± 0.5*	45.9 ± 0.7**
Reticulocytes ($10^6/\mu L$)	0.1 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.1 ± 0.0	0.2 ± 0.0	0.1 ± 0.0
Leukocytes ($10^3/\mu L$)	8.92 ± 0.57	8.31 ± 0.28	7.99 ± 0.33	7.88 ± 0.28	8.00 ± 0.21	10.34 ± 0.49
Segmented neutrophils ($10^3/\mu L$)	1.28 ± 0.17	1.23 ± 0.07	1.31 ± 0.12	1.00 ± 0.10	1.26 ± 0.13	3.08 ± 0.20**
Bands ($10^3/\mu L$)	0.02 ± 0.01	0.05 ± 0.02	0.05 ± 0.01[b]	0.05 ± 0.02	0.08 ± 0.02	0.03 ± 0.02[b]
Lymphocytes ($10^3/\mu L$)	7.18 ± 0.48	6.56 ± 0.18	6.18 ± 0.26	6.54 ± 0.22	6.34 ± 0.27	6.52 ± 0.37
Atypical lymphocytes ($10^3/\mu L$)	0.13 ± 0.04	0.13 ± 0.03	0.09 ± 0.04	0.12 ± 0.04	0.15 ± 0.03	0.26 ± 0.09
Monocytes ($10^3/\mu L$)	0.23 ± 0.04	0.17 ± 0.04	0.24 ± 0.06	0.11 ± 0.04	0.11 ± 0.03	0.34 ± 0.05
Eosinophils ($10^3/\mu L$)	0.09 ± 0.03	0.07 ± 0.03	0.09 ± 0.04	0.06 ± 0.02	0.13 ± 0.03	0.07 ± 0.04
Nucleated erythrocytes ($10^3/\mu L$)	0.02 ± 0.01	0.01 ± 0.01	0.03 ± 0.01	0.03 ± 0.02	0.03 ± 0.02	0.00 ± 0.00
Clinical Chemistry						
Urea nitrogen (mg/dL)	24.6 ± 1.1	19.8 ± 0.8	23.6 ± 1.1	20.6 ± 0.7	26.0 ± 0.8	26.7 ± 0.9
Creatinine (mg/dL)	0.45 ± 0.02	0.40 ± 0.02	0.44 ± 0.02	0.42 ± 0.01	0.45 ± 0.02	0.42 ± 0.02
Alkaline phosphatase (IU/L)	210 ± 13	171 ± 8	201 ± 8	202 ± 8	270 ± 13**	375 ± 16**
Alanine aminotransferase (IU/L)	77 ± 10	57 ± 3	65 ± 4	69 ± 7	380 ± 30**	535 ± 40**
γ-glutamyltranspeptidase (IU/L)	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.5 ± 0.2**

TABLE G2
Hematology and Clinical Chemistry Data for Rats in the 13-Week Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm	2,500 ppm	5,000 ppm
Female						
n	10	10	10	10	10	10
Hematology						
Hematocrit (%)	40.6 ± 0.6	41.1 ± 0.8	40.0 ± 0.6	39.4 ± 0.8	40.7 ± 0.7	39.6 ± 0.3
Hemoglobin (g/dL)	15.7 ± 0.2	15.8 ± 0.2	15.5 ± 0.2	15.7 ± 0.1	15.4 ± 0.2	15.3 ± 0.1
Erythrocytes ($10^6/\mu L$)	7.92 ± 0.11	7.86 ± 0.14	7.76 ± 0.11	7.74 ± 0.10	7.85 ± 0.12	8.31 ± 0.04**
Mean cell volume (fL)	51.5 ± 0.3	52.6 ± 0.2	51.8 ± 0.4	51.3 ± 0.5	52.2 ± 0.3	47.9 ± 0.4**
Reticulocytes ($10^6/\mu L$)	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
Leukocytes ($10^3/\mu L$)	6.34 ± 0.29	5.66 ± 0.26	5.92 ± 0.28	5.95 ± 0.38	6.16 ± 0.26	8.88 ± 0.24**
Segmented neutrophils ($10^3/\mu L$)	0.97 ± 0.13	0.84 ± 0.11	0.76 ± 0.11	0.61 ± 0.07[b]	0.92 ± 0.08	1.89 ± 0.23*
Bands ($10^3/\mu L$)	0.05 ± 0.02	0.14 ± 0.03*	0.24 ± 0.03**	0.18 ± 0.03**	0.22 ± 0.05**	0.59 ± 0.13**
Lymphocytes ($10^3/\mu L$)	5.04 ± 0.19	4.45 ± 0.17	4.63 ± 0.26	4.69 ± 0.25	4.86 ± 0.27	6.01 ± 0.34
Atypical lymphocytes ($10^3/\mu L$)	0.07 ± 0.02[b]	0.11 ± 0.03	0.25 ± 0.03**[b]	0.17 ± 0.02**	0.08 ± 0.03	0.26 ± 0.06**
Monocytes ($10^3/\mu L$)	0.12 ± 0.04	0.03 ± 0.01*	0.03 ± 0.01	0.04 ± 0.01	0.03 ± 0.01	0.05 ± 0.02[b]
Eosinophils ($10^3/\mu L$)	0.04 ± 0.02	0.10 ± 0.03	0.05 ± 0.02	0.06 ± 0.02	0.05 ± 0.02	0.06 ± 0.02
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.02 ± 0.01*	0.06 ± 0.01**	0.03 ± 0.01**	0.04 ± 0.02**	0.07 ± 0.02**
Clinical Chemistry						
Urea nitrogen (mg/dL)	23.9 ± 1.0	17.7 ± 0.7	18.2 ± 0.4	18.2 ± 0.7	20.3 ± 0.5	25.3 ± 0.9
Creatinine (mg/dL)	0.40 ± 0.02	0.39 ± 0.01	0.37 ± 0.02	0.37 ± 0.02	0.39 ± 0.02	0.44 ± 0.02
Alkaline phosphatase (IU/L)	184 ± 9	121 ± 6	132 ± 9	139 ± 5	171 ± 8	262 ± 11
Alanine aminotransferase (IU/L)	49 ± 5	37 ± 2	42 ± 3	43 ± 2	146 ± 16**	395 ± 28**
γ-glutamyltranspeptidase (IU/L)	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	3.4 ± 1.3**

* 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
[b] n=9

TABLE G3
Hematology, Clinical Chemistry, and Urinalysis Data for Rats at the 3-Month Interim Evaluation in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
Male				
n	15	15	15	15
Hematology				
Hematocrit (%)	50.1 ± 0.5	50.3 ± 0.3	50.4 ± 0.4	50.1 ± 0.4
Hemoglobin (g/dL)	16.0 ± 0.1	16.1 ± 0.1	15.9 ± 0.1	15.8 ± 0.1
Erythrocytes ($10^6/\mu L$)	9.64 ± 0.07	9.70 ± 0.10	9.63 ± 0.06	9.66 ± 0.09
Mean cell volume (fL)	52.0 ± 0.3	51.9 ± 0.3	52.2 ± 0.3	51.9 ± 0.2
Mean cell hemoglobin (pg)	16.6 ± 0.1	16.6 ± 0.1	16.5 ± 0.1	16.4 ± 0.1
Mean cell hemoglobin concentration (g/dL)	31.9 ± 0.1	32.1 ± 0.2	31.6 ± 0.2	31.6 ± 0.2
Platelets ($10^3/\mu L$)	491.7 ± 15.5	486.2 ± 13.8	484.3 ± 18.2	540.1 ± 9.6*
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
Leukocytes ($10^3/\mu L$)	5.88 ± 0.45	6.69 ± 0.31	5.19 ± 0.35	7.12 ± 0.50
Segmented neutrophils ($10^3/\mu L$)	0.88 ± 0.09	0.76 ± 0.08	0.66 ± 0.04	1.03 ± 0.07
Lymphocytes ($10^3/\mu L$)	4.95 ± 0.39	5.83 ± 0.29	4.46 ± 0.33	5.95 ± 0.47
Monocytes ($10^3/\mu L$)	0.02 ± 0.01	0.03 ± 0.01	0.02 ± 0.01	0.02 ± 0.01
Eosinophils ($10^3/\mu L$)	0.04 ± 0.01	0.07 ± 0.02	0.05 ± 0.01	0.07 ± 0.02
Nucleated erythrocytes ($10^3/\mu L$)	0.01 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01
Clinical Chemistry				
Urea nitrogen (mg/dL)	22.3 ± 0.5	21.8 ± 0.4	22.4 ± 0.3	20.4 ± 0.6*
Creatinine (IU/L)	0.65 ± 0.02	0.63 ± 0.03	0.64 ± 0.01	0.63 ± 0.01
Sodium (mEq/L)	143 ± 1	145 ± 1*[b]	144 ± 1	144 ± 1
Potassium (mEq/L)	4.7 ± 0.1	5.0 ± 0.1*[b]	5.0 ± 0.1*	5.0 ± 0.1*
Chloride (mEq/L)	101 ± 1	102 ± 0*[b]	103 ± 0**	102 ± 1*
Calcium (mg/dL)	5.44 ± 0.05	5.42 ± 0.05[c]	5.12 ± 0.15	5.29 ± 0.11
Total bilirubin (mg/dL)	0.1 ± 0.0	0.1 ± 0.0	0.0 ± 0.0	0.1 ± 0.0
Alkaline phosphatase (IU/L)	570 ± 12	574 ± 10	612 ± 9*	657 ± 20**
Alanine aminotransferase (IU/L)	75 ± 8	78 ± 6	80 ± 4[b]	606 ± 45**
Soribitol dehydrogenase (IU/L)	34 ± 3	44 ± 5	38 ± 2[b]	158 ± 8**
Urinalysis				
Creatinine (mg/dL)	69.00 ± 8.27	98.20 ± 9.15**	97.27 ± 7.47**	126.73 ± 9.23**
Volume (mL/16 hr)	9.7 ± 0.9	6.7 ± 0.7**	6.0 ± 0.6**	4.8 ± 0.3**
Alkaline phosphatase (IU/g creatinine)	382 ± 19	434 ± 27	401 ± 28	389 ± 33
Lactate dehydrogenase (IU/g creatinine)	38 ± 2	34 ± 2	39 ± 4	33 ± 2
N-acetyl-*β*-*D*-glucosaminidase (IU/g creatinine)	8.1 ± 0.6	7.7 ± 0.2	8.0 ± 0.4	7.9 ± 0.5
β-Galactosidase (IU/g creatinine)	4.79 ± 0.39	4.45 ± 0.10	4.86 ± 0.22	4.80 ± 0.22

TABLE G3
Hematology, Clinical Chemistry, and Urinalysis Data for Rats at the 3-Month Interim Evaluation in the 2-Year Feed Study of 4,4'-Thiobis(6-t-Butyl-m-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
Female				
n	15	15	15	14
Hematology				
Hematocrit (%)	49.5 ± 0.5	48.8 ± 0.4	49.0 ± 0.5	48.5 ± 0.5
Hemoglobin (g/dL)	16.0 ± 0.2	15.6 ± 0.2	15.7 ± 0.2	15.5 ± 0.2
Erythrocytes ($10^6/\mu L$)	8.96 ± 0.10	8.85 ± 0.08	8.89 ± 0.09	8.90 ± 0.10
Mean cell volume (fL)	55.3 ± 0.3	55.1 ± 0.3	55.1 ± 0.2	54.5 ± 0.2*
Mean cell hemoglobin (pg)	17.8 ± 0.1	17.6 ± 0.1	17.7 ± 0.1	17.4 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	32.2 ± 0.2	32.0 ± 0.2	32.1 ± 0.2	32.0 ± 0.2
Platelets ($10^3/\mu L$)	522.7 ± 12.0[b]	527.1 ± 22.1	541.9 ± 17.9	598.6 ± 20.7**
Reticulocytes ($10^6/\mu L$)	0.13 ± 0.01	0.12 ± 0.01	0.09 ± 0.01**	0.10 ± 0.01*
Leukocytes ($10^3/\mu L$)	4.57 ± 0.39	4.17 ± 0.36	4.58 ± 0.50	5.87 ± 0.62
Segmented neutrophils ($10^3/\mu L$)	0.53 ± 0.04[b]	0.66 ± 0.09	0.67 ± 0.11	0.94 ± 0.12**
Lymphocytes ($10^3/\mu L$)	3.78 ± 0.26	3.45 ± 0.29	3.86 ± 0.43	4.89 ± 0.53
Monocytes ($10^3/\mu L$)	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.00	0.01 ± 0.01
Eosinophils ($10^3/\mu L$)	0.04 ± 0.01	0.06 ± 0.01	0.04 ± 0.01	0.04 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01
n	15	15	15	15
Clinical Chemistry				
Urea nitrogen (mg/dL)	18.3 ± 0.5	17.4 ± 0.4	18.2 ± 0.4	18.7 ± 0.5
Creatinine (mg/dL)	0.61 ± 0.01	0.58 ± 0.01	0.58 ± 0.01[b]	0.61 ± 0.01[b]
Sodium (mEq/L)	143 ± 1	142 ± 1	142 ± 1	144 ± 1
Potassium (mEq/L)	4.4 ± 0.2	4.4 ± 0.1	4.6 ± 0.1	4.9 ± 0.2*
Chloride (mEq/L)	105 ± 0	105 ± 1	105 ± 1	106 ± 1
Calcium (mg/dL)	5.38 ± 0.05	5.31 ± 0.10	5.23 ± 0.13	5.19 ± 0.05*
Total bilirubin (mg/dL)	0.0 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
Alkaline phosphatase (IU/L)	445 ± 14[b]	432 ± 12[b]	412 ± 21	474 ± 17
Alanine aminotransferase (IU/L)	49 ± 3	46 ± 2	52 ± 2	275 ± 16**
Sorbitol dehydrogenase (IU/L)	27 ± 2	24 ± 3[b]	24 ± 2	123 ± 7**
n	15	15	14	15
Urinalysis				
Creatinine (mg/dL)	47.60 ± 5.32	58.60 ± 6.75	69.43 ± 9.98	86.00 ± 13.43*
Volume (mL/16 hr)	7.0 ± 0.9	5.1 ± 0.6*	4.7 ± 0.8**	5.0 ± 0.8**
Alkaline phosphatase (IU/g creatinine)	308 ± 18	414 ± 51	385 ± 27	300 ± 25
Lactate dehydrogenase (IU/g creatinine)	30 ± 2	29 ± 3	30 ± 2	30 ± 2
N-acetyl-β-*D*-glucosaminidase (IU/g creatinine)	8.6 ± 0.3	8.8 ± 0.8	9.2 ± 0.5	11.2 ± 0.8*
β-Galactosidase (IU/g creatinine)	5.99 ± 0.36	5.60 ± 0.38	5.73 ± 0.32	5.11 ± 0.32

* Significantly different (P≤0.05) from the control troup by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error
[b] n=14
[c] n=13

TABLE G4
Hematology, Clinical Chemistry, and Urinalysis Data for Rats at the 9-Month Interim Evaluation in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
Male				
n	15	15	14	15
Hematology				
Hematocrit (%)	50.6 ± 0.7	51.0 ± 0.6	49.8 ± 1.0	49.7 ± 0.8
Hemoglobin (g/dL)	15.3 ± 0.1	15.1 ± 0.2	15.0 ± 0.3	14.9 ± 0.2
Erythrocytes ($10^6/\mu L$)	9.47 ± 0.07	9.33 ± 0.10	9.31 ± 0.11	9.37 ± 0.11
Mean cell volume (fL)	53.5 ± 0.5	54.7 ± 0.3	53.5 ± 0.9	53.1 ± 0.7
Mean cell hemoglobin (pg)	16.2 ± 0.1	16.2 ± 0.1	16.1 ± 0.2	15.9 ± 0.2
Mean cell hemoglobin concentration (g/dL)	30.3 ± 0.3	29.7 ± 0.2	30.2 ± 0.3	30.0 ± 0.3
Platelets ($10^3/\mu L$)	581.3 ± 11.0	593.1 ± 20.2	570.1 ± 16.8	667.3 ± 14.9**
Reticulocytes ($10^6/\mu L$)	0.1 ± 0.0	0.2 ± 0.0	0.1 ± 0.0	0.2 ± 0.0
Leukocytes ($10^3/\mu L$)	8.51 ± 0.32	8.91 ± 0.47	8.37 ± 0.40	8.28 ± 0.26
Segmented neutrophils ($10^3/\mu L$)	1.99 ± 0.19	2.11 ± 0.21	2.00 ± 0.17	1.96 ± 0.20
Lymphocytes ($10^3/\mu L$)	6.31 ± 0.21	6.53 ± 0.31	6.19 ± 0.37	6.09 ± 0.21
Monocytes ($10^3/\mu L$)	0.07 ± 0.02	0.10 ± 0.03	0.08 ± 0.03	0.10 ± 0.03
Eosinophils ($10^3/\mu L$)	0.14 ± 0.04	0.17 ± 0.03	0.11 ± 0.03	0.13 ± 0.02
Nucleated erythrocytes ($10^3/\mu L$)	0.02 ± 0.01	0.01 ± 0.01	0.03 ± 0.02	0.01 ± 0.01
n	15	14	14	15
Clinical Chemistry				
Urea nitrogen (mg/dL)	20.0 ± 0.5	20.1 ± 0.4[b]	20.1 ± 0.5	20.0 ± 0.4
Creatinine (mg/dL)	0.67 ± 0.02	0.66 ± 0.03[b]	0.69 ± 0.01	0.67 ± 0.01
Sodium (mEq/L)	145 ± 1[c]	145 ± 1	146 ± 1	146 ± 0
Potassium (mEq/L)	5.3 ± 0.1[c]	5.0 ± 0.2	5.4 ± 0.2	5.3 ± 0.1
Chloride (mEq/L)	98 ± 1[c]	97 ± 0	99 ± 1	99 ± 1
Calcium (mg/dL)	5.21 ± 0.08	5.38 ± 0.06[d]	5.19 ± 0.09	5.24 ± 0.07
Total bilirubin (mg/dL)	0.0 ± 0.0[c]	0.0 ± 0.0	0.0 ± 0.0[e]	0.0 ± 0.0
Alkaline phosphatase (IU/L)	393 ± 10	390 ± 9[b]	388 ± 11*	467 ± 13**
Alanine aminotransferase (IU/L)	86 ± 3	87 ± 9[b]	111 ± 14	175 ± 8**
Sorbitol dehydrogenase (IU/L)	26 ± 1	24 ± 1	30 ± 2[d]	51 ± 2**
n	15	15	14	15
Urinalysis				
Creatinine (mg/dL)	107.3 ± 8.3	119.6 ± 10.8	140.1 ± 10.4*	128.0 ± 9.6*
Volume (mL/16 hr)	7.2 ± 0.6	7.1 ± 0.8	5.6 ± 0.6	6.0 ± 0.5[c]
Alkaline phosphatase (IU/g creatinine)	327.3 ± 17.9	309.4 ± 28.7	363.5 ± 19.5[d]	361.5 ± 11.2
Lactate dehydrogenase (IU/g creatinine)	36.9 ± 1.6	35.5 ± 3.4	34.5 ± 1.6	30.9 ± 1.1*
N-acetyl-*β*-*D*-glucosaminidase (IU/g creatinine)	6.71 ± 0.15	6.93 ± 0.42	6.44 ± 0.18	6.29 ± 0.25
β-Galactosidase (IU/g creatinine)	4.33 ± 0.14	4.06 ± 0.19	4.01 ± 0.12	4.29 ± 0.13

TABLE G4
Hematology, Clinical Chemistry, and Urinalysis Data for Rats at the 9-Month Interim Evaluation in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
Female				
n	15	15	14	14
Hematology				
Hematocrit (%)	48.8 ± 0.4	48.1 ± 0.5	48.0 ± 0.3	47.1 ± 0.3**
Hemoglobin (g/dL)	15.3 ± 0.1	15.1 ± 0.1	14.9 ± 0.1	14.5 ± 0.1**
Erythrocytes ($10^6/\mu L$)	8.29 ± 0.07	8.23 ± 0.08	8.17 ± 0.06	8.18 ± 0.05
Mean cell volume (fL)	58.9 ± 0.2	58.5 ± 0.2	58.7 ± 0.3	57.6 ± 0.3**
Mean cell hemoglobin (pg)	18.4 ± 0.1	18.3 ± 0.1	18.3 ± 0.1	17.7 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	31.3 ± 0.1	31.3 ± 0.1	31.1 ± 0.1	30.7 ± 0.1**
Platelets ($10^3/\mu L$)	538.7 ± 8.6	543.4 ± 9.6	583.9 ± 7.4**	648.6 ± 12.7**
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0	0.2 ± 0.0	0.1 ± 0.0	0.2 ± 0.0
Leukocytes ($10^3/\mu L$)	6.05 ± 0.25	5.54 ± 0.22	5.49 ± 0.22	6.21 ± 0.31
Segmented neutrophils ($10^3/\mu L$)	1.09 ± 0.06	1.09 ± 0.12	0.96 ± 0.09	1.16 ± 0.11
Lymphocytes ($10^3/\mu L$)	4.91 ± 0.22	4.38 ± 0.18	4.45 ± 0.20	4.96 ± 0.25
Monocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils ($10^3/\mu L$)	0.05 ± 0.02	0.08 ± 0.03	0.08 ± 0.02	0.09 ± 0.02
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00
n	15	14	15	14
Clinical Chemistry				
Urea nitrogen (mg/dL)	21.1 ± 0.5	21.9 ± 0.3	22.4 ± 0.5	20.6 ± 0.5
Creatinine (mg/dL)	0.76 ± 0.01	0.76 ± 0.01	0.76 ± 0.02	0.78 ± 0.02
Sodium (mEq/L)	145 ± 1	144 ± 1	145 ± 1	145 ± 1[d]
Potassium (mEq/L)	4.7 ± 0.1	4.7 ± 0.1	4.7 ± 0.1	4.7 ± 0.1[d]
Chloride (mEq/L)	100 ± 1	99 ± 1	101 ± 1	100 ± 1[d]
Calcium (mg/dL)	5.68 ± 0.04	5.70 ± 0.07	5.68 ± 0.07	5.58 ± 0.07
Total bilirubin (mg/dL)	0.07 ± 0.01	0.05 ± 0.01[b]	0.06 ± 0.01	0.08 ± 0.01
Alkaline phosphatase (IU/L)	334 ± 9	336 ± 9[b]	335 ± 7	318 ± 11
Alanine aminotransferase (IU/L)	53 ± 2	48 ± 2[b]	54 ± 3	110 ± 8**
Sorbitol dehydrogenase (IU/L)	25 ± 1	24 ± 2[b]	24 ± 2	44 ± 3**
n	15	15	15	14
Urinalysis				
Creatinine (mg/dL)	71.40 ± 6.10	69.00 ± 7.84	75.40 ± 5.15	68.29 ± 10.02
Volume (mL/16 hr)	4.6 ± 0.5	4.7 ± 0.6	4.5 ± 0.5	7.1 ± 1.2
Alkaline phosphatase (IU/g creatinine)	232.9 ± 27.2	265.4 ± 18.5	286.8 ± 19.2	295.2 ± 34.7
Lactate dehydrogenase (IU/g creatinine)	26.34 ± 0.52	27.33 ± 1.54[c]	28.16 ± 1.09	32.33 ± 1.19**
N-acetyl-β-*D*-glucosaminidase (IU/g creatinine)	8.02 ± 0.34	9.44 ± 0.53[c]	9.80 ± 0.44**	13.04 ± 0.55**
β-Galactosidase (IU/g creatinine)	4.07 ± 0.22	4.91 ± 0.25[c]	4.69 ± 0.15	3.65 ± 0.33

* Significantly different ($P \le 0.05$) from the control group by Dunn's or Shirley's test
** $P \le 0.01$
[a] Mean ± standard error
[b] n=15
[c] n=14
[d] n=13
[e] n=12

TABLE G5
Hematology, Clinical Chemistry, and Urinalysis Data for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
Male				
n	15	15	11	14
Hematology				
Hematocrit (%)	46.4 ± 0.3	46.4 ± 0.3	45.0 ± 0.5*	45.8 ± 0.4*
Hemoglobin (g/dL)	15.7 ± 0.1	15.7 ± 0.1	15.1 ± 0.1**	15.3 ± 0.1**
Erythrocytes ($10^6/\mu L$)	8.92 ± 0.07	8.91 ± 0.07	8.49 ± 0.12**	8.84 ± 0.08*
Mean cell volume (fL)	52.2 ± 0.4	52.0 ± 0.4	53.2 ± 0.6	51.9 ± 0.2
Mean cell hemoglobin (pg)	17.6 ± 0.1	17.6 ± 0.1	17.9 ± 0.2	17.3 ± 0.1
Mean cell hemoglobin concentration (g/dL)	33.81 ± 0.11	33.79 ± 0.14	33.65 ± 0.12	33.39 ± 0.09*
Platelets ($10^3/\mu L$)	541.3 ± 19.2	574.7 ± 17.3	572.4 ± 27.0	600.4 ± 9.7**
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0	0.3 ± 0.0	0.3 ± 0.0*	0.3 ± 0.0
Leukocytes ($10^3/\mu L$)	9.95 ± 0.46	9.51 ± 0.33	9.30 ± 0.36	8.85 ± 0.31
Segmented neutrophils ($10^3/\mu L$)	3.03 ± 0.24	2.36 ± 0.21*	2.42 ± 0.20	2.34 ± 0.11*
Lymphocytes ($10^3/\mu L$)	6.70 ± 0.34	6.91 ± 0.25	6.74 ± 0.31	6.34 ± 0.27
Eosinophils ($10^3/\mu L$)	0.16 ± 0.03	0.18 ± 0.03	0.13 ± 0.03	0.11 ± 0.03
Nucleated erythrocytes ($10^3/\mu L$)	0.02 ± 0.01	0.02 ± 0.01	0.05 ± 0.03	0.04 ± 0.01
n	15	15	12	14
Clinical Chemistry				
Urea nitrogen (mg/dL)	20.3 ± 0.5	20.2 ± 0.4	24.2 ± 2.6[d]	21.6 ± 0.5
Creatinine (mg/dL)	0.65 ± 0.02	0.68 ± 0.03	0.71 ± 0.05[d]	0.71 ± 0.03
Sodium (mEq/L)	146 ± 1	145 ± 1	148 ± 1[d]	147 ± 1
Potassium (mEq/L)	5.3 ± 0.1	5.5 ± 0.1	5.5 ± 0.1*[d]	5.5 ± 0.0*
Chloride (mEq/L)	97 ± 1	98 ± 0	99 ± 1[d]	99 ± 1
Calcium (mg/dL)	5.43 ± 0.04	5.44 ± 0.03	5.46 ± 0.04[d]	5.36 ± 0.03
Total bilirubin (mg/dL)	0.1 ± 0.0	0.2 ± 0.0	0.1 ± 0.0	0.2 ± 0.0
Direct bilirubin (mg/dL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Alkaline phosphatase (IU/L)	316 ± 7	335 ± 8	351 ± 10**	399 ± 7**
Alanine aminotransferase (IU/L)	64 ± 3	59 ± 2[b]	57 ± 3	144 ± 11**
Sorbitol dehydrogenase (IU/L)	27 ± 1	25 ± 1	30 ± 3	50 ± 3**
Bile salts (µm/L)	22 ± 3	21 ± 3	22 ± 2	17 ± 2
n	15	15	12	14
Urinalysis				
Creatinine (mg/dL)	120.1 ± 8.2	112.8 ± 5.4	106.8 ± 7.7	118.9 ± 9.1
Volume (mL/16 hr)	5.7 ± 0.5	6.8 ± 0.6	7.0 ± 0.7	7.4 ± 0.7
Alkaline phosphatase (IU/g creatinine)	448.6 ± 46.4	520.8 ± 40.9	415.0 ± 37.6	430.9 ± 41.4
Lactate dehydrogenase (IU/g creatinine)	39.2 ± 3.3	33.4 ± 2.3	47.1 ± 5.9	38.6 ± 2.7
N-acetyl-β-*D*-glucosaminidase (IU/g creatinine)	8.1 ± 0.4	7.5 ± 0.3	9.2 ± 0.6	7.8 ± 0.3
β-Galactosidase (IU/g creatinine)	4.85 ± 0.28	4.76 ± 0.17	5.23 ± 0.19	4.67 ± 0.13

TABLE G5
Hematology, Clinical Chemistry, and Urinalysis Data for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of 4,4'-Thiobis(6-t-Butyl-m-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
Female				
n	15	15	15	14
Hematology				
Hematocrit (%)	44.4 ± 0.4	44.8 ± 0.4	43.7 ± 0.4	43.7 ± 0.3
Hemoglobin (g/dL)	15.5 ± 0.1	15.5 ± 0.1	15.2 ± 0.2	15.0 ± 0.1*
Erythrocytes ($10^6/\mu L$)	8.19 ± 0.07	8.22 ± 0.07	8.02 ± 0.09	8.15 ± 0.07
Mean cell volume (fL)	54.1 ± 0.2	54.3 ± 0.2	54.4 ± 0.3	53.6 ± 0.2
Mean cell hemoglobin (pg)	18.9 ± 0.1	18.9 ± 0.1	19.0 ± 0.1	18.3 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	34.9 ± 0.1	34.7 ± 0.2	34.8 ± 0.1	34.3 ± 0.2*
Platelets ($10^3/\mu L$)	492.8 ± 10.6	462.3 ± 23.7	506.1 ± 38.8	524.3 ± 26.4
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0	0.1 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Leukocytes ($10^3/\mu L$)	4.93 ± 0.20	5.44 ± 0.26	5.85 ± 0.61	6.09 ± 0.26**
Segmented neutrophils ($10^3/\mu L$)	1.06 ± 0.08	1.30 ± 0.10	1.49 ± 0.17*	1.95 ± 0.10**
Lymphocytes ($10^3/\mu L$)	3.74 ± 0.18	4.03 ± 0.19	4.20 ± 0.49	3.94 ± 0.20
Eosinophils ($10^3/\mu L$)	0.07 ± 0.02	0.07 ± 0.02	0.11 ± 0.04	0.11 ± 0.02
Nucleated erythrocytes ($10^3/\mu L$)	0.05 ± 0.02	0.06 ± 0.02	0.04 ± 0.02	0.06 ± 0.03
Clinical Chemistry				
Urea nitrogen (mg/dL)	21.47 ± 0.40	19.87 ± 0.35*	21.33 ± 0.41	22.07 ± 0.43
Creatinine (mg/dL)	0.69 ± 0.03	0.65 ± 0.04	0.71 ± 0.01	0.74 ± 0.04
Sodium (mEq/L)	146.7 ± 0.6	145.5 ± 0.6[c]	146.2 ± 0.5	145.4 ± 0.5
Potassium (mEq/L)	5.0 ± 0.1	5.1 ± 0.1[c]	5.1 ± 0.1	5.2 ± 0.1
Chloride (mEq/L)	100.53 ± 0.42	99.54 ± 0.54[c]	101.07 ± 0.63	98.86 ± 0.42
Calcium (mg/dL)	5.51 ± 0.05	5.53 ± 0.05	5.47 ± 0.06	5.64 ± 0.04
Total bilirubin (mg/dL)	0.0 ± 0.0	0.0 ± 0.0[b]	0.0 ± 0.0[b]	0.0 ± 0.0
Direct bilirubin (mg/dL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00[b]	0.00 ± 0.00
Alkaline phosphatase (IU/L)	340 ± 8	345 ± 12	354 ± 16	303 ± 11*
Alanine aminotransferase (IU/L)	56 ± 2	59 ± 2	70 ± 4**	118 ± 9**
Sorbitol dehydrogenase (IU/L)	24 ± 3	33 ± 2*[c]	30 ± 3[c]	59 ± 5**
Bile salts (μm/L)	39 ± 4	31 ± 4	32 ± 3[b]	25 ± 3**
n	15	15	15	14
Urinalysis				
Creatinine (mg/dL)	55.7 ± 3.0	62.4 ± 3.7	69.5 ± 5.3*	63.5 ± 5.1
Volume (mL/16 hr)	5.7 ± 0.6	4.8 ± 0.5	5.1 ± 0.6	6.9 ± 0.4
Alkaline phosphatase (IU/g creatinine)	234.0 ± 11.8	249.3 ± 11.9	224.3 ± 9.8	293.6 ± 13.6**
Lactate dehydrogenase (IU/g creatinine)	42.4 ± 2.6	38.2 ± 1.1	36.2 ± 1.2	45.6 ± 2.2
N-acetyl-*β*-*D*-glucosaminidase (IU/g creatinine)	12.5 ± 0.5	10.7 ± 0.4	12.2 ± 0.5	16.5 ± 0.9**
β-Galactosidase (IU/g creatinine)	5.61 ± 0.25	5.03 ± 0.23	4.83 ± 0.19*	4.66 ± 0.18**

* 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
[b] n=14
[c] n=13
[d] n=11

TABLE G6
Hematology and Clinical Chemistry Data for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
Male				
n	10	10	7	10
Hematology				
Hematocrit (%)	43.6 ± 1.5	44.1 ± 1.2	45.1 ± 0.8	45.4 ± 0.6
Hemoglobin (g/dL)	14.1 ± 0.5	14.2 ± 0.3	14.5 ± 0.3	14.6 ± 0.2
Erythrocytes ($10^6/\mu L$)	8.17 ± 0.30	8.34 ± 0.23	8.44 ± 0.10	8.67 ± 0.11
Mean cell volume (fL)	53.3 ± 0.5	52.8 ± 0.3	53.3 ± 0.4	52.3 ± 0.2
Mean cell hemoglobin (pg)	17.3 ± 0.2	17.1 ± 0.1	17.2 ± 0.1	16.8 ± 0.1*
Mean cell hemoglobin concentration (g/dL)	32.4 ± 0.1	32.4 ± 0.2	32.1 ± 0.1	32.2 ± 0.1
Platelets ($10^3/\mu L$)	612.0 ± 40.2	557.0 ± 27.4	561.1 ± 21.4	565.1 ± 19.6
Reticulocytes ($10^6/\mu L$)	0.3 ± 0.3[b]	0.3 ± 0.0	0.2 ± 0.0	0.3 ± 0.2
Leukocytes ($10^3/\mu L$)	7.30 ± 0.49	6.54 ± 0.37	7.46 ± 0.40	7.36 ± 0.26
Segmented neutrophils ($10^3/\mu L$)	2.74 ± 0.33	2.00 ± 0.16	2.47 ± 0.36	2.42 ± 0.12
Lymphocytes ($10^3/\mu L$)	4.45 ± 0.28	4.45 ± 0.34	4.81 ± 0.22	4.75 ± 0.27
Monocytes ($10^3/\mu L$)	0.02 ± 0.01	0.01 ± 0.01	0.03 ± 0.01	0.02 ± 0.01
Eosinophils ($10^3/\mu L$)	0.09 ± 0.04	0.08 ± 0.01	0.15 ± 0.06	0.17 ± 0.05
Nucleated erythrocytes ($10^3/\mu L$)	0.08 ± 0.03	0.03 ± 0.02	0.04 ± 0.02	0.03 ± 0.02
n	9	9	6	10
Clinical Chemistry				
Urea nitrogen (mg/dL)	19.4 ± 0.7[c]	18.7 ± 0.4	18.8 ± 0.7	19.7 ± 0.6
Creatinine (mg/dL)	0.49 ± 0.06	0.48 ± 0.04	0.55 ± 0.07	0.52 ± 0.05
Sodium (mEq/L)	149 ± 1	150 ± 1	150 ± 1	151 ± 1[b]
Potassium (mEq/L)	5.3 ± 0.1	5.3 ± 0.1	5.5 ± 0.0	5.3 ± 0.1[b]
Chloride (mEq/L)	101 ± 1	100 ± 0*	102 ± 1	100 ± 1*[b]
Calcium (mg/dL)	5.16 ± 0.05	5.21 ± 0.07	5.02 ± 0.05	5.07 ± 0.05
Total bilirubin (mg/dL)	0.1 ± 0.1	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
Alkaline phosphatase (IU/L)	239 ± 13	329 ± 46*	336 ± 19**[d]	368 ± 17**
Alanine aminotransferase (IU/L)	66 ± 9	79 ± 7	81 ± 8[d]	172 ± 27**
Sorbitol dehydrogenase (IU/L)	32 ± 4[e]	42 ± 6[e]	40 ± 10	75 ± 10**
Bile salts (μm/L)	11 ± 2	24 ± 6[e]	12 ± 2[d]	11 ± 1

TABLE G6
Hematology and Clinical Chemistry Data for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
Female				
n	10	10	10	10
Hematology				
Hematocrit (%)	44.0 ± 0.4	43.8 ± 0.4	44.0 ± 0.4	42.6 ± 0.6
Hemoglobin (g/dL)	15.5 ± 0.1	15.4 ± 0.1	15.4 ± 0.1	14.7 ± 0.2**
Erythrocytes ($10^6/\mu L$)	8.08 ± 0.07	8.19 ± 0.05	8.24 ± 0.07	7.90 ± 0.13
Mean cell volume (fL)	54.4 ± 0.4	53.4 ± 0.4	53.5 ± 0.3	54.0 ± 0.4
Mean cell hemoglobin (pg)	19.2 ± 0.1	18.8 ± 0.1*	18.6 ± 0.0**	18.7 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	35.2 ± 0.2	35.2 ± 0.2	34.9 ± 0.2	34.6 ± 0.2*
Platelets ($10^3/\mu L$)	421.1 ± 34.6	492.8 ± 18.8	486.2 ± 21.5	546.6 ± 15.7**
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Leukocytes ($10^3/\mu L$)	5.40 ± 0.58	3.83 ± 0.18*	3.94 ± 0.23	4.57 ± 0.34
Segmented neutrophils ($10^3/\mu L$)	1.80 ± 0.29	1.15 ± 0.06	1.33 ± 0.10	1.42 ± 0.14
Lymphocytes ($10^3/\mu L$)	3.51 ± 0.32	2.60 ± 0.13	2.53 ± 0.19*	2.96 ± 0.25
Monocytes ($10^3/\mu L$)	0.01 ± 0.01	0.03 ± 0.01	0.03 ± 0.02	0.05 ± 0.02
Eosinophils ($10^3/\mu L$)	0.08 ± 0.02	0.05 ± 0.02	0.04 ± 0.02	0.14 ± 0.04
Nucleated erythrocytes ($10^3/\mu L$)	0.11 ± 0.03	0.05 ± 0.01	0.04 ± 0.01	0.07 ± 0.02
Clinical Chemistry				
Urea nitrogen (mg/dL)	20.0 ± 0.6	19.6 ± 0.7	19.8 ± 0.7	20.2 ± 0.4
Creatinine (mg/dL)	0.68 ± 0.01	0.73 ± 0.03	0.71 ± 0.03	0.74 ± 0.03
Sodium (mEq/L)	147 ± 1	148 ± 1	147 ± 0	147 ± 1
Potassium (mEq/L)	4.3 ± 0.1	4.2 ± 0.1	4.4 ± 0.1	4.4 ± 0.1
Chloride (mEq/L)	106 ± 0	106 ± 1	106 ± 0	104 ± 1*
Calcium (mg/dL)	5.02 ± 0.06	5.11 ± 0.04	5.16 ± 0.04	5.26 ± 0.05**
Total bilirubin (mg/dL)	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.04 ± 0.01
Alkaline phosphatase (IU/L)	316 ± 10	283 ± 7*	312 ± 10	253 ± 7**
Alanine aminotransferase (IU/L)	58 ± 4	55 ± 4	60 ± 6	104 ± 7**
Sorbitol dehydrogenase (IU/L)	16 ± 1	15 ± 1	20 ± 2	37 ± 4**
Bile salts ($\mu m/L$)	25 ± 4	24 ± 2	24 ± 3	24 ± 2

* 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
[b] n=9
[c] n=8
[d] n=7
[e] n=10

TABLE G7
Hematology Data for Mice in the 15-Day Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

	0 ppm	1,000 ppm	2,500 ppm	5,000 ppm
Male				
n	9	10	10	
Hematocrit (%)	40.7 ± 1.1	38.9 ± 0.5	40.1 ± 0.3	
Hemoglobin (g/dL)	13.6 ± 0.4	13.4 ± 0.2	13.9 ± 0.1*	
Erythrocytes (10^6/µL)	8.27 ± 0.20	7.98 ± 0.12	8.26 ± 0.07	
Mean cell volume (fL)	50.1 ± 0.2	49.8 ± 0.3	49.7 ± 0.2	
Mean cell hemoglobin (pg)	16.5 ± 0.1	16.8 ± 0.1	16.8 ± 0.1**	
Mean cell hemoglobin concentration (g/dL)	33.5 ± 0.2	34.3 ± 0.2*	34.6 ± 0.1**	
Reticulocytes (10^6/µL)	0.2 ± 0.0[b]	0.2 ± 0.0	0.2 ± 0.0	
Leukocytes (10^3/µL)	2.90 ± 0.49	3.13 ± 0.24	3.12 ± 0.23	
Segmented neutrophils (10^3/µL)	0.63 ± 0.16	0.70 ± 0.15	0.69 ± 0.11	
Lymphocytes (10^3/µL)	2.14 ± 0.32	2.14 ± 0.16	2.00 ± 0.18	
Atypical lymphocytes (10^3/µL)	0.00 ± 0.00	0.05 ± 0.02**	0.03 ± 0.01*	
Monocytes (10^3/µL)	0.00 ± 0.00	0.02 ± 0.01*	0.04 ± 0.02**	
Eosinophils (10^3/µL)	0.01 ± 0.01	0.01 ± 0.01	0.03 ± 0.01	
Nucleated erythrocytes (10^3/µL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	
Female				
n	10	10	10	2
Hematocrit (%)	40.0 ± 0.2	37.4 ± 0.4**	39.5 ± 1.2	35.8 ± 2.5
Hemoglobin (g/dL)	13.6 ± 0.1	13.2 ± 0.1	14.1 ± 0.4	13.1 ± 0.8
Erythrocytes (10^6/µL)	8.03 ± 0.06	7.63 ± 0.08	8.27 ± 0.26	7.83 ± 0.71
Mean cell volume (fL)	50.7 ± 0.3	50.1 ± 0.4	49.0 ± 0.2**	47.0 ± 1.0**
Mean cell hemoglobin (pg)	16.9 ± 0.1	17.2 ± 0.1	17.0 ± 0.1	16.8 ± 0.6
Mean cell hemoglobin concentration (g/dL)	34.0 ± 0.1	35.2 ± 0.4**	35.7 ± 0.2**	36.5 ± 0.5**
Reticulocytes (10^6/µL)	0.1 ± 0.0	0.2 ± 0.0	0.2 ± 0.0*	0.1 ± 0.0
Leukocytes (10^3/µL)	1.62 ± 0.21	1.90 ± 0.17	3.48 ± 0.29**	2.00 ± 0.30*
Segmented neutrophils (10^3/µL)	0.21 ± 0.05	0.26 ± 0.03	0.60 ± 0.06**	1.07 ± 0.15**
Lymphocytes (10^3/µL)	1.32 ± 0.22	1.49 ± 0.15	2.62 ± 0.26**	0.35 ± 0.01
Atypical lymphocytes (10^3/µL)	0.00 ± 0.00	0.01 ± 0.00	0.03 ± 0.01	0.06 ± 0.06
Monocytes (10^3/µL)	0.01 ± 0.01	0.01 ± 0.00	0.01 ± 0.01	0.01 ± 0.01
Eosinophils (10^3/µL)	0.05 ± 0.01	0.05 ± 0.02	0.03 ± 0.01	0.04 ± 0.04
Nucleated erythrocytes (10^3/µL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00

* 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; no measurements taken for males receiving 5,000, 10,000, or 25,000 ppm and females receiving 10,000 or 25,000 ppm due to 100% mortality in these groups.
[b] n=8

Table G8
Hematology Data for Mice in the 13-Week Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

	0 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm	2,500 ppm
Male						
n	9	10	10	10	10	10
Hematocrit (%)	44.3 ± 0.5	43.6 ± 0.7	41.7 ± 0.6*	43.4 ± 0.4	41.8 ± 0.7**	39.7 ± 0.5**
Hemoglobin (g/dL)	15.4 ± 0.2	15.3 ± 0.2	15.2 ± 0.2	15.6 ± 0.1	15.2 ± 0.2	14.2 ± 0.1**
Erythrocytes ($10^6/\mu L$)	9.40 ± 0.13	9.31 ± 0.17	8.87 ± 0.10**	9.17 ± 0.09	8.82 ± 0.15**	8.79 ± 0.09**
Mean cell volume (fL)	47.6 ± 0.3	47.0 ± 0.4	47.4 ± 0.3	47.7 ± 0.3	47.7 ± 0.2	45.6 ± 0.3**
Reticulocytes ($10^6/\mu L$)	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
Leukocytes ($10^3/\mu L$)	5.31 ± 0.32	5.87 ± 0.21	6.13 ± 0.37	6.18 ± 0.45	4.45 ± 0.47	3.95 ± 0.46
Segmented neutrophils ($10^3/\mu L$)	0.71 ± 0.11	0.79 ± 0.08	0.88 ± 0.05[b]	0.68 ± 0.11	0.47 ± 0.06	0.47 ± 0.08
Bands ($10^3/\mu L$)	0.26 ± 0.04	0.43 ± 0.06	0.36 ± 0.06	0.51 ± 0.07	0.38 ± 0.06	0.39 ± 0.07
Lymphocytes ($10^3/\mu L$)	4.14 ± 0.33	4.36 ± 0.19	4.59 ± 0.32	4.66 ± 0.28	3.32 ± 0.38	2.72 ± 0.36*
Atypical lymphocytes ($10^3/\mu L$)	0.08 ± 0.02	0.11 ± 0.03	0.18 ± 0.03**	0.15 ± 0.04*	0.09 ± 0.01[b]	0.16 ± 0.03*
Monocytes ($10^3/\mu L$)	0.03 ± 0.01	0.02 ± 0.01	0.06 ± 0.02	0.05 ± 0.01	0.05 ± 0.01	0.06 ± 0.01[b]
Eosinophils ($10^3/\mu L$)	0.10 ± 0.04	0.16 ± 0.05	0.18 ± 0.04	0.13 ± 0.04	0.13 ± 0.03	0.11 ± 0.04
Nucleated erythrocytes ($10^3/\mu L$)	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.00 ± 0.00
Female						
n	10	10	10	10	10	10
Hematocrit (%)	43.3 ± 0.8	43.1 ± 0.5	43.1 ± 0.6	42.2 ± 0.8	41.7 ± 0.4*	39.1 ± 0.5**
Hemoglobin (g/dL)	15.5 ± 0.2	15.7 ± 0.2	15.4 ± 0.2	15.1 ± 0.3	15.2 ± 0.1	14.4 ± 0.1**
Erythrocytes ($10^6/\mu L$)	9.16 ± 0.11	9.16 ± 0.10	9.00 ± 0.14	8.97 ± 0.19	8.81 ± 0.08*	8.68 ± 0.11*
Mean cell volume (fL)	47.5 ± 0.5	47.5 ± 0.2	48.4 ± 0.3	47.4 ± 0.2	47.7 ± 0.3	45.4 ± 0.3**
Reticulocytes ($10^6/\mu L$)	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.14 ± 0.02
Leukocytes ($10^3/\mu L$)	4.52 ± 0.25	3.89 ± 0.48	4.16 ± 0.24	3.65 ± 0.25	3.84 ± 0.28	4.56 ± 0.28
Segmented neutrophils ($10^3/\mu L$)	0.55 ± 0.10	0.57 ± 0.10	0.43 ± 0.08	0.49 ± 0.07	0.44 ± 0.06	0.63 ± 0.07
Bands ($10^3/\mu L$)	0.21 ± 0.03	0.14 ± 0.04	0.22 ± 0.04	0.13 ± 0.03	0.23 ± 0.03	0.32 ± 0.04
Lymphocytes ($10^3/\mu L$)	3.60 ± 0.18	2.98 ± 0.44*	3.30 ± 0.18	2.81 ± 0.18	2.89 ± 0.22	3.34 ± 0.23
Atypical lymphocytes ($10^3/\mu L$)	0.08 ± 0.02	0.08 ± 0.02	0.08 ± 0.02	0.09 ± 0.01	0.15 ± 0.03	0.14 ± 0.01*[b]
Monocytes ($10^3/\mu L$)	0.02 ± 0.01	0.03 ± 0.01	0.02 ± 0.01	0.03 ± 0.01	0.03 ± 0.02	0.08 ± 0.01**
Eosinophils ($10^3/\mu L$)	0.07 ± 0.02	0.10 ± 0.02	0.11 ± 0.02	0.10 ± 0.02	0.10 ± 0.02	0.06 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01

* 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 G9
Hematology and Clinical Chemistry Data for Mice at the 3-Month Interim Evaluation in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

	0 ppm	250 ppm	500 ppm	1,000 ppm
Male				
n	10	10	10	10
Hematology				
Hematocrit (%)	50.8 ± 0.5	51.3 ± 0.7	50.8 ± 0.5	50.8 ± 0.4
Hemoglobin (g/dL)	16.9 ± 0.2	17.0 ± 0.2	16.7 ± 0.2	16.8 ± 0.1
Erythrocytes ($10^6/\mu L$)	10.88 ± 0.10	10.93 ± 0.16	10.74 ± 0.11	10.71 ± 0.07
Mean cell volume (fL)	46.7 ± 0.2	47.0 ± 0.0	47.4 ± 0.3*	47.5 ± 0.2**
Mean cell hemoglobin (pg)	15.5 ± 0.1	15.5 ± 0.1	15.6 ± 0.1	15.7 ± 0.1
Mean cell hemoglobin concentration (g/dL)	33.3 ± 0.1	33.1 ± 0.1	32.9 ± 0.2	33.1 ± 0.2
Platelets ($10^3/\mu L$)	753.8 ± 41.0	761.3 ± 33.2	758.1 ± 30.0	739.9 ± 41.2
Reticulocytes ($10^6/\mu L$)	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
Leukocytes ($10^3/\mu L$)	4.88 ± 0.49	3.65 ± 0.33	4.13 ± 0.34	3.50 ± 0.32*
Segmented neutrophils ($10^3/\mu L$)	1.22 ± 0.26	1.00 ± 0.15	1.04 ± 0.18	0.98 ± 0.18
Lymphocytes ($10^3/\mu L$)	3.59 ± 0.31	2.61 ± 0.24*	3.03 ± 0.28	2.47 ± 0.27*
Eosinophils ($10^3/\mu L$)	0.07 ± 0.02	0.04 ± 0.02	0.07 ± 0.02	0.05 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00
n	10	9	10	10
Clinical Chemistry				
Urea nitrogen (mg/dL)	31.2 ± 1.8	30.7 ± 2.9	30.6 ± 1.7	32.0 ± 2.2
Creatinine (mg/dL)	0.35 ± 0.02	0.36 ± 0.02	0.32 ± 0.01	0.36 ± 0.02
Sodium (mEq/L)	151 ± 1[b]	151 ± 1	151 ± 1	153 ± 1
Potassium (mEq/L)	9.3 ± 0.3[b]	8.7 ± 0.5	9.0 ± 0.4	9.0 ± 0.3
Chloride (mEq/L)	103 ± 1[b]	105 ± 1	105 ± 1	105 ± 1
Calcium (mg/dL)	5.00 ± 0.06[b]	4.84 ± 0.06	4.86 ± 0.06	4.95 ± 0.06
Total bilirubin (mg/dL)	0.2 ± 0.0	0.2 ± 0.0[c]	0.2 ± 0.0	0.3 ± 0.0*
Direct bilirubin (mg/dL)	0.01 ± 0.01	0.02 ± 0.01	0.03 ± 0.01	0.02 ± 0.01
Alkaline phosphatase (IU/L)	144 ± 9	167 ± 7*[c]	156 ± 7	181 ± 4**
Alanine aminotransferase (IU/L)	116 ± 36	80 ± 11[c]	73 ± 9[b]	67 ± 8
Sorbitol dehydrogenase (IU/L)	100 ± 16	74 ± 6[c]	78 ± 7[b]	80 ± 5

TABLE G9
Hematology and Clinical Chemistry Data for Mice at the 3-Month Interim Evaluation in the 2-Year Feed Study of 4,4'-Thiobis(6-t-Butyl-m-Cresol) (continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm
Female				
n	10	10	10	10
Hematology				
Hematocrit (%)	51.4 ± 0.5	51.1 ± 0.7	51.5 ± 0.5	51.2 ± 0.3
Hemoglobin (g/dL)	17.0 ± 0.1	16.9 ± 0.1	17.0 ± 0.2	16.8 ± 0.2
Erythrocytes ($10^6/\mu L$)	10.85 ± 0.09	10.71 ± 0.10	10.74 ± 0.10	10.65 ± 0.09
Mean cell volume (fL)	47.3 ± 0.2	47.6 ± 0.3	48.1 ± 0.2*	48.1 ± 0.2*
Mean cell hemoglobin (pg)	15.7 ± 0.1	15.8 ± 0.1	15.9 ± 0.1	15.8 ± 0.1
Mean cell hemoglobin concentration (g/dL)	33.1 ± 0.2	33.1 ± 0.2	33.0 ± 0.3	32.9 ± 0.2
Platelets ($10^3/\mu L$)	710.2 ± 46.2	634.9 ± 60.5	632.3 ± 51.5	705.4 ± 43.7
Reticulocytes ($10^6/\mu L$)	0.1 ± 0.0	0.2 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
Leukocytes ($10^3/\mu L$)	4.31 ± 0.39	4.40 ± 0.31	4.59 ± 0.39	4.36 ± 0.40
Segmented neutrophils ($10^3/\mu L$)	0.92 ± 0.22	0.59 ± 0.09	0.70 ± 0.15	0.75 ± 0.15
Lymphocytes ($10^3/\mu L$)	3.29 ± 0.26	3.75 ± 0.28	3.79 ± 0.30	3.56 ± 0.35
Eosinophils ($10^3/\mu L$)	0.10 ± 0.03	0.07 ± 0.02	0.10 ± 0.03	0.05 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00
n	10	10	9	10
Clinical Chemistry				
Urea nitrogen (mg/dL)	27.8 ± 2.6	32.6 ± 2.4	26.9 ± 3.0	28.1 ± 1.5
Creatinine (mg/dL)	0.36 ± 0.02	0.36 ± 0.02	0.36 ± 0.02	0.32 ± 0.01
Sodium (mEq/L)	150 ± 1[d]	150 ± 1	151 ± 1	151 ± 1
Potassium (mEq/L)	8.5 ± 0.2[d]	8.7 ± 0.3	8.9 ± 0.2	8.7 ± 0.2
Chloride (mEq/L)	105 ± 1[d]	104 ± 1	105 ± 1	106 ± 1
Calcium (mg/dL)	4.97 ± 0.04	4.96 ± 0.07	4.94 ± 0.05	4.83 ± 0.07
Total bilirubin (mg/dL)	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.3 ± 0.0
Direct bilirubin (mg/dL)	0.01 ± 0.01	0.03 ± 0.01	0.02 ± 0.01	0.04 ± 0.01
Alkaline phosphatase (IU/L)	218 ± 9	218 ± 8	263 ± 28[c]	240 ± 14
Alanine aminotransferase (IU/L)	75 ± 4[b]	78 ± 11	57 ± 4	101 ± 11
Sorbitol dehydrogenase (IU/L)	74 ± 13	70 ± 6	55 ± 2[c]	74 ± 8

* 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
[b] n=9
[c] n=10
[d] n=8

Table G10
Hematology and Clinical Chemistry Data for Mice at the 9-Month Interim Evaluation in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

	0 ppm	250 ppm	500 ppm	1,000 ppm
Male				
n	10	10	10	9
Hematology				
Hematocrit (%)	57.6 ± 0.8	58.1 ± 0.9	58.6 ± 0.7	57.6 ± 0.6
Hemoglobin (g/dL)	15.9 ± 0.2	16.0 ± 0.2	16.1 ± 0.1	15.9 ± 0.2
Erythrocytes ($10^6/\mu L$)	10.64 ± 0.13	10.74 ± 0.19	10.75 ± 0.09	10.70 ± 0.11
Mean cell volume (fL)	53.6 ± 0.4	54.2 ± 0.3	54.6 ± 0.3	53.8 ± 0.3
Mean cell hemoglobin (pg)	14.8 ± 0.1	14.9 ± 0.1	14.9 ± 0.1	14.8 ± 0.1
Mean cell hemoglobin concentration (g/dL)	27.6 ± 0.2	27.6 ± 0.1	27.4 ± 0.1	27.6 ± 0.1
Platelets ($10^3/\mu L$)	856.7 ± 34.3	879.4 ± 51.6	834.8 ± 43.4	875.0 ± 56.0
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Leukocytes ($10^3/\mu L$)	6.22 ± 0.65	5.79 ± 0.54	6.81 ± 0.52	7.04 ± 0.66
Segmented neutrophils ($10^3/\mu L$)	1.87 ± 0.35	1.73 ± 0.26	1.71 ± 0.16	1.80 ± 0.17
Lymphocytes ($10^3/\mu L$)	4.25 ± 0.38	3.98 ± 0.37	4.98 ± 0.50	5.11 ± 0.57
Eosinophils ($10^3/\mu L$)	0.10 ± 0.05	0.09 ± 0.02	0.12 ± 0.03	0.14 ± 0.02*
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Clinical Chemistry				
Urea nitrogen (mg/dL)	22.4 ± 0.8	21.7 ± 0.6	20.0 ± 0.8*[b]	20.6 ± 0.3*
Creatinine (mg/dL)	0.37 ± 0.02	0.37 ± 0.02	0.37 ± 0.02	0.37 ± 0.02
Sodium (mEq/L)	154 ± 1[b]	153 ± 2[b]	155 ± 1[b]	156 ± 0.4*[c]
Potassium (mEq/L)	6.9 ± 0.2[b]	7.2 ± 0.4[b]	6.8 ± 0.2	7.4 ± 0.3[c]
Chloride (mEq/L)	110 ± 1[b]	108 ± 1[b]	108 ± 2	111 ± 0[c]
Calcium (mg/dL)	4.93 ± 0.06	4.87 ± 0.07[b]	4.87 ± 0.04[b]	4.89 ± 0.05
Total bilirubin (mg/dL)	0.17 ± 0.01	0.24 ± 0.01**	0.31 ± 0.01**	0.42 ± 0.03**
Direct bilirubin (mg/dL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01*
Alkaline phosphatase (IU/L)	129 ± 3[b]	139 ± 4	145 ± 4*	150 ± 6**
Alanine aminotransferase (IU/L)	58 ± 5	54 ± 7[b]	60 ± 8	84 ± 19
Sorbitol dehydrogenase (IU/L)	61 ± 3	58 ± 1	64 ± 3	67 ± 7

TABLE G10
Hematology and Clinical Chemistry Data for Mice at the 9-Month Interim Evaluation in the 2-Year Feed Study of 4,4'-Thiobis(6-t-Butyl-m-Cresol) (continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm
Female				
n	10	10	10	10
Hematology				
Hematocrit (%)	56.5 ± 0.5	56.7 ± 0.6	56.6 ± 0.5	56.1 ± 0.4
Hemoglobin (g/dL)	15.9 ± 0.1	16.0 ± 0.1	15.8 ± 0.1	15.7 ± 0.1
Erythrocytes ($10^6/\mu L$)	10.40 ± 0.09	10.40 ± 0.09	10.22 ± 0.11	10.28 ± 0.11
Mean cell volume (fL)	54.3 ± 0.3	54.6 ± 0.2	55.5 ± 0.3*	54.4 ± 0.5
Mean cell hemoglobin (pg)	15.3 ± 0.1	15.4 ± 0.1	15.5 ± 0.1	15.3 ± 0.1
Mean cell hemoglobin concentration (g/dL)	28.2 ± 0.1	28.2 ± 0.2	28.0 ± 0.1	28.0 ± 0.1
Platelets ($10^3/\mu L$)	896.2 ± 20.0	922.7 ± 21.5[b]	918.4 ± 12.3	907.0 ± 19.4[b]
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Leukocytes ($10^3/\mu L$)	4.92 ± 0.25	6.89 ± 0.87	4.54 ± 0.28	4.69 ± 0.23
Segmented neutrophils ($10^3/\mu L$)	1.37 ± 0.25	1.75 ± 0.20	1.56 ± 0.25	1.69 ± 0.23
Lymphocytes ($10^3/\mu L$)	3.47 ± 0.19	5.00 ± 0.91	2.88 ± 0.27	2.87 ± 0.23
Eosinophils ($10^3/\mu L$)	0.08 ± 0.02	0.14 ± 0.04	0.10 ± 0.03	0.13 ± 0.02
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
n	9	8	10	9
Clinical Chemistry				
Urea nitrogen (mg/dL)	27.2 ± 1.1	28.0 ± 1.3	25.9 ± 1.3	26.8 ± 0.7
Creatinine (mg/dL)	0.44 ± 0.02	0.44 ± 0.02	0.44 ± 0.02	0.41 ± 0.01
Sodium (mEq/L)	152 ± 1	153 ± 0	153 ± 0[b]	154 ± 1*
Potassium (mEq/L)	6.2 ± 0.1	6.7 ± 0.2	6.4 ± 0.2[b]	6.1 ± 0.2
Chloride (mEq/L)	110 ± 1	110 ± 1	110 ± 1[b]	111 ± 1
Calcium (mg/dL)	4.71 ± 0.04	4.73 ± 0.04	4.73 ± 0.02	4.68 ± 0.04
Total bilirubin (mg/dL)	0.1 ± 0.0	0.1 ± 0.0[d]	0.1 ± 0.0	0.2 ± 0.0*[d]
Direct bilirubin (mg/dL)	0.00 ± 0.00	0.00 ± 0.00[d]	0.00 ± 0.00	0.00 ± 0.00[d]
Alkaline phosphatase (IU/L)	223 ± 10[d]	222 ± 10[d]	236 ± 13	292 ± 15**[d]
Alanine aminotransferase (IU/L)	44 ± 4[d]	44 ± 3[d]	39 ± 5	54 ± 6
Sorbitol dehydrogenase (IU/L)	58 ± 3[d]	51 ± 2[d]	50 ± 2	57 ± 3

* 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=7
[d] n=10
[e] n=6

TABLE G11
Hematology and Clinical Chemistry Data for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

	0 ppm	250 ppm	500 ppm	1,000 ppm
Male				
n	10	10	10	10
Hematology				
Hematocrit (%)	52.2 ± 0.7	52.1 ± 0.7	51.5 ± 0.8	49.1 ± 0.7**
Hemoglobin (g/dL)	15.3 ± 0.2	15.2 ± 0.1	15.1 ± 0.2	14.5 ± 0.2**
Erythrocytes ($10^6/\mu L$)	9.97 ± 0.13	9.87 ± 0.13	9.83 ± 0.21	9.31 ± 0.12**
Mean cell volume (fL)	52.5 ± 0.2	52.7 ± 0.2	52.5 ± 0.4	52.7 ± 0.3
Mean cell hemoglobin (pg)	15.4 ± 0.1	15.4 ± 0.1	15.3 ± 0.1	15.6 ± 0.1
Mean cell hemoglobin concentration (g/dL)	29.3 ± 0.2	29.1 ± 0.2	29.3 ± 0.1	29.5 ± 0.2
Platelets ($10^3/\mu L$)	961.7 ± 47.4	955.5 ± 26.7	1,062.7 ± 62.2	937.6 ± 19.3
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Leukocytes ($10^3/\mu L$)	7.02 ± 0.64	6.20 ± 0.45	5.32 ± 0.52*	3.84 ± 0.54**
Segmented neutrophils ($10^3/\mu L$)	2.21 ± 0.41	1.44 ± 0.12	1.60 ± 0.26	0.90 ± 0.15**
Lymphocytes ($10^3/\mu L$)	4.66 ± 0.31	4.55 ± 0.36	3.54 ± 0.41	2.80 ± 0.39**
Monocytes ($10^3/\mu L$)	0.03 ± 0.02	0.02 ± 0.01	0.02 ± 0.01	0.03 ± 0.01
Eosinophils ($10^3/\mu L$)	0.11 ± 0.03	0.19 ± 0.03	0.17 ± 0.04	0.12 ± 0.02
Clinical Chemistry				
Urea nitrogen (mg/dL)	27.2 ± 1.2	26.2 ± 0.9	27.1 ± 1.6	28.5 ± 1.3
Creatinine (mg/dL)	0.36 ± 0.02	0.36 ± 0.02	0.36 ± 0.02	0.39 ± 0.02
Sodium (mEq/L)	155 ± 1	155 ± 0	157 ± 1	154 ± 0[b]
Potassium (mEq/L)	7.5 ± 0.2	7.2 ± 0.2	7.1 ± 0.2	7.0 ± 0.3[b]
Chloride (mEq/L)	112 ± 0	112 ± 1	113 ± 1	112 ± 0[b]
Calcium (mg/dL)	4.84 ± 0.04	4.76 ± 0.06	4.83 ± 0.10	4.52 ± 0.04**[b]
Total bilirubin (mg/dL)	0.11 ± 0.01	0.19 ± 0.02*	0.21 ± 0.01**	0.19 ± 0.01**
Direct bilirubin (mg/dL)	0.000 ± 0.000	0.015 ± 0.009	0.003 ± 0.003	0.019 ± 0.008*
Alkaline phosphatase (IU/L)	135 ± 4	135 ± 4	133 ± 9	141 ± 5
Alanine aminotransferase (IU/L)	43 ± 5	35 ± 3	38 ± 3	33 ± 3
Sorbitol dehydrogenase (IU/L)	70 ± 5	64 ± 4	66 ± 5	61 ± 3
Bile salts (μm/L)	20 ± 2	19 ± 1	20 ± 2	20 ± 3

TABLE G11
Hematology and Clinical Chemistry Data for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm
Female				
n	9	9	10	10
Hematology				
Hematocrit (%)	52.4 ± 0.7	51.5 ± 0.8	51.3 ± 0.7	50.7 ± 0.7
Hemoglobin (g/dL)	15.9 ± 0.2	15.7 ± 0.2	15.5 ± 0.2	15.4 ± 0.2
Erythrocytes ($10^6/\mu L$)	10.46 ± 0.16	10.22 ± 0.15	10.01 ± 0.13	9.94 ± 0.14*
Mean cell volume (fL)	50.2 ± 0.5	50.4 ± 0.2	51.3 ± 0.3*	51.0 ± 0.3
Mean cell hemoglobin (pg)	15.2 ± 0.1	15.4 ± 0.1	15.5 ± 0.1*	15.5 ± 0.1*
Mean cell hemoglobin concentration (g/dL)	30.3 ± 0.1	30.4 ± 0.1	30.3 ± 0.2	30.4 ± 0.3
Platelets ($10^3/\mu L$)	769.8 ± 52.9	745.1 ± 25.5	769.5 ± 34.5	728.5 ± 33.4
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Leukocytes ($10^3/\mu L$)	2.53 ± 0.19	2.68 ± 0.25	2.31 ± 0.18	2.52 ± 0.15
Segmented neutrophils ($10^3/\mu L$)	0.66 ± 0.12	0.66 ± 0.22	0.48 ± 0.06	0.50 ± 0.05
Lymphocytes ($10^3/\mu L$)	1.87 ± 0.13	1.99 ± 0.15	1.80 ± 0.16	2.00 ± 0.12
Monocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils ($10^3/\mu L$)	0.01 ± 0.00	0.03 ± 0.01	0.03 ± 0.01	0.02 ± 0.01
Clinical Chemistry				
Urea nitrogen (mg/dL)	23.3 ± 0.8	24.0 ± 0.9	23.9 ± 1.0[b]	25.9 ± 2.1
Creatinine (mg/dL)	0.39 ± 0.01	0.41 ± 0.01	0.39 ± 0.01[b]	0.39 ± 0.02
Sodium (mEq/L)	156 ± 0[c]	157 ± 0	157 ± 1[c]	157 ± 1[b]
Potassium (mEq/L)	6.4 ± 0.2[c]	6.4 ± 0.2	6.1 ± 0.2[c]	6.2 ± 0.1[b]
Chloride (mEq/L)	109.5 ± 0.7[c]	111.2 ± 0.5	110.5 ± 0.5[c]	111.3 ± 0.3*[b]
Calcium (mg/dL)	5.04 ± 0.09	4.86 ± 0.04	4.86 ± 0.03	4.75 ± 0.06**
Total bilirubin (mg/dL)	0.1 ± 0.0	0.1 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Direct bilirubin (mg/dL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Alkaline phosphatase (IU/L)	278 ± 17	297 ± 23	328 ± 13*	335 ± 14*
Alanine aminotransferase (IU/L)	37 ± 5	35 ± 3[c]	33 ± 1[b]	37 ± 5
Sorbitol dehydrogenase (IU/L)	64 ± 2	60 ± 2	58 ± 1*	57 ± 1*
Bile salts (µm/L)	31 ± 2	29 ± 3	29 ± 2	32 ± 2

* 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
[b] n=9
[c] n=8

APPENDIX H
NEUROTOXICITY EVALUATIONS

NEUROTOXICITY EVALUATIONS

Methods

13-Week Study

During the final 8 days of the 13-week study, male and female controls and rats administered 0, 1,000, and 2,500 ppm 4,4'-thiobis(6-*t*-butyl-*m*-cresol) were tested for forelimb and hindlimb grip strength, startle reflex, tailflick and foot splay.

Forelimb and hindlimb grip strength were measured using a method 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. While the backward motion continued, the animal was allowed to grasp a T-shaped bar with its hindpaws, then forced to release the bar by continued pulling. The maximum strain required to break the forelimb and hindlimb grip was recorded using Chatillon push-pull strain gauges (Kew Gardens, NY). Three trials were conducted with less than 1 minute between trials, so that the degree of habituation or fatigue could be observed.

Startle responsiveness was measured using an SR-LAB Startle Response System (San Diego Instruments, San Diego, CA) with four chambers equipped with a sound generation system and tactile (15 to 20 psi air puff) stimuli relay. Eighty trials were conducted, with 8-second intervals between trials. Twenty startle trials with the tactile stimulus (20 msec per trial) were followed by 40 trials in which a pre-pulse of 80 to 90 db(A) white noise preceded the tactile stimulus by 100 msec; the final 20 trials were tactile stimulus trials. Startle response for each trial, including data for initial reactivity, habituation, and pre-pulse inhibition of the startle response, was recorded after each tactile stimulus was turned off.

Hindlimb footsplay was tested using a modification of the method described by Edwards and Parker (1977). Animals with inked hind feet were held horizontally at a height of 32 cm and released; the distance between the outer digits of the two hind feet were measured for each of three trials.

2-Year Study

Neurotoxicity studies were conducted using 40 male rats per exposure group beginning at week 13. These rats were tested for startle reflex and forelimb and hindlimb grip strength. Ten rats per exposure group were administered electrophysiological evaluations and an additional ten rats per exposure group underwent whole body perfusion for neuropathology. The remaining neurotoxicity rats (20 per group) were placed on control feed for an additional 13 weeks to assess the reversibility of any effects noted after the original 13 weeks of exposure. At that time (26 weeks), all 20 rats per group were again tested for forelimb and hindlimb grip strength, then 10 per group were administered electrophysiological evaluations and 10 were perfused for neuropathology.

Startle response testing took place within environmentally controlled acoustic chambers (Industrial Acoustics Co., Inc., Model AC-15) housing four TEDEA (Model 1010) sensor plates set on a common lucite base and separated from each other by vertical transparent lucite partitions. Four horn tweeters, connected to an amplifier, were placed directly above and directed toward the sensors. Each sensor cable was connected to a startle reflex monitor (Columbus Instruments). Startle responses were relayed through the monitor to a Canon P10 printer which printed the amplitude and latency of the startle response received from each sensor. The sensors were calibrated before use.

During testing, a moderate level of white noise was maintained within the soundproof chamber, and this level was recorded along with the other stimuli and response parameter settings. The animals were placed onto the sensors and the cover was attached. A total of 10 startle stimuli were given with a 60 second interval between stimuli.

Forelimb and hindlimb grip strengths were measured as described for the 13-week studies except there were 8 trials in the 2-year study.

Gastrocnemius muscle tension was measured following dissection of the muscle from all other muscular and connective tissue attachments except for muscle origin on the femur, the sciatic nerve, and vascular supply to the muscle. A silk ligature from the gastrocnemius tendon was attached to a strain gauge transducer (Grass FT10). A plastic frame with electrodes was placed around the sciatic nerve as it followed the femur to the gastrocnemius muscle. Using a 1 Hz, 50 μs square wave pulse, the stimulus intensity (current) was increased stepwise until the maximum response (force) from the muscle was attained. Stimulation periods lasted approximately 5 seconds and were separated by 30 second rest periods. Supramaximal current values of 1.5 times the stimulus intensity required to produce maximum muscle response was used for all subsequent indirect muscle stimulations. Indirect stimulations were performed at six different frequencies: 1, 2, 4, 10, 20, and 40 Hertz. All individual stimulation pulses lasted 50 μs. Each stimulation period lasted approximately 5 seconds and periods were separated by a rest period of approximately 2 minutes.

Direct stimulation of the muscle was measured using a 1 Hertz, 1 ms pulse train of approximately 5 seconds duration separated by 30 seconds; the developed twitch response 1 mA step increases was recorded.

For neuropathology and histopathology muscle and sciatic nerve evaluations, animals were administered total body perfusion with a buffered glutaraldehyde fixative preceded by an initial flush with heparinized saline. Teased nerve preparations were made of the sciatic nerve; slides were examined and fibers were graded.

TABLE H1
Neurotoxicity Data for Rats in the 13-Week Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

	0 ppm	1,000 ppm	2,500 ppm
n	10	10	10
Male			
Hindlimb Footsplay Test (cm)	9.35 ± 0.54	9.72 ± 0.55	9.06 ± 0.46
Forelimb Grip Strength Test (kg)	0.594 ± 0.016	0.773 ± 0.027**	0.860 ± 0.019**
Startle Response Amplitude (g)	1.80 ± 0.13	2.05 ± 0.20	2.00 ± 0.20
Hindlimb Grip Strength Test (kg)	0.163 ± 0.009	0.280 ± 0.011**	0.281 ± 0.008**
Tailflick Latency Test (sec.)	2.12 ± 0.14	2.75 ± 0.15*	2.44 ± 0.11
Female			
Hindlimb Footsplay Test (cm)	7.23 ± 0.50	7.44 ± 0.56	7.88 ± 0.37
Forelimb Grip Strength Test (kg)	0.491 ± 0.018	0.585 ± 0.030*	0.717 ± 0.021**
Startle Response Amplitude (g)	1.90 ± 0.12	1.90 ± 0.19	1.95 ± 0.17
Hindlimb Grip Strength Test (kg)	0.182 ± 0.008	0.212 ± 0.006**	0.214 ± 0.008**
Tailflick Latency Test (sec.)	2.31 ± 0.16	2.36 ± 0.21	2.41 ± 0.14

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

TABLE H2
Neurotoxicity Data for Male Rats at the 3-Month Interim Evaluation in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
Forelimb Grip Strength Test (kg)				
n	40	40	40	40
Trial 1	1.26 ± 0.02	1.28 ± 0.02	1.31 ± 0.02	1.29 ± 0.02
Trial 2	1.24 ± 0.02	1.31 ± 0.02	1.29 ± 0.02	1.28 ± 0.02
Trial 3	1.24 ± 0.02	1.29 ± 0.02	1.30 ± 0.02*	1.27 ± 0.02
Trial 4	1.17 ± 0.02	1.27 ± 0.02**	1.27 ± 0.02**	1.27 ± 0.02**
Trial 5	1.13 ± 0.02	1.28 ± 0.02**	1.26 ± 0.02**	1.26 ± 0.02**
Trial 6	1.08 ± 0.02	1.26 ± 0.02**	1.23 ± 0.02**	1.22 ± 0.02**
Trial 7	1.00 ± 0.02	1.24 ± 0.02**	1.24 ± 0.02**	1.24 ± 0.02**
Trial 8	0.94 ± 0.02	1.24 ± 0.01**	1.24 ± 0.02**	1.21 ± 0.02**
Hindlimb Grip Strength Test (kg)				
n	40	40	40	40
Trial 1	0.874 ± 0.018	0.885 ± 0.015	0.917 ± 0.019	0.885 ± 0.015
Trial 2	0.877 ± 0.018	0.882 ± 0.013	0.892 ± 0.013	0.897 ± 0.016
Trial 3	0.865 ± 0.019	0.887 ± 0.011	0.912 ± 0.012	0.893 ± 0.012
Trial 4	0.824 ± 0.016	0.872 ± 0.013*	0.862 ± 0.013*	0.885 ± 0.014**
Trial 5	0.830 ± 0.019	0.863 ± 0.013	0.874 ± 0.011	0.877 ± 0.012
Trial 6	0.796 ± 0.017	0.867 ± 0.011**	0.861 ± 0.013**	0.869 ± 0.010**
Trial 7	0.795 ± 0.016	0.877 ± 0.011**	0.841 ± 0.012	0.844 ± 0.009
Trial 8	0.782 ± 0.018	0.851 ± 0.009**	0.857 ± 0.014**	0.851 ± 0.011**
Startle Response Amplitude (g)				
n	37	38	39	40
Trial 1	1,069 ± 60	1,033 ± 65[b]	1,034 ± 70	1,090 ± 58
Trial 2	959 ± 70[c]	887 ± 67[d]	1,039 ± 70[b]	1,004 ± 66
Trial 3	860 ± 69[d]	1,017 ± 64	975 ± 65	1,025 ± 79[d]
Trail 4	862 ± 68	833 ± 64	906 ± 70	771 ± 60
Trial 5	756 ± 71[e]	903 ± 70[f]	828 ± 63[g]	814 ± 70[d]
Trial 6	809 ± 75	781 ± 66[g]	799 ± 68[e]	778 ± 63
Trial 7	795 ± 69	834 ± 63[d]	709 ± 58[g]	824 ± 76[g]
Trial 8	784 ± 69[h]	720 ± 64[e]	838 ± 70[f]	731 ± 64[e]
Trial 9	737 ± 68[i]	7896 ± 859[i]	728 ± 721[f]	727 ± 64[g]
Trial 10	834 ± 57[f]	735 ± 67[e]	748 ± 67[e]	712 ± 72[e]

* 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
[b] n=40
[c] n=38
[d] n=39
[e] n=36
[f] n=35
[g] n=37
[h] n=34
[i] n=33

Table H3
Neurotoxicity Data for Male Rats at the 6-Month Interim Evaluation in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
n	20	20	20	20
Forelimb Grip Strength Test (kg)				
Trial 1	1.53 ± 0.02	1.51 ± 0.03	1.53 ± 0.03	1.52 ± 0.04
Trial 2	1.55 ± 0.03	1.54 ± 0.04	1.50 ± 0.03	1.53 ± 0.04
Trial 3	1.49 ± 0.03	1.48 ± 0.03	1.48 ± 0.03	1.43 ± 0.04
Trial 4	1.42 ± 0.04	1.50 ± 0.02	1.48 ± 0.04	1.45 ± 0.03
Trial 5	1.40 ± 0.04	1.42 ± 0.03	1.40 ± 0.03	1.43 ± 0.03
Trial 6	1.34 ± 0.04	1.38 ± 0.03	1.40 ± 0.03	1.38 ± 0.04
Trial 7	1.34 ± 0.04	1.35 ± 0.02	1.36 ± 0.03	1.39 ± 0.02
Trial 8	1.30 ± 0.04	1.31 ± 0.03	1.31 ± 0.03	1.37 ± 0.04
Hindlimb Grip Strength Test (kg)				
Trial 1	1.08 ± 0.03	1.09 ± 0.02	1.09 ± 0.02	1.12 ± 0.02
Trial 2	1.08 ± 0.02	1.09 ± 0.02	1.06 ± 0.02	1.07 ± 0.02
Trial 3	1.03 ± 0.02	1.08 ± 0.02	1.06 ± 0.02	1.03 ± 0.02
Trial 4	1.05 ± 0.02	1.04 ± 0.02	1.02 ± 0.02	1.01 ± 0.02
Trial 5	1.01 ± 0.02	1.06 ± 0.02	1.01 ± 0.02	1.02 ± 0.02
Trial 6	0.97 ± 0.02	1.00 ± 0.02	1.01 ± 0.02	1.00 ± 0.03
Trial 7	0.97 ± 0.02	0.98 ± 0.02	1.00 ± 0.02	0.99 ± 0.02
Trial 8	0.91 ± 0.02	0.98 ± 0.02*	0.96 ± 0.02	0.98 ± 0.03*

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

TABLE H4
Sciatic Nerve Conduction Time Data for Male Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
3-Month Interim Evaluation				
n	8	8	5	7
1 Hz	0.102 ± 0.003	0.106 ± 0.005	0.099 ± 0.002	0.104 ± 0.005
2 Hz	0.103 ± 0.003	0.107 ± 0.005	0.098 ± 0.002	0.104 ± 0.005
4 Hz	0.103 ± 0.003	0.106 ± 0.005	0.098 ± 0.002	0.105 ± 0.006
10 Hz	0.103 ± 0.003	0.105 ± 0.004	0.103 ± 0.005	0.107 ± 0.005
20 Hz	0.106 ± 0.005	0.106 ± 0.004	0.099 ± 0.003	0.110 ± 0.007
40 Hz	0.109 ± 0.008[b]	0.106 ± 0.004	0.101 ± 0.003	0.105 ± 0.004
6-Month Interim Evaluation				
n	7	9	9	7
1 Hz	0.121 ± 0.003	0.118 ± 0.005	0.107 ± 0.004	0.113 ± 0.005
2 Hz	0.123 ± 0.004	0.118 ± 0.005	0.107 ± 0.004*	0.112 ± 0.005
4 Hz	0.122 ± 0.003	0.119 ± 0.005	0.108 ± 0.004	0.112 ± 0.005
10 Hz	0.122 ± 0.003	0.118 ± 0.005	0.109 ± 0.004*	0.111 ± 0.005
20 Hz	0.122 ± 0.003	0.119 ± 0.004	0.112 ± 0.005	0.111 ± 0.005
40 Hz	0.123 ± 0.003	0.117 ± 0.004	0.111 ± 0.005	0.110 ± 0.005

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
[a] Mean ± standard error; times measured in milliseconds
[b] n=7

TABLE H5
Gastrocnemius Muscle Tension Data for Male Rats at the 3-Month Interim Evaluation in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
Sciatic Nerve Stimulation				
n	8	8	5	6
1.5 mA	36.34 ± 3.06	30.34 ± 4.22	28.28 ± 3.55	38.12 ± 3.16
2.0 mA	37.34 ± 2.80	31.31 ± 4.08	31.16 ± 3.10	38.97 ± 2.55[b]
2.5 mA	37.54 ± 2.63	31.68 ± 4.23	32.44 ± 3.62	39.61 ± 2.45[b]
3.0 mA	37.81 ± 2.52	32.31 ± 4.14	34.78 ± 3.89[c]	40.72 ± 3.08
3.5 mA	39.08 ± 2.24	32.28 ± 4.28	34.60 ± 4.96[c]	40.53 ± 3.14
4.0 mA	42.10 ± 2.32[b]	32.46 ± 4.37	35.10 ± 5.48[c]	43.22 ± 3.09[d]
4.5 mA	44.42 ± 3.14[e]	35.42 ± 5.06[e]	35.33 ± 5.36[c]	45.88 ± 3.95[c]
5.0 mA	46.18 ± 4.77[d]	35.88 ± 5.66[c]	38.87 ± 7.89[f]	47.00 ± 3.80[c]
5.5 mA	40.95 ± 2.65[g]	40.80 ± 12.30[g]	42.00 ± 13.10[g]	47.58 ± 3.80[c]
6.0 mA	50.70 ± 8.82[f]	37.70 ± 5.40[c]	43.30 ± 11.80[g]	47.40 ± 4.06[c]
6.5 mA	51.53 ± 9.65[f]	43.00 ± 10.70[g]	42.85 ± 10.55[g]	51.83 ± 2.54[f]
7.0 mA	52.60 ± 10.00[f]	42.40 ± 10.10[g]	42.40 ± 9.30[g]	51.53 ± 2.95[f]
7.5 mA	50.43 ± 9.28[f]	31.35 ± 1.65[g]	41.80 ± 7.00[g]	51.27 ± 2.74[f]
8.0 mA	41.70[h]	33.00[h]	35.70[h]	50.27 ± 2.44[f]
n	8	7	5	7
1 Hz	37.89 ± 2.14	32.80 ± 3.54	34.94 ± 3.90	39.77 ± 2.21
2 Hz	35.91 ± 1.81	34.13 ± 3.93	32.30 ± 3.23	38.54 ± 2.27
4 Hz	35.60 ± 2.22	34.59 ± 3.91	33.00 ± 3.34	38.56 ± 2.34
10 Hz	41.66 ± 4.01	35.99 ± 3.41	33.34 ± 3.33	42.93 ± 3.34
20 Hz	89.79 ± 9.98	86.96 ± 16.65	65.74 ± 10.87	85.63 ± 8.44
40 Hz	217.7 ± 11.1	216.5 ± 21.0	165.2 ± 14.8	242.6 ± 13.2
Gastrocnemius Muscle Stimulation				
n	7	5	5	6
1 Hz	22.76 ± 1.21	22.44 ± 3.27	21.98 ± 1.28	23.33 ± 1.36
2 Hz	22.43 ± 1.21	21.30 ± 3.38	21.34 ± 1.51	21.93 ± 1.02
4 Hz	22.30 ± 1.24	21.60 ± 3.23	21.92 ± 2.34	20.93 ± 0.92
10 Hz	23.39 ± 1.04	23.50 ± 3.47	23.12 ± 2.81	21.60 ± 0.94
20 Hz	35.51 ± 1.62	45.10 ± 7.04	38.50 ± 4.92	39.74 ± 6.69[d]
40 Hz	163.5 ± 6.5	161.4 ± 32.0	160.6 ± 17.6	168.4 ± 12.7

[a] Mean ± standard error; measurements in grams tension/ grams muscle mass
[b] n=7
[c] n=4
[d] n=5
[e] n=6
[f] n=3
[g] n=2
[h] n=1; No standard error calculated.

TABLE H6
Gastrocnemius Muscle Tension Data for Male Rats at the 6-Month Interim Evaluation in the 2-Year Feed Study of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)[a]

	0 ppm	500 ppm	1,000 ppm	2,500 ppm
Sciatic Nerve Stimulation				
n	9	8	9	8
1.5 mA	30.01 ± 5.79	32.26 ± 4.84	27.08 ± 2.41	32.70 ± 2.65
2.0 mA	38.71 ± 3.65	31.56 ± 2.91	32.50 ± 1.80[b]	34.84 ± 2.92
2.5 mA	39.89 ± 3.90[c]	32.03 ± 2.98	33.31 ± 1.87	35.43 ± 3.39
3.0 mA	39.44 ± 3.48	38.83 ± 6.42[d]	33.11 ± 1.97[c]	37.76 ± 2.52[e]
3.5 mA	41.13 ± 3.72[c]	40.43 ± 6.90	31.22 ± 1.36[f]	36.53 ± 2.55[g]
4.0 mA	41.48 ± 3.73[c]	36.60 ± 3.91[g]	30.05 ± 0.55[h]	36.63 ± 2.47[g]
4.5 mA	40.52 ± 3.50[f]	37.95 ± 3.87[g]	30.63 ± 0.27[i]	35.16 ± 3.46[f]
5.0 mA	37.03 ± 3.83[j]	38.50 ± 4.84[f]	29.95 ± 0.95[i]	26.50[k]
5.5 mA	35.50[k]	41.88 ± 4.68[h]	–[l]	–
6.0 mA	–	44.45 ± 10.25[i]	–	–
n	9	9	10	8
1 Hz	40.09 ± 3.20	38.71 ± 5.55	29.76 ± 0.82*	36.04 ± 2.73
2 Hz	38.63 ± 2.86	36.77 ± 5.10	29.48 ± 1.04	34.05 ± 2.76
4 Hz	38.41 ± 2.70	40.17 ± 5.94	30.06 ± 1.73	34.50 ± 2.55
10 Hz	42.38 ± 3.39	45.62 ± 7.11	32.29 ± 2.28	38.76 ± 3.16
20 Hz	78.24 ± 6.23	87.52 ± 16.06	62.62 ± 5.15	76.74 ± 9.43
40 Hz	199.0 ± 13.6	198.1 ± 25.5	167.5 ± 14.8[d]	189.9 ± 14.8
Gastrocnemius Muscle Stimulation				
n	9	9	10	9
3 mA	6.46 ± 0.57[f]	5.53 ± 0.46[g]	6.41 ± 0.59[c]	4.72 ± 0.20*[f]
4 mA	8.24 ± 0.77	7.97 ± 0.65	8.36 ± 0.91	7.52 ± 1.16
5 mA	11.02 ± 1.89[f]	9.02 ± 1.12[g]	9.14 ± 1.17[e]	7.13 ± 0.39[h]
6 mA	12.46 ± 1.34	11.87 ± 1.32	12.02 ± 1.50	10.69 ± 1.26
7 mA	15.25 ± 2.17[g]	11.58 ± 1.66[g]	12.36 ± 1.53[e]	10.15 ± 0.41[h]
8 mA	16.34 ± 1.58	15.11 ± 1.71	14.52 ± 1.78	13.34 ± 1.24
9 mA	18.50 ± 2.25[g]	14.38 ± 2.05[g]	14.59 ± 1.72[e]	13.60 ± 0.26[h]
10 mA	19.02 ± 1.88	17.90 ± 1.98	16.34 ± 1.98	14.90 ± 1.11
11 mA	20.77 ± 2.52[g]	15.98 ± 2.26[g]	15.34 ± 1.75[e]	15.05 ± 0.39[h]
12 mA	20.01 ± 2.00	18.76 ± 1.93	16.88 ± 2.03	16.06 ± 1.38
13 mA	22.50 ± 2.82[g]	17.15 ± 2.31[g]	16.36 ± 1.91[e]	16.10 ± 0.62[h]
14 mA	21.41 ± 2.26	20.11 ± 2.08	17.94 ± 2.15	17.33 ± 1.43
15 mA	24.35 ± 3.08[g]	18.55 ± 2.49[g]	17.24 ± 2.04[e]	17.70 ± 0.96[h]
16 mA	23.16 ± 2.64	21.62 ± 2.29	18.80 ± 2.26	18.44 ± 1.51
17 mA	25.40 ± 3.24[g]	19.87 ± 2.71[g]	17.86 ± 2.14[e]	18.78 ± 1.39[h]
18 mA	23.93 ± 2.63	22.77 ± 2.42	19.53 ± 2.37	19.21 ± 1.63
19 mA	26.38 ± 3.46[g]	20.70 ± 2.98[g]	18.57 ± 2.28[e]	20.00 ± 1.76[h]
20 mA	24.78 ± 2.78	23.86 ± 2.60	20.29 ± 2.54	20.12 ± 1.85
1 Hz	23.54 ± 2.66	25.64 ± 2.24	18.44 ± 2.39	19.38 ± 1.91
2 Hz	22.76 ± 2.56	24.64 ± 2.26	18.15 ± 2.15	19.04 ± 1.96
4 Hz	22.47 ± 2.57	24.46 ± 2.40	18.24 ± 2.24	19.26 ± 2.11
10 Hz	23.82 ± 2.70	25.18 ± 2.70	18.65 ± 2.17	20.46 ± 2.46
20 Hz	39.12 ± 4.54	40.46 ± 5.59	28.21 ± 3.24	34.29 ± 3.32
40 Hz	158.4 ± 18.9	175.6 ± 22.2	111.7 ± 16.3	130.3 ± 22.2

TABLE H6
Gastrocnemius Muscle Tension Data for Male Rats at the 6-Month Interim Evaluation in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
[a] Mean ± standard error; measurements in grams tension/grams muscle mass
[b] n=10
[c] n=8
[d] n=9
[e] n=7
[f] n=5
[g] n=6
[h] n=4
[i] n=2
[j] n=3
[k] n=1; no standard error calculated.
[l] No measurements taken

APPENDIX I
CHEMICAL CHARACTERIZATION AND DOSE FORMULATIONS

CHEMICAL CHARACTERIZATION AND DOSE FORMULATIONS

PROCUREMENT AND CHARACTERIZATION OF 4,4′-THIOBIS(6-T-BUTYL-M-CRESOL)

4,4′-Thiobis(6-*t*-butyl-*m*-cresol) was obtained from Monsanto Industrial Chemical Company (Akron, OH) in one lot (12), which was used throughout the studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the 4,4′-thiobis(6-*t*-butyl-*m*-cresol) studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a white powdered solid, was identified as 4,4′-thiobis(6-*t*-butyl-*m*-cresol) by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with the structure and with the literature spectra (*Sadtler Standard Spectra*) of 4,4′-thiobis(6-*t*-butyl-*m*-cresol) (Figures I1 and I2).

The purity of the chemical was determined by elemental analyses, Karl Fischer water analysis, functional group titration, thin-layer chromatography (TLC), and gas chromatography. Functional group titration was performed by dissolving 4,4′-thiobis(6-*t*-butyl-*m*-cresol) in chloroform, oxidizing to the corresponding sulfone with *m*-chloroperoxybenzoic acid, then reducing the unreacted peroxide with sodium iodide. The liberated iodine was then titrated with 0.1 N sodium thiosulfate. Thin-layer chromatography was performed on Silica Gel 60 F-254 plates using two solvent systems: 1) toluene:acetone (90:10) and 2) heptane:carbon tetrachloride:1,4-dioxane:chloroform (35:15:30:20). Plates were examined and referenced with *p*-*t*-butylphenol under ultraviolet light (254 nm) and a spray of 1% *p*-nitrobenzene diazonium fluoroborate in acetone, followed by 0.1 N potassium hydroxide in methanol. Gas chromatographic analysis was performed with a flame ionization detector (FID) with a nitrogen carrier gas at a flow rate of 70 mL/min. Two systems were used: A) 3% SP-2100 on 80/100 Supelcoport, and B) 3% SP-2401 on 100/120 Supelcoport, both with an oven temperature program of 50° C for 5 minutes, then 50° to 250° C at 10° C per minute.

Elemental analyses of the chemical for carbon, hydrogen, and sulfur were in agreement with the theoretical values for 4,4′-thiobis(6-*t*-butyl-*m*-cresol). Karl Fischer water analysis indicated 0.012% ± 0.001% water. Functional group titration indicated a purity of 100% ± 3%. TLC by system 1 indicated a major spot and two trace impurities, and system 2 indicated a major spot and two trace impurities. Gas chromatography using system A indicated a major peak and two impurities. Two impurities with a total area of 0.7% relative to the major peak area eluted before the major peak. System B indicated a major peak and one impurity that eluted before the major peak and had an area of 0.39% relative to the major peak. The overall purity was determined to be approximately 99%.

Stability studies on the chemical were performed by the analytical chemistry laboratory. Gas chromatography was performed using system A described above but with *n*-tetracosane added as an internal standard and an oven temperature program of 100° to 250° C. These studies indicated that 4,4′-thiobis(6-*t*-butyl-*m*-cresol) 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 formulations were prepared weekly by mixing 4,4′-thiobis(6-*t*-butyl-*m*-cresol) and feed to give the required concentrations (Table I1). Formulations were discarded 2 weeks after the date of preparation. The dose formulations were stored in sealed double plastic bags in plastic bins at −20° C or less for the 15-day studies and at −18° C or less for the 13-week studies and in plastic buckets lined with plastic bags, sealed with lids, and protected from light at −20° C for the 2-year studies.

Homogeneity and stability studies of the dose formulations were performed by the analytical chemistry laboratory. For the homogeneity studies at the 100 and 10,000 ppm concentration, aliquots were extracted with methanol and centrifuged. An aliquot of each extract was mixed with methanol and hexanophenone in methanol as an internal standard and diluted with water:methanol solution (25:75). High-performance liquid chromatography (HPLC) was then performed with a Brownlee RP-18 column. The mobile phase was a mixture of water:methanol at a ratio of 25:75 and a flow rate of 1 mL/minute. For the stability studies, aliquots were extracted with methanol and centrifuged. An aliquot of each extract was mixed with 100 ppm of nonanophenone in methanol as an internal standard and diluted with methanol. HPLC was then performed with a Brownlee RP-18 column. The mobile phase was a mixture of water:methanol at a ratio of 23:77 and a flow rate of 1 mL/minute. Homogeneity was confirmed and the stability of the dose formulations was confirmed for at least 3 weeks at −20° C when stored in the dark, as well as for at least 3 days when exposed to air and light.

Periodic analyses of the dose formulations of 4,4′-thiobis(6-*t*-butyl-*m*-cresol) were conducted at the study laboratory and analytical chemistry laboratory using high-performance liquid chromatography. During the 15-day studies, only the initial formulation was analyzed (Table I2). During the 13-week and the 2-year studies, the dose formulations were analyzed every 6 to 10 weeks (Tables I3 and I4). In the 2-year studies, all dose formulations were within 10% of the target concentrations. Results of the periodic referee analyses performed by the analytical chemistry laboratory were in good agreement with the results obtained by the study laboratory (Table I5).

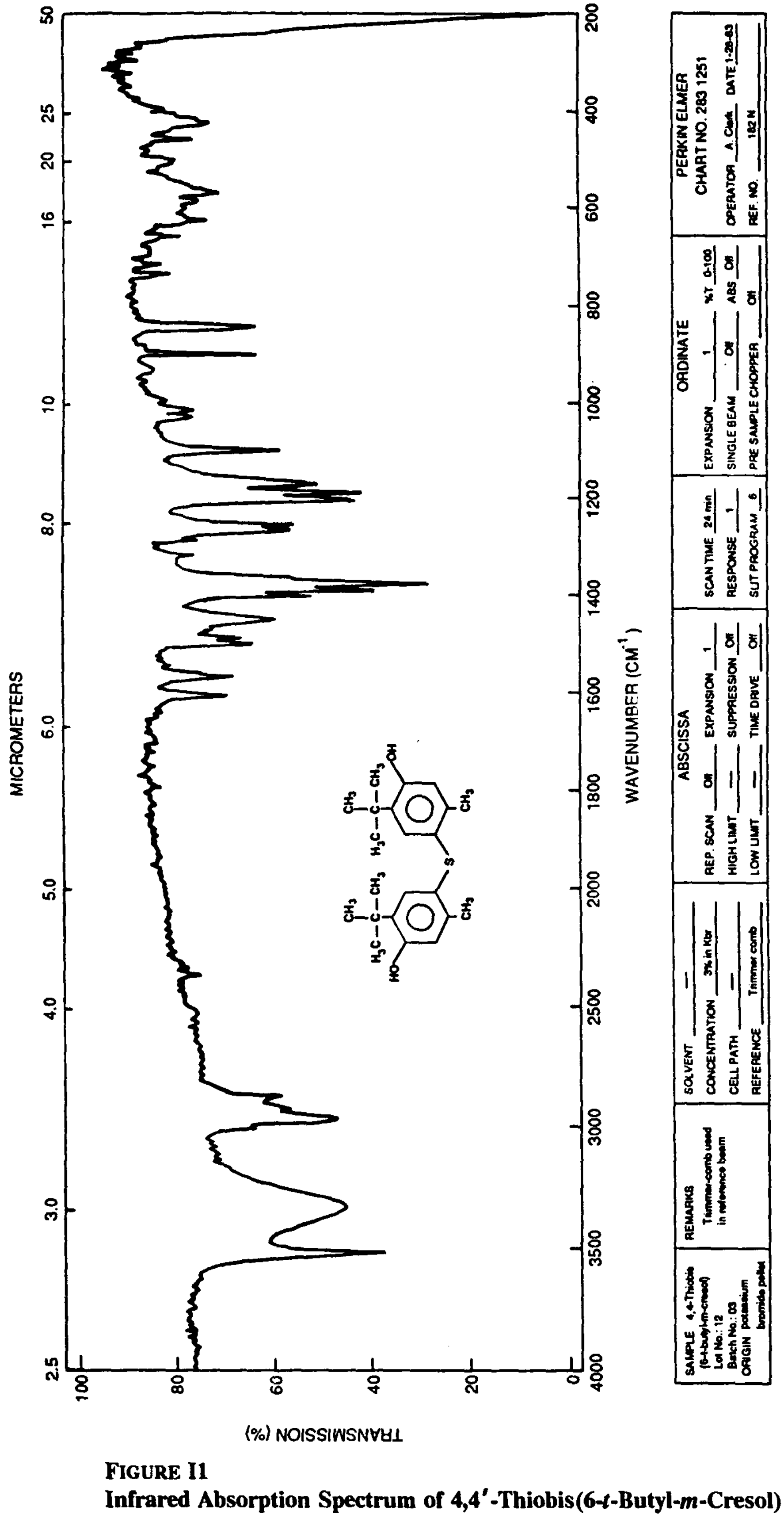

FIGURE I1
Infrared Absorption Spectrum of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol)

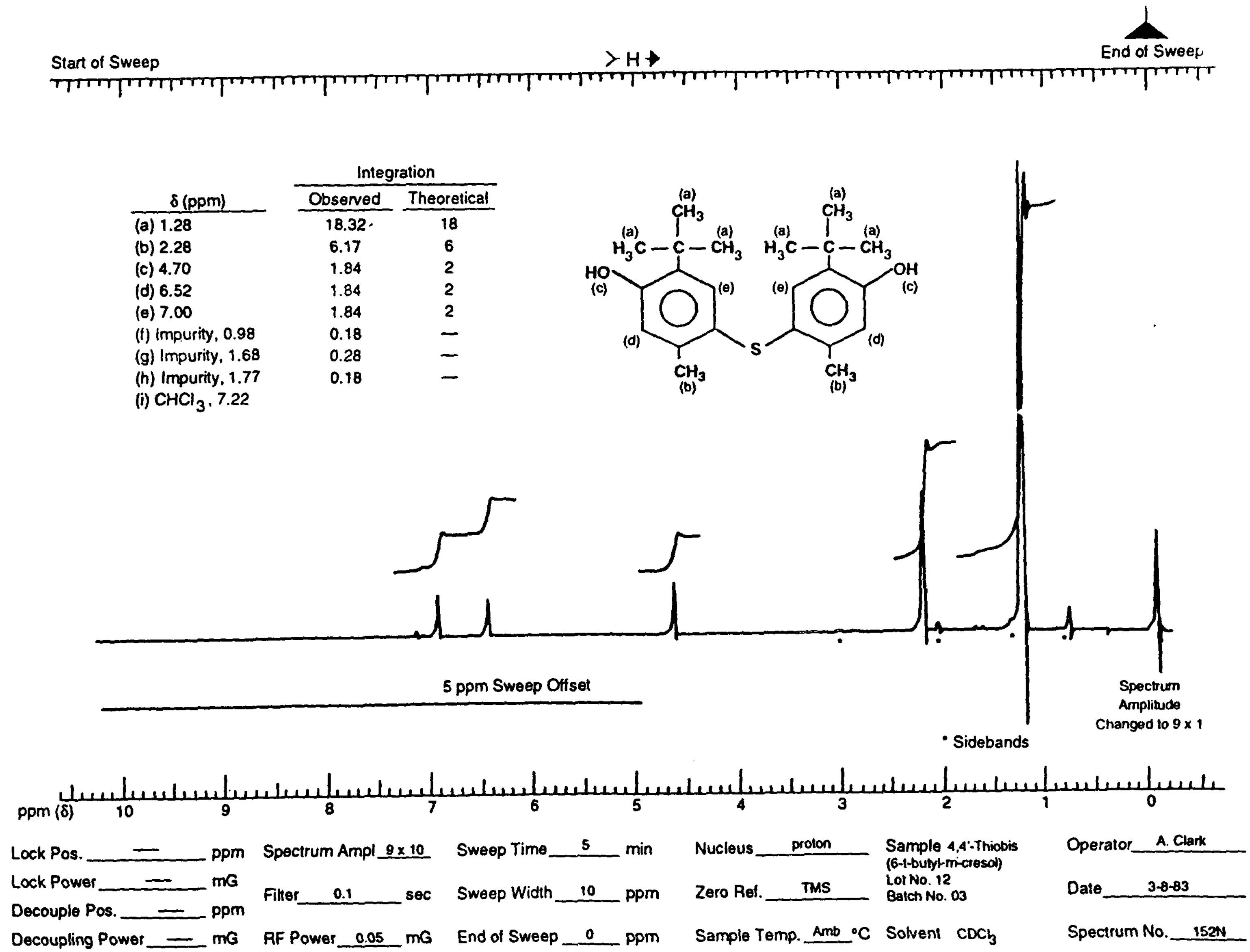

FIGURE 12
Nuclear Magnetic Resonance Spectrum of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)

TABLE I1
Preparation and Storage of Dose Formulations in the Feed Studies of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)

15-Day Studies	13-Week Studies	2-Year Studies
Preparation		
A premix of feed and 4,4'-thiobis(6-*t*-butyl-*m*-cresol) was prepared, then layered into the remaining feed and blended in a Patterson-Kelley twin-shell blender with the intensifier bar on for 5 minutes and off for 10 minutes. Doses were prepared weekly.	Same as 15-day studies	Same as 15-day studies
Chemical Lot Number		
12	12	12
Maximum Storage Time		
2 weeks	2 weeks	2 weeks
Storage Conditions		
Stored in sealed double plastic bags in plastic bins at –20° C or less.	Same as 15-day studies. Stored at –18° C or less.	Stored in plastic buckets lined with plastic bags, sealed with lids, and protected from light at –20° C or less.
Study Laboratory		
American Biogenics Corporation (Woburn, MA)	Same as 15-day studies	Battelle, Columbus Division (Columbus, OH)
Referee Laboratory		
Midwest Research Institute, Kansas City, MO	Same as 15-day studies	Same as 15-day studies

TABLE I2
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 15-Day Feed Studies of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	% Difference from Target
27 December 1983	28 December 1983	1,000	1,000	0
		2,500	2,500	0
		5,000	4,900	–2
		10,000	10,000	0
		25,000	25,400	+2
	30 December 1983	1,000	1,000	0
		2,500	2,400	–4
		5,000	4,800	–4
		10,000	10,200	+2
		25,000	24,400	–2
	3 January 1984	1,000	1,000	0
		2,500	2,400	–4
		5,000	4,800	–4
		10,000	10,100	+1
		25,000	24,400	–2
	6 January 1984	1,000	1,000	0
		2,500	2,500	0
		5,000	5,000	0
		10,000	9,800	–2
		25,000	24,700	–1

[a] Results of duplicate analyses

TABLE I3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week Feed Studies of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)

Date Prepared	Date Analyzed	Target Concentration[a] (ppm)	Determined Concentration[b] (ppm)	% Difference from Target
Rats				
30 July 1984	31 July 1984	250	271	+8
		500	481	–4
		1,000	1,026	+3
		2,500	2,631	+5
		5,000	5,226	+5
6 September 1984	7 September 1984	250	258	+3
		500	511	+2
		1,000	1,057	+6
		2,500	2,671	+7
		5,000	5,085	+2
25 October 1984	26 October 1984	250	263	+5
		500	471	–6
		1,000	992	–1
		2,500	2,470	–1
		5,000	4,987	0
Mice				
13 August 1984	13-14 August 1984	100	108	+8
		250	251	0
		500	464	–7
		1,000	1,089	+9
		2,500	2,458	–2
13 August 1984	7 September 1984	100	105	+5
		250	255	+2
		500	491	–2
		1,000	1,029	+3
		2,500	2,674	+7
20 September 1984	21 September 1984	100	93	–7
		250	260	+4
		500	526	+5
		1,000	1,019	+2
		2,500	2,542	+2
8 November 1984	9 November 1984	100	92	–8
		250	239	–4
		500	465	–7
		1,000	963	–4
		2,500	2,457	–2

[a] Results of duplicate analyses
[b] Archival reference samples

Table I4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	% Difference from Target
Rats				
15 December 1986	17 December 1986	500	501	0
		1,000	993	-1
		2,500[b]	2,533	+1
		2,500[c]	2,493	0
		2,500[d]	2,522	+1
2 February 1987	4 February 1987	500	505	+1
		1,000	974	-3
		2,500	2,439	-2
16 March 1987	17 March 1987	500	500	0
		1,000	977	-2
		2,500	2,565	+3
12 May 1987	13 May 1987	500	519	+4
		1,000	993	-1
		2,500	2,395	-4
6 July 1987	8 July 1987	500	497	-1
		1,000	996	0
		2,500	2,496	0
31 August 1987	1 September 1987	500	505	+1
		1,000	1,000	0
		2,500	2,481	-1
26 October 1987	28 October 1987	500	502	0
		1,000	1,011	+1
		2,500	2,534	+1
14 December 1987	16 December 1987	500	504	+1
		1,000	975	-3
		2,500	2,500	0
8 February 1988	11 February 1988	500	487	-3
		1,000	982	-2
		2,500	2,463	-1
4 April 1988	9 April 1988	500	473	-5
		1,000	1,008	+1
		2,500	2,567	+3
31 May 1988	1 June 1988	500	505	+1
		1,000	986	-1
		2,500	2,225	-11
2 June 1988[e]	2 June 1988	2,500	2,563	+3

TABLE I4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	% Difference from Target
Rats (continued)				
25 July 1988	28 July 1988	500	507	+1
		1,000	1,013	+1
		2,500	2,552	+2
27 September 1988	28 September 1988	500	522	+4
		1,000	1,039	+4
		2,500	2,598	+4
14 November 1988	16 November 1988	500	452	–10
		1,000	930	–7
		2,500	2,499	0
Mice				
15 December 1986	17 December 1986	250[b]	257	+3
		250[c]	251	+1
		250[d]	252	+1
12 January 1987	13 January 1987	250	249	–1
		500	496	–1
		1,000	995	0
16 March 1987	17 March 1987	250	253	+1
		500	498	0
		1,000	1,013	+1
12 May 1987	13 May 1987	250	233	–7
		500	506	+1
		1,000	1,003	0
6 July 1987	8 July 1987	250	248	–1
		500	500	0
		1,000	1,002	0
31 August 1987	1 September 1987	250	259	+4
		500	504	+1
		1,000	998	0
26 October 1987	28 October 1987	250	258	+3
		500	505	+1
		1,000	1,004	0
14 December 1987	16 December 1987	250	243	–3
		500	488	–2
		1,000	1,046	+5

TABLE I4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol) (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	% Difference from Target
Mice (continued)				
8 February 1988	11 February 1988	250	236	–6
		500	483	–3
		1,000	977	–2
4 April 1988	9 April 1988	250	266	+6
		500	516	+3
		1,000	1,006	+1
31 May 1988	1 June 1988	250	269	+8
		500	507	+1
		1,000	1,016	+2
25 July 1988	28 July 1988	250	274	+9
		500	501	0
		1,000	1,018	+2
27 September 1988	28 September 1988	250	285	+14
		500	518	+4
		1,000	1,044	+4
29 September 1988[e]	29 September 1988	250	220	–12
30 September 1988[e]	30 September 1988	250	257	+3
14 November 1988	16 November 1988	250	211	–16
		500	440	–12
		1,000	780	–22
18 November 1988[e]	19 November 1988	250	252	+1
		500	518	+4
		1,000	1,060	+6

[a] Results of duplicate analyses
[b] Sample selection from top left of twin-shell blender
[c] Sample selection from top right of twin-shell blender
[d] Sample selection from bottom of twin-shell blender
[e] Results of remix

TABLE I5
Results of Referee Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week and 2-Year Feed Studies of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)

Date Prepared	Target Concentration (ppm)	Determined Concentration (ppm) Study Laboratory[a]	Determined Concentration (ppm) Referee Laboratory[b]
13-Week Studies (American Biogenics Corporation)			
Rats			
30 July 1984	500	481	500 ± 11
Mice			
20 September 1984[d]	2,560	2,542	2,560 ± 30
2-Year Studies (Battelle Columbus)			
Rats			
15 December 1986	500	501	494 ± 11
12 May 1987	2,500	2,395	2,493 ± 60
14 November 1988	500	452	500 ± 5
Mice			
14 December 1987	250	243	242 ± 4
31 May 1988	1,000	1,016	979 ± 6

[a] Results of duplicate analyses
[b] Results of triplicate analyses (mean ± standard error)

APPENDIX J
FEED AND COMPOUND CONSUMPTION IN THE 2-YEAR FEED STUDIES

TABLE J1
Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-t-Butyl-m-Cresol)

Week	0 ppm Feed (g/day)[a]	0 ppm Body Weight (g)	500 ppm Feed (g/day)	500 ppm Body Weight (g)	500 ppm Dose/Day[b] (mg/kg/day)	1,000 ppm Feed (g/day)	1,000 ppm Body Weight (g)	1,000 ppm Dose/Day (mg/kg/day)	2,500 ppm Feed (g/day)	2,500 ppm Body Weight (g)	2,500 ppm Dose/Day (mg/kg/day)
3	17.8	215	18.2	218	42	18.1	218	83	19.2	216	222
4	17.2	245	17.4	246	35	17.5	246	71	18.6	246	190
7	17.2	292	16.7	295	28	17.0	298	57	17.5	294	149
8	18.1	310	17.7	307	29	18.0	312	58	18.0	305	147
11	17.1	342	16.9	341	25	16.8	343	49	16.7	332	126
12	17.6	350	16.9	349	24	16.3	351	46	16.8	338	124
13	17.6	355	16.8	358	23	24.5	360	68	25.1	346	182
17	16.8	383	16.5	377	22	16.5	383	43	16.7	365	114
21	16.0	421	15.5	420	19	15.2	402	38	15.2	382	100
22	15.5	397	16.2	389	21	15.7	395	40	15.0	378	99
25	16.8	412	16.5	405	20	17.1	406	42	16.9	392	108
29	18.6	419	17.9	412	22	17.7	417	42	17.8	405	110
33	17.4	431	19.9	425	23	18.6	428	44	19.3	413	117
37	16.5	438	17.9	434	21	16.9	437	39	16.0	425	94
41	16.0	441	15.5	442	18	15.0	440	34	15.4	428	90
45	17.9	444	16.2	444	18	16.7	440	38	15.6	431	91
49	16.3	451	16.2	451	18	15.9	449	35	16.1	436	92
53	17.2	453	16.9	455	19	15.8	453	35	15.9	440	90
57	16.1	461	15.6	462	17	15.2	456	33	15.7	447	88
61	15.0	464	16.1	462	17	14.9	455	33	15.1	445	85
64	14.6	497	15.6	489	16	14.3	477	30	15.0	447	84
65	15.6	454	17.1	453	19	15.7	452	35	15.5	445	87
69	15.1	462	14.9	458	16	15.0	455	33	14.7	443	83
73	14.3	459	14.6	458	16	13.8	453	30	14.1	444	79
77	14.5	455	14.5	457	16	12.5	453	28	13.7	437	78
81	13.8	455	14.1	451	16	14.8	445	33	13.9	436	80
85	13.3	448	13.5	453	15	14.6	442	33	14.3	431	83
89	13.7	442	13.6	447	15	12.8	441	29	13.2	429	77
93	13.8	445	13.0	435	15	13.9	430	32	13.0	416	78
97	15.3	437	14.4	432	17	13.1	427	31	13.1	413	79
101	14.1	446	13.0	428	15	12.2	410	30	13.4	418	80
104	13.5	441	12.0	417	14	12.1	413	29	12.7	417	76
Mean for weeks											
1-13	17.5	301	17.2	302	30	18.3	304	62	18.8	296	163
14-52	16.8	424	16.8	420	20	16.5	420	39	16.4	405	101
53-104	14.7	455	14.6	450	16	14.1	444	32	14.2	434	82

[a] Grams of feed consumed per animal per day.
[b] Milligrams of 4,4′-thiobis(6-t-butyl-m-cresol) consumed per kilogram body weight per day.

TABLE J2
Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol)

Week	0 ppm Feed (g/day)[a]	0 ppm Body Weight (g)	500 ppm Feed (g/day)	500 ppm Body Weight (g)	500 ppm Dose/ Day[b] (mg/kg/day)	1,000 ppm Feed (g/day)	1,000 ppm Body Weight (g)	1,000 ppm Dose/ Day (mg/kg/day)	2,500 ppm Feed (g/day)	2,500 ppm Body Weight (g)	2,500 ppm Dose/ Day (mg/kg/day)
3	12.6	146	12.3	148	41	12.6	147	86	12.6	149	211
4	11.7	156	11.7	159	37	12.0	158	76	12.3	160	193
7	10.9	178	11.1	182	30	11.6	178	65	11.8	180	164
8	11.3	182	12.0	186	32	11.9	184	65	11.9	184	162
11	10.5	192	10.8	197	27	10.9	194	56	10.4	193	135
12	10.5	196	10.6	200	26	10.8	196	55	10.1	193	130
13	12.3	199	11.2	203	28	10.7	198	54	21.5	197	274
17	10.3	209	10.3	211	24	10.2	208	49	9.2	202	114
21	10.1	213	10.3	218	24	10.2	207	49	9.5	213	112
22	9.9	216	10.1	219	23	10.2	215	47	9.5	209	114
25	10.4	219	11.0	223	25	10.8	218	49	10.6	212	125
29	11.6	225	11.8	228	26	11.8	223	53	10.4	216	121
33	11.8	235	12.5	236	26	12.1	232	52	11.2	221	126
37	10.7	242	11.5	244	24	10.4	237	44	10.6	225	117
41	11.4	246	10.7	249	22	10.3	241	43	10.3	228	113
45	12.9	252	12.1	253	24	12.0	248	49	11.1	231	120
49	12.4	266	12.5	263	24	12.1	261	46	11.2	240	116
53	12.6	277	12.2	277	22	12.4	272	46	11.6	246	118
57	12.0	293	12.1	287	21	12.6	284	44	11.5	257	112
61	11.2	304	12.4	297	21	11.5	294	39	11.5	262	110
64	11.4	311	11.9	308	19	11.5	290	40	11.4	278	103
65	11.9	312	13.4	303	22	12.6	301	42	11.9	268	111
69	11.2	322	12.2	316	19	11.9	312	38	12.0	278	108
73	10.7	326	11.6	324	18	10.7	319	33	10.9	286	96
77	11.6	330	12.0	327	18	11.8	320	37	11.6	286	101
81	11.3	334	11.3	335	17	11.7	328	36	11.4	293	98
85	11.6	336	11.1	335	17	12.3	326	38	12.8	295	109
89	10.9	335	11.2	331	17	10.9	327	33	11.7	304	96
93	11.3	339	11.5	327	18	12.1	324	37	11.7	305	96
97	11.6	341	10.1	327	15	11.0	328	34	12.1	305	100
101	10.0	338	9.9	336	15	10.6	331	32	11.3	307	92
104	10.1	333	9.5	326	15	10.3	327	32	11.6	311	93
Mean for weeks											
1-13	11.4	178	11.4	182	32	11.5	179	65	12.9	179	181
14-52	11.1	232	11.3	234	24	11.0	229	48	10.3	220	118
53-104	11.3	322	11.5	317	18	11.6	312	37	11.7	285	103

[a] Grams of feed consumed per animal per day.
[b] Milligrams of 4,4′-thiobis(6-*t*-butyl-*m*-cresol) consumed per kilogram body weight per day.

TABLE J3
Feed and Compound Consumption by Male Mice in the 2-Year Feed Study of 4,4′-Thiobis(6-t-Butyl-m-Cresol)

Week	0 ppm		250 ppm			500 ppm			1,000 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	5.6	24.7	5.2	24.8	52	5.2	25.1	104	5.8	25.2	231
4	5.6	25.4	5.5	25.5	54	5.8	25.9	112	6.3	25.9	245
7	6.2	27.8	5.0	27.8	45	5.8	27.8	104	6.7	28.0	238
8	6.9	28.8	5.4	28.5	47	6.2	28.6	108	6.8	28.4	240
11	5.4	30.6	5.2	30.4	43	5.6	30.2	93	6.4	29.9	212
12	5.1	31.6	5.0	31.2	40	5.9	31.0	95	6.4	30.5	209
13	4.7	32.0	4.8	31.5	38	5.2	31.1	83	5.8	30.9	189
17	5.0	35.1	5.0	34.5	36	5.6	33.8	82	6.0	33.3	179
21	4.1	37.0	4.8	36.4	33	5.2	35.7	73	6.1	34.8	175
25	4.5	38.0	4.5	37.2	30	5.4	36.2	75	5.9	35.6	167
29	4.6	38.9	5.0	37.8	33	4.8	36.7	65	5.6	35.8	158
33	4.3	41.1	4.4	40.1	27	4.4	39.3	56	5.3	37.6	142
37	4.0	41.5	4.1	42.0	24	4.4	40.6	54	5.8	37.9	153
41	4.4	42.3	4.6	42.2	27	4.7	41.1	57	5.6	38.5	147
45	4.4	44.2	4.3	43.5	25	4.8	42.2	56	5.5	39.9	138
49	4.3	45.6	4.4	44.7	25	4.5	43.6	52	5.4	41.3	130
53	4.6	46.8	4.5	46.1	24	4.3	44.5	48	5.2	42.3	124
57	3.9	47.5	4.0	46.9	21	4.1	45.6	45	4.8	43.3	112
61	4.1	48.0	4.1	46.9	22	4.2	45.8	46	4.8	43.2	112
65	4.4	48.3	4.2	47.5	22	4.0	45.9	44	4.9	44.1	111
69	4.4	47.7	4.4	47.1	23	4.5	46.0	49	5.6	43.7	129
73	4.5	47.8	4.5	47.5	24	4.7	46.0	51	5.6	43.4	129
77	4.4	48.8	4.5	49.0	23	4.6	47.5	49	5.9	44.9	131
81	4.5	48.3	4.3	48.8	22	4.3	47.5	45	4.6	43.9	104
85	4.0	47.5	4.2	48.5	22	4.4	45.8	48	4.4	42.8	102
89	4.4	46.9	4.6	47.2	24	5.2	45.3	57	5.6	42.8	131
93	4.8	46.4	4.5	47.4	24	4.5	44.5	51	5.4	42.3	127
97	3.7	46.5	4.0	49.2	20	4.2	45.2	47	5.6	42.6	132
101	4.2	46.0	4.5	48.3	23	4.4	45.0	49	5.5	42.8	128
104	4.4	47.0	4.5	49.5	23	4.5	46.2	48	5.5	43.2	127
Mean for weeks											
1-13	5.6	28.7	5.2	28.5	46	5.7	28.5	100	6.3	28.4	223
13-52	4.4	40.4	4.6	39.8	29	4.9	38.8	64	5.7	37.2	154
53-104	4.3	47.4	4.3	47.9	23	4.4	45.8	48	5.2	43.2	121

[a] Grams of feed consumed per animal per day.
[b] Milligrams of 4,4′-thiobis(6-t-butyl-m-cresol) consumed per kilogram body weight per day.

Table J4
Feed and Compound Consumption by Female Mice in the 2-Year Feed Study of 4,4′-Thiobis(6-*t*-Butyl-*m*-Cresol)

Week	0 ppm Feed (g/day)[a]	0 ppm Body Weight (g)	250 ppm Feed (g/day)	250 ppm Body Weight (g)	250 ppm Dose/Day[b] (mg/kg/day)	500 ppm Feed (g/day)	500 ppm Body Weight (g)	500 ppm Dose/Day (mg/kg/day)	1,000 ppm Feed (g/day)	1,000 ppm Body Weight (g)	1,000 ppm Dose/Day (mg/kg/day)
3	5.7	21.3	6.8	21.7	79	7.1	21.8	162	8.0	21.9	366
4	8.4	22.6	7.3	22.6	80	7.7	22.5	171	8.6	22.7	377
7	8.2	25.2	7.0	25.3	69	7.5	25.1	149	7.9	25.3	313
8	9.8	26.1	7.6	25.8	74	9.3	25.8	181	9.0	25.8	348
11	8.3	28.6	7.4	28.3	66	8.5	27.8	152	8.8	27.8	316
12	7.3	29.4	7.7	29.0	67	8.6	28.4	152	10.1	28.4	355
13	7.8	30.3	7.4	29.8	62	9.5	28.7	165	9.9	28.9	344
17	6.7	33.3	7.5	32.8	57	9.6	32.1	149	9.9	31.3	315
21	6.8	35.8	7.6	34.9	55	9.3	34.2	135	10.6	33.5	317
25	6.8	36.6	8.0	35.4	57	9.5	34.5	138	10.7	33.7	317
29	6.4	37.8	8.5	35.9	59	10.6	35.2	150	11.0	34.3	320
33	5.4	40.6	6.9	39.1	44	8.2	38.5	107	9.4	36.8	257
37	5.6	41.1	7.5	40.6	46	10.3	40.0	128	11.6	37.3	312
41	5.5	41.9	7.6	40.8	47	10.0	40.0	125	10.5	38.0	278
45	5.6	43.9	7.0	42.7	41	9.6	41.7	116	10.4	39.2	266
49	5.7	45.1	7.1	44.1	40	8.8	43.0	103	10.2	40.3	254
53	5.2	46.8	5.9	45.8	32	7.9	44.6	89	9.0	42.1	213
57	4.6	49.1	5.7	47.0	30	8.3	45.8	91	8.7	42.7	204
61	4.8	49.8	6.6	47.5	35	7.3	46.8	78	9.0	43.0	210
65	4.9	50.5	6.5	48.1	34	8.0	48.1	83	8.7	43.5	201
69	5.3	49.9	6.6	48.3	34	8.7	47.3	92	9.8	43.1	228
73	4.9	51.2	6.8	48.4	35	8.8	47.6	92	9.6	43.4	221
77	4.6	53.2	6.6	50.2	33	8.4	48.7	86	9.6	44.4	217
81	4.8	52.5	5.4	50.1	27	6.9	47.8	72	9.1	43.2	210
85	4.7	51.7	5.7	49.0	29	6.8	46.8	72	7.5	42.5	176
89	5.0	51.2	6.2	49.3	31	8.7	46.6	93	9.0	42.5	212
93	5.3	51.0	5.5	48.3	28	7.5	45.2	83	8.2	42.0	196
97	4.4	50.9	4.8	49.7	24	7.6	45.9	83	8.2	42.0	195
101	4.6	50.2	5.0	46.7	27	7.3	45.0	81	8.0	41.1	195
104	4.9	50.7	5.5	46.4	30	7.2	46.0	78	7.9	41.6	189
Mean for weeks											
1-13	7.9	26.2	7.3	26.1	71	8.3	25.7	162	8.9	25.8	345
13-52	6.1	39.6	7.5	38.5	50	9.5	37.7	128	10.5	36.0	293
53-104	4.9	50.6	5.9	48.2	31	7.8	46.6	84	8.7	42.6	205

[a] Grams of feed consumed per animal per day.
[b] Milligrams of 4,4′-thiobis(6-*t*-butyl-*m*-cresol) consumed per kilogram body weight per day.

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[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)	22.38 ± 0.83	21.30 - 24.00	21
Crude fat (% by weight)	5.40 ± 0.32	4.80 - 5.90	21
Crude fiber (% by weight)	3.54 ± 0.35	3.00 - 4.40	21
Ash (% by weight)	6.90 ± 0.24	6.49 - 7.27	21
Amino Acids (% of total diet)			
Arginine	1.308 ± 0.060	1.210 - 1.390	8
Cystine	0.306 ± 0.084	0.181 - 0.400	8
Glycine	1.150 ± 0.047	1.060 - 1.210	8
Histidine	0.576 ± 0.024	0.531 - 0.607	8
Isoleucine	0.917 ± 0.029	0.881 - 0.944	8
Leucine	1.946 ± 0.055	1.850 - 2.040	8
Lysine	1.270 ± 0.058	1.200 - 1.370	8
Methionine	0.448 ± 0.128	0.306 - 0.699	8
Phenylalanine	0.987 ± 0.140	0.665 - 1.110	8
Threonine	0.877 ± 0.042	0.824 - 0.940	8
Tryptophan	0.236 ± 0.176	0.107 - 0.671	8
Tyrosine	0.676 ± 0.105	0.564 - 0.794	8
Valine	1.103 ± 0.040	1.050 - 1.170	8
Essential Fatty Acids (% of total diet)			
Linoleic	2.393 ± 0.258	1.830 - 2.570	7
Linolenic	0.280 ± 0.040	0.210 - 0.320	7
Vitamins			
Vitamin A (IU/kg)	6,219 ± 1,145	4,100 - 8,240	21
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 - 6,300	4
α-Tocopherol (ppm)	37.95 ± 9.406	22.5 - 48.9	8
Thiamine (ppm)	20.00 ± 3.43	15.0 - 28.0	21
Riboflavin (ppm)	7.92 ± 0.87	6.10 - 9.00	8
Niacin (ppm)	103.38 ± 26.59	65.0 - 150.0	8
Pantothenic acid (ppm)	29.54 ± 3.60	23.0 - 34.0	8
Pyridoxine (ppm)	9.55 ± 3.48	5.60 - 14.0	8
Folic acid (ppm)	2.25 ± 0.73	1.80 - 3.70	8
Biotin (ppm)	0.25 ± 0.04	0.19 - 0.32	8
Vitamin B_{12} (ppb)	38.45 ± 22.01	10.6 - 65.0	8
Choline (ppm)	3,089 ± 328	2,400 - 3,430	8
Minerals			
Calcium (%)	1.28 ± 0.10	1.09 - 1.48	21
Phosphorus (%)	0.97 ± 0.06	0.85 - 1.10	21
Potassium (%)	0.883 ± 0.078	0.772 - 0.971	6
Chloride (%)	0.526 ± 0.092	0.380 - 0.635	8
Sodium (%)	0.313 ± 0.390	0.258 - 0.371	8
Magnesium (%)	0.168 ± 0.010	0.151 - 0.181	8
Sulfur (%)	0.280 ± 0.064	0.208 - 0.420	8
Iron (ppm)	360.54 ± 100	255.0 - 523.0	8
Manganese (ppm)	91.97 ± 6.01	81.70 - 99.40	8
Zinc (ppm)	54.72 ± 5.67	46.10 - 64.50	8
Copper (ppm)	11.06 ± 2.50	8.09 - 15.39	8
Iodine (ppm)	3.37 ± 0.92	1.52 - 4.13	6
Chromium (ppm)	1.79 ± 0.36	1.04 - 2.09	8
Cobalt (ppm)	0.681 ± 0.14	0.490 - 0.780	4

TABLE K4
Contaminant Levels in NIH-07 Rat and Mouse Ration

Contaminants	Mean ± Standard Deviation[a]	Range	Number of Samples
Arsenic (ppm)	0.23 ± 0.17	0.05 - 0.65	21
Cadmium (ppm)	<0.10		21
Lead (ppm)	0.23 ± 0.14	0.05 - 0.60	21
Mercury (ppm)[b]	0.05 ± 0.002	0.05 - 0.06	21
Selenium (ppm)	0.33 ± 0.09	0.20 - 0.55	21
Aflatoxins (ppb)	<5.0		21
Nitrate nitrogen (ppm)[c]	20.73 ± 9.30	0.30 - 34.0	21
Nitrite nitrogen (ppm)[c]	0.15 ± 0.14	<0.10 - 0.70	21
BHA (ppm)[d]	3.92 ± 6.10	<0.10 - 22.0	21
BHT (ppm)[d]	1.06 ± 0.56	<0.10 - 3.00	21
Aerobic plate count (CFU/g)[e]	281,000 ± 308,858	31,000 - 120,000	21
Coliform (MPN/g)[f]	161 ± 257	<3.00 - 1,100	21
E. coli (MPN/g)[g]	3.10 ± 0.30	<3.00 - 4.00	21
Total nitrosoamines (ppb)[h]	9.37 ± 4.18	3.90 - 19.40	21
N-Nitrosodimethylamine (ppb)[h]	7.10 ± 3.76	1.90 - 14.00	21
N-Nitrosopyrrolidine (ppb)[h]	2.28 ± 1.52	1.00 - 5.40	21
Pesticides (ppm)			
α-BHC[i]	<0.01		21
β-BHC	<0.02		21
γ-BHC	<0.01		21
δ-BHC	<0.01		21
Heptachlor	<0.01		21
Aldrin	<0.01		21
Heptachlor epoxide	<0.01		21
DDE	<0.01		21
DDD	<0.01		21
DDT	<0.01		21
HCB	<0.01		21
Mirex	<0.01		21
Methoxychlor	<0.05		21
Dieldrin	<0.01		21
Endrin	<0.01		21
Telodrin	<0.01		21
Chlordane	<0.05		21
Toxaphene	<0.1		21
Estimated PCBs	<0.2		21
Ronnel	<0.01		21
Ethion	<0.02		21
Trithion	<0.05		21
Diazinon	<0.1		21
Methyl parathion	<0.02		21
Ethyl parathion	<0.02		21
Malathion	0.15 ± 0.19	0.05 - 0.85	21
Endosulfan I	<0.01		21
Endosulfan 2	<0.01		21
Endosulfan sulfate	<0.03		21

[a] For values less than the limit of detection, the detection limit is given for the mean.
[b] The lot milled 4 December 1986 contained 0.06 ppm; all other lots contained 0.05 ppm or less.
[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] The lot milled 5 June 1987 contained 0.04 MPN/g; all others lots were less than or equal to the detection limit.
[h] All values were corrected for percent recovery.
[i] BHC is hexachlorocyclohexane or benzene hexachloride.

APPENDIX L
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via serology on sera from extra (sentinel) animals in the study rooms. These animals 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 first week of the 2-year study, serum samples were collected from 12 male and 10 female rats for murine virus assays. Inadequate blood samples were collected from two male rats due to their small size and two additional male rats were bled to provide adequate samples for analysis. Two shipments of rats were used in the study and serum samples were collected from rats of both shipments. Serum samples were also collected from as many as 10 male and 10 female rats at 6, 12, 15, and 18 months into the study and from five male and five female 2,500 ppm rats at the end of the study. Blood from each collection was appropriately processed, shipped to Microbiological Associates (Bethesda, MD), and screened for the following:

Method of Analysis	Time of Analysis
ELISA	
Mycoplasma arthritidis	24 months
Mycoplasma pulmonis	24 months
PVM (pneumonia virus of mice)	Study initiation, 6, 12, 15, 18, and 24 months
RCV/SDA	
(Rat coronavirus/sialodacryoadenitis virus)	Study initiation, 6, 12, 15, 18, and 24 months
Sendai	Study initiation, 6, 12, 15, 18, and 24 months
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	Study initiation, 6, 12, 15, 18, and 24 months
KRV (Kilham rat virus)	Study initiation, 6, 12, 15, 18, and 24 months

Mice

Serum samples for viral screening were collected from five male and five female mice prior to the beginning of the 2-year studies. Serum samples were also collected from sentinel animals at 6, 12, and 18 months into the study, and from five male and five female animals in the 1,000 ppm group at the end of the study. Sera were processed appropriately, shipped to Microbiological Associates, and screened for the following:

Method of Analysis	Time of Analysis
ELISA	
Ectromelia virus	Preinitiation, 6, 12, 18, and 24 months
GDVII (encephalomyelitis)	Preinitiation, 6, 12, 18, and 24 months
LCM (lymphocytic choriomeningitis virus)	6, 12, and 18 months
MVM (minute virus of mice)	6, 12, and 18 months
Mouse adenoma virus	Preinitiation, 6, 12, 18, and 24 months
MHV (mouse hepatitis virus)	Preinitiation, 6, 12, 18, and 24 months
M. pulmonis	24 months
PVM	Preinitiation, 6, 12, 18, and 24 months
Reovirus 3	Preinitiation, 6, 12, 18, and 24 months
Sendai	Preinitiation, 6, 12, 18, and 24 months
Hemagglutination Inhibition	
MVM	Preinitiation
Papovavirus	Preinitiation, 6, 12, 18, and 24 months
Polyoma virus	Preinitiation, 6, 12, 18, and 24 months
Immunofluorescent Assay	
EDIM (epizootic diarrhea of infant mice)	Preinitiation, 6, 12, 18, and 24 months
LCM	Preinitiation and 24 months
MVM	24 months
MCMV (murine cytomegalovirus)	24 months
Reovirus 3	18 months

The serology results for sentinel animals are presented in Table L1.

TABLE L1
Murine Virus Antibody Determinations for Rats and Mice in the 2-Year Feed Studies of 4,4'-Thiobis(6-*t*-Butyl-*m*-Cresol)

	Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
Rats			
	Study initiation	0/20	None positive
	6 months	0/20	None positive
	12 months	0/20	None positive
	15 months	0/10	None positive
	18 months	0/9	None positive
	24 months	0/10	None positive
Mice			
	Study initiation	0/10	None positive
	6 months	0/10	None positive
	12 months	0/10	None positive
	18 months	2/10	EDIM
	24 months	0/10	None positive

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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

TR No.	CHEMICAL
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
433	Tricresyl Phosphate
434	1,3-Butadiene
437	Hexachlorocyclopentadiene
440	Ozone and Ozone/NNK
443	Oxazepam

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