NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 332

TOXICOLOGY AND CARCINOGENESIS STUDIES OF 2-MERCAPTOBENZOTHIAZOLE

(CAS NO. 149-30-4)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

NATIONAL TOXICOLOGY PROGRAM

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

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF 2-MERCAPTOBENZOTHIAZOLE

(CAS NO. 149-30-4)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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May 1988

NTP TR 332

NIH Publication No. 88-2588

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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NOTE TO THE READER

This study was performed under the direction of the National Institute of Environmental Health Sciences as a function of the National Toxicology Program. The studies described in this Technical Report have been conducted in compliance with NTP chemical health and safety requirements and must meet or exceed all applicable Federal, state, and local health and safety regulations. Animal care and use were in accordance with the U.S. Public Health Service Policy on Humane Care and Use of Animals. All NTP toxicology and carcinogenesis studies are subjected to a data audit before being presented for public peer review.

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

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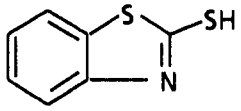

2-MERCAPTOBENZOTHIAZOLE

CAS No. 149-30-4

$C_7H_5NS_2$ Molecular weight 167.25

Synonyms and trade names: Captax, Dermacid, Mertax, Thiotax, 2(3H)-Benzothiazolethione, 2-Benzothiazolyl mercaptan

ABSTRACT

Toxicology and carcinogenesis studies of technical-grade 2-mercaptobenzothiazole (96%-97% pure), a rubber accelerant and preservative, were conducted by administering the chemical by gavage in a corn oil vehicle to groups of F344/N rats and B6C3F$_1$ mice of each sex for 16 days, 13 weeks, or 2 years. 2-Mercaptobenzothiazole was nominated for study by the National Institute of Environmental Health Sciences and the National Institute for Occupational Safety and Health.

Sixteen-Day and Thirteen-Week Studies: In 16-day studies, mean body weight gains of rats receiving 2,500 mg/kg were 6-7 g lower than those of vehicle controls; 4/5 male and 5/5 female mice dosed with 3,000 mg/kg and 4/5 female mice dosed with 1,500 mg/kg died; lethargy and prostration occurred in most of these animals after gavage. Based on these results, doses selected for both species in the 13-week studies were 0, 94 (mice only), 188, 375, 750, and 1,500 mg/kg.

In 13-week studies, no chemical-related deaths occurred in rats, but body weight gains in males dosed with 1,500 mg/kg and in females dosed with 750 or 1,500 mg/kg were lower than those in the vehicle control groups. Hepatomegaly occurred at the two highest doses in males and at all doses in females; however, no microscopic pathologic changes were noted in any tissue. More than half the mice dosed with 1,500 mg/kg died, but no compound-related body weight changes occurred. Clinical signs in mice were dose related and included lethargy in animals dosed with 375 mg/kg and lacrimation, salivation, and clonic seizure in some dosed with 750 or 1,500 mg/kg. No association between these clinical signs of toxicity and gross or microscopic pathologic effects was observed. Doses selected for the 2-year studies were 0, 375, and 750 mg/kg for male rats and for mice of each sex and 0, 188, or 375 mg/kg for female rats.

Body Weight and Survival in the Two-Year Studies: Fifty animals of each species and sex were administered 2-mercaptobenzothiazole in corn oil by gavage 5 days per week for 103 weeks. Administration of 2-mercaptobenzothiazole resulted in decreased survival in dosed male rats (vehicle control, 42/50; low dose, 22/50; high dose, 20/50) and in the high dose group of female mice (37/50; 39/50; 22/50) but not in female rats (28/50; 31/50; 25/50) or in male mice (38/50; 33/50; 30/50). No effect on body weight gain in dosed rats was observed; in dosed mice, minor reductions occurred between weeks 3 and 64, with recovery thereafter. Postgavage lethargy and prostration occurred frequently in dosed rats and mice.

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: The severity of nephropathy was increased in dosed male rats. Ulcers and inflammation of the forestomach were prevalent in dosed rats, as were increased incidences of epithelial hyperplasia and hyperkeratosis in male rats, but no neoplasms of the forestomach were observed. There were no increases of nonneoplastic lesions in mice which were considered to be compound related.

The incidences of a variety of tumors were increased in rats dosed with 2-mercaptobenzothiazole; some of the increased incidences were not dose related. In low dose male rats, increased incidences ($P<0.01$) were observed for mononuclear cell leukemia (7/50; 16/50; 3/50) and pancreatic acinar cell adenomas (2/50; 13/50; 6/49). Increased tumor incidences with dose-related trends ($P<0.05$) included pituitary gland adenomas in females (15/49; 24/50; 25/50), preputial gland adenomas or carcinomas (combined) in males (1/50; 6/50; 5/50), adrenal gland pheochromocytomas or malignant pheochromocytomas (combined) in males (18/50; 27/50; 24/49), and pheochromocytomas in females (1/50; 5/50; 6/50). These tumors were observed at significantly greater incidences ($P\leq0.05$) in the high dose groups than in the vehicle controls.

An increased incidence ($P=0.028$) of hepatocellular adenomas or carcinomas (combined) was observed only in low dose female mice (4/50; 12/49; 4/50). No significant increases in tumor incidences were seen in male mice.

Genetic Toxicology: 2-Mercaptobenzothiazole was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 with or without metabolic activation. In the presence of rat liver S9, 2-mercaptobenzothiazole increased the frequency of chromosomal aberrations and sister chromatid exchanges (SCEs) in Chinese hamster ovary (CHO) cells, as well as mutations at the TK locus of mouse L5178Y lymphoma cells.

Audit: The data, documents, and pathology materials from the 2-year studies of 2-mercaptobenzothiazole were audited at the NTP Archives. The audit findings show that the conduct of the studies is documented adequately and support the data and results given in this Technical Report.

Conclusions: Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenic activity** of 2-mercaptobenzothiazole for male F344/N rats, indicated by increased incidences of mononuclear cell leukemia, pancreatic acinar cell adenomas, adrenal gland pheochromocytomas, and preputial gland adenomas or carcinomas (combined). There was *some evidence of carcinogenic activity* for female F344/N rats, indicated by increased incidences of adrenal gland pheochromocytomas and pituitary gland adenomas. There was *no evidence of carcinogenic activity* of 2-mercaptobenzothiazole for male B6C3F$_1$ mice dosed with 375 or 750 mg/kg. There was *equivocal evidence of carcinogenic activity* for female B6C3F$_1$ mice, indicated by increased incidences of hepatocellular adenomas or carcinomas (combined).

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 8.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 11-12.

SUMMARY OF THE TWO-YEAR GAVAGE AND GENETIC TOXICOLOGY STUDIES OF 2-MERCAPTOBENZOTHIAZOLE

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Doses			
375 or 750 mg/kg 2-mercaptobenzothiazole in corn oil, 5 d/wk	188 or 375 mg/kg 2-mercaptobenzothiazole in corn oil, 5 d/wk	375 or 750 mg/kg 2-mercaptobenzothiazole in corn oil, 5 d/wk	375 or 750 mg/kg 2-mercaptobenzothiazole in corn oil, 5 d/wk
Survival rates in 2-year study			
42/50; 22/50; 20/50	28/50; 31/50; 25/50	38/50; 33/50; 30/50	37/50; 39/50; 22/50
Nonneoplastic effects			
Forestomach lesions; nephropathy	Forestomach lesions	None	None
Neoplastic effects			
Mononuclear cell leukemia and pancreatic acinar cell adenomas--low dose only; adrenal gland pheochromocytomas and malignant pheochromocytomas--trend and high dose; preputial gland adenomas or carcinomas (combined)--trend and dosed	Adrenal gland pheochromocytomas and pituitary gland adenomas--trend and high dose	None	Hepatocellular adenomas or carcinomas (combined)--low dose only
Level of evidence of carcinogenic activity			
Some evidence	Some evidence	No evidence	Equivocal evidence
Genetic toxicology			
Not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 with or without metabolic activation; significant increases in chromosomal aberrations and SCEs in CHO cells with S9; mutagenic at TK locus of mouse L5178Y lymphoma cells with S9.			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

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

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

These considerations together with the definitions as written should be used as composite guidelines for selecting one of the five categories. Additionally, the following concepts (as patterned from the International Agency for Research on Cancer Monographs) have been adopted by the NTP to give further clarification of these issues:

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

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of 2-Mercaptobenzothiazole is based on the 13-week studies that began in November 1980 (rats) or August 1980 (mice) and ended in February 1981 (rats) or November 1980 (mice) and on the 2-year studies that began in July 1981 and ended in July 1983 at Physiological Research Laboratories (Minneapolis, Minnesota).

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The members of the Peer Review Panel who evaluated the draft Technical Report on 2-mercaptobenzothiazole on March 4, 1987, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF 2-MERCAPTOBENZOTHIAZOLE

On March 4, 1987, the draft Technical Report on the toxicology and carcinogenesis studies of 2-mercaptobenzothiazole received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. M. Dieter, NTP, began the discussion by reviewing the experimental design, results, and proposed conclusions (some evidence of carcinogenic activity for male and female rats, no evidence of carcinogenic activity for male mice, equivocal evidence of carcinogenic activity for female mice).

Dr. Hooper, a principal reviewer, agreed with the conclusions as written. However, he argued that increased incidences of preputial gland adenomas or carcinomas (combined) should be included in support of the conclusion for male rats. Dr. Dieter agreed that it was valid to include the preputial gland tumors along with the mononuclear cell leukemia as some evidence of carcinogenic activity and that the conclusion and other appropriate sections of the Technical Report could be revised to reflect this change. Dr. S. Eustis, NIEHS, commented that this tumor was not originally included in the list of evidence because although the incidence of preputial gland tumors in this study was twice the historical mean, the incidence also fell within the historical range. Dr. Hooper noted the lack of tumors in high dose male rats compared with an elevated tumor incidence in low dose male rats for several neoplasms, including mononuclear cell leukemia. Dr. Dieter said that there was just one other tumor besides mononuclear cell leukemia, pancreatic acinar cell adenomas in male rats, for which there was an effect only at the low dose. Dose-related increases occurred in two tumor types, including adrenal gland tumors in male and female rats and pituitary gland tumors in female rats.

As a second principal reviewer, Dr. Popp agreed in principle with the conclusions. He said that the issue for decision was whether the conclusions for rats should remain as written or be lowered to equivocal evidence of carcinogenic activity.

As a third principal reviewer, Dr. Chinchilli agreed with the conclusions as written. He asked that an incidence table for mononuclear cell leukemia in female rats be added to the Results section.

Dr. Harold Grice, Cantox, Inc. Canada, representing the Chemical Manufacturers Association, mentioned several factors that he felt made interpretation of the increased tumor rates in male rats difficult. These factors included reduced survival in both dose groups, compound-induced kidney toxicity, gavage stress, and postgavage lethargy. Dr. Grice thought that the conclusion for male rats should be lowered to equivocal evidence of carcinogenic activity.

Since the low dose animals were placed in the cage racks nearest the room fluorescent lights and because cages were not rotated in these studies, there was speculation as to whether photoactivation of the chemical might have been a factor in toxicity/carcinogenicity. Although the incidence of eye lesions (retinopathy and cataracts) could be correlated with cage position, there was no consensus that increased tumor rates in low dose rats could be associated with exposure to light.

In other discussion, Dr. Hooper thought that the small but significant increase in renal neoplasms in male rats (tubular cell adenomas and transitional cell papillomas/carcinomas) might have been chemically associated. Dr. Eustis said that the renal tumors were not considered chemically related because the two cell types are generally not combined and the tumors were split between dose groups.

Dr. Hooper moved that the Technical Report on 2-mercaptobenzothiazole be accepted with the revisions discussed and the conclusions as written for male and female rats, some evidence of carcinogenic activity, for male mice, no evidence of carcinogenic activity, and for female mice, equivocal evidence of carcinogenic activity. He asked that the increased incidences of preputial gland adenomas or carcinomas (combined) in male rats be cited. Dr. Gallo seconded the motion, which was approved unanimously with seven votes.

I. INTRODUCTION

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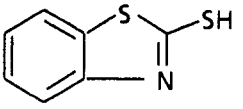

2-MERCAPTOBENZOTHIAZOLE

CAS No. 149-30-4

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Synonyms and trade names: Captax, Dermacid, Mertax, Thiotax, 2(3H)-Benzothiazolethione, 2-Benzothiazolyl mercaptan

2-Mercaptobenzothiazole forms pale, yellow, monoclinic needles or leaflets with a disagreeable odor; it has a melting point of 180.2°-181.7° C and a specific gravity of 1.42. The chemical is insoluble in water but soluble in alcohol, acetone, benzene, and chloroform (Hawley, 1981). The octanol:water partition coefficient is 41:1 (Hansch and Leo, 1979). 2-Mercaptobenzothiazole exists in the thioketo form in the solid crystalline state but converts to the thioenol form upon reaction with metals (Santodonato et al., 1976). 2-Mercaptobenzothiazole is a weak acid and will form salts in basic solutions with a wide variety of metal ions. In acid solutions in the presence of iron, 2-mercaptobenzothiazole is reduced to benzothiazole, whereas in the presence of ozone and potassium iodide, it dimerizes to 2-mercaptobenzothiazole disulfide.

Production, Use, and Exposure

2-Mercaptobenzothiazole is produced by reacting aniline, carbon disulfide, and sulfur at elevated temperature and pressure; generally, the product is then purified by dissolving it in a base to remove the dissolved organics. Reprecipitation is accomplished by the addition of acid (Kirk-Othmer, 1982).

2-Mercaptobenzothiazole is produced in the United States by two major tire companies (Goodyear and Uniroyal) and by Monsanto Company. Production in the United States was 6,531,000 pounds in 1984 (USITC, 1985), and 198,414 pounds was imported in 1981 (USITC, 1983). The use of smaller tires on cars and trends toward reduction in length of automobile trips may result in a decline in future needs for production of rubber-processing chemicals such as 2-mercaptobenzothiazole (Stinson, 1983). 2-Mercaptobenzothiazole, however, serves as an intermediate for other sulfenamide derivatives (Santadonato et al., 1976), so these production figures may be underestimated. 2-Mercaptobenzothiazole is used commercially as an accelerant in the rubber vulcanization process and as a preservative for textile or cordage materials; the sodium salt is used as a corrosion inhibitor in petroleum products.

2-Mercaptobenzothiazole was found to contaminate medicinal products that came in contact with rubber stoppers made with this accelerator (Petersen et al., 1981) and was found in aqueous extracts of rubber baby bottle nipples (Blosczyk and Doemling, 1982). Since manufacturing processes occur in closed, continuous systems (Santadonato et al., 1976), employee exposure to 2-mercaptobenzothiazole would probably occur through dermal contact or inhalation of dust during packaging, transport, or the use of rubber products. Consumer exposure occurs through direct contact with stretch garments (Bauer, 1972), shoes (Fisher, 1977), rubber pharmaceutical products (Petersen et al., 1981), and baby bottle nipples containing 2-mercaptobenzothiazole (Blosczyk and Doemling, 1982).

Acute Toxicity

The reported oral LD_{50} values in mice and rats range between 2,000 and 3,000 mg/kg (Vorob'eva and Mezentsera, 1968; Vanderbilt, 1975; Guess and O'Leary, 1969; Monsanto, 1982; Uniroyal, 1975), and intraperitoneal LD_{50} values range between 100 and 400 mg/kg in mice (Guess and O'Leary, 1969; Doull et al., 1962). 2-Mercaptobenzothiazole (110 or 300 mg/kg administered by intraperitoneal injection) was

shown to exert neurotoxic and hepatotoxic effects in mice after acute or short-term exposure (Johnson et al., 1970; Guess and O'Leary, 1969).

Dermal Toxicity

2-Mercaptobenzothiazole was shown to be a very strong contact allergen in guinea pigs (Maurer et al., 1979) but was judged a moderate contact sensitizer in humans (Goodwin et al., 1981). Rubber additives, such as salts of 2-mercaptobenzothiazole, have been reported to cause dermatitis in humans (Bauer, 1972). 2-Mercaptobenzothiazole was more soluble in a salt solution approximating human perspiration than in water (Ito et al., 1979). The sensitizing properties of 2-mercaptobenzothiazole were reviewed by Fisher (1973) and Santodonato et al. (1976), who noted that allergic contact dermatitis in humans is often caused by rubber products.

Reproductive Toxicity

Embryotoxic effects of 2-mercaptobenzothiazole in rats were reported (Aleksandrov, 1982), but these results were not corroborated in more extensive studies in rats administered 200 mg/kg 2-mercaptobenzothiazole by intraperitoneal injection on days 1-15 of gestation (Hardin et al., 1981). There were no chemically related histopathologic effects in maternal tissues, and no maternal toxicity, fetal toxicity, or teratogenesis was observed. In a long-term study, no cumulative effects on reproduction or lactation were observed in rats fed ad libitum 5,000 ppm of a formulation containing 2.4% 2-mercaptobenzothiazole and 27.6% dimethyldithiocarbamate through the second generation (Lehman, 1965).

Biochemical Effects

Biochemical studies suggested that 2-mercaptobenzothiazole was capable of enzyme inhibition in vivo and in vitro (Johnson et al., 1970; Grassetti et al., 1970). Dopamine β-hydroxylase, an enzyme in the pathway for norepinephrine biosynthesis, was inhibited 40% below control values in brain tissue taken from mice 1 hour after a 200 mg/kg intraperitoneal injection of 2-mercaptobenzothiazole. In the same tissues used for in vitro studies, there was 47% inhibition after less than 7 μM 2-mercaptobenzothiazole was added to the reaction mixture. Grassetti et al. (1970) showed that 1 mM 2-mercaptobenzothiazole added in vitro affected carbohydrate metabolism in Ehrlich ascites tumor cells, causing a slight inhibition of the hexose monophosphate shunt pathway and a moderate stimulation of the tricarboxylic acid cycle. An intraperitoneal injection of 100 mg/kg 2-mercaptobenzothiazole lowered blood glucose concentrations in rabbits 5 hours after administration (Chiba, 1969).

Absorption, Distribution, and Metabolism

Absorption, tissue distribution, and metabolism studies of radiolabeled 2-mercaptobenzothiazole in guinea pigs showed that the chemical was absorbed through the skin and that abrasion increased this rate; initially, the kidney, liver, and thyroid gland were the principal organs of uptake, with the thyroid gland ultimately attaining the highest concentration of 2-mercaptobenzothiazole 48 hours after subcutaneous injection; 90% of the compound was conjugated with glucuronides and sulfates and excreted in the urine 6 hours after injection (Nagamatsu et al., 1979). The urinary metabolites of [^{35}S-mercapto]2-mercaptobenzothiazole in rats dosed by intraperitoneal injection consisted of conjugates of glutathione, glucuronic acid, and inorganic sulfate (Colucci and Buyske, 1965); these authors proposed three possible metabolic pathways for 2-mercaptobenzothiazole which started with a benzothiazole-2-glutathione metabolite and proceeded either through benzothiazole-2-cysteine to benzothiazole-2-mercapturic acid that was eliminated in the urine, or to benzothiazole-2-mercaptan that then was eliminated in the urine as either benzothiazole-2-mercaptoglucuronide or as inorganic sulfate.

Genetic Toxicology

2-Mercaptobenzothiazole demonstrated no mutagenic activity in bacteria, but it is clearly clastogenic as well as genotoxic to mammalian cells in culture. Donner et al. (1983) found no increase in *Salmonella typhimurium his*$^+$ revertant colonies after exposure to 2-mercaptobenzothiazole; an early study by Szybalski (1958) showed no induction of mutations in *Escherichia coli* strain SD-4-73 after exposure to 2-mercaptobenzothiazole. Neither the doses used nor the source and purity of the 2-mercaptobenzothiazole were provided by the authors. Two laboratories investigated the mutagenicity of 2-mercaptobenzothiazole for NTP in the *S. typhimurium*/microsome assay with a preincubation protocol with strains TA98, TA100, TA1535, and TA1537 with and without Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9. In the study conducted at EG&G Mason Research Institute, questionable mutagenic activity was noted only in strain TA98 in the presence, but not in the absence, of S9 from either species. The Case Western Reserve University study detected no mutagenic activity in any of the four strains of *S. typhimurium* tested under any conditions (Zeiger et al., 1987; Appendix E, Table E1).

Exposure of V79 cells to doses of 50-300 µg/ml 2-mercaptobenzothiazole for 4 hours resulted in no increase in 6-thioguanine resistant mutants (Donner et al., 1983). Results from a CHO/HGPRT forward mutation assay conducted both with and without exogenous metabolic activation, at 2-mercaptobenzothiazole doses of up to 300 µg/ml, were negative (Pharmakon, 1984). The results of a mouse lymphoma forward mutation assay showed mutagenic activity for 2-mercaptobenzothiazole at the highest doses tested (100 and 150 µg/ml) in the absence of exogenous metabolic activation with concomitant extreme toxicity (Litton, 1985). With S9 activation, toxicity was reduced, and a significant increase in mutations was again noted at the highest doses tested (80 and 100 µg/ml). 2-Mercaptobenzothiazole induced forward mutations in mouse L5178Y lymphoma cells only in the presence of Aroclor 1254-induced male F344 rat liver S9 (Table E2).

In NTP cytogenetic assays, significant increases in chromosomal aberrations and sister chromatid exchanges (SCEs) were observed in cultured Chinese hamster ovary (CHO) cells after exposure to 2-mercaptobenzothiazole at 351-451 µg/ml in the presence of Aroclor 1254-induced male Sprague Dawley rat liver S9; no significant induction of chromosomal aberrations or SCEs was observed without S9 (Tables E3 and E4). Although the in vitro cytogenetic data indicate that the chemical is a clastogen, intraperitoneal injection of 300 mg/kg 2-mercaptobenzothiazole dissolved in corn oil did not produce a significant increase in the number of micronucleated polychromatic erythrocytes in the bone marrow of CD-1 mice (Pharmakon, 1984).

One published study presents data from a series of short-term tests designed to evaluate the genotoxic activity of four rubber accelerators, including 2-mercaptobenzothiazole disulfide, a structural analog resulting from the dimerization of 2-mercaptobenzothiazole (Hinderer et al., 1983). Results showed that 2-mercaptobenzothiazole disulfide (80% pure and containing 30 ppm morpholine, a nonmutagen in NTP Salmonella studies; Haworth et al., 1983) did not induce gene reversion in Salmonella and *E. coli* WP2 uvrA$^-$ with or without metabolic activation, was negative in the BALB/3T3 transformation assay in the absence of S9, and did not induce chromosomal aberrations in cultured CHO cells with or without S9. The maximum concentration of 2-mercaptobenzothiazole disulfide tested in the chromosomal aberration assay was 10.0 µg/ml, whereas the NTP cytogenetic tests used 2-mercaptobenzothiazole at concentrations in excess of 350 µg/ml. Exposure of mouse L5178Y lymphoma cells to 2-mercaptobenzothiazole disulfide in the absence of exogenous metabolic activation resulted in no increase in forward mutations at the TK$^{+/-}$ locus; in the presence of activation, the two highest doses (15 and 30 µg/ml) did produce a significant increase over background rates in the number of mutant colonies.

Carcinogenicity

2-Mercaptobenzothiazole did not cause increased tumor incidences in two hybrid mouse strains (C57BL/6 × C3H/Anf and C57BL/6 × AKR)

after 18 months of chemical administration (Innes et al., 1969). The F_1 generation of hybrids was administered 100 mg/kg 2-mercaptobenzothiazole in 0.5% gelatin by gavage from 7 to 28 days of age and then was fed 323 ppm 2-mercaptobenzothiazole ad libitum for the remainder of the study. There were 18 mice of each sex and strain per dose group and four untreated control groups containing 12-18 mice of each sex and strain. Lehman (1965) also reported no increase in tumor incidence in 10 rats (unspecified strain) of each sex fed a mixture of 5,000 ppm of a formulation containing 2.4% 2-mercaptobenzothiazole and 27.6% dimethyldithiocarbamate (a dietary 2-mercaptobenzothiazole concentration of 120 ppm) for 2 years.

Study Rationale

2-Mercaptobenzothiazole was nominated for study by the National Institute of Environmental Health Sciences and the National Institute for Occupational Safety and Health because of potential widespread human exposure and to determine structure-activity relationships with other sulfur-containing compounds. Since the salts of 2-mercaptobenzothiazole are hydrolyzed to the parent compound in vivo and these salts are marketed as fungicides and bactericides (Foltinova and Bloeckinger, 1970), the genotoxic effects of noncytocidal concentrations of 2-mercaptobenzothiazole were also examined.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF 2-MERCAPTOBENZOTHIAZOLE

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

FIRST SIXTEEN-DAY STUDIES

SECOND SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

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

PROCUREMENT AND CHARACTERIZATION OF 2-MERCAPTOBENZOTHIAZOLE

2-Mercaptobenzothiazole (Captax) was obtained in two lots from R.T. Vanderbilt Co., Inc. (Norwalk, Connecticut) (Table 1). Purity and identity analyses of both lots were conducted at Midwest Research Institute (MRI) (Kansas City, Missouri). MRI reports on the analyses performed in support of the 2-mercaptobenzothiazole studies are on file at NIEHS. Chemical identity was confirmed by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy (Figures 1 to 4).

Lot no. V10479 was obtained as a light green powder with a melting point of 175°-178° C; lot no. 39-7-D was obtained as a light green-yellow powder. The purity of the two lots was determined by elemental analysis, water analysis, nonaqueous titration of the sulfhydryl group, thin-layer chromatography, and high-performance liquid chromatography. Cumulative data indicated that lot no. V10479 was approximately 96% pure and lot no. 39-7-D was approximately 97% pure. The water content of lot no. V10479 by Karl Fischer titration was 1.35%, and that of lot no. 39-7-D was 0.25%. Titration of the sulfhydryl group with 0.1 N tetrabutylammonium hydroxide indicated that lot no. V10479 was 96.3% pure and lot no. 39-7-D, 96.8% pure. A major spot, three trace impurities, and one slight trace impurity in lot no. V10479 were detected by thin-layer chromatography with silica gel plates and a chloroform:methanol (96:4) solvent system; a major spot, a minor spot, a trace impurity, and a slight trace impurity in lot no. 39-7-D were detected by ultraviolet (254 and 366 nm) light and an iodoplatinate spray. Thin-layer chromatography with a hexanes:diethylether (40:60) solvent system detected a major spot, three trace impurities, and one slight trace impurity in lot no. V10479 and a major spot, a trace impurity, and a slight trace impurity in lot no. 39-7-D. High-performance liquid chromatography on a μBondapak C_{18} column with a water/1% acetic acid:acetonitrile/1% acetic acid (49:51) mobile phase at a flow rate of 1 ml/minute and detection at 313 nm indicated six impurities with peak areas greater than 0.1% that of the major peak and a relative combined area of 2.2% (lot no. V10479) and five impurities with peak areas greater than 0.1% and a relative combined area of 1.7% (lot no. 39-7-D).

Stability studies performed by the same high-performance liquid chromatographic system with a 50:50 solvent ratio at a flow rate of 1.5 ml/minute and detection at 254 nm indicated that 2-mercaptobenzothiazole was stable on storage for 2 weeks at 60° C. Further confirmation of the stability of the bulk chemical during the toxicity studies (storage at 25° C) was obtained by titration with 0.1 N tetrabutylammonium hydroxide and the same high-performance liquid chromatographic system that was used for the stability studies. No degradation was seen over the course of the studies.

TABLE 1. IDENTITY AND SOURCE OF 2-MERCAPTOBENZOTHIAZOLE USED IN THE GAVAGE STUDIES

First Sixteen-Day Studies	Second Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Lot Numbers Used V10479	V10479	V10479	V10479, 39-7-D
Date of Initial Use 2/11/80	4/28/80	Rats--11/17/80; mice--8/18/80	V10479--7/14/81 (rats), 7/28/81 (mice); 39-7-D--1/21/83
Supplier R.T. Vanderbilt Co., Inc. (Norwalk, CT)	Same as first 16-d studies	Same as first 16-d studies	Same as first 16-d studies

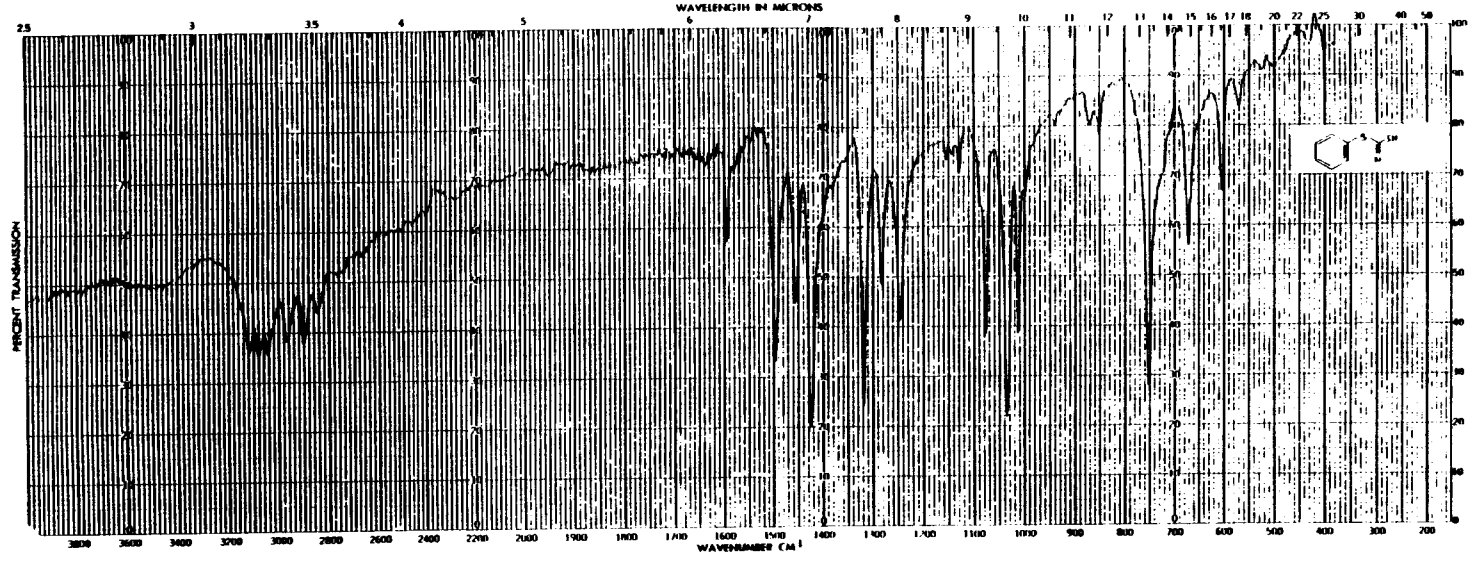


FIGURE 1. INFRARED ABSORPTION SPECTRUM OF 2-MERCAPTOBENZOTHIAZOLE (LOT NO. V10479)

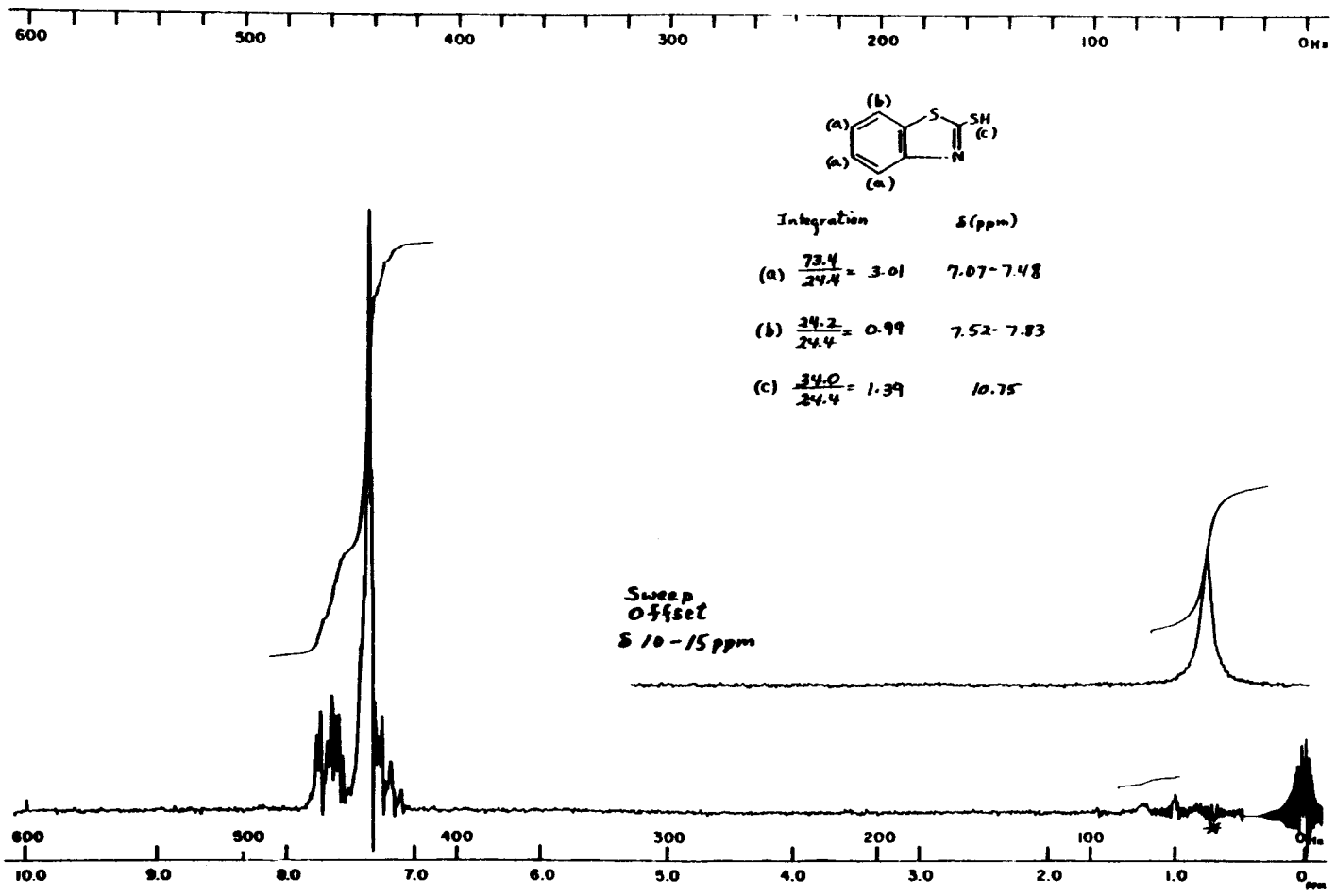


FIGURE 2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF 2-MERCAPTOBENZOTHIAZOLE (LOT NO. V10479)

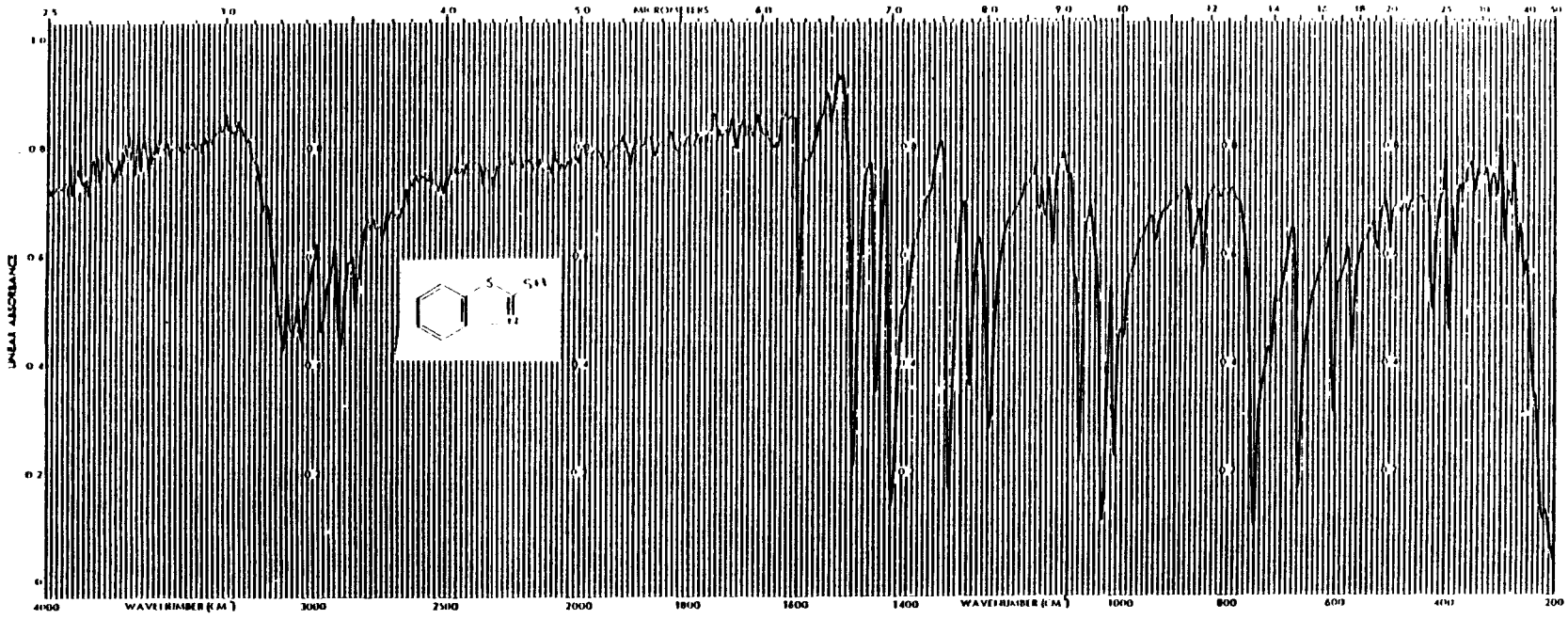


FIGURE 3. INFRARED ABSORPTION SPECTRUM OF 2-MERCAPTOBENZOTHIAZOLE (LOT NO. 39-7-D)

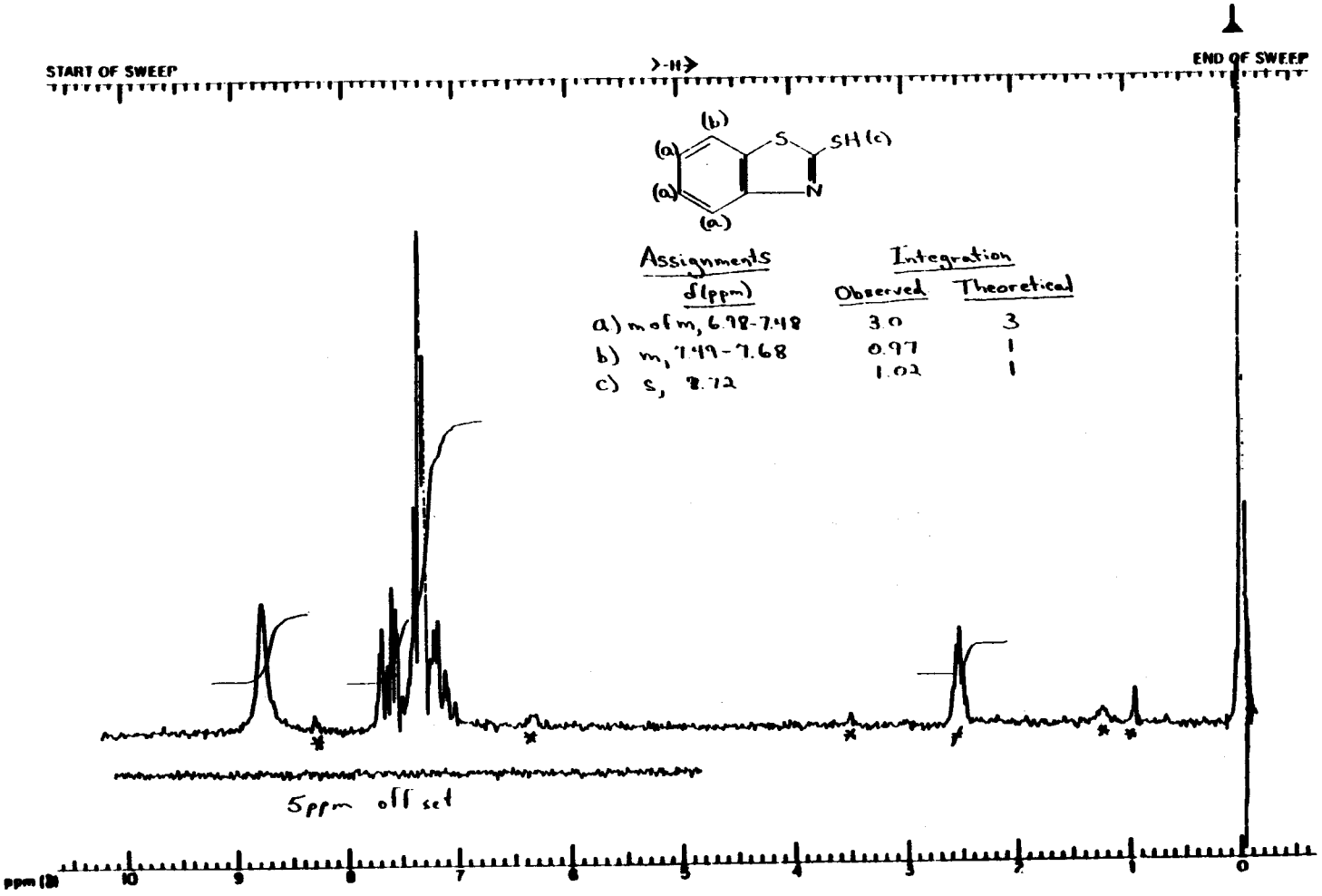


FIGURE 4. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF 2-MERCAPTOBENZOTHIAZOLE (LOT NO. 39-7-D)

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

Weighed amounts of 2-mercaptobenzothiazole and corn oil were mixed as described in Table 2. Stability studies of dose mixtures were performed with high-performance liquid chromatography on a μBondapak C_{18} column with a water:acetonitrile (65:35) mobile phase at a flow rate of 1 ml/minute and ultraviolet detection at 313 nm after extraction with methanol; the studies indicated that 2-mercaptobenzothiazole (20 mg/ml) in corn oil was stable for at least 14 days when stored in the dark at room temperature or 5° C. Samples exposed to air and light for 3 hours at room temperature also showed no loss of 2-mercaptobenzothiazole.

Analyses for 2-mercaptobenzothiazole in dose mixtures were performed by the study and analytical chemistry laboratories by extracting samples with methanol and determining the absorption at 320 nm (study laboratory) or 322 nm (analytical chemistry laboratory). Dose mixtures were analyzed three times during the 13-week studies; concentrations of 2-mercaptobenzothiazole ranged from 91% to 109% of the target concentration (Table 3).

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

First Sixteen-Day Studies	Second Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation			
A Polytron® homogenizer operated at low intensity for 2 min was used to suspend 2-mercaptobenzothiazole in corn oil	Same as first 16-d studies	Similar to first 16-d studies	Same as first 16-d studies
Maximum Storage Time			
14 d	14 d	14 d	14 d
Storage Conditions			
Room temperature in the dark	Same as first 16-d studies	Same as first 16-d studies	25° C in the dark

TABLE 3. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 2-MERCAPTOBENZOTHIAZOLE

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (mg/ml) (a)	Determined as Percent of Target
09/24/80	9.4	8.5	91
	18.8	17.5	93
	37.5	37.1	99
	75.0	73.7	98
	150.0	158.1	105
11/26/80	37.5	37.7	101
	75.0	73.7	98
	150.0	146.3	98
	300.0	290.5	97
02/04/81	37.5	40.8	109
	75.0	75.8	101
	150.0	152.5	102
	300.0	289.0	96

(a) Results of duplicate analysis

During the 2-year studies, periodic analysis of dose preparations indicated that concentrations varied from 93.3% to 108.0% of the target concentration (Table 4). Because 42/42 dose mixtures analyzed were within 10% of the target concentration, it is estimated that the dose mixtures were within specifications 100% of the time. Results of periodic referee analyses performed by the analytical chemistry laboratory indicated generally good agreement with the results from the study laboratory (Table 5).

TABLE 4. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF 2-MERCAPTOBENZOTHIAZOLE

Date Mixed	Concentration of 2-Mercaptobenzothiazole in Corn Oil for Target Concentration (mg/ml) (a)		
	37.5	75.0	150.0
07/08/81	37.8	74.8	140.0
08/12/81	37.8	76.9	149.0
10/20/81	36.6	72.8	147.5
10/28/81	38.2	72.6	146.7
01/13/82	39.1	70.2	157.5
04/07/82	38.7	74.2	146.1
05/05/82	39.8	76.0	147.2
06/23/82	38.3	76.2	144.3
09/08/82	37.1	74.4	144.0
11/17/82	35.4	76.7	149.3
12/01/82	37.8	79.4	156.9
02/16/83	39.9	78.3	158.3
04/27/83	37.7	75.7	151.4
06/08/83	39.0	81.0	147.2
Mean (mg/ml)	38.1	75.7	149.0
Standard deviation	1.22	2.83	5.39
Coefficient of variation (percent)	3.2	3.7	3.6
Range (mg/ml)	35.4-39.9	70.2-81.0	144.0-158.3
Number of samples	14	14	14

(a) Results of duplicate analysis

TABLE 5. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK AND TWO-YEAR GAVAGE STUDIES OF 2-MERCAPTOBENZOTHIAZOLE

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (mg/ml)	
		Study Laboratory (a)	Referee Laboratory (b)
Thirteen-Week Studies			
09/24/80	150.0	158.1	134.0
11/26/80	37.5	37.7	36.0
Two-Year Studies			
07/08/81	150.0	140.0	145.0
05/05/82	37.5	39.8	37.1
11/17/82	75.0	76.7	75.0
04/27/83	150.0	151.4	144.0

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

FIRST SIXTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for 14 days before the studies began. Rats were 6 weeks old when placed on study, and mice were 6-8 weeks old. Groups of five males and five females were administered 0, 156, 313, 625, 1,250, or 2,500 mg/kg 2-mercaptobenzothiazole in corn oil by gavage (12 doses over 16 days). Rats and mice were observed twice per day and were weighed on days 1, 8, and 15. A necropsy was performed on all animals. Details of animal maintenance are presented in Table 6.

SECOND SIXTEEN-DAY STUDIES

Male and female B6C3F$_1$ mice were obtained from Harlan Industries and held for 19 days before the studies began. Mice were 5-6 weeks old when placed on study. Groups of five males and five females were administered 0, 188, 375, 750, 1,500, or 3,000 mg/kg 2-mercaptobenzothiazole in corn oil by gavage (12 doses over 16 days). Mice were observed twice per day and were weighed on days 1, 8, and 15. A necropsy was performed on all animals. Details of animal maintenance are presented in Table 6.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated administration of 2-mercaptobenzothiazole and to determine the doses to be used in the 2-year studies.

Four- to five-week-old male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories, observed for 19 days (rats) or 18 days (mice), and distributed to weight classes and then to cages according to a table of random numbers. Cages were assigned to dosed and vehicle control groups according to a table of random numbers. Groups of 10 rats of each sex were administered 0, 188, 375, 750, or 1,500 mg/kg 2-mercaptobenzothiazole in corn oil by gavage, 5 days per week for 13 weeks. Groups of 10 mice of each sex were administered 0, 94, 188, 375, 750, or 1,500 mg/kg 2-mercaptobenzothiazole on the same schedule. (The 13-week study in rats reported in this Technical Report was a second study. In the first study in rats, 3,000 mg/kg groups all died during week 1.) Animals were housed five per cage. Feed and water were available ad libitum. Further experimental details are summarized in Table 6.

Animals were checked two times per day; moribund animals were killed. Individual animal weights were recorded weekly. At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 6.

TWO-YEAR STUDIES

Study Design

Groups of 50 male rats and 50 male and 50 female mice were administered 0, 375, or 750 mg/kg 2-mercaptobenzothiazole in corn oil by gavage, 5 days per week for 103 weeks. Groups of 50 female rats were administered 0, 188, or 375 mg/kg 2-mercaptobenzothiazole in corn oil by gavage on the same schedule.

Source and Specifications of Animals

The male and female F344/N rats and B6C3F$_1$ (C57BL/6N, female × C3H/HeN MTV$^-$, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the Carcinogenesis Program. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Rats were shipped to the study laboratory at 4-5 weeks of age and mice, at 6 weeks of age. The animals were quarantined at the study laboratory for 13 days. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rats were 46 days old and the mice, 56 days old when placed on study. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix F).

TABLE 6. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF 2-MERCAPTOBENZOTHIAZOLE

First Sixteen-Day Studies	Second Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN			
Size of Study Groups			
5 males and 5 females of each species	5 male and 5 female mice	10 males and 10 females of each species	50 males and 50 females of each species
Doses			
0, 156, 313, 625, 1,250, or 2,500 mg/kg 2-mercaptobenzothiazole in corn oil by gavage; dose vol--rats: 5 ml/kg except 10 ml/kg for 2,500 mg/kg groups; mice: 10 ml/kg	0, 188, 375, 750, 1,500, or 3,000 mg/kg 2-mercaptobenzothiazole in corn oil by gavage; dose vol--10 ml/kg	Rats--0, 188, 375, 750, or 1,500 mg/kg 2-mercaptobenzothiazole in corn oil by gavage; dose vol--5 mg/kg; mice--0, 94, 188, 375, 750, or 1,500 mg/kg; dose vol--10 ml/kg	Rats--male: 0, 375, or 750 mg/kg 2-mercaptobenzothiazole in corn oil by gavage; female: 0, 188, or 375 mg/kg; dose vol--5 ml/kg; mice--0, 375, or 750 mg/kg; dose vol--10 ml/kg
Date of First Dose			
2/11/80	4/28/80	Rats--11/17/80; mice--8/18/80	Rats--7/14/81; mice--7/28/81
Date of Last Dose			
2/26/80	5/13/80	Rats--2/13/81; mice--11/16/80	Rats--7/4/83; mice--7/19/83
Duration of Dosing			
5 d/wk, 12 doses over 16 d	Same as first 16-d studies	5 d/wk for 13 wk	5 d/wk for 103 wk
Type and Frequency of Observation			
Observed 2 × d; weighed initially and 1 × wk thereafter	Same as first 16-d studies	Same as first 16-d studies	Observed 2 × d; weighed 1 × wk for 12 wk and 1 × 4 wk thereafter
Necropsy and Histologic Examination			
Necropsy performed on all animals; histologic exams performed on all vehicle control and 2,500 mg/kg male rats, one rat from the 313 mg/kg group, and one female rat from the 2,500 mg/kg group; histologic exams not performed on mice	Necropsy performed on all animals; histologic exams not performed on rats or mice	Necropsy performed on all animals; histologic exams performed on some animals from all groups. Tissues examined include: adrenal glands, brain, colon, esophagus, eyes (if grossly abnormal), gallbladder (mice), gross lesions and tissue masses, heart, kidneys, liver, lungs and mainstem bronchi, mammary gland, mandibular or mesenteric lymph nodes, pancreas, parathyroids, pituitary gland, prostate/testes or ovaries/uterus, salivary glands, small intestine, spleen, spinal cord (if neurologic signs present), sternebrae or femur or vertebrae including marrow, stomach, thymus, thyroid gland, trachea, and urinary bladder	Necropsy and histologic exams performed on all animals; tissues examined: same as for 13-wk studies
ANIMALS AND ANIMAL MAINTENANCE			
Strain and Species			
F344/N rats; B6C3F$_1$ mice	B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice

TABLE 6. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

First Sixteen-Day Studies	Second Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)			
Animal Source			
Charles River Breeding Laboratories (Kingston, NY)	Harlan Industries (Indianapolis, IN)	Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)
Study Laboratory			
Physiological Research Laboratories	Physiological Research Laboratories	Physiological Research Laboratories	Physiological Research Laboratories
Method of Animal Identification			
Toe clip	Toe clip	Toe clip	Toe and ear clip
Time Held Before Study			
14 d	19 d	Rats--19 d; mice--18 d	13 d
Age When Placed on Study			
Rats--6 wk; mice--6-8 wk	5-6 wk	7-8 wk	Rats--6-7 wk; mice--8 wk
Age When Killed			
Rats--8-9 wk; mice--9-11 wk	7-8 wk	20-21 wk	Rats--111 wk; mice--112 wk
Necropsy Dates			
Rats--2/27/80-2/28/80; mice--2/28/80-2/29/80	5/13/80	Rats--2/17/81; mice--11/17/80	Rats--7/11/83-7/13/83; mice--7/25/83-7/27/83
Method of Animal Distribution			
Animals distributed to weight classes; assigned to cages and then to groups according to tables of random numbers	Same as first 16-d studies	Same as first 16-d studies	Same as first 16-d studies
Feed			
NIH 07 Rat and Mouse Ration (Zeigler Bros., Gardners, PA); available ad libitum	Same as first 16-d studies	Same as first 16-d studies	Same as first 16-d studies
Bedding			
Aspen wood chips (Minnesota Sawdust and Shavings Co., Anoka, MN)	Same as first 16-d studies	Same as first 16-d studies	Same as first 16-d studies
Water			
Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as first 16-d studies	Same as first 16-d studies	Same as first 16-d studies; softened to <1 grain/gal hardness with sodium zeolite; then filtered through spun polyethylene
Cages			
Polycarbonate (Hazleton Systems, Inc., Aberdeen, MD)	Same as first 16-d studies	Same as first 16-d studies	Same as first 16-d studies
Cage Filters			
Reemay® (Dupont, Style 2024) spun-bonded polyester (Snow Filtration Co., Cincinnati, OH)	Same as first 16-d studies	Same as first 16-d studies	Same as first 16-d studies

TABLE 6. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

First Sixteen-Day Studies	Second Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)			
Animals per Cage			
5	5	5	5
Other Chemicals on Study in the Same Room			
None	None	None	None
Animal Room Environment			
Temp--22.2°-24.4° C; hum--38%-50%; fluorescent light 12 h/d	Temp--17.8°-25.5° C; hum--35%-70%; fluorescent light 12 h/d	Temp--22.2°-26.6° C; hum--32%-50%; fluorescent light 12 h/d	Temp--generally 21°-23° C; hum--generally 40%-60%; fluorescent light 12 h/d; 15 room air changes/h

A quality control skin grafting program has been in effect since early 1978 to monitor the genetic integrity of the inbred mice used to produce the hybrid B6C3F$_1$ study animal. In mid-1981, data were obtained that showed incompatibility between the NIH C3H reference colony and the C3H colony from a Program supplier. In August 1981, inbred parental lines of mice were further tested for genetic integrity via isozyme and protein electrophoresis profiles that demonstrate phenotype expressions of known genetic loci.

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

Male mice from the C3H colony and female mice from the C57BL/6N colony were used as parents for the hybrid B6C3F$_1$ mice used in these studies. The influence of the potential genetic nonuniformity in the hybrid mice on these results is not known, but results of the studies are not affected because concurrent controls were included in each study.

Animal Maintenance

Animals were housed five per cage. Feed and water were available ad libitum. Further details of animal maintenance are given in Table 6.

Clinical Examinations and Pathology

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

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissues examined microscopically are listed in Table 6.

When the pathology evaluation was completed, the 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 sent to an independent

quality assessment laboratory. The individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assessment pathologist. The quality assessment report and slides were submitted to the Pathology Working Group (PWG) Chairperson, who reviewed all target tissues and those about which there was a disagreement between the laboratory and quality assessment pathologists.

Representative slides selected by the Chairperson were reviewed by the PWG without knowledge of previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the laboratory pathologist was asked to reconsider the original diagnosis. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final diagnoses represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

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

Statistical Methods

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

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

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

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

For studies in which compound administration has little effect on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the

cause of death. Continuity-corrected tests are used in the analysis of tumor incidence, and reported P values are one-sided.

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

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

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

Historical Control Data: Although the concurrent control group is always the first and most appropriate control group used for evaluation, there are certain instances in which historical control data can be helpful in the overall assessment of tumor incidence. Consequently, control tumor incidences from the NTP historical control data base (Haseman et al., 1984, 1985) are included for those tumors appearing to show compound-related effects.

III. RESULTS

RATS

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

SIXTEEN-DAY STUDIES

Although there were no chemically related deaths in the 16-day studies (Table 7), mean body weight gain in rats of each sex given the highest dose of 2-mercaptobenzothiazole (2,500 mg/kg) was 6-7 g (8%-14%) less than that in vehicle controls; for this reason, the highest dose chosen for the 13-week studies, 1,500 mg/kg, was between the two highest doses used in the 16-day studies (1,250 and 2,500 mg/kg). No compound-related gross pathologic effects were observed.

THIRTEEN-WEEK STUDIES

No compound-related deaths occurred in rats dosed with 2-mercaptobenzothiazole for 13 weeks (Table 8). The animals displayed irritable behavior that was more pronounced with increasing dose and was characterized as resistance to gavage. Body weight gain was reduced with increasing dose, with a maximum change of −15% compared with vehicle controls. Liver weight and liver weight to body weight ratios were increased in dosed rats with the greatest change occurring at the two highest doses (750 and 1,500 mg/kg) (Table 9). No gross or microscopic effects could be related to chemical administration.

Dose Selection Rationale: Because of lower weight gain at higher doses, doses selected for rats for the 2-year studies were 375 and 750 mg/kg 2-mercaptobenzothiazole for males and 188 and 375 mg/kg for females, administered in corn oil by gavage 5 days per week.

TABLE 7. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SIXTEEN-DAY GAVAGE STUDIES OF 2-MERCAPTOBENZOTHIAZOLE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	(d) 4/5	87 ± 1	159 ± 4	+72 ± 3	--
156	5/5	92 ± 2	166 ± 8	+74 ± 10	104
313	5/5	87 ± 1	163 ± 3	+76 ± 3	103
625	(e) 3/5	87 ± 1	171 ± 0	+85 ± 2	108
1,250	5/5	97 ± 1	164 ± 3	+67 ± 3	103
2,500	5/5	88 ± 1	154 ± 3	+66 ± 3	97
FEMALE					
0	5/5	78 ± 1	129 ± 1	+51 ± 2	--
156	5/5	81 ± 1	130 ± 3	+49 ± 2	101
313	(e) 4/5	75 ± 1	126 ± 1	+51 ± 1	98
625	5/5	71 ± 1	121 ± 1	+50 ± 1	94
1,250	5/5	83 ± 1	134 ± 1	+51 ± 1	104
2,500	5/5	84 ± 2	128 ± 3	+44 ± 3	99

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Day of death: 9
(e) Deaths due to gavage error

TABLE 8. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 2-MERCAPTOBENZOTHIAZOLE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	140 ± 2	355 ± 6	+215 ± 6	--
188	10/10	139 ± 2	357 ± 3	+218 ± 2	101
375	9/10	136 ± 2	336 ± 8	+200 ± 8	95
750	10/10	141 ± 3	342 ± 10	+201 ± 10	96
1,500	8/10	142 ± 2	325 ± 9	+182 ± 9	92
FEMALE					
0	10/10	115 ± 2	208 ± 5	+93 ± 5	--
188	9/10	115 ± 2	200 ± 5	+84 ± 5	96
375	10/10	116 ± 1	201 ± 4	+85 ± 3	97
750	8/10	115 ± 2	191 ± 3	+77 ± 2	92
1,500	10/10	115 ± 2	195 ± 4	+80 ± 3	94

(a) Number surviving/number initially in group; all deaths due to gavage error.
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean

TABLE 9. ANALYSIS OF LIVER WEIGHTS FOR RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 2-MERCAPTOBENZOTHIAZOLE (a)

Dose (mg/kg)	No. Examined	Final Mean Body Weight (grams)	Liver Weight (mg)	Liver Weight/Final Body Weight (mg/g)
MALE				
0	10	355 ± 19.1	13,593 ± 2,121	38.4 ± 6.07
188	10	357 ± 8.5	15,661 ± 793	(b) 43.9 ± 1.87
375	9	336 ± 23.1	15,861 ± 1,712	(c) 47.2 ± 2.79
750	10	342 ± 31.5	(c) 18,742 ± 2,631	(c) 54.8 ± 5.08
1,500	8	(b) 325 ± 26.8	(c) 16,759 ± 2,660	(c) 51.3 ± 5.42
FEMALE				
0	10	208 ± 15.9	6,606 ± 795	31.8 ± 3.28
188	9	200 ± 15.6	(c) 7,818 ± 814	(c) 39.3 ± 3.53
375	10	201 ± 11.3	(c) 8,027 ± 688	(c) 39.9 ± 2.99
750	8	(b) 191 ± 8.8	(c) 7,988 ± 591	(c) 41.8 ± 2.81
1,500	10	195 ± 12.1	(c) 8,413 ± 652	(c) 43.2 ± 2.61

(a) Mean ± standard deviation; P values are versus the vehicle controls by Dunnett's test (Dunnett, 1955).
(b) $P<0.05$
(c) $P<0.01$

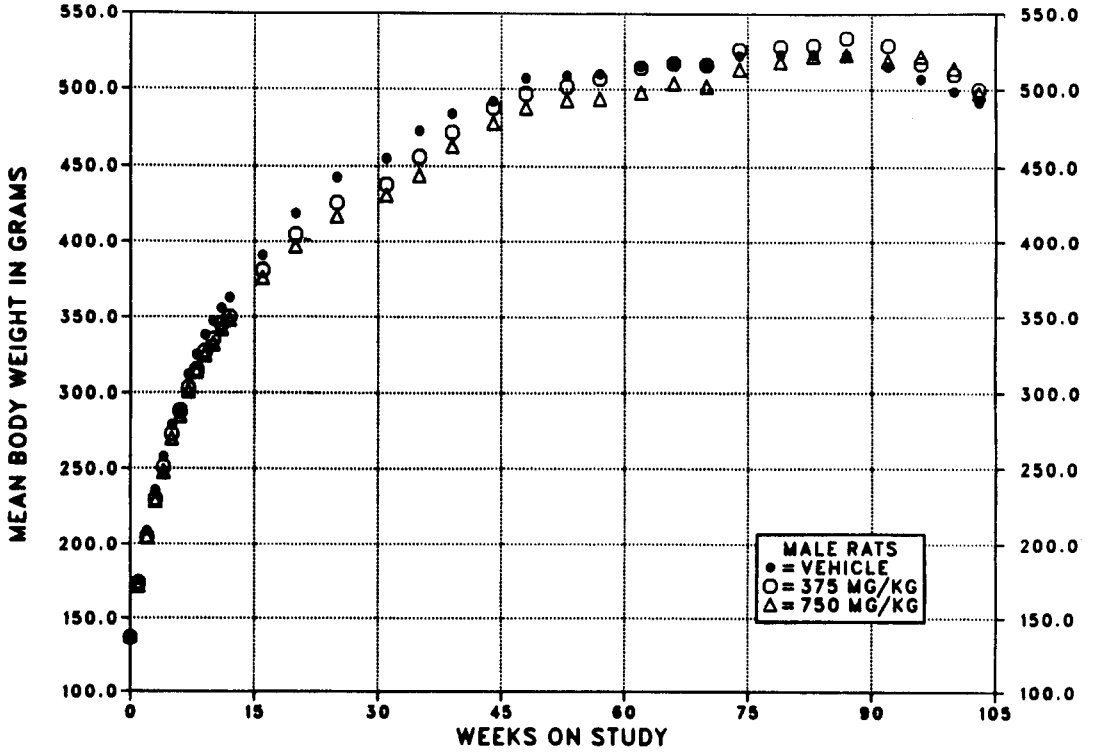
TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed male rats were similar to or greater than those of the vehicle controls (Table 10 and Figure 5). Mean body weights of dosed female rats were generally greater (up to 11%) than those of the vehicle controls. Rats were lethargic after they were dosed.

TABLE 10. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF 2-MERCAPTOBENZOTHIAZOLE

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	Low Dose Av. Wt. (grams)	Low Dose Wt. (percent of veh. controls)	Low Dose No. of Survivors	High Dose Av. Wt. (grams)	High Dose Wt. (percent of veh. controls)	High Dose No. of Survivors
MALE				**375 mg/kg**			**750 mg/kg**	
0	138	50	137	99	50	138	100	50
1	176	50	174	99	50	172	98	50
2	209	50	205	98	50	205	98	50
3	236	50	230	97	50	229	97	50
4	258	50	251	97	50	248	96	50
5	279	50	273	98	50	270	97	50
6	288	50	288	100	50	285	99	50
7	312	50	303	97	50	301	96	50
8	325	50	315	97	50	314	97	50
9	338	50	327	97	50	325	96	50
10	347	50	335	97	50	332	96	50
11	356	50	345	97	50	342	96	50
12	363	50	350	96	50	348	96	50
16	391	50	381	97	50	376	96	50
20	419	50	405	97	50	397	95	50
25	443	50	426	96	50	417	94	50
31	455	50	438	96	50	431	95	50
35	473	50	456	96	50	444	94	50
39	484	50	472	98	50	463	96	50
44	492	50	488	99	50	478	97	50
48	507	50	497	98	50	488	96	50
53	509	50	502	99	50	493	97	50
57	510	50	507	99	50	494	97	49
62	515	50	514	100	50	498	97	48
66	517	50	517	100	50	504	97	47
70	516	50	516	100	50	502	97	45
74	522	50	526	101	50	513	98	45
79	523	50	528	101	48	518	99	44
83	523	50	529	101	47	522	100	42
87	523	50	534	102	41	523	100	40
92	515	49	529	103	36	519	101	39
96	507	46	517	102	34	522	103	33
100	499	44	510	102	27	514	103	28
103	492	42	500	102	23	498	101	20
FEMALE				**188 mg/kg**			**375 mg/kg**	
0	112	50	112	100	50	112	100	50
1	131	50	131	100	50	129	98	50
2	148	50	148	100	50	147	99	50
3	159	50	160	101	50	159	100	50
4	168	50	169	101	50	168	100	50
5	179	50	181	101	50	179	100	50
6	186	50	188	101	50	186	100	50
7	191	50	194	102	50	193	101	50
8	196	50	201	103	50	199	102	50
9	198	50	204	103	50	201	102	50
10	200	50	206	103	50	203	102	50
11	206	50	212	103	50	209	101	50
12	205	50	211	103	50	208	101	50
16	216	50	222	103	50	219	101	50
20	225	50	231	103	49	232	103	50
25	233	50	239	103	49	238	102	48
31	238	49	246	103	48	247	104	46
35	246	48	254	103	48	255	104	45
39	250	48	262	105	48	263	105	44
44	255	46	271	106	48	273	107	43
48	262	46	278	106	48	281	107	43
53	269	44	287	107	48	290	108	42
57	274	43	293	107	47	298	109	42
62	283	42	305	108	47	306	108	42
66	295	41	317	107	47	318	108	41
70	300	41	325	108	46	326	109	41
74	309	40	337	109	46	338	109	41
79	322	39	349	108	46	348	108	41
83	332	35	356	107	46	358	108	38
87	336	35	364	108	44	365	109	36
92	340	31	368	108	40	371	109	32
96	345	31	371	108	39	381	110	27
100	343	30	371	108	35	378	110	26
103	340	29	370	109	31	378	111	25



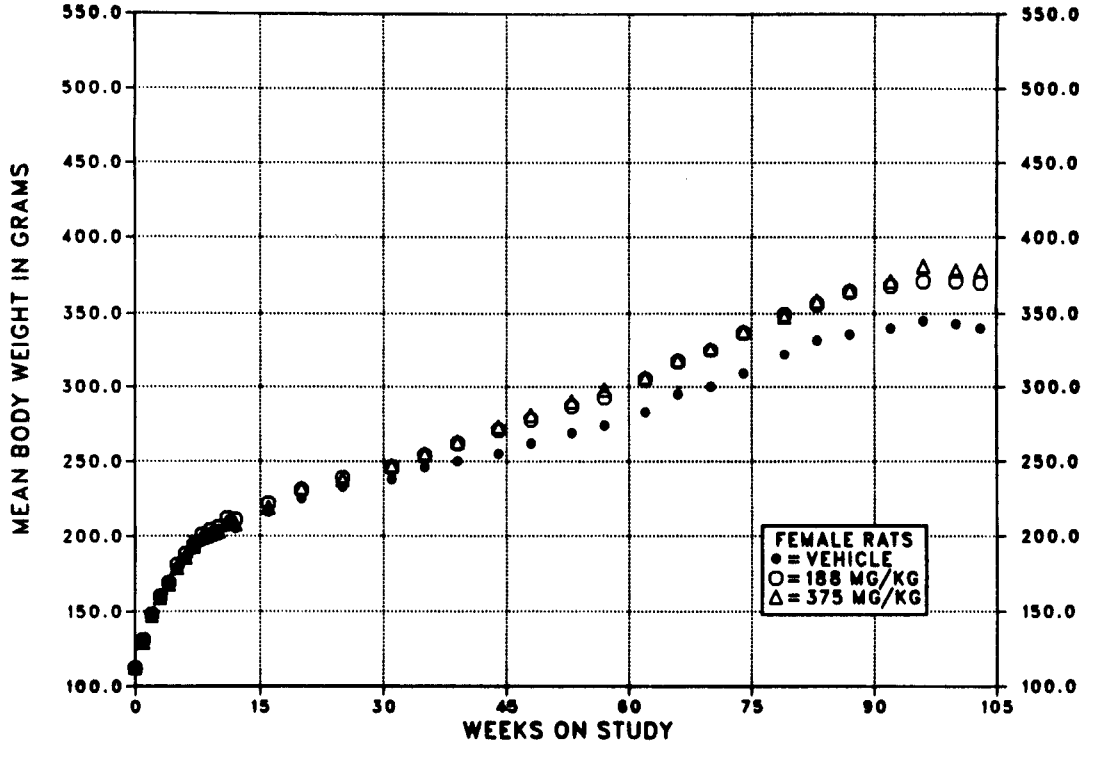


FIGURE 5. GROWTH CURVES FOR RATS ADMINISTERED 2-MERCAPTOBENZOTHIAZOLE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats administered 2-mercaptobenzothiazole at the doses used in these studies and for vehicle controls are shown in Table 11 and in the Kaplan and Meier curves in Figure 6. Survival of the low dose group of male rats was significantly lower than that of the vehicle controls after week 85. Survival of the high dose group of male rats was significantly lower than that of the vehicle controls after week 83 (except for weeks 94 and 95).

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the hematopoietic system, pituitary gland, adrenal gland, pancreas, preputial gland, multiple organs, subcutaneous tissue, kidney, forestomach, and eye.

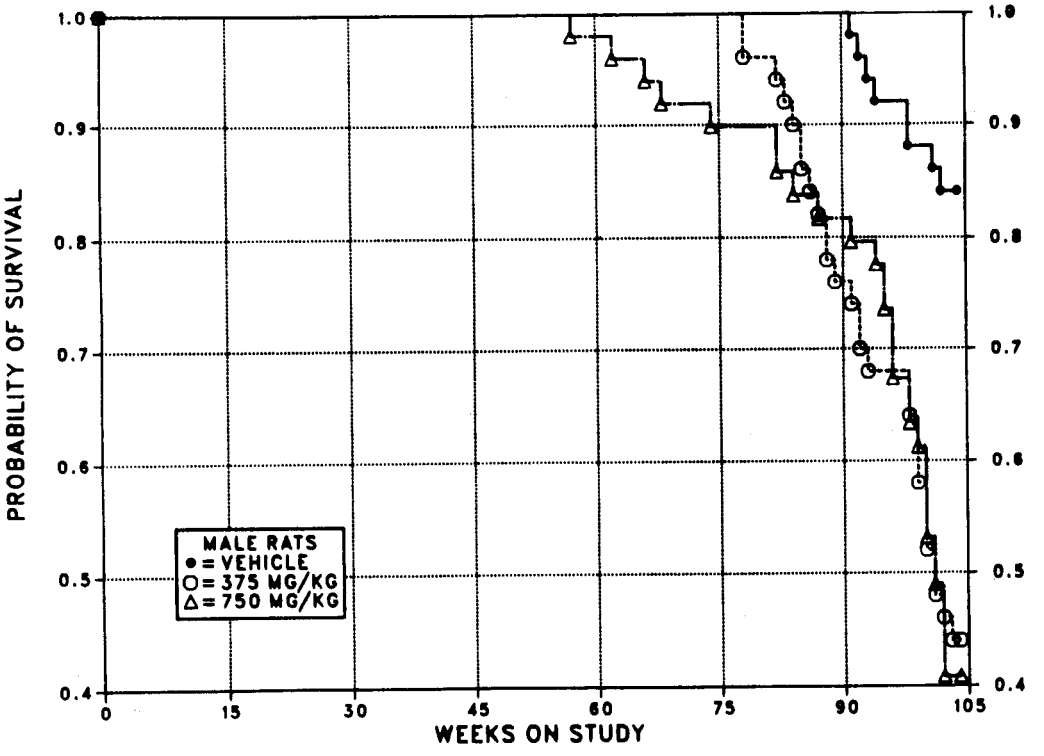
Lesions in male rats are summarized in Appendix A. Histopathologic findings on neoplasms are summarized in Table A1. Table A2 gives the survival and tumor status for individual male rats. Table A3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table A3 (footnotes). Historical incidences of tumors in corn oil vehicle control male rats are listed in Table A4. Findings on nonneoplastic lesions are summarized in Table A5.

Lesions in female rats are summarized in Appendix B. Histopathologic findings on neoplasms are summarized in Table B1. Table B2 gives the survival and tumor status for individual female rats. Table B3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table B3 (footnotes). Historical incidences of tumors in corn oil vehicle control female rats are listed in Table B4. Findings on nonneoplastic lesions are summarized in Table B5.

TABLE 11. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF 2-MERCAPTOBENZOTHIAZOLE

	Vehicle Control	188 mg/kg	375 mg/kg	750 mg/kg
MALE (a)				
Animals initially in study	50		50	50
Nonaccidental deaths before termination (b)	8		28	29
Accidentally killed	0		0	1
Killed at termination	42		22	20
Survival P values (c)	<0.001		<0.001	<0.001
FEMALE (a)				
Animals initially in study	50	50	50	
Nonaccidental deaths before termination (b)	21	18	25	
Accidentally killed	1	1	0	
Killed at termination	28	31	25	
Survival P values (c)	0.535	0.415	0.639	

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



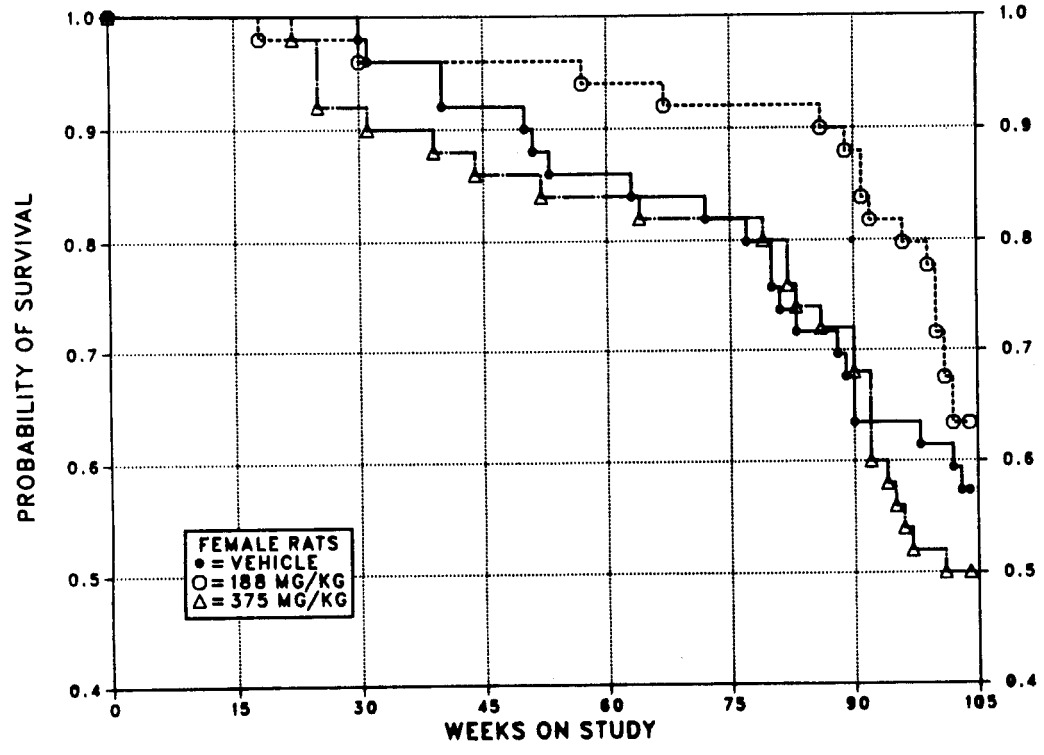


FIGURE 6. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED 2-MERCAPTOBENZOTHIAZOLE IN CORN OIL BY GAVAGE FOR TWO YEARS

Hematopoietic System: The incidence of leukemia in low dose male rats was significantly greater than that in the vehicle controls by the life table test and exceeded the high value for the historical corn oil vehicle control range (0/50-14/50) (Table 12).

Pituitary Gland: Adenomas and adenomas or adenocarcinomas (combined) in female rats occurred with significant positive trends; the incidences of adenomas in low dose males and of adenomas and adenomas or adenocarcinomas (combined) in high dose females were significantly greater than those in the vehicle controls (Table 13). The incidence of hyperplasia of the anterior pituitary was slightly increased in low dose male rats.

TABLE 12. ANALYSIS OF MONONUCLEAR CELL LEUKEMIA IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF 2-MERCAPTOBENZOTHIAZOLE (a)

	Vehicle Control	188 mg/kg	375 mg/kg	750 mg/kg
MALE (b)				
Overall Rates	7/50 (14%)		16/50 (32%)	3/50 (6%)
Adjusted Rates	15.1%		47.2%	12.3%
Terminal Rates	4/42 (10%)		6/22 (27%)	2/20 (10%)
Week of First Observation	91		78	91
Life Table Tests	P=0.475		P=0.002	P=0.449N
Incidental Tumor Tests	P=0.084N		P=0.103	P=0.157N
FEMALE (c)				
Overall Rates	6/50 (12%)	14/50 (28%)	9/50 (18%)	
Adjusted Rates	19.7%	35.4%	25.3%	
Terminal Rates	4/28 (14%)	6/31 (19%)	2/25 (8%)	
Week of First Observation	90	92	79	
Life Table Tests	P=0.221	P=0.099	P=0.279	
Incidental Tumor Tests	P=0.399	P=0.215	P=0.415	

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix A, Table A3 (footnotes).
(b) Historical incidence of leukemia in NTP studies (mean ± SD): 202/1,450 (14% ± 8%)
(c) Historical incidence of leukemia in NTP studies (mean ± SD): 271/1,450 (19% ± 9%)

TABLE 13. ANALYSIS OF PITUITARY GLAND LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF 2-MERCAPTOBENZOTHIAZOLE

	Vehicle Control	188 mg/kg	375 mg/kg	750 mg/kg
MALE				
Hyperplasia				
Overall Rates	10/50 (20%)		17/50 (34%)	12/48 (25%)
Adenoma (a)				
Overall Rates	14/50 (28%)		21/50 (42%)	12/48 (25%)
Adjusted Rates	30.9%		59.9%	40.1%
Terminal Rates	11/42 (26%)		10/22 (45%)	5/20 (25%)
Week of First Observation	94		82	82
Life Table Tests	P=0.106		P=0.003	P=0.171
Incidental Tumor Tests	P=0.506N		P=0.132	P=0.482N
FEMALE				
Hyperplasia				
Overall Rates	8/49 (16%)	10/50 (20%)	6/50 (12%)	
Adenoma				
Overall Rates	15/49 (31%)	24/50 (48%)	25/50 (50%)	
Adjusted Rates	44.6%	62.3%	73.2%	
Terminal Rates	10/28 (36%)	17/31 (55%)	16/25 (64%)	
Week of First Observation	72	67	82	
Life Table Tests	P=0.014	P=0.146	P=0.021	
Incidental Tumor Tests	P=0.015	P=0.139	P=0.027	
Adenocarcinoma				
Overall Rates	1/49 (2%)	0/50 (0%)	0/50 (0%)	
Adenoma or Adenocarcinoma (b)				
Overall Rates	16/49 (33%)	24/50 (48%)	25/50 (50%)	
Adjusted Rates	46.2%	62.3%	73.2%	
Terminal Rates	10/28 (36%)	17/31 (55%)	16/25 (64%)	
Week of First Observation	72	67	82	
Life Table Tests	P=0.024	P=0.206	P=0.036	
Incidental Tumor Tests	P=0.028	P=0.186	P=0.050	

(a) Historical incidence of adenomas in NTP studies (mean ± SD): 344/1,411 (24% ± 8%)
(b) Historical incidence of adenomas, carcinomas, or adenocarcinomas (combined) in NTP studies (mean ± SD): 561/1,407 (40% ± 8%)

Adrenal Gland: Pheochromocytomas in male and female rats occurred with significant positive trends; the incidences in dosed male and high dose female rats were significantly greater than those in the vehicle controls by the life table test (Table 14). The incidences for both low and high dose male rats exceeded the historical corn oil vehicle control values (mean historical incidence, 338/1,442, 23.4%; range, 2/50-20/49; Table A4c).

The incidence of medullary hyperplasia was slightly increased in low dose male rats. The hyperplasia was characterized by focal areas of somewhat darker staining cells with relatively larger nuclei; no invasion or compression of the surrounding medulla or cortex was observed. Benign pheochromocytomas were similar to the hyperplasia except that they were larger and compressed or displaced adjacent medulla and cortex. Malignant pheochromocytomas invaded the medulla and cortex and extended through the adrenal capsule.

TABLE 14. ANALYSIS OF ADRENAL GLAND LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF 2-MERCAPTOBENZOTHIAZOLE

	Vehicle Control	188 mg/kg	375 mg/kg	750 mg/kg
MALE				
Medullary Hyperplasia				
Overall Rates	9/50 (18%)		14/50 (28%)	10/49 (20%)
Pheochromocytoma				
Overall Rates	18/50 (36%)		25/50 (50%)	22/49 (45%)
Adjusted Rates	39.8%		70.3%	68.5%
Terminal Rates	15/42 (36%)		12/22 (55%)	11/20 (55%)
Week of First Observation	93		85	84
Life Table Tests	P=0.002		P<0.001	P=0.002
Incidental Tumor Tests	P=0.109		P=0.056	P=0.111
Malignant Pheochromocytoma				
Overall Rates	0/50 (0%)		2/50 (4%)	2/49 (4%)
Pheochromocytoma or Malignant Pheochromocytoma (a)				
Overall Rates	18/50 (36%)		27/50 (54%)	24/49 (49%)
Adjusted Rates	39.8%		74.1%	75.5%
Terminal Rates	15/42 (36%)		13/22 (59%)	13/20 (65%)
Week of First Observation	93		85	84
Life Table Tests	P<0.001		P<0.001	P<0.001
Incidental Tumor Tests	P=0.038		P=0.021	P=0.034
FEMALE				
Medullary Hyperplasia				
Overall Rates	5/50 (10%)	8/50 (16%)	2/50 (4%)	
Pheochromocytoma (b)				
Overall Rates	1/50 (2%)	5/50 (10%)	6/50 (12%)	
Adjusted Rates	3.6%	14.6%	23.0%	
Terminal Rates	1/28 (4%)	3/31 (10%)	5/25 (20%)	
Week of First Observation	104	96	97	
Life Table Tests	P=0.030	P=0.137	P=0.041	
Incidental Tumor Tests	P=0.038	P=0.214	P=0.052	

(a) Historical incidence in NTP studies (mean ± SD): 347/1,442 (24% ± 9%)
(b) Historical incidence in NTP studies (mean ± SD): 82/1,443 (6% ± 4%)

Pancreas: The incidence of acinar cell adenomas in low dose male rats was significantly greater than that in the vehicle controls by the incidental tumor test (Table 15). The incidence of pancreatic acinar cell hyperplasia was also increased in the low dose group. Acinar cell hyperplasia usually consisted of focal, circumscribed, round to oval lesions that slightly compressed the surrounding acini. The acinar pattern was prominent, and these areas were clearly demarcated from surrounding acinar tissue. Adenomas generally were similar in appearance to the hyperplasia but were distinguished primarily by their larger size and abnormal growth pattern.

Preputial Gland: Adenomas in male rats occurred with a significant positive trend by the incidental tumor test, and the incidences of adenomas or carcinomas (combined) in dosed groups were significantly greater than those in the vehicle controls by the life table tests (Table 16). The number of tumors for any group did not exceed the historical corn oil vehicle control range (0/50-9/50).

TABLE 15. ANALYSIS OF PANCREATIC ACINAR CELL LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE

	Vehicle Control	375 mg/kg	750 mg/kg
Hyperplasia			
Overall Rates	5/50 (10%)	15/50 (30%)	7/49 (14%)
Adenoma (a)			
Overall Rates	2/50 (4%)	13/50 (26%)	6/49 (12%)
Adjusted Rates	4.5%	45.7%	23.0%
Terminal Rates	1/42 (2%)	8/22 (36%)	3/20 (15%)
Week of First Observation	94	88	98
Life Table Tests	P=0.017	P<0.001	P=0.030
Incidental Tumor Tests	P=0.118	P<0.001	P=0.160

(a) Historical incidence of acinar cell neoplasms in NTP studies (mean ± SD): 80/1,381 (6% ± 8%)

TABLE 16. ANALYSIS OF PREPUTIAL GLAND LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE

	Vehicle Control	375 mg/kg	750 mg/kg
Hyperplasia			
Overall Rates	0/50 (0%)	0/50 (0%)	1/50 (2%)
Adenoma			
Overall Rates	0/50 (0%)	4/50 (8%)	4/50 (8%)
Adjusted Rates	0.0%	14.7%	14.4%
Terminal Rates	0/42 (0%)	2/22 (9%)	2/20 (10%)
Week of First Observation		88	87
Life Table Tests	P=0.016	P=0.019	P=0.021
Incidental Tumor Tests	P=0.042	P=0.076	P=0.063
Carcinoma (a)			
Overall Rates	1/50 (2%)	2/50 (4%)	1/50 (2%)
Adenoma or Carcinoma (b)			
Overall Rates	1/50 (2%)	6/50 (12%)	5/50 (10%)
Adjusted Rates	2.2%	18.5%	19.2%
Terminal Rates	0/42 (0%)	2/22 (9%)	3/20 (15%)
Week of First Observation	98	83	87
Life Table Tests	P=0.027	P=0.021	P=0.030
Incidental Tumor Tests	P=0.094	P=0.216	P=0.117

(a) Historical incidence in NTP studies (mean ± SD): 35/1,450 (2% ± 3%)
(b) Historical incidence in NTP studies (mean ± SD): 65/1,450 (4% ± 4%)

Multiple Organs: Mesotheliomas in male rats occurred with a significant positive trend; the incidences in the dosed groups were not significantly greater than that in the vehicle controls (Table 17) and did not exceed the historical corn oil vehicle control range for this neoplasm (0/50-6/50).

Subcutaneous Tissue: Fibromas and fibromas, neurofibromas, sarcomas, or fibrosarcomas (combined) in male rats occurred with significant positive trends by the life table test but not by the more appropriate incidental tumor test (Table 18).

TABLE 17. ANALYSIS OF MESOTHELIOMAS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (a)

	Vehicle Control	375 mg/kg	750 mg/kg
Overall Rates	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted Rates	0.0%	6.6%	9.5%
Terminal Rates	0/42 (0%)	1/22 (5%)	1/20 (5%)
Week of First Observation		84	84
Life Table Tests	P=0.039	P=0.163	P=0.066
Incidental Tumor Tests	P=0.041	P=0.310	P=0.158

(a) Historical incidence in NTP studies (mean ± SD): 55/1,450 (4% ± 3%)

TABLE 18. ANALYSIS OF SUBCUTANEOUS TISSUE TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE

	Vehicle Control	375 mg/kg	750 mg/kg
Fibroma			
Overall Rates	2/50 (4%)	3/50 (6%)	6/50 (12%)
Adjusted Rates	4.8%	9.2%	19.6%
Terminal Rates	2/42 (5%)	1/22 (5%)	2/20 (10%)
Week of First Observation	104	85	82
Life Table Tests	P=0.024	P=0.299	P=0.033
Incidental Tumor Tests	P=0.064	P=0.612	P=0.153
Neurofibroma			
Overall Rates	0/50 (0%)	1/50 (2%)	0/50 (0%)
Sarcoma			
Overall Rates	0/50 (0%)	1/50 (2%)	1/50 (2%)
Fibrosarcoma			
Overall Rates	1/50 (2%)	1/50 (2%)	0/50 (0%)
Fibroma, Neurofibroma, Sarcoma, or Fibrosarcoma (a)			
Overall Rates	3/50 (6%)	6/50 (12%)	7/50 (14%)
Adjusted Rates	7.1%	17.7%	21.4%
Terminal Rates	3/42 (7%)	2/22 (9%)	2/20 (10%)
Week of First Observation	104	85	74
Life Table Tests	P=0.031	P=0.084	P=0.037
Incidental Tumor Tests	P=0.129	P=0.396	P=0.237

(a) Historical incidence in NTP studies (mean ± SD): 126/1,450 (9% ± 4%)

Kidney: Nephropathy, characterized by tubular degeneration and regeneration, was present in all male rats and in more than 75% of the female rats; a severity grade from minimal to severe (1-4) was recorded for each animal. The mean severity of nephropathy was increased in dosed male rats (vehicle control: 2.3 [mild-moderate]; low dose and high dose: 3.4 [moderate-severe]).

Pelvic epithelial hyperplasia and transitional cell papillomas or carcinomas and tubular cell hyperplasia and tubular cell adenomas were observed in dosed male rats (Table 19). The historical incidence of transitional cell neoplasms in male F344/N corn oil vehicle control rats is 1/1,448 (<0.1%); the historical incidence of tubular cell neoplasms in male F344/N corn oil vehicle control rats is 8/1,448 (0.6%).

Forestomach: Ulcers and inflammation were observed at increased incidences in dosed rats, and epithelial hyperplasia and hyperkeratosis were observed at increased incidences in dosed male and low dose female rats (Table 20).

Eye: Retinopathy and cataracts were observed at increased incidences in low dose rats (retinopathy--male: vehicle control, 0/50; low dose, 10/50; high dose, 0/50; female: 1/50; 9/50; 0/50; cataracts--male: 1/50; 6/50; 0/50; female: 0/50; 8/50; 0/50). Low dose groups were on the top two rows of the racks near the fluorescent light source. The cage racks were not rotated in these studies.

TABLE 19. NUMBER OF RATS WITH KIDNEY LESIONS IN THE TWO-YEAR GAVAGE STUDIES OF 2-MERCAPTOBENZOTHIAZOLE

Site/Lesion	Male			Female		
	0	375 mg/kg	750 mg/kg	0	188 mg/kg	375 mg/kg
No. examined	50	50	49	50	50	50
Kidney/pelvis						
Epithelial hyperplasia	0	4	1	1	0	0
Transitional cell papilloma	0	1	1	0	0	0
Transitional cell carcinoma	0	1	0	0	0	0
Kidney/tubule						
Focal hyperplasia	0	3	3	1	0	0
Kidney						
Tubular cell adenoma	0	1	1	0	0	0

TABLE 20. NUMBER OF RATS WITH FORESTOMACH LESIONS IN THE TWO-YEAR GAVAGE STUDIES OF 2-MERCAPTOBENZOTHIAZOLE

Lesion	Male			Female		
	0	375 mg/kg	750 mg/kg	0	188 mg/kg	375 mg/kg
No. examined	50	50	49	49	50	50
Ulcer	0	5	5	0	3	5
Inflammation	0	11	14	2	4	7
Epithelial hyperplasia	1	12	17	1	4	1
Hyperkeratosis	0	12	17	1	4	1

SIXTEEN-DAY STUDIES

An initial 16-day study was repeated because an excessive number of gavage accidents occurred. In the second study, 4/5 males and 5/5 females that received 3,000 mg/kg and 4/5 females that received 1,500 mg/kg died before the end of the studies (Table 21). Mice that received 1,500 or 3,000 mg/kg were lethargic after day 1. Final mean body weights were not adversely affected by 2-mercaptobenzothiazole. No compound-related lesions were observed grossly. Since all but one of the male and female mice dosed with 3,000 mg/kg died, the highest dose used in the 13-week studies was 1,500 mg/kg for mice of each sex.

TABLE 21. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SECOND SIXTEEN-DAY GAVAGE STUDIES OF 2-MERCAPTOBENZOTHIAZOLE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	23.2 ± 0.8	24.1 ± 0.8	+0.9 ± 0.8	--
188	5/5	21.4 ± 0.6	24.2 ± 0.6	+2.8 ± 0.4	100.4
375	5/5	21.4 ± 0.7	25.0 ± 0.6	+3.6 ± 0.4	103.7
750	5/5	21.7 ± 0.8	24.5 ± 0.8	+2.8 ± 0.3	101.7
1,500	5/5	22.9 ± 0.3	25.0 ± 0.3	+2.1 ± 0.2	103.7
3,000	(d) 1/5	22.1 ± 0.4	27.0	+3.4	112.0
FEMALE					
0	5/5	19.0 ± 0.2	20.0 ± 0.1	+1.0 ± 0.1	--
188	5/5	20.3 ± 0.5	21.2 ± 0.5	+0.9 ± 0.2	106.0
375	5/5	20.3 ± 0.7	21.8 ± 0.7	+1.5 ± 0.4	109.0
750	5/5	20.3 ± 0.3	21.5 ± 0.3	+1.2 ± 0.3	107.5
1,500	(e) 1/5	19.8 ± 0.4	22.5	+1.3	112.5
3,000	(e) 0/5	18.6 ± 0.3	(f)	(f)	(f)

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Day of death: 2,2,2,3
(e) Day of death: all 2
(f) No data are reported because of the 100% mortality in this group.

THIRTEEN-WEEK STUDIES

Five of 10 males and 7/10 females that received 1,500 mg/kg died before the end of the studies (Table 22). Two of the deaths were related to gavage technique. Chemical administration did not affect body weight gain. Liver weight to body weight ratios of dosed groups were higher than those of the vehicle controls (Table 23). Clonic seizures, lacrimation, and salivation were observed in the 750 and 1,500 mg/kg groups. Lethargy and rough coats were observed in the 375 and 750 mg/kg groups. No compound-related gross or microscopic pathologic effects were observed.

Dose Selection Rationale: Because of the deaths observed at 1,500 mg/kg, doses selected for mice for the 2-year studies were 375 and 750 mg/kg 2-mercaptobenzothiazole, administered in corn oil by gavage, 5 days per week.

TABLE 22. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 2-MERCAPTOBENZOTHIAZOLE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	27.1 ± 0.3	36.7 ± 0.9	+9.6 ± 0.7	--
94	10/10	25.8 ± 0.4	37.0 ± 0.8	+11.2 ± 0.7	100.8
188	10/10	26.9 ± 0.3	37.7 ± 1.0	+10.8 ± 0.8	102.7
375	10/10	25.9 ± 0.5	35.1 ± 1.1	+9.2 ± 0.9	95.6
750	10/10	26.1 ± 0.5	34.4 ± 0.6	+8.3 ± 0.3	93.7
1,500	(d) 5/10	26.7 ± 0.4	35.2 ± 1.3	+8.5 ± 0.5	95.9
FEMALE					
0	10/10	20.6 ± 0.3	26.2 ± 0.4	+5.6 ± 0.4	--
94	10/10	20.4 ± 0.4	25.5 ± 0.4	+5.1 ± 0.3	97.3
188	10/10	20.3 ± 0.4	25.9 ± 0.6	+5.6 ± 0.2	98.9
375	10/10	20.0 ± 0.3	25.8 ± 0.4	+5.8 ± 0.2	98.5
750	(e) 8/10	20.5 ± 0.2	26.1 ± 0.4	+5.5 ± 0.4	99.6
1,500	(f) 3/10	20.1 ± 0.4	25.3 ± 0.2	+4.6 ± 0.4	96.6

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Week of death: 1,2,3,4,6
(e) Week of death: 7,8
(f) Week of death: 1,1,1,1,6,8,10

TABLE 23. ANALYSIS OF LIVER WEIGHTS FOR MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 2-MERCAPTOBENZOTHIAZOLE (a)

Dose (mg/kg)	No. Examined	Final Mean Body Weight (grams)	Liver Weight (mg)	Liver Weight/Final Body Weight (mg/g)
MALE				
0	10	36.7 ± 2.8	1,821 ± 213	49.6 ± 4.34
94	10	37.0 ± 2.6	1,942 ± 208	52.5 ± 4.02
188	10	37.7 ± 3.1	2,034 ± 184	(b) 54.0 ± 3.23
375	10	35.1 ± 3.4	1,855 ± 231	52.8 ± 3.51
750	10	34.4 ± 2.0	1,809 ± 115	52.6 ± 3.15
1,500	5	35.2 ± 2.8	2,090 ± 184	(c) 59.5 ± 3.94
FEMALE				
0	10	26.2 ± 1.3	1,129 ± 242	42.9 ± 7.71
94	10	25.5 ± 1.3	1,237 ± 123	48.6 ± 5.03
188	10	25.9 ± 1.7	1,238 ± 113	47.9 ± 3.61
375	10	25.8 ± 1.3	1,232 ± 124	47.8 ± 3.74
750	8	26.1 ± 1.3	1,281 ± 126	49.2 ± 4.70
1,500	3	25.3 ± 0.3	1,383 ± 96	(c) 54.7 ± 3.45

(a) Mean ± standard deviation; P values are versus the controls by Dunnett's test (Dunnett, 1955).
(b) $P<0.05$
(c) $P<0.01$

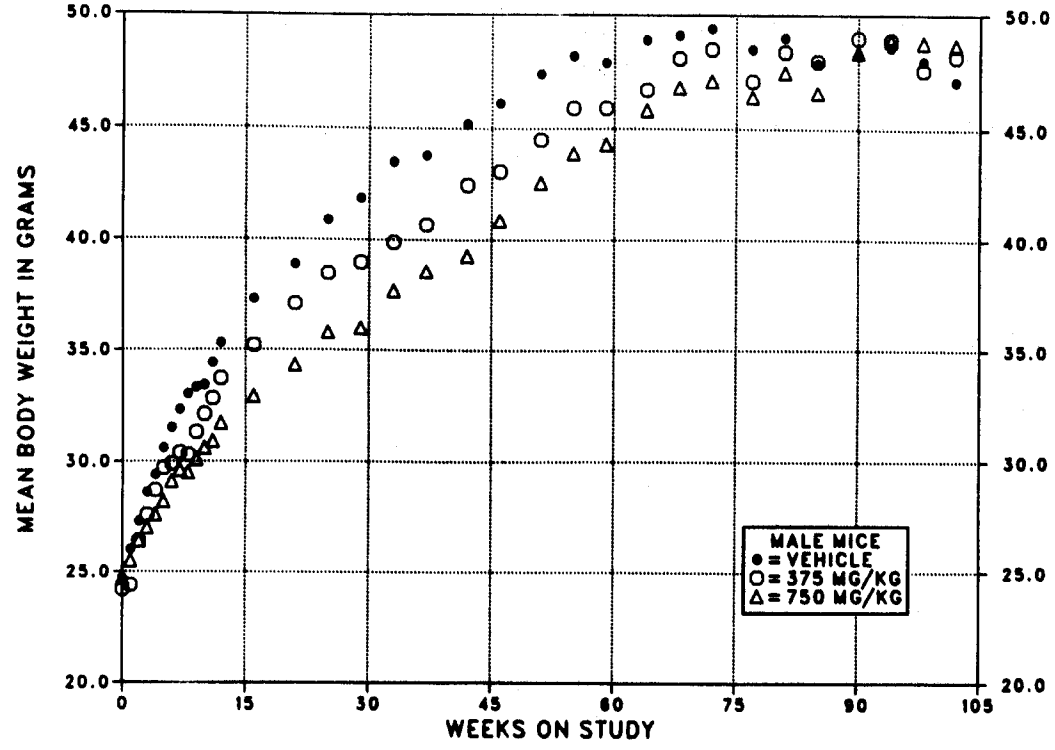
TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male mice were 6%-14% lower than those of the vehicle controls from week 3 to week 64 (Table 24 and Figure 7). Mean body weights of low dose male mice were 4%-8% lower than those of the vehicle controls from week 6 to week 64. Mean body weights of high dose female mice were within 6% of those of the vehicle controls throughout the studies. Mean body weights of low dose female mice were generally greater than those of the vehicle controls throughout the studies. Mice were lethargic after they were dosed.

TABLE 24. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF 2-MERCAPTOBENZOTHIAZOLE

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	375 mg/kg Av. Wt. (grams)	375 mg/kg Wt. (percent of veh. controls)	375 mg/kg No. of Survivors	750 mg/kg Av. Wt. (grams)	750 mg/kg Wt. (percent of veh. controls)	750 mg/kg No. of Survivors
MALE								
0	24.7	50	24.2	98	50	24.7	100	50
1	26.0	50	24.4	94	50	25.5	98	50
2	27.3	50	26.4	97	49	26.4	97	50
3	28.6	50	27.6	97	49	27.0	94	50
4	29.4	50	28.7	98	49	27.6	94	50
5	30.6	50	29.7	97	49	28.2	92	50
6	31.5	50	29.9	95	49	29.1	92	50
7	32.3	50	30.4	94	49	29.6	92	50
8	33.0	50	30.3	92	49	29.5	89	48
9	33.3	50	31.3	94	49	30.1	90	48
10	33.4	50	32.1	96	49	30.6	92	47
11	34.4	50	32.8	95	49	30.9	90	47
12	35.3	50	33.7	95	49	31.7	90	47
16	37.3	50	35.2	94	49	32.9	88	40
21	38.9	50	37.1	95	49	34.3	88	38
25	40.9	50	38.5	94	49	35.8	88	38
29	41.9	50	39.0	93	49	36.0	86	35
33	43.5	50	39.9	92	49	37.7	87	35
37	43.8	50	40.7	93	49	38.6	88	35
42	45.2	50	42.5	94	49	39.3	87	35
46	46.1	50	43.1	93	49	40.9	89	35
51	47.4	50	44.5	94	49	42.6	90	34
55	48.2	49	45.9	95	49	43.9	91	34
59	47.9	49	45.9	96	49	44.3	92	34
64	48.9	49	46.7	96	49	45.8	94	33
68	49.1	48	48.1	98	48	46.8	95	33
72	49.4	48	48.5	98	47	47.1	95	32
77	48.5	47	47.1	97	45	46.4	96	32
81	49.0	47	48.4	99	43	47.5	97	32
85	47.9	45	48.0	100	42	46.6	97	32
90	48.3	42	49.0	101	38	48.4	100	30
94	48.6	40	48.9	101	37	48.9	101	30
98	48.0	39	47.6	99	37	48.8	102	30
102	47.1	38	48.2	102	33	48.7	103	30
FEMALE								
0	20.8	50	20.5	99	50	20.9	100	50
1	20.8	50	20.4	98	50	21.1	101	50
2	21.6	50	21.8	101	50	21.8	101	50
3	22.2	50	22.4	101	50	22.4	101	49
4	23.3	50	23.2	100	50	23.0	99	49
5	23.7	50	23.5	99	50	22.9	97	49
6	24.0	50	23.7	99	50	23.9	100	49
7	23.9	50	24.1	101	50	24.1	101	49
8	24.0	50	24.5	102	50	24.2	101	49
9	24.4	50	24.4	100	50	24.6	101	49
10	25.2	50	24.9	99	50	24.9	99	49
11	26.1	50	25.8	99	50	25.7	98	49
12	26.6	50	26.0	98	50	26.0	98	49
16	27.7	50	27.6	100	50	27.0	97	44
21	29.1	50	28.4	98	50	28.1	97	40
25	30.6	50	30.3	99	50	29.5	96	40
29	30.3	50	31.0	102	50	30.2	100	39
33	31.1	50	31.8	102	50	30.9	99	39
37	32.6	50	33.0	101	50	32.2	99	39
42	34.6	50	33.3	96	50	32.6	94	39
46	35.6	50	34.6	97	50	33.4	94	37
51	37.4	50	36.7	98	50	35.0	94	35
55	39.4	50	38.6	98	50	37.2	94	34
59	39.9	49	39.3	98	50	38.9	97	33
64	41.3	49	41.1	100	50	40.3	98	31
68	42.5	49	42.3	100	50	40.5	95	31
72	43.3	48	43.2	100	50	41.5	96	31
77	42.8	48	43.5	102	49	41.9	98	29
81	43.3	48	44.9	104	48	42.7	99	27
85	44.0	45	45.2	103	48	42.4	96	27
90	45.4	43	46.7	103	45	43.5	96	27
94	45.3	41	47.3	104	45	44.1	97	27
98	44.5	38	46.2	104	43	43.4	98	25
102	44.8	37	46.7	104	40	46.6	104	22



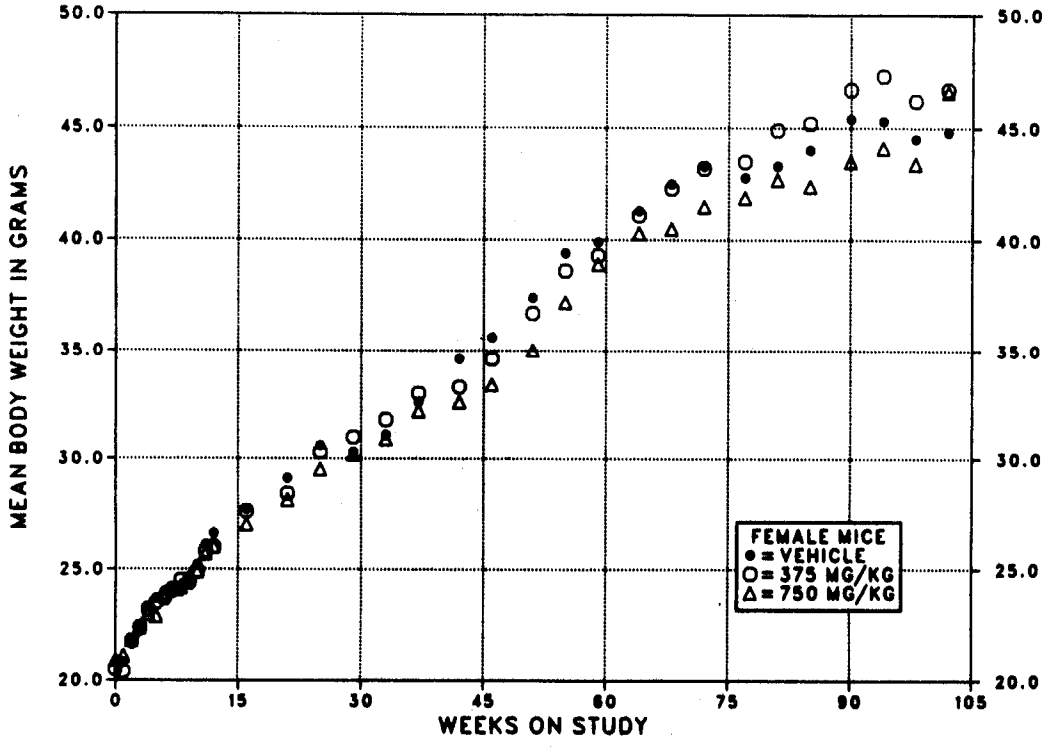


FIGURE 7. GROWTH CURVES FOR MICE ADMINISTERED 2-MERCAPTOBENZOTHIAZOLE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice administered 2-mercaptobenzothiazole at the doses used in these studies and for vehicle controls are shown in Table 25 and in the Kaplan and Meier curves in Figure 8. Survival of the high dose group of female mice was significantly lower than that of the vehicle controls after week 27. Six high dose male and four high dose female mice died on the same day during week 13. Since they were mistakenly dosed twice within a 16-hour period, these mice were censored from the statistical incidence of survival after week 12.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the liver, pituitary gland, hematopoietic system, and lung.

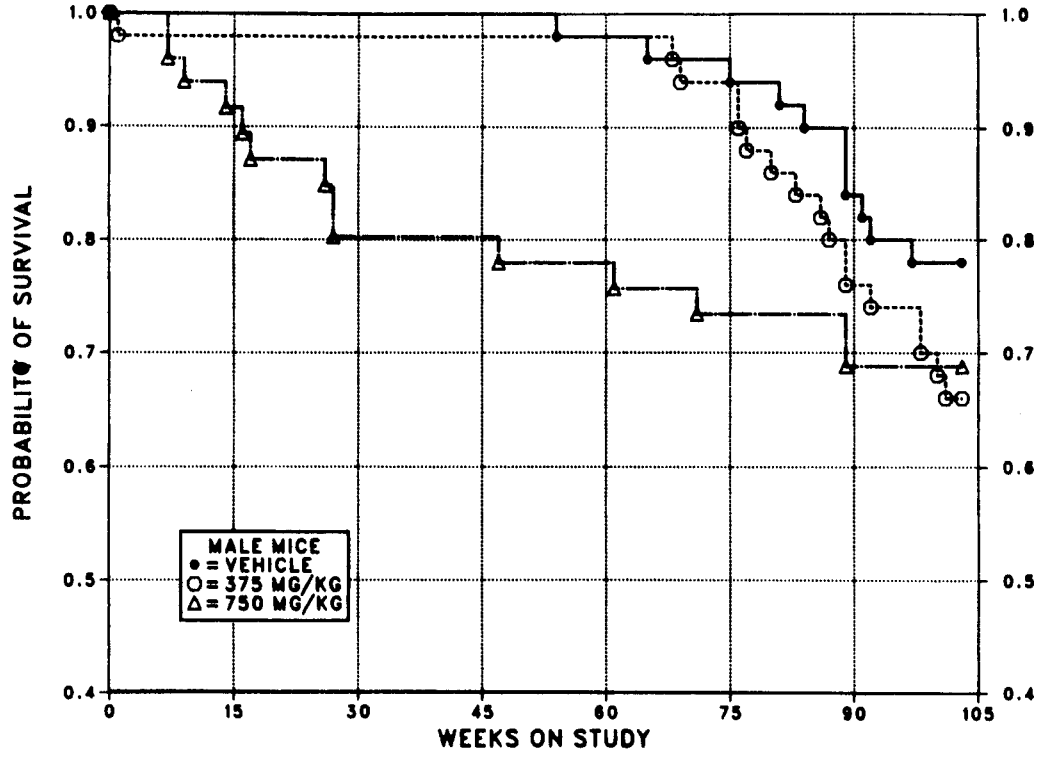
Lesions in male mice are summarized in Appendix C. Histopathologic findings on neoplasms are summarized in Table C1. Table C2 gives the survival and tumor status for individual male mice. Table C3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table C3 (footnotes). Findings on nonneoplastic lesions are summarized in Table C4.

Lesions in female mice are summarized in Appendix D. Histopathologic findings on neoplasms are summarized in Table D1. Table D2 gives the survival and tumor status for individual female mice. Table D3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table D3 (footnotes). Historical incidences of tumors in corn oil vehicle control female mice are listed in Table D4. Findings on nonneoplastic lesions are summarized in Table D5.

TABLE 25. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF 2-MERCAPTOBENZOTHIAZOLE

	Vehicle Control	375 mg/kg	750 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	11	17	14
Animals missing	1	0	0
Accidentally killed	0	0	6
Killed at termination	38	33	30
Survival P values (c)	0.204	0.262	0.254
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	13	10	24
Animals missing	0	1	0
Accidentally killed	0	0	4
Killed at termination	35	39	22
Died during termination period	2	0	0
Survival P values (c)	0.002	0.560	0.005

(a) Terminal-kill period: male, week 103; female, weeks 103-104
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.



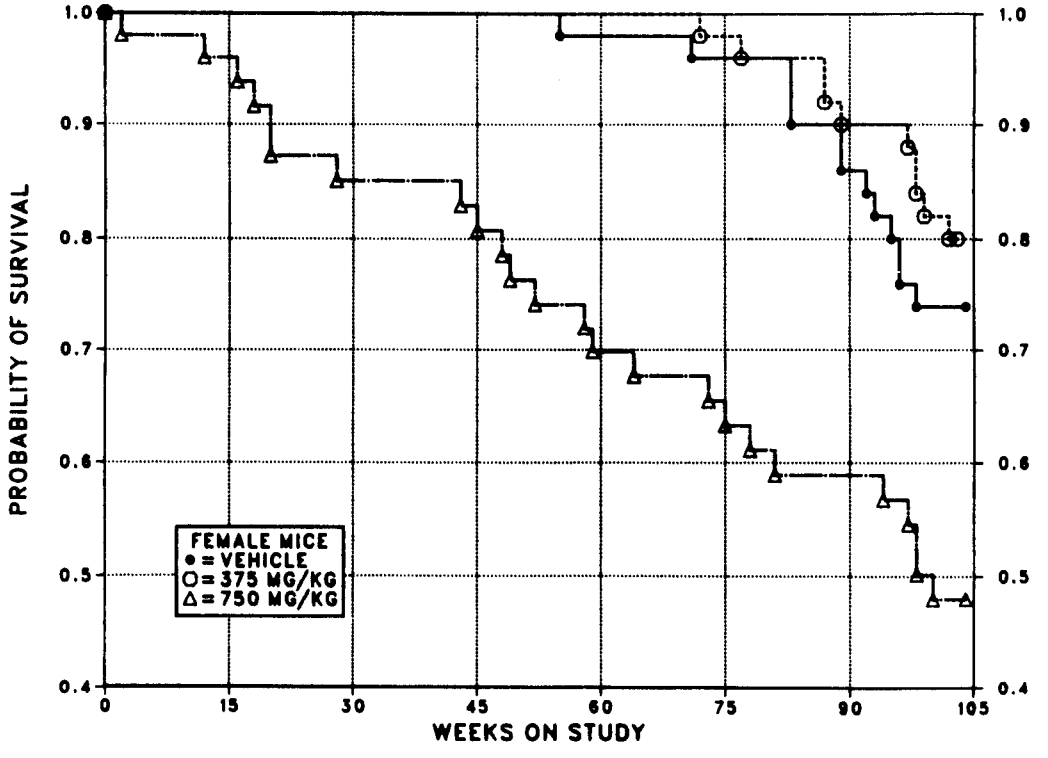


FIGURE 8. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED 2-MERCAPTOBENZOTHIAZOLE IN CORN OIL BY GAVAGE FOR TWO YEARS

Liver: The incidence of hepatocellular adenomas or carcinomas (combined) in low dose female mice was significantly greater than that in the vehicle controls (Table 26). Hepatocellular adenomas or carcinomas (combined) were seen in 16/49 vehicle control, 21/50 low dose, and 14/50 high dose male mice.

TABLE 26. ANALYSIS OF HEPATOCELLULAR TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (a)

	Vehicle Control	375 mg/kg	750 mg/kg
Adenoma			
Overall Rates	3/50 (6%)	7/49 (14%)	4/50 (8%)
Adjusted Rates	8.1%	17.9%	18.2%
Terminal Rates	3/37 (8%)	7/39 (18%)	4/22 (18%)
Week of First Observation	103	103	103
Life Table Tests	P=0.159	P=0.178	P=0.231
Incidental Tumor Tests	P=0.159	P=0.178	P=0.231
Carcinoma			
Overall Rates	1/50 (2%)	5/49 (10%)	0/50 (0%)
Adjusted Rates	2.7%	12.2%	0.0%
Terminal Rates	1/37 (3%)	4/39 (10%)	0/22 (0%)
Week of First Observation	103	89	
Life Table Tests	P=0.590N	P=0.116	P=0.604N
Incidental Tumor Tests	P=0.552	P=0.088	P=0.604N
Adenoma or Carcinoma (b)			
Overall Rates	4/50 (8%)	12/49 (24%)	4/50 (8%)
Adjusted Rates	10.8%	29.8%	18.2%
Terminal Rates	4/37 (11%)	11/39 (28%)	4/22 (18%)
Week of First Observation	103	89	103
Life Table Tests	P=0.204	P=0.035	P=0.343
Incidental Tumor Tests	P=0.171	P=0.028	P=0.343

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix D, Table D3 (footnotes).
(b) Historical incidence in NTP studies (mean ± SD): 116/1,489 (8% ± 6%)

Pituitary Gland: Adenomas and adenomas or carcinomas (combined) in female mice occurred with significant negative trends, and the incidences in the dosed groups were significantly lower than those in the vehicle controls (Table 27).

Hematopoietic System: Lymphomas in female mice occurred with a significant negative trend, and the incidence in the low dose group was significantly lower than that in the vehicle controls (Table 28).

Lung: The incidence of bronchopneumonia in all groups of mice varied from 24% to 49% (male: vehicle control, 12/49; low dose, 16/50; high dose, 16/50; female: 13/50; 24/49; 18/50). These lesions were of minimal to mild severity and consistent with those changes seen with viral infections. Serologic titers from sentinel animals were positive for Sendai virus antibody.

TABLE 27. ANALYSIS OF PITUITARY GLAND LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE

	Vehicle Control	375 mg/kg	750 mg/kg
Hyperplasia			
Overall Rates	16/49 (33%)	14/49 (29%)	12/49 (24%)
Adenoma			
Overall Rates	20/49 (41%)	11/49 (22%)	3/49 (6%)
Adjusted Rates	51.1%	26.4%	12.5%
Terminal Rates	18/37 (49%)	9/39 (23%)	2/22 (9%)
Week of First Observation	92	87	94
Life Table Tests	P=0.002N	P=0.028N	P=0.004N
Incidental Tumor Tests	P=0.001N	P=0.035N	P=0.003N
Carcinoma			
Overall Rates	1/49 (2%)	0/49 (0%)	0/49 (0%)
Adenoma or Carcinoma (a)			
Overall Rates	21/49 (43%)	11/49 (22%)	3/49 (6%)
Adjusted Rates	52.1%	26.4%	12.5%
Terminal Rates	18/37 (49%)	9/39 (23%)	2/22 (9%)
Week of First Observation	71	87	94
Life Table Tests	P<0.001N	P=0.019N	P=0.003N
Incidental Tumor Tests	P<0.001N	P=0.024N	P=0.001N

(a) Historical incidence of adenomas or carcinomas (combined) in NTP studies (mean ± SD): 257/1,324 (19% ± 9%)

TABLE 28. ANALYSIS OF HEMATOPOIETIC SYSTEM TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE

	Vehicle Control	375 mg/kg	750 mg/kg
Malignant Lymphoma (a)			
Overall Rates	19/50 (38%)	10/49 (20%)	6/50 (12%)
Adjusted Rates	48.5%	23.2%	25.3%
Terminal Rates	17/37 (46%)	7/39 (18%)	5/22 (23%)
Week of First Observation	89	72	75
Life Table Tests	P=0.032N	P=0.028N	P=0.076N
Incidental Tumor Tests	P=0.016N	P=0.035N	P=0.057N

(a) Historical incidence of lymphomas or leukemia in NTP studies (mean ± SD): 393/1,494 (26% ± 9%)

IV. DISCUSSION AND CONCLUSIONS

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2-Mercaptobenzothiazole is used in automobile tire production as an accelerant for the rubber vulcanization process and as a preservative for textile or cordage materials (Santadonato et al., 1976). The chemical is also contained in rubber medical devices and in baby bottle nipples, and it can leach into aqueous media (Petersen et al., 1981; Blosczyk and Doemling, 1982). Toxicity and carcinogenicity studies of 2-mercaptobenzothiazole were conducted by the NTP because of the high production volume (USITC, 1985), potential human exposure, and use of the salts of 2-mercaptobenzothiazole as fungicides and bactericides (Foltinova and Bloeckinger, 1970).

There was no indication from the short-term studies that the doses used in the 2-year studies would adversely affect survival of the rats. The dose selections were based on minimal toxic responses in the 13-week studies: minor decreases in body weight gain, small increases in liver weight to body weight ratios, and limited clinical observations. Despite this conservative approach, the 2-mercaptobenzothiazole doses selected proved to be toxic for both dose groups of male rats and for high dose female mice, although survival at 90 weeks ranged between 70% and 100% for all dosed groups of rats. A review of the individual animal records indicated that tumors were observed in most of the rats that died before study termination. Lung hemorrhage and congestion were associated with most of the mice that died early, and there was a consistent lack of tumors in these animals. However, final survival rates in these groups were 40%-50%, so a sufficient number of animals remained at risk to permit determination of the presence or absence of carcinogenicity.

There was a documented incident of unusual mortality in mice mistakenly dosed twice within a 16-hour period during week 13 of the 2-year studies. These animals were censored from the statistical analysis of survival after week 12; death may have been associated with the narcotic effect of the bolus doses given at short intervals.

The principal nonneoplastic lesions seen in these studies were nephropathy and inflammation and ulceration of the forestomach in rats. Although in earlier studies acute or short-term exposure to toxic doses of 2-mercaptobenzothiazole caused neurotoxicity (Johnson et al., 1970) and hepatoxicity (Guess and O'Leary, 1969; Litvinchuk, 1963; Vorob'eva and Mezentsera, 1968), there was no evidence from the present studies that long-term exposure to 2-mercaptobenzothiazole caused similar nonneoplastic lesions. Dosed mice had some clinical signs of neurotoxicity characterized as postgavage lethargy (at 375 and 750 mg/kg) and seizures (at 750 and 1,500 mg/kg) in the 13-week studies and as postgavage lethargy in rats and mice in the 2-year studies. Examination of tissues from the nervous system did not reveal lesions that were attributable to chemical administration.

Distribution studies after dermal application indicated that the thyroid gland, liver, and kidney were the principal organs that accumulated 2-mercaptobenzothiazole (Nagamatsu et al., 1979). In the present gavage studies, there was no evidence of lesions in the thyroid gland, where neoplastic and nonneoplastic responses to chemicals containing sulfur have most often occurred (NCI, 1978a, 1979).

Although a variety of neoplasms occurred in rats dosed with 2-mercaptobenzothiazole, their incidences were not always dose related. For example, the incidences of mononuclear cell leukemia and pancreatic acinar cell adenomas in male rats were increased only in the low dose groups. Comparable numbers of male rats were at risk at the end of the study (22 low dose and 20 high dose), so it is doubtful that survival rates affected the dose-response relationship for neoplasms. Examples of neoplasms with dose-related trends included pituitary gland adenomas in female rats and adrenal gland pheochromocytomas in each sex of rats. These responses suggested that 2-mercaptobenzothiazole expressed some carcinogenic activity in rats at doses sufficient to accelerate mortality.

There was equivocal evidence for the carcinogenicity of 2-mercaptobenzothiazole in female mice as shown by an increased incidence of hepatocellular adenomas or carcinomas (combined) in the low dose group. It is possible that low survival in the high dose group of female mice prevented the expression of hepatocellular tumorigenicity, since this is a late-appearing neoplasm in mice.

Some of the tumor responses to 2-mercaptobenzothiazole were comparable to those induced by other sulfur-containing chemicals in studies evaluated by the NCI (Griesemer and Cueto, 1980) and the NTP (Huff, 1982; Haseman et al., 1984). Of these chemicals, 2-mercaptobenzothiazole has the closest structural resemblance to 4,4'-thiodianiline. When administered in feed, 4,4'-thiodianiline caused hepatocellular carcinomas in male rats and in male and female mice (NCI, 1978a), whereas 2-mercaptobenzothiazole induced hepatocellular adenomas in female mice. Other responses to thio chemicals comparable to those induced by 2-mercaptobenzothiazole in the present studies included leukemia in male rats induced by intraperitoneal injection of thio-TEPA (NCI, 1978b) and forestomach neoplasms and nephropathy in male rats after the administration of sulfallate in feed (NCI, 1978c).

Neoplasms of the thyroid gland occurred in animals dosed with the other thio compounds but not after 2-mercaptobenzothiazole exposure. Thioacetamide, thiourea, and thiouracil are structurally similar to 2-mercaptobenzothiazole and cause neoplasms of the thyroid gland and sometimes the liver (Weisburger and Williams, 1980). For example, *N,N'*-diethylthiourea, which is structurally similar to the carcinogen ethylene thiourea (IARC, 1974), caused thyroid gland tumors in rats of each sex when administered in feed (NCI, 1979). The mechanism of action was hypothesized to be interference with thyroxine synthesis and subsequent stimulation of the pituitary gland-thyroid gland axis, causing enhanced secretion of thyrotropic hormone and possible neoplasia of the thyroid gland. Possible explanations for the lack of thyroid gland tumor expression by 2-mercaptobenzothiazole are the different route of administration or the comparatively lower doses used in the present studies. In the earlier studies, the thio chemicals were all given ad libitum in feed except for thio-TEPA, which was injected intraperitoneally three times per week. 4,4'-Thiodianiline, sulfallate, and thio-TEPA were administered at concentrations high enough to affect the thyroid gland, whereas this organ apparently was not affected by 2-mercaptobenzothiazole administered by gavage at lower concentrations. Although there was significant mortality in the present studies, even higher rates of mortality occurred in each of the earlier studies, such that there was either early termination of the studies or early withdrawal of chemical exposure.

Metabolism studies in F344 rats indicated that the half-life for 2-mercaptobenzothiazole after administration by gavage was less than 8 hours and possibly as short as 4-6 hours (CMA, 1986a). Absorption was rapid and unaffected by doses up to 55 mg/kg. The major products of metabolism were polar metabolites, a finding in agreement with those from earlier dermal absorption studies (Colucci and Buyske, 1965; Nagamatsu et al., 1979) in which glucuronide and sulfate conjugates of various proposed metabolites were demonstrated. In the CMA gavage study (1986a), 2-mercaptobenzothiazole-derived radioactivity in blood decreased very little between 24 and 96 hours, suggesting that residual 2-mercaptobenzothiazole-derived material accumulated in blood; no data were available for other tissues, so the potential accumulation of 2-mercaptobenzothiazole after long-term exposure is unknown. In a companion study, radiolabeled 2-mercaptobenzothiazole was administered intravenously to F344 rats (CMA, 1986b). Whole blood, plasma, urine, and feces were analyzed for radioactivity at 5 and 15 minutes and at 1, 2, 4, 24, and 72 hours. Most of the radioactivity (91%-101%) was excreted in the urine and 4%-8% was excreted in the feces by 72 hours. A small amount (1.5%-2%) of the radioactivity remained in the erythrocytes. The metabolites found in the urine samples were the same as those found in the gavage study (CMA, 1986a).

2-Mercaptobenzothiazole was clearly clastogenic to cultured Chinese hamster ovary (CHO) cells in the presence of S9 enzymes, inducing aberrations at frequencies comparable to and even exceeding those of the positive control chemical cyclophosphamide (Appendix E, Table E4). It also induced sister chromatid exchanges in CHO cells (Table E3) and thymidine kinase mutants in mouse L5178Y lymphoma cells in the presence of S9 (Table E2). In mouse lymphoma assays, the frequency of thymidine kinase mutants also was increased in the absence of S9 but only at toxic doses (Litton, 1985). Under these conditions, some of the mutant colonies produced were of small size, suggesting that 2-mercaptobenzothiazole is capable of inducing chromosomal

aberrations in this cell line as well. Although 2-mercaptobenzothiazole is clastogenic in vitro, the only reported study for in vivo mutagenicity, a mouse bone marrow micronucleus test, did not show an increase in the frequency of micronucleated polychromatic erythrocytes in these cells (Pharmakon, 1984).

The experimental and tabulated data for the NTP Technical Report on 2-mercaptobenzothiazole were examined for accuracy, consistency, completeness, and compliance with Good Laboratory Practice regulations. As summarized in Appendix H, the audit revealed no major problems with the conduct of the studies or with collection and documentation of the experimental data. No discrepancies were found that influenced the final interpretation of the results of these studies.

Conclusions: Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenic activity** of 2-mercaptobenzothiazole for male F344/N rats, indicated by increased incidences of mononuclear cell leukemia, pancreatic acinar cell adenomas, adrenal gland pheochromocytomas, and preputial gland adenomas or carcinomas (combined). There was *some evidence of carcinogenic activity* for female F344/N rats, indicated by increased incidences of adrenal gland pheochromocytomas and pituitary gland adenomas. There was *no evidence of carcinogenic activity* of 2-mercaptobenzothiazole for male $B6C3F_1$ mice dosed with 375 or 750 mg/kg. There was *equivocal evidence of carcinogenic activity* for female $B6C3F_1$ mice, indicated by increased incidences of hepatocellular adenomas or carcinomas (combined).

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 8.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 11-12.

V. REFERENCES

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APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)	2 (4%)	2 (4%)
Squamous cell carcinoma	1 (2%)		1 (2%)
Basal cell tumor	2 (4%)		
Keratoacanthoma	1 (2%)	2 (4%)	1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS		1 (2%)	1 (2%)
Fibroma	2 (4%)	3 (6%)	6 (12%)
Fibrosarcoma	1 (2%)	1 (2%)	
Fibrous histiocytoma, malignant			1 (2%)
Lipoma	1 (2%)		
Neurofibroma		1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	2 (4%)	1 (2%)	
Alveolar/bronchiolar carcinoma	1 (2%)	1 (2%)	
C-cell carcinoma, metastatic		1 (2%)	
Mucinous adenocarcinoma			1 (2%)
Pheochromocytoma, metastatic			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	7 (14%)	16 (32%)	3 (6%)
#Spleen	(50)	(50)	(49)
Sarcoma, NOS		1 (2%)	
#Thymus	(50)	(49)	(48)
Thymoma, benign	1 (2%)		
CIRCULATORY SYSTEM			
#Spleen	(50)	(50)	(49)
Hemangiosarcoma		1 (2%)	
#Heart	(50)	(50)	(50)
Pheochromocytoma, metastatic			1 (2%)
Neurilemoma, malignant		1 (2%)	
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Neoplastic nodule	3 (6%)	2 (4%)	1 (2%)
Mixed hepato/cholangio carcinoma			1 (2%)
#Pancreas	(50)	(50)	(49)
Acinar cell adenoma	2 (4%)	13 (26%)	6 (12%)
#Duodenum	(50)	(50)	(49)
Leiomyosarcoma		1 (2%)	

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
#Kidney	(50)	(50)	(49)
Transitional cell carcinoma		1 (2%)	
Tubular cell adenoma		1 (2%)	1 (2%)
#Kidney/pelvis	(50)	(50)	(49)
Transitional cell papilloma		1 (2%)	1 (2%)
Leiomyosarcoma	1 (2%)		
ENDOCRINE SYSTEM			
#Pituitary intermedia	(50)	(50)	(48)
Adenoma, NOS		1 (2%)	
#Anterior pituitary	(50)	(50)	(48)
Adenoma, NOS	14 (28%)	21 (42%)	12 (25%)
#Adrenal	(50)	(50)	(49)
Cortical adenoma		1 (2%)	1 (2%)
#Adrenal medulla	(50)	(50)	(49)
Pheochromocytoma	18 (36%)	25 (50%)	22 (45%)
Pheochromocytoma, malignant		2 (4%)	2 (4%)
#Thyroid	(50)	(50)	(50)
Follicular cell adenoma		1 (2%)	
Follicular cell carcinoma	1 (2%)	1 (2%)	
C-cell adenoma	2 (4%)	3 (6%)	1 (2%)
C-cell carcinoma	5 (10%)	2 (4%)	
#Pancreatic islets	(50)	(50)	(49)
Islet cell adenoma	4 (8%)	2 (4%)	1 (2%)
Islet cell carcinoma	1 (2%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Fibroadenoma	2 (4%)	1 (2%)	1 (2%)
*Preputial gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)	2 (4%)	1 (2%)
Adenoma, NOS		4 (8%)	4 (8%)
#Testis	(50)	(50)	(50)
Interstitial cell tumor	48 (96%)	48 (96%)	48 (96%)
Pheochromocytoma, metastatic			1 (2%)
#Tunica albuginea	(50)	(50)	(50)
Mesothelioma, NOS		1 (2%)	1 (2%)
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Astrocytoma			1 (2%)
Oligodendroglioma			1 (2%)
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS		1 (2%)	1 (2%)
Squamous cell carcinoma		1 (2%)	
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mesentery	(50)	(50)	(50)
Pheochromocytoma, invasive			1 (2%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	Low Dose	High Dose
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)		
Mesothelioma, malignant		1 (2%)	2 (4%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	2	2	5
Moribund sacrifice	6	26	24
Terminal sacrifice	42	22	20
Dosing accident			1
TUMOR SUMMARY			
Total animals with primary tumors**	49	50	48
Total primary tumors	123	169	125
Total animals with benign tumors	49	50	48
Total benign tumors	100	131	107
Total animals with malignant tumors	19	27	15
Total malignant tumors	20	35	16
Total animals with secondary tumors##		1	1
Total secondary tumors		1	4
Total animals with tumors uncertain--benign or malignant	3	3	2
Total uncertain tumors	3	3	2

* Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE: VEHICLE CONTROL

ANIMAL NUMBER	103	102	105	124	123	143	107	131	101	104	106	108	109	110	111	112	113	114	115	116	117	118	119	120	121
WEEKS ON STUDY	091	092	093	094	098	098	101	102	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																			X						
Squamous cell carcinoma																									
Basal cell tumor																							X		
Keratoacanthoma			X																						
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma									X					X											
Fibrosarcoma												X													
Lipoma															X										
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X													X									
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma, benign																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule				X											X										
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma				X																					X
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS				X	X	X									X	X								X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma			X		X		X		X						X		X					X	X	X	X
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																									X
C-cell adenoma						X															X				
C-carcinoma					X																X				
Parathyroid	–	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma								X	X																
Islet cell carcinoma																							X		
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS					X																				
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS								X																	
Leukemia, mononuclear cell	X		X			X			X										X						

+: Tissue examined microscopically
–: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
@: Multiple occurrence of morphology

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

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

ANIMAL NUMBER	122	125	126	127	128	129	130	132	133	134	135	136	137	138	139	140	141	142	144	145	146	147	148	149	150	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																										1
Squamous cell carcinoma															X											1
Basal cell tumor																								X		2
Keratoacanthoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										2
Fibrosarcoma																										1
Lipoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										2
Alveolar/bronchiolar carcinoma						X																				1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymoma, benign					X																					1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule														X												3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell adenoma																										2
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																	X									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS								X			X	X	X			X		X			X	X				14
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma	X	X	X					X			X			X	X		X					X				18
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell carcinoma																										1
C-cell adenoma																										2
C-cell carcinoma								X														X			X	5
Parathyroid	+	–	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	–	+	–	+	+	+	41
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma					X														X							4
Islet cell carcinoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma													X			X										2
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	48
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS																										1
Leukemia, mononuclear cell													X						X							7

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE: LOW DOSE

ANIMAL NUMBER	025	041	013	023	047	016	048	042	029	026	043	040	030	008	049	045	011	038	005	019	032	001	010	050	027
WEEKS ON STUDY	078	078	082	083	084	085	085	086	087	088	088	089	091	092	092	093	098	098	099	099	099	100	100	100	101
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																				X		X			
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS						X																			
Fibroma							X							X											
Fibrosarcoma													X												
Neurofibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma		X																							
Alveolar/bronchiolar carcinoma																									
C-cell carcinoma, metastatic														X											
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS													X												
Hemangiosarcoma													X												
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, malignant																								X	
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule		X																							
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma										X						X		X		X					
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma														X											
Tubular cell adenoma																									
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma																						X			
Urinary bladder	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS			X					X		X		X	X	X	X		X		X	X				X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma							X				X	X		X		X	X		X	X	X				X
Pheochromocytoma, malignant																		X							
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																								X	
Follicular cell carcinoma																									X
C-cell adenoma																									
C-cell carcinoma														X											
Parathyroid	+	+	+	+	+	+	+	+	–	–	–	+	+	–	+	–	+	–	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma		X																							
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	+	+	N	N	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma												X													
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Mesothelioma, NOS																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS				X				X																	
Adenoma, NOS										X															
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N
Carcinoma, NOS										X															
Squamous cell carcinoma																						X			
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, malignant					X																				
Leukemia, mononuclear cell	X								X			X						X	X	X			X	X	

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

ANIMAL NUMBER	0 3 9	0 3 1	0 2 4	0 0 2	0 0 3	0 0 4	0 0 6	0 0 7	0 0 9	0 1 2	0 1 4	0 1 5	0 1 7	0 1 8	0 2 0	0 2 1	0 2 2	0 2 8	0 3 3	0 3 4	0 3 5	0 3 6	0 3 7	0 4 4	0 4 6	TOTAL:
WEEKS ON STUDY	1 0 1	1 0 2	1 0 3	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma					X																		X			2
Keratoacanthoma																										2
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibroma									X																	3
Fibrosarcoma																										1
Neurofibroma																							X			1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma																	X									1
C-cell carcinoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS																										1
Hemangiosarcoma																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurilemoma, malignant																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule													X													2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell adenoma		X			X	X		X	X	X			X											X	X	13
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma				X																						1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional cell carcinoma																										1
Tubular cell adenoma																	X									1
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional cell papilloma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS						X	X	X	X				X			X	X				X		@X	X			21
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																			X							1
Pheochromocytoma	X	X	X		X	X	X	X	X			X	X	X		X		X			X		X			25
Pheochromocytoma, malignant																						X				2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																										1
Follicular cell carcinoma																										1
C-cell adenoma		X	X																				X			3
C-cell carcinoma																	X									2
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	43
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma												X														2
Islet cell carcinoma																	X									1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma																										1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	48
Mesothelioma, NOS																									X	1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										2
Adenoma, NOS	X																		X				X			4
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
Squamous cell carcinoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, malignant																										1
Leukemia, mononuclear cell	X		X		X	X																X	X	X	X	16

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE: HIGH DOSE

ANIMAL NUMBER	100	074	051	088	075	096	060	082	070	065	099	094	057	072	061	080	091	068	079	071	054	055	073	097	059
WEEKS ON STUDY	057	059	062	066	068	074	082	082	084	087	091	094	095	095	096	096	096	098	098	099	100	100	100	100	101
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Squamous cell carcinoma																									
Keratoacanthoma																									X
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS						X																			
Fibroma								X			X							X				X		
Fibrous histiocytoma, malignant																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mucinous adenocarcinoma																									
Pheochromocytoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma, metastatic																									
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Mixed hepato/cholangio carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Acinar cell adenoma																		X		X		X			
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Tubular cell adenoma																									
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Transitional cell papilloma						X																			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Adenoma, NOS							X		X					X								X		X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Cortical adenoma																									
Pheochromocytoma									X				X	X	X		X	X				X	X	X	X
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																									
Parathyroid	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pheochromocytoma, metastatic																									
Mesothelioma, NOS																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Adenoma, NOS										X		X													
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma		X																							
Oligodendroglioma	X																								
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
BODY CAVITIES																									
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pheochromocytoma, invasive																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, malignant									X	X															
Leukemia, mononuclear cell											X														

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

ANIMAL NUMBER	0098	0062	0076	0092	0095	0052	0053	0056	0058	0063	0064	0066	0067	0069	0077	0078	0081	0083	0084	0085	0086	0087	0089	0090	0093	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	101	102	102	102	102	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma													X											X		2
Squamous cell carcinoma																									X	1
Keratoacanthoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibroma										X									X							6
Fibrous histiocytoma, malignant		X																								1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mucinous adenocarcinoma								X																		1
Pheochromocytoma, metastatic										X																1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma, metastatic										X																1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule															X											1
Mixed hepato/cholangio carcinoma		X																								1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinar cell adenoma					X	X																X				6
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tubular cell adenoma							X																			1
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Transitional cell papilloma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS		X					X	X	X											X					X	12
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma																			X							1
Pheochromocytoma				X		X		X	X		X	X	X		X		X		X		X				X	22
Pheochromocytoma, malignant										X										X						2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell adenoma																							X			1
Parathyroid	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+		42
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma	X																									1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma																	X									1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	48
Pheochromocytoma, metastatic										X																1
Mesothelioma, NOS																							X			1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																		X								1
Adenoma, NOS								X													X					4
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma																										1
Oligodendroglioma																										1
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS			X																							1
BODY CAVITIES																										
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pheochromocytoma, invasive										X																1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, malignant																										2
Leukemia, mononuclear cell													X								X					3

* Animals necropsied

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE

	Vehicle Control	375 mg/kg	750 mg/kg
Skin: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	2/50 (4%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	4.8%	9.1%	15.0%
Terminal Rates (c)	2/42 (5%)	2/22 (9%)	3/20 (15%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.132	P=0.446	P=0.190
Incidental Tumor Tests (d)	P=0.132	P=0.446	P=0.190
Cochran-Armitage Trend Test (d)	P=0.406		
Fisher Exact Test (d)		P=0.691	P=0.500
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	6/50 (12%)
Adjusted Rates (b)	4.8%	9.2%	19.6%
Terminal Rates (c)	2/42 (5%)	1/22 (5%)	2/20 (10%)
Week of First Observation	104	85	82
Life Table Tests (d)	P=0.024	P=0.299	P=0.033
Incidental Tumor Tests (d)	P=0.064	P=0.612	P=0.153
Cochran-Armitage Trend Test (d)	P=0.090		
Fisher Exact Test (d)		P=0.500	P=0.134
Subcutaneous Tissue: Fibroma or Neurofibroma			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	6/50 (12%)
Adjusted Rates (b)	4.8%	13.5%	19.6%
Terminal Rates (c)	2/42 (5%)	2/22 (9%)	2/20 (10%)
Week of First Observation	104	85	82
Life Table Tests (d)	P=0.023	P=0.147	P=0.033
Incidental Tumor Tests (d)	P=0.060	P=0.353	P=0.153
Cochran-Armitage Trend Test (d)	P=0.099		
Fisher Exact Test (d)		P=0.339	P=0.134
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	4/50 (8%)	6/50 (12%)
Adjusted Rates (b)	7.1%	11.6%	19.6%
Terminal Rates (c)	3/42 (7%)	1/22 (5%)	2/20 (10%)
Week of First Observation	104	85	82
Life Table Tests (d)	P=0.055	P=0.266	P=0.064
Incidental Tumor Tests (d)	P=0.143	P=0.671	P=0.237
Cochran-Armitage Trend Test (d)	P=0.187		
Fisher Exact Test (d)		P=0.500	P=0.243
Subcutaneous Tissue: Fibroma, Neurofibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	6/50 (12%)	7/50 (14%)
Adjusted Rates (b)	7.1%	17.7%	21.4%
Terminal Rates (c)	3/42 (7%)	2/22 (9%)	2/20 (10%)
Week of First Observation	104	85	74
Life Table Tests (d)	P=0.031	P=0.084	P=0.037
Incidental Tumor Tests (d)	P=0.129	P=0.396	P=0.237
Cochran-Armitage Trend Test (d)	P=0.128		
Fisher Exact Test (d)		P=0.243	P=0.159
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	6.7%	6.5%	0.0%
Terminal Rates (c)	2/42 (5%)	1/22 (5%)	0/20 (0%)
Week of First Observation	93	78	
Life Table Tests (d)	P=0.190N	P=0.664	P=0.235N
Incidental Tumor Tests (d)	P=0.043N	P=0.409N	P=0.124N
Cochran-Armitage Trend Test (d)	P=0.082N		
Fisher Exact Test (d)		P=0.500N	P=0.121N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	375 mg/kg	750 mg/kg
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	7/50 (14%)	16/50 (32%)	3/50 (6%)
Adjusted Rates (b)	15.1%	47.2%	12.3%
Terminal Rates (c)	4/42 (10%)	6/22 (27%)	2/20 (10%)
Week of First Observation	91	78	91
Life Table Tests (d)	P=0.475	P=0.002	P=0.449N
Incidental Tumor Tests (d)	P=0.084N	P=0.103	P=0.157N
Cochran-Armitage Trend Test (d)	P=0.178N		
Fisher Exact Test (d)		P=0.028	P=0.159N
Liver: Neoplastic Nodule			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	6.8%	6.5%	5.0%
Terminal Rates (c)	2/42 (5%)	1/22 (5%)	1/20 (5%)
Week of First Observation	94	78	104
Life Table Tests (d)	P=0.431N	P=0.663	P=0.533N
Incidental Tumor Tests (d)	P=0.198N	P=0.409N	P=0.401N
Cochran-Armitage Trend Test (d)	P=0.222N		
Fisher Exact Test (d)		P=0.500N	P=0.309N
Pancreas: Acinar Cell Adenoma			
Overall Rates (a)	2/50 (4%)	13/50 (26%)	6/49 (12%)
Adjusted Rates (b)	4.5%	45.7%	23.0%
Terminal Rates (c)	1/42 (2%)	8/22 (36%)	3/20 (15%)
Week of First Observation	94	88	98
Life Table Tests (d)	P=0.017	P<0.001	P=0.030
Incidental Tumor Tests (d)	P=0.118	P<0.001	P=0.160
Cochran-Armitage Trend Test (d)	P=0.146		
Fisher Exact Test (d)		P=0.002	P=0.128
Pituitary Gland: Adenoma			
Overall Rates (a)	14/50 (28%)	21/50 (42%)	12/48 (25%)
Adjusted Rates (b)	30.9%	59.9%	40.1%
Terminal Rates (c)	11/42 (26%)	10/22 (45%)	5/20 (25%)
Week of First Observation	94	82	82
Life Table Tests (d)	P=0.106	P=0.003	P=0.171
Incidental Tumor Tests (d)	P=0.506N	P=0.132	P=0.482N
Cochran-Armitage Trend Test (d)	P=0.426N		
Fisher Exact Test (d)		P=0.104	P=0.458N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	18/50 (36%)	25/50 (50%)	22/49 (45%)
Adjusted Rates (b)	39.8%	70.3%	68.5%
Terminal Rates (c)	15/42 (36%)	12/22 (55%)	11/20 (55%)
Week of First Observation	93	85	84
Life Table Tests (d)	P=0.002	P<0.001	P=0.002
Incidental Tumor Tests (d)	P=0.109	P=0.056	P=0.111
Cochran-Armitage Trend Test (d)	P=0.213		
Fisher Exact Test (d)		P=0.113	P=0.243
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	18/50 (36%)	27/50 (54%)	24/49 (49%)
Adjusted Rates (b)	39.8%	74.1%	75.5%
Terminal Rates (c)	15/42 (36%)	13/22 (59%)	13/20 (65%)
Week of First Observation	93	85	84
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.038	P=0.021	P=0.034
Cochran-Armitage Trend Test (d)	P=0.115		
Fisher Exact Test (d)		P=0.054	P=0.135

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	375 mg/kg	750 mg/kg
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	4.5%	12.5%	5.0%
Terminal Rates (c)	1/42 (2%)	1/22 (5%)	1/20 (5%)
Week of First Observation	98	102	104
Life Table Tests (d)	P=0.526	P=0.264	P=0.703N
Incidental Tumor Tests (d)	P=0.346N	P=0.594	P=0.548N
Cochran-Armitage Trend Test (d)	P=0.399N		
Fisher Exact Test (d)		P=0.500	P=0.500N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	6/50 (12%)	5/50 (10%)	1/50 (2%)
Adjusted Rates (b)	13.5%	18.9%	5.0%
Terminal Rates (c)	4/42 (10%)	2/22 (9%)	1/20 (5%)
Week of First Observation	98	92	104
Life Table Tests (d)	P=0.249N	P=0.388	P=0.219N
Incidental Tumor Tests (d)	P=0.052N	P=0.454N	P=0.082N
Cochran-Armitage Trend Test (d)	P=0.049N		
Fisher Exact Test (d)		P=0.500N	P=0.056N
Pancreatic Islets: Islet Cell Adenoma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	1/49 (2%)
Adjusted Rates (b)	9.3%	6.5%	3.8%
Terminal Rates (c)	3/42 (7%)	1/22 (5%)	0/20 (0%)
Week of First Observation	102	78	101
Life Table Tests (d)	P=0.318N	P=0.591N	P=0.425N
Incidental Tumor Tests (d)	P=0.072N	P=0.295N	P=0.166N
Cochran-Armitage Trend Test (d)	P=0.122N		
Fisher Exact Test (d)		P=0.339N	P=0.187N
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	3/50 (6%)	1/49 (2%)
Adjusted Rates (b)	11.6%	10.9%	3.8%
Terminal Rates (c)	4/42 (10%)	2/22 (9%)	0/20 (0%)
Week of First Observation	102	78	101
Life Table Tests (d)	P=0.268N	P=0.626	P=0.324N
Incidental Tumor Tests (d)	P=0.069N	P=0.419N	P=0.118N
Cochran-Armitage Trend Test (d)	P=0.073N		
Fisher Exact Test (d)		P=0.357N	P=0.107N
Preputial Gland: Adenoma			
Overall Rates (a)	0/50 (0%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	0.0%	14.7%	14.4%
Terminal Rates (c)	0/42 (0%)	2/22 (9%)	2/20 (10%)
Week of First Observation		88	87
Life Table Tests (d)	P=0.016	P=0.019	P=0.021
Incidental Tumor Tests (d)	P=0.042	P=0.076	P=0.063
Cochran-Armitage Trend Test (d)	P=0.060		
Fisher Exact Test (d)		P=0.059	P=0.059
Preputial Gland: Adenoma or Carcinoma			
Overall Rates (a)	1/50 (2%)	6/50 (12%)	5/50 (10%)
Adjusted Rates (b)	2.2%	18.5%	19.2%
Terminal Rates (c)	0/42 (0%)	2/22 (9%)	3/20 (15%)
Week of First Observation	98	83	87
Life Table Tests (d)	P=0.027	P=0.021	P=0.030
Incidental Tumor Tests (d)	P=0.094	P=0.216	P=0.117
Cochran-Armitage Trend Test (d)	P=0.099		
Fisher Exact Test (d)		P=0.056	P=0.102

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	375 mg/kg	750 mg/kg
Testis: Interstitial Cell Tumor			
Overall Rates (a)	48/50 (96%)	48/50 (96%)	48/50 (96%)
Adjusted Rates (b)	96.0%	100.0%	100.0%
Terminal Rates (c)	40/42 (95%)	22/22 (100%)	20/20 (100%)
Week of First Observation	91	78	57
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.271	P=0.617	P=0.412
Cochran-Armitage Trend Test (d)	P=0.601		
Fisher Exact Test (d)		P=0.691N	P=0.691N
All Sites: Mesothelioma			
Overall Rates (a)	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	0.0%	6.6%	9.5%
Terminal Rates (c)	0/42 (0%)	1/22 (5%)	1/20 (5%)
Week of First Observation		84	84
Life Table Tests (d)	P=0.039	P=0.163	P=0.066
Incidental Tumor Tests (d)	P=0.041	P=0.310	P=0.158
Cochran-Armitage Trend Test (d)	P=0.082		
Fisher Exact Test (d)		P=0.247	P=0.121
All Sites: Benign Tumors			
Overall Rates (a)	49/50 (98%)	50/50 (100%)	48/50 (96%)
Adjusted Rates (b)	98.0%	100.0%	100.0%
Terminal Rates (c)	41/42 (98%)	22/22 (100%)	20/20 (100%)
Week of First Observation	91	78	57
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.604	P=0.629	P=0.648
Cochran-Armitage Trend Test (d)	P=0.360N		
Fisher Exact Test (d)		P=0.500	P=0.500N
All Sites: Malignant Tumors			
Overall Rates (a)	19/50 (38%)	27/50 (54%)	15/50 (30%)
Adjusted Rates (b)	40.2%	63.9%	48.1%
Terminal Rates (c)	14/42 (33%)	8/22 (36%)	7/20 (35%)
Week of First Observation	91	78	57
Life Table Tests (d)	P=0.137	P=0.002	P=0.199
Incidental Tumor Tests (d)	P=0.090N	P=0.431	P=0.209N
Cochran-Armitage Trend Test (d)	P=0.238N		
Fisher Exact Test (d)		P=0.080	P=0.264N
All Sites: All Tumors			
Overall Rates (a)	49/50 (98%)	50/50 (100%)	48/50 (96%)
Adjusted Rates (b)	98.0%	100.0%	100.0%
Terminal Rates (c)	41/42 (98%)	22/22 (100%)	20/20 (100%)
Week of First Observation	91	78	57
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.604	P=0.629	P=0.648
Cochran-Armitage Trend Test (d)	P=0.360N		
Fisher Exact Test (d)		P=0.500	P=0.500N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

TABLE A4a. HISTORICAL INCIDENCE OF LEUKEMIA IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls
No 2-year studies by Physiological Research Laboratories are included in the historical data base.	
Overall Historical Incidence	
TOTAL	202/1,450 (13.9%)
SD (b)	7.55%
Range (c)	
High	14/50
Low	1/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE A4b. HISTORICAL INCIDENCE OF PITUITARY GLAND TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Adenoma	Carcinoma or Adenocarcinoma	Adenoma, Carcinoma, or Adenocarcinoma
No 2-year studies by Physiological Research Laboratories are included in the historical data base.			
Overall Historical Incidence			
TOTAL	(b) 344/1,411 (24.4%)	(c) 26/1,411 (1.8%)	(b,c) 370/1,411 (26.2%)
SD (d)	7.92%	2.42%	8.34%
Range (e)			
High	19/50	4/47	22/50
Low	5/50	0/50	6/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Includes 34 chromophobe adenomas and 1 acidophil adenoma
(c) Includes four chromophobe carcinomas and two adenocarcinomas, NOS
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

TABLE A4c. HISTORICAL INCIDENCE OF ADRENAL GLAND TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Pheochromocytoma	Malignant Pheochromocytoma	Pheochromocytoma or Malignant Pheochromocytoma
No 2-year studies by Physiological Research Laboratories are included in the historical data base.			
Overall Historical Incidence			
TOTAL	338/1,442 (23.4%)	13/1,442 (0.9%)	347/1,442 (24.1%)
SD (b)	8.72%	1.27%	8.66%
Range (c)			
High	20/49	2/50	20/49
Low	2/50	0/50	2/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE A4d. HISTORICAL INCIDENCE OF PANCREATIC ACINAR CELL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence of Adenomas in Vehicle Controls
No 2-year studies by Physiological Research Laboratories are included in the historical data base.	
Overall Historical Incidence	
TOTAL	(b) 80/1,381 (5.8%)
SD (c)	8.00%
Range (d)	
High	14/50
Low	0/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks. An incidence of 22/50 for the benzyl acetate study for which multiple sections were examined has been deleted.
(b) Includes two carcinomas
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE A4e. HISTORICAL INCIDENCE OF PREPUTIAL GLAND TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies by Physiological Research Laboratories are included in the historical data base.			
Overall Historical Incidence			
TOTAL	30/1,450 (2.1%)	(b) 35/1,450 (2.4%)	(b) 65/1,450 (4.5%)
SD (c)	3.27%	2.53%	4.33%
Range (d)			
High	7/50	5/50	9/50
Low	0/50	0/50	0/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Includes 26 carcinomas, NOS, 3 squamous cell carcinomas, and 6 adenocarcinomas, NOS
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE A4f. HISTORICAL INCIDENCE OF SUBCUTANEOUS TISSUE TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Fibroma	Fibrosarcoma	Fibroma or Fibrosarcoma
No 2-year studies by Physiological Research Laboratories are included in the historical data base.			
Overall Historical Incidence			
TOTAL	(b) 93/1,450 (6.4%)	(c) 33/1,450 (2.3%)	(b,c) 126/1,450 (8.7%)
SD (d)	2.90%	2.86%	3.68%
Range (e)			
High	6/50	6/50	8/50
Low	0/50	0/50	1/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Includes five neurofibromas
(c) Includes 10 sarcomas, NOS, and 3 neurofibrosarcomas
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

TABLE A4g. HISTORICAL INCIDENCE OF MESOTHELIAL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Mesothelioma, NOS	Malignant Mesothelioma	All Mesothelioma
No 2-year studies by Physiological Research Laboratories are included in the historical data base.			
Overall Historical Incidence			
TOTAL	48/1,450 (3.3%)	8/1,450 (0.6%)	55/1,450 (3.8%)
SD (b)	3.04%	1.30%	2.74%
Range (c)			
High	6/50	2/50	6/50
Low	0/50	0/50	0/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE A4h. HISTORICAL INCIDENCE OF KIDNEY TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

No 2-year studies by Physiological Research Laboratories are included in the historical data base.

Overall Historical Incidence

	No. Examined	No. of Tumors	Diagnosis
	1,448	1	*Transitional cell papilloma*
		3	Tubular cell adenoma
		2	Adenocarcinoma, NOS
		3	Tubular cell adenocarcinoma
TOTAL		8 (0.6%)	Tubular cell
		1 (0.1%)	Transitional cell

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Mineralization			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Ulcer, NOS		1 (2%)	
Inflammation, active chronic		1 (2%)	
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Hemorrhage	2 (4%)		2 (4%)
Inflammation, acute	1 (2%)	1 (2%)	
Inflammation, chronic	1 (2%)	6 (12%)	1 (2%)
Foreign material, NOS		1 (2%)	
*Nasal turbinate	(50)	(50)	(50)
Inflammation, active chronic		2 (4%)	
Inflammation, chronic		2 (4%)	4 (8%)
#Lung	(50)	(50)	(50)
Mineralization			1 (2%)
Congestion, NOS	6 (12%)	6 (12%)	3 (6%)
Edema, NOS			1 (2%)
Hemorrhage	3 (6%)	6 (12%)	9 (18%)
Pneumonia, interstitial chronic	5 (10%)	1 (2%)	5 (10%)
Bronchopneumonia, chronic	1 (2%)	1 (2%)	2 (4%)
Granuloma, NOS		1 (2%)	
Hyperplasia, alveolar epithelium	1 (2%)	1 (2%)	1 (2%)
Histiocytosis	4 (8%)	2 (4%)	4 (8%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(50)	(48)
Hemorrhage		1 (2%)	
Fibrosis		3 (6%)	2 (4%)
Necrosis, NOS		2 (4%)	
Hyperplasia, megakaryocytic		2 (4%)	
#Spleen	(50)	(50)	(49)
Fibrosis	3 (6%)	7 (14%)	7 (14%)
Pigmentation, NOS	44 (88%)	39 (78%)	46 (94%)
Atrophy, NOS			3 (6%)
Hyperplasia, lymphoid	2 (4%)		3 (6%)
Hematopoiesis	44 (88%)	41 (82%)	43 (88%)
#Splenic capsule	(50)	(50)	(49)
Fibrosis	1 (2%)		
#Lymph node	(50)	(50)	(50)
Cyst, NOS	1 (2%)		
#Mandibular lymph node	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
Plasmacytosis		1 (2%)	
Hyperplasia, lymphoid	8 (16%)	12 (24%)	3 (6%)
#Mesenteric lymph node	(50)	(50)	(50)
Congestion, NOS	1 (2%)	2 (4%)	1 (2%)
Hyperplasia, reticulum cell		1 (2%)	
#Liver	(50)	(50)	(50)
Hematopoiesis	2 (4%)	1 (2%)	2 (4%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Thymus	(50)	(49)	(48)
Multiple cysts	1 (2%)		
Congestion, NOS	1 (2%)		
Hemosiderosis			1 (2%)
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Periarteritis			1 (2%)
#Heart	(50)	(50)	(50)
Mineralization		1 (2%)	
Inflammation, chronic	48 (96%)	46 (92%)	50 (100%)
#Heart/atrium	(50)	(50)	(50)
Dilatation, NOS	1 (2%)	1 (2%)	
Thrombus, organized	1 (2%)		
*Pulmonary artery	(50)	(50)	(50)
Mineralization	9 (18%)	3 (6%)	8 (16%)
*Pulmonary vein	(50)	(50)	(50)
Mineralization		1 (2%)	1 (2%)
#Pancreas	(50)	(50)	(49)
Periarteritis	2 (4%)	1 (2%)	5 (10%)
*Mesentery	(50)	(50)	(50)
Periarteritis			1 (2%)
#Testis	(50)	(50)	(50)
Periarteritis			1 (2%)
DIGESTIVE SYSTEM			
*Lip	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
*Tongue	(50)	(50)	(50)
Epidermal inclusion cyst		1 (2%)	
#Salivary gland	(50)	(50)	(50)
Mineralization		1 (2%)	
Inflammation, chronic		1 (2%)	1 (2%)
Atrophy, NOS	1 (2%)	5 (10%)	4 (8%)
#Liver	(50)	(50)	(50)
Accessory structure	1 (2%)		
Inflammation, chronic	1 (2%)		
Granuloma, NOS	2 (4%)	2 (4%)	
Necrosis, NOS	1 (2%)	2 (4%)	
Metamorphosis, fatty	6 (12%)	4 (8%)	2 (4%)
Cytoplasmic vacuolization	3 (6%)	4 (8%)	2 (4%)
Focal cellular change	45 (90%)	24 (48%)	18 (36%)
Hepatocytomegaly	1 (2%)		2 (4%)
Hyperplasia, NOS	2 (4%)	2 (4%)	
Angiectasis			1 (2%)
#Hepatic capsule	(50)	(50)	(50)
Mineralization		1 (2%)	
#Liver/centrilobular	(50)	(50)	(50)
Metamorphosis, fatty	2 (4%)		
Cytoplasmic vacuolization	1 (2%)		1 (2%)
#Liver/periportal	(50)	(50)	(50)
Inflammation, chronic	45 (90%)	46 (92%)	36 (72%)
Metamorphosis, fatty	5 (10%)		3 (6%)
Cytoplasmic vacuolization	1 (2%)		1 (2%)
#Bile duct	(50)	(50)	(50)
Multiple cysts	1 (2%)		
Hyperplasia, NOS	46 (92%)	49 (98%)	47 (94%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Pancreas	(50)	(50)	(49)
Cystic ducts		1 (2%)	
Inflammation, chronic		1 (2%)	1 (2%)
#Pancreatic acinus	(50)	(50)	(49)
Focal cellular change	2 (4%)		3 (6%)
Atrophy, NOS	19 (38%)	27 (54%)	20 (41%)
Hyperplasia, NOS	5 (10%)	15 (30%)	7 (14%)
#Stomach	(50)	(50)	(49)
Inflammation, active chronic		1 (2%)	
#Gastric fundal gland	(50)	(50)	(49)
Dilatation, NOS	38 (76%)	40 (80%)	34 (69%)
#Forestomach	(50)	(50)	(49)
Edema, NOS		1 (2%)	
Ulcer, NOS		5 (10%)	5 (10%)
Inflammation, acute		1 (2%)	
Inflammation, active chronic		2 (4%)	7 (14%)
Inflammation, chronic		8 (16%)	7 (14%)
Hyperplasia, epithelial	1 (2%)	12 (24%)	17 (35%)
Hyperkeratosis		12 (24%)	17 (35%)
#Duodenum	(50)	(50)	(49)
Ulcer, NOS		1 (2%)	
Inflammation, acute		1 (2%)	
Erosion		1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(49)
Hemorrhage	1 (2%)		
Nephropathy	50 (100%)	50 (100%)	49 (100%)
#Kidney/cortex	(50)	(50)	(49)
Cyst, NOS		1 (2%)	2 (4%)
#Kidney/tubule	(50)	(50)	(49)
Mineralization	25 (50%)	24 (48%)	33 (67%)
Multiple cysts		1 (2%)	
Inflammation, acute			2 (4%)
Pigmentation, NOS	46 (92%)	49 (98%)	42 (86%)
Hyperplasia, focal		3 (6%)	3 (6%)
#Kidney/pelvis	(50)	(50)	(49)
Calculus, microscopic examination	2 (4%)		2 (4%)
Hemorrhage	1 (2%)	1 (2%)	1 (2%)
Inflammation, acute			1 (2%)
Hyperplasia, epithelial		4 (8%)	1 (2%)
#Urinary bladder	(50)	(49)	(49)
Calculus, gross observation only			1 (2%)
Inflammation, hemorrhagic			1 (2%)
Inflammation, active chronic			1 (2%)
Inflammation, chronic	1 (2%)		
*Urethra	(50)	(50)	(50)
Calculus, microscopic examination	1 (2%)	3 (6%)	2 (4%)
ENDOCRINE SYSTEM			
#Pituitary intermedia	(50)	(50)	(48)
Cyst, NOS		3 (6%)	2 (4%)
Multiple cysts		1 (2%)	
#Anterior pituitary	(50)	(50)	(48)
Cyst, NOS	6 (12%)	5 (10%)	3 (6%)
Multiple cysts	1 (2%)	1 (2%)	
Hemorrhage			1 (2%)
Focal cellular change			1 (2%)
Hyperplasia, NOS	10 (20%)	17 (34%)	12 (25%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Adrenal cortex	(50)	(50)	(49)
Accessory structure	2 (4%)		3 (6%)
Mineralization			1 (2%)
Degeneration, lipoid	7 (14%)	10 (20%)	9 (18%)
Metamorphosis, fatty	3 (6%)	4 (8%)	6 (12%)
Pigmentation, NOS		1 (2%)	
Cytoplasmic vacuolization		1 (2%)	
Hyperplasia, NOS	7 (14%)	10 (20%)	5 (10%)
Angiectasis		1 (2%)	
#Adrenal medulla	(50)	(50)	(49)
Hyperplasia, NOS	9 (18%)	14 (28%)	10 (20%)
#Thyroid	(50)	(50)	(50)
Embryonal duct cyst	1 (2%)	1 (2%)	1 (2%)
Mineralization		2 (4%)	
Cystic follicles	6 (12%)	8 (16%)	12 (24%)
Pigmentation, NOS	1 (2%)	2 (4%)	2 (4%)
Hyperplasia, C-cell	28 (56%)	38 (76%)	34 (68%)
Hyperplasia, follicular cell		1 (2%)	
#Thyroid follicle	(50)	(50)	(50)
Atrophy, NOS			1 (2%)
#Thyroid colloid	(50)	(50)	(50)
Mineralization	1 (2%)		1 (2%)
#Pancreatic islets	(50)	(50)	(49)
Hyperplasia, NOS		3 (6%)	1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Cyst, NOS			3 (6%)
Multiple cysts	14 (28%)	11 (22%)	6 (12%)
Hyperplasia, cystic		2 (4%)	1 (2%)
*Preputial gland	(50)	(50)	(50)
Cystic ducts	2 (4%)	1 (2%)	
Lymphocytic inflammatory infiltration			1 (2%)
Inflammation, suppurative	1 (2%)	1 (2%)	1 (2%)
Abscess, NOS		1 (2%)	
Inflammation, active chronic	11 (22%)	7 (14%)	5 (10%)
Inflammation, chronic	34 (68%)	34 (68%)	33 (66%)
Hyperplasia, NOS			1 (2%)
#Prostate	(50)	(50)	(50)
Mineralization		1 (2%)	
Inflammation, active chronic	16 (32%)	20 (40%)	20 (40%)
Inflammation, chronic	10 (20%)	7 (14%)	7 (14%)
Hyperplasia, epithelial			1 (2%)
*Seminal vesicle	(50)	(50)	(50)
Dilatation, NOS		1 (2%)	
Hemorrhage			1 (2%)
Inflammation, active chronic			1 (2%)
Inflammation, chronic		1 (2%)	
Atrophy, NOS	3 (6%)	8 (16%)	4 (8%)
#Testis	(50)	(50)	(50)
Atrophy, NOS	48 (96%)	46 (92%)	44 (88%)
Hyperplasia, interstitial cell	46 (92%)	45 (90%)	45 (90%)
#Testis/tubule	(50)	(50)	(50)
Mineralization	35 (70%)	30 (60%)	37 (74%)
Oligospermia		2 (4%)	
*Epididymis	(50)	(50)	(50)
Mineralization			1 (2%)
Inflammation, chronic	1 (2%)		
*Scrotum	(50)	(50)	(50)
Steatitis	5 (10%)	4 (8%)	2 (4%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	Low Dose	High Dose
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Compression, NOS		1 (2%)	1 (2%)
Hemorrhage		1 (2%)	
Malacia			1 (2%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Hemorrhage		1 (2%)	
Inflammation, suppurative		1 (2%)	
Retinopathy		10 (20%)	
Phthisis bulbi		2 (4%)	
*Eye/sclera	(50)	(50)	(50)
Mineralization	1 (2%)	1 (2%)	
*Eye/cornea	(50)	(50)	(50)
Inflammation, active chronic		2 (4%)	
*Eye/crystalline lens	(50)	(50)	(50)
Cataract	1 (2%)	6 (12%)	
*Nasolacrimal duct	(50)	(50)	(50)
Hemorrhage	9 (18%)	2 (4%)	4 (8%)
Inflammation, acute			2 (4%)
*Harderian gland	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
*Ear canal	(50)	(50)	(50)
Inflammation, active chronic		1 (2%)	
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Epicardium	(50)	(50)	(50)
Inflammation, active chronic	1 (2%)		
*Mesentery	(50)	(50)	(50)
Ulcer, NOS		1 (2%)	
Steatitis	1 (2%)		
ALL OTHER SYSTEMS			
None			
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX B

SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell carcinoma			1 (2%)
Basal cell tumor		1 (2%)	
Keratoacanthoma		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)		
Fibroma	2 (4%)	3 (6%)	1 (2%)
Fibrosarcoma		1 (2%)	
Fibrous histiocytoma, malignant	1 (2%)		
Fibrous histiocytoma, metastatic	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma		2 (4%)	
Alveolar/bronchiolar carcinoma		1 (2%)	
Fibrous histiocytoma, metastatic	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	6 (12%)	13 (26%)	9 (18%)
#Spleen	(50)	(50)	(50)
Leukemia, mononuclear cell		1 (2%)	
CIRCULATORY SYSTEM			
None			
DIGESTIVE SYSTEM			
*Oral cavity	(50)	(50)	(50)
Squamous cell papilloma		1 (2%)	
*Tongue	(50)	(50)	(50)
Squamous cell papilloma		1 (2%)	
#Salivary gland	(50)	(50)	(50)
Fibrous histiocytoma, metastatic	1 (2%)		
#Liver	(50)	(50)	(50)
Neoplastic nodule	1 (2%)		
Fibrous histiocytoma, metastatic	1 (2%)		
#Esophagus	(50)	(50)	(50)
Fibrous histiocytoma, metastatic	1 (2%)		
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Pituitary intermedia	(49)	(50)	(50)
Adenoma, NOS		1 (2%)	
#Anterior pituitary	(49)	(50)	(50)
Adenoma, NOS	15 (31%)	24 (48%)	25 (50%)
Adenocarcinoma, NOS	1 (2%)		
#Adrenal	(50)	(50)	(50)
Cortical adenoma	2 (4%)	2 (4%)	

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma	1 (2%)	5 (10%)	6 (12%)
Ganglioneuroma		1 (2%)	
#Thyroid	(50)	(50)	(50)
Follicular cell adenoma		1 (2%)	
C-cell adenoma	5 (10%)	2 (4%)	3 (6%)
C-cell carcinoma		1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenoma, NOS			1 (2%)
Adenocarcinoma, NOS	1 (2%)		
Fibroadenoma	12 (24%)	17 (34%)	17 (34%)
*Clitoral gland	(50)	(50)	(50)
Carcinoma, NOS	4 (8%)	8 (16%)	1 (2%)
Adenoma, NOS	5 (10%)	2 (4%)	3 (6%)
#Uterus	(50)	(50)	(50)
Leiomyosarcoma			1 (2%)
Endometrial stromal polyp	13 (26%)	14 (28%)	8 (16%)
Endometrial stromal sarcoma	2 (4%)		2 (4%)
#Ovary	(50)	(50)	(50)
Fibrous histiocytoma, metastatic	1 (2%)		
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)	1 (2%)	
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	6	2	7
Moribund sacrifice	15	16	18
Terminal sacrifice	28	31	25
Dosing accident	1	1	

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	37	46	40
Total primary tumors	73	104	79
Total animals with benign tumors	31	41	36
Total benign tumors	55	78	64
Total animals with malignant tumors	14	21	13
Total malignant tumors	17	26	15
Total animals with secondary tumors##	1		
Total secondary tumors	6		
Total animals with tumors uncertain--benign or malignant	1		
Total uncertain tumors	1		

• Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE: VEHICLE CONTROL

ANIMAL NUMBER	14 06	10 04	12 01	12 02	13 07	11 09	11 05	12 05	10 01	13 08	11 08	12 00	13 06	12 04	13 04	11 13	11 12	12 06	14 00	11 11	13 09	11 07	10 02	10 03	10 05
WEEKS ON STUDY	03 00	03 01	04 00	04 00	05 00	05 01	05 03	05 08	06 03	07 02	07 07	08 00	08 00	08 01	08 03	08 08	08 89	09 00	09 00	09 98	10 02	10 03	10 04	10 04	10 04
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS						X																			
Fibroma																									
Fibrous histiocytoma, malignant																				X					
Fibrous histiocytoma, metastatic																				X					
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic																				X					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic																				X					
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																	X								
Fibrous histiocytoma, metastatic																				X					
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic																				X					
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS										X				X	X					X		X	X		
Adenocarcinoma, NOS																			X						
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma																								X	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma											X														
Parathyroid	+	–	+	–	+	+	–	+	+	+	–	–	–	+	–	–	+	+	+	–	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+
Adenocarcinoma, NOS																						X			
Fibroadenoma									X						X		X							X	
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS							X														X				
Adenoma, NOS											X							X						X	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp									X		X						X	X	X				X		
Endometrial stromal sarcoma						X						X													
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic																				X					
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																X									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell																		X			X				

+: Tissue examined microscopically
–: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

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

ANIMAL NUMBER	106	107	108	109	110	114	116	123	127	128	129	130	131	132	133	135	141	142	143	144	145	147	148	149	150	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibroma										X	X															2
Fibrous histiocytoma, malignant																										1
Fibrous histiocytoma, metastatic																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										1
Fibrous histiocytoma, metastatic																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS	X	X		X			X	X				X	X							X		X				15
Adenocarcinoma, NOS																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																						X		X		2
Pheochromocytoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C cell adenoma														X					X			X	X			5
Parathyroid	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	38
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										1
Fibroadenoma						X		X		X	X	X								X		X	X			12
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS						X																	X			4
Adenoma, NOS																			X			X				5
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp							X		X		X		X			X							X		X	13
Endometrial stromal sarcoma																										2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell		X				X							X	X												6

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE: LOW DOSE

ANIMAL NUMBER	0026	0008	0044	0041	0005	0028	0006	0016	0048	0036	0035	0037	0009	0020	0050	0002	0046	0001	0043	0003	0004	0007	0010	0011	0012
WEEKS ON STUDY	0188	0308	0557	0667	0885	0886	0899	0991	0991	0992	0996	0999	1000	1000	1000	1011	1011	1022	1022	1044	1044	1044	1044	1044	1044
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+
Basal cell tumor							X																		
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+
Fibroma																	X								
Fibrosarcoma									X																
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																									X
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma								X																	
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS				X			X			X		X	X			X	X			X	X			X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																			X						
Pheochromocytoma											X								X			X			
Ganglioneuroma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma														X											
C-cell adenoma																							X		
C-cell carcinoma																X									
Parathyroid	–	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma				X			X			X	X				X	X			X		X			X	
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS			X									X				X									
Adenoma, NOS														X											
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp							X	X			X											X			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS						X																			
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell										X		X	X	X	X	X	X	X							

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

ANIMAL NUMBER	0 1 3	0 1 4	0 1 5	0 1 7	0 1 8	0 1 9	0 2 1	0 2 2	0 2 3	0 2 4	0 2 5	0 2 7	0 2 9	0 3 0	0 3 1	0 3 2	0 3 3	0 3 4	0 3 8	0 3 9	0 4 0	0 4 2	0 4 5	0 4 7	0 4 9	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Basal cell tumor																										1
Keratoacanthoma				X																						1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma															X							X				3
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X				X														2
Alveolar/bronchiolar carcinoma																				X						1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia, mononuclear cell																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma																									X	2
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS	X	X	X	X		X	X		X	X						X		X		X	X	X	X		X	25
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma														X												2
Pheochromocytoma																		X		X						5
Ganglioneuroma						X																				1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																										1
C-cell adenoma																			X							2
C-cell carcinoma																										1
Parathyroid	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	43
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma			X	X	X			X				X							X			X	X			17
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS								X						X	X	X							X			8
Adenoma, NOS													X													2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp	X			X	X							X	X	X	X		X					X		X		14
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell				X				X				X								X	X					13

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE: HIGH DOSE

ANIMAL NUMBER	080	051	052	091	072	059	060	085	069	088	058	071	065	100	066	093	061	074	087	096	073	057	076	070	053
WEEKS ON STUDY	022	025	025	025	031	039	044	052	064	079	082	082	083	086	090	090	092	092	092	092	094	095	096	097	101
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																					X				
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS											X			X			X			X	X	X	X	X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																								X	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma											X														
C-cell carcinoma																									
Parathyroid	−	−	−	+	−	−	−	+	+	+	+	+	−	+	+	+	−	+	+	+	+	−	−	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Fibroadenoma									X						X	X		X		X			X	X	X
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Adenoma, NOS																	X								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																			X						
Endometrial stromal polyp											X						X				X				
Endometrial stromal sarcoma																					X				
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell										X		X	X				X	X	X						X

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

ANIMAL NUMBER	054	055	056	062	063	064	067	068	075	077	078	079	081	082	083	084	086	089	090	092	094	095	097	098	099	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell carcinoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma											X															1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS	X	X	X		X	X		X			X		X	X	X		X	X	X		X	X			X	25
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma									X						X					X			X	X		6
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell adenoma													X												X	3
C-cell carcinoma															X											1
Parathyroid	+	+	+	–	+	+	+	–	+	+	+	+	–	+	–	+	+	–	+	+	+	+	+	+	+	35
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS																			X							1
Fibroadenoma		X	X	X	X	X	X			X								X						X		17
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS			X																							1
Adenoma, NOS			X															X								3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Endometrial stromal polyp									X	X				X						X				X		8
Endometrial stromal sarcoma											X															2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell					X														X							9

* Animals necropsied

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE

	Vehicle Control	188 mg/kg	375 mg/kg
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	7.1%	9.1%	4.0%
Terminal Rates (c)	2/28 (7%)	2/31 (6%)	1/25 (4%)
Week of First Observation	104	101	104
Life Table Tests (d)	P=0.443N	P=0.551	P=0.540N
Incidental Tumor Tests (d)	P=0.407N	P=0.629	P=0.540N
Cochran-Armitage Trend Test (d)	P=0.400N		
Fisher Exact Test (d)		P=0.500	P=0.500N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	7.1%	11.2%	4.0%
Terminal Rates (c)	2/28 (7%)	2/31 (6%)	1/25 (4%)
Week of First Observation	104	91	104
Life Table Tests (d)	P=0.442N	P=0.408	P=0.540N
Incidental Tumor Tests (d)	P=0.393N	P=0.426	P=0.540N
Cochran-Armitage Trend Test (d)	P=0.407N		
Fisher Exact Test (d)		P=0.339	P=0.500N
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	9.2%	11.2%	4.0%
Terminal Rates (c)	2/28 (7%)	2/31 (6%)	1/25 (4%)
Week of First Observation	51	91	104
Life Table Tests (d)	P=0.280N	P=0.572	P=0.341N
Incidental Tumor Tests (d)	P=0.228N	P=0.510	P=0.310N
Cochran-Armitage Trend Test (d)	P=0.253N		
Fisher Exact Test (d)		P=0.500	P=0.309N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	0.0%	9.7%	0.0%
Terminal Rates (c)	0/28 (0%)	3/31 (10%)	0/25 (0%)
Week of First Observation		104	
Life Table Tests (d)	P=0.613	P=0.139	(e)
Incidental Tumor Tests (d)	P=0.613	P=0.139	(e)
Cochran-Armitage Trend Test (d)	P=0.638		
Fisher Exact Test (d)		P=0.121	(e)
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	6/50 (12%)	14/50 (28%)	9/50 (18%)
Adjusted Rates (b)	19.7%	35.4%	25.3%
Terminal Rates (c)	4/28 (14%)	6/31 (19%)	2/25 (8%)
Week of First Observation	90	92	79
Life Table Tests (d)	P=0.221	P=0.099	P=0.279
Incidental Tumor Tests (d)	P=0.399	P=0.215	P=0.415
Cochran-Armitage Trend Test (d)	P=0.263		
Fisher Exact Test (d)		P=0.039	P=0.288
Pituitary Gland: Adenoma			
Overall Rates (a)	15/49 (31%)	24/50 (48%)	25/50 (50%)
Adjusted Rates (b)	44.6%	62.3%	73.2%
Terminal Rates (c)	10/28 (36%)	17/31 (55%)	16/25 (64%)
Week of First Observation	72	67	82
Life Table Tests (d)	P=0.014	P=0.146	P=0.021
Incidental Tumor Tests (d)	P=0.015	P=0.139	P=0.027
Cochran-Armitage Trend Test (d)	P=0.033		
Fisher Exact Test (d)		P=0.059	P=0.039

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	188 mg/kg	375 mg/kg
Pituitary Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	16/49 (33%)	24/50 (48%)	25/50 (50%)
Adjusted Rates (b)	46.2%	62.3%	73.2%
Terminal Rates (c)	10/28 (36%)	17/31 (55%)	16/25 (64%)
Week of First Observation	72	67	82
Life Table Tests (d)	P=0.024	P=0.206	P=0.036
Incidental Tumor Tests (d)	P=0.028	P=0.186	P=0.050
Cochran-Armitage Trend Test (d)	P=0.051		
Fisher Exact Test (d)		P=0.088	P=0.061
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	1/50 (2%)	5/50 (10%)	6/50 (12%)
Adjusted Rates (b)	3.6%	14.6%	23.0%
Terminal Rates (c)	1/28 (4%)	3/31 (10%)	5/25 (20%)
Week of First Observation	104	96	97
Life Table Tests (d)	P=0.030	P=0.137	P=0.041
Incidental Tumor Tests (d)	P=0.038	P=0.214	P=0.052
Cochran-Armitage Trend Test (d)	P=0.049		
Fisher Exact Test (d)		P=0.102	P=0.056
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	5/50 (10%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	16.4%	6.5%	10.3%
Terminal Rates (c)	4/28 (14%)	2/31 (6%)	2/25 (8%)
Week of First Observation	77	104	82
Life Table Tests (d)	P=0.302N	P=0.175N	P=0.395N
Incidental Tumor Tests (d)	P=0.365N	P=0.227N	P=0.477N
Cochran-Armitage Trend Test (d)	P=0.274N		
Fisher Exact Test (d)		P=0.218N	P=0.357N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	3/50 (6%)	4/50 (8%)
Adjusted Rates (b)	16.4%	9.1%	14.2%
Terminal Rates (c)	4/28 (14%)	2/31 (6%)	3/25 (12%)
Week of First Observation	77	101	82
Life Table Tests (d)	P=0.473N	P=0.297N	P=0.546N
Incidental Tumor Tests (d)	P=0.512N	P=0.302N	P=0.628N
Cochran-Armitage Trend Test (d)	P=0.427N		
Fisher Exact Test (d)		P=0.357N	P=0.500N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	12/50 (24%)	17/50 (34%)	17/50 (34%)
Adjusted Rates (b)	37.5%	43.5%	50.4%
Terminal Rates (c)	9/28 (32%)	10/31 (32%)	9/25 (36%)
Week of First Observation	63	67	64
Life Table Tests (d)	P=0.121	P=0.336	P=0.150
Incidental Tumor Tests (d)	P=0.117	P=0.289	P=0.144
Cochran-Armitage Trend Test (d)	P=0.164		
Fisher Exact Test (d)		P=0.189	P=0.189
Clitoral Gland: Adenoma			
Overall Rates (a)	5/50 (10%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	15.6%	5.8%	10.7%
Terminal Rates (c)	3/28 (11%)	1/31 (3%)	2/25 (8%)
Week of First Observation	77	100	92
Life Table Tests (d)	P=0.297N	P=0.166N	P=0.383N
Incidental Tumor Tests (d)	P=0.319N	P=0.198N	P=0.445N
Cochran-Armitage Trend Test (d)	P=0.274N		
Fisher Exact Test (d)		P=0.218N	P=0.357N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	188 mg/kg	375 mg/kg
Clitoral Gland: Carcinoma			
Overall Rates (a)	4/50 (8%)	8/50 (16%)	1/50 (2%)
Adjusted Rates (b)	12.3%	22.3%	4.0%
Terminal Rates (c)	2/28 (7%)	5/31 (16%)	1/25 (4%)
Week of First Observation	53	57	
Life Table Tests (d)	P=0.231N	P=0.247	P=0.218N
Incidental Tumor Tests (d)	P=0.273N	P=0.258	P=0.249N
Cochran-Armitage Trend Test (d)	P=0.188N		
Fisher Exact Test (d)		P=0.178	P=0.181N
Clitoral Gland: Adenoma or Carcinoma			
Overall Rates (a)	9/50 (18%)	10/50 (20%)	3/50 (6%)
Adjusted Rates (b)	26.6%	27.2%	10.7%
Terminal Rates (c)	5/28 (18%)	6/31 (19%)	2/25 (8%)
Week of First Observation	53	57	92
Life Table Tests (d)	P=0.084N	P=0.574N	P=0.085N
Incidental Tumor Tests (d)	P=0.100N	P=0.592N	P=0.111N
Cochran-Armitage Trend Test (d)	P=0.060N		
Fisher Exact Test (d)		P=0.500	P=0.061N
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	13/50 (26%)	14/50 (28%)	8/50 (16%)
Adjusted Rates (b)	38.0%	40.0%	26.8%
Terminal Rates (c)	8/28 (29%)	11/31 (35%)	5/25 (20%)
Week of First Observation	63	89	82
Life Table Tests (d)	P=0.184N	P=0.509N	P=0.206N
Incidental Tumor Tests (d)	P=0.181N	P=0.490	P=0.226N
Cochran-Armitage Trend Test (d)	P=0.144N		
Fisher Exact Test (d)		P=0.500	P=0.163N
All Sites: Benign Tumors			
Overall Rates (a)	31/50 (62%)	41/50 (82%)	36/50 (72%)
Adjusted Rates (b)	81.3%	95.3%	94.7%
Terminal Rates (c)	21/28 (75%)	29/31 (94%)	23/25 (92%)
Week of First Observation	63	67	64
Life Table Tests (d)	P=0.081	P=0.219	P=0.123
Incidental Tumor Tests (d)	P=0.045	P=0.127	P=0.070
Cochran-Armitage Trend Test (d)	P=0.157		
Fisher Exact Test (d)		P=0.022	P=0.198
All Sites: Malignant Tumors			
Overall Rates (a)	14/50 (28%)	21/50 (42%)	13/50 (26%)
Adjusted Rates (b)	37.0%	49.3%	37.2%
Terminal Rates (c)	5/28 (18%)	10/31 (32%)	5/25 (20%)
Week of First Observation	51	57	79
Life Table Tests (d)	P=0.538N	P=0.274	P=0.547N
Incidental Tumor Tests (d)	P=0.329N	P=0.273	P=0.335N
Cochran-Armitage Trend Test (d)	P=0.459N		
Fisher Exact Test (d)		P=0.104	P=0.500N
All Sites: All Tumors			
Overall Rates (a)	37/50 (74%)	46/50 (92%)	40/50 (80%)
Adjusted Rates (b)	86.0%	97.9%	95.2%
Terminal Rates (c)	22/28 (79%)	30/31 (97%)	23/25 (92%)
Week of First Observation	51	57	64
Life Table Tests (d)	P=0.180	P=0.347	P=0.239
Incidental Tumor Tests (d)	P=0.088	P=0.091	P=0.173
Cochran-Armitage Trend Test (d)	P=0.257		
Fisher Exact Test (d)		P=0.015	P=0.317

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

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

TABLE B4a. HISTORICAL INCIDENCE OF LEUKEMIA IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls
No 2-year studies by Physiological Research Laboratories are included in the historical data base.	
Overall Historical Incidence	
TOTAL	271/1,450 (18.7%)
SD (b)	8.52%
Range (c)	
High	21/50
Low	2/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE B4b. HISTORICAL INCIDENCE OF PITUITARY GLAND TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Adenoma	Carcinoma or Adenocarcinoma	Adenoma, Carcinoma, or Adenocarcinoma
No 2-year studies by Physiological Research Laboratories are included in the historical data base.			
Overall Historical Incidence			
TOTAL	(b) 520/1,407 (37.0%)	(c) 43/1,407 (3.1%)	(b,c) 561/1,407 (39.9%)
SD (d)	8.35%	2.90%	8.47%
Range (e)			
High	27/49	5/47	30/49
Low	9/50	0/50	11/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Includes 449 adenomas, NOS, and 72 chromophobe adenomas
(c) Includes 33 carcinomas, NOS, 6 adenocarcinomas, NOS, and 4 chromophobe carcinomas
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

TABLE B4c. HISTORICAL INCIDENCE OF ADRENAL GLAND TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Pheochromocytoma	Malignant Pheochromocytoma	Pheochromocytoma or Malignant Pheochromocytoma
No 2-year studies by Physiological Research Laboratories are included in the historical data base.			
Overall Historical Incidence			
TOTAL	82/1,443 (5.7%)	5/1,443 (0.3%)	86/1,443 (6.0%)
SD (b)	3.59%	0.77%	3.56%
Range (c)			
High	7/50	1/50	8/50
Low	0/50	0/50	1/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
Steatitis	1 (2%)		
Inflammation, chronic	1 (2%)		1 (2%)
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Hemorrhage	2 (4%)		4 (8%)
Inflammation, acute	1 (2%)	2 (4%)	
Inflammation, chronic	4 (8%)	1 (2%)	2 (4%)
Foreign material, NOS	1 (2%)		1 (2%)
*Nasal turbinate	(50)	(50)	(50)
Inflammation, active chronic			2 (4%)
Inflammation, chronic		2 (4%)	3 (6%)
#Lung/bronchiole	(50)	(50)	(50)
Inflammation, acute			1 (2%)
#Lung	(50)	(50)	(50)
Mineralization		1 (2%)	
Congestion, NOS	3 (6%)	16 (32%)	7 (14%)
Edema, NOS	2 (4%)		3 (6%)
Hemorrhage	10 (20%)	10 (20%)	9 (18%)
Pneumonia, interstitial chronic	3 (6%)	2 (4%)	1 (2%)
Bronchopneumonia, chronic			2 (4%)
Granuloma, pyogenic			1 (2%)
Foreign material, NOS	1 (2%)		1 (2%)
Hyperplasia, alveolar epithelium	1 (2%)		
Histiocytosis	2 (4%)	5 (10%)	3 (6%)
HEMATOPOIETIC SYSTEM			
#Spleen	(50)	(50)	(50)
Hematoma, NOS		1 (2%)	
Pigmentation, NOS	50 (100%)	44 (88%)	49 (98%)
Hyperplasia, lymphoid	2 (4%)		1 (2%)
Hematopoiesis	38 (76%)	38 (76%)	41 (82%)
#Splenic capsule	(50)	(50)	(50)
Fibrosis		1 (2%)	
#Mandibular lymph node	(50)	(50)	(50)
Congestion, NOS			1 (2%)
Plasmacytosis			1 (2%)
Hyperplasia, lymphoid	4 (8%)	4 (8%)	2 (4%)
#Mesenteric lymph node	(50)	(50)	(50)
Congestion, NOS	1 (2%)	2 (4%)	1 (2%)
Hyperplasia, lymphoid	2 (4%)		
#Liver	(50)	(50)	(50)
Hematopoiesis	3 (6%)	1 (2%)	
#Thymus	(50)	(50)	(50)
Embryonal duct cyst	1 (2%)		
Multiple cysts			1 (2%)
Congestion, NOS		3 (6%)	1 (2%)
Hemorrhage			1 (2%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	Low Dose	High Dose
CIRCULATORY SYSTEM			
#Heart	(50)	(50)	(50)
Inflammation, chronic	46 (92%)	47 (94%)	47 (94%)
*Aorta	(50)	(50)	(50)
Periarteritis			1 (2%)
*Pulmonary artery	(50)	(50)	(50)
Mineralization	4 (8%)	2 (4%)	7 (14%)
*Pulmonary vein	(50)	(50)	(50)
Mineralization	2 (4%)		
DIGESTIVE SYSTEM			
*Intestinal tract	(50)	(50)	(50)
Bezoar		1 (2%)	
*Tongue	(50)	(50)	(50)
Hyperplasia, epithelial	1 (2%)		
#Salivary gland	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
Atrophy, NOS	5 (10%)	2 (4%)	5 (10%)
#Liver	(50)	(50)	(50)
Accessory structure	6 (12%)	8 (16%)	1 (2%)
Bile stasis			1 (2%)
Hemorrhage			1 (2%)
Inflammation, acute			1 (2%)
Inflammation, chronic	1 (2%)		
Granuloma, NOS	5 (10%)	12 (24%)	2 (4%)
Necrosis, NOS	1 (2%)	1 (2%)	3 (6%)
Pigmentation, NOS	1 (2%)		
Cytoplasmic vacuolization	5 (10%)	4 (8%)	4 (8%)
Focal cellular change	43 (86%)	42 (84%)	39 (78%)
Hepatocytomegaly	1 (2%)	1 (2%)	
Hyperplasia, NOS		3 (6%)	
Angiectasis	1 (2%)	2 (4%)	2 (4%)
#Liver/periportal	(50)	(50)	(50)
Inflammation, chronic	42 (84%)	45 (90%)	45 (90%)
#Bile duct	(50)	(50)	(50)
Hyperplasia, NOS	34 (68%)	42 (84%)	45 (90%)
#Pancreas	(50)	(50)	(50)
Cystic ducts	1 (2%)		
Lymphocytic inflammatory infiltration			1 (2%)
Inflammation, chronic		1 (2%)	1 (2%)
#Pancreatic acinus	(50)	(50)	(50)
Focal cellular change	1 (2%)		2 (4%)
Atrophy, NOS	15 (30%)	27 (54%)	16 (32%)
Hyperplasia, NOS	6 (12%)	4 (8%)	4 (8%)
#Esophagus	(50)	(50)	(50)
Ulcer, NOS			1 (2%)
Inflammation, acute	1 (2%)		1 (2%)
Necrosis, NOS			1 (2%)
#Stomach	(49)	(50)	(50)
Bezoar	1 (2%)		
#Gastric fundal gland	(49)	(50)	(50)
Dilatation, NOS	31 (63%)	41 (82%)	31 (62%)
#Glandular stomach	(49)	(50)	(50)
Inflammation, active chronic			1 (2%)
Dysplasia, epithelial			1 (2%)
#Forestomach	(49)	(50)	(50)
Ulcer, NOS		3 (6%)	5 (10%)
Inflammation, acute	1 (2%)	2 (4%)	6 (12%)
Inflammation, active chronic	1 (2%)	2 (4%)	1 (2%)
Necrosis, NOS	1 (2%)		
Hyperplasia, epithelial	1 (2%)	4 (8%)	1 (2%)
Hyperkeratosis	1 (2%)	4 (8%)	1 (2%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Small intestine	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
#Duodenum	(50)	(50)	(50)
Bezoar	1 (2%)		3 (6%)
#Ileum	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
#Cecum	(50)	(50)	(50)
Necrosis, NOS		1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Nephropathy	38 (76%)	42 (84%)	41 (82%)
#Kidney/tubule	(50)	(50)	(50)
Mineralization	46 (92%)	44 (88%)	46 (92%)
Pigmentation, NOS	46 (92%)	48 (96%)	46 (92%)
Hyperplasia, focal	1 (2%)		
#Kidney/pelvis	(50)	(50)	(50)
Calculus, microscopic examination			1 (2%)
Mineralization			1 (2%)
Hemorrhage			1 (2%)
Hyperplasia, epithelial	1 (2%)		
ENDOCRINE SYSTEM			
#Pituitary	(49)	(50)	(50)
Multiple cysts	1 (2%)		
Hematoma, organized		1 (2%)	
#Pituitary intermedia	(49)	(50)	(50)
Cyst, NOS	2 (4%)	1 (2%)	1 (2%)
Multiple cysts	1 (2%)		
Hemorrhagic cyst		1 (2%)	
#Anterior pituitary	(49)	(50)	(50)
Cyst, NOS	5 (10%)	6 (12%)	10 (20%)
Multiple cysts	20 (41%)	22 (44%)	11 (22%)
Congestion, NOS		1 (2%)	
Hemorrhage			1 (2%)
Hemorrhagic cyst		5 (10%)	1 (2%)
Pigmentation, NOS			1 (2%)
Hyperplasia, NOS	8 (16%)	10 (20%)	6 (12%)
Angiectasis	2 (4%)	1 (2%)	1 (2%)
#Adrenal	(50)	(50)	(50)
Accessory structure	1 (2%)		
#Adrenal cortex	(50)	(50)	(50)
Accessory structure			2 (4%)
Congestion, NOS		1 (2%)	1 (2%)
Hemorrhagic cyst		1 (2%)	
Inflammation, chronic		1 (2%)	
Degeneration, lipoid	8 (16%)	19 (38%)	15 (30%)
Necrosis, NOS		1 (2%)	1 (2%)
Metamorphosis, fatty			1 (2%)
Pigmentation, NOS	3 (6%)	1 (2%)	1 (2%)
Hypertrophy, focal	1 (2%)		2 (4%)
Hyperplasia, NOS	11 (22%)	8 (16%)	9 (18%)
#Adrenal medulla	(50)	(50)	(50)
Necrosis, NOS			1 (2%)
Hyperplasia, NOS	5 (10%)	8 (16%)	2 (4%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Thyroid	(50)	(50)	(50)
Embryonal duct cyst		2 (4%)	1 (2%)
Mineralization		1 (2%)	
Cystic follicles	4 (8%)	3 (6%)	6 (12%)
Inflammation, chronic		1 (2%)	
Hyperplasia, C-cell	30 (60%)	42 (84%)	34 (68%)
#Thyroid follicle	(50)	(50)	(50)
Atrophy, focal			1 (2%)
#Pancreatic islets	(50)	(50)	(50)
Focal cellular change			1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Multiple cysts	26 (52%)	40 (80%)	33 (66%)
Hyperplasia, NOS		1 (2%)	
*Preputial gland	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
*Clitoral gland	(50)	(50)	(50)
Cystic ducts	1 (2%)		
Inflammation, suppurative	3 (6%)		1 (2%)
Inflammation, active chronic	7 (14%)	7 (14%)	4 (8%)
Inflammation, chronic	18 (36%)	25 (50%)	18 (36%)
#Uterus	(50)	(50)	(50)
Dilatation, NOS	2 (4%)		3 (6%)
Hydrometra		1 (2%)	1 (2%)
Hematoma, NOS		1 (2%)	
Hematoma, organized	1 (2%)		1 (2%)
Inflammation, chronic		1 (2%)	
Hyperplasia, epithelial	1 (2%)		
#Cervix uteri	(50)	(50)	(50)
Polyp, NOS		1 (2%)	
#Uterus/endometrium	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
Hyperplasia, cystic	9 (18%)	14 (28%)	6 (12%)
#Ovary	(50)	(50)	(50)
Parovarian cyst	2 (4%)	5 (10%)	2 (4%)
Inflammation, chronic		1 (2%)	
#Mesovarium	(50)	(50)	(50)
Steatitis			1 (2%)
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Compression, NOS	6 (12%)	2 (4%)	5 (10%)
Mineralization		1 (2%)	
Malacia		1 (2%)	
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Retinopathy	1 (2%)	9 (18%)	
*Eye/sclera	(50)	(50)	(50)
Mineralization			1 (2%)
*Eye/crystalline lens	(50)	(50)	(50)
Cataract		8 (16%)	
*Nasolacrimal duct	(50)	(50)	(50)
Hemorrhage	3 (6%)	1 (2%)	1 (2%)
Inflammation, active chronic		1 (2%)	1 (2%)
*Harderian gland	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	Low Dose	High Dose
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mesentery	(50)	(50)	(50)
Steatitis	6 (12%)	7 (14%)	7 (14%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
Adipose tissue			
Steatitis		1	
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX C

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING	1		
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*Skin	(49)	(50)	(50)
Keratoacanthoma	1 (2%)		
*Subcutaneous tissue	(49)	(50)	(50)
Sarcoma, NOS	1 (2%)	2 (4%)	
Fibroma	1 (2%)	3 (6%)	1 (2%)
Fibrosarcoma	2 (4%)	2 (4%)	1 (2%)
RESPIRATORY SYSTEM			
*Nasal cavity	(49)	(50)	(50)
Fibroma		1 (2%)	
#Lung	(49)	(50)	(50)
Adenocarcinoma, NOS, metastatic	1 (2%)		
Hepatocellular carcinoma, metastatic			1 (2%)
Alveolar/bronchiolar adenoma	3 (6%)	4 (8%)	4 (8%)
Alveolar/bronchiolar carcinoma	5 (10%)	5 (10%)	1 (2%)
Sarcoma, NOS, metastatic	1 (2%)		
Neurilemoma, metastatic		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(49)	(50)	(50)
Malignant lymphoma, lymphocytic type		1 (2%)	
Malignant lymphoma, histiocytic type	3 (6%)		1 (2%)
Malignant lymphoma, mixed type	2 (4%)	1 (2%)	2 (4%)
#Mesenteric lymph node	(49)	(50)	(48)
Malignant lymphoma, mixed type			1 (2%)
#Liver	(49)	(50)	(50)
Malignant lymphoma, NOS		1 (2%)	
#Peyer's patch	(49)	(50)	(50)
Malignant lymphoma, mixed type	1 (2%)		
CIRCULATORY SYSTEM			
#Spleen	(49)	(50)	(50)
Hemangiosarcoma		1 (2%)	
#Liver	(49)	(50)	(50)
Hemangioma		1 (2%)	
Hemangiosarcoma			1 (2%)
#Testis	(49)	(50)	(50)
Hemangioma		1 (2%)	
DIGESTIVE SYSTEM			
#Salivary gland	(49)	(50)	(50)
Adenocarcinoma, NOS, metastatic	1 (2%)		
#Liver	(49)	(50)	(50)
Hepatocellular adenoma	11 (22%)	14 (28%)	9 (18%)
Hepatocellular carcinoma	5 (10%)	9 (18%)	6 (12%)
Sarcoma, NOS			2 (4%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
#Kidney	(49)	(50)	(50)
Tubular cell adenoma		1 (2%)	
#Kidney/cortex	(49)	(50)	(50)
Adenocarcinoma, NOS, metastatic	1 (2%)		
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(48)	(50)
Adenoma, NOS		1 (2%)	1 (2%)
#Adrenal	(49)	(50)	(48)
Cortical adenoma		1 (2%)	
#Adrenal medulla	(49)	(50)	(48)
Pheochromocytoma		3 (6%)	
#Thyroid	(49)	(50)	(47)
Follicular cell adenoma	2 (4%)		1 (2%)
#Pancreatic islets	(49)	(50)	(50)
Islet cell adenoma			1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(49)	(50)	(50)
Adenocarcinoma, NOS	1 (2%)		
#Testis	(49)	(50)	(50)
Interstitial cell tumor	1 (2%)		
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(49)	(50)	(50)
Adenoma, NOS	3 (6%)	2 (4%)	2 (4%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mediastinum	(49)	(50)	(50)
Alveolar/bronchiolar carcinoma, invasive		1 (2%)	
Neurilemoma, metastatic		1 (2%)	
*Pleura	(49)	(50)	(50)
Alveolar/bronchiolar carcinoma, invasive		2 (4%)	
ALL OTHER SYSTEMS			
Orbital region			
Neurilemoma, malignant		1	
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	4	6	12
Moribund sacrifice	7	11	2
Terminal sacrifice	38	33	30
Accidentally killed, NOS			6
Animal missing	1		

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	31	39	25
Total primary tumors	42	55	34
Total animals with benign tumors	20	24	16
Total benign tumors	22	32	19
Total animals with malignant tumors	20	21	14
Total malignant tumors	20	23	15
Total animals with secondary tumors##	2	3	1
Total secondary tumors	4	5	1

* Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE: VEHICLE CONTROL

ANIMAL NUMBER	120	101	109	108	127	117	118	145	111	112	131	121	102	103	104	105	106	107	110	113	114	115	116	119	122
WEEKS ON STUDY	054	065	075	081	084	089	089	089	091	092	097	102	103	103	103	103	103	103	103	103	103	103	103	103	103
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS	X																								
Fibroma																									
Fibrosarcoma				X		X																			
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic									X																
Alveolar/bronchiolar adenoma														X											
Alveolar/bronchiolar carcinoma														X											
Sarcoma, NOS, metastatic	X																								
Trachea	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	−	M	−	+	+	+	+	+	+	−	+	+	+	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic									X																
Liver	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma					X	X													X	X			X		
Hepatocellular carcinoma			X					X			X					X						X			
Bile duct	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic									X																
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma											X														
Parathyroid	−	+	+	+	−	−	+	−	+	−	−	M	−	+	+	+	+	+	+	−	+	+	+	−	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	+	N	N	M	N	N	N	N	N	N	N	N	+	N	N	N	+
Adenocarcinoma, NOS									X																
Testis	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS							X																		
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, histiocytic type																		X							
Malignant lymphoma, mixed type							X																		

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

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

ANIMAL NUMBER	123	124	125	126	128	129	130	132	133	134	135	136	137	138	139	140	141	142	143	144	146	147	148	149	150	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Keratoacanthoma																	X									1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Sarcoma, NOS																										1
Fibroma						X																				1
Fibrosarcoma																										2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS, metastatic																										1
Alveolar/bronchiolar adenoma										X		X														3
Alveolar/bronchiolar carcinoma						X	X									X						X				5
Sarcoma, NOS, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS, metastatic																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma			X	X									X	X	X				X							11
Hepatocellular carcinoma																										5
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, mixed type																			X							1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS, metastatic																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma																			X							2
Parathyroid	–	+	+	–	+	+	+	–	–	+	–	+	–	–	+	+	+	+	–	+	–	–	+	+	–	29
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Adenocarcinoma, NOS																										1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor																				X						1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Adenoma, NOS																				X		X				3
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Malignant lymphoma, histiocytic type											X						X									3
Malignant lymphoma, mixed type				X																						2

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE: LOW DOSE

ANIMAL NUMBER	0042	0041	0035	0117	0031	0040	0009	0022	0019	0018	0007	0015	0028	0043	0048	0008	0049	0001	0002	0003	0004	0005	0006	0010	0011
WEEKS ON STUDY	0001	0668	0669	0776	0776	0777	0800	0883	0886	0887	0889	0891	0992	0998	0998	1000	1001	1003	1003	1033	1033	1033	1033	1033	1033
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS			X				X																		
Fibroma																									
Fibrosarcoma					X								X												
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																			X		X				
Alveolar/bronchiolar carcinoma		X												X								X			
Neurilemoma, metastatic																	X								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																X									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma											X	X		X							X				
Hepatocellular carcinoma				X	X	X		X			X		X									X	X	X	
Hemangioma																									
Malignant lymphoma, NOS															X										
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Adenoma, NOS																									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma																						X			X
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	+	+	+	–	–	–	–	–	–	–	+	–	+	+	+	+	–	–	–	–	+	+	+	–
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS												X								X					
BODY CAVITIES																									
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Alveolar/bronchiolar carcinoma, invasive														X											
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Alveolar/bronchiolar carcinoma, invasive																									
Neurilemoma, metastatic																	X								
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, lymphocytic type																X									
Malignant lymphoma, mixed type																									
Orbital region																									
Neurilemoma, malignant																	X								

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

ANIMAL NUMBER	0121	0131	0141	0161	0201	0211	0223	0244	0255	0266	0277	0299	0300	0322	0333	0344	0366	0377	0388	0399	0441	0455	0466	0477	0500	TOTAL:
WEEKS ON STUDY	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										2
Fibroma									X	X								X								3
Fibrosarcoma																										2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X																					X	4
Alveolar/bronchiolar carcinoma	X																		X							5
Neurilemoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	*50
Fibroma																										1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma								X																		1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	44
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma		X			X					X	X								X	X				X		14
Hepatocellular carcinoma				X												X				X						9
Hemangioma												X														1
Malignant lymphoma, NOS																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma												X														1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	48
Adenoma, NOS													X													1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma														X												1
Pheochromocytoma											X															3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid	+	+	+	+	–	–	+	+	+	+	+	+	+	+	–	+	+	–	+	+	–	+	+	+	–	31
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma										X																1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																										2
BODY CAVITIES																										
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Alveolar/bronchiolar carcinoma, inv	X																									2
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Alveolar/bronchiolar carcinoma, inv	X																									1
Neurilemoma, metastatic																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malig. lymphoma, lymphocytic type																										1
Malignant lymphoma, mixed type															X											1
Orbital region																										
Neurilemoma, malignant																										1

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE: HIGH DOSE

ANIMAL NUMBER	05 55	08 83	05 54	05 58	06 62	06 65	08 88	08 89	09 97	09 99	09 98	07 76	09 90	08 86	08 87	09 93	08 82	09 91	05 53	08 84	05 51	05 52	05 56	05 57	05 59
WEEKS ON STUDY	00 07	00 07	00 09	01 13	01 13	01 13	01 13	01 13	01 13	01 14	01 16	01 17	02 26	02 27	02 27	04 47	06 61	07 71	08 89	08 89	10 03	10 03	10 03	10 03	10 03
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Fibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																				X					
Alveolar/bronchiolar adenoma																									X
Alveolar/bronchiolar carcinoma																									
Trachea	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	−	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																					X				
Hepatocellular carcinoma																		X		X	X				
Sarcoma, NOS																									
Hemangiosarcoma																								X	
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	N	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																			X						
Adrenal	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	−	−	−	+	+	+	+	+	−	−	−	+	−	−	−	−	+	+	+	+	−	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																					X				
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, histiocytic type																									
Malignant lymphoma, mixed type																									

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

ANIMAL NUMBER	060	061	063	064	066	067	068	069	070	071	072	073	074	075	077	078	079	080	081	085	092	094	095	096	100	TOTAL TISSUES TUMORS
WEEKS ON STUDY	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma												X														1
Fibrosarcoma																								X		1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma				X								X								X					4
Alveolar/bronchiolar carcinoma							X																			1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Malignant lymphoma, mixed type									X																	1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	46
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma			X		X		X			X			X			X						X	X			9
Hepatocellular carcinoma								X			X				X											6
Sarcoma, NOS					X				X																	2
Hemangiosarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Follicular cell adenoma														X												1
Parathyroid	–	+	+	+	+	+	–	–	–	+	+	–	+	–	+	+	–	–	+	+	+	+	–	–	+	29
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS	X																						X			2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malig lymphoma, histiocytic type																						X				1
Malignant lymphoma, mixed type														X					X							2

* Animals necropsied

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE

	Vehicle Control	375 mg/kg	750 mg/kg
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	1/49 (2%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	2.6%	9.1%	3.3%
Terminal Rates (c)	1/38 (3%)	3/33 (9%)	1/30 (3%)
Week of First Observation	103	103	103
Life Table Tests (d)	P=0.523	P=0.256	P=0.708
Incidental Tumor Tests (d)	P=0.523	P=0.256	P=0.708
Cochran-Armitage Trend Test (d)	P=0.603N		
Fisher Exact Test (d)		P=0.316	P=0.747N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	3/49 (6%)	5/50 (10%)	2/50 (4%)
Adjusted Rates (b)	6.8%	13.4%	6.7%
Terminal Rates (c)	1/38 (3%)	3/33 (9%)	2/30 (7%)
Week of First Observation	81	76	103
Life Table Tests (d)	P=0.568N	P=0.305	P=0.627N
Incidental Tumor Tests (d)	P=0.498	P=0.351	P=0.605
Cochran-Armitage Trend Test (d)	P=0.410N		
Fisher Exact Test (d)		P=0.369	P=0.490N
Subcutaneous Tissue: Sarcoma or Fibrosarcoma			
Overall Rates (a)	3/49 (6%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	6.2%	8.8%	3.3%
Terminal Rates (c)	0/38 (0%)	0/33 (0%)	1/30 (3%)
Week of First Observation	54	69	103
Life Table Tests (d)	P=0.393N	P=0.472	P=0.433N
Incidental Tumor Tests (d)	P=0.528N	P=0.630	P=0.595N
Cochran-Armitage Trend Test (d)	P=0.244N		
Fisher Exact Test (d)		P=0.511	P=0.301N
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	4/49 (8%)	7/50 (14%)	2/50 (4%)
Adjusted Rates (b)	8.7%	17.1%	6.7%
Terminal Rates (c)	1/38 (3%)	3/33 (9%)	2/30 (7%)
Week of First Observation	54	69	103
Life Table Tests (d)	P=0.470N	P=0.227	P=0.484N
Incidental Tumor Tests (d)	P=0.574	P=0.304	P=0.616N
Cochran-Armitage Trend Test (d)	P=0.286N		
Fisher Exact Test (d)		P=0.274	P=0.329N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	3/49 (6%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	7.9%	12.1%	13.3%
Terminal Rates (c)	3/38 (8%)	4/33 (12%)	4/30 (13%)
Week of First Observation	103	103	103
Life Table Tests (d)	P=0.297	P=0.423	P=0.371
Incidental Tumor Tests (d)	P=0.297	P=0.423	P=0.371
Cochran-Armitage Trend Test (d)	P=0.435		
Fisher Exact Test (d)		P=0.511	P=0.511
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	5/49 (10%)	5/50 (10%)	1/50 (2%)
Adjusted Rates (b)	13.2%	13.4%	3.3%
Terminal Rates (c)	5/38 (13%)	3/33 (9%)	1/30 (3%)
Week of First Observation	103	68	103
Life Table Tests (d)	P=0.160N	P=0.555	P=0.163N
Incidental Tumor Tests (d)	P=0.158N	P=0.595N	P=0.163N
Cochran-Armitage Trend Test (d)	P=0.085N		
Fisher Exact Test (d)		P=0.617N	P=0.098N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	375 mg/kg	750 mg/kg
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	7/49 (14%)	9/50 (18%)	5/50 (10%)
Adjusted Rates (b)	18.4%	24.9%	16.7%
Terminal Rates (c)	7/38 (18%)	7/33 (21%)	5/30 (17%)
Week of First Observation	103	68	103
Life Table Tests (d)	P=0.524N	P=0.292	P=0.552N
Incidental Tumor Tests (d)	P=0.537N	P=0.376	P=0.552N
Cochran-Armitage Trend Test (d)	P=0.318N		
Fisher Exact Test (d)		P=0.410	P=0.365N
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	3/49 (6%)	0/50 (0%)	1/50 (2%)
Adjusted Rates (b)	7.9%	0.0%	3.3%
Terminal Rates (c)	3/38 (8%)	0/33 (0%)	1/30 (3%)
Week of First Observation	103		103
Life Table Tests (d)	P=0.231N	P=0.147N	P=0.393N
Incidental Tumor Tests (d)	P=0.231N	P=0.147N	P=0.393N
Cochran-Armitage Trend Test (d)	P=0.171N		
Fisher Exact Test (d)		P=0.117N	P=0.301N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	3/49 (6%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	7.4%	3.0%	10.0%
Terminal Rates (c)	2/38 (5%)	1/33 (3%)	3/30 (10%)
Week of First Observation	89	103	103
Life Table Tests (d)	P=0.484	P=0.356N	P=0.541
Incidental Tumor Tests (d)	P=0.445	P=0.345N	P=0.475
Cochran-Armitage Trend Test (d)	P=0.585N		
Fisher Exact Test (d)		P=0.301N	P=0.651N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	6/49 (12%)	3/50 (6%)	4/50 (8%)
Adjusted Rates (b)	15.1%	8.3%	13.3%
Terminal Rates (c)	5/38 (13%)	1/33 (3%)	4/30 (13%)
Week of First Observation	89	98	103
Life Table Tests (d)	P=0.440N	P=0.311N	P=0.531N
Incidental Tumor Tests (d)	P=0.501N	P=0.155N	P=0.583N
Cochran-Armitage Trend Test (d)	P=0.286N		
Fisher Exact Test (d)		P=0.233N	P=0.357N
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	0/49 (0%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	0.0%	9.1%	3.3%
Terminal Rates (c)	0/38 (0%)	3/33 (9%)	1/30 (3%)
Week of First Observation		103	103
Life Table Tests (d)	P=0.306	P=0.097	P=0.453
Incidental Tumor Tests (d)	P=0.306	P=0.097	P=0.453
Cochran-Armitage Trend Test (d)	P=0.384		
Fisher Exact Test (d)		P=0.125	P=0.505
Liver: Hepatocellular Adenoma			
Overall Rates (a)	11/49 (22%)	14/50 (28%)	9/50 (18%)
Adjusted Rates (b)	27.0%	38.4%	30.0%
Terminal Rates (c)	9/38 (24%)	11/33 (33%)	9/30 (30%)
Week of First Observation	84	89	103
Life Table Tests (d)	P=0.468	P=0.203	P=0.555
Incidental Tumor Tests (d)	P=0.376	P=0.255	P=0.476
Cochran-Armitage Trend Test (d)	P=0.339N		
Fisher Exact Test (d)		P=0.343	P=0.382N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	375 mg/kg	750 mg/kg
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	5/49 (10%)	9/50 (18%)	6/50 (12%)
Adjusted Rates (b)	11.6%	21.1%	18.6%
Terminal Rates (c)	2/38 (5%)	3/33 (9%)	4/30 (13%)
Week of First Observation	75	76	71
Life Table Tests (d)	P=0.243	P=0.164	P=0.312
Incidental Tumor Tests (d)	P=0.120	P=0.295	P=0.130
Cochran-Armitage Trend Test (d)	P=0.457		
Fisher Exact Test (d)		P=0.205	P=0.514
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	16/49 (33%)	21/50 (42%)	14/50 (28%)
Adjusted Rates (b)	36.6%	50.1%	43.6%
Terminal Rates (c)	11/38 (29%)	13/33 (39%)	12/30 (40%)
Week of First Observation	75	76	71
Life Table Tests (d)	P=0.343	P=0.126	P=0.422
Incidental Tumor Tests (d)	P=0.196	P=0.233	P=0.219
Cochran-Armitage Trend Test (d)	P=0.348N		
Fisher Exact Test (d)		P=0.226	P=0.388N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	0/49 (0%)	3/50 (6%)	0/48 (0%)
Adjusted Rates (b)	0.0%	9.1%	0.0%
Terminal Rates (c)	0/38 (0%)	3/33 (9%)	0/30 (0%)
Week of First Observation		103	
Life Table Tests (d)	P=0.574	P=0.097	(e)
Incidental Tumor Tests (d)	P=0.574	P=0.097	(e)
Cochran-Armitage Trend Test (d)	P=0.635		
Fisher Exact Test (d)		P=0.125	(e)
Harderian Gland: Adenoma			
Overall Rates (a)	3/49 (6%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	7.4%	5.5%	6.7%
Terminal Rates (c)	2/38 (5%)	1/33 (3%)	2/30 (7%)
Week of First Observation	89	89	103
Life Table Tests (d)	P=0.522N	P=0.559N	P=0.616N
Incidental Tumor Tests (d)	P=0.594	P=0.539N	P=0.678
Cochran-Armitage Trend Test (d)	P=0.398N		
Fisher Exact Test (d)		P=0.490N	P=0.490N
All Sites: Benign Tumors			
Overall Rates (a)	20/49 (41%)	24/50 (48%)	16/50 (32%)
Adjusted Rates (b)	47.2%	64.6%	51.6%
Terminal Rates (c)	16/38 (42%)	20/33 (61%)	15/30 (50%)
Week of First Observation	84	89	89
Life Table Tests (d)	P=0.460	P=0.121	P=0.545
Incidental Tumor Tests (d)	P=0.322	P=0.215	P=0.332
Cochran-Armitage Trend Test (d)	P=0.212N		
Fisher Exact Test (d)		P=0.303	P=0.241N
All Sites: Malignant Tumors			
Overall Rates (a)	20/49 (41%)	21/50 (42%)	14/50 (28%)
Adjusted Rates (b)	42.9%	45.0%	43.6%
Terminal Rates (c)	12/38 (32%)	8/33 (24%)	12/30 (40%)
Week of First Observation	54	68	71
Life Table Tests (d)	P=0.467N	P=0.363	P=0.466N
Incidental Tumor Tests (d)	P=0.409	P=0.379N	P=0.430
Cochran-Armitage Trend Test (d)	P=0.111N		
Fisher Exact Test (d)		P=0.534	P=0.129N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	375 mg/kg	750 mg/kg
All Sites: All Tumors			
Overall Rates (a)	31/49 (63%)	39/50 (78%)	25/50 (50%)
Adjusted Rates (b)	65.6%	82.9%	75.8%
Terminal Rates (c)	22/38 (58%)	25/33 (76%)	22/30 (73%)
Week of First Observation	54	68	71
Life Table Tests (d)	P=0.372	P=0.037	P=0.479
Incidental Tumor Tests (d)	P=0.119	P=0.104	P=0.158
Cochran-Armitage Trend Test (d)	P=0.100N		
Fisher Exact Test (d)		P=0.082	P=0.130N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the 750 mg/kg and vehicle control groups.

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING	1		
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*Skin	(49)	(50)	(50)
Mineralization	1 (2%)		
Ulcer, NOS	3 (6%)	1 (2%)	
Inflammation, chronic	3 (6%)	3 (6%)	
Exfoliative dermatitis			1 (2%)
Hyperkeratosis			1 (2%)
*Subcutaneous tissue	(49)	(50)	(50)
Steatitis	1 (2%)		
Abscess, NOS	1 (2%)		
Inflammation, chronic	2 (4%)		
Granuloma, NOS	1 (2%)		
Granuloma, foreign body	2 (4%)		
Granulation tissue		1 (2%)	
RESPIRATORY SYSTEM			
*Nasal cavity	(49)	(50)	(50)
Hemorrhage	10 (20%)	7 (14%)	7 (14%)
Lymphocytic inflammatory infiltration	2 (4%)	1 (2%)	1 (2%)
Inflammation, acute		3 (6%)	
*Nasal turbinate	(49)	(50)	(50)
Inflammation, chronic		1 (2%)	
#Lung	(49)	(50)	(50)
Mineralization	1 (2%)	2 (4%)	3 (6%)
Emphysema, alveolar			1 (2%)
Congestion, NOS	1 (2%)		8 (16%)
Hemorrhage	11 (22%)	7 (14%)	16 (32%)
Bronchopneumonia, NOS	12 (24%)	16 (32%)	16 (32%)
Lymphocytic inflammatory infiltration	1 (2%)	1 (2%)	10 (20%)
Pneumonia, interstitial chronic			1 (2%)
Cholesterol deposit	2 (4%)	5 (10%)	8 (16%)
Hemosiderosis		1 (2%)	
Hyperplasia, alveolar epithelium	12 (24%)	19 (38%)	13 (26%)
Histiocytosis	13 (27%)	20 (40%)	13 (26%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(49)	(48)	(50)
Hemorrhage		1 (2%)	
Fibrosis	2 (4%)		1 (2%)
Hyperplasia, granulocytic	40 (82%)	40 (83%)	28 (56%)
#Spleen	(49)	(50)	(50)
Pigmentation, NOS	4 (8%)	5 (10%)	4 (8%)
Hyperplasia, lymphoid	12 (24%)	6 (12%)	10 (20%)
Hematopoiesis	12 (24%)	10 (20%)	4 (8%)
#Lymph node	(49)	(50)	(48)
Hyperplasia, lymphoid	3 (6%)	1 (2%)	1 (2%)
#Mandibular lymph node	(49)	(50)	(48)
Pigmentation, NOS	1 (2%)		2 (4%)
Hyperplasia, lymphoid	3 (6%)	2 (4%)	4 (8%)
#Mesenteric lymph node	(49)	(50)	(48)
Congestion, NOS	13 (27%)	2 (4%)	1 (2%)
Hemorrhage		1 (2%)	
Inflammation, acute			1 (2%)
Inflammation, active chronic	1 (2%)		
Hyperplasia, lymphoid	3 (6%)	7 (14%)	2 (4%)

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Liver	(49)	(50)	(50)
Hematopoiesis	2 (4%)	1 (2%)	2 (4%)
#Peyer's patch	(49)	(50)	(50)
Hyperplasia, lymphoid		1 (2%)	
#Thymus	(45)	(44)	(46)
Embryonal duct cyst			1 (2%)
Cyst, NOS	1 (2%)		1 (2%)
Necrosis, NOS			1 (2%)
Hyperplasia, reticulum cell		1 (2%)	
Hyperplasia, lymphoid	2 (4%)		1 (2%)
CIRCULATORY SYSTEM			
#Heart	(49)	(50)	(50)
Lymphocytic inflammatory infiltration		1 (2%)	
Inflammation, chronic	4 (8%)	2 (4%)	1 (2%)
*Artery	(49)	(50)	(50)
Mineralization	1 (2%)		
Periarteritis			1 (2%)
*Aorta	(49)	(50)	(50)
Mineralization			1 (2%)
DIGESTIVE SYSTEM			
*Root of tooth	(49)	(50)	(50)
Inflammation, active chronic	1 (2%)		
*Pulp of tooth	(49)	(50)	(50)
Dysplasia, NOS	1 (2%)	1 (2%)	
#Salivary gland	(49)	(50)	(50)
Mineralization			1 (2%)
Lymphocytic inflammatory infiltration	1 (2%)	1 (2%)	2 (4%)
Inflammation, chronic	1 (2%)	5 (10%)	
Atrophy, NOS	1 (2%)	3 (6%)	3 (6%)
#Liver	(49)	(50)	(50)
Mineralization	1 (2%)		
Cyst, NOS		1 (2%)	
Congestion, NOS	1 (2%)		
Lymphocytic inflammatory infiltration		2 (4%)	
Inflammation, acute	1 (2%)	1 (2%)	1 (2%)
Inflammation, active chronic	2 (4%)		
Necrosis, coagulative		1 (2%)	
Cytoplasmic vacuolization	7 (14%)	7 (14%)	9 (18%)
Focal cellular change	2 (4%)	3 (6%)	2 (4%)
Hepatocytomegaly	1 (2%)	3 (6%)	1 (2%)
#Liver/centrilobular	(49)	(50)	(50)
Necrosis, coagulative			1 (2%)
#Liver/periportal	(49)	(50)	(50)
Inflammation, chronic		1 (2%)	
*Gallbladder	(49)	(50)	(50)
Cyst, NOS	2 (4%)	1 (2%)	
Inflammation, acute		1 (2%)	
#Pancreas	(49)	(50)	(50)
Cyst, NOS	1 (2%)		
Necrosis, NOS			1 (2%)
#Pancreatic acinus	(49)	(50)	(50)
Focal cellular change	1 (2%)	3 (6%)	3 (6%)
Atrophy, NOS	2 (4%)		1 (2%)
Hyperplasia, NOS		1 (2%)	1 (2%)
#Stomach	(49)	(50)	(50)
Inflammation, chronic		1 (2%)	
#Gastric fundal gland	(49)	(50)	(50)
Dilatation, NOS	6 (12%)	1 (2%)	2 (4%)

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Glandular stomach	(49)	(50)	(50)
Mineralization	1 (2%)		
Lymphocytic inflammatory infiltration		1 (2%)	
Inflammation, acute	2 (4%)		
Inflammation, active chronic			1 (2%)
Inflammation, chronic			1 (2%)
Metaplasia, squamous	1 (2%)		
Dysplasia, epithelial	1 (2%)	3 (6%)	
#Forestomach	(49)	(50)	(50)
Mineralization		1 (2%)	1 (2%)
Inflammation, acute	1 (2%)		1 (2%)
Inflammation, active chronic		2 (4%)	1 (2%)
Hyperplasia, epithelial	1 (2%)		
Hyperkeratosis	2 (4%)	1 (2%)	1 (2%)
Acanthosis			1 (2%)
URINARY SYSTEM			
#Kidney	(49)	(50)	(50)
Lymphocytic inflammatory infiltration	1 (2%)		8 (16%)
Inflammation, chronic	3 (6%)	8 (16%)	3 (6%)
#Kidney/cortex	(49)	(50)	(50)
Cyst, NOS	4 (8%)	3 (6%)	
Multiple cysts	4 (8%)		
Metaplasia, osseous	1 (2%)	2 (4%)	
#Kidney/tubule	(49)	(50)	(50)
Mineralization	32 (65%)	29 (58%)	26 (52%)
Dilatation, NOS	5 (10%)	5 (10%)	6 (12%)
Cyst, NOS			1 (2%)
Necrosis, NOS	9 (18%)	6 (12%)	5 (10%)
Cytoplasmic vacuolization	3 (6%)		
Regeneration, NOS	39 (80%)	42 (84%)	34 (68%)
#Kidney/pelvis	(49)	(50)	(50)
Hemorrhage	1 (2%)		
#Urinary bladder	(49)	(50)	(48)
Calculus, gross observation only			2 (4%)
Calculus, microscopic examination			1 (2%)
Mineralization			1 (2%)
Cast, NOS		1 (2%)	
Lymphocytic inflammatory infiltration			2 (4%)
Inflammation, acute		1 (2%)	
Inflammation, chronic	2 (4%)		
*Urethra	(49)	(50)	(50)
Cast, NOS	19 (39%)	13 (26%)	24 (48%)
ENDOCRINE SYSTEM			
#Pituitary intermedia	(49)	(48)	(50)
Cyst, NOS			1 (2%)
#Anterior pituitary	(49)	(48)	(50)
Cyst, NOS		1 (2%)	3 (6%)
Multiple cysts	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, NOS	1 (2%)	3 (6%)	1 (2%)
Hyperplasia, focal		1 (2%)	
#Adrenal/capsule	(49)	(50)	(48)
Hyperplasia, NOS	48 (98%)	45 (90%)	39 (81%)
#Adrenal cortex	(49)	(50)	(48)
Accessory structure	1 (2%)		
Cyst, NOS	1 (2%)		
Focal cellular change		1 (2%)	
Hypertrophy, focal			1 (2%)
Hyperplasia, NOS	5 (10%)	3 (6%)	4 (8%)

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Adrenal medulla	(49)	(50)	(48)
Hyperplasia, NOS	2 (4%)	3 (6%)	
#Thyroid	(49)	(50)	(47)
Cystic follicles	14 (29%)	11 (22%)	11 (23%)
Inflammation, chronic			1 (2%)
Hyperplasia, C-cell	4 (8%)	1 (2%)	
Hyperplasia, follicular cell	2 (4%)		
#Thyroid follicle	(49)	(50)	(47)
Atrophy, NOS		1 (2%)	
#Parathyroid	(29)	(31)	(29)
Metaplasia, osseous	1 (3%)		
#Pancreatic islets	(49)	(50)	(50)
Hyperplasia, NOS	20 (41%)	20 (40%)	13 (26%)
REPRODUCTIVE SYSTEM			
*Preputial gland	(49)	(50)	(50)
Cystic ducts	8 (16%)	6 (12%)	4 (8%)
Inflammation, suppurative	1 (2%)		
Abscess, NOS	1 (2%)		
Inflammation, active chronic		1 (2%)	
Inflammation, chronic	10 (20%)	9 (18%)	3 (6%)
#Prostate	(49)	(50)	(50)
Inflammation, chronic	2 (4%)	2 (4%)	
*Seminal vesicle	(49)	(50)	(50)
Dilatation, NOS	2 (4%)	1 (2%)	
Cyst, NOS			1 (2%)
Inflammation, chronic		1 (2%)	
#Testis	(49)	(50)	(50)
Atrophy, NOS	1 (2%)		
Hyperplasia, interstitial cell		2 (4%)	
#Testis/tubule	(49)	(50)	(50)
Mineralization	3 (6%)	1 (2%)	
*Epididymis	(49)	(50)	(50)
Inflammation, chronic	1 (2%)	1 (2%)	1 (2%)
Granuloma, spermatic			2 (4%)
*Scrotum	(49)	(50)	(50)
Steatitis	1 (2%)		2 (4%)
NERVOUS SYSTEM			
*Choroid plexus	(49)	(50)	(50)
Mineralization			1 (2%)
#Brain	(49)	(50)	(50)
Compression, NOS			1 (2%)
Mineralization	37 (76%)	27 (54%)	22 (44%)
Congestion, NOS			1 (2%)
SPECIAL SENSE ORGANS			
*Eye	(49)	(50)	(50)
Cataract		1 (2%)	
*Eye/cornea	(49)	(50)	(50)
Inflammation, active chronic		1 (2%)	
*Eyelid	(49)	(50)	(50)
Inflammation, chronic	1 (2%)		
*Nasolacrimal duct	(49)	(50)	(50)
Hemorrhage	4 (8%)	8 (16%)	5 (10%)
Lymphocytic inflammatory infiltration	1 (2%)		3 (6%)
Inflammation, acute	1 (2%)		

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	Low Dose	High Dose
MUSCULOSKELETAL SYSTEM			
*Knee joint	(49)	(50)	(50)
Osteoarthritis	1 (2%)		
*Tarsal joint	(49)	(50)	(50)
Ankylosis	18 (37%)	15 (30%)	12 (24%)
BODY CAVITIES			
*Peritoneum	(49)	(50)	(50)
Steatitis			1 (2%)
*Pericardium	(49)	(50)	(50)
Inflammation, chronic		1 (2%)	
*Mesentery	(49)	(50)	(50)
Cyst, NOS	1 (2%)		
Steatitis	3 (6%)	4 (8%)	3 (6%)
ALL OTHER SYSTEMS			
*Multiple organs	(49)	(50)	(50)
Lymphocytic inflammatory infiltration	43 (88%)	40 (80%)	31 (62%)
SPECIAL MORPHOLOGY SUMMARY			
Animal missing/no necropsy	1		

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

APPENDIX D

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(49)	(50)
Fibrosarcoma	†2 (4%)	1 (2%)	
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(49)	(50)
Carcinoma, NOS, invasive	1 (2%)		
#Lung	(50)	(49)	(50)
Carcinoma, NOS, metastatic	1 (2%)		
Adenocarcinoma, NOS, metastatic		1 (2%)	
Alveolar/bronchiolar adenoma	2 (4%)	1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma	1 (2%)		1 (2%)
Endometrial stromal sarcoma, metastatic	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(49)	(50)
Malignant lymphoma, histiocytic type		1 (2%)	
Malignant lymphoma, mixed type	17 (34%)	6 (12%)	6 (12%)
#Spleen	(50)	(49)	(50)
Malignant lymphoma, mixed type	1 (2%)	1 (2%)	
#Lymph node	(50)	(47)	(48)
Malignant lymphoma, mixed type		1 (2%)	
#Liver	(50)	(49)	(50)
Malignant lymphoma, mixed type	1 (2%)		
#Jejunum	(50)	(49)	(48)
Malignant lymphoma, mixed type		1 (2%)	
CIRCULATORY SYSTEM			
#Liver	(50)	(49)	(50)
Hemangiosarcoma		1 (2%)	
#Uterus	(50)	(49)	(50)
Hemangioma	1 (2%)		
DIGESTIVE SYSTEM			
*Tongue	(50)	(49)	(50)
Squamous cell carcinoma	1 (2%)		
#Liver	(50)	(49)	(50)
Carcinoma, NOS, metastatic			1 (2%)
Hepatocellular adenoma	3 (6%)	7 (14%)	4 (8%)
Hepatocellular carcinoma	1 (2%)	5 (10%)	
Endometrial stromal sarcoma, metastatic	1 (2%)		
#Stomach	(50)	(48)	(50)
Sarcoma, NOS			1 (2%)
#Jejunum	(50)	(49)	(48)
Carcinoma, NOS	1 (2%)		
URINARY SYSTEM			
None			

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(49)	(49)
Carcinoma, NOS	1 (2%)		
Adenoma, NOS	20 (41%)	11 (22%)	3 (6%)
#Adrenal/capsule	(50)	(47)	(50)
Carcinoma, NOS			1 (2%)
Adenoma, NOS	1 (2%)		
#Adrenal medulla	(50)	(47)	(50)
Pheochromocytoma	1 (2%)		
#Thyroid	(50)	(49)	(49)
Follicular cell adenoma		1 (2%)	
Follicular cell carcinoma			1 (2%)
#Pancreatic islets	(50)	(49)	(50)
Islet cell adenoma	1 (2%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(49)	(50)
Adenocarcinoma, NOS		2 (4%)	
*Vagina	(50)	(49)	(50)
Squamous cell carcinoma	1 (2%)		
#Uterus	(50)	(49)	(50)
Endometrial stromal polyp	1 (2%)		
Endometrial stromal sarcoma	1 (2%)		
#Ovary	(50)	(48)	(46)
Cystadenoma, NOS		1 (2%)	2 (4%)
Granulosa cell tumor		1 (2%)	
NERVOUS SYSTEM			
#Brain/meninges	(50)	(49)	(50)
Fibrosarcoma, invasive		1 (2%)	
*Spinal dura mater	(50)	(49)	(50)
Fibrosarcoma, invasive	1 (2%)		
#Brain	(50)	(49)	(50)
Carcinoma, NOS, invasive	1 (2%)		
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(49)	(50)
Carcinoma, NOS	1 (2%)		
Adenoma, NOS	2 (4%)	5 (10%)	2 (4%)
MUSCULOSKELETAL SYSTEM			
*Vertebra	(50)	(49)	(50)
Fibrosarcoma, invasive	1 (2%)		
BODY CAVITIES			
*Mesentery	(50)	(49)	(50)
Sarcoma, NOS, invasive			1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(49)	(50)
Sarcoma, NOS	1 (2%)		
Fibrosarcoma, metastatic	1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	Low Dose	High Dose
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	4	2	22
Moribund sacrifice	11	8	2
Terminal sacrifice	35	39	22
Accidentally killed, NOS			4
Animal missing		1	
TUMOR SUMMARY			
Total animals with primary tumors**	38	33	15
Total primary tumors	63	46	22
Total animals with benign tumors	25	21	11
Total benign tumors	32	26	12
Total animals with malignant tumors	27	18	9
Total malignant tumors	31	19	10
Total animals with secondary tumors##	5	2	2
Total secondary tumors	8	2	2
Total animals with tumors uncertain-- benign or malignant		1	
Total uncertain tumors		1	

* Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
† Multiple occurrence of morphology in the same organ; tissue is counted once only.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE: VEHICLE CONTROL

ANIMAL NUMBER	1 3 4	1 4 6	1 0 2	1 0 3	1 4 5	1 1 3	1 2 1	1 2 4	1 4 8	1 2 9	1 1 1	1 3 7	1 3 8	1 1 9	1 2 2	1 0 1	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 4
WEEKS ON STUDY	0 5 5	0 7 1	0 8 3	0 8 3	0 8 3	0 8 9	0 8 9	0 9 2	0 9 3	0 9 5	0 9 6	0 9 6	0 9 8	1 0 3	1 0 3	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma										X	@X														
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic												X													
Alveolar/bronchiolar adenoma									X																
Alveolar/bronchiolar carcinoma																									
Endometrial stromal sarcoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive												X													
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	−	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma					X																				
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																								X	
Hepatocellular carcinoma																	X								
Endometrial stromal sarcoma, metastatic																									
Malignant lymphoma, mixed type																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS		X																							
Adenoma, NOS								X				X				X	X								
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	−	+	−	+	−	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vagina	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																								X	
Endometrial stromal sarcoma																									
Hemangioma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive		X																							
Spinal cord	+	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma, invasive										X															
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS												X													
Adenoma, NOS																									
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma, invasive										X															
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS																									
Fibrosarcoma, metastatic											X														
Malignant lymphoma, mixed type						X							X		X		X		X	X			X	X	

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

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

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

ANIMAL NUMBER	115	116	117	118	120	123	125	126	127	128	130	131	132	133	135	136	139	140	141	142	143	144	147	149	150	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																										2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, metastatic																										1
Alveolar/bronchiolar adenoma											X															2
Alveolar/bronchiolar carcinoma																									X	1
Endometrial stromal sarcoma, meta																								X		1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Carcinoma, NOS, invasive																										1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, mixed type																X										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	44
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma																										1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																					X	X				3
Hepatocellular carcinoma																										1
Endometrial stromal sarcoma, meta																								X		1
Malignant lymphoma, mixed type				X																						1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																					X					1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS																										1
Adenoma, NOS	X	X	X						X	X		X	X	X		X	X	X	X		X	X	X	X		20
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS		X																								1
Pheochromocytoma											X															1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid	+	+	−	+	−	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	−	+	+	−	36
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																X										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Vagina	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma										X																1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp																										1
Endometrial stromal sarcoma																								X		1
Hemangioma										X																1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																										1
Spinal cord	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma, invasive																										1
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
Adenoma, NOS								X																	X	2
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma, invasive																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS									X																	1
Fibrosarcoma, metastatic																										1
Malignant lymphoma, mixed type					X					X			X	X	X			X				X	X		X	17

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE: LOW DOSE

ANIMAL NUMBER	0024	0007	0035	0040	0447	0443	0331	0488	0912	0113	0223	0001	0002	0003	0004	0005	0006	0008	0009	0010	0111	0114	0115	0116	0117
WEEKS ON STUDY	072	077	087	087	089	097	098	098	099	102	102	103	103	103	103	103	103	103	103	103	103	103	103	103	103
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma									X																
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic										X															
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Lymph nodes	+	–	+	+	+	+	+	+	+	–	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Thymus	+	+	+	–	+	+	+	+	+	+	M	+	+	+	+	+	–	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma												X							X					X	
Hepatocellular carcinoma					X													X		X					
Hemangiosarcoma															X										
Bile duct	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	–	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																	X								
Large intestine	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS			X				X					X	X								X				
Adrenal	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Thyroid	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma			X																						
Parathyroid	+	+	–	+	–	+	+	–	+	–	M	–	+	+	+	+	+	–	+	–	–	+	+	–	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS										X															
Uterus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma, NOS																		X							
Granulosa cell tumor																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, invasive									X																
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS								X				X							X	X					
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, histiocytic type													X												
Malignant lymphoma, mixed type	X					X	X									X				X					

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

ANIMAL NUMBER	018	019	020	021	022	025	026	027	028	029	030	032	033	034	036	037	038	039	041	042	044	045	046	049	050	TOTAL:
WEEKS ON STUDY	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS, metastatic																										1
Alveolar/bronchiolar adenoma															X											1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, mixed type											X															1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Malignant lymphoma, mixed type						X																				1
Thymus	+	+	+	+	+	–	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	44
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma						X		X				X			X											7
Hepatocellular carcinoma																		X						X		5
Hemangiosarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, mixed type																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS		X			X				X					X						X		X				11
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	47
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma																										1
Parathyroid	+	+	+	+	+	+	+	–	+	+	–	+	–	–	+	+	–	+	+	–	–	–	+	+	+	32
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Adenocarcinoma, NOS																						X				2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ovary	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cystadenoma, NOS																										1
Granulosa cell tumor																									X	1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, invasive																										1
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Adenoma, NOS					X																					5
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Malignant lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type									X																	6

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE: HIGH DOSE

ANIMAL NUMBER	0065	1000	0076	0078	0094	0096	0052	0066	0056	0091	0053	0080	0069	0058	0092	0073	0075	0088	0089	0081	0077	0055	0063	0062	0064
WEEKS ON STUDY	002	012	013	013	013	013	016	018	020	020	028	043	045	048	049	052	058	059	064	073	075	078	081	094	097
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																							X		
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic																									
Hepatocellular adenoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																								X	
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																								X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																									
Parathyroid	+	+	+	+	+	+	+	−	+	+	+	−	−	−	−	−	−	+	−	+	+	−	−	+	−
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+
Cystadenoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
BODY CAVITIES																									
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS, invasive																								X	
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, mixed type																					X				

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

ANIMAL NUMBER	0090	0097	0061	0051	0054	0057	0059	0060	0067	0068	0070	0071	0072	0074	0079	0082	0083	0084	0085	0086	0087	0093	0095	0098	0099	TOTAL:
WEEKS ON STUDY	098	098	100	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma																								X		1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	49
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, metastatic							X																			1
Hepatocellular adenoma									X		X			X									X			4
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS									X														X			3
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS							X																			1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell carcinoma														X												1
Parathyroid	+	+	+	+	−	+	+	+	−	+	−	−	+	+	−	+	+	+	+	−	+	−	+	+	+	32
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	46
Cystadenoma, NOS										X						X										2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS					X																	X				2
BODY CAVITIES																										
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS, invasive																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, mixed type					X				X				X	X								X				6

* Animals necropsied

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE

	Vehicle Control	375 mg/kg	750 mg/kg
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	1/49 (2%)	2/50 (4%)
Adjusted Rates (b)	7.7%	2.6%	8.0%
Terminal Rates (c)	2/37 (5%)	1/39 (3%)	1/22 (5%)
Week of First Observation	93	103	81
Life Table Tests (d)	P=0.587N	P=0.287N	P=0.638
Incidental Tumor Tests (d)	P=0.584	P=0.293N	P=0.601
Cochran-Armitage Trend Test (d)	P=0.400N		
Fisher Exact Test (d)		P=0.316N	P=0.500N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	19/50 (38%)	9/49 (18%)	6/50 (12%)
Adjusted Rates (b)	48.5%	20.8%	25.3%
Terminal Rates (c)	17/37 (46%)	6/39 (15%)	5/22 (23%)
Week of First Observation	89	72	75
Life Table Tests (d)	P=0.028N	P=0.016N	P=0.076N
Incidental Tumor Tests (d)	P=0.014N	P=0.020N	P=0.057N
Cochran-Armitage Trend Test (d)	P=0.001N		
Fisher Exact Test (d)		P=0.025N	P=0.003N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	19/50 (38%)	10/49 (20%)	6/50 (12%)
Adjusted Rates (b)	48.5%	23.2%	25.3%
Terminal Rates (c)	17/37 (46%)	7/39 (18%)	5/22 (23%)
Week of First Observation	89	72	75
Life Table Tests (d)	P=0.032N	P=0.028N	P=0.076N
Incidental Tumor Tests (d)	P=0.016N	P=0.035N	P=0.057N
Cochran-Armitage Trend Test (d)	P=0.002N		
Fisher Exact Test (d)		P=0.044N	P=0.003N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	3/50 (6%)	7/49 (14%)	4/50 (8%)
Adjusted Rates (b)	8.1%	17.9%	18.2%
Terminal Rates (c)	3/37 (8%)	7/39 (18%)	4/22 (18%)
Week of First Observation	103	103	103
Life Table Tests (d)	P=0.159	P=0.178	P=0.231
Incidental Tumor Tests (d)	P=0.159	P=0.178	P=0.231
Cochran-Armitage Trend Test (d)	P=0.432		
Fisher Exact Test (d)		P=0.151	P=0.500
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	1/50 (2%)	5/49 (10%)	0/50 (0%)
Adjusted Rates (b)	2.7%	12.2%	0.0%
Terminal Rates (c)	1/37 (3%)	4/39 (10%)	0/22 (0%)
Week of First Observation	103	89	
Life Table Tests (d)	P=0.590N	P=0.116	P=0.604N
Incidental Tumor Tests (d)	P=0.552	P=0.088	P=0.604N
Cochran-Armitage Trend Test (d)	P=0.400N		
Fisher Exact Test (d)		P=0.098	P=0.500N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	12/49 (24%)	4/50 (8%)
Adjusted Rates (b)	10.8%	29.8%	18.2%
Terminal Rates (c)	4/37 (11%)	11/39 (28%)	4/22 (18%)
Week of First Observation	103	89	103
Life Table Tests (d)	P=0.204	P=0.035	P=0.343
Incidental Tumor Tests (d)	P=0.171	P=0.028	P=0.343
Cochran-Armitage Trend Test (d)	P=0.558		
Fisher Exact Test (d)		P=0.024	P=0.643

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	375 mg/kg	750 mg/kg
Pituitary Gland: Adenoma			
Overall Rates (a)	20/49 (41%)	11/49 (22%)	3/49 (6%)
Adjusted Rates (b)	51.1%	26.4%	12.5%
Terminal Rates (c)	18/37 (49%)	9/39 (23%)	2/22 (9%)
Week of First Observation	92	87	94
Life Table Tests (d)	P=0.002N	P=0.028N	P=0.004N
Incidental Tumor Tests (d)	P=0.001N	P=0.035N	P=0.003N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.041N	P<0.001N
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	21/49 (43%)	11/49 (22%)	3/49 (6%)
Adjusted Rates (b)	52.1%	26.4%	12.5%
Terminal Rates (c)	18/37 (49%)	9/39 (23%)	2/22 (9%)
Week of First Observation	71	87	94
Life Table Tests (d)	P<0.001N	P=0.019N	P=0.003N
Incidental Tumor Tests (d)	P<0.001N	P=0.024N	P=0.001N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.026N	P<0.001N
Harderian Gland: Adenoma			
Overall Rates (a)	2/50 (4%)	5/49 (10%)	2/50 (4%)
Adjusted Rates (b)	5.4%	12.3%	9.1%
Terminal Rates (c)	2/37 (5%)	4/39 (10%)	2/22 (9%)
Week of First Observation	103	98	103
Life Table Tests (d)	P=0.351	P=0.245	P=0.496
Incidental Tumor Tests (d)	P=0.372	P=0.237	P=0.496
Cochran-Armitage Trend Test (d)	P=0.583		
Fisher Exact Test (d)		P=0.210	P=0.691
Harderian Gland: Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	5/49 (10%)	2/50 (4%)
Adjusted Rates (b)	7.8%	12.3%	9.1%
Terminal Rates (c)	2/37 (5%)	4/39 (10%)	2/22 (9%)
Week of First Observation	96	98	103
Life Table Tests (d)	P=0.505	P=0.398	P=0.642
Incidental Tumor Tests (d)	P=0.547	P=0.378	P=0.678
Cochran-Armitage Trend Test (d)	P=0.421N		
Fisher Exact Test (d)		P=0.346	P=0.500N
All Sites: Benign Tumors			
Overall Rates (a)	25/50 (50%)	21/49 (43%)	11/50 (22%)
Adjusted Rates (b)	62.3%	49.7%	45.1%
Terminal Rates (c)	22/37 (59%)	18/39 (46%)	9/22 (41%)
Week of First Observation	92	87	81
Life Table Tests (d)	P=0.129N	P=0.193N	P=0.178N
Incidental Tumor Tests (d)	P=0.143N	P=0.242N	P=0.186N
Cochran-Armitage Trend Test (d)	P=0.003N		
Fisher Exact Test (d)		P=0.305N	P=0.003N
All Sites: Malignant Tumors			
Overall Rates (a)	27/50 (54%)	18/49 (37%)	9/50 (18%)
Adjusted Rates (b)	61.1%	39.6%	36.5%
Terminal Rates (c)	20/37 (54%)	12/39 (31%)	7/22 (32%)
Week of First Observation	71	72	75
Life Table Tests (d)	P=0.023N	P=0.048N	P=0.044N
Incidental Tumor Tests (d)	P=0.005N	P=0.054N	P=0.013N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.064N	P<0.001N

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	375 mg/kg	750 mg/kg
All Sites: All Tumors			
Overall Rates (a)	38/50 (76%)	33/49 (67%)	15/50 (30%)
Adjusted Rates (b)	82.6%	70.1%	59.2%
Terminal Rates (c)	29/37 (78%)	25/39 (64%)	12/22 (55%)
Week of First Observation	71	72	75
Life Table Tests (d)	P=0.025N	P=0.142N	P=0.034N
Incidental Tumor Tests (d)	P=0.006N	P=0.197N	P=0.009N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.232N	P<0.001N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

TABLE D4a. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies by Physiological Research Laboratories are included in the historical data base.			
Overall Historical Incidence			
TOTAL	71/1,489 (4.8%)	46/1,489 (3.1%)	116/1,489 (7.8%)
SD (b)	4.29%	2.62%	5.56%
Range (c)			
High	9/50	5/50	(d) 14/50
Low	0/50	0/50	0/49

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Second highest: 9/50

TABLE D4b. HISTORICAL INCIDENCE OF PITUITARY GLAND TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies by Physiological Research Laboratories are included in the historical data base.			
Overall Historical Incidence			
TOTAL	(b) 237/1,324 (17.9%)	(c) 20/1,324 (1.5%)	(b,c) 257/1,324 (19.4%)
SD (d)	8.44%	2.79%	8.95%
Range (e)			
High	18/49	5/47	18/49
Low	2/44	0/49	2/44

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Includes 198 adenomas, NOS, 38 chromophobe adenomas, and 1 acidophil adenoma
(c) Includes 14 carcinomas, NOS, 5 adenocarcinomas, NOS, and 1 acidophil carcinoma
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

TABLE D4c. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls	
	Lymphoma	Lymphoma or Leukemia
No 2-year studies by Physiological Research Laboratories are included in the historical data base.		
Overall Historical Incidence		
TOTAL	379/1,494 (25.4%)	393/1,494 (26.3%)
SD (b)	9.16%	9.25%
Range (c)		
High	21/50	21/50
Low	4/50	4/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(49)	(50)
Ulcer, NOS	1 (2%)		
Inflammation, chronic	1 (2%)		
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(49)	(50)
Hemorrhage	6 (12%)	1 (2%)	1 (2%)
Lymphocytic inflammatory infiltration	3 (6%)	3 (6%)	8 (16%)
Inflammation, acute	1 (2%)	1 (2%)	
Inflammation, chronic		2 (4%)	
Metaplasia, squamous			1 (2%)
*Nasal turbinate	(50)	(49)	(50)
Hemorrhage			1 (2%)
Inflammation, chronic	3 (6%)		
#Trachea	(50)	(49)	(50)
Mineralization	1 (2%)		
#Lung/bronchiole	(50)	(49)	(50)
Hyperplasia, NOS			1 (2%)
#Lung	(50)	(49)	(50)
Mineralization	1 (2%)	1 (2%)	
Congestion, NOS		1 (2%)	11 (22%)
Hemorrhage	12 (24%)	3 (6%)	12 (24%)
Bronchopneumonia, NOS	13 (26%)	24 (49%)	18 (36%)
Lymphocytic inflammatory infiltration	2 (4%)	1 (2%)	9 (18%)
Pneumonia, interstitial chronic	1 (2%)		
Cholesterol deposit	4 (8%)	5 (10%)	6 (12%)
Hyperplasia, alveolar epithelium	11 (22%)	28 (57%)	16 (32%)
Histiocytosis	16 (32%)	30 (61%)	17 (34%)
HEMATOPOIETIC SYSTEM			
#Brain	(50)	(49)	(50)
Lymphocytosis	1 (2%)		
*Multiple organs	(50)	(49)	(50)
Hyperplasia, lymphoid	1 (2%)		
#Bone marrow	(50)	(49)	(50)
Fibrosis	15 (30%)	16 (33%)	12 (24%)
Hyperplasia, granulocytic	32 (64%)	28 (57%)	10 (20%)
#Spleen	(50)	(49)	(50)
Pigmentation, NOS	5 (10%)	4 (8%)	5 (10%)
Hyperplasia, lymphoid	19 (38%)	15 (31%)	6 (12%)
Hematopoiesis	10 (20%)	9 (18%)	2 (4%)
#Lymph node	(50)	(47)	(48)
Hyperplasia, lymphoid	1 (2%)		
#Mandibular lymph node	(50)	(47)	(48)
Hemosiderosis			1 (2%)
Hyperplasia, lymphoid	8 (16%)	4 (9%)	1 (2%)
#Mesenteric lymph node	(50)	(47)	(48)
Congestion, NOS	1 (2%)		
Inflammation, acute	2 (4%)		
Hyperplasia, reticulum cell			1 (2%)
Hyperplasia, lymphoid	8 (16%)	6 (13%)	
Hematopoiesis			1 (2%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Renal lymph node	(50)	(47)	(48)
Congestion, NOS	1 (2%)		
Hyperplasia, lymphoid	1 (2%)		
#Liver	(50)	(49)	(50)
Hematopoiesis	3 (6%)	3 (6%)	3 (6%)
#Ovary/parovarian	(50)	(48)	(46)
Hyperplasia, lymphoid		1 (2%)	
#Thymus	(44)	(44)	(49)
Cyst, NOS	2 (5%)		
Hyperplasia, lymphoid	3 (7%)	1 (2%)	1 (2%)
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(49)	(50)
Periarteritis	2 (4%)		
#Mesenteric lymph node	(50)	(47)	(48)
Thrombosis, NOS	1 (2%)		
#Heart	(50)	(49)	(50)
Mineralization	1 (2%)	1 (2%)	
Thrombosis, NOS		1 (2%)	
Embolus, septic		1 (2%)	
Inflammation, acute	1 (2%)		
Inflammation, chronic	7 (14%)	2 (4%)	1 (2%)
*Pulmonary vein	(50)	(49)	(50)
Mineralization		1 (2%)	
Thrombosis, NOS		1 (2%)	
#Ovary	(50)	(48)	(46)
Thrombosis, NOS		1 (2%)	
DIGESTIVE SYSTEM			
*Pulp of tooth	(50)	(49)	(50)
Inflammation, chronic	1 (2%)		
#Salivary gland	(50)	(49)	(50)
Lymphocytic inflammatory infiltration	1 (2%)	1 (2%)	
Inflammation, chronic	2 (4%)	2 (4%)	
#Liver	(50)	(49)	(50)
Accessory structure		1 (2%)	
Bile stasis		1 (2%)	
Congestion, NOS	1 (2%)		
Lymphocytic inflammatory infiltration			2 (4%)
Inflammation, acute	1 (2%)	1 (2%)	
Inflammation, chronic	1 (2%)		
Necrosis, NOS	2 (4%)	2 (4%)	
Hemosiderosis			1 (2%)
Cytoplasmic vacuolization	5 (10%)	8 (16%)	9 (18%)
Focal cellular change	1 (2%)	1 (2%)	1 (2%)
Hepatocytomegaly	1 (2%)		
#Liver/periportal	(50)	(49)	(50)
Inflammation, chronic	2 (4%)		
*Gallbladder	(50)	(49)	(50)
Multiple cysts		1 (2%)	
#Bile duct	(50)	(49)	(50)
Hyperplasia, NOS	1 (2%)		
#Pancreas	(50)	(49)	(50)
Cystic ducts	2 (4%)	1 (2%)	
Inflammation, chronic	2 (4%)	2 (4%)	
Atrophy, NOS	1 (2%)		

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Pancreatic acinus	(50)	(49)	(50)
Cytoplasmic vacuolization	1 (2%)		
Focal cellular change	1 (2%)		1 (2%)
Atrophy, NOS		3 (6%)	
Hyperplasia, NOS	3 (6%)	1 (2%)	2 (4%)
#Esophagus	(50)	(49)	(49)
Hyperkeratosis			1 (2%)
#Stomach	(50)	(48)	(50)
Inflammation, acute	1 (2%)		
#Gastric fundal gland	(50)	(48)	(50)
Dilatation, NOS	7 (14%)		3 (6%)
#Glandular stomach	(50)	(48)	(50)
Mineralization	1 (2%)	1 (2%)	1 (2%)
Cyst, NOS	1 (2%)		1 (2%)
Inflammation, acute	1 (2%)		
Inflammation, chronic	2 (4%)		
#Forestomach	(50)	(48)	(50)
Ulcer, NOS			1 (2%)
Inflammation, acute	1 (2%)		
Inflammation, active chronic		1 (2%)	1 (2%)
Hyperkeratosis	2 (4%)		
Acanthosis		1 (2%)	
#Cecum	(50)	(49)	(48)
Edema, NOS	1 (2%)		
*Rectum	(50)	(49)	(50)
Infection, protozoan		1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(49)	(50)
Lymphocytic inflammatory infiltration	1 (2%)	3 (6%)	9 (18%)
Pyelonephritis, acute		1 (2%)	
Inflammation, chronic	3 (6%)	3 (6%)	2 (4%)
Glomerulonephritis, chronic	1 (2%)		
Infarct, focal	1 (2%)		
#Kidney/cortex	(50)	(49)	(50)
Metaplasia, osseous	1 (2%)	1 (2%)	1 (2%)
#Kidney/glomerulus	(50)	(49)	(50)
Amyloidosis		1 (2%)	
#Kidney/tubule	(50)	(49)	(50)
Mineralization	1 (2%)	6 (12%)	4 (8%)
Dilatation, NOS	2 (4%)	5 (10%)	5 (10%)
Nephrosis, cholemic		1 (2%)	
Necrosis, NOS	4 (8%)	7 (14%)	4 (8%)
Pigmentation, NOS		1 (2%)	
Regeneration, NOS	18 (36%)	15 (31%)	14 (28%)
#Urinary bladder	(50)	(49)	(49)
Calculus, microscopic examination	1 (2%)		
Hemorrhage	1 (2%)		
Lymphocytic inflammatory infiltration		1 (2%)	2 (4%)
Inflammation, chronic	1 (2%)		
Hyperplasia, epithelial	1 (2%)		

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(49)	(49)
Cyst, NOS	2 (4%)	1 (2%)	
Multiple cysts	1 (2%)		
Hemorrhagic cyst			2 (4%)
Focal cellular change	1 (2%)		
Hyperplasia, NOS	16 (33%)	14 (29%)	12 (24%)
Angiectasis		1 (2%)	
#Adrenal	(50)	(47)	(50)
Degeneration, lipoid			1 (2%)
#Adrenal/capsule	(50)	(47)	(50)
Hyperplasia, NOS	50 (100%)	46 (98%)	49 (98%)
#Adrenal cortex	(50)	(47)	(50)
Accessory structure		1 (2%)	
Congestion, NOS	1 (2%)		1 (2%)
Degeneration, lipoid	1 (2%)	2 (4%)	
Necrosis, NOS	1 (2%)		
Amyloidosis	1 (2%)		
Metamorphosis, fatty		2 (4%)	
Pigmentation, NOS		1 (2%)	1 (2%)
Focal cellular change	1 (2%)		
Hyperplasia, NOS	3 (6%)	2 (4%)	1 (2%)
#Adrenal medulla	(50)	(47)	(50)
Hyperplasia, NOS	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, focal	1 (2%)		
#Thyroid	(50)	(49)	(49)
Embryonal duct cyst		1 (2%)	
Cystic follicles	20 (40%)	15 (31%)	6 (12%)
Hyperplasia, C-cell	1 (2%)	1 (2%)	
Hyperplasia, follicular cell	2 (4%)	1 (2%)	
#Parathyroid	(36)	(32)	(32)
Embryonal duct cyst	1 (3%)		
Hyperplasia, NOS	1 (3%)		
#Pancreatic islets	(50)	(49)	(50)
Hyperplasia, NOS	4 (8%)	7 (14%)	3 (6%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(49)	(50)
Multiple cysts	11 (22%)	5 (10%)	1 (2%)
Inflammation, acute	1 (2%)		
Inflammation, chronic	1 (2%)		
#Uterus	(50)	(49)	(50)
Hydrometra		3 (6%)	5 (10%)
Hematoma, organized		1 (2%)	
Inflammation, acute	2 (4%)		
#Uterus/endometrium	(50)	(49)	(50)
Inflammation, acute	3 (6%)		
Hyperplasia, cystic	47 (94%)	42 (86%)	25 (50%)
#Ovary	(50)	(48)	(46)
Follicular cyst, NOS	1 (2%)	2 (4%)	2 (4%)
Parovarian cyst	5 (10%)	5 (10%)	1 (2%)
Hemorrhagic cyst		1 (2%)	
Abscess, NOS	1 (2%)		
Amyloidosis	1 (2%)		
Cytomegaly			1 (2%)
Hyperplasia, epithelial	1 (2%)	2 (4%)	
Angiectasis		1 (2%)	

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-MERCAPTOBENZOTHIAZOLE (Continued)

	Vehicle Control	Low Dose	High Dose
NERVOUS SYSTEM			
#Brain	(50)	(49)	(50)
Compression, NOS	2 (4%)	1 (2%)	
Mineralization	23 (46%)	26 (53%)	9 (18%)
Congestion, NOS			1 (2%)
Infarct, NOS	1 (2%)		
#Brain/thalamus	(50)	(49)	(50)
Malacia	1 (2%)		
SPECIAL SENSE ORGANS			
*Nasolacrimal duct	(50)	(49)	(50)
Hemorrhage	13 (26%)	4 (8%)	3 (6%)
Lymphocytic inflammatory infiltration	1 (2%)		6 (12%)
Inflammation, acute		1 (2%)	
Inflammation, chronic		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(49)	(50)
Fibrous osteodystrophy		1 (2%)	
BODY CAVITIES			
*Pleura	(50)	(49)	(50)
Vegetable foreign body	1 (2%)		
*Mesentery	(50)	(49)	(50)
Steatitis	6 (12%)	7 (14%)	2 (4%)
Inflammation, chronic			1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(49)	(50)
Lymphocytic inflammatory infiltration	43 (86%)	42 (86%)	29 (58%)
SPECIAL MORPHOLOGY SUMMARY			
Animal missing/no necropsy		1	

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

APPENDIX E

GENETIC TOXICOLOGY OF

2-MERCAPTOBENZOTHIAZOLE

TABLE E1. MUTAGENICITY OF 2-MERCAPTOBENZOTHIAZOLE IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/plate (b) −S9	+10% S9 (hamster)	+10% S9 (rat)
Study Performed at EG&G Mason Research Institute				
TA100	0	136 ± 10.5	133 ± 3.2	106 ± 7.4
	3.3	125 ± 9.9	--	--
	10	133 ± 10.4	138 ± 3.8	103 ± 13.3
	33	118 ± 9.8	115 ± 9.8	131 ± 7.2
	100	131 ± 5.6	109 ± 3.8	123 ± 10.1
	333	(c) 63 ± 0.9	105 ± 11.9	130 ± 4.9
	1,000	--	(c) 53 ± 7.9	(c) 67 ± 9.0
	Trial summary	Negative	Negative	Negative
	Positive control (d)	1,109 ± 29.4	927 ± 16.4	878 ± 4.5
TA1535	0	23 ± 1.0	10 ± 0.9	9 ± 1.2
	3.3	25 ± 1.2	--	--
	10	29 ± 5.6	9 ± 2.1	9 ± 0.9
	33	23 ± 0.6	9 ± 0.9	11 ± 0.0
	100	28 ± 3.6	11 ± 1.3	8 ± 0.6
	333	(c) 20 ± 2.8	6 ± 2.0	6 ± 0.7
	1,000	--	(c) 9 ± 0.9	(c) 4 ± 0.7
	Trial summary	Negative	Negative	Negative
	Positive control (d)	866 ± 2.8	89 ± 5.9	78 ± 7.5
TA1537	0	8 ± 0.3	6 ± 0.3	8 ± 2.0
	3.3	6 ± 1.2	--	--
	10	5 ± 0.9	5 ± 0.6	7 ± 1.0
	33	6 ± 0.9	5 ± 1.3	10 ± 1.5
	100	6 ± 0.3	11 ± 2.3	7 ± 2.6
	333	(c) 6 ± 0.7	7 ± 0.7	7 ± 1.5
	1,000	--	(c) 0 ± 0.3	(c) 0 ± 0
	Trial summary	Negative	Negative	Negative
	Positive control (d)	563 ± 42.3	74 ± 13.6	75 ± 2.2

		Revertants/plate (b)							
		−S9		+10% S9 (hamster)			+10% S9 (rat)		
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 3	Trial 1	Trial 2	Trial 3
TA98	0	22 ± 3.5	21 ± 1.9	28 ± 2.9	26 ± 2.9	36 ± 2.6	24 ± 3.2	28 ± 3.1	33 ± 0.9
	3.3	15 ± 2.2	18 ± 3.4	--	--	--	--	--	--
	10	21 ± 2.3	25 ± 4.1	29 ± 6.1	29 ± 1.2	31 ± 0.7	24 ± 1.5	28 ± 0.6	31 ± 3.4
	33	19 ± 2.6	18 ± 4.4	26 ± 1.3	--	--	28 ± 5.9	--	--
	100	14 ± 3.1	17 ± 3.8	35 ± 3.2	33 ± 2.3	23 ± 3.2	36 ± 2.6	32 ± 2.6	36 ± 4.4
	200	--	--	--	44 ± 1.3	29 ± 4.1	--	31 ± 2.5	33 ± 2.2
	333	12 ± 1.9	15 ± 1.2	42 ± 1.2	49 ± 2.3	26 ± 3.2	49 ± 2.9	40 ± 2.3	33 ± 2.5
	400	--	--	--	43 ± 3.6	32 ± 5.4	--	48 ± 2.2	28 ± 5.3
	500	--	--	--	46 ± 8.8	27 ± 5.3	--	37 ± 3.3	30 ± 5.9
	600	--	--	--	43 ± 4.3	18 ± 2.6	--	38 ± 3.5	30 ± 5.5
	700	--	--	--	40 ± 0.9	28 ± 4.1	--	29 ± 2.0	23 ± 0.9
	1,000	--	--	21 ± 3.8	22 ± 0.9	14 ± 0.3	21 ± 1.2	34 ± 4.8	14 ± 2.3
	Trial summary	Negative	Negative	Equivocal	Weakly Positive	Negative	Weakly Positive	Equivocal	Negative
	Positive control (d)	1,399 ± 48.1	1,408 ± 141.7	944 ± 37.8	1,187 ± 62.3	553 ± 39.4	818 ± 8.4	1,001 ± 58.5	418 ± 21.8

TABLE E1. MUTAGENICITY OF 2-MERCAPTOBENZOTHIAZOLE IN *SALMONELLA TYPHIMURIUM* (Continued)

Strain	Dose (µg/plate)	Revertants/plate (b) −S9 Trial 1	−S9 Trial 2	+10% S9 (hamster) Trial 1	+10% S9 (hamster) Trial 2	+10% S9 (rat) Trial 1	+10% S9 (rat) Trial 2
Study performed at Case Western Reserve University							
TA100	0	92 ± 1.3	104 ± 8.1	127 ± 6.0	109 ± 7.9	129 ± 5.5	92 ± 7.1
	10	--	97 ± 4.3	--	104 ± 4.6	--	89 ± 4.1
	33	97 ± 7.6	100 ± 6.2	--	89 ± 4.0	--	98 ± 6.5
	100	92 ± 6.7	109 ± 4.6	85 ± 7.8	93 ± 7.3	91 ± 15.1	81 ± 11.7
	333	67 ± 3.8	56 ± 12.9	95 ± 8.8	61 ± 15.0	82 ± 14.8	72 ± 1.9
	1,000	(e) 20 ± 10.2	--	74 ± 2.8	(e) 0 ± 0.0	22 ± 11.7	(e) 0 ± 0.0
	3,333	(e) 0 ± 0.0	--	(e) 11 ± 1.2	--	(e) 0 ± 0.0	--
	10,000	--	(e) 0 ± 0.0	(e) 0 ± 0.0	--	(e) 0 ± 0.0	--
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	420 ± 16.9	440 ± 30.4	2,102 ±164.8	2,286 ± 43.9	1,660 ± 54.6	2,162 ± 59.6
TA1535	0	6 ± 1.2	4 ± 1.5	11 ± 0.9	4 ± 1.3	11 ± 1.2	8 ± 2.2
	10	--	4 ± 2.3	--	4 ± 1.0	--	7 ± 1.0
	33	8 ± 2.2	2 ± 0.3	--	2 ± 0.7	--	5 ± 1.3
	100	5 ± 1.5	1 ± 0.3	8 ± 3.1	6 ± 2.8	6 ± 0.9	5 ± 1.2
	333	4 ± 0.9	3 ± 1.5	6 ± 1.8	6 ± 3.0	10 ± 3.0	2 ± 0.9
	1,000	7 ± 3.5	Toxic	Toxic	Toxic	Toxic	Toxic
	3,333	(e) 0 ± 0.0	--	(e) 0 ± 0.0	--	(e) 0 ± 0.0	--
	10,000	--	--	(e) 0 ± 0.0	--	(e) 0 ± 0.0	--
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	409 ±192.4	100 ± 14.9	67 ± 6.6	86 ± 7.5	148 ± 11.8	95 ± 13.1
TA1537	0	6 ± 0.0	5 ± 2.7	9 ± 1.5	7 ± 1.5	6 ± 1.7	8 ± 3.5
	3.3	--	4 ± 0.0	--	--	--	--
	10	--	3 ± 2.0	--	11 ± 2.6	--	7 ± 1.9
	33	6 ± 1.9	3 ± 0.6	--	8 ± 2.4	--	5 ± 0.6
	100	3 ± 1.0	4 ± 0.0	9 ± 0.3	6 ± 1.7	5 ± 1.8	3 ± 0.9
	333	Toxic	6 ± 1.5	6 ± 0.3	6 ± 0.9	5 ± 0.7	4 ± 0.7
	1,000	Toxic	--	6 ± 3.0	(e) 0 ± 0.0	2 ± 0.3	(e) 0 ± 0.0
	3,333	(e) 0 ± 0.0	--	(e) 0 ± 0.0	--	(e) 0 ± 0.0	--
	10,000	--	--	(e) 0 ± 0.0	--	(e) 0 ± 0.0	--
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	182 ± 55.1	271 ± 32.8	306 ± 94.4	164 ± 21.8	431 ± 13.6	365 ± 17.4
TA98	0	16 ± 0.6	14 ± 4.4	21 ± 2.2	20 ± 1.9	19 ± 2.4	13 ± 0.7
	10	--	8 ± 1.2	--	17 ± 1.5	--	18 ± 3.1
	33	13 ± 1.5	17 ± 1.5	--	14 ± 4.2	--	15 ± 3.5
	100	18 ± 1.0	15 ± 3.0	15 ± 1.2	23 ± 2.0	18 ± 3.8	18 ± 3.5
	333	20 ± 2.3	12 ± 2.0	15 ± 1.9	12 ± 2.1	12 ± 1.9	17 ± 0.9
	1,000	7 ± 6.5	(e) 0 ± 0.0	Toxic	Toxic	Toxic	--
	3,333	(e) 0 ± 0.0	--	(e) 0 ± 0.0	--	(e) 0 ± 0.0	--
	10,000	--	--	(e) 0 ± 0.0	--	(e) 0 ± 0.0	Toxic
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	277 ± 22.0	169 ± 31.3	1,937 ± 32.6	1,126 ± 71.3	1,388 ± 78.5	1,153 ± 72.4

(a) The detailed protocol is presented in Haworth et al. (1983). Cells and study compound or solvent (dimethyl sulfoxide) were incubated in the absence of exogenous metabolic activation (−S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 µg/plate dose is the solvent control.
(b) Revertants are presented as mean ± standard error from three plates.
(c) Slight toxicity
(d) Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation 4-nitro-o-phenylenediamine was used with TA98, sodium azide was used with TA100 and TA1535, and 9-aminoacridine was used with TA1537.
(e) Precipitate on plate

TABLE E2. MUTAGENICITY OF 2-MERCAPTOBENZOTHIAZOLE IN MOUSE L5178Y LYMPHOMA CELLS (a,b)

Compound	Concentration (µg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutant Count	Mutant Fraction (c)
-S9					
Trial 1					
Ethanol (d)		91.5 ± 3.6	100.0 ± 3.4	61.5 ± 3.7	22.5 ± 1.7
2-Mercaptobenzothiazole	30	84.3 ± 5.5	86.7 ± 5.5	68.0 ± 4.0	27.0 ± 2.1
	40	76.0 ± 7.2	74.3 ± 3.4	62.0 ± 2.1	28.0 ± 2.5
	50	81.0 ± 11.0	57.0 ± 5.0	74.5 ± 8.5	31.5 ± 7.5
	60	85.7 ± 4.4	63.3 ± 3.8	54.0 ± 5.3	21.3 ± 3.2
	80	82.7 ± 4.7	51.0 ± 5.6	81.7 ± 8.3	32.7 ± 2.9
	100	76.7 ± 3.5	33.7 ± 0.7	77.3 ± 8.1	34.0 ± 5.0
	150	Lethal	--	--	--
Methyl methanesulfonate	5	47.0 ± 7.9	28.0 ± 6.2	264.3 ± 21.3	(e) 197.0 ± 34.6
Trial 2					
Ethanol (d)		103.5 ± 4.6	100.3 ± 2.4	80.5 ± 4.7	26.0 ± 0.8
2-Mercaptobenzothiazole	40	84.0 ± 12.8	26.3 ± 10.3	63.3 ± 3.8	26.7 ± 4.1
	60	91.3 ± 11.5	18.0 ± 3.2	51.7 ± 12.7	19.0 ± 4.0
	80	89.7 ± 12.8	14.3 ± 2.4	100.3 ± 28.3	36.0 ± 5.5
	(f) 100	63.0 ± 3.0	6.0 ± 0.0	64.5 ± 4.5	34.5 ± 0.5
	120	Lethal	--	--	--
Methyl methanesulfonate	5	56.7 ± 2.7	31.0 ± 2.1	662.7 ± 16.2	(e) 393.0 ± 19.3
+S9 (g)					
Trial 1					
Ethanol (d)		84.3 ± 6.8	100.0 ± 4.4	196.5 ± 8.9	79.0 ± 7.4
2-Mercaptobenzothiazole	1.25	68.0 ± 4.5	65.3 ± 1.5	137.3 ± 33.5	65.7 ± 13.0
	2.5	67.3 ± 4.7	69.7 ± 2.0	103.7 ± 6.4	51.7 ± 1.3
	5	90.0 ± 12.1	56.7 ± 3.9	101.0 ± 19.1	38.0 ± 5.9
	7.5	88.7 ± 3.8	33.3 ± 2.4	192.7 ± 6.0	72.7 ± 4.3
	10	86.7 ± 3.3	24.0 ± 1.0	226.7 ± 12.3	87.7 ± 7.3
	15	79.0 ± 4.2	12.0 ± 2.0	307.3 ± 55.5	(e) 130.3 ± 24.3
Methylcholanthrene	2.5	36.0 ± 10.7	19.0 ± 10.0	528.3 ± 74.0	(e) 537.0 ± 74.1
Trial 2					
Ethanol		81.0 ± 3.0	100.3 ± 6.1	86.3 ± 5.2	35.7 ± 0.9
2-Mercaptobenzothiazole	5	79.0 ± 6.1	85.0 ± 10.5	155.7 ± 5.0	(e) 66.0 ± 4.2
	6	73.3 ± 4.7	59.7 ± 10.7	149.0 ± 10.1	(e) 69.7 ± 9.7
	8	81.0 ± 8.7	48.3 ± 4.2	140.0 ± 16.0	(e) 58.0 ± 3.6
	10	83.0 ± 9.9	35.7 ± 2.2	250.3 ± 9.0	(e) 104.0 ± 14.4
	12	75.0 ± 9.0	29.0 ± 4.5	218.3 ± 15.2	(e) 100.0 ± 15.6
	16	68.3 ± 4.8	21.3 ± 2.3	144.0 ± 57.4	(e) 69.3 ± 28.0
Methylcholanthrene	2.5	73.0 ± 13.1	46.0 ± 9.0	589.0 ± 55.5	(e) 277.3 ± 25.1
Trial 3					
Ethanol (d)		97.5 ± 3.7	100.3 ± 4.8	113.8 ± 1.0	39.0 ± 1.8
2-Mercaptobenzothiazole	4	82.7 ± 2.2	71.0 ± 5.5	139.3 ± 5.9	56.0 ± 1.5
	8	87.3 ± 13.3	59.0 ± 8.0	140.7 ± 24.5	53.3 ± 2.7
	10	87.3 ± 10.5	49.0 ± 4.2	146.7 ± 18.2	56.7 ± 5.5
	12	70.3 ± 4.1	33.7 ± 0.9	141.3 ± 18.7	(e) 66.7 ± 7.2
	16	82.3 ± 3.9	30.3 ± 2.2	184.3 ± 15.0	(e) 74.7 ± 2.8
	20	87.7 ± 8.3	21.0 ± 1.7	189.0 ± 16.7	(e) 72.0 ± 4.0
Methylcholanthrene	2.5	72.7 ± 4.2	42.3 ± 3.4	706.7 ± 81.4	(e) 324.7 ± 31.4

TABLE E2. MUTAGENICITY OF 2-MERCAPTOBENZOTHIAZOLE IN MOUSE L5178Y LYMPHOMA CELLS (Continued)

(a) Study performed at Litton Bionetics, Inc. The experimental protocol is presented in detail by Myhr et al. (1985) and follows the basic format of Clive et al. (1979). The highest dose of study compound is determined by solubility or toxicity and may not exceed 5 mg/ml. All doses are tested in triplicate; unless otherwise specified, the average for the three tests is presented in the table. Cells (6×10^5/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency.
(b) Mean ± standard error of replicate trials for approximately 3×10^6 cells each. All data are evaluated statistically for both trend and peak response ($P<0.05$ for at least one of the three highest dose sets). Both responses must be significantly ($P<0.05$) positive for a chemical to be considered mutagenic. If only one of these responses is significant, the call is "questionable"; the absence of both trend and peak response results in a "negative" call.
(c) Mutant fraction (frequency) is a ratio of the mutant count to the cloning efficiency, divided by 3 (to arrive at MF per 1×10^6 cells treated); MF = mutant fraction.
(d) Data presented are the average of four tests.
(e) Significant positive response; occurs when the relative mutant fraction (average MF of treated culture/average MF of solvent control) is greater than or equal to 1.6.
(f) Data presented are the average of two tests; doses in one test were lethal.
(g) Tests conducted with metabolic activation were performed as described in (a) except that S9, prepared from the liver of Aroclor 1254-induced F344 rats, was added at the same time as the study chemical and/or solvent (ethanol).

TABLE E3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY 2-MERCAPTOBENZOTHIAZOLE (a)

Compound	Dose (µg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
-S9 (c)								
Trial No. 1--Summary: Negative								
Dimethyl sulfoxide		50	1,035	500	0.48	10.0	25.3	--
2-Mercaptobenzothiazole	12.5	50	1,036	471	0.45	9.4	(d) 32.6	94.0
	14.9	50	1,027	515	0.50	10.3	(d) 32.6	103.0
	20.1	50	1,025	568	0.55	11.4	(d) 32.6	114.0
	24.8	0	--	--	--	--	--	--
Mitomycin C	0.001	50	1,027	741	0.72	14.8	25.3	148.0
	0.010	5	104	205	1.97	41.0	25.3	410.0
+S9 (e)								
Trial No. 1--Summary: Positive								
Dimethyl sulfoxide		50	1,038	477	0.46	9.5	25.3	--
2-Mercaptobenzothiazole	99.2	50	1,028	531	0.52	10.6	25.3	111.6
	247.5	50	1,026	536	0.52	10.7	25.3	112.6
	501.5	50	1,045	640	0.61	12.8	(d) 32.6	134.7
	750	0	--	--	--	--	--	--
Cyclophosphamide	0.4	50	1,020	634	0.62	12.7	25.3	133.7
	2.0	5	104	142	1.37	28.4	25.3	298.9
Trial No. 2--Summary: Positive								
Dimethyl sulfoxide		50	1,025	454	0.44	9.1	25.6	--
2-Mercaptobenzothiazole	351.6	50	1,032	558	0.54	11.2	(d) 36.6	123.1
	401.6	50	1,035	624	0.60	12.5	(d) 36.6	137.4
	445.3	50	1,041	588	0.56	11.8	(d) 36.6	129.7
	502.3	0	--	--	--	--	--	--
Cyclophosphamide	0.4	50	1,035	702	0.68	14.0	25.6	153.8
	2.0	5	108	183	1.69	36.6	25.6	402.2

(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. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as described in (c) or (d) below and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air-dried, and stained.
(b) SCEs/cell in treated culture expressed as a percent of the SCEs/cell in the control culture
(c) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then BrdU was added, and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and colcemid was added, and incubation was continued for 2-3 hours.
(d) Because of significant chemically induced cell cycle delay, incubation time before addition of colcemid was lengthened to provide sufficient metaphases at harvest.
(e) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Then cells were washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with colcemid present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

TABLE E4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY 2-MERCAPTOBENZOTHIAZOLE (a)

−S9 (b)					+S9 (c)				
Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Trial 1--Harvest time 20.5 h (d)					**Trial 1**--Harvest time 20.5 h (d)				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	0	0.00	0		100	1	0.01	1
2-Mercaptobenzothiazole					2-Mercaptobenzothiazole				
10	100	1	0.01	1	351.8	100	18	0.18	9
14.9	100	1	0.01	1	400.8	100	14	0.14	9
19.9	100	2	0.02	2	451.0	50	24	0.48	16
30.1	0				500.5	0			
Summary: Negative					Summary: Positive				
Mitomycin C					Cyclophosphamide				
0.025	100	12	0.12	10	2.5	100	4	0.04	4
0.062	25	14	0.56	10	12.5	25	12	0.48	36
					Trial 2--Harvest time 20.5 h (d)				
					Dimethyl sulfoxide				
						50	1	0.02	2
					2-Mercaptobenzothiazole				
					373.5	25	12	0.48	24
					399	25	17	0.68	28
					425	25	21	0.84	28
					450	0			
					Summary: Positive				
					Cyclophosphamide				
					3.8	50	3	0.06	6
					12.5	25	9	0.36	20

(a) Study performed at Litton Bionetics, Inc. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as indicated in (b) or (c). Cells were arrested in first metaphase by addition of colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.
(b) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid was added for an additional 2-3 hours followed by harvest.
(c) In the presence of S9, cells were incubated with study compound or solvent (dimethyl sulfoxide) for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8-10 hours. Colcemid was added for the last 2-3 hours of incubation before harvest. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.
(d) Because of significant chemically induced cell cycle delay, incubation time before addition of colcemid was lengthened to provide sufficient metaphases at harvest.

APPENDIX F

SENTINEL ANIMAL PROGRAM

APPENDIX F. SENTINEL ANIMAL PROGRAM

I. Methods

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

Fifteen B6C3F$_1$ mice and 15 F344/N rats of each sex are selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group are killed at 6, 12, and 18 months on study. Data from animals surviving 24 months are collected from 5/50 randomly selected control animals of each sex and species. The blood from each animal is collected and clotted, and the serum is separated. The serum is cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the antibody titers. The following tests are performed:

	Hemagglutination Inhibition	Complement Fixation	ELISA
Mice	PVM (pneumonia virus of mice) Reo 3 (reovirus type 3) GDVII (Theiler's encephalomyelitis virus) Poly (polyoma virus) MVM (minute virus of mice) Ectro (infectious ectromelia) Sendai	M. Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus)	MHV (mouse hepatitis virus) *M. pul.* (*Mycoplasma pulmonis*) (24 mo)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai	RCV (rat coronavirus)	*M. pul.* (24 mo)

II. Results

Results are presented in Table F1.

TABLE F1. MURINE ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF 2-MERCAPTOBENZOTHIAZOLE (a)

Interval (months)	No. of Animals	Positive Serologic Reaction for
RATS		
6	8/10	Sendai
12	10/10	Sendai
18	1/10	Sendai
24	10/10	(b) *M. pul.*
	4/10	Sendai
MICE		
6	9/10	Sendai
12	10/10	Sendai
18	5/10	Sendai
24	6/10	Sendai

(a) Blood samples were taken from sentinel animals at 6, 12, and 18 months after the start of dosing and from the vehicle control animals just before they were killed; samples were sent to Microbiological Associates (Bethesda, MD) for determination of antibody titers.
(b) Further evaluation of this assay indicated that it is not specific for *M. pulmonis*, and these results are considered false positive.

APPENDIX G

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

Pelleted Diet: July 1981 to July 1983

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

TABLE G1. INGREDIENTS OF NIH 07 RAT AND MOUSE RATION (a)

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

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

TABLE G2. 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 activity
d-α-Tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	*d*-Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B_{12}	4,000 µg	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	*d*-Biotin
Minerals		
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 G3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	23.6 ± 0.87	22.2-25.3	25
Crude fat (percent by weight)	4.92 ± 0.54	3.3-5.7	25
Crude fiber (percent by weight)	3.30 ± 0.26	2.9-3.8	25
Ash (percent by weight)	6.43 ± 0.39	5.7-7.2	25
Amino Acids (percent of total diet)			
Arginine	1.323 ± 0.830	1.21-1.39	4
Cystine	0.310 ± 0.099	0.218-0.400	4
Glycine	1.155 ± 0.069	1.06-1.21	4
Histidine	0.572 ± 0.030	0.530-0.603	4
Isoleucine	0.910 ± 0.033	0.881-0.944	4
Leucine	1.949 ± 0.065	1.85-1.99	4
Lysine	1.275 ± 0.076	1.20-1.37	4
Methionine	0.422 ± 0.187	0.306-0.699	4
Phenylalanine	0.909 ± 0.167	0.665-1.04	4
Threonine	0.844 ± 0.029	0.824-0.886	4
Tryptophan	0.187	0.171-0.211	3
Tyrosine	0.631 ± 0.094	0.566-0.769	4
Valine	1.11 ± 0.050	1.05-1.17	4
Essential Fatty Acids (percent of total diet)			
Linoleic	2.44	2.37-2.52	3
Linolenic	0.274	0.256-0.308	3
Arachidonic	0.008	--	1
Vitamins			
Vitamin A (IU/kg)	12,088 ± 4,119	7,500-24,000	25
Vitamin D (IU/kg)	4,650	3,000-6,300	2
α-Tocopherol (ppm)	41.53 ± 7.52	31.1-48.9	4
Thiamine (ppm) (a)	16.2 ± 2.30	12.0-21.0	24
Riboflavin (ppm)	7.5 ± 0.96	6.1-8.2	4
Niacin (ppm)	85.0 ± 14.2	65.0-97.0	4
Pantothenic acid (ppm)	29.3 ± 4.6	23.0-34.0	4
Pyridoxine (ppm)	7.6 ± 1.5	5.6-8.8	4
Folic acid (ppm)	2.8 ± 0.88	1.8-3.7	4
Biotin (ppm)	0.27 ± 0.05	0.21-0.32	4
Vitamin B_{12} (ppb)	21.0 ± 11.9	11.0-38.0	4
Choline (ppm)	3,302.0 ± 120.0	3,200.0-3,430.0	4
Minerals			
Calcium (percent)	1.23 ± 0.10	1.08-1.44	25
Phosphorus (percent)	0.98 ± 0.05	0.88-1.11	25
Potassium (percent)	0.862 ± 0.100	0.772-0.974	3
Chloride (percent)	0.546 ± 0.100	0.442-0.635	4
Sodium (percent)	0.311 ± 0.038	0.258-0.350	4
Magnesium (percent)	0.169 ± 0.133	0.151-0.181	4
Sulfur (percent)	0.316 ± 0.070	0.270-0.420	4
Iron (ppm)	447.0 ± 57.3	409.0-523.0	4
Manganese (ppm)	90.6 ± 8.20	81.7-95.5	4
Zinc (ppm)	53.6 ± 5.27	46.1-58.6	4
Copper (ppm)	10.77 ± 3.19	8.09-15.39	4
Iodine (ppm)	2.95 ± 1.05	1.52-3.82	4
Chromium (ppm)	1.81 ± 0.28	1.44-2.09	4
Cobalt (ppm)	0.68 ± 0.14	0.49-0.80	4

(a) One batch (7/22/81) not analyzed for thiamine.

TABLE G4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.50 ± 0.13	0.29-0.77	25
Cadmium (ppm)	<0.10	<0.10-0.10	25
Lead (ppm) (a)	0.74 ± 0.42	0.33-1.97	23
Lead (ppm) (b)	0.92 ± 0.75	0.33-3.37	25
Mercury (ppm) (c)	<0.05		25
Selenium (ppm)	0.29 ± 0.07	0.14-0.40	25
Aflatoxins (ppb)	<10	<5.0-<10.0	25
Nitrate nitrogen (ppm) (d)	9.22 ± 4.39	1.9-17.0	25
Nitrite nitrogen (ppm) (d)	2.19 ± 1.55	<0.6-6.9	25
BHA (ppm) (e)	5.86 ± 4.87	2.0-17.0	25
BHT (ppm) (e)	3.0 ± 2.7	<1.0-12.0	25
Aerobic plate count (CFU/g) (f)	43,936 ± 31,267	4,900-110,000	25
Coliform (MPN/g) (g)	14.96 ± 22.36	<3-93	24
Coliform (MPN/g) (h)	32.76 ± 91.66	<3-460	25
E. coli (MPN/g) (i)	<3		25
Total nitrosamines (ppb)	3.42 ± 2.72	0.8-9.3	25
N-Nitrosodimethylamine (ppb)	2.68 ± 2.37	0.8-8.3	25
N-Nitrosopyrrolidine (ppb)	1.14 ± 0.48	<0.5-2.9	25
Pesticides (ppm)			
α-BHC (c, j)	<0.01		25
β-BHC (c)	<0.02		25
γ-BHC-Lindane (c)	<0.01		25
δ-BHC (c)	<0.01		25
Heptachlor (c)	<0.01		25
Aldrin (c)	<0.01		25
Heptachlor epoxide (c)	<0.01		25
DDE (c)	<0.01		25
DDD (c)	<0.01		25
DDT (c)	<0.01		25
HCB (c)	<0.01		25
Mirex (c)	<0.01		25
Methoxychlor (k)	<0.05	0.09 (8/26/81); 0.06 (7/26/83)	25
Dieldrin (c)	<0.01		25
Endrin (c)	<0.01		25
Telodrin (c)	<0.01		25
Chlordane (c)	<0.05		25
Toxaphene (c)	<0.1		25
Estimated PCBs (c)	<0.2		25
Ronnel (c)	<0.01		25
Ethion (c)	<0.02		25
Trithion (c)	<0.05		25
Diazinon (c)	<0.1		25
Methyl parathion (c)	<0.02		25
Ethyl parathion (c)	<0.02		25
Malathion (l)	0.09 ± 0.06	<0.05-0.27	25
Endosulfan I (m)	<0.01		20
Endosulfan II (m)	<0.01		20
Endosulfan sulfate (m)	<0.03		20

TABLE G4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION (Continued)

(a) Mean, standard deviation, and range exclude two high values of 2.65 ppm and 3.37 ppm obtained for batches produced on 8/26/81 and on 7/21/82.
(b)Mean, standard deviation, and range include the high values given in (a).
(c) All values were less than the detection limit. The detection limit is given as the mean.
(d) Sources of contamination: alfalfa, grains, and fish meal
(e) Sources of contamination: soy oil and fish meal
(f) CFU = colony forming unit
(g) MPN = most probable number; mean, standard deviation, and range exclude one high value of 460 MPN/g obtained for the batch produced on 9/23/82.
(h) Mean, standard deviation, and range include the high value listed in (g).
(i) All values were less than 3 MPN/g.
(j) BHC = hexachlorocyclohexane or benzene hexachloride
(k) Two observations were above the detection limit. The values and the dates they were obtained are given under the range.
(l) Eleven batches contained more than 0.05 ppm.
(m) Four batches (7/22/81-11/25/81) were not analyzed for endosulfan I, endosulfan II, or endosulfan sulfate.

APPENDIX H

AUDIT SUMMARY

APPENDIX H. AUDIT SUMMARY

The experimental data, pathology materials, and draft NTP Technical Report for the 2-year studies of 2-mercaptobenzothiazole in F344/N rats and B6C3F$_1$ mice were examined for accuracy, consistency, and completeness. The studies were conducted for the NTP by Physiological Research Laboratories (Minneapolis, Minnesota) under a subcontract with Tracor Jitco, Inc. (Rockville, Maryland), until February 28, 1983, and then under a contract with the National Institute of Environmental Health Sciences (NIEHS). Animal exposures for the 2-year studies began in July 1981, about 3 months prior to the date (October 1, 1981) when the NTP required studies to be conducted in full compliance with the FDA Good Laboratory Practice regulations for nonclinical laboratory studies. The retrospective audit was conducted for the NIEHS at the NTP Archives in September and October 1986 by Dynamac Corporation, J.C. Bhandari, D.V.M., Ph.D., Principal Investigator. Other individuals who conducted the audit are listed in the full report, which is on file at the NIEHS. The data audit included a review of:

(1) All records concerning animal receipt, quarantine, randomization, and disposition prior to study start.
(2) All chemistry records.
(3) Body weight and clinical observation data for a random 10% sample of the study animals.
(4) A random 50% percent sample of the dose records.
(5) All inlife records concerning environmental conditions, palpable masses, mortality, and animal identification.
(6) All postmortem records for individual animals concerning identification, disposition codes, condition codes, and correlation between necropsy observations and histopathologic findings.
(7) Wet tissues from a random 10% sample of the study animals to verify animal identification and to examine for untrimmed potential lesions.
(8) Slides and blocks of tissues from all vehicle control and high dose animals to examine for proper match and inventory.

The audit showed that inlife procedures were documented in the Materials and Methods Report submitted by the study laboratory and by archival records with the exception of periodic animal room procedures for cage and rack changes, equipment sanitization, light cycle, twice daily morbidity and moribundity checks, and animal dosing for the first several months. The analytical chemistry records from the study laboratory were complete and accurate, but raw data for the initial characterization of 2-mercaptobenzothiazole by Midwest Research Institute were not present at the Archives for the audit. Review of the pathology documents resulted in a change in disposition code for 10 mice from natural death or moribund kill to accidental death because of gavage trauma. Review of the pathology specimens revealed only miscellaneous findings that were not significant to the interpretation of the study results.

In summary, the findings of the data audit were adequately resolved or were considered not to affect the interpretation of these studies. Thus, the retrospective audit, coupled with audit of the draft Technical Report, shows that the records and specimens for the 2-year studies of 2-mercaptobenzothiazole support the data and results presented in this NTP Technical Report.

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NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS PUBLISHED AS OF APRIL 1988

TR No.	CHEMICAL
200	2,6-Toluenediamine Dihydrochloride
201	2,3,7,8-Tetrachlorodibenzo-p-dioxin (Dermal)
202	1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin and 1,2,3,7,8,9-Hexachlorodibenzo-p-dioxin (Dermal)
203	Phenol
204	Benzoin
205	4,4'-Oxydianiline
206	Dibromochloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane (Inhalation)
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butylbenzyl Phthalate
214	Caprolactam
215	Bisphenol A
216	11-Aminoundecanoic Acid
217	Di(2-ethylhexyl)phthalate
219	2,6-Dichloro-*p*-phenylenediamine
220	C.I. Acid Red 14
221	Locust Bean Gum
222	C.I. Disperse Yellow 3
223	Eugenol
224	Tara Gum
225	D & C Red No. 9
226	C.I. Solvent Yellow 14
227	Gum Arabic
228	Vinylidene Chloride
229	Guar Gum
230	Agar
231	Stannous Chloride
232	Pentachloroethane
233	2-Biphenylamine Hydrochloride
234	Allyl Isothiocyanate
235	Zearalenone
236	D-Mannitol
237	1,1,1,2-Tetrachloroethane
238	Ziram
239	Bis(2-chloro-1-methylethyl)ether
240	Propyl Gallate
242	Diallyl Phthalate (Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
247	L-Ascorbic Acid
248	4,4'-Methylenedianiline Dihydrochloride
249	Amosite Asbestos
250	Benzyl Acetate
251	Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
267	Propylene Oxide
269	Telone II®
271	HC Blue No. 1
272	Propylene
273	Trichloroethylene (Four strains of rats)
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
281	H.C. Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No. 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethy)phosphonium Sulfate and Tetrakis(hydroxymethy)phosphonium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	*o*-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane
307	Ephedrine Sulfate
308	Chlorinated Paraffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	*n*-Butyl Chloride
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
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
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol

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