NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 388

TOXICOLOGY AND CARCINOGENESIS STUDIES OF ETHYLENE THIOUREA

(CAS NO. 96-45-7)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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

FOREWORD

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

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

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

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

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NTP TECHNICAL REPORT

ON THE PERINATAL

TOXICOLOGY AND CARCINOGENESIS

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P.O. Box 12233
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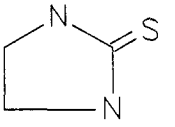
ABSTRACT



ETHYLENE THIOUREA

CAS No. 96-45-7

Chemical Formula: $C_3H_6N_2S$ Molecular Weight: 102.17

Chemical Names: 2-Imidazolidinethione; Imidazoline-2-thiol
Synonyms: 2-mercaptoimidazoline; *N,N'*-ethylenethiourea; 1,3-ethylenethiourea; 2-imadazoline-2-thiol

Ethylene thiourea is a white crystalline solid used extensively in the rubber industry as an accelerator in the vulcanization of elastomers. It is also a trace contaminant and metabolic degradation product of a widely used class of ethylene bisdithiocarbamate fungicides. Ethylene thiourea is known to produce thyroid neoplasms in rats and liver neoplasms in mice following long-term administration; thus, it was chosen by the National Toxicology Program in an investigation of the potential value of perinatal exposures in assessing chemical carcinogenicity.

Chronic toxicity and carcinogenicity studies of ethylene thiourea, 99% pure, were conducted in F344/N rats and B6C3F$_1$ mice of each sex. The studies were designed to determine 1) the effects of ethylene thiourea in rats and mice receiving adult exposure only (a typical carcinogenicity study), 2) the toxic and carcinogenic effects of ethylene thiourea on rats and mice receiving perinatal exposure only (dietary exposure of dams prior to breeding and throughout gestation and lactation), and 3) the effects of combined perinatal and adult exposure to ethylene thiourea.

Studies in F344/N Rats

In a preliminary study to determine the perinatal dietary concentrations for the 2-year studies, female F344/N rats were fed 0, 8, 25, 83, or 250 ppm ethylene thiourea in the feed beginning 2 weeks prior to breeding and continuing throughout gestation and lactation, and the pups were fed at these same concentrations up to 9 weeks postweaning. Based on decreased survival of rat pups between postnatal days 0 to 4 and reduction in body weight gains in male weanling rats receiving 250 ppm, dietary concentrations of 0, 9, 30, and 90 ppm were selected for the perinatal (F_0) exposure levels in the 2-year studies. Groups of 10 male and 10 female rats, 8 to 9 weeks of age, were fed diets containing 0, 60, 125, 250, 500, or 750 ppm ethylene thiourea for 13 weeks to determine the adult dietary concentrations. Because of reduced weight gains and decreased feed consumption in rats receiving 500 or 750 ppm ethylene thiourea, dietary concentrations of 0, 25, 83, and 250 ppm were selected for the adult (F_1) exposure during the 2-year studies.

In the 2-year studies, perinatal and adult exposures to ethylene thiourea were applied separately and together to groups of male or female rats as shown in the following table.

The principal toxic effects of ethylene thiourea involved the thyroid gland. Serum levels of thyroxine (T_4) and/or triiodothyronine (T_3) were significantly decreased in rats receiving adult concentrations of 83 or 250 ppm, and thyrotropin

(thyroid-stimulating hormone, TSH) was significantly increased at these concentrations. In male and female rats receiving adult-only exposure of 83 or 250 ppm, the incidences of follicular cell hyperplasia or follicular cell adenoma of the thyroid gland were significantly increased relative to the controls. The incidences of follicular cell carcinoma were significantly increased in the 250 ppm groups, and carcinomas occurred more frequently in males than in females.

Exposure Groups of Rats in the 2-Year Feed Studies of Ethylene Thiourea[a]

	F_1 Concentration[b] (ppm)			
F_0[c] (ppm)	0	25	83	250
0	60	–	60	60
9	–	60	–	–
30	–	–	60	–
90	60	–	60	60

[a] Ten rats from each group were sacrificed and evaluated at 9 months.
[b] Concentration of ethylene thiourea in feed given to rats beginning at 8 weeks of age for 24 months
[c] Concentration of ethylene thiourea in feed through breeding, gestation, and lactation until pups were 8 weeks of age

Perinatal-only exposure to 90 ppm had no effect on the incidence of thyroid neoplasms in these studies, although there was a marginal increase in follicular cell hyperplasia relative to the controls. However, for groups of rats receiving combined perinatal and adult exposure (F_0:F_1), males and females receiving concentrations of 90:250 ppm ethylene thiourea had significantly increased incidences of thyroid follicular cell neoplasms relative to those receiving adult-only exposure to 250 ppm. Further, groups of male rats receiving 90:83 ppm showed a significantly increased incidence of follicular cell hyperplasia. Final mean body weights of males and survival of males and females receiving combined perinatal (90 ppm) and adult (250 ppm) exposure were lower than those receiving adult-only exposure of 250 ppm.

Thus, in rats, combined perinatal and adult exposure slightly enhanced the toxicity and proliferative effects on the thyroid gland observed with adult-only exposure to ethylene thiourea.

Neoplasms of the Zymbal's gland were marginally increased in rats receiving 90:250 ppm (males - 0:0, 1/50; 90:250, 5/50; females - 0:0, 1/50; 90:250, 4/50). Mononuclear cell leukemia occurred with a significant trend in groups of male and female rats receiving perinatal exposure of 90 ppm and increasing adult concentrations (90:0, 90:83, and 90:250 ppm), and for female rats without perinatal exposure (0:0, 0:83, and 0:250 ppm). The incidences of mononuclear cell leukemia in males receiving 90:83 ppm and males and females receiving 90:250 ppm were statistically significant relative to the respective 0:0 ppm groups. Low incidences of renal tubule cell adenomas occurred in most dose groups of male rats, but not in the highest dose group or the controls.

Studies in B6C3F$_1$ Mice

In a preliminary study to determine the perinatal dietary concentrations for the 2-year studies, adult female C57BL/6N mice were fed 0, 33, 100, 330, or 1,000 ppm ethylene thiourea in the feed beginning 2 weeks prior to breeding and continuing throughout gestation and lactation and up to 9 weeks postweaning. Because of reduced survival of mouse pups at postnatal day 28 and lower final mean body weights in weanlings receiving perinatal exposure of 1,000 ppm, dietary concentrations of 0, 33, 110, and 330 ppm were selected for the perinatal exposure levels in the 2-year studies. Groups of 10 male and 10 female mice, 8 to 9 weeks of age, were fed diets containing 0, 125, 250, 500, 1,000, or 2,000 ppm ethylene thiourea for 13 weeks to determine the adult dietary concentrations. Moderately severe diffuse follicular cell hyperplasia in the thyroid gland and centrilobular cytomegaly of the liver occurred in mice receiving 2,000 ppm. Because the severity of the thyroid lesion (and degree of hypothyroidism) at this concentration was considered potentially life threatening in 2-year studies, dietary concentrations of 0, 100, 330, and 1,000 ppm ethylene thiourea were selected for adult exposure during the 2-year studies.

In the 2-year studies, perinatal and adult exposures to ethylene thiourea were applied separately and together to groups of male or female mice as shown in the following table.

Exposure Groups of Mice in the 2-Year Feed Studies of Ethylene Thiourea[a]

	F_1 Concentration[b] (ppm)			
F_0[c] (ppm)	0	100	330	1,000
0	60	–	60	60
33	–	34/29[d]	–	–
110	–	–	60	–
330	60	–	60	60

[a] Ten mice from each group except the 33:100 ppm group were sacrificed and evaluated at 9 months.
[b] Concentration of ethylene thiourea in feed given to mice beginning at 8 weeks of age for 24 months
[c] Concentration of ethylene thiourea in feed through breeding, gestation, and lactation until pups were 8 weeks of age
[d] 34 males and 29 females assigned to group

The principal toxic effects of ethylene thiourea in mice occurred in the thyroid gland, liver, and pituitary gland. Serum levels of T_3 were significantly decreased in groups of mice receiving adult concentrations of 1,000 ppm; TSH was significantly increased in mice receiving 330 and 1,000 ppm. The incidences of follicular cell hyperplasia and neoplasia increased principally in males receiving 1,000 ppm and in females receiving 330 or 1,000 ppm. Follicular cell carcinomas were significantly increased in mice receiving 1,000 ppm. Incidences of centrilobular hepatocellular cytomegaly (males and females), hepatocellular adenoma (females), hepatocellular carcinoma (males and females), and adenoma or carcinoma combined (males and females) also were significantly increased in mice receiving F_1 concentrations of 330 or 1,000 ppm. In the pituitary gland, incidences of focal hyperplasia (males) or adenoma (males and females) of the pars distalis were significantly increased in groups of mice receiving 1,000 ppm ethylene thiourea.

Perinatal exposure to concentrations of 330 ppm had no effect on the incidences of nonneoplastic lesions or neoplasms in mice. For groups of mice receiving combined perinatal and adult exposure, females receiving F_0:F_1 concentrations of 330:330 ppm had significantly increased incidences of follicular cell adenoma relative to those receiving adult-only exposure to 330 ppm. Similarly, male mice receiving F_0:F_1 concentrations of 330:330 ppm had significantly increased incidences of follicular cell hyperplasia. Thus, in mice, perinatal exposure slightly enhanced the proliferative effects on the thyroid gland of adult exposure. There were no effects of perinatal exposure in mice at sites other than in the thyroid gland.

Conclusions

2-Year Adult-Only Exposure: Under the conditions of these 2-year adult-only dietary exposures, there was *clear evidence of carcinogenic activity** of ethylene thiourea in male and female F344/N rats, as shown by increased incidences of thyroid follicular cell neoplasms. There was *clear evidence of carcinogenic activity* of ethylene thiourea in male and female $B6C3F_1$ mice as shown by increased incidences of thyroid follicular cell neoplasms, hepatocellular neoplasms, and adenomas of the pars distalis of the pituitary gland.

Nonneoplastic lesions associated with the administration of ethylene thiourea included follicular cell hyperplasia in rats and mice and follicular cell cytoplasmic vacuolation, centrilobular hepatocellular cytomegaly, and focal hyperplasia of the pars distalis of the pituitary gland in mice. Other effects associated with the administration of ethylene thiourea included decreased serum levels of T_4 and/or T_3 in rats and increased serum levels of TSH in rats and mice.

Perinatal-Only Exposure: Perinatal exposure alone had no effect on the incidences of neoplasms in rats or mice after 2 years. Animals may have been able to tolerate higher perinatal exposure concentrations.

Combined Perinatal and 2-Year Adult Exposures: Combined perinatal and 2-year adult dietary exposure to ethylene thiourea confirmed the findings of the 2-year adult-only exposures for the incidences of neoplasms in the thyroid gland of rats and mice and the liver and pituitary gland of mice. In male and female rats, combined perinatal and adult exposure to 90:250 ppm was associated with marginal increases, relative to the untreated (0:0 ppm) controls, in Zymbal's gland neoplasms and mononuclear cell leukemia, which may have been related to chemical administration. In rats receiving adult exposure to 250 ppm ethylene thiourea, perinatal exposure to 90 ppm was associated with a slightly enhanced incidence of thyroid neoplasms compared to adult-only exposure. However, increasing perinatal exposure from 0 to 90 ppm had no effect on incidences of thyroid neoplasms in rats receiving

adult exposure to 83 ppm. Increasing perinatal exposure from 0 to 330 ppm was associated with a marginally increased incidence of thyroid neoplasms in female mice receiving adult exposure to 330 ppm, but there were no enhancing effects of perinatal exposure in mice receiving adult exposure to 1,000 ppm.

[1] Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of peer review comments and the public discussion on this Technical Report appears on page 11.

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on ethylene thiourea on November 20, 1989, and on April 25, 1990, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities:

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

National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee

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SUMMARY OF PEER REVIEW COMMENTS

On November 20, 1989, the draft Technical Report on the perinatal toxicology and carcinogenesis studies of ethylene thiourea (ETU) received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Committee and associated Panel of Experts. The review meeting was held at the National Institute of Health Sciences, Research Triangle Park, North Carolina.

The study designs included conventional 2-year exposure of adult animals, perinatal exposure only, and perinatal plus adult exposure. The studies were intended to compare and evaluate the potential value of perinatal exposures in assessing chemical carcinogenicity. After much discussion, the consensus of the Subcommittee was that there was not an overwhelming effect of perinatal exposure to ETU on increased incidences of neoplasms. However, Dr. Gold suggested that the results should be reorganized and reported in terms of three questions addressed by the experimental design: (1) were there effects of perinatal exposure?, (2) were there carcinogenic effects in a typical 2-year bioassay?, and (3) did perinatal exposure enhance or potentiate carcinogenic effects seen in a subsequent 2-year bioassay? The Subcommittee recommended unanimously that the Technical Report be deferred for further consideration so that the questions raised could be addressed in a revision of the report.

The Technical Report was reevaluated on April 25, 1990. Dr. S.L. Eustis, NIEHS, began by addressing the three questions raised. The conclusions of the staff were that 1) perinatal exposure alone had no effect on incidence of neoplasms; 2) in rats and mice receiving adult-only exposure, there was *clear evidence of carcinogenic activity* for males and females; and 3) in groups of rats receiving the highest combined perinatal exposure of 90 ppm and adult exposure of 250 ppm, there was a slight enhancement of the toxicity and thyroid proliferative effects as compared to adult-only exposure at 250 ppm, while in mice, perinatal exposure at 330 ppm slightly enhanced the thyroid proliferative effects seen with adult-only exposure at 330 ppm.

Public comment was taken from representatives of member companies from the EBDC/ETU Task Force. Dr. Peter Chan, Rohm and Haas Company, presented information which he claimed supported conclusions that the NTP studies did not provide evidence for carcinogenicity of ETU in the Zymbal's gland, for mononuclear cell leukemias, or for renal tubule cell tumors in rats. He felt the NTP studies did not show a potentiation of tumorigenesis by perinatal exposure, and also, the weight of evidence indicated that ETU is not mutagenic or genotoxic. Dr. Ray Brown, Research Pathology Services, Inc., representing the Task Force, discussed the data and statistics used by the NTP. He noted that the life table test, which was the only test to yield statistical significance for Zymbal's gland tumors and mononuclear cell leukemia, was not the appropriate test, as these neoplasms are often not lethal. Further, he claimed that there was insufficient evidence to support increases in renal tubule cell tumors in male rats as being chemically related. Dr. Greg Sykes, E.I. du Pont de Nemours and Company, added that there was insufficient evidence to indicate that increases in the three types of neoplasms may have been chemical related. Dr. Harvey Scribner, Rohm and Haas Company, spoke of the socio-economic importance of the EBDC fungicides and stressed the need for the NTP conclusions to be as accurate as possible. He stated that the term "may have been chemical related" as applied to the three tumor types was unsupported by the data and should be removed from the report.

Dr. Gold, a principal reviewer, said the report was much improved. She stated that the conclusions on thyroid tumors related to the 2-year studies alone, while the association with Zymbal's gland neoplasms and mononuclear cell leukemia in rats related only to perinatal plus adult exposure. Dr. Gold said there needed to be more discussion of the possible enhancing effects of perinatal exposure to ETU on the incidence of thyroid neoplasms in high-dose adult rats and female mice. She suggested that information should be added about exposure of pups between four and eight weeks of age, as contrasted to the adult-only exposure with feeding of ETU beginning at 8 weeks.

Dr. Hayden, the second principal reviewer, agreed with the conclusions that the principal neoplastic effects of ETU were on the thyroid in adult rats and mice and supported the conclusions that there

were enhancing effects of perinatal exposure to ETU on the incidence of thyroid neoplasms in high-dose male and female rats. With regard to Zymbal's gland tumors, mononuclear cell leukemia, and kidney neoplasms, he felt there was insufficient evidence to discern an effect of the chemical.

Dr. Zeise agreed with the speakers for the EBDC/ETU Task Force that it was important to make accurate interpretations of the other tumors. She thought the Abstract should include a description of the observations of leukemia and Zymbal's gland neoplasms of both sexes, and renal tubule cell neoplasms in male rats. She asked whether resectioning could be done with the Zymbal's gland and renal tumors, noting a precedent for this with renal tumors in other NTP studies where there were marginal increases in incidence observed. Dr. Eustis responded that there was usually not enough tissue from Zymbal's glands to resection, and that past experience indicated the likelihood of finding additional tumors was very small. With regard to the kidney, the sectioning technique used in this study left only the margins of the kidneys, which would not be very good samples for step sectioning. Dr. Zeise commented that the enhancing effect of perinatal exposure should not be referred to as "only slight" because the incidence of thyroid tumors in female rats doubled, increased by 70% in male rats, and more than doubled in adult female mice.

Dr. Zeise commented that the lack of effect on tumor incidence for perinatal-only exposure may indicate that a maximum tolerated dose was not achieved. Dr. R.S. Chhabra, NIEHS, pointed out the high mortality at the highest dose (250 ppm) in the study used to determine the maximum perinatal dose.

Dr. Gold moved that the conclusions be accepted as written with respect to the 2-year studies, *clear evidence of carcinogenic activity* in male and female rats based on thyroid follicular cell neoplasms, and *clear evidence of carcinogenic activity* in male and female mice based on thyroid follicular cell neoplasms, hepatocellular neoplasms, and adenomas of the pituitary gland. Dr. Hayden seconded the motion, which was accepted with nine yes votes and one abstention (Dr. Ashby). Dr. Ashby's abstention on this and subsequent motions was for reasons of company affiliation.

Dr. Gold moved that the first and second paragraphs of the conclusions refer only to the 2-year studies in adult animals, and that the statement, "marginal increases in Zymbal's gland neoplasms and mononuclear cell leukemia in males and females and renal tubule cell neoplasms in males may have been chemically related," should be deleted. She claimed that the sentence to be deleted related to tumor increases based on combined perinatal and adult exposure. Dr. Longnecker seconded the motion. There ensued a lengthy discussion as to whether the incidences of any of these tumors may have been associated with 2-year exposure of adults only. Dr. J.K. Haseman, NIEHS, commented that in his judgment a *no evidence* call was not indicated for renal tumors because the incidence in the low-dose group was above the historical range and the incidence in the high-dose group was at the historical limit; further, the high-dose group had seven renal tubule hyperplasias. After additional discussion, Dr. Gold's motion was accepted by six yes votes (Drs. Davis, Gold, Garman, Goodman, Hayden, and Longnecker) to three no votes (Drs. Carlson, McKnight, and Zeise) with one abstention (Dr. Ashby).

The Subcommittee and NTP staff discussed whether there should be separate conclusionary statements for results of perinatal exposure alone and results of combined perinatal and adult exposure, or whether these results should be published in separate reports. Dr. Hayden moved that the perinatal exposure studies and combined exposure studies as experimental protocols be published as a separate technical report. Dr. Davis seconded the motion. After discussion, Dr. Hayden withdrew the motion. Dr. R.A. Griesemer, NIEHS, noted that the ETU study was the first of three to use the experimental protocols for perinatal and perinatal plus adult exposure, and that the other two would be brought to the Subcommittee later.

Dr. Longnecker moved that the following statement be included in the conclusions: "Perinatal exposure alone had no effect on the incidences of neoplasms after 2 years." Dr. Gold seconded the motion. Dr. Eustis cautioned against taking the perinatal exposure alone as a carcinogenicity study. Dr. Zeise offered an amendment that the lack of neoplastic effect may have been due to the low doses used. She noted that in the gestational study conducted to determine the dietary concentrations for perinatal exposure, there were thyroid follicular cell adenomas

in 4 of 10 male rats at the highest dose (250 ppm). Yet, 90 ppm was chosen as the highest dose for perinatal exposure in the 2-year studies. Drs. Longnecker and Gold agreed to accept the amendment. The amended motion was accepted by nine yes votes with one abstention (Dr. Ashby).

Dr. Longnecker moved that the statement: "in male and female rats, combined perinatal and adult exposure, compared with untreated control animals, was associated with a marginal increase in Zymbal's gland neoplasms and mononuclear cell leukemia that may have been chemically related" be included in the conclusions. Dr. Zeise seconded the motion. Dr. Gold added for clarification that in the combined exposure groups, exposure in the diet to young animals began at four weeks of age. The motion was accepted by seven yes votes (Drs. Carlson, Davis, Hayden, Longnecker, McKnight, Silbergeld, and Zeise) to three no votes (Drs. Garman, Gold, and Goodman) with one abstention (Dr. Ashby).

Dr. Gold moved that the following be added to the conclusions: "in rats, compared with adult-only exposure at 250 ppm, perinatal exposure at 90 ppm marginally increased the incidence of thyroid neoplasms in adults exposed to 250 ppm; however, increasing perinatal exposure from 0 to 30 to 90 ppm had no effect on the incidence of such neoplasms in adult animals exposed to 83 ppm." Dr. Garman seconded the motion, which was accepted by six yes votes (Drs. Davis, Garman, Gold, Hayden, McKnight, and Zeise) to three no votes (Drs. Carlson, Goodman, and Silbergeld) with two abstentions (Drs. Ashby and Longnecker).

Dr. Gold moved that the statement: "in female mice, increasing perinatal exposure from 0 to 330 ppm marginally increased the incidence of thyroid neoplasms in adult animals exposed to 330 ppm, but there were no enhancing effects of perinatal exposure on adult animals exposed to 1,000 ppm" be included in the conclusions. Dr. Davis seconded the motion, which was accepted by nine yes votes with two abstentions (Drs. Ashby and Silbergeld).

INTRODUCTION

A series of mishaps with certain therapeutic agents and environmental toxicants has focused attention on the responses of developing organisms to diverse types of biologically active molecules. The occurrence of congenital defects in children resulting from the use of thalidomide by pregnant women, cancer in the daughters of women exposed to diethylstilbestrol during pregnancy, and episodes of congenital methylmercury poisoning have stimulated research in perinatal toxicology (Herbst *et al.*, 1971, 1975; Amin-Zaki *et al.*, 1974). During the perinatal period from conception to birth or weaning, some physiologic barriers such as the blood-brain barrier and certain aspects of the excretory, metabolizing, and gastrointestinal systems are not fully developed. Therefore, developing organisms can be more susceptible to the toxic effects of environmental or therapeutic agents (Lewerenz, 1982; Miller, 1983).

Recognition of the heightened sensitivity of developing organisms to chemical toxicity has led to a number of human and laboratory animal studies. Examples of epidemiological studies include evaluations of the relationships between brain tumors in children and the occupational exposure of parents to carcinogens (Peters *et al.*, 1981), childhood cancer and parental cigarette smoking (Grufferman *et al.*, 1983; Stjernfeldt *et al.*, 1986; Pershagen, 1989), and childhood leukemia and occupational and home exposure of parents to carcinogens (Lowengart *et al.*, 1987). Arundel and Kinnier-Wilson (1986) have reviewed 14 epidemiology studies that investigate a possible association between childhood cancer and parental occupational exposure to carcinogens. The contradictory observations suggest that more investigations are needed in this field.

Although human data are limited, information on perinatal toxicology and carcinogenesis in laboratory animals began accumulating when Larsen *et al.* (1947) reported a high incidence of lung tumors in offspring when pregnant strain A mice were administered urethane 1 day before delivery. This finding of an increased susceptibility of the fetal lung to urethane carcinogenesis was confirmed by Klein (1952). Pietra *et al.* (1959) reported that 12-hour-old mice given a single injection of 9,10-dimethyl-1,2-benzanthracene (DMBA) had a 32% incidence of lymphomas at 15.3 weeks of age, a relatively short period for expression of a tumorigenic effect. Similar decreases in the latency period for expression of tumorigenic effects were obtained with benzo(a)pyrene, 3-methylcholanthrene, and urethane (Pietra *et al.*, 1961). Druckery *et al.* (1966) reported that the teratogen ethylenenitrosourea (ENU), administered by a single injection to pregnant rats, produced brain tumors in offspring at an average age of 160 days, compared to an average age of 360 days for animals exposed to ENU as young adults. The increased sensitivity of fetal nervous tissue to ENU was further studied in Fischer and Sprague-Dawley rats by Swenberg *et al.* (1972), who evaluated the dose-relationship of transplacental brain tumor development and concluded that the age at which an animal develops neoplasia following exposure is a function of the dose levels used. Spontaneous tumors of the brain and nerves are rare in mice. However, perinatal exposure of several mouse strains to ENU caused a 6% incidence of neurogenic tumors, whereas postnatal ENU exposure resulted in an incidence of only 0.33% (Wechsler *et al.*, 1979). Furthermore, certain types of tumors, such as medulloblastomas, astrocytomas, and meningeal tumors, were observed only in mice exposed to ENU perinatally.

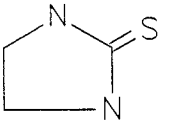
The carcinogenic response of various tissues following transplacental, neonatal-infant, or adult exposure of mice to a single administration of ENU was studied by Vesselinovitch *et al.* (1979). These studies showed that the age of the animals at the time of exposure to a carcinogen is the most effective modulator of carcinogenesis in the liver, lung, stomach, ovary, and lymphoreticular tissues. Tomatis (1979) reported that exposure of mice to DMBA and of rats to ENU or methylnitrosourea during pregnancy resulted in a high incidence of tumors in animals of the first generation and in an increased incidence of tumors at specific sites in untreated animals of the second and third generations. Germ cell mutation caused by perinatal exposure to a carcinogen was reported by Nomura (1982). The exposure of parent ICR mice to X-rays or urethane resulted in a 90% incidence of lung

tumors in the offspring; the inheritability of carcinogenic effects in the F_1 and F_2 generations was shown. Yamasaki *et al.* (1987) reported that fetal c-Ha-*ras* can be transplacentally activated through a specific point mutation by a carcinogen. Also, when administered to pregnant ICR mice on day 18 of gestation, safrole, 4-aminobiphenyl, and benzo(a)pyrene bind to the DNA of the maternal uterus and placenta and the maternal and fetal liver, lung, kidney, heart, brain, intestine, and skin (Lu *et al.*, 1986).

Toxicology endpoints other than carcinogenicity have also been studied in laboratory animals after perinatal exposure. The toxicity of chemicals to the nervous (Adams and Buelke-Sam, 1981), reproductive (McLachlan *et al.*, 1981), and immune systems (Roberts and Chapman, 1981) are subjects of continuing scientific interest. The field of perinatal toxicology and carcinogenesis has been extensively reviewed (IARC, 1973; NCI, 1979; Alexandrov, 1983; Miller, 1983; Tomatis, 1988). A recent review of environmental, occupational, and therapeutic exposure data by Schardein and Keller (1989) has identified 54 chemicals as potential developmental toxicants in humans.

STUDY RATIONALE

The evaluation of chemicals for carcinogenicity in rodents is usually accomplished by exposing animals to a chemical for 2 years, beginning when the animals are approximately 6 to 8 weeks of age (Chhabra *et al.*, 1990). In 1976, a symposium was organized by the National Cancer Institute on perinatal carcinogenesis (NCI, 1979); this group recommended that the perinatal period be incorporated into the period of exposure for conventional carcinogenicity studies (Swenberg, 1979; Vesselinovitch *et al.*, 1979). Therefore, the National Institute of Environmental Health Sciences designed the present studies to incorporate the perinatal period, including exposure of maternal animals prior to breeding, through gestation, lactation, and weaning, followed by conventional exposure of the offspring for 2 years, to compare the sensitivity of the combined perinatal and adult exposure bioassay with the conventional bioassay for detecting carcinogenicity. Three chemicals, ethylene thiourea, diphenylhydantoin (phenytoin), and polybrominated biphenyls (Firemaster FF-1), were selected for these combined perinatal and adult exposure studies. These chemicals can cross the placenta and be secreted in the milk so that developing fetuses and neonates are exposed during the gestation and lactation periods. This report describes the results of the carcinogenicity studies of ethylene thiourea.



ETHYLENE THIOUREA

CAS No. 96-45-7

Chemical Formula: $C_3H_6N_2S$ Molecular Weight: 102.17

Chemical Names: 2-Imidazolidinethione; Imidazoline-2-thiol

Synonyms: 2-mercaptoimidazoline; *N,N'*-ethylenethiourea; 1,3-ethylenethiourea; 2-imadazoline-2-thiol

PHYSICAL AND CHEMICAL PROPERTIES

Ethylene thiourea (ETU) is prepared by the reaction of ethylenediamine with carbon disulfide in aqueous alcohol. It is a white, needle-like crystalline powder which melts at 203° to 204° C. Commercial ETU is available as a powder, as a dispersion in oil, and "encapsulated" in a matrix of compatible elastomers. ETU is moderately soluble in methanol, ethanol, ethylene glycol, and pyridine, but is insoluble in acetone, ether, chloroform, benzene, and ligroin (*Merck Index*, 1983; Sittig, 1985).

USE, PRODUCTION, AND EXPOSURE

ETU has been widely used as an accelerator in neoprene rubber production and as part of a curing system for polyacrylate rubber. It is a major degradation product of the metal salts of ethylenebisdithiocarbamic acid, which are widely used as agricultural fungicides. ETU has been found in 28 different ethylenebisdithiocarbamate commercial products (IARC, 1974). It is also used as an intermediate for antioxidants and in the manufacture of synthetic resins. U.S. production for 1980 was probably greater than 1 million pounds; no current data on production are available. Ethylenebisdithiocarbamate (EBDC) fungicide production has been estimated to be 500,000 tons (Moller *et al.*, 1986).

The introduction of ETU into the environment occurs primarily through its formation as a degradation product of widely used EBDC fungicides. It is also present as a small-volume impurity in these fungicides. Exposure of the general population to ETU is by contaminated food. Occupational exposure by the dermal route is related to the use of EBDCs containing small amounts of ETU. Workers in the rubber industry also have potential occupational exposure to ETU. From a survey conducted from 1981 to 1983, NIOSH has estimated that 10,749 workers, including 1,800 women, have been exposed to ETU (NIOSH, 1990). However, this survey did not include agricultural workers, a number of whom may also be exposed.

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

ETU is rapidly absorbed by the oral route of exposure in laboratory animals and distributed throughout the body. The compound accumulates in the thyroid gland independent of the route of exposure. Mice respond to ETU with increased hepatic cytochrome P_{450} and aniline hydroxylase activities, while these enzymes are markedly reduced in the rat following ETU exposure (Lewerenz and Plass, 1984). The mouse, but not the rat, metabolizes ETU via the flavin-dependent mono-oxygenase (FMO) system (Hui *et al.*, 1988). The rapid metabolism of ETU by the mouse may contribute to the lack of teratogenicity in this species as compared to the rat, but the FMO-mediated binding of ETU metabolites to mouse liver proteins may contribute to the chronic hepatotoxicity of this compound in this species (Hui *et al.*, 1988).

The major route of elimination in Rhesus monkeys is by urine (Allen *et al.*, 1978). The major metabolites identified in the urine of male rats given 4 mg/kg ^{14}C-labeled ETU were imidazoline, ethylene urea, and 4-imidazoline2-one (Iverson *et al.*, 1980). Ruddick *et al.* (1977) studied distribution, metabolism, and excretion of ETU in the pregnant mouse and rat by oral gavage of a single dose (240 mg/kg) of ^{14}C-labeled ETU. Maternal and fetal tissue levels of ETU were similar 3 hours after treatment; thereafter, the mouse (maternal and fetal) had lower ETU levels than the rat. The half-life for ETU elimination from the maternal blood was 9.4 and 5.5 hours for the rat and mouse, respectively. The rate of metabolism was greater in mice than in rats and involved different pathways.

GENERAL TOXICITY

The acute oral LD_{50} values for rats, mice, and hamsters are 1,832, 3,000, and greater than 3,000 mg/kg body weight, respectively (Graham and Hansen, 1972; Teramoto *et al.*, 1978). Toxicological studies of ETU have generally shown that its primary effect is on the thyroid gland. The feeding of ETU to rats causes significant increases in thyroid weights (Gak *et al.*, 1976). In Charles River rats fed diets containing 125, 250, or 500 ppm ETU for 2, 6, or 12 months, uptake of iodine-131 was significantly decreased in male rats after 12 months of exposure to 500 ppm but was increased in females. Microscopic examination of the thyroids revealed the development of nodular hyperplasia at dose levels of 125 ppm and higher; a mild degree of thyroid hyperplasia and an excess of vascularity was observed in rats fed 5 or 25 ppm (Graham *et al.*, 1973).

In a study reported by Freudenthal *et al.* (1977), ETU was administered to young adult male and female Sprague-Dawley rats at concentrations of 0, 125, 250, and 625 ppm for up to 12 weeks. Thereafter, the rats were maintained on the control diet for an additional 12 weeks. The toxicity of ETU in rats was demonstrated by reduction in serum triiodothyronine (T_3) and thyroxine (T_4) levels and concomitant increases in serum thyroid-stimulating hormone (TSH). These changes correlated closely with elevations in thyroid weights and histopathologic alteration observed in the thyroid (hyperplasia)

and pituitary (hypertrophy in the pars distalis) glands after the first 2 weeks of the studies. Rats administered the highest dose of ETU (625 ppm) were placed on the control diet after the fourth week of the studies due to systemic toxicity; alterations in their hormone function parameters quickly returned to normal. Prolonged feeding of ETU for 12 weeks did not, however, alter the degree of thyroid hyperplasia and pituitary cell swelling beyond that observed after the second week of the studies in rats receiving 125 or 250 ppm. Two weeks after withdrawal of ETU (125 and 250 ppm), the pituitary and thyroid morphologies were similar to those of the control group. Thus these findings demonstrated a plateau and reversibility of the effects by the feeding and withdrawal of ETU in the diet.

ETU is a structurally related analogue of antithyroid drugs that act by inhibiting the synthesis of T_4. As T_4 secretion diminishes, the store of organic iodide decreases because of a lack of resynthesis. The possibility that ETU may also inhibit synthesis of TSH by blocking the coupling of iodotyrosines to form iodothyronines has been suggested by Taurog and Howells (1966). In response to decreased T_3 and T_4 levels, the pituitary gland increases the level of TSH, resulting in hyperplastic, highly vascularized thyroid glands. If hyperstimulation of the thyroid gland by TSH is severe and prolonged, it provides conditions conducive to the formation of tumors (O'Neil and Marshall, 1984). Astwood *et al.* (1943) have reported that thyroid iodine concentrations are decreased by ETU exposure in rats. However, Graham *et al.* (1973) found that the effects of ETU on radioactive iodine uptake were complex, with an increase in radioactive iodine uptake reported in both male and female rats receiving radioactive iodine intraperitoneally after being fed 5, 25, or 125 ppm ETU in diet over a 2-month period. The increases were significantly higher for male rats. For longer exposure periods, the changes in uptake of iodine fluctuated, particularly in female rats.

While the thyroid gland is a major target organ of toxicity, effects have also been observed in the liver. Liver triglycerides in rats were increased fourfold after a single ETU exposure of 92 mg/100 g by gavage, and liver cytochrome P_{450} was significantly reduced after a long-term exposure (Ugazio *et al.*, 1985). Moller *et al.* (1986) have reported liver morphology changes in Sprague-Dawley rats exposed to 500 ppm ETU in drinking water for 4 months. There have been no reports of acute toxicity from exposure to ETU in humans. Reports of contact dermatitis, skin sensitization, and a case of severe laryngeal edema have been noted in workers exposed to EBDCs (Rose *et al.*, 1980).

Developmental Toxicity and Teratogenicity

ETU was evaluated for developmental toxicity in a short-term *in vivo* animal bioassay (Hardin *et al.*, 1987). Pregnant CD-1 mice, 50 per group, were exposed to ETU dose levels ranging from 100 to 600 mg/kg per day in water by gavage on days 6 through 13 of gestation and were allowed to deliver. Pup birth weight and litter size were reduced at the 300 mg/kg dose level, while at 600 mg/kg the number of viable litters was reduced. ETU is highly teratogenic in rats (Chernoff *et al.*, 1979; Khera, 1973, 1987). A wide variety of central nervous system and skeletal defects have been observed in litters of animals receiving daily doses of ETU as low as 10 mg/kg during organogenesis. Khera (1973) reported the induction of meningoencephalocele, hydrocephalus, agenesis of the cerebellum, obliterated neural canal, abnormal limb posture with equinovarus, and short or kinky tail. Skeletal abnormalities associated with ETU administration observed in the rat include micrognathia, micromelia, oligodactyly, and kyphosis (Chernoff *et al.*, 1979). Teramoto *et al.* (1975) proposed that ETU-induced CNS abnormalities result from extensive cell necrosis of the neural tube at an early stage of fetal development and are not caused by the direct action of ETU on the affected organs. Khera (1987) has reviewed teratogenicity and reproductive risk posed by ETU. Teratogenic effects of ETU administration have not been demonstrated in the mouse, guinea pig, rabbit, hamster, or cat (Ruddick *et al.*, 1976; Khera and Iverson, 1978; Chernoff *et al.*, 1979; Iverson *et al.*, 1980). ETU has been shown to cross the placenta; however, its lack of teratogenicity in species other than the rat may be due to its rate of elimination or differences in metabolism. Using ^{14}C-labeled ETU, Iverson *et al.* (1980) demonstrated that the total elimination of radioactivity and the half-life of ETU in the cat and rat are similar. They suggested that the difference in teratogenic effects between species was not due to a difference in the rate of excretion, but to the extensive metabolism of ETU to its 5-methyl derivative in the cat. The more rapid ETU elimination and different metabolic pathway in the mouse compared to the rat may explain the lack of teratogenic effects of ETU in the mouse (Ruddick *et al.*, 1977;

Hui *et al.*, 1988). However, Teramoto *et al.* (1980) demonstrated that ETU was teratogenic when given in combination with sodium nitrite in mice. When sodium nitrite was given to females immediately after treatment with ETU on gestation day 6 or 8, fetal survival was decreased and various types of malformation were observed in the fetuses.

Genetic Toxicology

ETU has been tested extensively for genotoxicity in a variety of *in vitro* and *in vivo* systems, and the results, with few exceptions, are negative. Results of bacterial gene mutation studies with several strains of *Escherichia coli* and *Salmonella typhimurium* were negative (Baker and Bonin, 1981; Brooks and Dean, 1981; Gatehouse, 1981; MacDonald, 1981; Matsushima *et al.*, 1981; Richold and Jones, 1981; Rowland and Severn, 1981; Trueman, 1981; Moriya *et al.*, 1983; Falck *et al.*, 1985), except for isolated positive responses reported with *S. typhimurium* strain TA1535 (Teramoto *et al.*, 1977; Shirasu *et al.*, 1982; Moriya *et al.*, 1983; Mortelmans *et al.*, 1986). Results from studies of genetic effects in yeast showed some potential for induction of mitotic aneuploidy (Parry and Sharp, 1981), gene conversion (Sharp and Parry, 1981a), and DNA damage (Sharp and Parry, 1981b). No induction of sex-linked recessive lethal mutations was observed in germ cells of male *Drosophila melanogaster* treated with ethylene thiourea by feeding or injection (Valencia and Houtchens, 1981; Woodruff *et al.*, 1985).

ETU was tested in mammalian cells *in vitro* for induction of chromosomal aberrations (Carver *et al.*, 1981; Dean, 1981), sister chromatid exchanges (Evans and Mitchell, 1981; Perry and Thomson, 1981), and unscheduled DNA synthesis (Robinson and Mitchell, 1981; Althaus *et al.*, 1982); all results were negative. Positive results were reported in a mouse lymphoma assay for induction of trifluorothymidine resistance in L5178Y cells (McGregor *et al.*, 1988). *In vivo* mammalian tests for induction of micronuclei or sister chromatid exchanges in bone marrow cells of mice were negative (Seiler, 1975; Schuepbach and Hummler, 1977; Kirkhart, 1981; Salamone *et al.*, 1981; Tsuchimoto and Matter, 1981), as were tests for induction of dominant lethal mutations or sperm abnormalities (Teramoto *et al.*, 1977, 1978; Topham, 1981; Wyrobek *et al.*, 1981).

In contrast to the generally negative genotoxicity test results seen with ETU, its nitrosated metabolite, *N*-nitroso-ethylenethiourea, was positive for all genotoxicity endpoints for which it was tested, both *in vitro* and *in vivo*. It induced gene mutations in *S. typhimurium* (Seiler, 1977; Shirasu *et al.*, 1977), sister chromatid exchanges in Chinese hamster V79 cells, and chromosomal aberrations (Seiler, 1977), micronuclei (Seiler, 1977), and dominant lethal mutations (Teramoto *et al.*, 1978) in mice *in vivo*.

Long-Term Toxicity and Carcinogenicity

A number of previous studies have shown that ETU induces thyroid neoplasms in the rat. Graham *et al.* (1973) fed ETU to male and female Charles River rats for 2, 6, or 12 months at concentrations of 0, 5, 25, 125, 250, or 500 ppm in the diet. After 12 months of exposure, histopathologic examination of the thyroid gland revealed the development of thyroid carcinomas at concentrations of 250 and 500 ppm in both male and female rats. In a later study, Graham *et al.* (1975) exposed male and female Charles River rats to ETU in the diet for 24 months at concentrations of 0, 5, 25, 125, 250, and 500 ppm. They confirmed their earlier observation and reported that ETU is a thyroid gland carcinogen at 125 ppm and higher concentrations. Thyroid hyperplasia was noticed at the 5 and 25 ppm dose levels. Thyroid hyperplasia was not reversible in those rats in each group that were changed to the control diet after 66 weeks on a diet containing ETU. However, Arnold *et al.* (1983) reported that toxicologic effects induced by ETU are partially reversible. The magnitude of the changes in body weight, thyroid weight, and T_4 blood levels observed during the first 7 weeks of the studies decreased after ETU was removed from the diet. Gak *et al.* (1976) showed that ETU was carcinogenic at doses of 60 mg/kg in male rats and 200 mg/kg in female rats. ETU was not carcinogenic in hamsters even at the 200 mg/kg level. In an 18- to 24-month study in Charles River CD-1 rats, administration of ETU in the diet led to a dose-related induction of follicular and papillary thyroid carcinomas with pulmonary metastases, thyroid adenomas, hyperplasia, and simple goiters (Ulland *et al.*, 1972). Weisburger *et al.* (1981) showed that ETU exposure induced follicular cell carcinomas, papillary carcinomas and hyperplasia of the thyroid gland in male and female CD-1 rats. Innes *et al.* (1969) studied the carcinogenic potential of ETU in two strains of

mice. The animals were given 215 mg/kg of ETU by gavage daily from day 7 to day 28 after birth. This regimen was followed by dietary exposure of 646 ppm ETU for 18 months. Increased incidences of hepatomas were observed in males and females.

EPIDEMIOLOGY

An epidemiology study in Britain by Smith (1976) found no evidence of increased incidences of congenital defects or cancer in 699 female industrial users of rubber containing ETU. A survey of male rubber workers in Britain by Smith (1984) found no evidence that thyroid function was affected by exposure to ETU in the workplace, nor was there any clinical evidence of an effect. IARC (1982, 1987) has classified ETU as an animal carcinogen based on sufficient experimental evidence from animal studies. The evidence for carcinogenicity to humans was considered inadequate.

MATERIALS AND METHODS

DIETARY FORMULATION

Dietary formulations were prepared weekly by mixing appropriate amounts of ETU (99% pure) and feed; mixtures were analyzed at least every 2 months. It is estimated that the formulated diets were prepared within 10% of the target concentrations approximately 90% of the time (for complete details of chemical analysis and stability studies see Appendix A).

EXPERIMENTAL DESIGN

13-Week Studies

Thirteen-week studies were conducted in F344/N rats and B6C3F$_1$ mice to evaluate the cumulative toxic effects of repeated exposure to ETU and to determine the concentrations to be used in the 2-year studies. Exposure concentrations were selected on the basis of reports in the literature regarding the toxicity of ETU in rats and mice and 14-day repeated dose studies (not reported here). Groups of 10 rats of each sex, 8 to 9 weeks of age, were fed diets containing 0, 60, 125, 250, 500, or 750 ppm ETU for 13 weeks. Similarly, groups of 10 mice of each sex, 8 to 9 weeks of age, were fed diets containing 0, 125, 250, 500, 1,000, or 2,000 ppm on the same schedule. Animals were observed twice daily and feed consumption was measured weekly by cage. Individual animal weights were recorded weekly. At the end of the 13-week studies, survivors were humanely killed. A necropsy was performed on all animals, including those found dead or moribund during the course of the studies. Histologic examinations were performed on all controls, all rats fed 750 ppm, all mice fed 2,000 ppm, and all mice that died before the end of the studies. Selected tissues were examined for animals receiving lower concentrations. Tissues and groups examined are listed in Table 1.

Gestational Studies and Determination of Maximum Perinatal Dose

Exposure concentrations for the gestational and perinatal studies in rats were selected to preclude the known teratogenic effects of ETU in this species. Female F344/N rats were given 0, 8, 25, 83, or 250 ppm ETU in feed for 2 weeks prior to breeding, throughout gestation and lactation, and up to 9 weeks postweaning. Female C57BL/6N mice were fed 0, 33, 100, 330, or 1,000 ppm on the same schedule. Females were bred to previously unexposed male F344/N rats or C3H/HeN mice. Four pregnant animals from each group were humanely killed on gestation day 17 (mice) or 18 (rats) and evaluated for chemical-related reproductive effects, including fetal anomalies and differences in the number of implantations, mean number of fetuses per litter, numbers of live or dead fetuses, mean fetal weights, and mean placental weights. After weaning on postpartum day 28, selected dams and their offspring (10 per group) were continued at the same exposure level for 9 weeks. A necropsy was performed on all weanling rats at the end of the 9-week exposure, and tissues were examined histologically to help determine the appropriate maximum perinatal exposure concentration. Tissues examined are listed in Table 1.

2-Year Studies

The experimental design of the 2-year studies consisted of groups of rats and mice receiving perinatal exposure (F_0), adult exposure (F_1), or both, to different concentrations of ETU (Table 1).

Female F344/N rats were exposed to 0, 9, 30, or 90 ppm in feed for 1 week before breeding. Female C57BL/6N mice were exposed to 0, 33, 110, or 330 ppm on the same schedule. All males (rats, F344/N; mice, C3H/HeN) received control feed. All females were naturally inseminated by males, housed individually, and continued on their previous diet. ETU exposure continued throughout pregnancy and lactation. Weaning occurred on day 28 postpartum and dietary exposure at these same concentrations continued until the pups were 8 weeks of age.

On postpartum day 4 (rats) or 7 (mice), litters were culled to a maximum of eight pups. Pups were separated by sex after weaning, and litter mates were cohoused. At approximately 8 weeks of age, the pups were separated into groups of 60 males and 60 females to receive the adult dietary concentrations (rats - 0, 25, 83, or 250 ppm; mice - 0, 330, or

1,000 ppm) for up to 2 years. Groups of 34 male and 29 female mice that were fed 33 ppm ETU before weaning received 100 ppm for up to 2 years. Animals were housed five per cage and feed and water were available *ad libitum*. Cages were not rotated during these studies.

Clinical Examinations and Pathology

All animals were observed twice daily, and clinical findings were recorded. Body weights were recorded weekly for the first 13 weeks of the studies and monthly thereafter. Mean body weights were calculated for each group.

After 9 months, 10 rats and 10 mice of each sex were humanely killed. Triiodothyronine (T_3), thyroxine (T_4), and thyroid-stimulating hormone (TSH) were measured in serum from rats and mice. Necropsy was performed on each animal and the adrenal gland, brain, heart, kidney, liver, lung, pituitary gland, testis, prostate gland, uterus, ovary, thyroid gland, and thymus were weighed. Complete histopathologic examinations were performed on all rats, on mice that died early, and on mice fed 0:1,000 or 330:1,000 ppm ETU. The thyroid gland, pituitary gland, and lung were examined from all mice in the lower exposure groups.

A necropsy was performed on animals found dead or moribund prior to study termination and on those surviving to the end of the 2-year studies. 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. Complete histopathologic examinations were performed on all rats, all control animals, all mice fed 0:1,000 ppm or 330:1,000 ppm, and all mice that died before the end of the studies. The liver, pituitary gland, and thyroid gland were examined for all exposure groups of male and female mice, and the lung was examined for all groups of male mice. Tissues examined are listed in Table 1.

After the pathology examinations were completed and the data entered into the Toxicology Data Management System, the pathology specimens were audited and the histopathological diagnoses were reviewed by an independent quality assessment pathologist. A pathology working group consisting of experienced toxicologic pathologists also reviewed the pathology findings. Details of the audits and histopathology quality assessment are presented in Appendix A.

Statistical Methods

The experimental design of these studies was complex (a 4 x 4 matrix with missing cells), and both perinatal and postnatal effects were evaluated. The effect of adult-only exposure to ETU (i.e., the standard 2-year study design) was analyzed by comparison of the 0:0, 0:83, and 0:250 ppm groups (rats) or 0:0, 0:330, and 0:1000 ppm groups (mice). To determine perinatal effects, supplemental analyses were carried out in addition to the usual comparison of exposed groups with controls. Specifically, for a fixed adult exposure concentration, the effect of varying perinatal exposure was evaluated. For example, in rats, comparisons were made between the 0:0 and 90:0 ppm groups, among the 0:83, 30:83, and 90:83 ppm groups, and between the 0:250 and 90:250 ppm groups. Comparisons also were made between groups with varying perinatal and adult exposure concentrations and the 0:0 ppm group. It is recognized that these multiple comparisons are not all strictly independent, but taken collectively, they should provide a reasonable evaluation of the overall effects of perinatal and adult exposure to ETU.

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. 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.

The majority of tumors in these studies were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was a logistic regression analysis, which assumed that the diagnosed tumors were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In addition to logistic regression, alternative methods of statistical analysis were used, and the results of these tests are summarized in the appendixes. These include the life table test (Cox, 1972; Tarone, 1975), appropriate for rapidly lethal tumors, and the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart *et al.*, 1979), procedures based on the overall proportion of tumor-bearing animals. For further details see Appendix A.

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of Ethylene Thiourea

13-Week Studies	Gestation and Maximum Perinatal Dose Studies	9-Month and 2-Year Studies
Study Laboratory Battelle Columbus Laboratories	Battelle Columbus Laboratories	Battelle Columbus Laboratories
Strain and Species F344/N rats; B6C3F_1 mice	Rats: F344/N; mice: C3H/HeN males and C57BL/6N females	F344/N rats; B6C3F_1 mice
Animal Source Charles River Breeding Laboratories (Kingston, NY)	Male rats and all mice: Charles River Breeding Laboratories (Kingston, NY); female rats: Charles River Breeding Laboratories (Portage, MI)	F_0 rats and mice: Charles River Breeding Laboratories (Kingston, NY) F_1: bred at the study laboratory from F_0 animals
Time Held Before Study 21 days	Male: 4-5 weeks; female: at least 5 weeks	
Age When Placed on Study 8-9 weeks		F_1: 8 weeks
Date of First Dose Rats: 19 February 1980 (male) or 20 February 1980 (female) Mice: 21 February 1980 (male) or 22 February 1980 (female)	F_0: 22 April 1981 (rats) or 8 May 1981 (mice)	F_0 (females before breeding): 18 October 1982 (rats) or 12 August 1982 (mice)
Duration of Dosing 13 weeks	Up to 13 weeks (9 weeks post weaning)	F_0 doses through gestation, lactation, and 4 weeks post weaning; F_1 doses from 8 weeks to 2 years
Necropsy Date Male: 19 May 1980 Female: 20 May 1980	Rats: 5-14 August 1981 Mice: 28 September-27 October 1981	9 months: 1-4 November 1983 (rats) or 15-18 August 1983 (mice) 2 years: 1-8 February 1985 (rats) or 26 November-06 December 1984 (mice)
Age When Killed 21-22 weeks	F_0: 18-19 weeks; F_1: 8 weeks	11 or 26 months

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of Ethylene Thiourea (continued)

13-Week Studies	Gestation and Maximum Perinatal Dose Studies	9-Month and 2-Year Studies
Method of Animal Distribution		
Distributed to weight classes and then assigned to cages by one table of random numbers and to groups by another	Randomized by weight	Randomized by weight
Animals per Cage		
5	1-3 females and 1 male; females housed individually after becoming pregnant	5 after weaning
Method of Animal Identification		
Ear tag	Ear tag	Ear tag and toe clip
Other Chemicals on Test in Same Room		
None	None	None
Size of Study Groups		
10 males and 10 females of each species		9 months: 10 males and 10 females of each species 2 years: 50 males and 50 females of each species except 34 males and 29 females in the 33:100 ppm (F_0:F_1) groups of mice
Doses		
Rats: 0, 125, 250, 500, or 750 ppm ethylene thiourea in feed Mice: 0, 125, 250, 500, 1,000, or 2,000 ppm	Rats: 0, 8, 25, 83, or 250 ppm ethylene thiourea in feed Mice: 0, 33, 100, 330, or 1,000 ppm	F_0 females administered perinatal (F_0) doses in feed from 1 week before breeding through the weaning of the F_1 generation; pups administered same diet as the dams from weaning at week 4 until 8 weeks of age and then administered adult (F_1) doses. The following concentrations (ppm) of ethylene thiourea were administered in feed:

Rats		Mice	
F_0	F_1	F_0	F_1
0	0	0	0
0	83	0	330
0	250	0	1,000
9	25	33	100
30	83	110	330
90	0	330	0
90	83	330	330
90	250	330	1,000

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of Ethylene Thiourea (continued)

13-Week Studies	Gestation and Maximum Perinatal Dose Studies	9-Month and 2-Year Studies
Frequency of Observation Observed twice daily; weighed weekly	F_0: weighed once weekly F_1: weighed on day 4 and day 28 and then once weekly after week 8; feed consumption measured once weekly after week 8	Observed twice daily; weighed initially, once weekly for 13 weeks, and once monthly thereafter
Necropsy Necropsy performed on all animals	**Necropsy** Necropsy performed on all animals	**Necropsy** Necropsy performed on all animals
Histopathology The following tissues were examined histologically for all control and high-dose animals and all animals dying before the end of the studies: adrenal gland, brain, epididymis/prostate gland/testis or ovary/uterus, esophagus, bone including marrow, gross lesions, heart, kidneys, large intestine, liver, lung, mammary gland, lymph node, nasal cavity, pancreas, parathyroid gland, pituitary gland, preputial or clitoral gland, salivary gland, skin, small intestine, spleen, stomach, thymus, thyroid gland, trachea, and urinary bladder. The following tissues were examined for all lower dose groups of rats: bone marrow, esophagus, forestomach, liver, pituitary gland, and thyroid gland. The esophagus, liver, and thyroid gland were examined for all lower dose groups of mice.	**Histopathology** Histologic exams performed on all controls, all high-dose rats, and all mice administered 330 or 1,000 ppm. Tissues examined include adrenal glands, bone including marrow, brain, epididymis/prostate gland/testis or ovaries/uterus, esophagus, gross lesions, heart, kidney, large intestine, liver, lung, mammary gland, lymph nodes, nasal cavity, pancreas, parathyroid gland, pituitary gland, preputial or clitoral gland, salivary gland, skin, small intestine, spleen, stomach, thymus, thyroid gland, trachea, and urinary bladder. Tissues examined at lower doses include thyroid gland for rats; kidneys, liver, lung, lymph node, spleen, testis, thymus, and thyroid gland for male mice administered 330 ppm; kidney, lung, and thyroid gland for female mice administered 330 ppm; and lung for mice administered 33 or 100 ppm. Tissue distribution studies performed at day 18 of gestation and day 12 postpartum.	**Histopathology** The following tissues were examined histologically for all controls, all rats, and all mice that died before the end of the studies or were administered 1,000 ppm: adrenal glands, brain, cecum, colon, duodenum, epididymis/prostate gland/testis or ovary/uterus, esophagus, femur including marrow, gross lesions, heart, ileum, jejunum, kidney, liver, lung, mammary gland (female), mandibular or mesenteric lymph node, nasal turbinate, pancreas, parathyroid glands, pituitary gland, preputial or clitoral gland, rectum, salivary glands, skin, spleen, stomach, thymus, thyroid gland, trachea, and urinary bladder. The following tissues were examined for lower dose animals: thyroid gland for rats; liver, lung, pituitary gland, and thyroid gland for male mice; and adrenal gland, liver, pituitary gland, and thyroid gland for female mice. **Clinical Pathology** Thyroid function studies carried out on 9-month and 2-year study animals.

RESULTS

RATS

13-Week Studies

During the 13-week studies, there were no clinical signs of toxicity and all rats survived to study termination (Table 2). The final mean body weights of male rats that received 500 or 750 ppm ETU were 10% or 32% lower than the final mean body weight of the controls. The final mean body weights of female rats that received 60 to 500 ppm were about 10% lower than the final mean body weight of the controls, and that of females receiving 750 ppm was 28% lower. Feed consumption relative to controls was clearly reduced in male rats receiving concentrations of 500 or 750 ppm and in female rats receiving 250 ppm or higher.

Lesions related to chemical administration were observed in the thyroid gland, pituitary gland, and liver of exposed rats. Focal and/or diffuse follicular cell hyperplasia occurred in the thyroid glands of male and female rats at all exposure levels (Table 3). The hyperplasia ranged from minimal at the lower concentrations to marked at the highest concentration. Minimal diffuse changes were characterized by slightly increased cytoplasmic basophilia of follicular cells and decreased intensity of colloid staining, whereas the mild to marked hyperplasia was characterized by increased height and cellularity of the follicular epithelium. The follicles were often irregular in shape, with hypertrophic epithelial cells occasionally forming blunt papillary projections into the lumens. Focal

TABLE 2
Survival, Mean Body Weights, and Feed Consumption of Rats in the 13-Week Feed Studies of Ethylene Thiourea

Concentration (ppm)	Survival[a]	Mean Body Weights (g) Initial[b]	Final	Change[c]	Final Weight Relative to Controls (%)	Feed Consumption[d] Week 1	Week 13	Mean
Male								
0	10/10	183	332	+149	-	142	67	116
60	10/10	176	324	+148	98	132	84	116
125	10/10	183	326	+143	98	143	87	106
250	10/10	181	323	+142	97	134	95	111
500	10/10	179	300	+121	90	134	97	98
750	10/10	180	226	+ 46	68	125	88	88
Female								
0	10/10	139	217	+ 78	-	106	74	97
60	10/10	139	194	+ 55	89	105	66	97
125	10/10	139	197	+ 58	91	113	72	91
250	10/10	139	199	+ 60	92	109	60	84
500	10/10	140	191	+ 51	88	96	61	80
750	10/10	138	157	+ 19	72	111	56	73

[a] Number surviving/number initially in the group
[b] Initial group mean body weight. Subsequent calculations are based on animals surviving to the end of the studies.
[c] Mean body weight change of the survivors
[d] Feed consumption in grams/animal per week

TABLE 3
Incidences of Selected Lesions in Rats in the 13-Week Feed Studies of Ethylene Thiourea[a]

	Concentration (ppm)					
	0	60	125	250	500	750
Male						
Thyroid Gland						
Focal Follicular Cell Hyperplasia	0	0	0	5*	5*	6**
Diffuse Follicular Cell Hyperplasia	0	10**	10**	10**	10**	10**
Follicular Cell Adenoma	0	0	0	3	3	6**
Pituitary Gland, Pars Distalis						
Cellular Vacuolization	0	0	0	6**	7**	10**
Liver						
Centrilobular Cytomegaly[b]	0	0	0	0	0	7**
Female						
Thyroid Gland						
Focal Follicular Cell Hyperplasia	0	0	0	0	1	4*
Diffuse Follicular Cell Hyperplasia	0	10**	10**	10**	10**	10**
Follicular Cell Adenoma	0	0	0	0	3	3
Pituitary Gland, Pars Distalis						
Cellular Vacuolization	0	0	0	0	1	10**
Liver						
Centrilobular Cytomegaly[b]	0	0	0	0	0	10**

* Significantly different ($P<0.05$) from the control group
** $P<0.01$
[a] n=10
[b] Diagnosed as "cellular atypia" or "altered stain affinity" by the study pathologist

follicular cell hyperplasia consisted of poorly demarcated lesions with more complex folding of the follicular epithelium than is seen with diffuse hyperplasia. Single thyroid follicular cell adenomas occurred in male rats in the 250 to 750 ppm groups and in female rats in the 500 and 750 ppm groups. The adenomas were generally larger and better circumscribed, with a more complex growth pattern than focal hyperplasia.

Cytoplasmic vacuolization of cells in the pars distalis of the pituitary gland was seen in male rats in the 250 to 750 ppm exposure groups and in female rats in the 500 and 750 ppm groups. The affected cells were enlarged by single or multiple clear vacuoles. Sections of pituitary gland from selected male and female rats in the control and 750 ppm groups were examined for thyroid-stimulating hormone (TSH) by an immunogold-silver technique and appropriate positive and negative controls. There were no observed differences in number or morphology of TSH-positive cells between the control and exposed rats. The vacuolated cells in the pars distalis did not stain preferentially for TSH.

Centrilobular hepatocellular cytomegaly (hypertrophy) occurred in the liver of male and female rats receiving 750 ppm. Centrilobular hepatocytes were minimally to mildly enlarged, with a homogeneous eosinophilic granular cytoplasm.

Gestational Study: Determination of Maximum Perinatal Dose

The gestational study was conducted to determine the dietary concentrations for perinatal exposure in the 2-year studies. Selected dams from each dose group were evaluated at gestation day 18 for chemical-related reproductive effects (Appendix G, Table G1). No external gross fetal anomalies or differences in the number of implantations, mean number of fetuses per litter, numbers of live or dead fetuses, mean fetal weights, or mean placental weights were seen among the dose groups (Table G1). All rat dams not designated for interim evaluation survived to the end of the study.

The number of rat pups surviving to postnatal day 4 was decreased in the 250 ppm dose group (Table G2). Survival of rat pups from postnatal days 4 to 28 and mean body weights on day 28 were similar among exposed and control groups. All weanling rats receiving ETU in the feed survived until the scheduled necropsy at 8 weeks (Table 4). Dose-related decreased body weight gains were noted in male rats, especially in the two highest exposure groups. Dose-related, minimal to moderate, diffuse follicular cell hyperplasia was observed in the thyroid glands of male rats receiving 25, 83, or 250 ppm ETU and in female rats receiving 83 or 250 ppm (Table 5). Bilateral follicular cell adenomas occurred in three males receiving 250 ppm, and single, unilateral adenomas occurred in one male receiving 83 ppm and another receiving 250 ppm. Minimal to moderate cytoplasmic vacuolization of cells in the pars distalis was seen in males in the 250 ppm group. The thyroid and pituitary lesions were similar to those described above for the 13-week studies.

Dose Selection Rationale for the 2-Year Studies

Selection of dietary concentrations for the adult (F_1) exposures in the 2-year studies in rats was based primarily on the decreased weight gains and lower feed consumption in the 13-week studies. Because the final mean body weights of male and female rats receiving 500 or 750 ppm were 10% to 30% lower than those of the controls and feed consumption was clearly decreased at these concentrations, 250 ppm was considered appropriate as the highest dose for the 2-year studies. The severity of the thyroid lesions at this concentration was not believed to be potentially life threatening in 2-year studies. Further, a concentration level sufficient to produce an effect was necessary to meet one of the objectives of these studies, that is, to compare the effects of combined perinatal and adult exposure with the standard carcinogenicity study protocol.

The maximum perinatal exposure concentration selected for the 2-year studies was one that did not produce greater mortality or reduce body weight more than 10% compared to controls. The decreased survival of rat pups between postnatal days 0 and 4 at 250 ppm and the reduction in body weight gain in male weanling rats at this concentration resulted in the selection of 90 ppm as the highest dose for perinatal exposure in the 2-year studies.

2-Year Studies

9-Month Interim Evaluation

Body and organ weights were generally similar among exposed and control rats evaluated at 9 months. Absolute and relative liver weights were marginally increased in males receiving 0:83, 0:250, 90:83, or 90:250 ppm (Table 6). Thyroid gland weights were marginally increased in males and females in the 0:250 and 90:250 ppm groups, but the increases were not statistically significant.

Thyroid follicular cell hyperplasia was observed in most groups of exposed male and female rats (Table 7). The severity increased in a dose-related manner from minimal in the lower dose groups to moderate in the higher dose groups. Follicular cell adenomas were found in the thyroid glands of three males and one female receiving 90:250 ppm. In general, serum thyroxine (T_4) levels were decreased in exposed rats and TSH levels were increased; triiodothyronine (T_3) levels were variable but were decreased in some exposure groups (Appendix H, Tables H1-H4).

Clinical Findings, Body Weights and Survival in the 2-Year Studies

Serum T_3, T_4, and TSH were also measured at the end of the studies, and the results were similar to those at 9 months (Tables H1-H4). Although hypothyroidism was detected in groups of rats evaluated at 9 months or 2 years, there were no clinical findings attributed to derangement of thyroid function or other toxicity. There were no differences in feed consumption between groups of exposed rats and the 0:0 ppm controls throughout

TABLE 4
Survival and Mean Body Weights of Weanling Rats in the Maximum Perinatal Dose Determination Feed Study of Ethylene Thiourea

Concentration (ppm)	Survival[a]	Mean Body Weights (grams) Initial[b]	Final	Change[c]	Final Weight Relative to Controls (%)
Male					
0	10/10	57	336	+279	-
8	10/10	57	321	+264	96
25	10/10	55	317	+262	94
83	10/10	56	299	+243	89
250	10/10	56	296	+240	88
Female					
0	10/10	50	188	+138	-
8	10/10	53	189	+136	101
25	10/10	51	192	+141	102
83	10/10	51	188	+137	100
250	10/10	50	186	+136	99

[a] Number surviving/number initially in the group
[b] Initial group mean body weight. Final mean body weights based on number of animals surviving to the end of the studies.
[c] Mean body weight change of the survivors

TABLE 5
Incidences of Selected Lesions in Weanling Rats in the Maximum Perinatal Dose Determination Feed Study of Ethylene Thiourea[a]

	Concentration (ppm) 0	8	25	83	250
Male					
Thyroid Gland					
Diffuse Follicular Cell Hyperplasia	0	1	4*	10**	9**
Follicular Cell Adenoma	0	0	0	1	4*
Pituitary Gland, Pars Distalis					
Cellular Vacuolization	0	0	0	0	7**
Female					
Thyroid Gland					
Diffuse Follicular Cell Hyperplasia	0	0	0	10**	10**
Multifocal Follicular Cell Hyperplasia	0	0	2	0	0

* Significantly different ($P<0.05$) from the control group
** $P<0.01$
[a] n=10

TABLE 6
Liver Weights in Rats at the 9-Month Interim Evaluations in the 2-Year Feed Studies of Ethylene Thiourea[a]

F_0 Concentration (ppm)	F_1 Concentration (ppm) 0	25	83	250
Male				
0	14.66 ± 0.25	–[b]	16.28 ± 0.28	17.01 ± 0.33*
9	–	15.01 ± 0.42	–	–
30	–	–	15.48 ± 0.48	–
90	14.51 ± 0.46[c]	–	15.99 ± 1.68[c]	17.19 ± 0.73*
Female				
0	8.92 ± 0.34	–	8.19 ± 0.19*	8.59 ± 0.14
9	–	8.08 ± 0.29*	–	–
30	–	–	7.96 ± 0.18*	–
90	8.44 ± 0.18	–	8.47 ± 0.16	8.46 ± 0.31

* Significantly different (P≤0.05) from the 0:0 ppm group by Fisher's least significant difference test
[a] Mean weight ± standard error (grams); n=10 unless otherwise specified.
[b] Animals were not exposed at these concentrations.
[c] n=9

TABLE 7
Incidences of Thyroid Gland Lesions in Rats at the 9-Month Interim Evaluations in the 2-Year Feed Studies of Ethylene Thiourea[a]

F_0 Concentration (ppm)	Male F_1 Concentration (ppm) 0[b]	25	83	250	Female F_1 Concentration (ppm) 0	25	83	250
Follicular Cell Hyperplasia								
0	0	–[c]	10**	10**	0	–	5*	10**
9	–	1	–	–	–	0	–	–
30	–	–	8**	–	–	–	10**	–
90	4	–	10**	10**	0	–	10**	10**
Follicular Cell Adenoma								
0	0	–	0	0	0	–	0	0
9	–	0	–	–	–	0	–	–
30	–	–	0	–	–	–	0	–
90	0	–	0	3	0	–	0	1

* Significantly different (P≤0.05) from the 0:0 ppm group
** P≤0.01
[a] Diagnoses represent the consensus of the study pathologist, quality assessment pathologist, and PWG Chair; n=10 for all groups unless otherwise specified.
[b] n=9 for male rats receiving 90:0 ppm
[c] Animals were not exposed at these concentrations.

TABLE 8
Final Mean Body Weights of Rats at 105 Weeks in the 2-Year Feed Studies of Ethylene Thiourea

F_0:F_1 Concentration (ppm)	Male			Female		
	Number	Mean[a]	Ratio[b]	Number	Mean[a]	Ratio[b]
0:0	19	415.2 ± 3.9	-	24	331.3 ± 3.7	-
0:83	19	395.3 ± 8.7	95	33	330.5 ± 3.0	100
0:250	14	398.0 ± 11.1	96	21	317.0 ± 7.1	96
9:25	22	406.2 ± 7.3	98	35	336.1 ± 2.4	101
30:83	20	409.5 ± 2.9	99	28	326.9 ± 4.7	99
90:0	18	383.4 ± 12.8	92	30	330.4 ± 3.6	100
90:83	15	387.7 ± 13.7	93	33	332.1 ± 3.4	100
90:250	7	324.9 ± 14.6**	78	14	325.6 ± 4.1	98

** Significantly different ($P \leq 0.01$) from the 0:0 ppm group by Fisher's least significant difference test
[a] Mean ± standard error in grams
[b] Percent final weight relative to 0:0 ppm group

the studies, except for a decrease in that of the 90:250 ppm group of males during the last month of exposure. Mean body weights of rats receiving adult-only exposure to ETU were similar to those of the 0:0 ppm controls throughout the studies. Mean body weights of females were not affected by perinatal exposure, but the mean body weight of males receiving 90:250 ppm ETU was 18% lower than that of the 0:250 ppm group and 22% lower than that of the 0:0 ppm group at the end of the studies. Mean body weights of males receiving lower F_0:F_1 concentrations of ETU were generally similar to the mean body weight of the controls (Table 8 and Figure 1). Estimates of the probabilities of survival for male and female rats fed diets containing ETU at the concentrations used in these studies and for controls are shown in Table 9 and in the Kaplan and Meier curves in Figure 2. Survival of rats receiving adult-only exposure was similar to that of the controls. However, survival of male rats in the 90:250 ppm dose group was significantly decreased, probably due to aging changes compounded by hypothyroidism, thyroid follicular cell neoplasms, and/or mononuclear cell leukemia.

Pathology and Statistical Analysis of Results

This section describes the statistically significant or biologically noteworthy change in the incidences of rats with neoplastic or nonneoplastic lesions of the thyroid gland, Zymbal's gland, hematopoietic system, kidney, adrenal gland, and subcutaneous tissue.

The incidences of neoplasms in rats are summarized in Appendix B, Table B1 (males) and Appendix C, Table C1 (females). The statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one exposure group are presented in Tables B2 through B6 (males) and C2 through C6 (females). The statistical analyses used are discussed in Appendix A (Materials and Methods). Historical incidences of neoplasms in control rats are listed in Tables B7 (males) and C7 (females). The incidences of nonneoplastic lesions in rats are summarized in Tables B8 (males) and C8 (females).

Effects of Adult-Only Exposure of Rats to Ethylene Thiourea

Thyroid Gland: The neoplastic and nonneoplastic effects of adult-only exposure were determined by comparison of the incidences of lesions in the 0:0, 0:83, and 0:250 ppm groups (e.g., the groups corresponding to a standard carcinogenicity study). The principal toxic effects in rats were observed in the thyroid gland (Table 10). The incidence of follicular cell hyperplasia was markedly increased relative to controls in both exposure groups and occurred in 60% to 90% of the exposed rats. The incidence of adenomas was marginally increased in the 0:83 ppm groups; this lesion was seen in 46% to 56% of rats in the 0:250 ppm groups. Follicular cell carcinomas were increased only in the high-dose (0:250 ppm) groups and were more frequent in males than in females. Thus, male rats were more sensitive to the

effects of ETU than were female rats. Male rats receiving 83 or 250 ppm (F_1) had higher incidences of follicular cell neoplasms than females at these concentrations, and male rats receiving 250 ppm had higher incidences of carcinoma than females. Most of the affected rats receiving 0:250 ppm had bilateral or multiple thyroid neoplasms.

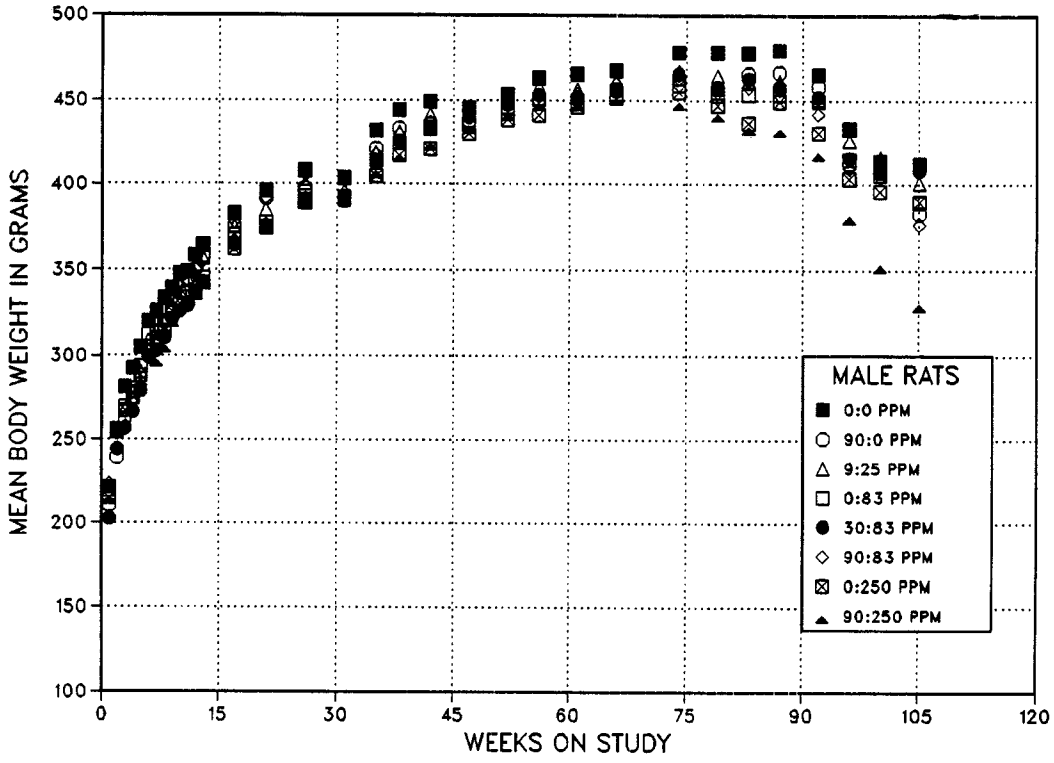
Follicular cell hyperplasia in exposed rats was similar to that described above for the 13-week studies. Hyperplasia was generally diffuse, with more severely altered single or multiple foci.

The follicles were variable in size, often smaller than normal, and contained pale-staining colloid. The follicular epithelial cells were enlarged and crowded, forming papillary projections into the lumens. Follicular cysts and micro-follicle formation within the walls of existing follicles were seen. Follicular cell hyperplasia in control rats was minimal in severity, focal, and occurred at the periphery of the lobe.

TABLE 9
Survival of Rats in the 2-Year Feed Studies of Ethylene Thiourea

	F_0:F_1 Concentration (ppm)							
	0:0	90:0	9:25	0:83	30:83	90:83	0:250	90:250
Male[a]								
Animals initially in study	50	50	50	50	50	50	50	50
Moribund sacrifice	21	29	22	28	24	25	23	31
Natural death	11	6	11	7	8	11	8	15
Terminal sacrifice	18	15	17	15	18	14	14	4
Accidental deaths							5	
Survival analysis[b]		P=1.000	P=0.555	P=0.732	P=0.917	P=0.644	P=0.730	P=0.009
Female[a]								
Animals initially in study	50	50	50	50	50	50	50	50
Moribund sacrifice	20	15	13	10	11	13	26	30
Natural death	7	5	3	10	13	5	4	7
Terminal sacrifice	23	30	34	30	26	32	20	13
Survival analysis[b]		P=0.287	P=0.052	P=0.080	P=0.604	P=0.065	P=0.849	P=0.069

[a] Day of first terminal sacrifice: 738 for males and 740 for females
[b] Results of the life table pairwise comparison with the 0:0 ppm group



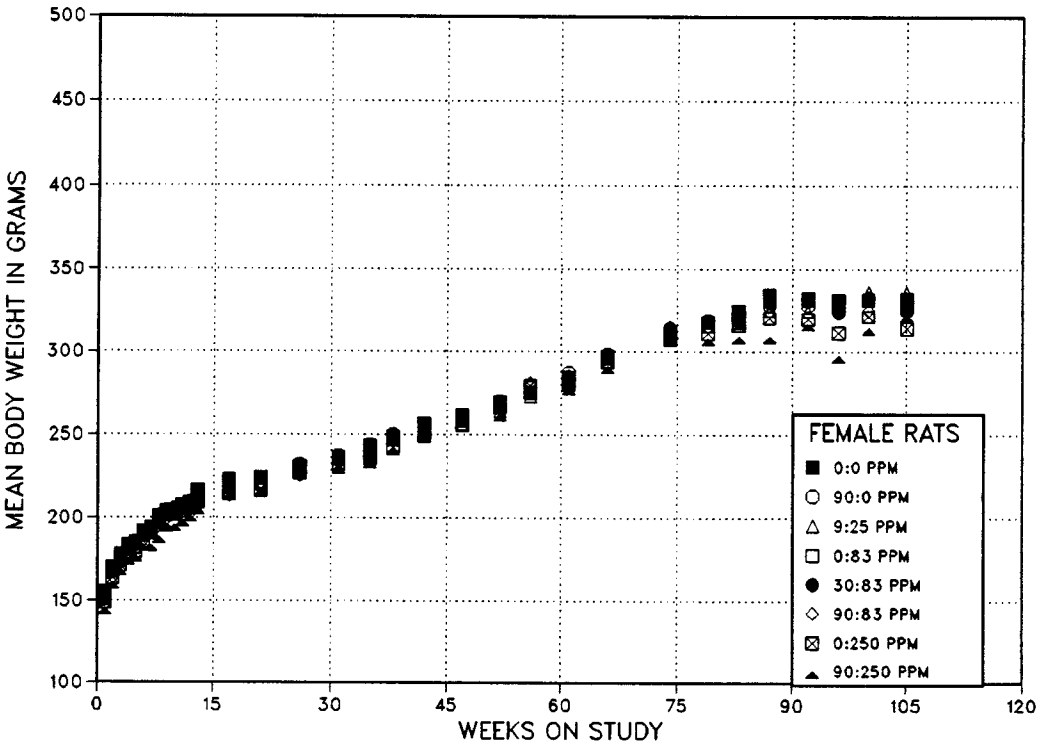


FIGURE 1
Growth Curves for Male and Female Rats Administered Ethylene Thiourea in Feed for 2 Years

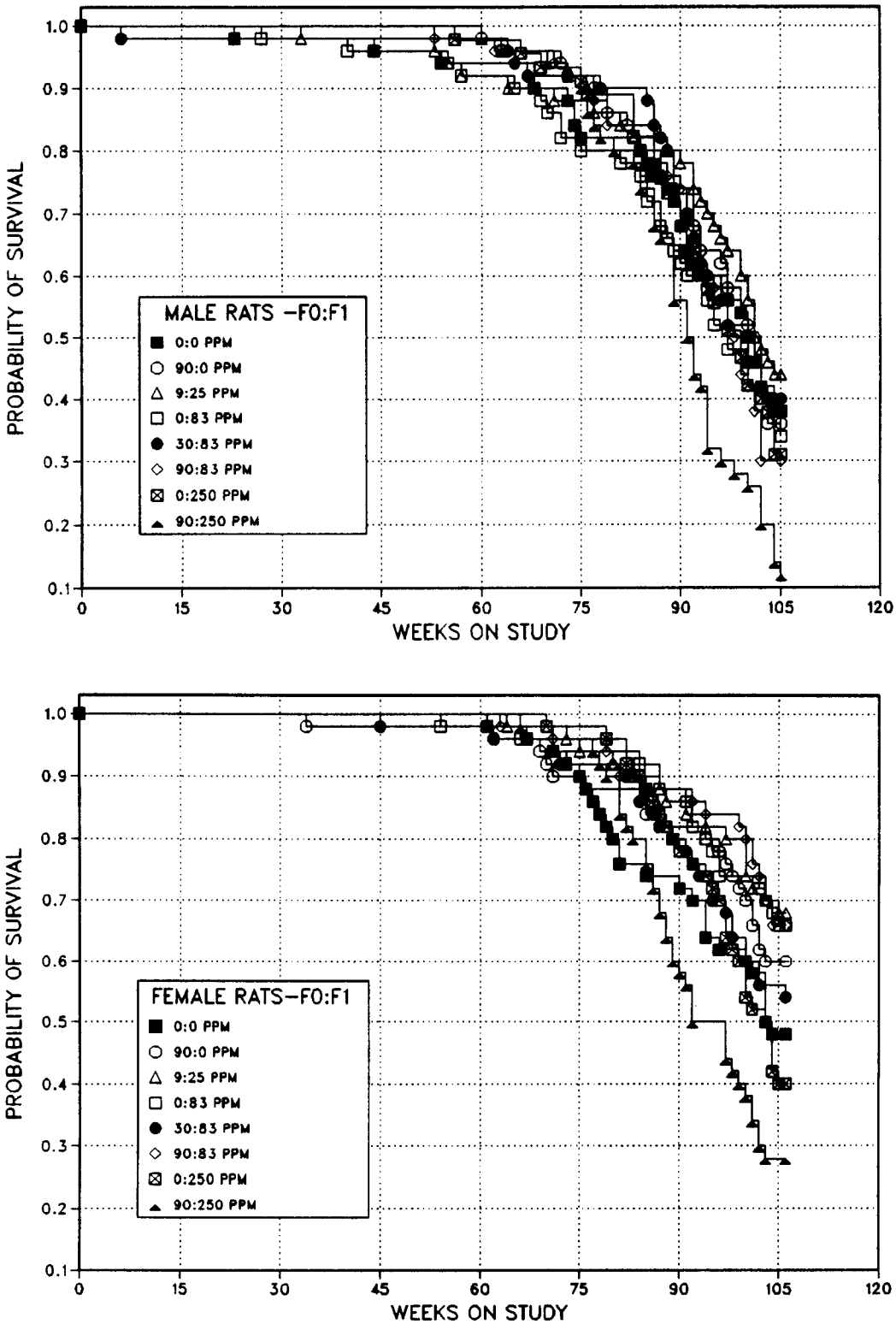


FIGURE 2
Kaplan-Meier Survival Curves for Male and Female Rats Administered Ethylene Thiourea in Feed for 2 Years

TABLE 10
Incidences of Follicular Cell Lesions of the Thyroid Gland in Rats in the 2-Year Feed Studies of Ethylene Thiourea: Comparison of the 0:0, 0:83, and 0:250 ppm Groups[a]

	Male F_0:F_1 Concentration (ppm)			Female F_0:F_1 Concentration (ppm)		
	0:0	0:83	0:250	0:0	0:83	0:250
Hyperplasia	4/49** (1.3[b])	30/46** (2.1)	41/50** (3.9)	0/50**	33/44** (1.8)	45/49** (2.7)
Adenoma	0/49**	9/46**	23/50**	1/50**	6/44	28/49**
Carcinoma	1/49**	3/46	26/50**	2/50**	1/44	8/49*
Adenoma or Carcinoma	1/49**	12/46**	37/50**	3/50**	7/44	30/49**

* Significant ($P \leq 0.05$) by the logistic regression tests
** $P \leq 0.01$
[a] Number of lesions observed/number of animals with thyroid gland examined microscopically; indications of statistical significance appearing adjacent to the incidences in the 0:0 ppm column represent the trend test, whereas those adjacent to the incidences in other columns represent pairwise comparisons vs the 0:0 ppm group. The thyroid gland neoplasms were not considered fatal; thus, the logistic regression tests were considered the most appropriate analyses.
[b] Mean severity grade (minimal=1, mild=2, moderate=3, marked=4)

Focal follicular cell hyperplasia, adenoma, and carcinoma constituted a morphologic continuum. Adenomas generally were well-circumscribed nodular masses that compressed adjacent normal tissue and consisted of follicle-like structures, papillary projections, and solid nests of well-differentiated epithelium; cystic areas were often present. Follicular cell carcinomas displayed increased architectural disorganization and greater cellular pleomorphism and atypia than adenomas. Some carcinomas invaded the adjacent parenchyma and/or esophagus and trachea, and two metastasized to the lungs.

Effects of Perinatal-Only Exposure of Rats to Ethylene Thiourea

Thyroid Gland: Comparison of the 90:0 ppm groups with the 0:0 ppm controls showed that perinatal-only exposure had no effect on the incidences of neoplasms in the thyroid gland or any other organ (Appendixes B and C, Tables B3 and C3). However, the incidences of male and female rats with follicular cell hyperplasia were marginally but significantly increased in the 90:0 ppm groups (Table 11). Whether these increases are chemical related is uncertain, but similar effects in both sexes support the association with dietary exposure.

Effects of Combined Perinatal and Adult Exposure of Rats to ETU

Combined perinatal exposure of 30 or 90 ppm ETU with adult exposure of 83 or 250 ppm was associated with increased incidences of nonneoplastic lesions and neoplasms of the thyroid gland similar to those of adult-only exposure. The effect of perinatal exposure was determined by comparing groups with varying F_0 concentrations and constant adult F_1 exposure of 83 or 250 ppm. At the adult exposure level of 83 ppm, there was no increase in neoplasms of the thyroid gland or of any other tissue due to perinatal exposure (Table 12). However, the incidence of follicular cell hyperplasia in males, but not females, receiving 90:83 ppm was significantly greater than that in the 0:83 ppm group. In contrast, comparison of the 90:250 and 0:250 ppm groups showed statistically significant increased incidences of follicular cell adenomas and of follicular cell carcinomas in male rats and of follicular cell carcinomas in female rats perinatally exposed at 90 ppm (Table 13).

Miscellaneous Organs: Although adult-only or perinatal-only exposure to ETU had no clear effects on the incidences of neoplasms or nonneoplastic lesions at sites other than the thyroid gland, some

TABLE 11
Incidences of Follicular Cell Lesions of the Thyroid Gland in Rats in the 2-Year Feed Studies of Ethylene Thiourea: Comparison of the 0:0 and 90:0 ppm Groups[a]

	Male F_0:F_1 Concentration (ppm)		Female F_0:F_1 Concentration (ppm)	
	0:0	90:0	0:0	90:0
Hyperplasia	4/49 (1.3[b])	12/49* (1.3)	0/50	8/48** (1.3)
Adenoma	0/49	1/49	1/50	0/48
Carcinoma	1/49	3/49	2/50	0/48
Adenoma or Carcinoma	1/49	4/49	3/50	0/48

* Significantly different ($P \leq 0.05$) from the 0:0 ppm group by the logistic regression tests
** $P \leq 0.01$
[a] Number of lesions observed/number of animals with thyroid gland examined microscopically
[b] Mean severity grade (minimal=1, mild=2, moderate=3, marked=4)

TABLE 12
Incidences of Follicular Cell Lesions of the Thyroid Gland in Rats in the 2-Year Feed Studies of Ethylene Thiourea: Comparison of the 0:83, 30:83, and 90:83 ppm Groups[a]

	Male F_0:F_1 Concentration (ppm)			Female F_0:F_1 Concentration (ppm)		
	0:83	30:83	90:83	0:83	30:83	90:83
Hyperplasia	30/46** (2.1[b])	35/47 (2.1)	47/50** (2.1)	33/44 (1.8)	30/46 (2.0)	41/47 (2.1)
Adenoma	9/46	10/47	8/50	6/44	5/46	7/47
Carcinoma	3/46	4/47	6/50	1/44	1/46	2/47
Adenoma or Carcinoma	12/46	14/47	13/50	7/44	6/46	9/47

** Significant ($P \leq 0.01$) by the logistic regression tests
[a] Number of lesions observed/number of animals with thyroid gland examined microscopically; indications of statistical significance appearing adjacent to the incidences in the 0:83 ppm column represent the trend test, whereas those adjacent to the other columns represent pairwise comparisons vs the 0:83 ppm group.
[b] Mean severity grade (minimal=1, mild=2, moderate=3, marked=4)

TABLE 13
Incidences of Follicular Cell Lesions of the Thyroid Gland in Rats in the 2-Year Feed Studies of Ethylene Thiourea: Comparison of the 0:250 and 90:250 ppm Groups[a]

	Male F_0:F_1 Concentration (ppm)		Female F_0:F_1 Concentration (ppm)	
	0:250	90:250	0:250	90:250
Hyperplasia	41/50[b] (3.9[c])	39/50 (3.5)	45/49 (2.7)	47/50 (2.8)
Adenoma	23/50	34/50*	28/49	29/50
Carcinoma	26/50	44/50**	8/49	17/50*
Adenoma or Carcinoma	37/50	48/50**	30/49	37/50*

* Significantly different ($P \leq 0.05$) from the 0:0 ppm group by the logistic regression tests
** $P \leq 0.01$
[a] Number of lesions observed/number of animals with thyroid gland examined microscopically
[b] Five males in the 0:250 ppm group were accidentally killed on day 30 and were not at risk for lesions; however, the logistic regression tests adjust for mortality.
[c] Mean severity grade (minimal=1, mild=2, moderate=3, marked=4)

groups receiving both perinatal and adult exposure showed statistically significant increases relative to the 0:0 ppm controls in neoplasms of the Zymbal's gland, hematopoietic system, adrenal medulla, and lung. There also were slight increases in rare renal tubule cell neoplasms that were not statistically significant.

Neoplasms of the Zymbal's gland, a specialized sebaceous gland which empties into the external auditory canal, were marginally increased in groups of rats receiving 83 or 250 ppm ETU (Table 14). Three of the five males in the 90:250 ppm group with Zymbal's gland carcinomas had leukemia, two had follicular cell carcinomas of the thyroid gland, and one had an hepatocellular carcinoma. Thus, the cause of death of these rats could not be attributed solely to the Zymbal's gland neoplasms. However, they are rapidly growing neoplasms that are potentially fatal, and the life table test is generally considered the most appropriate statistical analysis. The incidence of adenoma or carcinoma (combined) in males receiving 90:250 ppm was significantly increased ($P<0.05$) relative to the 0:0 ppm group. Furthermore, the incidences of Zymbal's gland neoplasms in groups receiving perinatal exposure of 90 ppm and increasing adult exposure levels (90:0, 90:83, and 90:250) were significant by the trend test (males $P=0.01$, females $P=0.03$). The incidences in males and females receiving 90:250 ppm ETU exceed the historical ranges for untreated control rats from 2-year NTP studies [males, 18/1,596 (1%), range 0/50-4/50; females, 14/1,643 (1%), range 0/50-3/50] (Tables B7 and C7).

Mononuclear cell leukemia occurred with greater frequency in rats receiving ETU (Table 15). The majority of cases of leukemia were advanced, and the life table test was considered the most appropriate analysis. There were significant trends ($P<0.01$) for groups of female rats receiving perinatal exposure of 90 ppm and increasing adult exposure levels (90:0, 90:83, and 90:250 ppm) and for female rats without perinatal exposure (0:0, 0:83, and 0:250 ppm). The incidences of leukemia in males receiving 90:83 ppm and in males and females receiving 90:250 ppm were significantly increased relative to their respective 0:0 ppm controls.

Renal tubule cell hyperplasia, adenoma, or carcinoma occurred in one or several male rats from each of the exposed groups, but not in controls (Table 16). The incidence of hyperplasia was highest in the 0:250 ppm group, but the incidences of tubule cell neoplasms did not increase in a dose-related manner. Further, the incidence in the 90:250 ppm group was the same as that in the controls. Two of the three carcinomas (0:250 and 9:25 ppm exposure groups) occurred in rats with adenomas. Although the low incidences of tubule cell neoplasms in rats receiving ETU were not significantly increased relative to the 0:0 ppm controls, they are uncommon in historical controls. The incidence for historical untreated controls (all NTP laboratories) is 13/1,590 or 0.8% (Table B7). Furthermore, the incidence of adenomas in the 0:83 ppm group exceeds the historical range for controls (3/50). Tubule cell adenomas also occurred in one female in the 0:83 ppm group and in one

TABLE 14
Incidences of Zymbal's Gland Neoplasms in Rats in the 2-Year Feed Studies of Ethylene Thiourea[a]

F_0 Concentration (ppm)	F_1 Concentration (ppm) 0	25	83	250
Male				
Adenoma or Carcinoma				
0	1/50	–[b]	3/50	3/50
9	–	1/50	–	–
30	–	–	1/50	–
90	1/50	–	2/50	5/50*▲
Female				
Adenoma or Carcinoma				
0	1/50	–	0/50	2/50
9	–	0/50	–	–
30	–	–	0/50	–
90	0/50	–	3/50	4/50▲

* Significantly different (P≤0.05) from the 0:0 ppm group by the life table tests
▲ Significantly different (P≤0.05) from the 90:0 ppm group by the life table tests
[a] Number of lesions observed/number of animals necropsied; Zymbal's glands were examined microscopically only if observed to be enlarged.
[b] Animals were not exposed at these concentrations.

TABLE 15
Incidences of Mononuclear Cell Leukemia in Rats in the 2-Year Feed Studies of Ethylene Thiourea[a]

F_0 Concentration (ppm)	F_1 Concentration (ppm) 0	25	83	250
Male				
Mononuclear Cell Leukemia				
0	22/50	–[b]	25/50	26/50
9	–	29/50	–	–
30	–	–	31/50	–
90	32/50	–	35/50*	29/50**
Female				
Mononuclear Cell Leukemia				
0	18/50	–	22/50	27/50
9	–	19/50	–	–
30	–	–	29/50	–
90	18/50	–	23/50	25/50*▲▲

* Significantly different (P≤0.05) from the 0:0 ppm group by the life table tests
** Significantly different (P≤0.01) from the 0:0 ppm group by the life table tests
▲▲ Significantly different (P≤0.01) from the 90:0 ppm group by the life table tests
[a] Number of lesions observed/number of animals examined
[b] Animals were not exposed at these concentrations.

TABLE 16
Incidences of Kidney Tubule Cell Lesions in Male Rats in the 2-Year Feed Study of Ethylene Thiourea[a]

F_0 Concentrations (ppm)	F_1 Concentrations (ppm)			
	0	25	83	250
Hyperplasia				
0	0/50	-[b]	0/50	7/50**
9	-	1/49	-	-
30	-	-	1/50	-
90	3/50	-	3/50	2/50
Adenoma				
0	0/50	-	4/50	3/50
9	-	1/49	-	-
30	-	-	1/50	-
90	1/50	-	2/50	0/50
Carcinoma				
0	0/50	-	0/50	1/50
9	-	1/49	-	-
30	-	-	0/50	-
90	0/50	-	1/50[c]	0/50
Adenoma or Carcinoma				
0	0/50	-	4/50	3/50
9	-	1/49[d]	-	-
30	-	-	1/50	-
90	1/50	-	3/50	0/50

** Significantly different ($P \leq 0.01$) from the 0:0 ppm group by the logistic regression tests
[a] Number of lesions observed/number of animals with kidney examined microscopically
[b] Animals were not exposed at these concentrations.
[c] Diagnosed as cystadenocarcinoma by the laboratory pathologist
[d] Adenoma and carcinoma occurred in the same animal.

female in the 30:83 ppm group. It is uncertain if these renal neoplasms in the exposed rats are related to the administration of ETU.

Adrenal Medulla: Incidences of benign pheochromocytoma and benign or malignant pheochromocytoma (combined) were marginally increased in the 90:83 ppm group of female rats relative to the 0:0 ppm controls [0:0 ppm, 2/50; 90:83 ppm, 10/50 ($P<0.05$)]. However, the incidence of pheochromocytomas did not increase in a dose-related manner, nor was there a dose-related increase in focal hyperplasia in the adrenal medulla. All incidences except that of the 90:83 ppm group fall within the range for historical control female rats from NTP 2-year studies [females, 93/1634 (6%), range 0/50-8/50]. The slight increase in the incidence of pheochromocytomas was not considered to be related to chemical administration.

Subcutaneous Tissue: The incidences of fibroma and fibroma or fibrosarcoma (combined) were increased in males receiving 30:83 ppm relative to the controls [fibroma or fibrosarcoma (combined): 0:0 ppm, 0/50; 30:83 ppm, 9/50 ($P<0.01$)]. Although the incidences in this group exceed the range for historical untreated control male rats [fibroma: 87/1,596 (5%), range 0%-6%; fibroma or fibrosarcoma (combined): 105/1,596 (7%), range 0%-7%], there was no dose-related trend and the incidences in the highest dose groups (0:250 and 90:250 ppm) were similar to the incidence in the controls. Consequently, the increased incidences in this single group were not considered to be related to chemical administration.

MICE

13-Week Studies

There were no clinical signs of chemical toxicity in the 13-week studies in mice. Six male and two female mice died before the end of the studies (Table 17). The causes of death were not determined, but they were not dose related and thus were not attributed to the administration of ETU. All surviving animals gained weight during the studies, and there was no obvious chemical effect on weight gain. The final mean body weights of the 1,000 ppm males and 2,000 ppm males and females were marginally decreased relative to controls. Feed consumption data were variable and were not corrected for spillage. Feed consumption by mice at the higher exposure concentrations was marginally less than that of controls.

Diffuse thyroid follicular cell hyperplasia occurred in nearly all male and female mice receiving dietary concentrations of 500 ppm or greater (Table 18). The severity increased from minimal to moderate in a dosed-related manner. Follicular cell hyperplasia was characterized by increased cellularity of the follicles and enlargement of the cells. The follicles were of varying diameter and the colloid had increased granularity and decreased eosinophilia relative to that of controls.

Centrilobular hepatocyte cytomegaly (hypertrophy) occurred in the liver of male and female mice receiving ETU concentrations of 500 ppm or greater. The hepatocytes surrounding the central venules were enlarged with homogeneously staining, finely granular, eosinophilic cytoplasm.

Gestational Study: Determination of Maximum Perinatal Dose

A total of 10 mouse dams of the 490 assigned to dose groups died before the end of the study. There were three each from the 33 and 330 ppm groups and two each from the control and 1,000 ppm dose groups. Selected dams from each dose group except the 1,000 ppm group were sacrificed at gestation day 17 and evaluated for chemical-related reproductive effects. No external gross fetal anomalies were observed, nor were there significant differences relative to controls in the number of implantations, numbers of live or dead fetuses, mean fetal weights, mean placental weights, or mean number of fetuses per litter (Appendix G, Table G3).

Survival of mouse pups to postnatal day 7 was not affected by exposure to ETU in the milk, but the number of pups surviving in the 1,000 ppm dose group at postnatal day 28 was significantly decreased (Table G4). The cause of the increased mortality was not determined, although cannibalization was not a primary factor. Four weanling mice died before the end of the studies, but the causes of death were not determined. Because of the relatively low number of deaths, it is uncertain whether they were related to ETU administration. Mean body weights of the exposed pups were slightly lower than those of controls, but the decrements were not dose related. Most dose groups had marginally decreased body weight gains relative to the controls (Table 19). Diffuse follicular cell hyperplasia of the thyroid gland and centrilobular hepatocellular cytomegaly occurred in mice receiving 1,000 ppm ETU (Table 20). The lesions were similar to those seen in exposed mice in the 13-week studies.

Dose Selection Rationale for the 2-Year Studies

In the 13-week studies there was no clear dose-related effect on weight gain or feed consumption. However, because of the severity of the thyroid and liver lesions at 2,000 ppm, 1,000 ppm was selected as the highest dose for the adult exposures. For the perinatal exposures, 330 ppm was selected as the highest dose because 1,000 ppm caused a decrease in the number of mouse pups surviving until postnatal day 28 and caused reduced final mean body weights in surviving weanling mice.

TABLE 17
Survival, Mean Body Weights, and Feed Consumption of Mice in the 13-Week Feed Studies of Ethylene Thiourea

Concentration (ppm)	Survival[a]	Mean Body Weights (g) Initial[b]	Final	Change[c]	Final Weight Relative to Controls (%)	Feed Consumption Week 1[d]	Week 13[d]	Mean[e]
Male								
0	7/10	24	34	+10	-	755	585	74
125	10/10	26	32	+ 6	94	700	864	77
250	9/10	25	33	+ 8	97	486	654	66
500	8/10	28	33	+ 5	97	570	471	61
1,000	10/10	27	31	+ 4	91	572	463	59
2,000	10/10	25	31	+ 6	91	602	508	66
Female								
0	10/10	19	25	+ 5	-	782	639	80
125	8/10	19	24	+ 5	96	720	649	88
250	10/10	19	24	+ 5	96	592	680	75
500	10/10	19	25	+ 6	100	629	578	79
1,000	10/10	19	24	+ 5	96	589	518	73
2,000	10/10	18	22	+ 4	88	526	550	67

[a] Number surviving/number initially in the group
[b] Initial group mean body weight. Subsequent calculations are based on animals surviving to the end of the studies.
[c] Mean body weight change of the survivors
[d] Mean consumption in grams/group per week
[e] Mean consumption in grams/animal per week

TABLE 18
Incidences of Selected Lesions in Mice in the 13-Week Feed Studies of Ethylene Thiourea[a]

	Concentration (ppm) 0	125	250	500	1,000	2,000
Male						
Thyroid Gland						
Diffuse Follicular Cell Hyperplasia	0	0	0	7**	10**	10**
Liver						
Hepatocellular Cytomegaly[b]	0	0	0	10**	10**	10**
Female						
Thyroid Gland						
Diffuse Follicular Cell Hyperplasia	1	0	0	8**	9**	10**
Liver						
Hepatocellular Cytomegaly[b]	0	0	0	4*	9**	9**

* Significantly different ($P \leq 0.05$) from the control group
** $P \leq 0.01$
[a] n=10
[b] Diagnosed as "cellular atypia" or "altered stain affinity" by the study pathologist

TABLE 19
Survival and Mean Body Weights of Weanling Mice in the Maximum Perinatal Dose Determination Feed Study of Ethylene Thiourea

Concentration (ppm)	Survival[a]	Mean Body Weights (grams) Initial[b]	Final	Change[c]	Final Weight Relative to Controls (%)
Male					
0	10/10	13	27	+14	-
33	10/10	12	24	+12	89
100	10/10	11	24	+13	89
330	8/10	10	23	+13	85
1,000	9/10	11	23	+12	85
Female					
0	10/10	12	22	+10	-
33	10/10	11	20	+ 9	91
100	10/10	10	20	+10	91
330	9/10	11	20	+ 9	91
1,000	10/10	11	19	+ 8	86

[a] Number surviving/number initially in the group
[b] Initial group mean body weight. Final mean body weights are based on number of animals surviving to the end of the studies.
[c] Mean body weight change of the survivors

TABLE 20
Incidences of Selected Lesions in Weanling Mice in the Maximum Perinatal Dose Determination Feed Study of Ethylene Thiourea[a]

	Concentration (ppm) 0	33	100	330	1,000
Male					
Thyroid Gland					
Diffuse Follicular Cell Hyperplasia	0	0	0	0	7**
Liver					
Centrilobular Cytomegaly	0	0	0	0	8**
Female					
Thyroid Gland					
Diffuse Follicular Cell Hyperplasia	0	0	0	0	7**
Liver					
Centrilobular Cytomegaly	0	0	0	0	7**

** Significantly different ($P \leq 0.01$) from the control group
a n=10

2-Year Studies

9-Month Interim Evaluations

In mice evaluated at 9 months, there were significant increases in absolute and relative liver weights in groups receiving adult exposure concentrations of 330 or 1,000 ppm ETU, regardless of perinatal exposure levels (Table 21). Absolute thyroid weights of mice were increased in the 0:1,000 ppm and 330:1,000 ppm dose groups.

Diffuse cytoplasmic vacuolization of the follicular epithelium occurred in the thyroid gland of mice receiving ETU, except those only exposed perinatally (Table 22). Generally, the severity was minimal or mild in the 0:330 ppm groups and mild or moderate in the others. Multifocal follicular cell hyperplasia was seen in two male mice receiving 0:1,000 ppm. T_3 levels were increased in males and females at the highest F_1 exposure level, whereas TSH levels were increased only in males (Appendix I, Tables I1 and I2).

Centrilobular hepatocellular cytomegaly similar to that noted in the short-term studies was observed in the livers of exposed mice. Eosinophilic foci of cellular alteration were observed in several female mice in the 1,000 ppm groups. The eosinophilic foci were characterized by the altered staining properties (increased eosinophilia) of the hepatocyte cytoplasm. Hepatocellular adenomas also occurred in several exposed mice. The adenomas compressed adjacent parenchyma and lacked well-organized cords. In males the adenomas generally were composed of small cells with basophilic cytoplasm, while those in females were composed of eosinophilic cells larger than normal hepatocytes.

TABLE 21
Liver Weights in Mice at the 9-Month Interim Evaluations in the 2-Year Feed Studies of Ethylene Thiourea[a]

F_0 Concentration (ppm)	F_1 Concentration (ppm) 0	330	1,000
Male			
0	1.86 ± 0.06[b]	2.00 ± 0.08	2.23 ± 0.06**
110	–[c]	2.14 ± 0.05**	–
330	1.93 ± 0.06	2.11 ± 0.05**	2.29 ± 0.08**▲▲
Female			
0	1.38 ± 0.03	1.72 ± 0.05**	1.95 ± 0.07**
110	–	1.82 ± 0.06**	–
330	1.34 ± 0.05	1.72 ± 0.09**▲▲	1.86 ± 0.05**▲▲

** Significantly different (P≤0.01) from the 0:0 ppm group by Fisher's least significant difference test
▲▲ Significantly different (P≤0.01) from the 330:0 ppm group by Fisher's least significant difference test
[a] Mean weight ± standard error (grams); n=10 unless otherwise specified.
[b] n=9
[c] Animals were not exposed at these concentrations.

TABLE 22
Incidences of Selected Lesions in Mice at the 9-Month Interim Evaluations in the 2-Year Feed Studies of Ethylene Thiourea[a]

	Male			Female		
	F_1 Concentration (ppm)			F_1 Concentration (ppm)		
F_0 Concentration (ppm)	0	330	1,000	0	330	1,000
Thyroid Gland						
Follicular Cell Vacuolization						
0	0	10**	10**	0	10**	10**
110	–[b]	9**	–	–	9**	–
330	0	10**	10**	0	10**	10**
Follicular Cell Hyperplasia						
0	0	0	2	0	0	0
110	–	0	–	–	0	–
330	0	0	0	0	0	0
Liver						
Hepatocellular Adenoma						
0	0	0	2	0	0	2
110	–	0	–	–	–	–
330	1	0	1	–	–	1
Centrilobular Cytomegaly						
0	0	0	10**	0	0	10**
110	–	8**	–	–	–	–
330	0	5*	10**	–	–	9**
Eosinophilic Focus						
0	0	0	0	0	0	4*
110	–	0	–	–	–	–
330	0	0	0	–	–	5*

* Significantly different ($P \leq 0.05$) from the 0:0 ppm group
** $P \leq 0.01$
[a] Diagnoses represent the consensus of the study pathologist, quality assessment pathologist, and PWG Chair; n=10 for all groups.
[b] No animals exposed at these concentrations or livers not examined at these concentrations

Body Weights and Survival in the 2-Year Studies

There were no clinical findings observed in mice that could be attributed to hypothyroidism or other toxicity. There were no differences in feed consumption between exposed groups of mice and the controls (0:0 ppm) throughout the studies. Final mean body weights of groups of mice receiving ETU postnatally, regardless of the level of perinatal exposure, were 6% to 15% lower than the 0:0 ppm controls for males and 18% to 30% lower for females. Comparison of groups receiving perinatal and adult exposure with those receiving adult-only exposure showed no effect of the perinatal exposure. Mice receiving perinatal but not adult exposure (330:0 ppm) did not have significantly decreased body weights (Table 23 and Figure 3). Estimates of the probabilities of survival for male and female mice fed diets containing ETU at the concentrations used in these studies and for controls are shown in Table 24 and in the Kaplan and Meier curves in Figure 4. Survival of mice receiving ETU was similar to that of the controls.

TABLE 23
Final Mean Body Weights of Mice at 105 Weeks in the 2-Year Feed Studies of Ethylene Thiourea

F_0:F_1 Concentration (ppm)	Male			Female		
	Number	Mean[a]	Ratio[b]	Number	Mean[a]	Ratio[b]
0:0	31	36.0 ± 0.65	-	35	40.5 ± 0.57	-
0:330	34	33.9 ± 0.31**	94	43	33.1 ± 0.27**	82
0:1,000	23	31.0 ± 0.23**	86	31	32.0 ± 0.23**	79
30:100	26	34.2 ± 0.43**	95	21	32.8 ± 0.41**	81
110:330	32	34.2 ± 0.34**	95	36	32.7 ± 0.25**	81
330:0	28	35.8 ± 0.47	99	39	40.7 ± 0.64	101
330:330	32	33.9 ± 0.19**	94	40	32.7 ± 0.36**	81
330:1,000	26	30.4 ± 0.47**	85	30	28.5 ± 0.27**	70

** Significantly different ($P \leq 0.01$) from the 0:0 ppm group by Fisher's least significant difference test
[a] Mean ± standard error in grams
[b] Percent final weight relative to the 0:0 ppm group

TABLE 24
Survival of Mice in the 2-Year Feed Studies of Ethylene Thiourea

	F_0:F_1 Concentration (ppm)							
	0:0	330:0	33:100	0:330	110:330	330:330	0:1,000	330:1,000
Male[a]								
Animals in study	50	50	34	50	50	50	50	50
Moribund sacrifice	8	7	5	8	10	6	14	10
Natural death	12	10	3	11	8	13	14	16
Terminal sacrifice	30	27	25	31	32	30	22	24
Missing		1	1			1		
Accidental deaths		5						
Survival analysis[b]		P=0.887	P=0.148	P=0.726	P=0.894	P=0.757	P=0.353	P=0.553
Female[a]								
Animals in study	50	50	29	50	50	50	50	50
Moribund sacrifice	9	4	6	6	11	10	10	14
Natural death	7	9	2	2	5	4	10	7
Terminal sacrifice	34	37	21	42	34	36	30	29
Survival analysis[b]		P=0.622	P=1.000	P=0.087	P=0.904	P=0.849	P=0.566	P=0.327

[a] Day of first terminal sacrifice: 742 for males and 740 for females
[b] Results of the life table pairwise comparison with the 0:0 ppm group

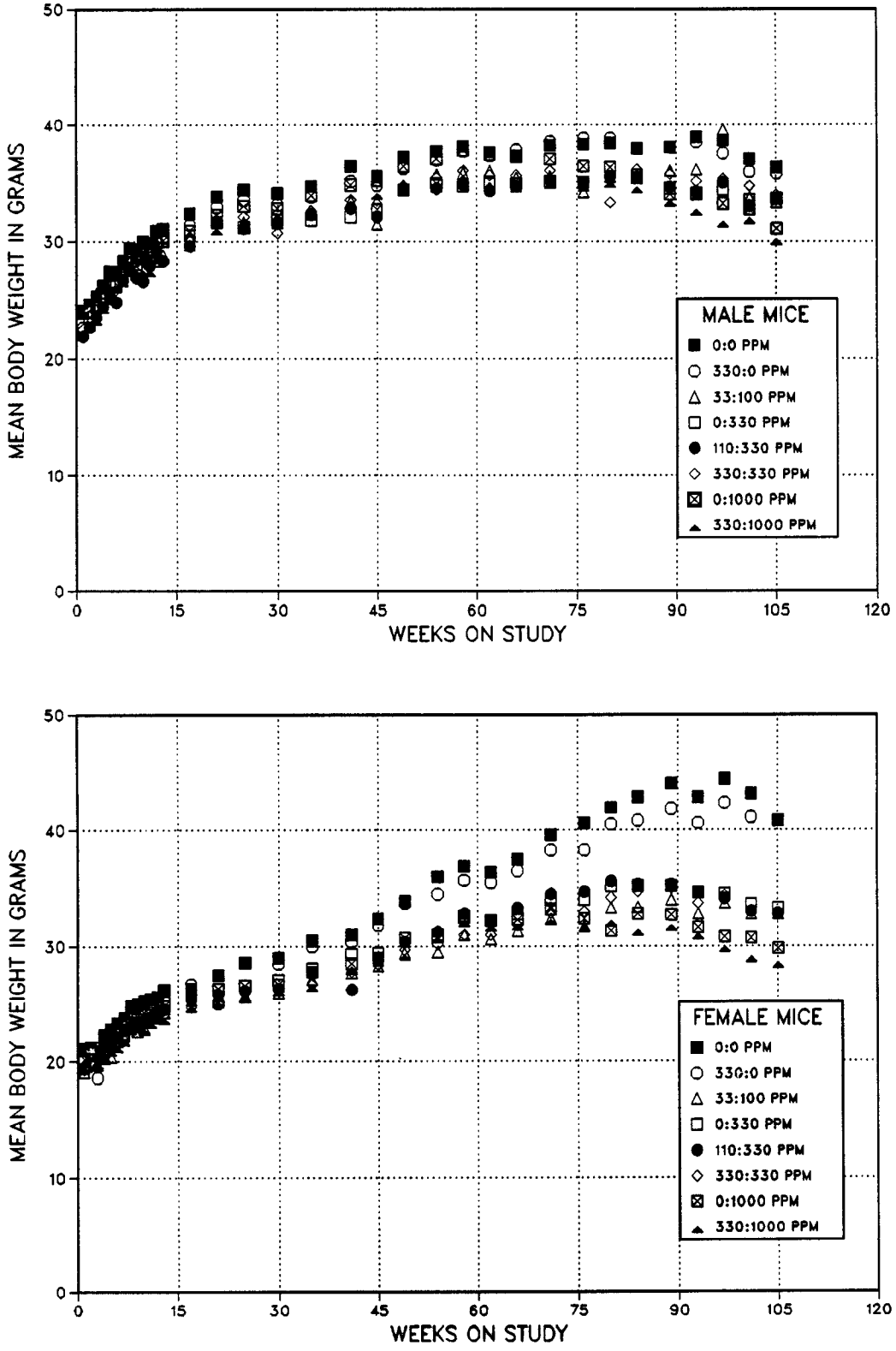
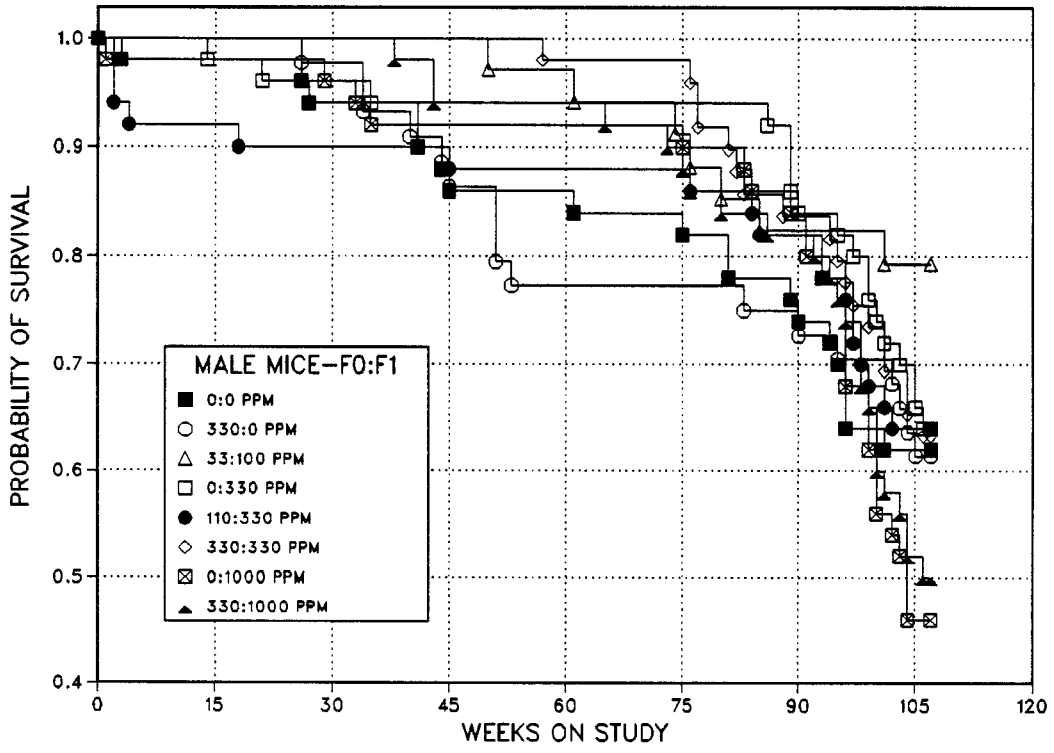


FIGURE 3
Growth Curves for Male and Female Mice Administered Ethylene Thiourea in Feed for 2 Years



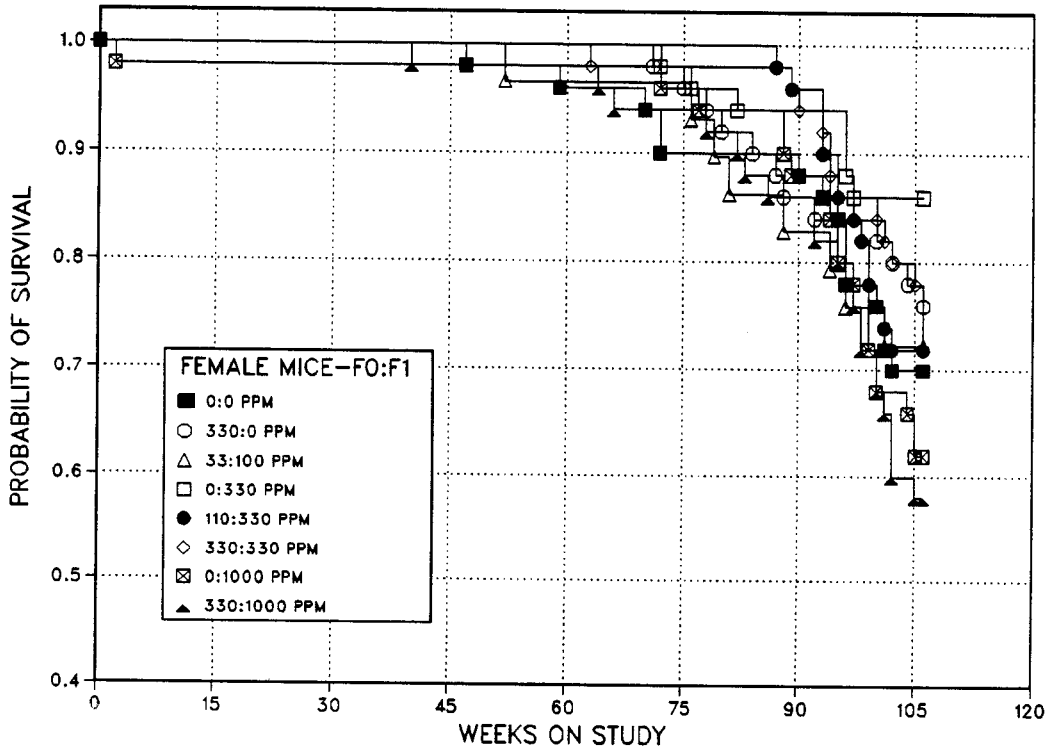


FIGURE 4
Kaplan-Meier Survival Curves for Male and Female Mice Administered Ethylene Thiourea in Feed for 2 Years

Pathology and Statistical Analysis of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the thyroid gland, liver, pituitary gland, and lung. Details are presented in Appendix D (males) and Appendix E (females).

The incidences of neoplasms in mice are summarized in Tables D1 and E1. The statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one exposure group are presented in Tables D2 through D6 and E2 through E6. The statistical analyses used are discussed in Appendix A (Materials and Methods). Historical incidences of selected neoplastic lesions are summarized in Tables D7 and E7. Incidences of nonneoplastic lesions are summarized in Tables D8 and E8.

Effects of Adult-Only Exposure to Ethylene Thiourea

Thyroid Gland: Effects of adult-only exposure to ETU were determined by comparison of the incidences of mice with neoplasms or nonneoplastic lesions in the 0:0, 0:330, and 0:1,000 ppm groups. Administration of dietary concentrations of 330 and 1,000 ppm ETU to F_1 mice was associated with diffuse cytoplasmic vacuolization of the follicular epithelium, diffuse and focal hyperplasia, and neoplasia (Table 25). The cytoplasmic vacuolization was characterized by the accumulation of many small clear vacuoles in the follicular epithelium throughout the gland, and nearly all exposed mice were affected. Diffuse and/or focal follicular cell hyperplasia also occurred in most male and female mice receiving 1,000 ppm ETU, but was significantly increased relative to controls only in females receiving 330 ppm. Approximately 70% of mice receiving 1,000 ppm ETU had follicular cell adenomas or carcinomas; most affected mice had multiple or bilateral neoplasms. Follicular cell carcinomas were significantly increased only in female mice receiving 1,000 ppm ETU, although there was also a significant positive trend in males. Females were more susceptible than males to the effects of ETU on the thyroid gland since hyperplasia occurred at a lower exposure concentration and the incidence of follicular cell neoplasms at the highest concentration was increased in female mice. The follicular lesions were similar to those described for rats.

Liver: Diffuse centrilobular hepatocellular cytomegaly (hypertrophy or enlargement of hepatocytes surrounding the central venules of each lobule) was observed in the liver of male mice receiving F_1 concentrations of 330 or 1,000 ppm and in some females receiving 330 ppm (Table 26). The incidence of male mice with hepatocellular carcinomas was significantly increased at 1,000 ppm; the incidence of benign and malignant hepatocellular neoplasms combined was slightly but significantly increased at 330 ppm. In contrast, the incidences of hepatocellular adenomas, hepatocellular carcinomas, and adenomas or carcinomas (combined) were markedly increased in female mice receiving 330 or 1,000 ppm. Multiple hepatocellular neoplasms occurred in many of the exposed mice, and many of the carcinomas metastasized to the lung. Rare hepatoblastomas also occurred in exposed mice, particularly males. Hepatoblastomas were anaplastic hepatocellular neoplasms usually occurring as part of or associated with hepatocellular carcinomas.

Pituitary Gland: The incidences of male mice with focal hyperplasia or adenoma of the pars distalis were significantly increased in the 1,000 ppm group (Table 27). In female mice, the incidence of adenoma, but not the incidence of hyperplasia, was significantly increased at this exposure concentration as well. Focal hyperplasia and adenoma are part of a morphologic continuum. Hyperplasia was characterized by a focal increase in cells of similar cytologic features. Generally, other cell types were interspersed within foci of hyperplasia and the lesion blended with the surrounding parenchyma. Lesions that were well delineated, monomorphic, and showed some compression of the surrounding parenchyma were diagnosed as adenomas. The carcinoma that occurred in a female in the 0:0 ppm group was characterized by large size and cellular pleomorphism.

Effects of Perinatal-Only Exposure of Mice to Ethylene Thiourea

The effects of perinatal-only exposure were determined by comparison of the incidences of mice with neoplasms and nonneoplastic lesions in the 0:0 and 0:330 ppm groups (Tables D3 and D8 and Tables E3 and E8). The incidences of neoplasms or nonneoplastic lesions in the thyroid gland, liver, pituitary gland, and all other organs in the 0:330 ppm groups were not significantly increased relative to the 0:0 ppm controls. Thus, perinatal-only exposure to ETU had no effect on mice.

TABLE 25
Incidences of Selected Follicular Cell Lesions of the Thyroid Gland in Mice in the 2-Year Feed Studies of Ethylene Thiourea: Comparison of the 0:0, 0:330, and 0:1,000 ppm Groups[a]

	Male F_0:F_1 Concentration (ppm)			Female F_0:F_1 Concentration (ppm)		
	0:0	0:330	0:1,000	0:0	0:330	0:1,000
Cytoplasmic Vacuolization	0/50**	46/49** (2.7[b])	47/50** (3.2)	3/50** (2.0)	49/50** (2.8)	47/50** (2.7)
Hyperplasia	0/50**	0/49	44/50** (2.5)	2/50** (2.5)	13/50** (2.1)	46/50** (2.8)
Adenoma	0/50**	1/49	26/50**	0/50**	2/50	35/50**
Carcinoma	1/50*	0/49	5/50	0/50**	0/50	8/50**
Adenoma or Carcinoma	1/50**	1/49	29/50**	0/50**	2/50	38/50**

* Significant (P≤0.05) by the logistic regression tests
** P≤0.01
[a] Number of lesions observed/number of animals with thyroid examined microscopically; indications of statistical significance appearing adjacent to the incidences in the 0:0 ppm column represent the trend test, whereas those adjacent to the incidences in other columns represent pairwise comparisons vs the 0:0 ppm group.
[b] Mean severity grade (minimal=1, mild=2, moderate=3, marked=4)

TABLE 26
Incidences of Selected Hepatocellular Lesions in Mice in the 2-Year Feed Studies of Ethylene Thiourea: Comparison of the 0:0, 0:330, and 0:1,000 ppm Groups[a]

	Male F_0:F_1 Concentration (ppm)			Female F_0:F_1 Concentration (ppm)		
	0:0	0:330	0:1,000	0:0	0:330	0:1,000
Centrilobular Cytomegaly	0/49**	36/50**	25/50**	0/50	11/50**	0/50
Hepatocellular Adenoma	11/49	16/50	9/50	2/50**	33/50**	14/50**
Hepatocellular Carcinoma	13/49**	19/50	45/50**	2/50**	29/50**	47/50**
Adenoma or Carcinoma	20/49**	32/50*	46/50**	4/50**	44/50**	48/50**
Hepatoblastoma	0/49**	1/50	6/50*	0/50	0/50	2/50

* Significant (P≤0.05) by the logistic regression tests
** P≤0.01
[a] Number of lesions observed/number of animals with liver examined microscopically; indications of statistical significance appearing adjacent to the incidences in the 0:0 ppm column represent the trend test, whereas those adjacent to the incidences in other columns represent pairwise comparisons vs the 0:0 ppm group.

TABLE 27
Incidences of Lesions of the Pituitary Gland Pars Distalis in Mice in the 2-Year Feed Studies of Ethylene Thiourea: Comparison of the 0:0, 0:330, and 0:1,000 ppm Groups[a]

	Male F_0:F_1 Concentration (ppm)			Female F_0:F_1 Concentration (ppm)		
	0:0	0:330	0:1,000	0:0	0:330	0:1,000
Focal Hyperplasia	0/44**	2/42	32/41**	19/47	22/49	27/49
Adenoma	0/44**	0/42	8/41**	10/47**	19/49	26/49**
Carcinoma	0/44	0/42	0/41	1/47	0/49	0/49

** Significant (P≤0.01) by the logistic regression tests
a Number of lesions observed/number of animals with pituitary examined microscopically; indications of statistical significance appearing adjacent to the incidences in the 0:0 ppm column represent the trend test, whereas those adjacent to the incidences in other columns represent pairwise comparisons vs the 0:0 ppm group.

Effects of Combined Perinatal and Adult Exposure of Mice to Ethylene Thiourea

Thyroid Gland, Liver, and Pituitary Gland: Combined perinatal exposure of 330 ppm ETU with adult exposure of 330 or 1,000 ppm was associated with increased incidences of nonneoplastic lesions and/or neoplasms in the thyroid gland, liver, and pituitary gland relative to the 0:0 ppm group, similar to those of adult-only exposure. Comparison of groups with varying F_0 concentrations and constant adult F_1 exposure of 330 ppm ETU showed marginally increased incidences of follicular cell hyperplasia in males (Table 28). It is uncertain if these slight increases are biologically significant. There was also an increase relative to the 0:330 ppm group in follicular cell adenomas in females receiving 330:330 ppm. Comparison of groups with varying F_0 exposure and constant F_1 exposure of 1,000 ppm showed no significant effects on the thyroid gland due to perinatal exposure (Table 29). Similar comparisons of the incidences of mice with lesions in the liver or pituitary gland also showed no effects of perinatal exposure (Tables 30-33).

TABLE 28
Incidences of Follicular Cell Lesions of the Thyroid Gland in Mice in the 2-Year Feed Studies of Ethylene Thiourea: Comparison of the 0:330, 110:330, and 330:330 ppm Groups[a]

	Male F_0:F_1 Concentration (ppm)			Female F_0:F_1 Concentration (ppm)		
	0:330	110:330	330:330	0:330	110:330	330:330
Hyperplasia	0/49**	3/47 (2.3[b])	7/48** (2.0)	13/50 (2.1)	17/50 (2.0)	22/49 (2.2)
Adenoma	1/49	1/47	2/48	2/50**	5/50	10/49*
Carcinoma	0/49	0/47	0/48	0/50	0/50	1/49
Adenoma or Carcinoma	1/49	1/47	2/48	2/50**	5/50	10/49*

* Significant (P≤0.05) by the logistic regression tests
** P≤0.01
a Number of lesions observed/number of animals with thyroid gland examined microscopically; indications of statistical significance appearing adjacent to the incidences in the 0:330 ppm column represent the trend test, whereas those adjacent to the incidences in other columns represent pairwise comparisons vs the 0:330 ppm group.
b Mean severity grade of hyperplasia (minimal=1, mild=2, moderate=3, marked=4)

TABLE 29
Incidences of Follicular Cell Lesions of the Thyroid Gland in Mice in the 2-Year Feed Studies of Ethylene Thiourea: Comparison of the 0:1,000 and 330:1,000 ppm Groups[a]

	Male F_0:F_1 Concentration (ppm)		Female F_0:F_1 Concentration (ppm)	
	0:1,000	330:1,000	0:1,000	330:1,000
Hyperplasia	44/50 (2.5[b])	47/49 (2.8)	46/50 (2.8)	46/50 (2.9)
Adenoma	26/50	33/49	35/50	38/50
Carcinoma	5/50	9/49	8/50	4/50
Adenoma or Carcinoma	29/50	35/49	38/50	38/50

[a] Number of lesions observed/number of animals with thyroid gland examined microscopically
[b] Mean severity grade of hyperplasia (minimal=1, mild=2, moderate=3, marked=4); no statistically significant differences were observed.

TABLE 30
Incidences of Hepatocellular Neoplasms in Mice in the 2-Year Feed Studies of Ethylene Thiourea: Comparison of the 0:330, 110:330, and 330:330 ppm Groups[a]

	Male F_0:F_1 Concentration (ppm)			Female F_0:F_1 Concentration (ppm)		
	0:330	110:330	330:330	0:330	110:330	330:330
Adenoma	16/50	15/47	20/49	33/50	34/50	35/50
Carcinoma	19/50	15/47	19/49	29/50	31/50	23/50
Adenoma or Carcinoma	32/50	26/47	34/49	44/50	46/50	46/50

[a] Number of lesions observed/number of animals with liver examined microscopically; no statistically significant differences were observed.

TABLE 31
Incidences of Hepatocellular Neoplasms in Mice in the 2-Year Feed Studies of Ethylene Thiourea: Comparison of the 0:1,000 ppm and 330:1,000 ppm Groups[a]

	Male F_0:F_1 Concentration (ppm)		Female F_0:F_1 Concentration (ppm)	
	0:1,000	330:1,000	0:1,000	330:1,000
Adenoma	9/50	15/49	14/50	17/50
Carcinoma	45/50	45/49	47/50	48/50
Adenoma or Carcinoma	46/50	47/49	48/50	49/50

[a] Number of lesions observed/number of animals with liver examined microscopically; no statistically significant differences were observed.

TABLE 32
Selected Lesions of the Pituitary Gland Pars Distalis in Mice in the 2-Year Feed Studies of Ethylene Thiourea: Comparison of the 0:330, 110:330, and 330:330 ppm Groups[a]

	Male F_0:F_1 Concentration (ppm)			Female F_0:F_1 Concentration (ppm)		
	0:330	110:330	330:330	0:330	110:330	330:330
Hyperplasia	2/42	2/41	1/45	22/49	23/48	18/47
Adenoma	0/42	0/41	0/45	19/49	14/48	26/47

[a] Number of lesions observed/number of animals with pituitary gland examined microscopically; no statistically significant differences were observed.

TABLE 33
Selected Lesions of the Pituitary Gland Pars Distalis in Mice in the 2-Year Feed Studies of Ethylene Thiourea: Comparison of the 0:1,000 and 330:1,000 ppm Groups[a]

	Male F_0:F_1 Concentration (ppm)		Female F_0:F_1 Concentration (ppm)	
	0:1,000	330:1,000	0:1,000	330:1,000
Hyperplasia	32/41	25/39	27/49	28/47
Adenoma	8/41	4/39	26/49	24/47

[a] Number of lesions observed/number of animals with pituitary gland examined microscopically; no statistically significant differences were observed.

Lung: The combined incidences of alveolar/bronchiolar adenoma or carcinoma were marginally increased relative to the controls in the 33:100, 110:330, and 330:330 ppm groups of male mice (Table 34). The incidences of lung neoplasms did not increase in a dose-related manner and all fell within the range for historical untreated control male mice from NTP 2-year studies (277/1,684 or 16%, range 4/50-17/50). The marginal increase in lung neoplasms in male mice was not considered to be related to chemical administration.

TABLE 34
Incidences of Alveolar/bronchiolar Neoplasms in Male Mice in the 2-Year Feed Study of Ethylene Thiourea[a]

	F_1 Concentration (ppm)			
F_0 Concentration (ppm)	0	100	330	1,000
Adenoma				
0	4/50	–[b]	6/50	6/50
33	–	10/33*	–	–
110	–	–	12/47*	–
330	7/49	–	11/49	6/49
Carcinoma				
0	1/50	–	1/50	2/50
33	–	1/33	–	–
110	–	–	1/47	–
330	0/49	–	7/49*▲▼	0/49
Adenoma or Carcinoma				
0	5/50	–	6/50	8/50
33	–	11/33*	–	–
110	–	–	12/47	–
330	7/49	–	17/49**▼▼	6/49

* Significantly different (P≤0.05) from the 0:0 ppm group by the logistic regression tests
** Significantly different (P≤0.01) from the 0:0 ppm group by the logistic regression tests
▲ Significantly different (P≤0.05) from the 330:0 ppm group by the logistic regression tests
▼ Significantly different (P≤0.05) from the 0:330 ppm group by the logistic regression tests
▼▼ Significantly different (P≤0.01) from the 0:330 ppm group by the logistic regression tests
[a] Number of mice with lesions/number of animals examined microscopically
[b] Animals were not exposed at these concentrations.

DISCUSSION AND CONCLUSIONS

One of the principal objectives of these studies was to investigate the potential value of perinatal (prenatal and neonatal periods) exposure in assessing chemical carcinogenicity. ETU was chosen by the NTP as one of three chemicals for perinatal studies because a) it is known to be a carcinogen in rodents at concentrations that are not teratogenic, b) it is an example of a carcinogen generally believed to be nongenotoxic, and c) it readily crosses the placenta and is secreted into the milk. Results of studies conducted by the NTP of two other chemicals, diphenylhydantoin and polybrominated biphenyls, will be published in subsequent Technical Reports.

Thirteen-week and gestational exposure studies were conducted to determine the dietary concentrations for the 2-year studies. ETU is teratogenic in rats, inducing skeletal and brain abnormalities when given at daily doses as low as 10 mg/kg, but not in mice (Khera, 1973; Chernoff *et al.*, 1979). Because of these teratogenic effects in rats, dietary concentrations selected for the maximum perinatal exposure determination study were considerably lower than those selected for mice. F344/N rat and C57BL/6 mouse dams were exposed to the highest perinatal dose or fractions thereof for one week prior to breeding and throughout gestation and lactation until the F_1 litters were weaned on postnatal day 28. The pups were exposed to perinatal dose levels for an additional 4 weeks postweaning and then administered the highest adult dose or fractions thereof for 2 years.

EFFECTS OF PERINATAL EXPOSURE

Perinatal exposure alone had no effect on body weights or survival of rats or mice. However, the final mean body weight of male rats receiving 90:250 ppm ETU was 18% lower than that of males in the 0:250 ppm group. Furthermore, survival of rats, particularly males, was decreased in the 90:250 ppm group relative to that of rats receiving adult-only exposure (0:250 ppm). Thus, perinatal exposure to dietary concentrations of 90 ppm appeared to enhance the toxicity of ETU in rats receiving 250 ppm in the diet as adults. There was no evidence of perinatal effects on body weight or survival of mice receiving adult exposure in the 2-year studies.

Perinatal-only exposure to ETU had no effect on the incidences of rats or mice with neoplasms after 2 years. These findings suggest that the few follicular cell adenomas found in the 8-week-old male rats receiving 83 or 250 ppm ETU in the maximum perinatal dose determination study were likely hormone dependent and not autonomous. For male and female rats fed dietary concentrations of 250 ppm ETU, perinatal exposure to 90 ppm increased the incidence of thyroid follicular cell neoplasms when compared with rats not receiving perinatal exposure (e.g., the 0:250 ppm group). However, no increase in the incidence of thyroid neoplasms relative to the 0:83 ppm group was observed in rats receiving 83 ppm as adults and 90 ppm perinatally. For mice receiving adult exposure of 330 ppm ETU, perinatal exposure to 330 ppm increased the incidence of follicular cell adenomas in females and hyperplasia in males. A similar enhancing effect could not be discerned in mice receiving adult exposure of 1,000 ppm and perinatal exposure of 330 ppm because nearly all mice in the 0:1,000 ppm group had follicular cell neoplasms. Thus perinatal exposure slightly enhanced the proliferative response of the follicular epithelium to ETU administered in the diet for 2 years. It is unknown if the increased incidences associated with perinatal exposure are the result of the longer exposure period or if it reflects a greater sensitivity of the developing thyroid gland to ETU. There was no evidence of perinatal effects on any other organs in rats or mice.

The reasons for the weak enhancing effects of perinatal exposure on the carcinogenic activity of ETU are unknown. Although at least 38 chemicals have been shown to induce neoplasms in experimental animals following *in utero* exposure, the neonatal period (up to approximately 3 weeks of age in mice) has been shown to be the most susceptible period for the carcinogenicity of a variety of agents (Vesselinovitch *et al.*, 1979). The transplacental

effect of chemicals depends on many factors, including strain and sex of the species studied, precise time of *in utero* exposure, mutagenicity or genotoxicity of the chemical, and whether the chemical requires metabolic activation or is direct acting (Alexandrov, 1983; Rice *et al.*, 1989).

Direct-acting alkylating agents are the most potent of the known transplacental carcinogens, perhaps because of their independence from enzyme-mediated metabolism and activation. In general, sensitivity to chemical-induced neoplasia starts in the second half of pregnancy, and tumors appear in offspring with a somewhat shorter latency and higher incidence compared to those induced in adults (Tomatis, 1979). The high rate of cell proliferation and high ratio of differentiating cells in the fetus appear to be major factors in the greater susceptibility of the fetus and neonate in comparison to the adult.

Toxicity of Ethylene Thiourea

The thyroid gland and liver are the major organs in the adult rat affected by ETU (Graham *et al.*, 1973; Gak *et al.*, 1976; Ugazio *et al.*, 1985; Moller *et al.*, 1986); this chemical has not been as thoroughly studied in mice. ETU is a structural analog of compounds (thionamides) that act by inhibiting the synthesis of thyroxine (Davidson *et al.*, 1978; Engler *et al.*, 1982). It has been shown to affect the uptake of iodine by the thyroid gland, reduce serum levels of triiodothyronine (T_3) and thyroxine (T_4), and increase production of thyroid-stimulating hormone (TSH) by the pituitary gland (Frudenthal *et al.*, 1977). With repeated or continuous dietary exposure, ETU causes an increase in thyroid weight, hyperplasia of the follicular epithelium, and eventually thyroid neoplasms.

The current studies in F344/N rats and B6C3F_1 mice confirm these findings. In the 13-week studies, thyroid follicular cell hyperplasia was seen in rats at all exposure concentrations and adenomas were seen at concentrations of 250 ppm (males) or 500 ppm (females) and higher. The cytoplasmic vacuolization of cells in the pars distalis of the pituitary gland is consistent with the known physiological effects of ETU on the gland. The vacuolated cells are likely those stimulated to produce TSH as a result of interference in the feedback mechanisms regulating its production. Follicular cell hyperplasia was seen in mice receiving concentrations of 500 ppm or higher, but no adenomas were observed in mice exposed for 13 weeks, consistent with the known greater sensitivity of the rat thyroid gland to ETU.

In the studies reported here, serum T_3, T_4, and TSH levels were determined in rats and mice after 9 and 24 months of ETU administration. Alterations included an F_1 dose-related decrease in T_4 and an increase in TSH concentrations in both sexes of rats and mice. The changes observed for perinatal plus adult exposure and for adult-only exposure were similar for both species, with the females being slightly more sensitive than the males. Rarely, the analysis of some samples within a sex and time point produced results that are not consistent with the predominant chemical effect (examples include decreases in T_3 concentrations at middle doses and not at the highest dose and increases in T_3 concentrations relative to those of control animals). These sporadic variations are thought to result from the complexity of the study design, which required that sample collection or analysis be performed on different days or at different times of the day. Even with these constraints, however, the detection of this important chemical-related effect was not compromised.

Centrilobular hepatocellular cytomegaly (hypertrophy) was seen in rats receiving 750 ppm and in mice receiving 500 ppm or higher in the 13-week studies. This change is commonly associated with microsomal enzyme induction (increases in xenobiotic metabolizing enzymes) and increased amounts of hepatic smooth endoplasmic reticulum. Although measurements of microsomal enzymes or ultrastructural examination of the liver were not performed in these studies, Lewerenz and Plass (1984) reported an increase in hepatic cytochrome P_{450} in mice given ETU. Histologic evidence of liver toxicity was not observed in the gestational and perinatal dose determination studies in rats primarily because the exposure concentrations were lower than those used in the 13-week studies.

Carcinogenicity of ETU

Several studies have shown that the prolonged administration of ETU to rats causes thyroid neoplasms (Ulland *et al.*, 1972; Graham *et al.*, 1973; Gak *et al.*, 1976; and Weisburger *et al.*, 1981). Graham *et al.* (1973) reported the development of thyroid neoplasms in Charles River rats receiving dietary concentrations of 125 ppm or higher.

Thyroid hyperplasia was not reversible in rats that received control diet after 66 weeks of dietary ETU exposure. Innes *et al.* (1969) reported the induction of liver neoplasms in mice exposed to dietary concentrations of 646 ppm ETU for 18 months, but apparently the thyroid glands of mice were not examined in that study.

The perinatal and adult exposure studies of ETU reported here confirm the induction of thyroid neoplasms in rats and identify similar thyroid effects in mice. ETU was carcinogenic in both male and female rats receiving dietary concentrations of 83 or 250 ppm, regardless of the level of perinatal exposure. Males were more sensitive than females, as demonstrated by higher incidences of follicular cell neoplasms (adenoma or adenocarcinoma combined) at 83 ppm and follicular cell adenocarcinomas at 250 ppm. A sex difference in sensitivity was also reported in previous studies.

There are no reports in the literature on the induction of thyroid neoplasms in mice by ETU. This study shows that the thyroid gland is one of the major target sites for ETU in mice, as it is in rats. However, mice are less sensitive to the thyroid effects of ETU; concentrations required to induce follicular cell neoplasms in mice were about two to four times those for rats. This species difference may be partially explained by qualitative and quantitative differences in the metabolism of ETU in rats and mice. Ruddick *et al.* (1977) reported that mice and rats metabolize ETU by different pathways and the rate of ETU metabolism is higher in mice than in rats.

There is a considerable body of evidence to support the role of hypothyroidism and prolonged elevation of blood TSH levels in the development of thyroid neoplasms (McClain *et al.*, 1988, 1989; Capen and Martin, 1989; Hill *et al.*, 1989). Conditions inducing hypothyroidism and associated with the development of thyroid neoplasms include iodine deficiency (Bielschowsky, 1955; Schaller and Stevenson, 1966) and subtotal thyroidectomy (Dent *et al.*, 1956). Also, transplantation of TSH-secreting pituitary tumors cause the development of thyroid neoplasms (Dent *et al.*, 1956; Sinha *et al.*, 1965). The factor common to these conditions is the increased production of TSH and prolonged stimulation of the thyroid gland by this hormone. Hypothyroidism characterized by a reduction in circulating levels of T_4 and T_3 and elevated levels of TSH also occurs following the administration of several groups of natural and synthetic compounds loosely designated as "goitrogens." ETU is a representative of one group of structurally related compounds generally referred to as thionamides, which have been shown to inhibit synthesis of thyroid hormones and to produce thyroid neoplasms. It has been shown that thyroid follicular cell hyperplasia and neoplasia caused by several of these compounds can be prevented by the concurrent administration of exogenous thyroid hormone, which reestablishes normal pituitary function, or by hypophysectomy (Yamada and Lewis, 1968; Jemec, 1980). Overall, the results of thyroid hormone assays in the studies of ETU reported here are consistent with primary hypothyroidism related to F_1 exposure. This possible nongenetic mechanism of thyroid carcinogenicity is further supported by the fact that ETU has not been positive in most of the microbial and mammalian mutagenesis tests (Appendix J).

Follicular cell adenomas were identified in the thyroid gland of rats in the 13-week and perinatal dose determination studies, but not in mice. Although the adenomas seen in these short-term studies had morphologic features consistent with this diagnosis, it is unknown if they had autonomous growth. Similar focal thyroid lesions induced in rats by the administration of methimazole for 6 months were reversible following removal of the compound (Todd, 1986). In general, thyroid neoplasms induced in animals by excessive TSH stimulation are hormone-dependent (Doniach, 1970). At some undefined point, some of the neoplasms lose that dependency and become autonomous. There was no significant increase in the number of rats with follicular cell adenomas in groups exposed to 250 ppm ETU in the 13-week studies (males, 3/10; females, 0/10) and the 9-month interim evaluations (90:250 ppm groups: males, 3/10; females, 1/10). However, by the end of the 2-year studies, nearly all male rats (96%) and most female rats (74%) in the 90:250 ppm dose groups and most mice (males, 71%; females, 76%) in the 330:1,000 ppm groups had thyroid follicular cell neoplasms. Further, over half the animals had bilateral or multiple neoplasms. Many were malignant, and some metastasized to the lung or other tissues.

These observations are consistent with those in the literature concerning the progression of thyroid changes in response to prolonged elevated levels of TSH. Following initiation of TSH stimulation, the

thyroid gland exhibits an initial lag phase of several days followed by a period of rapid growth and later a period of declining growth rate as a plateau is reached (Hill *et al.*, 1989). The phase of rapid growth is accompanied by an increase in mitotic activity of the follicular cells and the number of follicular cells per gland. However, even with sustained increases in TSH and stimulation of the thyroid gland, the mitotic activity declines and thyroid size and weight reach a plateau (Wynford-Thomas *et al.*, 1982a,b). Despite this plateau, with continued stimulation further morphological changes occur in the thyroid with the formation of follicular cell adenomas and carcinomas.

The current study confirms the report by Innes *et al.* (1969) that ETU is a hepatocarcinogen in mice. At the highest F_1 exposure concentration (1,000 ppm), nearly all male and female mice had multiple hepatocellular carcinomas. At the next lower concentration (330 ppm), nearly all female mice had carcinomas; 75% of the males had carcinomas. Further, hepatoblastomas (phenotypic variants of carcinoma) were seen in mice exposed to these concentrations. There was no effect of perinatal exposure on liver tumor incidences. Two other thionamides, 2-thiouracil and 6-methyluracil, also produced thyroid neoplasms in rats and mice and liver neoplasms in mice (IARC, 1974). The mechanisms by which ETU and other nongenotoxic (*in vitro*) chemicals cause liver neoplasms in mice is not known.

The incidence of adenomas of the pars distalis of the pituitary gland was significantly increased in female mice receiving an adult exposure concentration of 1,000 ppm; in males, the incidence was significantly increased at 0:1,000 ppm but not 330:1,000 ppm. These increases are considered chemical related and are consistent with the pathophysiology of toxicity associated with the administration of "antithyroid" compounds. Secretion of TSH from cells in the pars distalis is regulated by the amount of TSH-releasing hormone from the hypothalamus and by circulating levels of T_3 and T_4. Diminished circulating levels of T_3 and/or T_4 cause an increase in the secretion of TSH and proliferation of TSH-producing cells (Furth *et al.*, 1973). The reason that mice, but not rats, are affected in these studies is unknown.

In addition to the chemical-related increases in the incidences of thyroid neoplasms in rats, there were slight increases in the incidences of Zymbal's gland neoplasms and mononuclear cell leukemia in male and female rats and kidney neoplasms in male rats. Zymbal's gland neoplasms are uncommon in NTP untreated historical controls, and the incidences of five males and four females with this neoplasm in the 90:250 ppm groups exceed the highest incidence reported in a single group of historical controls (males, 4/50; females, 3/50). In male rats, there were marginally increased incidences of mononuclear cell leukemia in the 90:83 and 90:250 ppm exposure groups, but there was no clear dose-related pattern. There was also a marginal increase in the incidence of this neoplasm in females receiving 90:250 ppm. Mononuclear cell leukemia has occurred in untreated historical control groups with variable and sometimes very high incidences. The marginal increases in Zymbal's gland neoplasms and mononuclear cell leukemia may be related to chemical administration. Although renal tubule cell neoplasms are also uncommon, there was no dose response, and the exposure group with the highest incidence was the 0:83 ppm group. Further, the group receiving the highest perinatal and adult exposure concentrations (90:250 ppm) had no tubule cell neoplasms. The renal neoplasms were late appearing (first incidence 632 days); however, and the impact of lowered survival in the 90:250 ppm group on the incidence of renal neoplasms is unknown.

CONCLUSIONS

2-Year Adult-Only Exposure

Under the conditions of these 2-year adult-only dietary exposures, there was *clear evidence of carcinogenic activity** of ethylene thiourea in male and female F344/N rats, as shown by increased incidences of thyroid follicular cell neoplasms. There was *clear evidence of carcinogenic activity* of ethylene thiourea in male and female $B6C3F_1$ mice as shown by increased incidences of thyroid follicular cell neoplasms, hepatocellular neoplasms, and adenomas of the pars distalis of the pituitary gland.

Nonneoplastic lesions associated with the administration of ethylene thiourea included follicular cell hyperplasia in rats and mice and follicular cell cytoplasmic vacuolation, centrilobular hepatocellular cytomegaly, and focal hyperplasia of the pars distalis of the pituitary gland in mice. Other effects associated with the administration of ethylene thiourea

included decreased serum levels of T_4 and/or T_3 in rats and increased serum levels of TSH in rats and mice.

Perinatal-Only Exposure

Perinatal exposure alone had no effect on the incidences of neoplasms in rats or mice after 2 years. Animals may have been able to tolerate higher perinatal exposure concentrations.

Combined Perinatal and 2-Year Adult Exposures

Combined perinatal and 2-year adult dietary exposure to ethylene thiourea confirmed the findings of the 2-year adult-only exposures for the incidences of neoplasms in the thyroid gland of rats and mice and the liver and pituitary gland of mice. In male and female rats, combined perinatal and adult exposure to 90:250 ppm was associated with marginal increases, relative to the untreated (0:0 ppm) controls, in Zymbal's gland neoplasms and mononuclear cell leukemia, which may have been related to chemical administration. In rats receiving adult exposure to 250 ppm ethylene thiourea, perinatal exposure to 90 ppm was associated with a slightly enhanced incidence of thyroid neoplasms compared to adult-only exposure. However, increasing perinatal exposure from 0 to 90 ppm had no effect on incidences of thyroid neoplasms in rats receiving adult exposure to 83 ppm. Increasing perinatal exposure from 0 to 330 ppm was associated with a marginally increased incidence of thyroid neoplasms in female mice receiving adult exposure to 330 ppm, but there were no enhancing effects of perinatal exposure in mice receiving adult exposure to 1,000 ppm.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of peer review comments and the public discussion on this Technical Report appears on page 11.

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APPENDIX A
MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF ETHYLENE THIOUREA

Ethylene thiourea (ETU) was obtained in one lot (labeled 97% pure) from Aldrich Chemical Company. Purity and identity analyses were conducted at the study laboratory (Battelle Columbus Laboratories, Columbus, OH). The reports on analyses performed in support of the ethylene thiourea studies are on file at the National Institute of Environmental Health Sciences, Bethesda, MD.

The study chemical was identified as ETU by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with those expected for the structure and with the literature spectra of ETU (Figures A1 and A2); a resonance in the nuclear magnetic resonance spectrum at 3.31 ppm representing a trace impurity was present in both the sample and the reference spectra, but the impurity was not further characterized.

The purity of ETU was determined by elemental analysis, Karl Fischer water analysis (performed at Galbraith Laboratories, Knoxville, TN), ashing to determine inorganic content, thin-layer chromatography, and high-performance liquid chromatography. Thin-layer chromatography was performed on silica gel plates with a chloroform:*n*-butyl alcohol:methanol:water (100:5:1:0.5) solvent system, and visualization was performed by charring with 50% aqueous sulfuric acid. High-performance liquid chromatography was performed with a μBondapak NH_2 column and mobile phase systems of 40% or 80% acetonitrile in chloroform (v/v) and ultraviolet detection at 254 nm.

The results of elemental analysis for nitrogen were slightly high, those for sulfur were slightly low, and those for carbon and hydrogen were in agreement with the theoretical values. Ashing indicated 0.03% organic material. The water content was 0.55%. No impurities were detected by thin-layer chromatography. High-performance liquid chromatography indicated no impurities present at a concentration greater than 0.001%. The overall purity was estimated as 99%.

Periodic reanalysis of ETU by infrared spectroscopy and gas chromatography of the *S*-benzyl derivative performed with a 3% OV-17 column, flame ionization detection, and a nitrogen flow rate of 30 mL/minute indicated no significant deterioration during the studies.

PREPARATION AND CHARACTERIZATION OF DOSE FORMULATIONS

Dose formulations were prepared weekly by mixing the appropriate quantities of ETU with feed in a twin-shell blender. The formulations were stored in plastic bags for no longer than 2 weeks, and stability studies showed no decrease in the concentration of ETU in the formulated diets after 14 days of storage in the dark at room temperature. Dose formulations of ETU were analyzed periodically at the study laboratory. During the 13-week studies, the ETU content of the administered diet was determined by gas chromatographic analysis of the *S*-benzyl derivative prepared from the methanol extracts of formulated feed samples. Specifically, the dose formulations were extracted with methanol followed by an evaporative step to reduce the volume. The extracts were filtered, water was added, and the analyte was derivatized with benzyl chloride. After derivatization, 1.2N HCl was added and the sample was made basic with 1N KOH and extracted with chloroform. The derivatized ETU content was then determined by gas chromatography performed with a flame ionization detector, with a 3% OV-17 on a Gas Chrom Q column and with helium as the carrier at 30 mL/minute. The measured concentrations ranged from 93.5% to 110% of the target concentrations (Table A1).

During the 2-year studies, feed samples were extracted with acetonitrile and analyzed by high-performance liquid chromatography with a μBondpak NH_2 column, a mobile phase system of ethanol:hexane (20:80), and ultraviolet detection at 240 nm. On 25 July 1983, the method was changed to improve the precision of the dose analysis method by using a Lichrosorb RP-2 column and a mobile phase system of $ZnSO_4$ (2.87 g/L) and 4-dodecyldiethylene triamine (2.71 g/L) in distilled water: NH_4OAc (17 g/L) in distilled water:methanol (100:585:315). Formulated diets were analyzed approximately every 2 months (Table A2).

Because 90 of 100 analyzed formulated diets were prepared within 10% of the target concentrations, it is estimated that the formulated diets were prepared within specifications 90% of the time.

SOURCE AND SPECIFICATIONS OF ANIMALS

Male and female F344/N rats were obtained in two shipments and male CeH/HeN and female C57Bl/6N mice were obtained in three shipments from Charles River Breeding Laboratories (Kingston, NY). These rats and mice were produced under strict barrier conditions. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Rats were 4 to 5 weeks of age and mice were 4 to 6 weeks of age when shipped. Rats were held 14 weeks before receiving formulated diets and mice were held 4 to 6 weeks. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program.

ANIMAL MAINTENANCE

Animals were housed five per cage. Feed and water were available *ad libitum*. Cages were not rotated during these studies.

CLINICAL EXAMINATIONS AND PATHOLOGY

All animals were observed twice daily, and clinical signs were recorded. Body weights were recorded weekly for the first weeks of the studies and monthly 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 prior to study termination.

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. Generally, single transverse (thyroid gland and others) or longitudinal sections of each tissue were prepared, except for nose (three sections), brain (three sections), and liver (two sections). Tissues examined are listed in Materials and Methods.

When the pathology evaluation was completed by the laboratory pathologist and the pathology data entered into the Toxicology Data Management System, the slides, paraffin blocks, and residual formalin-fixed tissues were sent to the NTP Archives. The slides, blocks, and residual wet tissues were audited for accuracy of labeling and animal identification and for thoroughness of tissue trimming. The slides, individual animal necropsy records, and pathology tables were sent to an independent pathology quality assessment laboratory. The individual animal records and pathology tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tissues with a tumor diagnosis, all potential target tissues, and all tissues from a randomly selected 10% of the animals were reevaluated microscopically by a quality assessment pathologist. For rats, the potential target tissues for this review were thyroid gland, liver and spleen (for mononuclear cell leukemia), and kidney (males only). In mice, the liver, thyroid gland, pituitary gland, and lung (males only) were reviewed. Nonneoplastic lesions were evaluated for accuracy and consistency of diagnosis only in the potential target organs and in a randomly selected 10% of animals.

The quality assessment report and slides were submitted to the Pathology Working Group (PWG) chair, who reviewed microscopically all potential target tissues and any other tissues for which there was a disagreement in diagnosis between the laboratory and quality assessment pathologists. Representative examples of potential chemical-related nonneoplastic lesions and neoplasms and examples of disagreements in diagnosis between the laboratory and quality assessment pathologists were shown to the PWG. The PWG, which included the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology, examined the tissues without knowledge of dose group or previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the diagnosis was

changed to reflect the opinion of the PWG. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). The final pathology data 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).

STATISTICAL METHODS

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses 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 neoplasms 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

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

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

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

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 database (Haseman *et al.*, 1984, 1985) are included for those tumors appearing to show compound-related effects.

Thyroid Gland Function Data

The chemical-related response in thyroid gland weight and thyroid function data (triiodothyronine, thyroxine, and thyroid-stimulating hormone) were examined using analysis of variance methods. If the F-statistic from the one-way analysis of variance of the experimental groups was significant ($P \leq 0.05$), individual pairwise comparisons of means were performed using Duncan's Multiple Range Test (Duncan, 1955). Transformation of some of the thyroid function data was deemed necessary to satisfy the homogeneity of variance assumptions of these statistical tests. A reciprocal square root transformation was used to stabilize the variance of thyroid-stimulating hormone data taken from both rats and mice at 9 months and 2 years. Triiodothyronine data taken at 24 months from male mice and female rats were analyzed on a logarithmic scale.

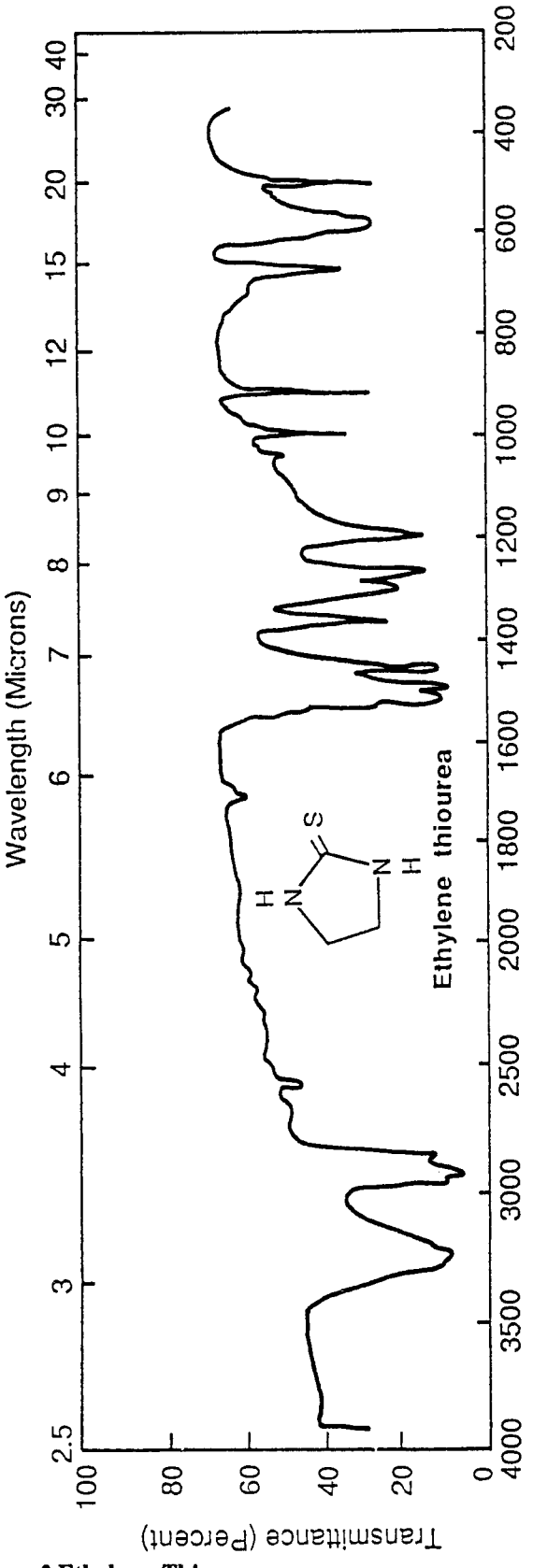
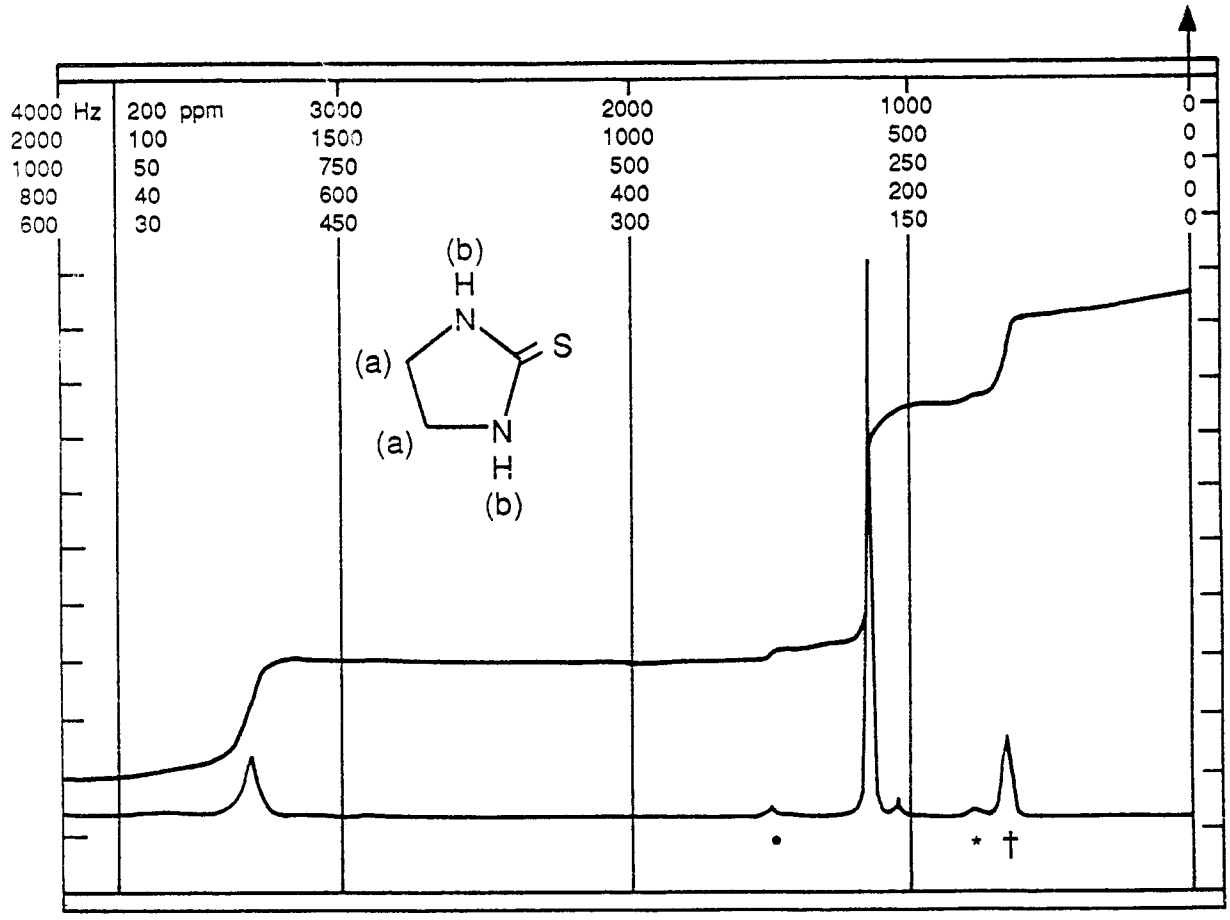


FIGURE A1
Infrared Spectrum of Ethylene Thiourea



Sample: Ethylene Thiourea
Lot No.: PC 081687
Solvent: DMSO - d_6

Remarks:
• Sideband
† Solvent

FIGURE A2
Nuclear Magnetic Resonance Spectrum of Ethylene Thiourea

TABLE A1
Results of Analysis of Dose Formulations in the 13-Week Feed Studies of Ethylene Thiourea

Date Mixed	Concentration of Ethylene Thiourea in Feed (ppm)		
	Target	Determined[a]	Percent of Target
4/16/80	60	56.1[b]	93.5
	60	58.8[c]	98.0
	60	66.2[d]	110.3
	125	118.0	94.4
	250	262.0	104.8
	500	503.8	100.8
	750	736.3	98.2
	1,000	1,007.0	100.7
	2,000	1,887.0[b]	94.4
	2,000	2,178.0[c]	108.9
	2,000	2,163.0[d]	108.2

[a] Results of duplicate analysis
[b] Sample taken from upper left section of blender
[c] Sample taken from upper right section of blender
[d] Sample taken from bottom of blender

TABLE A2
Results of Analysis of Dose Formulations in the 2-Year Feed Studies of Ethylene Thiourea

Date Mixed	Concentration of Ethylene Thiourea in Feed for Target Concentration (ppm)										
	9	25	30	33	83	90	100	110	250	330	1,000
09/09/82				27.9				115		638	
09/16/82				33.7				127		328	
11/11/82						98.7		72.2		348	
12/03/82	9.1		21.3			74.1	102			350	1,054
02/02/83		25.3			77.7		88.6		231	338	1,089
03/30/83		27.4			72.7		99.6		268	354	1,150
03/31/83					115						950
06/09/83		26.3			82.4		102		263	337	1,085
					83.1						
07/20/83		26.0			84.8		99.0		236	334	955
09/14/83		24.7			75.9		103		263	352	983
					83.2						
11/09/83		24.8			79.7	90.2					
		26.1			78.4						
		24.8									
11/16/83									255	340	986
											982
											912
01/12/84		25.3			86.8		101		236	302	942
03/16/84		22.6			76.5		93.3		245	328	1,009
04/25/84		26.9			87.3		102		255	346	1,001
06/27/84		25.4			78.9		93.6		241	352	995
					77.7						
08/22/84		22.7			79.5		93.5		228	318	964
					77.1						
10/10/84		23.6			78.2		95.7		255	349	1,036
12/17/84		27.4			91.0						
Mean	9.1	25.3	21.3	30.8	82.4	87.7	97.8	105	248	357	1,006
%RSD	-	5.9	-	13.3	11.0	14.2	4.8	27.5	5.5	21.3	6.2

APPENDIX B
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR FEED STUDY OF ETHYLENE THIOUREA

TABLE B1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Ethylene Thiourea[a]

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	90 ppm 0 ppm	9 ppm 25 ppm	0 ppm 83 ppm	30 ppm 83 ppm	90 ppm 83 ppm
Disposition Summary						
Animals initially in study	50	50	50	50	50	50
Early deaths						
Natural death	11	6	11	7	8	11
Moribund sacrifice	21	29	22	28	24	25
Survivors						
Terminal sacrifice	18	15	17	15	18	14
Animals examined microscopically	50	50	50	50	50	50
Alimentary System						
Intestine large, cecum	(45)	(47)	(40)	(44)	(43)	(43)
Intestine large, colon	(48)	(49)	(42)	(45)	(45)	(50)
Polyp adenomatous			1 (2%)			
Intestine large, rectum	(47)	(46)	(40)	(43)	(44)	(45)
Intestine small, duodenum	(48)	(49)	(46)	(47)	(49)	(49)
Intestine small, ileum	(45)	(47)	(42)	(43)	(45)	(46)
Intestine small, jejunum	(48)	(49)	(44)	(46)	(47)	(50)
Leiomyoma					1 (2%)	
Liver	(50)	(50)	(50)	(50)	(50)	(50)
Hepatocellular adenoma						3 (6%)
Hepatocellular adenoma, multiple		1 (2%)				
Mesentery	(3)	(5)	(6)	(2)	(2)	(3)
Sarcoma						1 (33%)
Pancreas	(48)	(50)	(50)	(50)	(49)	(50)
Sarcoma, metastatic, mesentery						1 (2%)
Pharynx					(1)	
Palate, papilloma squamous					1 (100%)	
Salivary glands	(50)	(49)	(50)	(50)	(50)	(50)
Adenoma		1 (2%)				
Stomach, forestomach	(49)	(50)	(47)	(50)	(48)	(49)
Stomach, glandular	(49)	(50)	(47)	(49)	(49)	(49)
Tongue		(2)			(1)	
Papilloma squamous		1 (50%)			1 (100%)	
Tooth	(50)	(50)	(49)	(50)	(50)	(50)
Gingiva, squamous cell carcinoma			1 (2%)			
Cardiovascular System						
Heart	(50)	(50)	(50)	(50)	(50)	(50)
Schwannoma malignant				1 (2%)		

TABLE B1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 250 ppm	90 ppm 250 ppm
Disposition Summary		
Animals initially in study	50	50
Early deaths		
Natural death	8	15
Moribund sacrifice	23	31
Accidental deaths	5	
Survivors		
Terminal sacrifice	14	4
Animals examined microscopically	50	50
Alimentary System		
Esophagus	(50)	(50)
Adenocarcinoma, metastatic, thyroid gland		1 (2%)
Intestine small, jejunum	(42)	(45)
Adenocarcinoma	1 (2%)	
Liver	(50)	(50)
Hepatocellular carcinoma		1 (2%)
Hepatocellular adenoma	1 (2%)	1 (2%)
Osteosarcoma, metastatic, uncertain primary site		1 (2%)
Mesentery	(2)	(3)
Pancreas	(49)	(50)
Salivary glands	(50)	(49)
Adenocarcinoma, metastatic, thyroid gland		1 (2%)
Stomach, forestomach	(49)	(50)
Stomach, glandular	(49)	(49)
Tongue	(1)	
Papilloma squamous	1 (100%)	
Cardiovascular System		
Heart	(50)	(50)

TABLE B1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	90 ppm 0 ppm	9 ppm 25 ppm	0 ppm 83 ppm	30 ppm 83 ppm	90 ppm 83 ppm
Endocrine System						
Adrenal gland, cortex	(50)	(50)	(49)	(50)	(49)	(50)
Adenoma		1 (2%)			1 (2%)	1 (2%)
Adrenal gland, medulla	(50)	(50)	(49)	(49)	(49)	(50)
Pheochromocytoma malignant	2 (4%)	1 (2%)	1 (2%)	1 (2%)	4 (8%)	1 (2%)
Pheochromocytoma benign	16 (32%)	16 (32%)	18 (37%)	15 (31%)	13 (27%)	19 (38%)
Bilateral, pheochromocytoma benign	6 (12%)	15 (30%)	6 (12%)	7 (14%)	11 (22%)	5 (10%)
Islets, pancreatic	(48)	(50)	(50)	(50)	(49)	(50)
Adenoma	2 (4%)	2 (4%)		1 (2%)	1 (2%)	2 (4%)
Carcinoma	1 (2%)	1 (2%)	2 (4%)	1 (2%)		
Parathyroid gland	(44)	(46)	(48)	(45)	(45)	(47)
Adenoma	1 (2%)	1 (2%)	2 (4%)		1 (2%)	1 (2%)
Pituitary gland	(50)	(50)	(48)	(47)	(49)	(49)
Pars distalis, adenoma	19 (38%)	15 (30%)	10 (21%)	10 (21%)	13 (27%)	11 (22%)
Pars distalis, adenoma, multiple						1 (2%)
Pars distalis, carcinoma		1 (2%)		1 (2%)		
Pars intermedia, adenoma	1 (2%)					
Thyroid gland	(49)	(49)	(46)	(46)	(47)	(50)
Bilateral, C-cell, adenoma	2 (4%)	1 (2%)	1 (2%)			1 (2%)
Bilateral, follicular cell, adenoma				1 (2%)	1 (2%)	1 (2%)
C-cell, adenoma	8 (16%)	10 (20%)	9 (20%)	12 (26%)	16 (34%)	12 (24%)
C-cell, carcinoma	2 (4%)	1 (2%)	1 (2%)			
Follicular cell, carcinoma	1 (2%)	3 (6%)	2 (4%)	3 (7%)	4 (9%)	6 (12%)
Follicular cell, adenoma		1 (2%)	1 (2%)	8 (17%)	9 (19%)	7 (14%)
General Body System						
Tissue NOS					(1)	
Carcinoma					1 (100%)	
Genital System						
Epididymis	(50)	(50)	(50)	(50)	(49)	(50)
Sarcoma, metastatic, mesentery						1 (2%)
Preputial gland	(49)	(49)	(49)	(49)	(46)	(50)
Adenoma	2 (4%)	4 (8%)	1 (2%)			1 (2%)
Carcinoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)		
Bilateral, adenoma		1 (2%)				
Prostate	(50)	(50)	(50)	(50)	(50)	(49)
Seminal vesicle	(1)	(1)	(4)	(1)		
Testes	(50)	(50)	(50)	(50)	(50)	(50)
Sarcoma, metastatic, mesentery						1 (2%)
Bilateral, interstitial cell, adenoma	35 (70%)	34 (68%)	39 (78%)	36 (72%)	40 (80%)	40 (80%)
Interstitial cell, adenoma	7 (14%)	11 (22%)	5 (10%)	4 (8%)	5 (10%)	8 (16%)

TABLE B1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 250 ppm	90 ppm 250 ppm
Endocrine System		
Adrenal gland, cortex	(50)	(50)
Osteosarcoma, metastatic, uncertain primary site		1 (2%)
Bilateral, adenoma	1 (2%)	
Adrenal gland, medulla	(50)	(50)
Pheochromocytoma malignant	1 (2%)	2 (4%)
Pheochromocytoma benign	11 (22%)	15 (30%)
Bilateral, pheochromocytoma benign	13 (26%)	7 (14%)
Islets, pancreatic	(50)	(50)
Adenoma		2 (4%)
Carcinoma	1 (2%)	1 (2%)
Parathyroid gland	(33)	(21)
Adenoma	1 (3%)	
Pituitary gland	(50)	(49)
Pars distalis, adenoma	11 (22%)	11 (22%)
Thyroid gland	(50)	(50)
Bilateral, follicular cell, carcinoma	11 (22%)	23 (46%)
Bilateral, follicular cell, carcinoma, multiple	1 (2%)	1 (2%)
Bilateral, follicular cell, adenoma	6 (12%)	2 (4%)
Bilateral, follicular cell, adenoma, multiple	2 (4%)	4 (8%)
C-cell, adenoma	9 (18%)	3 (6%)
Follicular cell, carcinoma	14 (28%)	20 (40%)
Follicular cell, adenoma	11 (22%)	20 (40%)
Follicular cell, adenoma, multiple	4 (8%)	8 (16%)
General Body System		
None		
Genital System		
Epididymis	(49)	(50)
Preputial gland	(49)	(50)
Adenoma		3 (6%)
Carcinoma	1 (2%)	
Squamous cell carcinoma	1 (2%)	
Prostate	(49)	(50)
Seminal vesicle		(2)
Testes	(50)	(50)
Bilateral, interstitial cell, adenoma	30 (60%)	33 (66%)
Interstitial cell, adenoma	10 (20%)	12 (24%)

TABLE B1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	90 ppm 0 ppm	9 ppm 25 ppm	0 ppm 83 ppm	30 ppm 83 ppm	90 ppm 83 ppm
Hematopoietic System						
Blood	(17)	(25)	(24)	(21)	(24)	(26)
Bone marrow	(50)	(50)	(50)	(50)	(49)	(50)
Lymph node	(50)	(50)	(50)	(50)	(48)	(50)
Deep cervical carcinoma, metastatic, thyroid gland		1 (2%)				
Deep cervical, mediastinal, mandibular, fibrous histiocytoma, metastatic, skin	1 (2%)					
Lumbar, fibrosarcoma, metastatic, skin		1 (2%)				
Mandibular, carcinoma, metastatic, Zymbal's gland	1 (2%)					
Mediastinal, pheochromocytoma malignant, metastatic, adrenal gland					1 (2%)	
Mediastinal, sarcoma, metastatic, mesentery						1 (2%)
Lymph node, mesenteric	(2)	(10)	(14)	(10)	(9)	(10)
Hemangiosarcoma		1 (10%)				
Spleen	(50)	(50)	(50)	(50)	(50)	(50)
Fibrosarcoma		1 (2%)			1 (2%)	
Hemangiosarcoma	1 (2%)					
Thymus	(40)	(39)	(45)	(42)	(40)	(38)
Integumentary System						
Mammary gland	(42)	(40)	(42)	(37)	(45)	(41)
Adenocarcinoma					1 (2%)	
Adenoma				1 (3%)		
Fibroadenoma		1 (3%)	4 (10%)	2 (5%)	1 (2%)	1 (2%)
Skin	(50)	(49)	(50)	(50)	(49)	(50)
Basal cell adenoma, multiple				1 (2%)		
Basosquamous tumor benign	1 (2%)		2 (4%)			
Basosquamous tumor benign, multiple					1 (2%)	
Keratoacanthoma	1 (2%)	2 (4%)		1 (2%)	1 (2%)	
Lipoma	1 (2%)					
Papilloma squamous		1 (2%)			1 (2%)	
Squamous cell carcinoma					1 (2%)	
Trichoepithelioma					1 (2%)	
Subcutaneous tissue, fibroma		2 (4%)	3 (6%)	1 (2%)	8 (16%)	1 (2%)
Subcutaneous tissue, fibrosarcoma	1 (2%)	1 (2%)	2 (4%)	2 (4%)	1 (2%)	3 (6%)
Subcutaneous tissue, fibrous histiocytoma	1 (2%)					
Subcutaneous tissue, leiomyosarcoma				1 (2%)		
Subcutaneous tissue, neurofibrosarcoma			1 (2%)		1 (2%)	
Subcutaneous tissue, osteosarcoma, metastatic, bone		1 (2%)				

TABLE B1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 250 ppm	90 ppm 250 ppm
Hematopoietic System		
Blood	(14)	(22)
Bone marrow	(49)	(50)
Femoral, osteosarcoma, metastatic, uncertain primary site		1 (2%)
Lymph node	(50)	(49)
Mediastinal, adenocarcinoma, metastatic, thyroid gland		1 (2%)
Lymph node, mesenteric	(14)	(10)
Spleen	(50)	(50)
Thymus	(43)	(44)
Thymoma benign		2 (5%)
Integumentary System		
Skin	(49)	(49)
Keratoacanthoma	1 (2%)	1 (2%)
Subcutaneous tissue, adenocarcinoma, metastatic, thyroid gland	1 (2%)	
Subcutaneous tissue, fibroma		1 (2%)
Subcutaneous tissue, fibrosarcoma		1 (2%)
Subcutaneous tissue, hemangiosarcoma	1 (2%)	

TABLE B1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	90 ppm 0 ppm	9 ppm 25 ppm	0 ppm 83 ppm	30 ppm 83 ppm	90 ppm 83 ppm
Musculoskeletal System						
Bone	(50)	(50)	(50)	(50)	(50)	(50)
Squamous cell carcinoma, metastatic, skin					1 (2%)	
Cervical, osteoma				1 (2%)		
Femur, osteosarcoma		1 (2%)				1 (2%)
Skeletal muscle	(1)				(1)	(1)
Diaphragm, sarcoma, metastatic, mesentery						1 (100%)
Nervous System						
Brain	(50)	(50)	(50)	(50)	(50)	(50)
Carcinoma, metastatic, pituitary gland		1 (2%)		1 (2%)		
Meningioma benign					1 (2%)	
Oligodendroglioma malignant			1 (2%)			
Respiratory System						
Lung	(50)	(50)	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma			2 (4%)		1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma	1 (2%)				1 (2%)	1 (2%)
Carcinoma, metastatic, thyroid gland	1 (2%)					
Carcinoma, metastatic, Zymbal's gland	1 (2%)					
Fibrosarcoma, metastatic, skin		1 (2%)				
Pheochromocytoma malignant, metastatic, adrenal gland					1 (2%)	
Schwannoma malignant, metastatic, heart				1 (2%)		
Nose	(50)	(50)	(50)	(50)	(49)	(50)
Squamous cell carcinoma, metastatic, skin					1 (2%)	
Trachea	(50)	(50)	(50)	(50)	(50)	(50)
Adenocarcinoma, metastatic, thyroid gland			1 (2%)			1 (2%)
Special Senses System						
Ear	(1)			(2)	(1)	
Papilloma squamous				1 (50%)		
Harderian gland	(48)	(50)	(49)	(49)	(50)	(50)
Zymbal's gland	(1)	(1)	(1)	(3)	(2)	(2)
Carcinoma	1 (100%)	1 (100%)	1 (100%)	3 (100%)	1 (50%)	2 (100%)

TABLE B1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 250 ppm	90 ppm 250 ppm
Musculoskeletal System		
Skeletal muscle	(5)	(2)
Nervous System		
Brain	(50)	(50)
Respiratory System		
Lung	(50)	(50)
Adenocarcinoma, metastatic, thyroid gland	1 (2%)	1 (2%)
Osteosarcoma, metastatic, uncertain primary site	1 (2%)	1 (2%)
Pheochromocytoma malignant, metastatic, adrenal gland		1 (2%)
Nose	(50)	(50)
Nasolacrimal duct, squamous cell carcinoma	1 (2%)	
Trachea	(50)	(50)
Adenocarcinoma, metastatic, thyroid gland		2 (4%)
Special Senses System		
Harderian gland	(49)	(50)
Zymbal's gland	(3)	(5)
Adenoma	1 (33%)	
Carcinoma	2 (67%)	4 (80%)
Bilateral, carcinoma		1 (20%)

TABLE B1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	90 ppm 0 ppm	9 ppm 25 ppm	0 ppm 83 ppm	30 ppm 83 ppm	90 ppm 83 ppm
Urinary System						
Kidney	(50)	(50)	(49)	(50)	(50)	(50)
Cystadenocarcinoma						1 (2%)
Myxoma			1 (2%)			
Nephroblastoma				1 (2%)		
Capsule, sarcoma, metastatic, mesentery						1 (2%)
Renal tubule, adenoma		1 (2%)	1 (2%)	4 (8%)	1 (2%)	1 (2%)
Renal tubule, adenoma, multiple						1 (2%)
Renal tubule, carcinoma, multiple			1 (2%)			
Urinary bladder	(49)	(50)	(48)	(49)	(48)	(50)
Systemic Lesions						
Multiple organs[b]	(50)	(50)	(50)	(50)	(50)	(50)
Leukemia monocytic						1 (2%)
Leukemia mononuclear	22 (44%)	32 (64%)	29 (58%)	25 (50%)	31 (62%)	34 (68%)
Mesothelioma malignant		2 (4%)	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Tumor Summary						
Total animals with primary neoplasms[c]	48	50	49	49	49	50
Total primary neoplasms	136	173	151	147	179	170
Total animals with benign neoplasms	48	50	46	48	49	49
Total benign neoplasms	102	126	106	106	130	118
Total animals with malignant neoplasms	26	40	36	37	39	40
Total malignant neoplasms	34	47	45	41	49	52
Total animals with secondary neoplasms[d]	3	4	1	2	2	2
Total secondary neoplasms	4	5	1	2	4	7

TABLE B1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 250 ppm	90 ppm 250 ppm
Urinary System		
Kidney	(50)	(50)
Renal tubule, adenoma	3 (6%)	
Renal tubule, carcinoma	1 (2%)	
Transitional epithelium, carcinoma		1 (2%)
Urinary bladder	(49)	(50)
Systemic Lesions		
Multiple organs[b]	(50)	(50)
Leukemia mononuclear	26 (52%)	29 (58%)
Lymphoma malignant histiocytic	1 (2%)	
Mesothelioma malignant		3 (6%)
Tumor Summary		
Total animals with primary neoplasms	45	50
Total primary neoplasms	179	212
Total animals with benign neoplasms	45	49
Total benign neoplasms	116	125
Total animals with malignant neoplasms	41	50
Total malignant neoplasms	63	87
Total animals with secondary neoplasms	3	6
Total secondary neoplasms	3	11
Total animals with malignant neoplasms of uncertain primary site	1	1

[a] Effects on rats exposed to ethylene thiourea perinatally through 8 weeks of age (F_0 concentration) and for 2 years postnatally (F_1 concentration)
[b] The number in parentheses is the number of animals with any tissue examined microscopically.
[c] Primary tumors: all tumors except metastatic tumors
[d] Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

TABLE B2
Statistical Analysis of Primary Tumors in Male Rats in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 0:83, and 0:250 ppm Groups

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	0 ppm 83 ppm	0 ppm 250 ppm
Adrenal Gland, Medulla: Benign or Malignant Pheochromocytoma			
Overall rates[a]	22/50 (44%)	22/49 (45%)	24/50 (48%)
Adjusted rates[b]	74.1%	72.6%	73.6%
Terminal rates[c]	12/19 (63%)	9/17 (53%)	6/14 (43%)
First incidence (days)	507	585	580
Life table tests[d]	P=0.138	P=0.446	P=0.168
Logistic regression tests[d]	P=0.225	P=0.456	P=0.260
Cochran-Armitage test[d]	P=0.387		
Fisher exact test[d]		P=0.545	P=0.421
Islets, Pancreatic: Adenoma or Carcinoma			
Overall rates	3/48 (6%)	2/50 (4%)	1/50 (2%)
Adjusted rates	11.2%	6.0%	2.7%
Terminal rates	1/19 (5%)	0/17 (0%)	0/14 (0%)
First incidence (days)	628	585	596
Life table tests	P=0.308N	P=0.545N	P=0.375N
Logistic regression tests	P=0.254N	P=0.491N	P=0.314N
Cochran-Armitage test	P=0.241N		
Fisher exact test		P=0.480N	P=0.293N
Kidney, Renal Tubule: Adenoma			
Overall rates	0/50 (0%)	4/50 (8%)	3/50 (6%)
Adjusted rates	0.0%	17.9%	12.1%
Terminal rates	0/19 (0%)	2/17 (12%)	0/14 (0%)
First incidence (days)	-[e]	632	631
Life table tests	P=0.161	P=0.054	P=0.107
Logistic regression tests	P=0.176	P=0.056	P=0.107
Cochran-Armitage test	P=0.205		
Fisher exact test		P=0.059	P=0.121
Mammary Gland: Fibroadenoma or Adenoma			
Overall rates	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted rates	0.0%	17.6%	0.0%
Terminal rates	0/19 (0%)	3/17 (18%)	0/14 (0%)
First incidence (days)	-	733 (T)	-
Life table tests	P=0.587N	P=0.098	-
Logistic regression tests	P=0.587N	P=0.098	-
Cochran-Armitage test	P=0.499N		
Fisher exact test		P=0.121	-
Pituitary Gland, Pars Distalis: Adenoma			
Overall rates	19/50 (38%)	10/47 (21%)	11/50 (22%)
Adjusted rates	51.1%	32.9%	51.9%
Terminal rates	4/19 (21%)	2/17 (12%)	5/14 (36%)
First incidence (days)	472	276	603
Life table tests	P=0.223N	P=0.094N	P=0.212N
Logistic regression tests	P=0.103N	P=0.056N	P=0.092N
Cochran-Armitage test	P=0.079N		
Fisher exact test		P=0.057N	P=0.063N

TABLE B2
Statistical Analysis of Primary Tumors in Male Rats in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 0:83, and 0:250 ppm Groups (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	0 ppm 83 ppm	0 ppm 250 ppm
Pituitary Gland, Pars Distalis: Adenoma or Carcinoma			
Overall rates	19/50 (38%)	11/47 (23%)	11/50 (22%)
Adjusted rates	51.1%	34.8%	51.9%
Terminal rates	4/19 (21%)	2/17 (12%)	5/14 (36%)
First incidence (days)	472	276	603
Life table tests	P=0.215N	P=0.135N	P=0.212N
Logistic regression tests	P=0.095N	P=0.089N	P=0.092N
Cochran-Armitage test	P=0.073N		
Fisher exact test		P=0.091N	P=0.063N
Preputial Gland: Adenoma or Carcinoma			
Overall rates	3/49 (6%)	1/49 (2%)	1/49 (2%)
Adjusted rates	12.5%	4.2%	3.4%
Terminal rates	2/19 (11%)	0/16 (0%)	0/14 (0%)
First incidence (days)	507	695	650
Life table tests	P=0.332N	P=0.357N	P=0.372N
Logistic regression tests	P=0.286N	P=0.315N	P=0.318N
Cochran-Armitage test	P=0.272N		
Fisher exact test		P=0.309N	P=0.309N
Skin, Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall rates	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted rates	4.5%	12.7%	0.0%
Terminal rates	0/19 (0%)	1/17 (6%)	0/14 (0%)
First incidence (days)	712	503	-
Life table tests	P=0.353N	P=0.295	P=0.529N
Logistic regression tests	P=0.312N	P=0.296	P=0.528N
Cochran-Armitage test	P=0.293N		
Fisher exact test		P=0.309	P=0.500N
Testes: Adenoma			
Overall rates	42/50 (84%)	40/50 (80%)	40/50 (80%)
Adjusted rates	97.6%	100.0%	100.0%
Terminal rates	18/19 (95%)	17/17 (100%)	14/14 (100%)
First incidence (days)	372	381	461
Life table tests	P=0.215	P=0.481	P=0.249
Logistic regression tests	P=0.442	P=0.484N	P=0.521
Cochran-Armitage test	P=0.390N		
Fisher exact test		P=0.398N	P=0.398N
Thyroid Gland: C-cell Adenoma			
Overall rates	10/49 (20%)	12/46 (26%)	9/50 (18%)
Adjusted rates	39.5%	44.8%	37.8%
Terminal rates	6/19 (32%)	4/17 (24%)	2/14 (14%)
First incidence (days)	628	486	580
Life table tests	P=0.506	P=0.328	P=0.510
Logistic regression tests	P=0.470N	P=0.331	P=0.565
Cochran-Armitage test	P=0.380N		
Fisher exact test		P=0.340	P=0.480N

TABLE B2
Statistical Analysis of Primary Tumors in Male Rats in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 0:83, and 0:250 ppm Groups (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	0 ppm 83 ppm	0 ppm 250 ppm
Thyroid Gland: C-cell Adenoma or Carcinoma			
Overall rates	11/49 (22%)	12/46 (26%)	9/50 (18%)
Adjusted rates	44.1%	44.8%	37.8%
Terminal rates	7/19 (37%)	4/17 (24%)	2/14 (14%)
First incidence (days)	628	486	580
Life table tests	P=0.544N	P=0.410	P=0.590
Logistic regression tests	P=0.388N	P=0.422	P=0.467
Cochran-Armitage test	P=0.303N		
Fisher exact test		P=0.431	P=0.382N
Thyroid Gland: Follicular Cell Adenoma			
Overall rates	0/49 (0%)	9/46 (20%)	23/50 (46%)
Adjusted rates	0.0%	35.3%	76.1%
Terminal rates	0/19 (0%)	4/17 (24%)	8/14 (57%)
First incidence (days)	-	503	391
Life table tests	P<0.001	P=0.002	P<0.001
Logistic regression tests	P<0.001	P=0.002	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001
Thyroid Gland: Follicular Cell Carcinoma			
Overall rates	1/49 (2%)	3/46 (7%)	26/50 (52%)
Adjusted rates	2.3%	9.2%	92.1%
Terminal rates	0/19 (0%)	0/17 (0%)	12/14 (86%)
First incidence (days)	512	592	391
Life table tests	P<0.001	P=0.276	P<0.001
Logistic regression tests	P<0.001	P=0.265	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.285	P<0.001
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall rates	1/49 (2%)	12/46 (26%)	37/50 (74%)
Adjusted rates	2.3%	41.3%	100.0%
Terminal rates	0/19 (0%)	4/17 (24%)	14/14 (100%)
First incidence (days)	512	503	391
Life table tests	P<0.001	P=0.002	P<0.001
Logistic regression tests	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001
Zymbal's Gland: Carcinoma			
Overall rates	1/50 (2%)	3/50 (6%)	2/50 (4%)
Adjusted rates	2.8%	6.4%	8.0%
Terminal rates	0/19 (0%)	0/17 (0%)	0/14 (0%)
First incidence (days)	628	395	677
Life table tests	P=0.468	P=0.294	P=0.464
Logistic regression tests	P=0.577	P=0.324	P=0.479
Cochran-Armitage test	P=0.501		
Fisher exact test		P=0.309	P=0.500

TABLE B2
Statistical Analysis of Primary Tumors in Male Rats in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 0:83, and 0:250 ppm Groups (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	0 ppm 83 ppm	0 ppm 250 ppm
Zymbal's Gland: Adenoma or Carcinoma			
Overall rates	1/50 (2%)	3/50 (6%)	3/50 (6%)
Adjusted rates	2.8%	6.4%	13.4%
Terminal rates	0/19 (0%)	0/17 (0%)	0/14 (0%)
First incidence (days)	628	395	677
Life table tests	P=0.270	P=0.294	P=0.267
Logistic regression tests	P=0.347	P=0.324	P=0.277
Cochran-Armitage test	P=0.303		
Fisher exact test		P=0.309	P=0.309
All Organs: Mononuclear Cell Leukemia			
Overall rates	22/50 (44%)	25/50 (50%)	26/50 (52%)
Adjusted rates	63.5%	74.9%	76.7%
Terminal rates	8/19 (42%)	9/17 (53%)	7/14 (50%)
First incidence (days)	372	565	579
Life table tests	P=0.111	P=0.269	P=0.121
Logistic regression tests	P=0.149	P=0.281	P=0.165
Cochran-Armitage test	P=0.271		
Fisher exact test		P=0.344	P=0.274
All Organs: Benign Tumors			
Overall rates	48/50 (96%)	48/50 (96%)	45/50 (90%)
Adjusted rates	100.0%	100.0%	100.0%
Terminal rates	19/19 (100%)	17/17 (100%)	14/14 (100%)
First incidence (days)	372	276	391
Life table tests	P=0.274	P=0.362	P=0.277
Logistic regression tests	P=0.636	P=0.740	P=0.217
Cochran-Armitage test	P=0.135N		
Fisher exact test		P=0.691N	P=0.218N
All Organs: Malignant Tumors			
Overall rates	26/50 (52%)	37/50 (74%)	41/50 (82%)
Adjusted rates	71.6%	85.5%	97.6%
Terminal rates	10/19 (53%)	11/17 (65%)	13/14 (93%)
First incidence (days)	372	395	391
Life table tests	P=0.003	P=0.041	P=0.002
Logistic regression tests	P<0.001	P=0.015	P<0.001
Cochran-Armitage test	P=0.002		
Fisher exact test		P=0.019	P=0.001
All Organs: Benign or Malignant Tumors			
Overall rates	48/50 (96%)	49/50 (98%)	45/50 (90%)
Adjusted rates	100.0%	100.0%	100.0%
Terminal rates	19/19 (100%)	17/17 (100%)	14/14 (100%)
First incidence (days)	372	276	391
Life table tests	P=0.283	P=0.316	P=0.277
Logistic regression tests	P=0.707	P=0.378	P=0.350
Cochran-Armitage test	P=0.103N		
Fisher exact test		P=0.500	P=0.218N

TABLE B2
Statistical Analysis of Primary Tumors in Male Rats in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 0:83, and 0:250 ppm Groups (continued)

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

TABLE B3
Statistical Analysis of Primary Tumors in Male Rats in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 90:0, 9:25, 30:83, 90:83, and 90:250 ppm Groups

F_0 Concentration	0 ppm	90 ppm	9 ppm	30 ppm	90 ppm	90 ppm
F_1 Concentration	0 ppm	0 ppm	25 ppm	83 ppm	83 ppm	250 ppm
Adrenal Gland, Medulla: Benign Pheochromocytoma						
Overall rates[a]	22/50 (44%)	31/50 (62%)	24/49 (49%)	24/49 (49%)	24/50 (48%)	22/50 (44%)
Adjusted rates[b]	74.1%	90.4%	75.7%	66.5%	72.9%	84.6%
Terminal rates[c]	12/19 (63%)	15/18 (83%)	15/22 (68%)	9/20 (45%)	8/15 (53%)	3/6 (50%)
First incidence (days)	507	538	497	453	507	486
Life table tests[d]		P=0.080	P=0.508N	P=0.489	P=0.255	P=0.013
Logistic regression tests[d]		P=0.069	P=0.528	P=0.484	P=0.454	P=0.322
Fisher exact test[d]		P=0.054	P=0.384	P=0.384	P=0.421	P=0.580N
Adrenal Gland, Medulla: Malignant Pheochromocytoma						
Overall rates	2/50 (4%)	1/50 (2%)	1/49 (2%)	4/49 (8%)	1/50 (2%)	2/50 (4%)
Adjusted rates	6.3%	5.6%	2.4%	12.9%	6.7%	11.8%
Terminal rates	0/19 (0%)	1/18 (6%)	0/22 (0%)	1/20 (5%)	1/15 (7%)	0/6 (0%)
First incidence (days)	619	733 (T)	580	617	733 (T)	438
Life table tests		P=0.503N	P=0.476N	P=0.357	P=0.548N	P=0.554
Logistic regression tests		P=0.487N	P=0.519N	P=0.330	P=0.496N	P=0.691N
Fisher exact test		P=0.500N	P=0.508N	P=0.329	P=0.500N	P=0.691N
Adrenal Gland, Medulla: Benign or Malignant Pheochromocytoma						
Overall rates	23/50 (46%)	31/50 (62%)	25/49 (51%)	28/49 (57%)	24/50 (48%)	23/50 (46%)
Adjusted rates	74.8%	90.4%	76.3%	72.0%	72.9%	84.9%
Terminal rates	12/19 (63%)	15/18 (83%)	15/22 (68%)	10/20 (50%)	8/15 (53%)	3/6 (50%)
First incidence (days)	507	538	497	453	507	438
Life table tests		P=0.112	P=0.504N	P=0.312	P=0.317	P=0.015
Logistic regression tests		P=0.105	P=0.511	P=0.253	P=0.539	P=0.389
Fisher exact test		P=0.080	P=0.383	P=0.182	P=0.500	P=0.579N
Islets, Pancreatic: Adenoma or Carcinoma						
Overall rates	3/48 (6%)	3/50 (6%)	2/50 (4%)	1/49 (2%)	2/50 (4%)	3/50 (6%)
Adjusted rates	11.2%	12.7%	9.1%	3.8%	10.6%	12.2%
Terminal rates	1/19 (5%)	0/18 (0%)	2/22 (9%)	0/19 (0%)	1/15 (7%)	0/6 (0%)
First incidence (days)	628	711	733 (T)	696	692	619
Life table tests		P=0.651N	P=0.444N	P=0.316N	P=0.568N	P=0.421
Logistic regression tests		P=0.632N	P=0.454N	P=0.292N	P=0.491N	P=0.660
Fisher exact test		P=0.641N	P=0.480N	P=0.301N	P=0.480N	P=0.641N
Liver: Neoplastic Nodule or Hepatocellular Adenoma						
Overall rates	0/50 (0%)	1/50 (2%)	0/50 (0%)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted rates	0.0%	5.0%	0.0%	0.0%	18.4%	2.9%
Terminal rates	0/19 (0%)	0/18 (0%)	0/22 (0%)	0/20 (0%)	2/15 (13%)	0/6 (0%)
First incidence (days)	-[e]	720	-	-	713	604
Life table tests		P=0.500	-	-	P=0.085	P=0.478
Logistic regression tests		P=0.506	-	-	P=0.086	P=0.500
Fisher exact test		P=0.500	-	-	P=0.121	P=0.500
Liver: Neoplastic Nodule, Hepatocellular Adenoma, or Hepatocellular Carcinoma						
Overall rates	0/50 (0%)	1/50 (2%)	0/50 (0%)	0/50 (0%)	3/50 (6%)	2/50 (4%)
Adjusted rates	0.0%	5.0%	0.0%	0.0%	18.4%	7.4%
Terminal rates	0/19 (0%)	0/18 (0%)	0/22 (0%)	0/20 (0%)	2/15 (13%)	0/6 (0%)
First incidence (days)	-	720	-	-	713	604
Life table tests		P=0.500	-	-	P=0.085	P=0.191
Logistic regression tests		P=0.506	-	-	P=0.086	P=0.240
Fisher exact test		P=0.500	-	-	P=0.121	P=0.247

TABLE B3
Statistical Analysis of Primary Tumors in Male Rats in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 90:0, 9:25, 30:83, 90:83, and 90:250 ppm Groups (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	90 ppm 0 ppm	9 ppm 25 ppm	30 ppm 83 ppm	90 ppm 83 ppm	90 ppm 250 ppm
Mammary Gland: Fibroadenoma						
Overall rates	0/50 (0%)	1/50 (2%)	4/50 (8%)	1/50 (2%)	1/50 (2%)	0/50 (0%)
Adjusted rates	0.0%	3.7%	17.4%	5.0%	6.7%	0.0%
Terminal rates	0/19 (0%)	0/18 (0%)	3/22 (14%)	1/20 (5%)	1/15 (7%)	0/6 (0%)
First incidence (days)	-	698	728	733 (T)	733 (T)	-
Life table tests		P=0.508	P=0.085	P=0.510	P=0.453	-
Logistic regression tests		P=0.508	P=0.077	P=0.510	P=0.453	-
Fisher exact test		P=0.500	P=0.059	P=0.500	P=0.500	-
Mammary Gland: Fibroadenoma or Adenocarcinoma						
Overall rates	0/50 (0%)	1/50 (2%)	4/50 (8%)	2/50 (4%)	1/50 (2%)	0/50 (0%)
Adjusted rates	0.0%	3.7%	17.4%	10.0%	6.7%	0.0%
Terminal rates	0/19 (0%)	0/18 (0%)	3/22 (14%)	2/20 (10%)	1/15 (7%)	0/6 (0%)
First incidence (days)	-	698	728	733 (T)	733 (T)	-
Life table tests		P=0.508	P=0.085	P=0.248	P=0.453	-
Logistic regression tests		P=0.508	P=0.077	P=0.248	P=0.453	-
Fisher exact test		P=0.500	P=0.059	P=0.247	P=0.500	-
Pituitary Gland, Pars Distalis: Adenoma						
Overall rates	19/50 (38%)	15/50 (30%)	10/48 (21%)	13/49 (27%)	12/49 (24%)	11/49 (22%)
Adjusted rates	51.1%	47.3%	39.9%	45.8%	49.4%	48.1%
Terminal rates	4/19 (21%)	5/18 (28%)	8/22 (36%)	6/20 (30%)	5/15 (33%)	1/6 (17%)
First incidence (days)	472	435	382	447	552	555
Life table tests		P=0.281N	P=0.029N	P=0.159N	P=0.193N	P=0.454N
Logistic regression tests		P=0.273N	P=0.047N	P=0.153N	P=0.102N	P=0.078N
Fisher exact test		P=0.263N	P=0.050N	P=0.157N	P=0.109N	P=0.071N
Pituitary Gland, Pars Distalis: Adenoma or Carcinoma						
Overall rates	19/50 (38%)	16/50 (32%)	10/48 (21%)	13/49 (27%)	12/49 (24%)	11/49 (22%)
Adjusted rates	51.1%	49.0%	39.9%	45.8%	49.4%	48.1%
Terminal rates	4/19 (21%)	5/18 (28%)	8/22 (36%)	6/20 (30%)	5/15 (33%)	1/6 (17%)
First incidence (days)	472	435	382	447	552	555
Life table tests		P=0.344N	P=0.029N	P=0.159N	P=0.193N	P=0.454N
Logistic regression tests		P=0.347N	P=0.047N	P=0.153N	P=0.102N	P=0.078N
Fisher exact test		P=0.338N	P=0.050N	P=0.157N	P=0.109N	P=0.071N
Preputial Gland: Adenoma						
Overall rates	2/49 (4%)	5/49 (10%)	1/49 (2%)	0/46 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rates	7.4%	23.5%	3.6%	0.0%	5.9%	9.6%
Terminal rates	1/19 (5%)	3/17 (18%)	0/22 (0%)	0/18 (0%)	0/15 (0%)	0/6 (0%)
First incidence (days)	507	650	703	-	713	527
Life table tests		P=0.206	P=0.463N	P=0.243N	P=0.546N	P=0.374
Logistic regression tests		P=0.228	P=0.502N	P=0.273N	P=0.493N	P=0.512
Fisher exact test		P=0.218	P=0.500N	P=0.263N	P=0.492N	P=0.510
Preputial Gland: Adenoma or Carcinoma						
Overall rates	3/49 (6%)	6/49 (12%)	2/49 (4%)	0/46 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rates	12.5%	25.2%	5.6%	0.0%	5.9%	9.6%
Terminal rates	2/19 (11%)	3/17 (18%)	0/22 (0%)	0/18 (0%)	0/15 (0%)	0/6 (0%)
First incidence (days)	507	552	395	-	713	527
Life table tests		P=0.232	P=0.458N	P=0.127N	P=0.365N	P=0.463
Logistic regression tests		P=0.254	P=0.516N	P=0.130N	P=0.293N	P=0.649N
Fisher exact test		P=0.243	P=0.500N	P=0.133N	P=0.301N	P=0.651N

TABLE B3
Statistical Analysis of Primary Tumors in Male Rats in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 90:0, 9:25, 30:83, 90:83, and 90:250 ppm Groups (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	90 ppm 0 ppm	9 ppm 25 ppm	30 ppm 83 ppm	90 ppm 83 ppm	90 ppm 250 ppm
Skin, Subcutaneous Tissue Fibroma						
Overall rates	0/50 (0%)	2/50 (4%)	3/50 (6%)	8/50 (16%)	1/50 (2%)	1/50 (2%)
Adjusted rates	0.0%	8.3%	13.6%	26.6%	3.0%	10.0%
Terminal rates	0/19 (0%)	1/18 (6%)	3/22 (14%)	2/20 (10%)	0/15 (0%)	0/6 (0%)
First incidence (days)	-	640	733 (T)	594	647	723
Life table tests		P=0.244	P=0.145	P=0.008	P=0.512	P=0.362
Logistic regression tests		P=0.246	P=0.145	P=0.005	P=0.499	P=0.370
Fisher exact test		P=0.247	P=0.121	P=0.003	P=0.500	P=0.500
Skin, Subcutaneous Tissue: Fibrosarcoma						
Overall rates	1/50 (2%)	1/50 (2%)	2/50 (4%)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted rates	4.5%	5.0%	6.6%	3.6%	10.7%	3.6%
Terminal rates	0/19 (0%)	0/18 (0%)	0/22 (0%)	0/20 (0%)	0/15 (0%)	0/6 (0%)
First incidence (days)	712	720	642	678	536	634
Life table tests		P=0.755N	P=0.554	P=0.755	P=0.283	P=0.687
Logistic regression tests		P=0.756N	P=0.517	P=0.755N	P=0.305	P=0.741
Fisher exact test		P=0.753N	P=0.500	P=0.753N	P=0.309	P=0.753N
Skin, Subcutaneous Tissue: Fibroma or Fibrosarcoma						
Overall rates	1/50 (2%)	3/50 (6%)	5/50 (10%)	9/50 (18%)	4/50 (8%)	2/50 (4%)
Adjusted rates	4.5%	12.8%	19.4%	29.3%	13.5%	13.2%
Terminal rates	0/19 (0%)	1/18 (6%)	3/22 (14%)	2/20 (10%)	0/15 (0%)	0/6 (0%)
First incidence (days)	712	640	642	594	536	634
Life table tests		P=0.316	P=0.145	P=0.015	P=0.171	P=0.348
Logistic regression tests		P=0.319	P=0.124	P=0.011	P=0.179	P=0.415
Fisher exact test		P=0.309	P=0.102	P=0.008	P=0.181	P=0.500
Testes: Adenoma						
Overall rates	42/50 (84%)	45/50 (90%)	44/50 (88%)	45/50 (90%)	48/50 (96%)	45/50 (90%)
Adjusted rates	97.6%	100.0%	97.8%	100.0%	100.0%	100.0%
Terminal rates	18/19 (95%)	18/18 (100%)	21/22 (95%)	20/20 (100%)	15/15 (100%)	6/6 (100%)
First incidence (days)	372	416	444	541	429	438
Life table tests		P=0.409	P=0.382N	P=0.483	P=0.101	P=0.001
Logistic regression tests		P=0.432	P=0.451	P=0.420	P=0.085	P=0.285
Fisher exact test		P=0.277	P=0.387	P=0.277	P=0.046	P=0.277
Thyroid Gland: C-cell Adenoma						
Overall rates	10/49 (20%)	11/49 (22%)	10/46 (22%)	16/47 (34%)	13/50 (26%)	3/50 (6%)
Adjusted rates	39.5%	42.9%	33.9%	57.1%	44.4%	23.7%
Terminal rates	6/19 (32%)	6/18 (33%)	4/21 (19%)	8/19 (42%)	3/15 (20%)	1/6 (17%)
First incidence (days)	628	507	642	618	552	538
Life table tests		P=0.499	P=0.489N	P=0.141	P=0.245	P=0.336N
Logistic regression tests		P=0.546	P=0.589N	P=0.127	P=0.352	P=0.063N
Fisher exact test		P=0.500	P=0.536	P=0.101	P=0.337	P=0.033N
Thyroid Gland: C-cell Adenoma or Carcinoma						
Overall rates	11/49 (22%)	12/49 (24%)	11/46 (24%)	16/47 (34%)	13/50 (26%)	3/50 (6%)
Adjusted rates	44.1%	47.6%	37.8%	57.1%	44.4%	23.7%
Terminal rates	7/19 (37%)	7/18 (39%)	5/21 (24%)	8/19 (42%)	3/15 (20%)	1/6 (17%)
First incidence (days)	628	507	642	618	552	538
Life table tests		P=0.494	P=0.480N	P=0.197	P=0.311	P=0.284N
Logistic regression tests		P=0.550	P=0.578N	P=0.186	P=0.446	P=0.043N
Fisher exact test		P=0.500	P=0.529	P=0.150	P=0.430	P=0.018N

TABLE B3
Statistical Analysis of Primary Tumors in Male Rats in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 90:0, 9:25, 30:83, 90:83, and 90:250 ppm Groups (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	90 ppm 0 ppm	9 ppm 25 ppm	30 ppm 83 ppm	90 ppm 83 ppm	90 ppm 250 ppm
Thyroid Gland: Follicular Cell Adenoma						
Overall rates	0/49 (0%)	1/49 (2%)	1/46 (2%)	10/47 (21%)	8/50 (16%)	34/50 (68%)
Adjusted rates	0.0%	5.6%	4.8%	34.0%	37.4%	100.0%
Terminal rates	0/19 (0%)	1/18 (6%)	1/21 (5%)	4/19 (21%)	3/15 (20%)	6/6 (100%)
First incidence (days)	-	733 (T)	733 (T)	466	681	438
Life table tests		P=0.489	P=0.520	P=0.002	P=0.003	P<0.001
Logistic regression tests		P=0.489	P=0.520	P=0.001	P=0.003	P<0.001
Fisher exact test		P=0.500	P=0.484	P<0.001	P=0.003	P<0.001
Thyroid Gland: Follicular Cell Carcinoma						
Overall rates	1/49 (2%)	3/49 (6%)	2/46 (4%)	4/47 (9%)	6/50 (12%)	44/50 (88%)
Adjusted rates	2.3%	11.0%	5.1%	17.9%	26.9%	100.0%
Terminal rates	0/19 (0%)	1/18 (6%)	0/21 (0%)	3/19 (16%)	3/15 (20%)	6/6 (100%)
First incidence (days)	512	633	497	617	552	418
Life table tests		P=0.321	P=0.514	P=0.189	P=0.048	P<0.001
Logistic regression tests		P=0.290	P=0.439	P=0.171	P=0.061	P<0.001
Fisher exact test		P=0.309	P=0.476	P=0.168	P=0.059	P<0.001
Thyroid Gland: Follicular Cell Adenoma or Carcinoma						
Overall rates	1/49 (2%)	4/49 (8%)	3/46 (7%)	14/47 (30%)	13/50 (26%)	48/50 (96%)
Adjusted rates	2.3%	16.2%	9.6%	48.6%	52.4%	100.0%
Terminal rates	0/19 (0%)	2/18 (11%)	1/21 (5%)	7/19 (37%)	5/15 (33%)	6/6 (100%)
First incidence (days)	512	633	497	466	552	418
Life table tests		P=0.189	P=0.328	P<0.001	P<0.001	P<0.001
Logistic regression tests		P=0.179	P=0.261	P<0.001	P<0.001	P<0.001
Fisher exact test		P=0.181	P=0.285	P<0.001	P<0.001	P<0.001
Zymbal's Gland: Carcinoma						
Overall rates	1/50 (2%)	1/50 (2%)	1/50 (2%)	1/50 (2%)	2/50 (4%)	5/50 (10%)
Adjusted rates	2.8%	4.3%	3.3%	2.6%	9.2%	25.0%
Terminal rates	0/19 (0%)	0/18 (0%)	0/22 (0%)	0/20 (0%)	1/15 (7%)	0/6 (0%)
First incidence (days)	628	712	696	619	640	640
Life table tests		P=0.752N	P=0.740N	P=0.754N	P=0.493	P=0.041
Logistic regression tests		P=0.758N	P=0.761N	P=0.758	P=0.504	P=0.089
Fisher exact test		P=0.753N	P=0.753N	P=0.753N	P=0.500	P=0.102
All Organs: Mononuclear Cell Leukemia						
Overall rates	22/50 (44%)	32/50 (64%)	29/50 (58%)	31/50 (62%)	35/50 (70%)	29/50 (58%)
Adjusted rates	63.5%	78.1%	70.9%	82.0%	84.3%	94.7%
Terminal rates	8/19 (42%)	10/18 (56%)	11/22 (50%)	14/20 (70%)	10/15 (67%)	5/6 (83%)
First incidence (days)	372	507	444	447	371	486
Life table tests		P=0.102	P=0.318	P=0.138	P=0.020	P=0.002
Logistic regression tests		P=0.044	P=0.132	P=0.063	P=0.008	P=0.088
Fisher exact test		P=0.035	P=0.115	P=0.054	P=0.007	P=0.115
All Organs: Mesothelioma (Benign, Malignant, or NOS)						
Overall rates	0/50 (0%)	2/50 (4%)	2/50 (4%)	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted rates	0.0%	6.8%	7.1%	8.7%	3.4%	7.9%
Terminal rates	0/19 (0%)	0/18 (0%)	1/22 (5%)	1/20 (5%)	0/15 (0%)	0/6 (0%)
First incidence (days)	-	650	646	696	678	506
Life table tests		P=0.268	P=0.276	P=0.241	P=0.507	P=0.113
Logistic regression tests		P=0.245	P=0.247	P=0.241	P=0.503	P=0.109
Fisher exact test		P=0.247	P=0.247	P=0.247	P=0.500	P=0.121

TABLE B3
Statistical Analysis of Primary Tumors in Male Rats in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 90:0, 9:25, 30:83, 90:83, and 90:250 ppm Groups (continued)

F_0 Concentration	0 ppm	90 ppm	9 ppm	30 ppm	90 ppm	90 ppm
F_1 Concentration	0 ppm	0 ppm	25 ppm	83 ppm	83 ppm	250 ppm
All Organs: Benign Tumors						
Overall rates	48/50 (96%)	50/50 (100%)	46/50 (92%)	49/50 (98%)	49/50 (98%)	49/50 (98%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Terminal rates	19/19 (100%)	18/18 (100%)	22/22	20/20 (100%)	15/15 (100%)	6/6 (100%)
First incidence (days)	372	416	382	447	429	438
Life table tests		P=0.474	P=0.186N	P=0.510N	P=0.273	P=0.003
Logistic regression tests		-[f]	P=0.230N	-	P=0.469N	P=0.392N
Fisher exact test		P=0.247	P=0.339N	P=0.500	P=0.500	P=0.500
All Organs: Malignant Tumors						
Overall rates	26/50 (52%)	40/50 (80%)	36/50 (72%)	39/50 (78%)	40/50 (80%)	50/50 (100%)
Adjusted rates	71.6%	86.7%	79.2%	90.0%	91.7%	100.0%
Terminal rates	10/19 (53%)	12/18 (67%)	13/22 (59%)	16/20 (80%)	12/15 (80%)	6/6 (100%)
First incidence (days)	372	416	368	447	371	418
Life table tests		P=0.044	P=0.214	P=0.061	P=0.014	P<0.001
Logistic regression tests		P=0.004	P=0.035	P=0.007	P=0.003	P<0.001
Fisher exact test		P=0.003	P=0.032	P=0.006	P=0.003	P<0.001
All Organs: Benign or Malignant Tumors						
Overall rates	48/50 (96%)	50/50 (100%)	49/50 (98%)	49/50 (98%)	50/50 (100%)	50/50 (100%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Terminal rates	19/19 (100%)	18/18 (100%)	22/22 (100%)	20/20 (100%)	15/15 (100%)	6/6 (100%)
First incidence (days)	372	416	368	447	371	418
Life table tests		P=0.474	P=0.319N	P=0.510N	P=0.235	P=0.002
Logistic regression tests		-	-	-	-	-
Fisher exact test		P=0.247	P=0.500	P=0.500	P=0.247	P=0.247

(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no tumors in animal group
[f] Value of statistic cannot be computed

TABLE B4
Statistical Analysis of Selected Primary Tumors in Male Rats in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 90:0, 90:83, and 90:250 ppm Groups

F_0 Concentration F_1 Concentration	90 ppm 0 ppm	90 ppm 83 ppm	90 ppm 250 ppm
Thyroid Gland: Follicular Cell Adenoma			
Overall rates[a]	1/49 (2%)	8/50 (16%)	34/50 (68%)
Life table tests[b]	P<0.001	P=0.010	P<0.001
Logistic regression tests[b]	P<0.001	P=0.011	P<0.001
Cochran-Armitage test[b]	P<0.001		
Fisher exact test[b]		P=0.017	P<0.001
Thyroid Gland: Follicular Cell Carcinoma			
Overall rates	3/49 (6%)	6/50 (12%)	44/50 (88%)
Life table tests	P<0.001	P=0.199	P<0.001
Logistic regression tests	P<0.001	P=0.245	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.254	P<0.001
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall rates	4/49 (8%)	13/50 (26%)	48/50 (96%)
Life table tests	P<0.001	P=0.010	P<0.001
Logistic regression tests	P<0.001	P=0.014	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.017	P<0.001
Zymbal's Gland: Carcinoma			
Overall rates	1/50 (2%)	2/50 (4%)	5/50 (10%)
Life table tests	P=0.010	P=0.451	P=0.030
Logistic regression tests	P=0.036	P=0.483	P=0.067
Cochran-Armitage test	P=0.060		
Fisher exact test		P=0.500	P=0.102
All Organs: Mononuclear Cell or Monocytic Leukemia			
Overall rates	32/50 (64%)	35/50 (70%)	29/50 (58%)
Life table tests	P=0.040	P=0.231	P=0.043
Logistic regression tests	P=0.280N	P=0.344	P=0.471N
Cochran-Armitage test	P=0.247N		
Fisher exact test		P=0.335	P=0.341N

[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.

[b] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

TABLE B5
Statistical Analysis of Selected Primary Tumors in Male Rats in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:83, 30:83, and 90:83 ppm Groups

F_0 Concentration F_1 Concentration	0 ppm 83 ppm	30 ppm 83 ppm	90 ppm 83 ppm
Thyroid Gland: Follicular Cell Adenoma			
Overall rates[a]	9/46 (20%)	10/47 (21%)	8/50 (16%)
Life table tests[b]	P=0.501N	P=0.591	P=0.567N
Logistic regression tests[b]	P=0.347N	P=0.541	P=0.411N
Cochran-Armitage test[b]	P=0.354N		
Fisher exact test[b]		P=0.521	P=0.424N
Thyroid Gland: Follicular Cell Carcinoma			
Overall rates	3/46 (7%)	4/47 (9%)	6/50 (12%)
Life table tests	P=0.185	P=0.574	P=0.262
Logistic regression tests	P=0.239	P=0.527	P=0.286
Cochran-Armitage test	P=0.237		
Fisher exact test		P=0.512	P=0.287
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall rates	12/46 (26%)	14/47 (30%)	13/50 (26%)
Life table tests	P=0.438	P=0.537	P=0.459
Logistic regression tests	P=0.508N	P=0.460	P=0.569N
Cochran-Armitage test	P=0.516N		
Fisher exact test		P=0.434	P=0.587N
Zymbal's Gland: Carcinoma			
Overall rates	3/50 (6%)	1/50 (2%)	2/50 (4%)
Life table tests	P=0.479N	P=0.285N	P=0.477N
Logistic regression tests	P=0.591N	P=0.343N	P=0.649N
Cochran-Armitage test	P=0.500N		
Fisher exact test		P=0.309N	P=0.500N
All Organs: Mononuclear Cell or Monocytic Leukemia			
Overall rates	25/50 (50%)	31/50 (62%)	35/50 (70%)
Life table tests	P=0.066	P=0.403	P=0.092
Logistic regression tests	P=0.048	P=0.259	P=0.050
Cochran-Armitage test	P=0.034		
Fisher exact test		P=0.157	P=0.033

[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.

[b] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

TABLE B6
Statistical Analysis of Selected Primary Tumors in Male Rats in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:250 and 90:250 ppm Groups

F_0 Concentration F_1 Concentration	0 ppm 250 ppm	90 ppm 250 ppm
Thyroid Gland: Follicular Cell Adenoma		
Overall rates[a]	23/50 (46%)	34/50 (68%)
Life table tests[b]		P=0.002
Logistic regression tests[b]		P=0.032
Fisher exact test[b]		P=0.021
Thyroid Gland: Follicular Cell Carcinoma		
Overall rates	26/50 (52%)	44/50 (88%)
Life table tests		P<0.001
Logistic regression tests		P<0.001
Fisher exact test		P<0.001
Thyroid Gland: Follicular Cell Adenoma or Carcinoma		
Overall rates	37/50 (74%)	48/50 (96%)
Life table tests		P<0.001
Logistic regression tests		P=0.010
Fisher exact test		P=0.002
Zymbal's Gland: Adenoma or Carcinoma		
Overall rates	3/50 (6%)	5/50 (10%)
Life table tests		P=0.180
Logistic regression tests		P=0.320
Fisher exact test		P=0.357
All Organs: Leukemia, Mononuclear or Monocytic		
Overall rates	26/50 (52%)	29/50 (58%)
Life table tests		P=0.045
Logistic regression tests		P=0.397
Fisher exact test		P=0.344

[a] Number of tumor-bearing animals/number of animals examined at microscopically at site
[b] Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates.

TABLE B7a
Historical Incidence of Zymbal's Gland Adenomas and Carcinomas in Untreated Male F344/N Rats[a]

Study	Incidence in Untreated Controls
Historical Incidence at Battelle Columbus Laboratories	
Chlorobenzene	0/50
N-Phenyl-2-Naphthylamine	1/50
Rotenone	1/50
l-Ascorbic Acid	1/50
Total	3/200 (1.5%)
Standard deviation	1.0%
Range	
High	1/50
Low	0/50
Overall Historical Incidence	
Total	18/1596 (1.1%)
Standard deviation	1.8%
Range	
High	4/50
Low	0/50

[a] Data as of 1 March 1989 for studies of at least 104 weeks. Standard deviation and range are presented for groups of 35 or more animals.

TABLE B7b
Historical Incidence of Renal Tubule Cell Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	0/50	0/50	0/50
N-Phenyl-2-Naphthylamine	2/50	1/50	3/50
Rotenone	0/50	1/50	1/50
l-Ascorbic Acid	0/49	0/49	0/49
Total	2/199 (1.0%)	2/199 (1.0%)	4/199 (2.0%)
Standard deviation	2.0%	1.2%	2.8%
Range			
High	2/50	1/50	3/50
Low	0/50	0/50	0/50
Overall Historical Incidence			
Total	11/1590 (0.7%)	3/1590 (0.2%)	14/1590 (0.9%)
Standard deviation	1.4%	0.6%	1.7%
Range			
High	3/50	1/50	3/50
Low	0/50	0/50	0/50

[a] Data as of 1 March 1989 for studies of at least 104 weeks. Standard deviation and range are presented for groups of 35 or more animals.

TABLE B7c
Historical Incidence of Subcutaneous Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Untreated Controls		
	Fibroma	Fibrosarcoma	Fibroma or Fibrosarcoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	4/50	0/50	4/50
N-Phenyl-2-Naphthylamine	1/50	1/50	2/50
Rotenone	4/50	1/50	5/50
l-Ascorbic Acid	1/50	2/50	3/50
Total	10/200 (5.0%)	4/200 (2.0%)	14/200 (7.0%)
Standard deviation	3.5%	1.6%	2.6%
Range			
High	4/50	2/50	5/50
Low	1/50	0/50	2/50
Overall Historical Incidence			
Total	87/1596 (5.5%)	20/1596 (1.3%)	105/1596 (6.6%)
Standard deviation	2.8%	1.9%	3.2%
Range			
High	6/50	4/50	7/50
Low	0/49	0/50	0/49

[a] Data as of 1 March 1989 for studies of at least 104 weeks. Standard deviation and range are presented for groups of 35 or more animals.

TABLE B7d
Historical Incidence of Leukemia in Untreated Male F344/N Rats[a]

Study	Incidence in Untreated Controls
Historical Incidence at Battelle Columbus Laboratories	
Chlorobenzene	19/50
N-Phenyl-2-Naphthylamine	21/50
Rotenone	24/50
l-Ascorbic Acid	17/50
Total	81/200 (40.5%)
Standard deviation	6.0%
Range	
High	24/50
Low	17/50
Overall Historical Incidence	
Total	594/1596 (37.2%)
Standard deviation	16.4%
Range	
High	36/50
Low	5/50

[a] Data as of 1 March 1989 for studies of at least 104 weeks. Standard deviation and range are presented for groups of 35 or more animals.

TABLE B8
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Ethylene Thiourea

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	90 ppm 0 ppm	9 ppm 25 ppm	0 ppm 83 ppm	30 ppm 83 ppm	90 ppm 83 ppm
Disposition Summary						
Animals initially in study	50	50	50	50	50	50
Animals removed	50	50	50	50	50	50
Animals examined histopathologically	50	50	50	50	50	50
Alimentary System						
Esophagus	(50)	(50)	(50)	(50)	(50)	(50)
Hemorrhage						1 (2%)
Intestine large, cecum	(45)	(47)	(40)	(44)	(43)	(43)
Inflammation, chronic active	1 (2%)	1 (2%)		2 (5%)	1 (2%)	
Parasite metazoan			1 (3%)	1 (2%)		
Perivascular, inflammation, chronic active		5 (11%)				
Intestine large, colon	(48)	(49)	(42)	(45)	(45)	(50)
Necrosis, coagulative				1 (2%)		
Parasite metazoan	3 (6%)	1 (2%)	3 (7%)	3 (7%)	2 (4%)	3 (6%)
Intestine large, rectum	(47)	(46)	(40)	(43)	(44)	(45)
Edema					1 (2%)	
Inflammation, chronic active		1 (2%)				
Parasite metazoan	7 (15%)	2 (4%)	3 (8%)	9 (21%)	5 (11%)	5 (11%)
Artery, necrosis, fibrinoid	1 (2%)					
Perivascular, inflammation, chronic active	1 (2%)					
Intestine small, duodenum	(48)	(49)	(46)	(47)	(49)	(49)
Inflammation, chronic active	1 (2%)		1 (2%)	1 (2%)		
Necrosis, coagulative						1 (2%)
Intestine small, ileum	(45)	(47)	(42)	(43)	(45)	(46)
Edema					1 (2%)	
Necrosis, coagulative				1 (2%)		
Intestine small, jejunum	(48)	(49)	(44)	(46)	(47)	(50)
Dilatation				1 (2%)		
Edema					1 (2%)	
Inflammation, chronic active			1 (2%)	1 (2%)		
Metaplasia, osseous				1 (2%)		
Liver	(50)	(50)	(50)	(50)	(50)	(50)
Basophilic focus	12 (24%)	4 (8%)	9 (18%)	7 (14%)	14 (28%)	5 (10%)
Clear cell focus	1 (2%)	2 (4%)		2 (4%)	2 (4%)	1 (2%)
Cyst					1 (2%)	
Degeneration, cystic	17 (34%)	19 (38%)	18 (36%)	13 (26%)	20 (40%)	21 (42%)
Eosinophilic focus		1 (2%)				
Hematopoietic cell proliferation	1 (2%)					
Hepatodiaphragmatic nodule	1 (2%)					
Hepatodiaphragmatic nodule, multiple				1 (2%)		
Hyperplasia			1 (2%)			2 (4%)
Inflammation, chronic	2 (4%)	3 (6%)	7 (14%)	3 (6%)	1 (2%)	1 (2%)
Leukocytosis				1 (2%)	1 (2%)	
Necrosis, coagulative	2 (4%)	4 (8%)	3 (6%)	4 (8%)		6 (12%)
Vacuolization cytoplasmic	1 (2%)	1 (2%)	2 (4%)		2 (4%)	
Bile duct, hyperplasia		4 (8%)		1 (2%)	1 (2%)	
Mesentery	(3)	(5)	(6)	(2)	(2)	(3)
Hemorrhage			1 (17%)			
Inflammation, chronic active	3 (100%)	2 (40%)	4 (67%)	1 (50%)	1 (50%)	1 (33%)
Thrombus					1 (50%)	

TABLE B8
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 250 ppm	90 ppm 250 ppm
Disposition Summary		
Animals initially in study	50	50
Animals removed	50	50
Animals examined histopathologically	50	50
Alimentary System		
Esophagus	(50)	(50)
Inflammation, chronic active		1 (2%)
Intestine large, cecum	(44)	(39)
Artery, inflammation, chronic active		1 (3%)
Intestine large, colon	(47)	(47)
Parasite metazoan	2 (4%)	3 (6%)
Intestine large, rectum	(43)	(45)
Parasite metazoan	4 (9%)	3 (7%)
Artery, inflammation, chronic active		1 (2%)
Intestine small, duodenum	(50)	(49)
Inflammation, chronic active		1 (2%)
Necrosis, coagulative		1 (2%)
Liver	(50)	(50)
Angiectasis	2 (4%)	2 (4%)
Basophilic focus	15 (30%)	3 (6%)
Clear cell focus		4 (8%)
Degeneration, cystic	25 (50%)	17 (34%)
Inflammation, chronic	10 (20%)	3 (6%)
Leukocytosis		1 (2%)
Necrosis, coagulative	6 (12%)	4 (8%)
Thrombus		1 (2%)
Vacuolization cytoplasmic	2 (4%)	1 (2%)
Mesentery	(2)	(3)
Inflammation, chronic active	2 (100%)	
Artery, inflammation, chronic active		1 (33%)

TABLE B8
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration	0 ppm	90 ppm	9 ppm	0 ppm	30 ppm	90 ppm
F_1 Concentration	0 ppm	0 ppm	25 ppm	83 ppm	83 ppm	83 ppm
Alimentary System (continued)						
Pancreas	(48)	(50)	(50)	(50)	(49)	(50)
Cyst	1 (2%)		1 (2%)			1 (2%)
Inflammation, chronic active		1 (2%)				1 (2%)
Acinus, atrophy	20 (42%)	30 (60%)	24 (48%)	24 (48%)	27 (55%)	18 (36%)
Acinus, hyperplasia	1 (2%)					
Acinus, hyperplasia, focal			1 (2%)		1 (2%)	
Artery, necrosis, fibrinoid	1 (2%)					
Perivascular, inflammation, chronic active	1 (2%)	3 (6%)	1 (2%)	1 (2%)	5 (10%)	
Salivary glands	(50)	(49)	(50)	(50)	(50)	(50)
Inflammation, chronic active	1 (2%)				1 (2%)	
Stomach, forestomach	(49)	(50)	(47)	(50)	(48)	(49)
Acanthosis	4 (8%)		3 (6%)	2 (4%)	4 (8%)	3 (6%)
Hyperkeratosis	4 (8%)		3 (6%)	2 (4%)	4 (8%)	3 (6%)
Hyperplasia				1 (2%)		
Hyperplasia, squamous	1 (2%)					1 (2%)
Inflammation, chronic active	3 (6%)	4 (8%)	3 (6%)	5 (10%)	6 (13%)	3 (6%)
Stomach, glandular	(49)	(50)	(47)	(49)	(49)	(49)
Cyst epithelial inclusion				1 (2%)		
Inflammation, chronic active	1 (2%)	2 (4%)	3 (6%)	4 (8%)	6 (12%)	
Mineralization	2 (4%)	4 (8%)	1 (2%)	2 (4%)	2 (4%)	3 (6%)
Necrosis, coagulative	1 (2%)					1 (2%)
Tooth	(50)	(50)	(49)	(50)	(50)	(50)
Cyst	1 (2%)					
Cardiovascular System						
Heart	(50)	(50)	(50)	(50)	(50)	(50)
Cardiomyopathy, chronic	46 (92%)	44 (88%)	47 (94%)	41 (82%)	44 (88%)	47 (94%)
Inflammation, chronic active	1 (2%)	1 (2%)		1 (2%)		
Mineralization	2 (4%)		1 (2%)	2 (4%)	1 (2%)	3 (6%)
Atrium, thrombus	3 (6%)	8 (16%)	1 (2%)	7 (14%)	1 (2%)	4 (8%)
Ventricle, thrombus		1 (2%)				
Endocrine System						
Adrenal gland, cortex	(50)	(50)	(49)	(50)	(49)	(50)
Accessory adrenal cortical nodule						1 (2%)
Degeneration, fatty	14 (28%)	15 (30%)	11 (22%)	15 (30%)	13 (27%)	10 (20%)
Hyperplasia	15 (30%)	18 (36%)	19 (39%)	17 (34%)	21 (43%)	16 (32%)
Hypertrophy	4 (8%)	2 (4%)	5 (10%)	2 (4%)	5 (10%)	5 (10%)
Necrosis, coagulative		1 (2%)			1 (2%)	
Adrenal gland, medulla	(50)	(50)	(49)	(49)	(49)	(50)
Hematocyst						1 (2%)
Hyperplasia	21 (42%)	21 (42%)	23 (47%)	21 (43%)	30 (61%)	21 (42%)
Necrosis, coagulative		1 (2%)				
Islets, pancreatic	(48)	(50)	(50)	(50)	(49)	(50)
Hyperplasia, focal						1 (2%)
Parathyroid gland	(44)	(46)	(48)	(45)	(45)	(47)
Hyperplasia	8 (18%)	5 (11%)	3 (6%)	4 (9%)	6 (13%)	5 (11%)

TABLE B8
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 250 ppm	90 ppm 250 ppm
Alimentary System (continued)		
Pancreas	(49)	(50)
Necrosis, coagulative	1 (2%)	
Acinus, atrophy	17 (35%)	19 (38%)
Artery, inflammation, chronic active		1 (2%)
Salivary glands	(50)	(49)
Inflammation, chronic active		2 (4%)
Necrosis		1 (2%)
Artery, inflammation, chronic active		1 (2%)
Stomach, forestomach	(49)	(50)
Necrosis, coagulative		3 (6%)
Stomach, glandular	(49)	(49)
Inflammation, chronic active		2 (4%)
Mineralization	1 (2%)	2 (4%)
Artery, inflammation, chronic active		1 (2%)
Tooth	(49)	(50)
Inflammation, chronic active	1 (2%)	
Cardiovascular System		
Heart	(50)	(50)
Cardiomyopathy, chronic	39 (78%)	43 (86%)
Mineralization	1 (2%)	
Artery, inflammation, chronic active		1 (2%)
Atrium, thrombus	3 (6%)	4 (8%)
Endocrine System		
Adrenal gland, cortex	(50)	(50)
Degeneration, fatty	14 (28%)	13 (26%)
Hyperplasia	9 (18%)	6 (12%)
Hypertrophy, focal		1 (2%)
Necrosis, coagulative		1 (2%)
Vacuolization cytoplasmic	1 (2%)	
Adrenal gland, medulla	(50)	(50)
Hyperplasia	14 (28%)	17 (34%)
Necrosis, coagulative		1 (2%)
Islets, pancreatic	(50)	(50)
Hyperplasia		3 (6%)
Necrosis, coagulative	1 (2%)	

TABLE B8
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	90 ppm 0 ppm	9 ppm 25 ppm	0 ppm 83 ppm	30 ppm 83 ppm	90 ppm 83 ppm
Endocrine System (continued)						
Pituitary gland	(50)	(50)	(48)	(47)	(49)	(49)
Pars distalis, angiectasis		1 (2%)				
Pars distalis, cyst	4 (8%)	3 (6%)	4 (8%)	4 (9%)	7 (14%)	3 (6%)
Pars distalis, hemorrhage				2 (4%)	4 (8%)	
Pars distalis, hyperplasia	12 (24%)	9 (18%)	12 (25%)	9 (19%)	10 (20%)	12 (24%)
Pars distalis, vacuolization cytoplasmic		1 (2%)				
Pars intermedia, cyst	1 (2%)	2 (4%)	3 (6%)	4 (9%)	5 (10%)	4 (8%)
Rathke's cleft, cyst			1 (2%)			
Thyroid gland	(49)	(49)	(46)	(46)	(47)	(50)
Inflammation, chronic active		1 (2%)				
Ultimobranchial cyst		3 (6%)				
C-cell, hyperplasia	29 (59%)	33 (67%)	22 (48%)	30 (65%)	35 (74%)	27 (54%)
Follicle, cyst	1 (2%)					
Follicular cell, hyperplasia	4 (8%)	12 (24%)	13 (28%)	30 (65%)	35 (74%)	47 (94%)
General Body System						
None						
Genital System						
Coagulating gland		(3)				
Inflammation, chronic active		2 (67%)				
Epididymis	(50)	(50)	(50)	(50)	(49)	(50)
Inflammation, chronic active	1 (2%)		1 (2%)			
Perivascular, inflammation, chronic active		1 (2%)				
Preputial gland	(49)	(49)	(49)	(49)	(46)	(50)
Hyperplasia	3 (6%)	1 (2%)	1 (2%)		1 (2%)	2 (4%)
Hypertrophy						1 (2%)
Inflammation, chronic		1 (2%)				
Inflammation, chronic active	45 (92%)	45 (92%)	46 (94%)	46 (94%)	42 (91%)	47 (94%)
Duct, dilatation		1 (2%)	1 (2%)		1 (2%)	
Prostate	(50)	(50)	(50)	(50)	(50)	(49)
Cyst			1 (2%)	3 (6%)		1 (2%)
Inflammation, chronic active	29 (58%)	27 (54%)	23 (46%)	24 (48%)	21 (42%)	25 (51%)
Epithelium, hyperplasia				1 (2%)		2 (4%)
Seminal vesicle	(1)	(1)	(4)	(1)		
Inflammation, chronic active			1 (25%)	1 (100%)		
Testes	(50)	(50)	(50)	(50)	(50)	(50)
Cyst			1 (2%)			
Inflammation, chronic active	1 (2%)					
Necrosis, coagulative	1 (2%)					1 (2%)
Interstitial cell, hyperplasia	9 (18%)	12 (24%)	9 (18%)	7 (14%)	4 (8%)	5 (10%)
Seminiferous tubule, atrophy	9 (18%)	8 (16%)	11 (22%)	11 (22%)	8 (16%)	6 (12%)

TABLE B8
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 250 ppm	90 ppm 250 ppm
Endocrine System (continued)		
Pituitary gland	(50)	(49)
Pars distalis, atypical cells	1 (2%)	
Pars distalis, cyst		8 (16%)
Pars distalis, hyperplasia	6 (12%)	16 (33%)
Pars distalis, vacuolization cytoplasmic	1 (2%)	
Thyroid gland	(50)	(50)
Inflammation, chronic active		1 (2%)
Artery, inflammation, chronic active		1 (2%)
C-cell, hyperplasia	12 (24%)	9 (18%)
Follicular cell, hyperplasia	41 (82%)	39 (78%)
General Body System		
None		
Genital System		
Epididymis	(49)	(50)
Mineralization	1 (2%)	
Preputial gland	(49)	(50)
Inflammation, chronic active	41 (84%)	42 (84%)
Prostate	(49)	(50)
Cyst	2 (4%)	1 (2%)
Inflammation, chronic active	27 (55%)	27 (54%)
Seminal vesicle		(2)
Artery, inflammation, chronic active		1 (50%)
Testes	(50)	(50)
Artery, inflammation, chronic active		1 (2%)
Interstitial cell, hyperplasia	6 (12%)	8 (16%)
Seminiferous tubule, atrophy	8 (16%)	7 (14%)

TABLE B8
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	90 ppm 0 ppm	9 ppm 25 ppm	0 ppm 83 ppm	30 ppm 83 ppm	90 ppm 83 ppm
Hematopoietic System						
Bone marrow	(50)	(50)	(50)	(50)	(49)	(50)
Femoral, hyperplasia, reticulum cell		1 (2%)		1 (2%)		
Femoral, myelofibrosis	1 (2%)	1 (2%)		1 (2%)	1 (2%)	
Femoral, myeloid cell, atrophy						1 (2%)
Femoral, myeloid cell, hyperplasia	1 (2%)					
Lymph node	(50)	(50)	(50)	(50)	(48)	(50)
Inguinal, necrosis					1 (2%)	
Mandibular, cyst	1 (2%)	2 (4%)	1 (2%)		3 (6%)	2 (4%)
Mandibular, hyperplasia, lymphoid		1 (2%)		1 (2%)		
Mandibular, hyperplasia, plasma cell	2 (4%)			1 (2%)		1 (2%)
Mandibular, necrosis		1 (2%)			1 (2%)	
Mediastinal, cyst		2 (4%)			1 (2%)	
Mediastinal, inflammation, chronic active	1 (2%)					
Mediastinal, inflammation, suppurative				1 (2%)		
Renal, infiltration cellular, histiocytic				1 (2%)		
Lymph node, mesenteric	(2)	(10)	(14)	(10)	(9)	(10)
Cyst						1 (10%)
Necrosis		1 (10%)				
Spleen	(50)	(50)	(50)	(50)	(50)	(50)
Fibrosis	6 (12%)	8 (16%)	2 (4%)	4 (8%)	3 (6%)	4 (8%)
Hematopoietic cell proliferation	1 (2%)	3 (6%)	1 (2%)	1 (2%)		2 (4%)
Necrosis, coagulative			2 (4%)	1 (2%)	1 (2%)	1 (2%)
Thrombus	1 (2%)				2 (4%)	
Thymus	(40)	(39)	(45)	(42)	(40)	(38)
Cyst				1 (2%)		
Ectopic parathyroid gland						1 (3%)
Necrosis					1 (3%)	
Integumentary System						
Mammary gland	(42)	(40)	(42)	(37)	(45)	(41)
Hyperplasia, cystic	42 (100%)	36 (90%)	39 (93%)	35 (95%)	40 (89%)	37 (90%)
Skin	(50)	(49)	(50)	(50)	(49)	(50)
Abscess					1 (2%)	
Acanthosis		1 (2%)		1 (2%)		
Cyst epithelial inclusion					1 (2%)	1 (2%)
Hyperkeratosis		1 (2%)				
Hyperplasia, basal cell				1 (2%)		
Inflammation, chronic active	1 (2%)		2 (4%)			1 (2%)
Subcutaneous tissue, fibrosis		1 (2%)				
Vein, dilatation				1 (2%)		
Musculoskeletal System						
Bone	(50)	(50)	(50)	(50)	(50)	(50)
Cranium, fibrous osteodystrophy	4 (8%)	4 (8%)	3 (6%)	1 (2%)	6 (12%)	3 (6%)
Femur, fibrous osteodystrophy	4 (8%)	4 (8%)	3 (6%)	1 (2%)	6 (12%)	3 (6%)

TABLE B8
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 250 ppm	90 ppm 250 ppm
Hematopoietic System		
Bone marrow	(49)	(50)
Femoral, myelofibrosis		1 (2%)
Lymph node	(50)	(49)
Mandibular, hyperplasia, plasma cell	2 (4%)	3 (6%)
Lymph node, mesenteric	(14)	(10)
Cyst	1 (7%)	
Spleen	(50)	(50)
Fibrosis	8 (16%)	6 (12%)
Hematopoietic cell proliferation	1 (2%)	
Necrosis, coagulative	2 (4%)	
Artery, inflammation, chronic active		1 (2%)
Thymus	(43)	(44)
Ectopic parathyroid gland		1 (2%)
Hemorrhage		1 (2%)
Integumentary System		
Mammary gland	(36)	(37)
Hyperplasia, cystic	31 (86%)	37 (100%)
Skin	(49)	(49)
Hyperkeratosis		1 (2%)
Inflammation, chronic active	1 (2%)	1 (2%)
Musculoskeletal System		
Bone	(49)	(50)
Femur, fibrous osteodystrophy	1 (2%)	
Skeletal muscle	(5)	(2)
Artery, inflammation, chronic active		1 (50%)

TABLE B8
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	90 ppm 0 ppm	9 ppm 25 ppm	0 ppm 83 ppm	30 ppm 83 ppm	90 ppm 83 ppm
Nervous System						
Brain	(50)	(50)	(50)	(50)	(50)	(50)
Compression	5 (10%)	5 (10%)	1 (2%)	5 (10%)	3 (6%)	
Hemorrhage	1 (2%)	2 (4%)	1 (2%)	3 (6%)	3 (6%)	1 (2%)
Hydrocephalus	4 (8%)	5 (10%)	2 (4%)	5 (10%)	3 (6%)	
Necrosis	1 (2%)	1 (2%)				
Peripheral nerve	(2)			(1)	(1)	
Sciatic, degeneration				1 (100%)		
Spinal cord	(2)			(1)	(2)	
Hemorrhage	1 (50%)					
White matter, degeneration	2 (100%)			1 (100%)	1 (50%)	
Respiratory System						
Lung	(50)	(50)	(50)	(50)	(50)	(50)
Granuloma	1 (2%)					
Hemorrhage	1 (2%)				1 (2%)	
Inflammation, chronic active	9 (18%)	4 (8%)	5 (10%)	5 (10%)	5 (10%)	3 (6%)
Leukocytosis				1 (2%)		
Metaplasia, osseous			1 (2%)		1 (2%)	
Mineralization	1 (2%)					
Necrosis, coagulative				1 (2%)		
Alveolar epithelium, hyperplasia	1 (2%)	1 (2%)		2 (4%)	2 (4%)	
Artery, mediastinum, necrosis, fibrinoid					1 (2%)	
Mediastinum, mineralization						1 (2%)
Mediastinum, perivascular, inflammation, chronic active		1 (2%)			1 (2%)	
Nose	(50)	(50)	(50)	(50)	(49)	(50)
Cyst				1 (2%)		
Fungus	5 (10%)		1 (2%)	5 (10%)		1 (2%)
Hemorrhage		1 (2%)				
Inflammation, chronic active	15 (30%)	10 (20%)	12 (24%)	11 (22%)	13 (27%)	13 (26%)
Nasolacrimal duct, hyperkeratosis					1 (2%)	
Nasolacrimal duct, inflammation, suppurative	6 (12%)	4 (8%)	7 (14%)	5 (10%)	8 (16%)	5 (10%)
Trachea	(50)	(50)	(50)	(50)	(50)	(50)
Cyst			1 (2%)			
Hemorrhage						1 (2%)
Inflammation, chronic active						1 (2%)
Special Senses System						
Eye	(11)	(10)	(6)	(8)	(4)	(5)
Hemorrhage	1 (9%)					1 (20%)
Inflammation, chronic active	1 (9%)					1 (20%)
Lens, cataract	9 (82%)	7 (70%)	4 (67%)	6 (75%)	3 (75%)	3 (60%)
Retina, atrophy	10 (91%)	9 (90%)	4 (67%)	6 (75%)	3 (75%)	3 (60%)

TABLE B8
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 250 ppm	90 ppm 250 ppm
Nervous System		
Brain	(50)	(50)
Compression	1 (2%)	
Hemorrhage		1 (2%)
Hydrocephalus	1 (2%)	
Artery, inflammation, chronic active		1 (2%)
Peripheral nerve	(6)	
Sciatic, degeneration	2 (33%)	
Spinal cord	(7)	
White matter, degeneration	2 (29%)	
Respiratory System		
Lung	(50)	(50)
Congestion		1 (2%)
Hemorrhage		1 (2%)
Inflammation, chronic active	6 (12%)	10 (20%)
Thrombus	1 (2%)	1 (2%)
Artery, mediastinum, inflammation, chronic active		1 (2%)
Vein, mediastinum, thrombus	1 (2%)	
Nose	(50)	(50)
Foreign body		1 (2%)
Fungus	1 (2%)	5 (10%)
Hemorrhage	3 (6%)	
Inflammation, chronic active	9 (18%)	16 (32%)
Nasolacrimal duct, foreign body		1 (2%)
Nasolacrimal duct, inflammation, suppurative	7 (14%)	6 (12%)
Trachea	(50)	(50)
Inflammation, chronic active		1 (2%)
Special Senses System		
Eye	(11)	(10)
Lens, cataract	5 (45%)	9 (90%)
Retina, atrophy	5 (45%)	8 (80%)

TABLE B8
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration	0 ppm	90 ppm	9 ppm	0 ppm	30 ppm	90 ppm
F_1 Concentration	0 ppm	0 ppm	25 ppm	83 ppm	83 ppm	83 ppm
Urinary System						
Kidney	(50)	(50)	(49)	(50)	(50)	(50)
Bacterium			1 (2%)			
Hydronephrosis	1 (2%)					
Infarct		1 (2%)				
Infiltration cellular, mixed cell					1 (2%)	
Inflammation, chronic active			1 (2%)		1 (2%)	
Necrosis, coagulative				2 (4%)		
Nephropathy, chronic	49 (98%)	50 (100%)	47 (96%)	49 (98%)	49 (98%)	50 (100%)
Artery, necrosis, fibrinoid	1 (2%)					
Perivascular, inflammation, chronic active	1 (2%)					
Renal tubule, hyperplasia					1 (2%)	
Renal tubule, mineralization			1 (2%)			
Renal tubule, epithelium, hyperplasia		3 (6%)	1 (2%)			3 (6%)
Urethra	(1)					
Transitional epithelium, hyperplasia	1 (100%)					
Urinary bladder	(49)	(50)	(48)	(49)	(48)	(50)
Dilatation	1 (2%)					
Hemorrhage	1 (2%)					
Inflammation, chronic active		1 (2%)	1 (2%)			

TABLE B8
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 250 ppm	90 ppm 250 ppm
Urinary System		
Kidney	(50)	(50)
Necrosis, coagulative	1 (2%)	1 (2%)
Nephropathy, chronic	45 (90%)	50 (100%)
Artery, inflammation, chronic active		1 (2%)
Renal tubule, epithelium, hyperplasia	7 (14%)	2 (4%)

APPENDIX C
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR FEED STUDY OF ETHYLENE THIOUREA

TABLE C1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Ethylene Thiourea[a]

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	90 ppm 0 ppm	9 ppm 25 ppm	0 ppm 83 ppm	30 ppm 83 ppm	90 ppm 83 ppm
Disposition Summary						
Animals initially in study	50	50	50	50	50	50
Early deaths						
Natural death	7	5	3	10	13	5
Moribund sacrifice	20	15	13	10	11	13
Survivors						
Terminal sacrifice	23	30	34	30	26	32
Animals examined microscopically	50	50	50	50	50	50
Alimentary System						
Esophagus	(50)	(50)	(49)	(50)	(49)	(50)
Intestine large, colon	(47)	(47)	(50)	(45)	(43)	(47)
Intestine small, duodenum	(49)	(49)	(50)	(48)	(48)	(49)
Intestine small, ileum	(45)	(47)	(48)	(42)	(42)	(44)
Jejunum, sarcoma stromal, metastatic		1 (2%)				
Intestine small, jejunum	(47)	(47)	(50)	(44)	(45)	(48)
Leiomyoma					1 (2%)	
Liver	(50)	(50)	(50)	(50)	(50)	(50)
Adenocarcinoma, metastatic, uterus	1 (2%)					
Hepatocellular adenoma		1 (2%)		1 (2%)	1 (2%)	
Histiocytic sarcoma		1 (2%)				
Neoplastic nodule		1 (2%)				
Mesentery	(3)	(2)	(2)	(1)	(4)	(8)
Adenocarcinoma, metastatic, uterus	1 (33%)					
Sarcoma stromal, metastatic, uterus		1 (50%)				
Pancreas	(50)	(49)	(50)	(49)	(49)	(50)
Adenocarcinoma, metastatic, uterus	1 (2%)					
Salivary glands	(50)	(50)	(50)	(50)	(50)	(49)
Stomach, forestomach, glandular	(49)	(49)	(50)	(49)	(48)	(50)
Adenocarcinoma, metastatic, uterus	1 (2%)					
Stomach, glandular	(48)	(49)	(50)	(48)	(48)	(50)
Tongue	(1)		(1)	(1)	(1)	(1)
Papilloma squamous	1 (100%)			1 (100%)	1 (100%)	1 (100%)
Squamous cell carcinoma			1 (100%)			
Cardiovascular System						
Heart	(50)	(50)	(50)	(50)	(50)	(50)
Endocrine System						
Adrenal gland, cortex	(50)	(49)	(49)	(48)	(49)	(50)
Adenoma	2 (4%)	1 (2%)	6 (12%)			2 (4%)
Capsule, adenocarcinoma, metastatic, uterus	1 (2%)					
Adrenal gland, medulla	(50)	(49)	(49)	(49)	(49)	(50)
Pheochromocytoma malignant				2 (4%)		
Pheochromocytoma benign	2 (4%)	8 (16%)	1 (2%)	1 (2%)	5 (10%)	7 (14%)
Bilateral, pheochromocytoma benign			2 (4%)	1 (2%)	1 (2%)	3 (6%)
Islets, pancreatic	(50)	(49)	(50)	(50)	(50)	(50)
Adenoma			1 (2%)	1 (2%)		
Carcinoma					1 (2%)	

TABLE C1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 250 ppm	90 ppm 250 ppm
Disposition Summary		
Animals initially in study	50	50
Early deaths		
Natural death	4	7
Moribund sacrifice	26	30
Survivors		
Terminal sacrifice	20	13
Animals examined microscopically	50	50
Alimentary System		
Intestine large, rectum	(45)	(49)
Polyp adenomatous		1 (2%)
Intestine small, ileum	(45)	(50)
Liver	(50)	(50)
Hepatocellular carcinoma		1 (2%)
Pancreas	(49)	(50)
Salivary glands	(50)	(50)
Stomach, forestomach	(50)	(50)
Stomach, glandular	(50)	(50)
Tongue	(1)	
Papilloma squamous	1 (100%)	
Cardiovascular System		
Heart	(50)	(49)
Endocrine System		
Adrenal gland, cortex	(50)	(50)
Adenoma	1 (2%)	1 (2%)
Carcinoma	1 (2%)	
Adrenal gland, medulla	(50)	(50)
Pheochromocytoma benign	6 (12%)	4 (8%)
Bilateral, pheochromocytoma benign		1 (2%)

TABLE C1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	90 ppm 0 ppm	9 ppm 25 ppm	0 ppm 83 ppm	30 ppm 83 ppm	90 ppm 83 ppm
Endocrine System (continued)						
Parathyroid gland	(46)	(47)	(48)	(46)	(46)	(47)
Adenoma		1 (2%)	2 (4%)		1 (2%)	1 (2%)
Pituitary gland	(50)	(50)	(49)	(49)	(49)	(49)
Pars distalis, adenoma	24 (48%)	23 (46%)	26 (53%)	25 (51%)	20 (41%)	25 (51%)
Pars distalis, adenoma, multiple			1 (2%)			1 (2%)
Pars distalis, carcinoma			1 (2%)	1 (2%)		1 (2%)
Thyroid gland	(50)	(48)	(49)	(44)	(46)	(47)
Bilateral, C-cell, adenoma			3 (6%)		2 (4%)	
Bilateral, follicular cell, adenoma, multiple				1 (2%)		
C-cell, adenoma	11 (22%)	10 (21%)	14 (29%)	12 (27%)	6 (13%)	6 (13%)
C-cell, carcinoma	1 (2%)	3 (6%)	1 (2%)		1 (2%)	2 (4%)
Follicular cell, carcinoma	2 (4%)		1 (2%)	1 (2%)	1 (2%)	2 (4%)
Follicular cell, adenoma	1 (2%)			5 (11%)	5 (11%)	7 (15%)
General Body System						
None						
Genital System						
Clitoral gland	(48)	(50)	(49)	(47)	(49)	(45)
Adenoma	3 (6%)	1 (2%)		2 (4%)	1 (2%)	
Carcinoma		1 (2%)		1 (2%)		1 (2%)
Ovary	(50)	(50)	(50)	(50)	(50)	(50)
Adenocarcinoma, metastatic, uterus	1 (2%)					
Cystadenoma						1 (2%)
Granulosa-theca tumor malignant				1 (2%)		
Uterus	(50)	(50)	(50)	(50)	(50)	(50)
Adenocarcinoma	1 (2%)					
Leiomyoma	1 (2%)		1 (2%)	1 (2%)		
Polyp stromal	8 (16%)	6 (12%)	13 (26%)	15 (30%)	7 (14%)	6 (12%)
Polyp stromal, multiple	1 (2%)					
Sarcoma stromal		1 (2%)			1 (2%)	
Cervix, squamous cell carcinoma		1 (2%)				
Hematopoietic System						
Blood	(10)	(10)	(16)	(14)	(18)	(11)
Bone marrow	(50)	(50)	(49)	(50)	(47)	(50)
Lymph node	(50)	(49)	(50)	(50)	(50)	(50)
Deep cervical, carcinoma, metastatic, thyroid gland		1 (2%)				
Lymph node, mesenteric	(5)	(8)	(6)	(14)	(14)	(6)
Spleen	(50)	(50)	(50)	(50)	(50)	(50)
Adenocarcinoma, metastatic, uterus	1 (2%)					
Fibrosarcoma						2 (4%)
Hemangiosarcoma				1 (2%)		
Thymus	(43)	(46)	(44)	(44)	(45)	(42)

TABLE C1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 250 ppm	90 ppm 250 ppm
Endocrine System (continued)		
Pituitary gland	(50)	(50)
Pars distalis, adenoma	18 (36%)	24 (48%)
Pars distalis, carcinoma	3 (6%)	2 (4%)
Pars intermedia, adenoma	1 (2%)	
Thyroid gland	(49)	(50)
Bilateral, C-cell, adenoma	1 (2%)	2 (4%)
Bilateral, follicular cell, carcinoma	1 (2%)	4 (8%)
Bilateral, follicular cell, adenoma	6 (12%)	9 (18%)
Bilateral, follicular cell, adenoma, multiple	7 (14%)	2 (4%)
C-cell, adenoma	9 (18%)	6 (12%)
C-cell, carcinoma	1 (2%)	
Follicular cell, carcinoma	7 (14%)	13 (26%)
Follicular cell, adenoma	12 (24%)	11 (22%)
Follicular cell, adenoma, multiple	3 (6%)	7 (14%)
General Body System		
None		
Genital System		
Clitoral gland	(47)	(47)
Adenoma	2 (4%)	2 (4%)
Ovary	(50)	(50)
Granulosa-theca tumor benign	1 (2%)	
Uterus	(50)	(50)
Polyp stromal	7 (14%)	3 (6%)
Sarcoma stromal		1 (2%)
Hematopoietic System		
Blood	(22)	(17)
Bone marrow	(49)	(50)
Lymph node	(50)	(50)
Lymph node, mesenteric	(3)	(8)
Spleen	(50)	(50)
Thymus	(41)	(44)

TABLE C1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	90 ppm 0 ppm	9 ppm 25 ppm	0 ppm 83 ppm	30 ppm 83 ppm	90 ppm 83 ppm
Integumentary System						
Mammary gland	(50)	(47)	(50)	(50)	(50)	(50)
Adenocarcinoma			1 (2%)	1 (2%)	2 (4%)	
Adenoma		1 (2%)	1 (2%)			2 (4%)
Fibroadenoma	10 (20%)	11 (23%)	7 (14%)	11 (22%)	11 (22%)	9 (18%)
Fibroadenoma, multiple	3 (6%)	2 (4%)	1 (2%)	2 (4%)		
Mixed tumor malignant						1 (2%)
Skin	(50)	(49)	(50)	(50)	(50)	(48)
Basal cell adenoma		1 (2%)				
Basal cell carcinoma		1 (2%)				
Keratoacanthoma	1 (2%)		1 (2%)			
Squamous cell carcinoma					1 (2%)	
Subcutaneous tissue, fibroma					1 (2%)	1 (2%)
Subcutaneous tissue, fibrosarcoma	1 (2%)					1 (2%)
Subcutaneous tissue, lip, osteosarcoma, metastatic, bone	1 (2%)					
Musculoskeletal System						
Bone	(50)	(49)	(50)	(50)	(50)	(50)
Chondrosarcoma			2 (4%)			
Mandible, osteosarcoma	1 (2%)					
Skeletal muscle		(1)				
Diaphragm, sarcoma stromal, metastatic, uterus		1 (100%)				
Nervous System						
Brain	(50)	(50)	(50)	(50)	(50)	(50)
Astrocytoma malignant	1 (2%)		1 (2%)			
Carcinoma, metastatic, pituitary gland			1 (2%)			1 (2%)
Meningioma benign					1 (2%)	
Respiratory System						
Lung	(50)	(50)	(50)	(50)	(50)	(50)
Adenocarcinoma, metastatic, uterus	1 (2%)					
Alveolar/bronchiolar carcinoma						1 (2%)
Carcinoma, metastatic, thyroid gland					1 (2%)	
Chordoma, metastatic, uncertain primary site	1 (2%)			1 (2%)		
Histiocytic sarcoma		1 (2%)				
Mixed tumor malignant, metastatic, mammary gland						1 (2%)
Pheochromocytoma malignant, metastatic, adrenal gland				1 (2%)		
Nose	(50)	(50)	(49)	(50)	(49)	(50)
Trachea	(50)	(50)	(49)	(50)	(50)	(50)

TABLE C1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Ethylene Thiourea[a] (continued)

F_0 Concentration F_1 Concentration	0 ppm 250 ppm	90 ppm 250 ppm
Integumentary System		
Mammary gland	(50)	(50)
Adenocarcinoma	2 (4%)	2 (4%)
Fibroadenoma	7 (14%)	9 (18%)
Fibroadenoma, multiple	1 (2%)	
Skin	(49)	(50)
Subcutaneous tissue, fibroma		1 (2%)
Subcutaneous tissue, fibrosarcoma	1 (2%)	
Musculoskeletal System		
Skeletal muscle		(1)
Nervous System		
Brain	(50)	(50)
Carcinoma, metastatic, pituitary gland	3 (6%)	1 (2%)
Respiratory System		
Lung	(50)	(50)
Carcinoma, metastatic		1 (2%)
Nose	(50)	(50)
Nasolacrimal duct, papilloma squamous		1 (2%)
Trachea	(50)	(50)
Adenocarcinoma, metastatic, thyroid gland		1 (2%)

TABLE C1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	90 ppm 0 ppm	9 ppm 25 ppm	0 ppm 83 ppm	30 ppm 83 ppm	90 ppm 83 ppm
Special Senses System						
Ear				(1)		
Fibrosarcoma				1 (100%)		
Harderian gland	(50)	(50)	(50)	(50)	(50)	(50)
Zymbal's gland	(1)					(3)
Adenoma						2 (67%)
Carcinoma	1 (100%)					1 (33%)
Urinary System						
Kidney	(50)	(49)	(50)	(50)	(50)	(50)
Adenocarcinoma, metastatic, uterus	1 (2%)					
Lipoma		1 (2%)				
Mixed tumor benign				1 (2%)		
Renal tubule, adenoma				1 (2%)	1 (2%)	
Urinary bladder	(49)	(48)	(50)	(47)	(48)	(50)
Adenocarcinoma, metastatic, uterus	1 (2%)					
Hemangioma		1 (2%)				
Sarcoma stromal, metastatic, uterus		1 (2%)				
Transitional epithelium, carcinoma					1 (2%)	
Systemic Lesions						
Multiple organs[b]	(50)	(50)	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)				
Leukemia mononuclear	18 (36%)	18 (36%)	19 (38%)	22 (44%)	29 (58%)	23 (46%)
Mesothelioma malignant	1 (2%)					
Tumor Summary						
Total animals with primary neoplasms[c]	48	46	46	46	46	47
Total primary neoplasms	95	95	107	112	102	109
Total animals with benign neoplasms	40	38	39	39	40	38
Total benign neoplasms	68	69	80	81	65	74
Total animals with malignant neoplasms	25	23	24	28	35	30
Total malignant neoplasms	27	26	27	31	37	35
Total animals with secondary neoplasms[d]	3	2	1	2	1	2
Total secondary neoplasms	12	5	1	2	1	2
Total animals with malignant neoplasms of uncertain primary site	1			1		

TABLE C1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Ethylene Thiourea[a] (continued)

F_0 Concentration F_1 Concentration	0 ppm 250 ppm	90 ppm 250 ppm
Special Senses System		
Ear	(1)	(1)
Papilloma squamous	1 (100%)	
Eye	(12)	(8)
Harderian gland	(50)	(50)
Zymbal's gland	(2)	(4)
Carcinoma	2 (100%)	4 (100%)
Urinary System		
Kidney	(50)	(50)
Urinary bladder	(49)	(50)
Systemic Lesions		
Multiple organs[b]	(50)	(50)
Leukemia mononuclear	27 (54%)	25 (50%)
Tumor Summary		
Total animals with primary neoplasms	49	50
Total primary neoplasms	129	136
Total animals with benign neoplasms	44	42
Total benign neoplasms	84	84
Total animals with malignant neoplasms	35	41
Total malignant neoplasms	45	52
Total animals with secondary neoplasms	3	3
Total secondary neoplasms	3	3

[a] Effects on rats exposed to ethylene thiourea perinatally through 8 weeks of age (F_0 concentration) and for 2 years postnatally (F_1 concentration)
[b] The number in parentheses is the number of animals with any tissue examined microscopically.
[c] Primary tumors: all tumors except metastatic tumors
[d] Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

TABLE C2
Statistical Analysis of Primary Tumors in Female Rats in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 0:83, and 0:250 ppm Groups

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	0 ppm 83 ppm	0 ppm 250 ppm
Adrenal Gland, Medulla: Benign Pheochromocytoma			
Overall rates[a]	2/50 (4%)	2/49 (4%)	6/50 (12%)
Adjusted rates[b]	7.7%	6.1%	20.3%
Terminal rates[c]	1/24 (4%)	2/33 (6%)	2/20 (10%)
First incidence (days)	721	740 (T)	605
Life table tests[d]	P=0.044	P=0.581N	P=0.130
Logistic regression tests[d]	P=0.071	P=0.609N	P=0.148
Cochran-Armitage test[d]	P=0.070		
Fisher exact test[d]		P=0.684	P=0.134
Adrenal Gland, Medulla: Malignant Pheochromocytoma			
Overall rates	0/50 (0%)	2/49 (4%)	0/50 (0%)
Adjusted rates	0.0%	5.3%	0.0%
Terminal rates	0/24 (0%)	1/33 (3%)	0/20 (0%)
First incidence (days)	-[e]	638	-
Life table tests	P=0.602N	P=0.296	-
Logistic regression tests	P=0.573N	P=0.233	-
Cochran-Armitage test	P=0.573N		
Fisher exact test		P=0.242	-
Adrenal Gland, Medulla: Benign or Malignant Pheochromocytoma			
Overall rates	2/50 (4%)	4/49 (8%)	6/50 (12%)
Adjusted rates	7.7%	11.2%	20.3%
Terminal rates	1/24 (4%)	3/33 (9%)	2/20 (10%)
First incidence (days)	721	638	605
Life table tests	P=0.077	P=0.475	P=0.130
Logistic regression tests	P=0.120	P=0.401	P=0.148
Cochran-Armitage test	P=0.116		
Fisher exact test		P=0.329	P=0.134
Clitoral Gland: Adenoma			
Overall rates	3/48 (6%)	2/47 (4%)	2/47 (4%)
Adjusted rates	13.0%	6.5%	5.0%
Terminal rates	3/23 (13%)	2/31 (6%)	0/17 (0%)
First incidence (days)	740 (T)	740 (T)	570
Life table tests	P=0.557N	P=0.364N	P=0.552N
Logistic regression tests	P=0.465N	P=0.364N	P=0.499N
Cochran-Armitage test	P=0.467N		
Fisher exact test		P=0.510N	P=0.510N
Clitoral Gland: Adenoma or Carcinoma			
Overall rates	3/48 (6%)	3/47 (6%)	2/47 (4%)
Adjusted rates	13.0%	9.7%	5.0%
Terminal rates	3/23 (13%)	3/31 (10%)	0/17 (0%)
First incidence (days)	740 (T)	740 (T)	570
Life table tests	P=0.535N	P=0.519N	P=0.552N
Logistic regression tests	P=0.432N	P=0.519N	P=0.499N
Cochran-Armitage test	P=0.432N		
Fisher exact test		P=0.651	P=0.510N

TABLE C2
Statistical Analysis of Primary Tumors in Female Rats in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 0:83, and 0:250 ppm Groups (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	0 ppm 83 ppm	0 ppm 250 ppm
Mammary Gland: Fibroadenoma			
Overall rates	13/50 (26%)	13/50 (26%)	8/50 (16%)
Adjusted rates	43.9%	36.5%	30.5%
Terminal rates	9/24 (38%)	11/33 (33%)	4/20 (20%)
First incidence (days)	494	638	605
Life table tests	P=0.239N	P=0.280N	P=0.243N
Logistic regression tests	P=0.107N	P=0.459N	P=0.132N
Cochran-Armitage test	P=0.126N		
Fisher exact test		P=0.590N	P=0.163N
Mammary Gland: Adenoma, Fibroadenoma, or Adenocarcinoma			
Overall rates	13/50 (26%)	13/50 (26%)	10/50 (20%)
Adjusted rates	43.9%	36.5%	36.4%
Terminal rates	9/24 (38%)	11/33 (33%)	5/20 (25%)
First incidence (days)	494	638	605
Life table tests	P=0.444N	P=0.280N	P=0.420N
Logistic regression tests	P=0.242N	P=0.459N	P=0.272N
Cochran-Armitage test	P=0.270N		
Fisher exact test		P=0.590N	P=0.318N
Pituitary Gland, Pars Distalis: Adenoma			
Overall rates	24/50 (48%)	25/49 (51%)	18/50 (36%)
Adjusted rates	66.8%	66.7%	52.9%
Terminal rates	13/24 (54%)	21/33 (64%)	7/20 (35%)
First incidence (days)	466	372	487
Life table tests	P=0.283N	P=0.200N	P=0.253N
Logistic regression tests	P=0.097N	P=0.553	P=0.146N
Cochran-Armitage test	P=0.106N		
Fisher exact test		P=0.460	P=0.156N
Pituitary Gland, Pars Distalis: Adenoma or Carcinoma			
Overall rates	24/50 (48%)	26/49 (53%)	21/50 (42%)
Adjusted rates	66.8%	67.5%	60.1%
Terminal rates	13/24 (54%)	21/33 (64%)	8/20 (40%)
First incidence (days)	466	372	487
Life table tests	P=0.515N	P=0.253N	P=0.458N
Logistic regression tests	P=0.247N	P=0.453	P=0.317N
Cochran-Armitage test	P=0.263N		
Fisher exact test		P=0.381	P=0.344N
Thyroid Gland: C-cell Adenoma			
Overall rates	11/50 (22%)	12/44 (27%)	10/49 (20%)
Adjusted rates	33.6%	34.2%	40.8%
Terminal rates	5/24 (21%)	10/33 (30%)	7/20 (35%)
First incidence (days)	424	718	601
Life table tests	P=0.503	P=0.402N	P=0.592N
Logistic regression tests	P=0.399N	P=0.472	P=0.478N
Cochran-Armitage test	P=0.433N		
Fisher exact test		P=0.361	P=0.521N

TABLE C2
Statistical Analysis of Primary Tumors in Female Rats in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 0:83, and 0:250 ppm Groups (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	0 ppm 83 ppm	0 ppm 250 ppm
Thyroid Gland: C-cell Adenoma or Carcinoma			
Overall rates	12/50 (24%)	12/44 (27%)	10/49 (20%)
Adjusted rates	35.8%	34.2%	40.8%
Terminal rates	5/24 (21%)	10/33 (30%)	7/20 (35%)
First incidence (days)	424	718	601
Life table tests	P=0.546N	P=0.312N	P=0.503N
Logistic regression tests	P=0.320N	P=0.568	P=0.381N
Cochran-Armitage test	P=0.354N		
Fisher exact test		P=0.449	P=0.426N
Thyroid Gland: Follicular Cell Adenoma			
Overall rates	1/50 (2%)	6/44 (14%)	28/49 (57%)
Adjusted rates	4.2%	18.2%	84.2%
Terminal rates	1/24 (4%)	6/33 (18%)	15/20 (75%)
First incidence (days)	740 (T)	740 (T)	588
Life table tests	P<0.001	P=0.120	P<0.001
Logistic regression tests	P<0.001	P=0.120	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.038	P<0.001
Thyroid Gland: Follicular Cell Carcinoma			
Overall rates	2/50 (4%)	1/44 (2%)	8/49(16%)
Adjusted rates	8.3%	3.0%	31.9%
Terminal rates	2/24 (8%)	1/33 (3%)	5/20 (25%)
First incidence (days)	740 (T)	740 (T)	657
Life table tests	P=0.003	P=0.389N	P=0.033
Logistic regression tests	P=0.008	P=0.389N	P=0.047
Cochran-Armitage test	P=0.011		
Fisher exact test		P=0.548N	P=0.043
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall rates	3/50 (6%)	7/44 (16%)	30/49 (61%)
Adjusted rates	12.5%	21.2%	85.0%
Terminal rates	3/24 (13%)	7/33 (21%)	15/20 (75%)
First incidence (days)	740 (T)	740 (T)	588
Life table tests	P<0.001	P=0.310	P<0.001
Logistic regression tests	P<0.001	P=0.310	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.111	P<0.001
Uterus: Stromal Polyp			
Overall rates	9/50 (18%)	15/50 (30%)	7/50 (14%)
Adjusted rates	35.2%	41.2%	24.3%
Terminal rates	8/24 (33%)	12/33 (36%)	3/20 (15%)
First incidence (days)	642	638	570
Life table tests	P=0.405N	P=0.361	P=0.481N
Logistic regression tests	P=0.224N	P=0.262	P=0.351N
Cochran-Armitage test	P=0.241N		
Fisher exact test		P=0.121	P=0.393N

TABLE C2
Statistical Analysis of Primary Tumors in Female Rats in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 0:83, and 0:250 ppm Groups (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	0 ppm 83 ppm	0 ppm 250 ppm
All Organs: Mononuclear Cell Leukemia			
Overall rates	18/50 (36%)	22/50 (44%)	27/50 (54%)
Adjusted rates	48.2%	50.6%	70.0%
Terminal rates	6/24 (25%)	12/33 (36%)	10/20 (50%)
First incidence (days)	523	461	547
Life table tests	P=0.037	P=0.502N	P=0.082
Logistic regression tests	P=0.050	P=0.287	P=0.060
Cochran-Armitage test	P=0.048		
Fisher exact test		P=0.270	P=0.054
All Organs: Benign Tumors			
Overall rates	40/50 (80%)	39/50 (78%)	44/50 (88%)
Adjusted rates	92.8%	92.7%	95.6%
Terminal rates	21/24 (88%)	30/33 (91%)	18/20 (90%)
First incidence (days)	424	372	487
Life table tests	P=0.062	P=0.037N	P=0.215
Logistic regression tests	P=0.217	P=0.335N	P=0.290
Cochran-Armitage test	P=0.153		
Fisher exact test		P=0.500N	P=0.207
All Organs: Malignant Tumors			
Overall rates	26/50 (52%)	28/50 (56%)	35/50(70%)
Adjusted rates	64.1%	61.9%	84.6%
Terminal rates	10/24 (42%)	16/33 (48%)	14/20 (70%)
First incidence (days)	424	461	547
Life table tests	P=0.031	P=0.282N	P=0.086
Logistic regression tests	P=0.043	P=0.446	P=0.064
Cochran-Armitage test	P=0.038		
Fisher exact test		P=0.421	P=0.050
All Organs: Benign or Malignant Tumors			
Overall rates	48/50 (96%)	46/50 (92%)	49/50 (98%)
Adjusted rates	96.0%	95.8%	100.0%
Terminal rates	22/24 (92%)	31/33 (94%)	20/20 (100%)
First incidence (days)	424	372	487
Life table tests	P=0.170	P=0.029N	P=0.378
Logistic regression tests	P=0.350	P=0.339N	P=0.490
Cochran-Armitage test	P=0.339		
Fisher exact test		P=0.339N	P=0.500

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

TABLE C3
Statistical Analysis of Primary Tumors in Female Rats in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 90:0, 9:25, 30:83, 90:83, and 90:250 ppm Groups

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	90 ppm 0 ppm	9 ppm 25 ppm	30 ppm 83 ppm	90 ppm 83 ppm	90 ppm 250 ppm
Adrenal Gland, Medulla: Benign Pheochromocytoma						
Overall rates[a]	2/50 (4%)	8/49 (16%)	3/49 (6%)	6/49 (12%)	10/50 (20%)	5/50 (10%)
Adjusted rates[b]	7.7%	24.3%	8.5%	19.7%	24.8%	17.0%
Terminal rates[c]	1/24 (4%)	6/30 (20%)	2/33 (6%)	4/27 (15%)	4/33 (12%)	0/14 (0%)
First incidence (days)	721	592	699	622	550	564
Life table tests[d]		P=0.091	P=0.634	P=0.171	P=0.060	P=0.121
Logistic regression tests[d]		P=0.065	P=0.587	P=0.148	P=0.024	P=0.213
Fisher exact test[d]		P=0.043	P=0.490	P=0.128	P=0.014	P=0.218
Clitoral Gland: Adenoma						
Overall rates	3/48 (6%)	1/50 (2%)	0/49 (0%)	1/49 (2%)	0/45 (0%)	2/47 (4%)
Adjusted rates	13.0%	3.3%	0.0%	3.7%	0.0%	7.1%
Terminal rates	3/23 (13%)	1/30 (3%)	0/34 (0%)	1/27 (4%)	0/30 (0%)	0/13 (0%)
First incidence (days)	740 (T)	740 (T)	-[e]	740 (T)	-	548
Life table tests		P=0.214N	P=0.061N	P=0.247N	P=0.077N	P=0.679N
Logistic regression tests		P=0.214N	P=0.061N	P=0.247N	P=0.077N	P=0.566N
Fisher exact test		P=0.293N	P=0.117N	P=0.301N	P=0.133N	P=0.510N
Clitoral Gland: Adenoma or Carcinoma						
Overall rates	3/48 (6%)	2/50 (4%)	0/49 (0%)	1/49 (2%)	1/45 (2%)	2/47 (4%)
Adjusted rates	13.0%	5.7%	0.0%	3.7%	3.3%	7.1%
Terminal rates	3/23 (13%)	1/30 (3%)	0/34 (0%)	1/27 (4%)	1/30 (3%)	0/13 (0%)
First incidence (days)	740 (T)	658	-	740 (T)	740 (T)	548
Life table tests		P=0.384N	P=0.061N	P=0.247N	P=0.214N	P=0.679N
Logistic regression tests		P=0.426N	P=0.061N	P=0.247N	P=0.214N	P=0.566N
Fisher exact test		P=0.480N	P=0.117N	P=0.301N	P=0.333N	P=0.510N
Mammary Gland: Fibroadenoma						
Overall rates	13/50 (26%)	13/50 (26%)	8/50 (16%)	11/50 (22%)	9/50 (18%)	9/50 (18%)
Adjusted rates	43.9%	36.2%	22.7%	34.1%	25.4%	40.3%
Terminal rates	9/24 (38%)	9/30 (30%)	7/34 (21%)	7/27 (26%)	7/33 (21%)	4/14 (29%)
First incidence (days)	494	431	700	622	704	565
Life table tests		P=0.393N	P=0.040N	P=0.312N	P=0.071N	P=0.578
Logistic regression tests		P=0.567N	P=0.093N	P=0.354N	P=0.138N	P=0.296N
Fisher exact test		P=0.590N	P=0.163N	P=0.408N	P=0.235N	P=0.235N
Mammary Gland: Fibroadenoma, Adenoma, Adenocarcinoma, or Carcinoma						
Overall rates	13/50 (26%)	14/50 (28%)	9/50 (18%)	13/50 (26%)	11/50 (22%)	11/50 (22%)
Adjusted rates	43.9%	39.3%	25.5%	40.7%	31.1%	47.4%
Terminal rates	9/24 (38%)	10/30 (33%)	8/34 (24%)	9/27 (33%)	9/33 (27%)	5/14 (36%)
First incidence (days)	494	431	700	622	704	544
Life table tests		P=0.471N	P=0.063N	P=0.477N	P=0.149N	P=0.370
Logistic regression tests		P=0.530	P=0.138N	P=0.529N	P=0.259N	P=0.475N
Fisher exact test		P=0.500	P=0.235N	P=0.590N	P=0.408N	P=0.408N
Pituitary Gland, Pars Distalis: Adenoma						
Overall rates	24/50 (48%)	23/50 (46%)	27/49 (55%)	20/49 (41%)	26/49 (53%)	24/50 (48%)
Adjusted rates	66.8%	61.2%	65.6%	54.2%	67.7%	77.1%
Terminal rates	13/24 (54%)	16/30 (53%)	20/34 (59%)	11/27 (41%)	20/32 (63%)	8/14 (57%)
First incidence (days)	466	480	610	574	494	462
Life table tests		P=0.227N	P=0.271N	P=0.184N	P=0.271N	P=0.100
Logistic regression tests		P=0.437N	P=0.482	P=0.262N	P=0.529	P=0.507
Fisher exact test		P=0.500N	P=0.307	P=0.303N	P=0.381	P=0.579N

TABLE C3
Statistical Analysis of Primary Tumors in Female Rats in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 90:0, 9:25, 30:83, 90:83, and 90:250 ppm Groups (continued)

F_0 Concentration	0 ppm	90 ppm	9 ppm	30 ppm	90 ppm	90 ppm
F_1 Concentration	0 ppm	0 ppm	25 ppm	83 ppm	83 ppm	250 ppm
Pituitary Gland, Pars Distalis: Adenoma or Carcinoma						
Overall rates	24/50 (48%)	23/50 (46%)	28/49 (57%)	20/49 (41%)	27/49 (55%)	26/50 (52%)
Adjusted rates	66.8%	61.2%	68.0%	54.2%	70.4%	78.7%
Terminal rates	13/24 (54%)	16/30 (53%)	21/34 (62%)	11/27 (41%)	21/32 (66%)	8/14 (57%)
First incidence (days)	466	480	610	574	494	462
Life table tests		P=0.227N	P=0.321N	P=0.184N	P=0.325N	P=0.056
Logistic regression tests		P=0.437N	P=0.410	P=0.262N	P=0.456	P=0.356
Fisher exact test		P=0.500N	P=0.239	P=0.303N	P=0.307	P=0.421
Thyroid Gland: C-cell Adenoma						
Overall rates	11/50 (22%)	10/48 (21%)	17/49 (35%)	8/46 (17%)	6/47 (13%)	8/50 (16%)
Adjusted rates	33.6%	30.1%	44.2%	29.6%	16.7%	25.5%
Terminal rates	5/24 (21%)	8/30 (27%)	13/34 (38%)	8/27 (30%)	4/32 (13%)	1/14 (7%)
First incidence (days)	424	488	581	740 (T)	558	564
Life table tests		P=0.338N	P=0.423	P=0.238N	P=0.062N	P=0.581N
Logistic regression tests		P=0.517N	P=0.176	P=0.323N	P=0.184N	P=0.295N
Fisher exact test		P=0.542N	P=0.119	P=0.379N	P=0.177N	P=0.306N
Thyroid Gland: C-cell Carcinoma						
Overall rates	1/50 (2%)	3/48 (6%)	1/49 (2%)	1/46 (2%)	2/47 (4%)	0/50 (0%)
Adjusted rates	3.3%	8.7%	2.9%	3.7%	6.3%	0.0%
Terminal rates	0/24 (0%)	1/30 (3%)	1/34 (3%)	1/27 (4%)	2/32 (6%)	0/14 (0%)
First incidence (days)	707	674	740 (T)	740 (T)	740 (T)	-
Life table tests		P=0.370	P=0.701N	P=0.747N	P=0.593	P=0.591N
Logistic regression tests		P=0.318	P=0.727N	P=0.755N	P=0.570	P=0.539N
Fisher exact test		P=0.293	P=0.747	P=0.731	P=0.477	P=0.500N
Thyroid Gland: C-cell Adenoma or Carcinoma						
Overall rates	12/50 (24%)	11/48 (23%)	18/49 (37%)	8/46 (17%)	8/47 (17%)	8/50 (16%)
Adjusted rates	35.8%	32.2%	46.9%	29.6%	22.6%	25.5%
Terminal rates	5/24 (21%)	8/30 (27%)	14/34 (41%)	8/27 (30%)	6/32 (19%)	1/14 (7%)
First incidence (days)	424	488	581	740 (T)	558	564
Life table tests		P=0.337N	P=0.447	P=0.175N	P=0.098N	P=0.507N
Logistic regression tests		P=0.513N	P=0.190	P=0.240N	P=0.258N	P=0.222N
Fisher exact test		P=0.545N	P=0.123	P=0.294N	P=0.276N	P=0.227N
Thyroid Gland: Follicular Cell Adenoma						
Overall rates	1/50 (2%)	0/48 (0%)	0/49 (0%)	5/46 (11%)	7/47 (15%)	29/50 (58%)
Adjusted rates	4.2%	0.0%	0.0%	16.2%	21.9%	89.1%
Terminal rates	1/24 (4%)	0/30 (0%)	0/34 (0%)	3/27 (11%)	7/32 (22%)	11/14 (79%)
First incidence (days)	740 (T)	-	-	597	740 (T)	469
Life table tests		P=0.455N	P=0.431N	P=0.131	P=0.070	P<0.001
Logistic regression tests		P=0.455N	P=0.431N	P=0.102	P=0.070	P<0.001
Fisher exact test		P=0.510N	P=0.505N	P=0.084	P=0.024	P<0.001
Thyroid Gland: Follicular Cell Carcinoma						
Overall rates	2/50 (4%)	0/48 (0%)	1/49 (2%)	1/46 (2%)	2/47 (4%)	17/50 (34%)
Adjusted rates	8.3%	0.0%	2.9%	3.7%	5.8%	66.5%
Terminal rates	2/24 (8%)	0/30 (0%)	1/34 (3%)	1/27 (4%)	1/32 (3%)	7/14 (50%)
First incidence (days)	740 (T)	-	740 (T)	740 (T)	721	462
Life table tests		P=0.190N	P=0.379N	P=0.459N	P=0.587N	P<0.001
Logistic regression tests		P=0.190N	P=0.379N	P=0.459N	P=0.603N	P<0.001
Fisher exact test		P=0.258N	P=0.508N	P=0.532N	P=0.668	P<0.001

TABLE C3
Statistical Analysis of Primary Tumors in Female Rats in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 90:0, 9:25, 30:83, 90:83, and 90:250 ppm Groups (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	90 ppm 0 ppm	9 ppm 25 ppm	30 ppm 83 ppm	90 ppm 83 ppm	90 ppm 250 ppm
Thyroid Gland: Follicular Cell Adenoma or Carcinoma						
Overall rates	3/50 (6%)	0/48 (0%)	1/49 (2%)	6/46 (13%)	9/47 (19%)	37/50 (74%)
Adjusted rates	12.5%	0.0%	2.9%	19.7%	27.1%	94.3%
Terminal rates	3/24 (13%)	0/30 (0%)	1/34 (3%)	4/27 (15%)	8/32 (25%)	12/14 (86%)
First incidence (days)	740 (T)	-	740 (T)	597	721	462
Life table tests		P=0.084N	P=0.189N	P=0.298	P=0.147	P<0.001
Logistic regression tests		P=0.084N	P=0.189N	P=0.256	P=0.137	P<0.001
Fisher exact test		P=0.129N	P=0.316N	P=0.203	P=0.048	P<0.001
Uterus: Stromal Polyp						
Overall rates	9/50 (18%)	6/50 (12%)	13/50 (26%)	7/50 (14%)	6/50 (12%)	3/50 (6%)
Adjusted rates	35.2%	16.5%	34.1%	20.9%	16.4%	17.2%
Terminal rates	8/24 (33%)	3/30 (10%)	9/34 (26%)	4/27 (15%)	4/33 (12%)	2/14 (14%)
First incidence (days)	642	494	679	312	558	637
Life table tests		P=0.175N	P=0.556	P=0.316N	P=0.114N	P=0.240N
Logistic regression tests		P=0.251N	P=0.446	P=0.381N	P=0.169N	P=0.154N
Fisher exact test		P=0.288N	P=0.235	P=0.393N	P=0.288N	P=0.061N
Uterus: Stromal Polyp or Stromal Sarcoma						
Overall rates	9/50 (18%)	7/50 (14%)	13/50 (26%)	8/50 (16%)	6/50 (12%)	4/50 (8%)
Adjusted rates	35.2%	18.3%	34.1%	23.3%	16.4%	19.3%
Terminal rates	8/24 (33%)	3/30 (10%)	9/34 (26%)	4/27 (15%)	4/33 (12%)	2/14 (14%)
First incidence (days)	642	480	679	312	558	592
Life table tests		P=0.264N	P=0.556	P=0.420N	P=0.114N	P=0.359N
Logistic regression tests		P=0.378N	P=0.446	P=0.487N	P=0.169N	P=0.216N
Fisher exact test		P=0.393N	P=0.235	P=0.500N	P=0.288N	P=0.117N
Zymbal's Gland: Carcinoma						
Overall rates	1/50 (2%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%)	4/50 (8%)
Adjusted rates	4.2%	0.0%	0.0%	0.0%	2.0%	12.4%
Terminal rates	1/24 (4%)	0/30 (0%)	0/34 (0%)	0/27 (0%)	0/33 (0%)	0/14 (0%)
First incidence (days)	740 (T)	-	-	-	494	565
Life table tests		P=0.455N	P=0.431N	P=0.477N	P=0.723N	P=0.142
Logistic regression tests		P=0.455N	P=0.431N	P=0.477N	P=0.693	P=0.191
Fisher exact test		P=0.500N	P=0.500N	P=0.500N	P=0.753N	P=0.181
Zymbal's Gland: Adenoma or Carcinoma						
Overall rates	1/50 (2%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	3/50 (6%)	4/50 (8%)
Adjusted rates	4.2%	0.0%	0.0%	0.0%	7.6%	12.4%
Terminal rates	1/24 (4%)	0/30 (0%)	0/34 (0%)	0/27 (0%)	1/33 (3%)	0/14 (0%)
First incidence (days)	740 (T)	-	-	-	494	565
Life table tests		P=0.455N	P=0.431N	P=0.477N	P=0.396	P=0.142
Logistic regression tests		P=0.455N	P=0.431N	P=0.477N	P=0.274	P=0.191
Fisher exact test		P=0.500N	P=0.500N	P=0.500N	P=0.309	P=0.181
All Organs: Mononuclear Cell Leukemia						
Overall rates	18/50 (36%)	18/50 (36%)	19/50 (38%)	29/50 (58%)	23/50 (46%)	25/50 (50%)
Adjusted rates	48.2%	45.2%	45.0%	66.7%	50.6%	70.2%
Terminal rates	6/24 (25%)	9/30 (30%)	12/34 (35%)	13/27 (48%)	11/33 (33%)	5/14 (36%)
First incidence (days)	523	592	523	312	550	469
Life table tests		P=0.357N	P=0.304N	P=0.107	P=0.540N	P=0.022
Logistic regression tests		P=0.548N	P=0.490	P=0.023	P=0.210	P=0.111
Fisher exact test		P=0.582N	P=0.500	P=0.022	P=0.208	P=0.113

TABLE C3
Statistical Analysis of Primary Tumors in Female Rats in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 90:0, 9:25, 30:83, 90:83, and 90:250 ppm Groups (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	90 ppm 0 ppm	9 ppm 25 ppm	30 ppm 83 ppm	90 ppm 83 ppm	90 ppm 250 ppm
All Organs: Benign Tumors						
Overall rates	40/50 (80%)	38/50 (76%)	39/50 (78%)	40/50 (80%)	38/50 (76%)	42/50 (84%)
Adjusted rates	92.8%	90.2%	88.6%	88.7%	84.3%	97.4%
Terminal rates	21/24 (88%)	26/30 (87%)	29/34 (85%)	22/27 (81%)	26/33 (79%)	13/14 (93%)
First incidence (days)	424	431	581	312	494	462
Life table tests		P=0.107N	P=0.028N	P=0.342N	P=0.033N	P=0.021
Logistic regression tests		P=0.364N	P=0.245N	P=0.572N	P=0.264N	P=0.357
Fisher exact test		P=0.405N	P=0.500N	P=0.598N	P=0.405N	P=0.398
All Organs: Malignant Tumors						
Overall rates	26/50 (52%)	23/50 (46%)	24/50 (48%)	35/50 (70%)	30/50 (60%)	42/50 (84%)
Adjusted rates	64.1%	54.0%	53.7%	77.4%	63.4%	93.0%
Terminal rates	10/24 (42%)	11/30 (37%)	14/34 (41%)	17/27 (63%)	16/33 (48%)	11/14 (79%)
First incidence (days)	424	480	447	312	437	462
Life table tests		P=0.170N	P=0.116N	P=0.224	P=0.371N	P<0.001
Logistic regression tests		P=0.323N	P=0.472N	P=0.052	P=0.219	P<0.001
Fisher exact test		P=0.345N	P=0.421N	P=0.050	P=0.273	P<0.001
All Organs: Benign or Malignant Tumors						
Overall rates	48/50 (96%)	46/50 (92%)	46/50 (92%)	46/50 (92%)	47/50 (94%)	50/50 (100%)
Adjusted rates	96.0%	93.9%	95.8%	92.0%	94.0%	100.0%
Terminal rates	22/24 (92%)	27/30 (90%)	32/34 (94%)	23/27 (85%)	30/33 (91%)	14/14 (100%)
First incidence (days)	424	431	447	312	437	462
Life table tests		P=0.109N	P=0.019N	P=0.237N	P=0.037N	P=0.024
Logistic regression tests		P=0.325N	P=0.316N	P=0.390N	P=0.645N	P=0.362
Fisher exact test		P=0.339N	P=0.339N	P=0.339N	P=0.500N	P=0.247

(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no tumors in animal group

TABLE C4
Statistical Analysis of Selected Primary Tumors in Female Rats in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 90:0, 90:83, and 90:250 ppm Groups

F_0 Concentration F_1 Concentration	90 ppm 0 ppm	90 ppm 83 ppm	90 ppm 250 ppm
Thyroid Gland: Follicular Cell Adenoma			
Overall rates[a]	0/48 (0%)	7/47 (15%)	29/50 (58%)
Life table tests[b]	P<0.001	P=0.011	P<0.001
Logistic regression tests[b]	P<0.001	P=0.011	P<0.001
Cochran-Armitage test[b]	P<0.001		
Fisher exact test[b]		P=0.006	P<0.001
Thyroid Gland: Follicular Cell Carcinoma			
Overall rates	0/48 (0%)	2/47 (4%)	17/50 (34%)
Life table tests	P<0.001	P=0.264	P<0.001
Logistic regression tests	P<0.001	P=0.252	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.242	P<0.001
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall rates	0/48 (0%)	9/47 (19%)	37/50 (74%)
Life table tests	P<0.001	P=0.003	P<0.001
Logistic regression tests	P<0.001	P=0.003	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.001	P<0.001
Zymbal's Gland: Adenoma or Carcinoma			
Overall rates	0/50 (0%)	3/50 (6%)	4/50 (8%)
Life table tests	P=0.031	P=0.145	P=0.044
Logistic regression tests	P=0.099	P=0.093	P=0.068
Cochran-Armitage test	P=0.074		
Fisher exact test		P=0.121	P=0.059
All Organs: Mononuclear Cell or Monocytic Leukemia			
Overall rates	18/50 (36%)	23/50 (46%)	25/50 (50%)
Life table tests	P=0.001	P=0.368	P=0.004
Logistic regression tests	P=0.106	P=0.227	P=0.093
Cochran-Armitage test	P=0.118		
Fisher exact test		P=0.208	P=0.113

[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.

[b] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

TABLE C5
Statistical Analysis of Selected Primary Tumors in Female Rats in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:83, 30:83, and 90:83 ppm Groups

F_0 Concentration F_1 Concentration	0 ppm 83 ppm	30 ppm 83 ppm	90 ppm 83 ppm
Thyroid Gland: Follicular Cell Adenoma			
Overall rates[a]	6/44 (14%)	5/46 (11%)	7/47 (15%)
Life table tests[b]	P=0.427	P=0.621	P=0.475
Logistic regression tests[b]	P=0.483	P=0.535	P=0.475
Cochran-Armitage test[b]	P=0.465		
Fisher exact test[b]		P=0.468N	P=0.552
Thyroid Gland: Follicular Cell Carcinoma			
Overall rates	1/44 (2%)	1/46 (2%)	2/47 (4%)
Life table tests	P=0.404	P=0.717	P=0.496
Logistic regression tests	P=0.419	P=0.717	P=0.520
Cochran-Armitage test	P=0.413		
Fisher exact test		P=0.742N	P=0.525
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall rates	7/44 (16%)	6/46 (13%)	9/47 (19%)
Life table tests	P=0.321	P=0.590	P=0.366
Logistic regression tests	P=0.376	P=0.549N	P=0.386
Cochran-Armitage test	P=0.357		
Fisher exact test		P=0.465N	P=0.449
Zymbal's Gland: Adenoma or Carcinoma			
Overall rates	0/50 (0%)	0/50 (0%)	3/50 (6%)
Life table tests	P=0.039	-[c]	P=0.129
Logistic regression tests	P=0.024	-	P=0.106
Cochran-Armitage test	P=0.031		
Fisher exact test		-	P=0.121
All Organs: Mononuclear Cell or Monocytic Leukemia			
Overall rates	22/50 (44%)	29/50 (58%)	23/50 (46%)
Life table tests	P=0.440N	P=0.059	P=0.517
Logistic regression tests	P=0.534N	P=0.124	P=0.493
Cochran-Armitage test	P=0.517N		
Fisher exact test		P=0.115	P=0.500

[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.

[b] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

[c] Not applicable; no tumors in animal group

TABLE C6
Statistical Analysis of Selected Primary Tumors in Female Rats in the 2-Year Feed Study of Ethylene Thiourea

F_0 Concentration F_1 Concentration	0 ppm 250 ppm	90 ppm 250 ppm
Thyroid Gland: Follicular Cell Adenoma		
Overall rates[a]	28/49 (57%)	29/50 (58%)
Life table tests[b]		P=0.057
Logistic regression tests[b]		P=0.201
Fisher exact test[b]		P=0.547
Thyroid Gland: Follicular Cell Carcinoma		
Overall rates	8/49 (16%)	17/50 (34%)
Life table tests		P=0.003
Logistic regression tests		P=0.011
Fisher exact test		P=0.036
Thyroid Gland: Follicular Cell Adenoma or Carcinoma		
Overall rates	30/49 (61%)	37/50 (74%)
Life table tests		P=0.006
Logistic regression tests		P=0.026
Fisher exact test		P=0.126
Zymbal's Gland: Adenoma or Carcinoma		
Overall rates	2/50 (4%)	4/50 (8%)
Life table tests		P=0.236
Logistic regression tests		P=0.433
Fisher exact test		P=0.339
All Organs: Mononuclear Cell or Monocytic Leukemia		
Overall rates	27/50 (54%)	25/50 (50%)
Life table tests		P=0.226
Logistic regression tests		P=0.427N
Fisher exact test		P=0.421N

[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.

[b] Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

TABLE C7a
Historical Incidence of Zymbal's Gland Adenomas and Carcinomas in Untreated Female F344/N Rats[a]

Study	Incidence in Untreated Controls
Historical Incidence at Battelle Columbus Laboratories	
Chlorobenzene	0/49
N-Phenyl-2-Naphthylamine	0/50
Rotenone	2/50
l-Ascorbic Acid	1/50
Total	3/199 (1.5%)
Standard deviation	1.9%
Range	
High	2/50
Low	0/50
Overall Historical Incidence	
Total	14/1643 (0.9%)
Standard deviation	1.5%
Range	
High	3/50
Low	0/50

[a] Data as of 1 March 1989 for studies of at least 104 weeks. Standard deviation and range are presented for groups of 35 or more animals.

TABLE C7b
Historical Incidence of Leukemia in Untreated Female F344/N Rats[a]

Study	Incidence in Untreated Controls
Historical Incidence at Battelle Columbus Laboratories	
Chlorobenzene	9/49
N-Phenyl-2-Naphthylamine	14/50
Rotenone	15/50
l-Ascorbic Acid	6/50
Total	44/199 (22.1%)
Standard deviation	8.4%
Range	
High	15/50
Low	6/50
Overall Historical Incidence	
Total	324/1643 (19.7%)
Standard deviation	8.2%
Range	
High	20/50
Low	3/50

[a] Data as of 1 March 1989 for studies of at least 104 weeks. Standard deviation and range are presented for groups of 35 or more animals.

TABLE C7c
Historical Incidence of Benign and Malignant Pheochromocytomas of the Adrenal Medulla in Untreated Female F344/N Rats[a]

Study	Incidence in Untreated Controls
Historical Incidence at Battelle Columbus Laboratories	
Chlorobenzene	3/49
N-Phenyl-2-Naphthylamine	4/50
Rotenone	4/50
l-Ascorbic Acid	4/50
Total	15/199 (7.5%)
Standard deviation	0.9%
Range	
High	4/50
Low	3/49
Overall Historical Incidence	
Total	93/1643 (5.7%)
Standard deviation	3.9%
Range	
High	8/50
Low	0/50

[a] Data as of 1 March 1989 for studies of at least 104 weeks. Standard deviation and range are presented for groups of 35 or more animals.

TABLE C8
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Ethylene Thiourea

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	90 ppm 0 ppm	9 ppm 25 ppm	0 ppm 83 ppm	30 ppm 83 ppm	90 ppm 83 ppm
Disposition Summary						
Animals initially in study	50	50	50	50	50	50
Animals removed	50	50	50	50	50	50
Animals examined histopathologically	50	50	50	50	50	50
Alimentary System						
Esophagus	(50)	(50)	(49)	(50)	(49)	(50)
Foreign body						1 (2%)
Intestine large, cecum	(46)	(46)	(48)	(42)	(39)	(46)
Artery, necrosis, fibrinoid			1 (2%)			
Perivascular, inflammation, chronic active			1 (2%)			
Intestine large, colon	(47)	(47)	(50)	(45)	(43)	(47)
Parasite metazoan		1 (2%)		1 (2%)	1 (2%)	1 (2%)
Intestine large, rectum	(48)	(46)	(49)	(43)	(41)	(47)
Parasite metazoan	2 (4%)	6 (13%)	4 (8%)	2 (5%)	7 (17%)	4 (9%)
Intestine small, duodenum	(49)	(49)	(50)	(48)	(48)	(49)
Inflammation, chronic active				1 (2%)	2 (4%)	
Liver	(50)	(50)	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)					
Atrophy						1 (2%)
Basophilic focus	36 (72%)	31 (62%)	34 (68%)	31 (62%)	23 (46%)	28 (56%)
Clear cell focus	2 (4%)	4 (8%)	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Degeneration, cystic	1 (2%)	2 (4%)	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Eosinophilic focus		1 (2%)				
Fibrosis	1 (2%)					
Hematopoietic cell proliferation		1 (2%)				
Hepatodiaphragmatic nodule	2 (4%)	1 (2%)		1 (2%)	2 (4%)	1 (2%)
Hyperplasia			1 (2%)	1 (2%)		
Inflammation, chronic	14 (28%)	17 (34%)	21 (42%)	18 (36%)	16 (32%)	20 (40%)
Leukocytosis					1 (2%)	
Necrosis, coagulative	2 (4%)	1 (2%)	2 (4%)	3 (6%)	3 (6%)	1 (2%)
Thrombus			1 (2%)			
Vacuolization cytoplasmic	8 (16%)	4 (8%)	9 (18%)		1 (2%)	
Hepatocyte, hyperplasia						1 (2%)
Mesentery	(3)	(2)	(2)	(1)	(4)	(8)
Inflammation, chronic active	1 (33%)	1 (50%)	1 (50%)	1 (100%)	2 (50%)	5 (63%)
Artery, inflammation, chronic active					1 (25%)	
Artery, necrosis, fibrinoid					1 (25%)	
Pancreas	(50)	(49)	(50)	(49)	(49)	(50)
Cyst		1 (2%)				
Ectopic liver					1 (2%)	
Acinus, atrophy	16 (32%)	12 (24%)	17 (34%)	15 (31%)	14 (29%)	17 (34%)
Artery, necrosis, fibrinoid			1 (2%)			
Perivascular, inflammation, chronic active			3 (6%)			
Salivary glands	(50)	(50)	(50)	(50)	(50)	(49)
Inflammation, chronic active						1 (2%)
Acinus, atrophy	1 (2%)					
Stomach, forestomach	(49)	(49)	(50)	(49)	(48)	(50)
Acanthosis		2 (4%)	3 (6%)	3 (6%)		1 (2%)
Hyperkeratosis		2 (4%)	3 (6%)	3 (6%)		1 (2%)
Hyperplasia, squamous, focal			1 (2%)			
Inflammation, chronic active	3 (6%)	3 (6%)	5 (10%)	3 (6%)	1 (2%)	2 (4%)
Necrosis, coagulative						2 (4%)

TABLE C8
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 250 ppm	90 ppm 250 ppm
Disposition Summary		
Animals initially in study	50	50
Animals removed	50	50
Animals examined histopathologically	50	50
Alimentary System		
Intestine large, cecum	(46)	(48)
Inflammation, chronic active		1 (2%)
Parasite metazoan	1 (2%)	
Intestine large, colon	(46)	(49)
Parasite metazoan	2 (4%)	2 (4%)
Intestine large, rectum	(45)	(49)
Inflammation, chronic active		1 (2%)
Intestine small, duodenum	(48)	(50)
Hyperplasia, glandular	1 (2%)	
Liver	(50)	(50)
Basophilic focus	16 (32%)	11 (22%)
Clear cell focus	2 (4%)	4 (8%)
Cyst		1 (2%)
Degeneration, cystic	3 (6%)	
Hepatodiaphragmatic nodule	3 (6%)	
Inflammation, chronic	15 (30%)	15 (30%)
Leukocytosis	3 (6%)	
Necrosis, coagulative	4 (8%)	4 (8%)
Vacuolization cytoplasmic	4 (8%)	2 (4%)
Bile duct, hyperplasia	1 (2%)	
Mesentery	(2)	
Inflammation, chronic active	2 (100%)	
Pancreas	(49)	(50)
Acinus, atrophy	14 (29%)	10 (20%)
Salivary glands	(50)	(50)
Granuloma		1 (2%)

TABLE C8
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	90 ppm 0 ppm	9 ppm 25 ppm	0 ppm 83 ppm	30 ppm 83 ppm	90 ppm 83 ppm
Alimentary System (continued)						
Stomach, glandular	(48)	(49)	(50)	(48)	(48)	(50)
Infiltration cellular, lymphocytic		1 (2%)				
Inflammation, chronic active	4 (8%)	4 (8%)	3 (6%)	9 (19%)	9 (19%)	5 (10%)
Mineralization	1 (2%)	3 (6%)	5 (10%)	2 (4%)	4 (8%)	6 (12%)
Necrosis, coagulative	1 (2%)					
Mucosa, degeneration, chronic		1 (2%)				
Tooth	(50)	(49)	(50)	(49)	(50)	(49)
Caries					1 (2%)	
Inflammation, chronic active	1 (2%)			1 (2%)		
Cardiovascular System						
Heart	(50)	(50)	(50)	(50)	(50)	(50)
Bacterium						1 (2%)
Cardiomyopathy, chronic	30 (60%)	25 (50%)	27 (54%)	38 (76%)	33 (66%)	35 (70%)
Inflammation, chronic active						1 (2%)
Mineralization	1 (2%)	1 (2%)		1 (2%)		
Artery, necrosis, fibrinoid						1 (2%)
Atrium, thrombus		2 (4%)	1 (2%)	2 (4%)	1 (2%)	
Perivascular, inflammation, chronic active						1 (2%)
Ventricle, thrombus			1 (2%)			
Endocrine System						
Adrenal gland	(50)	(49)	(50)	(50)	(49)	(50)
Accessory adrenal cortical nodule				1 (2%)		
Capsule, inflammation, chronic						1 (2%)
Adrenal gland, cortex	(50)	(49)	(49)	(48)	(49)	(50)
Atypical cells			2 (4%)		1 (2%)	1 (2%)
Degeneration, fatty	16 (32%)	20 (41%)	23 (47%)	22 (46%)	20 (41%)	23 (46%)
Hematocyst		1 (2%)		2 (4%)		1 (2%)
Hyperplasia	25 (50%)	33 (67%)	26 (53%)	31 (65%)	27 (55%)	36 (72%)
Hypertrophy	3 (6%)	11 (22%)	8 (16%)	7 (15%)	8 (16%)	4 (8%)
Hypertrophy, focal						1 (2%)
Necrosis, coagulative	2 (4%)	1 (2%)		2 (4%)		2 (4%)
Adrenal gland, medulla	(50)	(49)	(49)	(49)	(49)	(50)
Hematocyst		1 (2%)				
Hyperplasia	11 (22%)	16 (33%)	8 (16%)	14 (29%)	15 (31%)	13 (26%)
Infiltration cellular, lymphocytic						1 (2%)
Islets, pancreatic	(50)	(49)	(50)	(50)	(50)	(50)
Hyperplasia						1 (2%)
Parathyroid gland	(46)	(47)	(48)	(46)	(46)	(47)
Hyperplasia	2 (4%)	3 (6%)	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Pituitary gland	(50)	(50)	(49)	(49)	(49)	(49)
Pars distalis, angiectasis		1 (2%)		1 (2%)		2 (4%)
Pars distalis, atypical cells				1 (2%)		
Pars distalis, cyst	27 (54%)	17 (34%)	27 (55%)	28 (57%)	29 (59%)	31 (63%)
Pars distalis, fibrosis					1 (2%)	
Pars distalis, hemorrhage				1 (2%)		
Pars distalis, hyperplasia	18 (36%)	12 (24%)	13 (27%)	13 (27%)	12 (24%)	12 (24%)
Pars distalis, vacuolization cytoplasmic					1 (2%)	
Pars intermedia, angiectasis	1 (2%)					
Pars intermedia, cyst	1 (2%)	1 (2%)	1 (2%)	1 (2%)		

TABLE C8
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 250 ppm	90 ppm 250 ppm
Alimentary System (continued)		
Stomach, forestomach	(50)	(50)
Acanthosis		1 (2%)
Hyperkeratosis		1 (2%)
Inflammation, chronic active	5 (10%)	6 (12%)
Stomach, glandular	(50)	(50)
Inflammation, chronic active	6 (12%)	6 (12%)
Mineralization	2 (4%)	
Tooth	(50)	(50)
Inflammation, chronic active	2 (4%)	
Cardiovascular System		
Heart	(50)	(49)
Cardiomyopathy, chronic	29 (58%)	27 (55%)
Inflammation, chronic active	1 (2%)	1 (2%)
Atrium, thrombus	2 (4%)	3 (6%)
Endocrine System		
Adrenal gland, cortex	(50)	(50)
Atypical cells	1 (2%)	
Degeneration, fatty	22 (44%)	15 (30%)
Hyperplasia	22 (44%)	23 (46%)
Hypertrophy	4 (8%)	3 (6%)
Necrosis, coagulative	1 (2%)	
Adrenal gland, medulla	(50)	(50)
Hyperplasia	8 (16%)	10 (20%)
Parathyroid gland	(37)	(42)
Hyperplasia	3 (8%)	2 (5%)
Pituitary gland	(50)	(50)
Pars distalis, atypical cells		2 (4%)
Pars distalis, cyst	17 (34%)	25 (50%)
Pars distalis, hyperplasia	12 (24%)	11 (22%)
Pars intermedia, cyst	1 (2%)	3 (6%)
Pars nervosa, cyst		1 (2%)

TABLE C8
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	90 ppm 0 ppm	9 ppm 25 ppm	0 ppm 83 ppm	30 ppm 83 ppm	90 ppm 83 ppm
Endocrine System (continued)						
Thyroid gland	(50)	(48)	(49)	(44)	(46)	(47)
Inflammation, chronic active		1 (2%)				
Ultimobranchial cyst	1 (2%)	3 (6%)	1 (2%)	3 (7%)	2 (4%)	
Artery, inflammation, chronic active					1 (2%)	
Artery, necrosis, fibrinoid					1 (2%)	
C-cell, hyperplasia	31 (62%)	36 (75%)	41 (84%)	35 (80%)	33 (72%)	39 (83%)
Follicular cell, hyperplasia		8 (17%)	15 (31%)	33 (75%)	30 (65%)	41 (87%)
General Body System						
None						
Genital System						
Clitoral gland	(48)	(50)	(49)	(47)	(49)	(45)
Hyperplasia	3 (6%)	4 (8%)	3 (6%)	3 (6%)	2 (4%)	
Inflammation, chronic active	11 (23%)	11 (22%)	9 (18%)	15 (32%)	8 (16%)	14 (31%)
Duct, dilatation	11 (23%)	14 (28%)	8 (16%)	8 (17%)	6 (12%)	13 (29%)
Ovary	(50)	(50)	(50)	(50)	(50)	(50)
Atrophy		2 (4%)	3 (6%)	3 (6%)	2 (4%)	1 (2%)
Cyst	11 (22%)	19 (38%)	18 (36%)	21 (42%)	14 (28%)	13 (26%)
Inflammation, chronic active			1 (2%)		1 (2%)	
Uterus	(50)	(50)	(50)	(50)	(50)	(50)
Dilatation		5 (10%)	3 (6%)	6 (12%)	1 (2%)	1 (2%)
Hemorrhage	2 (4%)	1 (2%)		3 (6%)		2 (4%)
Inflammation, chronic active		3 (6%)	1 (2%)	1 (2%)	1 (2%)	
Prolapse		1 (2%)				
Cervix, diverticulum	1 (2%)	3 (6%)	1 (2%)	1 (2%)	1 (2%)	
Cervix, inflammation, suppurative		2 (4%)	1 (2%)	1 (2%)	1 (2%)	
Endometrium, hyperplasia, cystic, glandular	12 (24%)	12 (24%)	10 (20%)	14 (28%)	11 (22%)	15 (30%)
Vagina		(2)				(1)
Dilatation						1 (100%)
Epithelium, hyperplasia						1 (100%)
Hematopoietic System						
Bone marrow	(50)	(50)	(49)	(50)	(47)	(50)
Femoral, hyperplasia, reticulum cell	1 (2%)	1 (2%)		2 (4%)	1 (2%)	
Femoral, myelofibrosis	1 (2%)				1 (2%)	1 (2%)
Lymph node	(50)	(49)	(50)	(50)	(50)	(50)
Mandibular, cyst	1 (2%)					
Mediastinal, infiltration cellular, histiocytic				1 (2%)		
Spleen	(50)	(50)	(50)	(50)	(50)	(50)
Atrophy	1 (2%)	1 (2%)			1 (2%)	
Fibrosis	1 (2%)		2 (4%)	2 (4%)	1 (2%)	1 (2%)
Hematopoietic cell proliferation	3 (6%)	4 (8%)	1 (2%)		1 (2%)	2 (4%)
Necrosis, coagulative		1 (2%)	2 (4%)		1 (2%)	1 (2%)

TABLE C8
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 250 ppm	90 ppm 250 ppm
Endocrine System (continued)		
Thyroid gland	(49)	(50)
Ultimobranchial cyst	1 (2%)	
C-cell, hyperplasia	33 (67%)	27 (54%)
Follicular cell, hyperplasia	45 (92%)	47 (94%)
General Body System		
None		
Genital System		
Clitoral gland	(47)	(47)
Hyperplasia	2 (4%)	1 (2%)
Inflammation, chronic active	9 (19%)	8 (17%)
Duct, dilatation	6 (13%)	9 (19%)
Ovary	(50)	(50)
Atrophy		1 (2%)
Cyst	9 (18%)	16 (32%)
Uterus	(50)	(50)
Dilatation	1 (2%)	
Inflammation, chronic active	1 (2%)	
Cervix, diverticulum	2 (4%)	1 (2%)
Cervix, inflammation, suppurative	2 (4%)	1 (2%)
Endometrium, hyperplasia, cystic, glandular	4 (8%)	8 (16%)
Vagina	(1)	
Inflammation, suppurative	1 (100%)	
Hematopoietic System		
Lymph node	(50)	(50)
Lumbar, inflammation, chronic active		1 (2%)
Mandibular, hyperplasia, lymphoid		1 (2%)
Mandibular, hyperplasia, plasma cell		1 (2%)
Pancreatic, cyst	1 (2%)	
Spleen	(50)	(50)
Fibrosis	1 (2%)	
Hematopoietic cell proliferation	3 (6%)	2 (4%)
Thymus	(41)	(44)
Cyst	2 (5%)	

TABLE C8
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	90 ppm 0 ppm	9 ppm 25 ppm	0 ppm 83 ppm	30 ppm 83 ppm	90 ppm 83 ppm
Integumentary System						
Mammary gland	(50)	(47)	(50)	(50)	(50)	(50)
Hyperplasia, cystic	48 (96%)	45 (96%)	50 (100%)	47 (94%)	49 (98%)	47 (94%)
Inflammation, chronic active			2 (4%)	1 (2%)		
Skin	(50)	(49)	(50)	(50)	(50)	(48)
Alopecia	1 (2%)			1 (2%)		
Cyst epithelial inclusion			1 (2%)		1 (2%)	
Inflammation, chronic active				1 (2%)		
Musculoskeletal System						
Bone	(50)	(49)	(50)	(50)	(50)	(50)
Cranium, fibrous osteodystrophy	1 (2%)	2 (4%)		2 (4%)	1 (2%)	1 (2%)
Femur, fibrous osteodystrophy	1 (2%)	2 (4%)		2 (4%)	1 (2%)	1 (2%)
Nervous System						
Brain	(50)	(50)	(50)	(50)	(50)	(50)
Compression	11 (22%)	7 (14%)	8 (16%)	9 (18%)	3 (6%)	5 (10%)
Hemorrhage	1 (2%)				4 (8%)	
Hydrocephalus	10 (20%)	6 (12%)	9 (18%)	8 (16%)	3 (6%)	4 (8%)
Inflammation, chronic active						1 (2%)
Thrombus				1 (2%)		
Artery, inflammation, chronic active					1 (2%)	
Artery, necrosis, fibrinoid					1 (2%)	
Spinal cord	(1)				(1)	(1)
Hemorrhage	1 (100%)					
White matter, degeneration					1 (100%)	1 (100%)
Respiratory System						
Lung	(50)	(50)	(50)	(50)	(50)	(50)
Inflammation, chronic active	7 (14%)	11 (22%)	13 (26%)	12 (24%)	10 (20%)	9 (18%)
Leukocytosis					1 (2%)	
Necrosis, coagulative					1 (2%)	
Alveolar epithelium, hyperplasia		1 (2%)	2 (4%)			
Artery, mediastinum, mineralization		1 (2%)				
Artery, mediastinum, necrosis, fibrinoid			1 (2%)			
Bronchiole, epithelium, hyperplasia						1 (2%)
Mediastinum, perivascular, inflammation, chronic active	1 (2%)		2 (4%)			
Nose	(50)	(50)	(49)	(50)	(49)	(50)
Foreign body				1 (2%)		
Fungus					2 (4%)	1 (2%)
Inflammation, chronic active	3 (6%)	3 (6%)	1 (2%)		4 (8%)	3 (6%)
Nasolacrimal duct, inflammation, suppurative	7 (14%)	4 (8%)	5 (10%)	4 (8%)	7 (14%)	6 (12%)

TABLE C8
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 250 ppm	90 ppm 250 ppm
Integumentary System		
Mammary gland	(50)	(50)
Hyperplasia, cystic	47 (94%)	49 (98%)
Musculoskeletal System		
Bone	(50)	(50)
Cranium, fibrous osteodystrophy	2 (4%)	1 (2%)
Femur, fibrous osteodystrophy	2 (4%)	1 (2%)
Nervous System		
Brain	(50)	(50)
Compression	7 (14%)	13 (26%)
Hemorrhage	1 (2%)	1 (2%)
Hydrocephalus	8 (16%)	11 (22%)
Respiratory System		
Lung	(50)	(50)
Fungus		1 (2%)
Inflammation, chronic active	5 (10%)	10 (20%)
Leukocytosis	2 (4%)	
Alveolar epithelium, hyperplasia	1 (2%)	1 (2%)
Artery, mediastinum, inflammation, chronic active	1 (2%)	
Artery, mediastinum, necrosis, fibrinoid	1 (2%)	
Mediastinum, hemorrhage	1 (2%)	
Nose	(50)	(50)
Foreign body	1 (2%)	
Fungus	2 (4%)	2 (4%)
Hemorrhage	1 (2%)	
Inflammation, chronic active	4 (8%)	6 (12%)
Mucosa, nasolacrimal duct, hyperplasia		1 (2%)
Nasolacrimal duct, dilatation		1 (2%)
Nasolacrimal duct, hyperkeratosis		1 (2%)
Nasolacrimal duct, inflammation, suppurative	4 (8%)	5 (10%)

TABLE C8
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	90 ppm 0 ppm	9 ppm 25 ppm	0 ppm 83 ppm	30 ppm 83 ppm	90 ppm 83 ppm
Special Senses System						
Eye	(8)	(9)	(7)	(7)	(12)	(10)
Hemorrhage	3 (38%)		1 (14%)			
Inflammation, chronic active			1 (14%)	1 (14%)		1 (10%)
Lens, cataract	6 (75%)	7 (78%)	4 (57%)	6 (86%)	11 (92%)	9 (90%)
Retina, atrophy	6 (75%)	8 (89%)	5 (71%)	6 (86%)	10 (83%)	7 (70%)
Harderian gland	(50)	(50)	(50)	(50)	(50)	(50)
Inflammation, chronic active				1 (2%)		
Urinary System						
Kidney	(50)	(49)	(50)	(50)	(50)	(50)
Cyst			1 (2%)		1 (2%)	2 (4%)
Fibrosis	1 (2%)					
Hydronephrosis					1 (2%)	
Inflammation, chronic active				1 (2%)		
Mineralization	1 (2%)					
Necrosis, coagulative	1 (2%)					2 (4%)
Nephropathy, chronic	49 (98%)	43 (88%)	46 (92%)	43 (86%)	41 (82%)	45 (90%)
Urinary bladder	(49)	(48)	(50)	(47)	(48)	(50)
Dilatation					1 (2%)	
Inflammation, chronic active						1 (2%)
Transitional epithelium, hyperplasia						1 (2%)

TABLE C8
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 250 ppm	90 ppm 250 ppm
Special Senses System		
Eye	(12)	(8)
Hemorrhage	1 (8%)	
Lens, cataract	9 (75%)	5 (63%)
Retina, atrophy	8 (67%)	5 (63%)
Harderian gland	(50)	(50)
Inflammation, chronic active		1 (2%)
Urinary System		
Kidney	(50)	(50)
Cyst	1 (2%)	1 (2%)
Inflammation, chronic active		1 (2%)
Necrosis, coagulative		1 (2%)
Nephropathy, chronic	48 (96%)	47 (94%)
Urinary bladder	(49)	(50)
Transitional epithelium, hyperplasia		1 (2%)

APPENDIX D
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR FEED STUDY OF ETHYLENE THIOUREA

TABLE D1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Ethylene Thiourea[a]

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	330 ppm 0 ppm	33 ppm 100 ppm	0 ppm 330 ppm	110 ppm 330 ppm	330 ppm 330 ppm
Disposition Summary						
Animals initially in study	50	50	34	50	50	50
Early deaths						
Natural death	12	10	3	11	8	13
Moribund sacrifice	8	7	5	8	10	6
Accidental deaths		5				
Survivors						
Terminal sacrifice	30	27	25	31	32	30
Missing		1	1			1
Animals examined microscopically	50	49	33	50	50	49
Alimentary System						
Esophagus	(50)	(22)	(8)	(18)	(15)	(19)
Periesophageal tissue, sarcoma, metastatic, skin			1 (13%)			
Gallbladder	(40)	(12)	(6)	(10)	(13)	(11)
Fibrosarcoma, metastatic, skin		1 (8%)				
Intestine large, colon	(50)	(21)	(8)	(17)	(16)	(16)
Intestine large, rectum	(48)	(19)	(8)	(17)	(15)	(16)
Squamous cell carcinoma	1 (2%)					
Intestine small, ileum	(44)	(18)	(7)	(16)	(14)	(13)
Intestine small, jejunum	(45)	(20)	(10)	(18)	(16)	(18)
Adenocarcinoma	1 (2%)	1 (5%)	1 (10%)			
Liver	(49)	(49)	(33)	(50)	(47)	(49)
Fibrosarcoma, metastatic, skin		1 (2%)			1 (2%)	
Hemangioma				1 (2%)		
Hemangiosarcoma	2 (4%)	1 (2%)	1 (3%)	2 (4%)		1 (2%)
Hemangiosarcoma, multiple	1 (2%)			1 (2%)	2 (4%)	
Hepatoblastoma			1 (3%)	1 (2%)		3 (6%)
Hepatoblastoma, multiple						1 (2%)
Hepatocellular carcinoma	9 (18%)	6 (12%)	3 (9%)	11 (22%)	7 (15%)	12 (24%)
Hepatocellular carcinoma, multiple	4 (8%)	2 (4%)	1 (3%)	8 (16%)	8 (17%)	7 (14%)
Hepatocellular adenoma	8 (16%)	2 (4%)	4 (12%)	12 (24%)	12 (26%)	14 (29%)
Hepatocellular adenoma, multiple	3 (6%)	4 (8%)	2 (6%)	4 (8%)	3 (6%)	6 (12%)
Histiocytic sarcoma		1 (2%)	1 (3%)	1 (2%)	2 (4%)	1 (2%)
Mesentery	(6)	(1)			(1)	(1)
Fibrosarcoma, metastatic, skin		1 (100%)				
Histiocytic sarcoma					1 (100%)	
Pancreas	(48)	(20)	(7)	(17)	(15)	(17)
Pharynx	(1)					
Papilloma squamous	1 (100%)					
Salivary glands	(50)	(21)	(8)	(19)	(15)	(17)
Sarcoma, metastatic, skin			1 (13%)			
Stomach, forestomach	(49)	(24)	(7)	(17)	(16)	(22)
Papilloma squamous		2 (8%)				2 (9%)
Stomach, glandular	(48)	(21)	(7)	(17)	(15)	(18)
Tooth	(5)					

TABLE D1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 1,000 ppm	330 ppm 1,000 ppm
Disposition Summary		
Animals initially in study	50	50
Early deaths		
Natural death	14	16
Moribund sacrifice	14	10
Survivors		
Terminal sacrifice	22	24
Animals examined microscopically	50	50
Alimentary System		
Intestine small, jejunum	(44)	(40)
Liver	(50)	(49)
Fibrosarcoma, metastatic, skin	1 (2%)	
Hemangiosarcoma	1 (2%)	2 (4%)
Hemangiosarcoma, multiple		1 (2%)
Hepatoblastoma	4 (8%)	7 (14%)
Hepatoblastoma, multiple	2 (4%)	3 (6%)
Hepatocellular carcinoma	3 (6%)	5 (10%)
Hepatocellular carcinoma, multiple	42 (84%)	40 (82%)
Hepatocellular adenoma	4 (8%)	9 (18%)
Hepatocellular adenoma, multiple	5 (10%)	6 (12%)
Histiocytic sarcoma	1 (2%)	1 (2%)
Sarcoma, metastatic	1 (2%)	
Mesentery	(5)	(3)
Pancreas	(45)	(47)
Salivary glands	(50)	(49)
Stomach, glandular	(48)	(44)
Tooth	(4)	(1)

TABLE D1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	330 ppm 0 ppm	33 ppm 100 ppm	0 ppm 330 ppm	110 ppm 330 ppm	330 ppm 330 ppm
Cardiovascular System						
Heart	(50)	(23)	(8)	(19)	(15)	(19)
Adenocarcinoma, metastatic, uncertain primary site				2 (9%)		
Endocrine System						
Adrenal gland	(50)	(21)	(8)	(18)	(15)	(18)
Spindle cell, subcapsular, adenoma	1 (2%)					
Spindle cell, subcapsular, adenoma, multiple	1 (2%)					
Adrenal gland, medulla	(50)	(21)	(8)	(18)	(15)	(18)
Pheochromocytoma benign	1 (2%)					
Islets, pancreatic	(48)	(20)	(7)	(17)	(15)	(17)
Pituitary gland	(44)	(42)	(28)	(42)	(41)	(45)
Pars intermedia, adenoma	1 (2%)					
Thyroid gland	(50)	(46)	(33)	(49)	(47)	(48)
Follicular cell, adenoma		1 (2%)	1 (3%)	1 (2%)	1 (2%)	2 (4%)
Follicular cell, carcinoma	1 (2%)					
General Body System						
None						
Genital System						
Epididymis	(49)	(22)	(8)	(18)	(15)	(19)
Preputial gland	(2)	(2)	(1)	(2)	(4)	(3)
Carcinoma					1 (25%)	
Prostate	(50)	(22)	(8)	(18)	(15)	(19)
Seminal vesicle	(4)	(2)		(1)	(1)	(1)
Testes	(50)	(22)	(8)	(20)	(14)	(19)
Interstitial cell, adenoma				1 (5%)		
Hematopoietic System						
Blood	(1)					
Bone marrow	(49)	(21)	(8)	(18)	(13)	(19)
Lymph node	(48)	(25)	(15)	(22)	(20)	(22)
Axillary, fibrosarcoma, metastatic, skin						1 (5%)
Axillary, sarcoma, metastatic		1 (4%)				
Deep cervical, sarcoma, metastatic, skin			1 (7%)			
Inguinal, hepatoblastoma, metastatic, liver						1 (5%)
Mandibular, histiocytic sarcoma					1 (5%)	
Lymph node, mesenteric	(14)	(11)	(7)	(4)	(8)	(6)
Fibrosarcoma, metastatic, skin			1 (13%)			
Histiocytic sarcoma			1 (14%)		1 (13%)	
Spleen	(49)	(25)	(12)	(21)	(24)	(24)
Hemangiosarcoma	1 (2%)				1 (4%)	
Histiocytic sarcoma					1 (4%)	
Thymus	(29)	(11)	(4)	(11)	(11)	(11)

TABLE D1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 1,000 ppm	330 ppm 1,000 ppm
Cardiovascular System		
Heart	(50)	(50)
Fibrosarcoma, metastatic, skin		1 (2%)
Hemangioma	2 (4%)	
Hepatocellular carcinoma, metastatic, liver		1 (2%)
Endocrine System		
Adrenal gland, cortex	(50)	(49)
Adrenal gland, medulla	(50)	(49)
Pheochromocytoma benign	1 (2%)	2 (4%)
Pituitary gland	(41)	(39)
Pars distalis, adenoma	8 (20%)	4 (10%)
Pars intermedia, adenoma	1 (2%)	
Thyroid gland	(50)	(49)
Follicular cell, adenoma	8 (16%)	11 (22%)
Follicular cell, adenoma, multiple	18 (36%)	22 (45%)
Follicular cell, carcinoma		8 (16%)
Follicular cell, carcinoma, multiple	5 (10%)	1 (2%)
General Body System		
None		
Genital System		
Epididymis	(49)	(49)
Preputial gland	(2)	(1)
Prostate	(47)	(49)
Seminal vesicle	(2)	
Testes	(50)	(49)
Hematopoietic System		
Blood	(1)	
Bone marrow	(49)	(47)
Lymph node	(47)	(48)
Pancreatic, sarcoma, metastatic, skin	1 (2%)	
Lymph node, mesenteric	(7)	(5)
Histiocytic sarcoma	1 (14%)	
Spleen	(48)	(47)
Fibrosarcoma, metastatic, skin	1 (2%)	
Hemangiosarcoma	2 (4%)	1 (2%)

TABLE D1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	330 ppm 0 ppm	33 ppm 100 ppm	0 ppm 330 ppm	110 ppm 330 ppm	330 ppm 330 ppm
Integumentary System						
Skin	(50)	(26)	(14)	(23)	(25)	(26)
Papilloma squamous					1 (4%)	
Schwannoma malignant					1 (4%)	
Squamous cell carcinoma				1 (4%)		
Subcutaneous tissue, fibroma	1 (2%)					
Subcutaneous tissue, fibrosarcoma	1 (2%)	5 (19%)	4 (29%)	6 (26%)	6 (24%)	8 (31%)
Subcutaneous tissue, fibrosarcoma, multiple					1 (4%)	
Subcutaneous tissue, fibrous histiocytoma	1 (2%)		1 (7%)		2 (8%)	
Subcutaneous tissue, histiocytic sarcoma					1 (4%)	
Subcutaneous tissue, neurofibrosarcoma					1 (4%)	1 (4%)
Subcutaneous tissue, sarcoma	2 (4%)	1 (4%)	1 (7%)	1 (4%)		3 (12%)
Subcutaneous tissue, schwannoma malignant			1 (7%)			1 (4%)
Musculoskeletal System						
None						
Nervous System						
Brain	(50)	(21)	(8)	(19)	(15)	(19)
Respiratory System						
Lung	(50)	(49)	(33)	(50)	(47)	(49)
Adenocarcinoma, metastatic, uncertain primary site		1 (2%)				
Alveolar/bronchiolar adenoma	4 (8%)	6 (12%)	10 (30%)	6 (12%)	11 (23%)	8 (16%)
Alveolar/bronchiolar adenoma, multiple		1 (2%)			1 (2%)	3 (6%)
Alveolar/bronchiolar carcinoma	1 (2%)		1 (3%)	1 (2%)		6 (12%)
Alveolar/bronchiolar carcinoma, multiple					1 (2%)	1 (2%)
Fibrosarcoma, metastatic, skin						1 (2%)
Hepatoblastoma, metastatic, liver						1 (2%)
Hepatocellular carcinoma, metastatic	10 (20%)	1 (2%)	1 (3%)	2 (4%)	1 (2%)	1 (2%)
Histiocytic sarcoma					2 (4%)	1 (2%)
Nose	(50)	(21)	(8)	(19)	(16)	(18)
Special Senses System						
Harderian gland	(4)	(1)	(3)	(3)	(1)	(3)
Adenocarcinoma						1 (33%)
Adenoma	1 (25%)	1 (100%)	3 (100%)	2 (67%)	1 (100%)	1 (33%)

TABLE D1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 1,000 ppm	330 ppm 1,000 ppm
Integumentary System		
Skin	(49)	(50)
Basosquamous tumor malignant	1 (2%)	
Squamous cell carcinoma		1 (2%)
Subcutaneous tissue, fibrosarcoma	5 (10%)	5 (10%)
Subcutaneous tissue, sarcoma	1 (2%)	
Subcutaneous tissue, sarcoma, multiple	1 (2%)	
Musculoskeletal System		
None		
Nervous System		
Brain	(50)	(49)
Respiratory System		
Lung	(50)	(49)
Alveolar/bronchiolar adenoma	4 (8%)	6 (12%)
Alveolar/bronchiolar adenoma, multiple	2 (4%)	
Alveolar/bronchiolar carcinoma	2 (4%)	
Carcinoma, metastatic, thyroid gland	1 (2%)	2 (4%)
Carcinoma, metastatic, uncertain primary site	1 (2%)	
Fibrosarcoma, metastatic, skin	1 (2%)	1 (2%)
Hepatoblastoma, metastatic, liver	2 (4%)	3 (6%)
Hepatoblastoma, metastatic, uncertain primary site	1 (2%)	
Hepatocellular carcinoma, metastatic, liver	11 (22%)	21 (43%)
Histiocytic sarcoma	1 (2%)	
Nose	(50)	(49)
Special Senses System		
Ear		(1)
Pinna, hemangioma	1 (100%)	
Harderian gland	(18)	(6)
Adenocarcinoma	1 (17%)	
Adenoma	4 (22%)	1 (17%)

TABLE D1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	330 ppm 0 ppm	33 ppm 100 ppm	0 ppm 330 ppm	110 ppm 330 ppm	330 ppm 330 ppm
Urinary System						
Kidney	(49)	(23)	(11)	(21)	(17)	(19)
Hepatocellular carcinoma, metastatic				1 (5%)	1 (6%)	
Urinary bladder	(49)	(20)	(8)	(17)	(15)	(16)
Systemic Lesions						
Multiple organs[b]	(50)	(49)	(33)	(50)	(50)	(49)
Histiocytic sarcoma		1 (2%)	1 (3%)	1 (2%)	2 (4%)	1 (2%)
Lymphoma malignant histiocytic	1 (2%)				1 (2%)	
Lymphoma malignant lymphocytic	4 (8%)	1 (2%)	1 (3%)	3 (6%)	1 (2%)	2 (4%)
Lymphoma malignant mixed	2 (4%)	3 (6%)	3 (9%)	2 (4%)	6 (12%)	6 (12%)
Lymphoma malignant undifferentiated cell	2 (4%)				1 (2%)	
Total Summary						
Total animals with primary neoplasms[c]	35	28	25	40	39	48
Total primary neoplasms	56	38	40	65	72	90
Total animals with benign neoplasms	16	14	15	23	25	30
Total benign neoplasms	22	17	20	27	30	36
Total animals with malignant neoplasms	28	19	16	31	30	41
Total malignant neoplasms	34	21	20	38	42	54
Total animals with secondary neoplasms[d]	10	3	2	3	2	4
Total secondary neoplasms	10	8	4	3	4	5
Total animals with malignant neoplasms of uncertain primary site		2				

TABLE D1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 1,000 ppm	330 ppm 1,000 ppm
Urinary System		
Kidney	(50)	(49)
Fibrosarcoma, metastatic, skin	1 (2%)	
Renal tubule, adenoma	1 (2%)	
Urinary bladder	(48)	(48)
Systemic Lesions		
Multiple organs[b]	(50)	(50)
Histiocytic sarcoma	1 (2%)	1 (2%)
Lymphoma malignant lymphocytic	3 (6%)	2 (4%)
Lymphoma malignant mixed	3 (6%)	3 (6%)
Lymphoma malignant undifferentiated cell	1 (2%)	1 (2%)
Tumor Summary		
Total animals with primary neoplasms	47	47
Total primary neoplasms	136	143
Total animals with benign neoplasms	36	41
Total benign neoplasms	59	61
Total animals with malignant neoplasms	46	46
Total malignant neoplasms	77	82
Total animals with secondary neoplasms	17	27
Total secondary neoplasms	21	30
Total animals with malignant neoplasms of uncertain primary site	1	1

[a] Effects on rats exposed to ethylene thiourea perinatally through 8 weeks of age (F_0 concentration) and for 2 years postnatally (F_1 concentration)
[b] The number in parentheses is the number of animals with any tissue examined microscopically.
[c] Primary tumors: all tumors except metastatic tumors
[d] Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

TABLE D2
Statistical Analysis of Primary Tumors in Male Mice in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 0:330, and 0:1,000 ppm Groups

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	0 ppm 330 ppm	0 ppm 1,000 ppm
Harderian Gland: Adenoma			
Overall rates[a]	1/50 (2%)	2/50 (4%)	4/50 (8%)
Adjusted rates[b]	2.9%	5.7%	15.8%
Terminal rates[c]	0/31 (0%)	1/32 (3%)	3/23 (13%)
First incidence (days)	666	704	694
Life table tests[d]	P=0.081	P=0.539	P=0.137
Logistic regression tests[d]	P=0.124	P=0.528	P=0.187
Cochran-Armitage test[d]	P=0.128		
Fisher exact test[d]		P=0.500	P=0.181
Liver: Hepatocellular Adenoma			
Overall rates	11/49 (22%)	16/50 (32%)	9/50 (18%)
Adjusted rates	31.6%	43.3%	32.8%
Terminal rates	8/31 (26%)	12/32 (38%)	6/23 (26%)
First incidence (days)	618	602	576
Life table tests	P=0.511N	P=0.245	P=0.594N
Logistic regression tests	P=0.247N	P=0.285	P=0.361N
Cochran-Armitage test	P=0.253N		
Fisher exact test		P=0.200	P=0.382N
Liver: Hepatocellular Carcinoma			
Overall rates	13/49 (27%)	19/50 (38%)	45/50(90%)
Adjusted rates	36.4%	50.6%	100.0%
Terminal rates	9/31 (29%)	14/32 (44%)	23/23 (100%)
First incidence (days)	520	602	525
Life table tests	P<0.001	P=0.208	P<0.001
Logistic regression tests	P<0.001	P=0.239	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.157	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rates	20/49 (41%)	32/50 (64%)	46/50 (92%)
Adjusted rates	54.9%	79.6%	100.0%
Terminal rates	15/31 (48%)	24/32 (75%)	23/23 (100%)
First incidence (days)	520	602	525
Life table tests	P<0.001	P=0.037	P<0.001
Logistic regression tests	P<0.001	P=0.045	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.017	P<0.001
Lung: Alveolar/bronchiolar Adenoma			
Overall rates	4/50 (8%)	6/50 (12%)	6/50(12%)
Adjusted rates	12.9%	17.9%	20.1%
Terminal rates	4/31 (13%)	5/32 (16%)	3/23 (13%)
First incidence (days)	743 (T)	704	650
Life table tests	P=0.213	P=0.396	P=0.261
Logistic regression tests	P=0.345	P=0.456	P=0.383
Cochran-Armitage test	P=0.362		
Fisher exact test		P=0.370	P=0.370

TABLE D2
Statistical Analysis of Primary Tumors in Male Mice in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 0:330, and 0:1,000 ppm Groups (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	0 ppm 330 ppm	0 ppm 1,000 ppm
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rates	5/50 (10%)	6/50 (12%)	8/50(16%)
Adjusted rates	16.1%	17.9%	26.1%
Terminal rates	5/31(16%)	5/32 (16%)	4/23 (17%)
First incidence (days)	743 (T)	704	650
Life table tests	P=0.116	P=0.530	P=0.176
Logistic regression tests	P=0.221	P=0.596	P=0.290
Cochran-Armitage test	P=0.235		
Fisher exact test		P=0.500	P=0.277
Pituitary Gland, Pars Distalis: Adenoma			
Overall rates	0/44 (0%)	0/42 (0%)	8/41 (20%)
Adjusted rates	0.0%	0.0%	31.4%
Terminal rates	0/30 (0%)	0/31 (0%)	5/20 (25%)
First incidence (days)	-[e]	-	669
Life table tests	P<0.001	-	P=0.002
Logistic regression tests	P<0.001	-	P=0.003
Cochran-Armitage test	P<0.001		
Fisher exact test		-	P=0.002
Skin, Subcutaneous Tissue: Fibrosarcoma			
Overall rates	1/50 (2%)	6/50 (12%)	5/50 (10%)
Adjusted rates	3.1%	16.2%	13.0%
Terminal rates	0/31 (0%)	3/32 (9%)	0/23 (0%)
First incidence (days)	705	677	525
Life table tests	P=0.132	P=0.086	P=0.113
Logistic regression tests	P=0.170	P=0.076	P=0.101
Cochran-Armitage test	P=0.167		
Fisher exact test		P=0.056	P=0.102
Skin, Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall rates	2/50 (4%)	6/50 (12%)	5/50 (10%)
Adjusted rates	6.3%	16.2%	13.0%
Terminal rates	1/31 (3%)	3/32 (9%)	0/23 (0%)
First incidence (days)	705	677	525
Life table tests	P=0.210	P=0.178	P=0.212
Logistic regression tests	P=0.272	P=0.173	P=0.218
Cochran-Armitage test	P=0.268		
Fisher exact test		P=0.134	P=0.218
Skin, Subcutaneous Tissue: Fibrosarcoma or Sarcoma			
Overall rates	3/50 (6%)	7/50 (14%)	7/50 (14%)
Adjusted rates	8.0%	18.5%	18.7%
Terminal rates	0/31 (0%)	3/32 (9%)	1/23 (4%)
First incidence (days)	565	677	525
Life table tests	P=0.150	P=0.224	P=0.172
Logistic regression tests	P=0.188	P=0.181	P=0.156
Cochran-Armitage test	P=0.186		
Fisher exact test		P=0.159	P=0.159

TABLE D2
Statistical Analysis of Primary Tumors in Male Mice in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 0:330, and 0:1,000 ppm Groups (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	0 ppm 330 ppm	0 ppm 1,000 ppm
Skin, Subcutaneous Tissue: Fibroma, Fibrosarcoma, or Sarcoma			
Overall rates	4/50 (8%)	7/50 (14%)	7/50 (14%)
Adjusted rates	11.0%	18.5%	18.7
Terminal rates	1/31 (3%)	3/32 (9%)	1/23 (4%)
First incidence (days)	565	677	525
Life table tests	P=0.217	P=0.339	P=0.259
Logistic regression tests	P=0.277	P=0.300	P=0.262
Cochran-Armitage test	P=0.273		
Fisher exact test		P=0.262	P=0.262
Thyroid Gland: Follicular Cell Adenoma			
Overall rates	0/50 (0%)	1/49 (2%)	26/50 (52%)
Adjusted rates	0.0%	3.1%	68.9%
Terminal rates	0/31 (0%)	1/32 (3%)	12/23 (52%)
First incidence (days)	-	743 (T)	241
Life table tests	P<0.001	P=0.506	P<0.001
Logistic regression tests	P<0.001	P=0.506	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.495	P<0.001
Thyroid Gland: Follicular Cell Carcinoma			
Overall rates	1/50 (2%)	0/49 (0%)	5/50 (10%)
Adjusted rates	3.2%	0.0%	18.0%
Terminal rates	1/31 (3%)	0/32 (0%)	3/23 (13%)
First incidence (days)	743 (T)	-	669
Life table tests	P=0.011	P=0.494N	P=0.070
Logistic regression tests	P=0.021	P=0.494N	P=0.105
Cochran-Armitage test	P=0.023		
Fisher exact test		P=0.505N	P=0.102
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall rates	1/50 (2%)	1/49 (2%)	29/50 (58%)
Adjusted rates	3.2%	3.1%	77.4%
Terminal rates	1/31 (3%)	1/32 (3%)	15/23 (65%)
First incidence (days)	743 (T)	743 (T)	241
Life table tests	P<0.001	P=0.755N	P<0.001
Logistic regression tests	P<0.001	P=0.755N	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.747	P<0.001
All Organs: Hemangioma			
Overall rates	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rates	0.0%	2.4%	11.8%
Terminal rates	0/31 (0%)	0/32 (0%)	2/23 (9%)
First incidence (days)	-	662	700
Life table tests	P=0.046	P=0.531	P=0.085
Logistic regression tests	P=0.067	P=0.500	P=0.116
Cochran-Armitage test	P=0.068		
Fisher exact test		P=0.500	P=0.121

TABLE D2
Statistical Analysis of Primary Tumors in Male Mice in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 0:330, and 0:1,000 ppm Groups (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	0 ppm 330 ppm	0 ppm 1,000 ppm
All Organs: Hemangiosarcoma			
Overall rates	4/50 (8%)	3/50 (6%)	3/50 (6%)
Adjusted rates	11.9%	8.0%	10.3%
Terminal rates	3/31 (10%)	1/32 (3%)	1/23 (4%)
First incidence (days)	565	623	690
Life table tests	P=0.559N	P=0.457N	P=0.586N
Logistic regression tests	P=0.456N	P=0.464N	P=0.481N
Cochran-Armitage test	P=0.465N		
Fisher exact test		P=0.500N	P=0.500N
All Organs: Hemangioma or Hemangiosarcoma			
Overall rates	4/50 (8%)	4/50 (8%)	6/50(12%)
Adjusted rates	11.9%	10.1%	21.3%
Terminal rates	3/31 (10%)	1/32 (3%)	3/23 (13%)
First incidence (days)	565	623	690
Life table tests	P=0.208	P=0.591N	P=0.266
Logistic regression tests	P=0.307	P=0.614N	P=0.391
Cochran-Armitage test	P=0.300		
Fisher exact test		P=0.643N	P=0.370
All Organs: Malignant Lymphoma (all types)			
Overall rates	9/50 (18%)	5/50 (10%)	7/50 (14%)
Adjusted rates	25.5%	12.0%	23.5%
Terminal rates	6/31 (19%)	1/32 (3%)	3/23 (13%)
First incidence (days)	427	619	671
Life table tests	P=0.541N	P=0.157N	P=0.520N
Logistic regression tests	P=0.415N	P=0.178N	P=0.365N
Cochran-Armitage test	P=0.425N		
Fisher exact test		P=0.194N	P=0.393N
All Organs: Benign Tumors			
Overall rates	16/50 (32%)	23/50 (46%)	36/50 (72%)
Adjusted rates	45.2%	61.4%	89.6%
Terminal rates	12/31 (39%)	18/32 (56%)	19/23 (83%)
First incidence (days)	618	602	241
Life table tests	P<0.001	P=0.166	P<0.001
Logistic regression tests	P<0.001	P=0.221	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.109	P<0.001
All Organs: Malignant Tumors			
Overall rates	28/50 (56%)	31/50 (62%)	46/50 (92%)
Adjusted rates	68.1%	68.5%	100.0%
Terminal rates	18/31 (58%)	18/32 (56%)	23/23 (100%)
First incidence (days)	427	602	525
Life table tests	P<0.001	P=0.521	P<0.001
Logistic regression tests	P<0.001	P=0.523	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.342	P<0.001

TABLE D2
Statistical Analysis of Primary Tumors in Male Mice in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 0:330, and 0:1,000 ppm Groups (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	0 ppm 330 ppm	0 ppm 1,000 ppm
All Organs: Benign or Malignant Tumors			
Overall rates	35/50 (70%)	40/50 (80%)	47/50 (94%)
Adjusted rates	83.3%	86.9%	100.0%
Terminal rates	24/31 (77%)	26/32 (81%)	23/23 (100%)
First incidence (days)	427	602	241
Life table tests	P<0.001	P=0.410	P=0.003
Logistic regression tests	P=0.001	P=0.436	P=0.002
Cochran-Armitage test	P=0.002		
Fisher exact test		P=0.178	P=0.002

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

TABLE D3
Statistical Analysis of Primary Tumors in Male Mice in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 330:0, 33:100, 110:330, 330:330, and 330:1,000 ppm Groups

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	330 ppm 0 ppm	33 ppm 100 ppm	110 ppm 330 ppm	330 ppm 330 ppm	330 ppm 1,000 ppm
Harderian Gland: Adenoma						
Overall rates[a]	1/50 (2%)	1/49 (2%)	3/33 (9%)	1/50 (2%)	1/49 (2%)	1/50 (2%)
Adjusted rates[b]	2.9%	3.7%	11.5%	3.1%	2.6%	3.1%
Terminal rates[c]	0/31 (0%)	1/27 (4%)	3/26 (12%)	1/32 (3%)	0/31 (0%)	0/25 (0%)
First incidence (days)	666	743 (T)	743 (T)	743 (T)	669	697
Life table tests[d]		P=0.731	P=0.239	P=0.745N	P=0.730N	P=0.751N
Logistic regression tests[d]		P=0.734	P=0.208	P=0.757N	P=0.762	P=0.756N
Fisher exact test[d]		P=0.747	P=0.171	P=0.753N	P=0.747	P=0.753N
Harderian Gland: Adenoma or Carcinoma						
Overall rates	1/50 (2%)	1/49 (2%)	3/33 (9%)	1/50 (2%)	2/49 (4%)	2/50 (4%)
Adjusted rates	2.9%	3.7%	11.5%	3.1%	5.7%	7.0%
Terminal rates	0/31 (0%)	1/27 (4%)	3/26 (12%)	1/32 (3%)	1/31 (3%)	1/25 (4%)
First incidence (days)	666	743 (T)	743 (T)	743 (T)	669	697
Life table tests		P=0.731	P=0.239	P=0.745N	P=0.532	P=0.485
Logistic regression tests		P=0.734	P=0.208	P=0.757N	P=0.515	P=0.516
Fisher exact test		P=0.747	P=0.171	P=0.753N	P=0.492	P=0.500
Liver: Hepatocellular Adenoma						
Overall rates	11/49 (22%)	6/49 (12%)	6/33 (18%)	15/47 (32%)	20/49 (41%)	15/49(31%)
Adjusted rates	31.6%	19.6%	21.9%	40.9%	53.3%	39.3%
Terminal rates	8/31 (26%)	4/27 (15%)	5/26 (19%)	11/32 (34%)	14/31 (45%)	5/25 (20%)
First incidence (days)	618	351	532	526	573	449
Life table tests		P=0.231N	P=0.276N	P=0.300	P=0.060	P=0.199
Logistic regression tests		P=0.206N	P=0.345N	P=0.276	P=0.074	P=0.274
Fisher exact test		P=0.143N	P=0.429N	P=0.208	P=0.041	P=0.246
Liver: Hepatocellular Carcinoma						
Overall rates	13/49 (27%)	8/49 (16%)	4/33 (12%)	15/47 (32%)	19/49 (39%)	45/49 (92%)
Adjusted rates	36.4%	28.6%	14.1%	45.1%	55.5%	100.0%
Terminal rates	9/31 (29%)	7/27 (26%)	2/26 (8%)	14/32 (44%)	16/31 (52%)	25/25 (100%)
First incidence (days)	520	735	532	649	535	507
Life table tests		P=0.267N	P=0.054N	P=0.462	P=0.160	P<0.001
Logistic regression tests		P=0.253N	P=0.072N	P=0.472	P=0.225	P<0.001
Fisher exact test		P=0.162N	P=0.095N	P=0.361	P=0.141	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma						
Overall rates	20/49 (41%)	13/49 (27%)	9/33 (27%)	26/47 (55%)	34/49 (69%)	47/49 (96%)
Adjusted rates	54.9%	42.7%	32.0%	69.8%	84.8%	100.0%
Terminal rates	15/31 (48%)	10/27 (37%)	7/26 (27%)	21/32 (66%)	25/31 (81%)	25/25 (100%)
First incidence (days)	520	351	532	526	535	449
Life table tests		P=0.217N	P=0.059N	P=0.216	P=0.011	P<0.001
Logistic regression tests		P=0.193N	P=0.087N	P=0.193	P=0.013	P<0.001
Fisher exact test		P=0.100N	P=0.153N	P=0.112	P=0.004	P<0.001
Lung: Alveolar/bronchiolar Adenoma						
Overall rates	4/50 (8%)	7/49 (14%)	10/33 (30%)	12/47 (26%)	11/49 (22%)	6/49 (12%)
Adjusted rates	12.9%	24.8%	38.5%	36.0%	33.0%	17.6%
Terminal rates	4/31 (13%)	6/27 (22%)	10/26 (38%)	11/32 (34%)	9/31 (29%)	2/25 (8%)
First incidence (days)	743 (T)	716	743 (T)	649	705	641
Life table tests		P=0.188	P=0.028	P=0.029	P=0.047	P=0.318
Logistic regression tests		P=0.207	P=0.028	P=0.033	P=0.060	P=0.396
Fisher exact test		P=0.251	P=0.010	P=0.019	P=0.041	P=0.357

TABLE D3
Statistical Analysis of Primary Tumors in Male Mice in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 330:0, 33:100, 110:330, 330:330, and 330:1,000 ppm Groups (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	330 ppm 0 ppm	33 ppm 100 ppm	110 ppm 330 ppm	330 ppm 330 ppm	330 ppm 1,000 ppm
Lung: Alveolar/bronchiolar Carcinoma						
Overall rates	1/50 (2%)	0/49 (0%)	1/33 (3%)	1/47 (2%)	7/49 (14%)	0/49 (0%)
Adjusted rates	3.2%	0.0%	3.7%	3.1%	19.0%	0.0%
Terminal rates	1/31 (3%)	0/27 (0%)	0/26 (0%)	1/32 (3%)	4/31 (13%)	0/25 (0%)
First incidence (days)	743 (T)	-[e]	705	743 (T)	562	-
Life table tests		P=0.528N	P=0.722	P=0.755N	P=0.041	P=0.543N
Logistic regression tests		P=0.528N	P=0.700	P=0.755N	P=0.035	P=0.543N
Fisher exact test		P=0.505N	P=0.640	P=0.737	P=0.028	P=0.505N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma						
Overall rates	5/50 (10%)	7/49 (14%)	11/33 (33%)	12/47 (26%)	17/49 (35%)	6/49 (12%)
Adjusted rates	16.1%	24.8%	40.7%	36.0%	46.2%	17.6%
Terminal rates	5/31 (16%)	6/27 (22%)	10/26 (38%)	11/32 (34%)	12/31 (39%)	2/25 (8%)
First incidence (days)	743 (T)	716	705	649	562	641
Life table tests		P=0.288	P=0.033	P=0.058	P=0.005	P=0.431
Logistic regression tests		P=0.316	P=0.025	P=0.065	P=0.007	P=0.530
Fisher exact test		P=0.365	P=0.010	P=0.040	P=0.003	P=0.486
Pituitary Gland, Pars Distalis: Adenoma						
Overall rates	0/44 (0%)	0/42 (0%)	0/28 (0%)	0/41 (0%)	0/45 (0%)	4/39 (10%)
Adjusted rates	0.0%	0.0%	0.0%	0.0%	0.0%	15.7%
Terminal rates	0/30 (0%)	0/24 (0%)	0/22 (0%)	0/31 (0%)	0/31 (0%)	2/20 (10%)
First incidence (days)	-	-	-	-	-	697
Life table tests		-	-	-	-	P=0.041
Logistic regression tests		-	-	-	-	P=0.054
Fisher exact test		-	-	-	-	P=0.045
Skin, Subcutaneous Tissue: Fibrosarcoma						
Overall rates	1/50 (2%)	5/49 (10%)	4/33 (12%)	7/50 (14%)	8/49 (16%)	5/50 (10%)
Adjusted rates	3.1%	15.5%	13.9%	19.4%	21.7%	14.0%
Terminal rates	0/31 (0%)	1/27 (4%)	2/26 (8%)	4/32 (13%)	4/31 (13%)	1/25 (4%)
First incidence (days)	705	578	516	595	576	557
Life table tests		P=0.092	P=0.122	P=0.044	P=0.027	P=0.107
Logistic regression tests		P=0.077	P=0.073	P=0.035	P=0.022	P=0.108
Fisher exact test		P=0.098	P=0.079	P=0.030	P=0.014	P=0.102
Skin, Subcutaneous Tissue: Sarcoma						
Overall rates	2/50 (4%)	1/49 (2%)	1/33 (3%)	0/50 (0%)	3/49 (6%)	0/50 (0%)
Adjusted rates	5.1%	3.4%	3.8%	0.0%	8.5%	0.0%
Terminal rates	0/31 (0%)	0/27 (0%)	1/26 (4%)	0/32 (0%)	1/31 (3%)	0/25 (0%)
First incidence (days)	565	722	743 (T)	-	693	-
Life table tests		P=0.546N	P=0.600N	P=0.229N	P=0.539	P=0.229N
Logistic regression tests		P=0.526N	P=0.652N	P=0.237N	P=0.495	P=0.251N
Fisher exact test		P=0.508N	P=0.653N	P=0.247N	P=0.490	P=0.247N
Skin, Subcutaneous Tissue: Fibrosarcoma or Sarcoma						
Overall rates	3/50 (6%)	6/49 (12%)	5/33 (15%)	7/50 (14%)	11/49 (22%)	5/50 (10%)
Adjusted rates	8.0%	18.4%	17.4%	19.4%	28.7%	14.0%
Terminal rates	0/31 (0%)	1/27 (4%)	3/26 (12%)	4/32 (13%)	5/31 (16%)	1/25 (4%)
First incidence (days)	565	578	516	595	576	557
Life table tests		P=0.207	P=0.235	P=0.193	P=0.0	P=0.363
Logistic regression tests		P=0.191	P=0.151	P=0.164	P=0.025	P=06358
Fisher exact test		P=0.233	P=0.158	P=0.159	P=0.018	P=0.357

TABLE D3
Statistical Analysis of Primary Tumors in Male Mice in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 330:0, 33:100, 110:330, 330:330, and 330:1,000 ppm Groups (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	330 ppm 0 ppm	33 ppm 100 ppm	110 ppm 330 ppm	330 ppm 330 ppm	330 ppm 1,000 ppm
Skin, Subcutaneous Tissue: Fibroma, Fibrosarcoma, or Sarcoma						
Overall rates	4/50 (8%)	6/49 (12%)	5/33 (15%)	7/50 (14%)	11/49 (22%)	5/50 (10%)
Adjusted rates	11.0%	18.4%	17.4%	19.4%	28.7%	14.0%
Terminal rates	1/31 (3%)	1/27 (4%)	3/26 (12%)	4/32 (13%)	5/31 (16%)	1/25 (4%)
First incidence (days)	565	578	516	595	576	557
Life table tests		P=0.315	P=0.355	P=0.301	P=0.075	P=0.487
Logistic regression tests		P=0.299	P=0.257	P=0.271	P=0.055	P=0.510
Fisher exact test		P=0.357	P=0.250	P=0.262	P=0.041	P=0.500
Thyroid Gland: Follicular Cell Adenoma						
Overall rates	0/50 (0%)	1/46 (2%)	1/33 (3%)	1/47 (2%)	2/48 (4%)	33/49 (67%)
Adjusted rates	0.0%	4.2%	3.8%	3.1%	6.5%	82.1%
Terminal rates	0/31 (0%)	1/24 (4%)	1/26 (4%)	1/32 (3%)	2/31 (6%)	18/25 (72%)
First incidence (days)	-	743 (T)	743 (T)	743 (T)	743 (T)	557
Life table tests		P=0.449	P=0.465	P=0.506	P=0.238	P<0.001
Logistic regression tests		P=0.449	P=0.465	P=0.506	P=0.238	P<0.001
Fisher exact test		P=0.479	P=0.398	P=0.485	P=0.237	P<0.001
Thyroid Gland: Follicular Cell Carcinoma						
Overall rates	1/50 (2%)	0/46 (0%)	0/33 (0%)	0/47 (0%)	0/48 (0%)	9/49 (18%)
Adjusted rates	3.2%	0.0%	0.0%	0.0%	0.0%	29.9%
Terminal rates	1/31 (3%)	0/24 (0%)	0/26(0%)	0/32 (0%)	0/31 (0%)	5/25 (20%)
First incidence (days)	743 (T)	-	-	-	-	685
Life table tests		P=0.551N	P=0.535N	P=0.494N	P=0.500N	P=0.006
Logistic regression tests		P=0.551N	P=0.535N	P=0.494N	P=0.500N	P=0.010
Fisher exact test		P=0.521N	P=0.602N	P=0.515N	P=0.510N	P=0.007
Thyroid Gland: Follicular Cell Adenoma or Carcinoma						
Overall rates	1/50 (2%)	1/46 (2%)	1/33 (3%)	1/47 (2%)	2/48 (4%)	35/49 (71%)
Adjusted rates	3.2%	4.2%	3.8%	3.1%	6.5%	87.2%
Terminal rates	1/31 (3%)	1/24 (4%)	1/26 (4%)	1/32 (3%)	2/31 (6%)	20/25 (80%)
First incidence (days)	743 (T)	743 (T)	743 (T)	743 (T)	743 (T)	557
Life table tests		P=0.704	P=0.723	P=0.755N	P=0.500	P<0.001
Logistic regression tests		P=0.704	P=0.723	P=0.755N	P=0.500	P<0.001
Fisher exact test		P=0.731	P=0.640	P=0.737	P=0.485	P<0.001
All Organs: Hemangioma or Hemangiosarcoma						
Overall rates	4/50 (8%)	1/49 (2%)	1/33 (3%)	3/50 (6%)	1/49 (2%)	4/50 (8%)
Adjusted rates	11.9%	3.7%	3.8%	8.9%	3.2%	14.4%
Terminal rates	3/31 (10%)	1/27 (4%)	1/26 (4%)	2/32 (6%)	1/31 (3%)	3/25 (12%)
First incidence (days)	565	743 (T)	743 (T)	690	743 (T)	685
Life table tests		P=0.227N	P=0.251N	P=0.477N	P=0.177N	P=0.565
Logistic regression tests		P=0.219N	P=0.284N	P=0.482N	P=0.156N	P=0.619N
Fisher exact test		P=0.187N	P=0.335N	P=0.500N	P=0.187N	P=0.643N
All Organs: Malignant Lymphoma (all types)						
Overall rates	9/50 (18%)	4/49 (8%)	4/33 (12%)	9/50 (18%)	8/49 (16%)	6/50 (12%)
Adjusted rates	25.5%	13.1%	15.4%	25.1%	22.5%	16.2%
Terminal rates	6/31 (19%)	3/27 (11%)	4/26 (15%)	6/32 (19%)	5/31 (16%)	0/25 (0%)
First incidence (days)	427	180	743 (T)	666	658	522
Life table tests		P=0.182N	P=0.212N	P=0.551N	P=0.463N	P=0.346N
Logistic regression tests		P=0.150N	P=0.283N	P=0.583N	P=0.448N	P=0.274N
Fisher exact test		P=0.125N	P=0.345N	P=0.602N	P=0.518N	P=0.288N

TABLE D3
Statistical Analysis of Primary Tumors in Male Mice in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 330:0, 33:100, 110:330, 330:330, and 330:1,000 ppm Groups (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	330 ppm 0 ppm	33 ppm 100 ppm	110 ppm 330 ppm	330 ppm 330 ppm	330 ppm 1,000 ppm
All Organs: Benign Tumors						
Overall rates	16/50 (32%)	14/49 (29%)	15/33 (45%)	26/50 (52%)	30/49 (61%)	41/50 (82%)
Adjusted rates	45.2%	45.9%	55.4%	69.8%	76.7%	93.0%
Terminal rates	12/31 (39%)	11/27 (41%)	14/26 (54%)	21/32 (66%)	22/31 (71%)	22/25 (88%)
First incidence (days)	618	351	532	526	573	449
Life table tests		P=0.584	P=0.406	P=0.053	P=0.009	P<0.001
Logistic regression tests		P=0.585	P=0.278	P=0.042	P=0.011	P<0.001
Fisher exact test		P=0.440N	P=0.157	P=0.034	P=0.003	P<0.001
All Organs: Malignant Tumors						
Overall rates	28/50 (56%)	19/49 (39%)	16/33 (48%)	30/50 (60%)	41/49 (84%)	46/50 (92%)
Adjusted rates	68.1%	57.1%	51.6%	71.4%	87.2%	100.0%
Terminal rates	18/31 (58%)	13/27 (48%)	11/26 (42%)	20/32 (63%)	25/31 (81%)	25/25 (100%)
First incidence (days)	427	180	516	584	532	507
Life table tests		P=0.187N	P=0.123N	P=0.531	P=0.046	P<0.001
Logistic regression tests		P=0.142N	P=0.211N	P=0.473	P=0.012	P<0.001
Fisher exact test		P=0.065N	P=0.327N	P=0.420	P=0.002	P<0.001
All Organs: Benign or Malignant Tumors						
Overall rates	35/50 (70%)	28/49 (57%)	25/33 (76%)	39/50 (78%)	48/49 (98%)	47/50 (94%)
Adjusted rates	83.3%	77.6%	80.6%	88.6%	100.0%	100.0%
Terminal rates	24/31 (77%)	19/27 (70%)	20/26 (77%)	27/32 (84%)	31/31 (100%)	25/25 (100%)
First incidence (days)	427	180	516	526	532	449
Life table tests		P=0.371N	P=0.292N	P=0.415	P=0.037	P=0.007
Logistic regression tests		P=0.351N	P=0.566N	P=0.275	P=0.003	P=0.003
Fisher exact test		P=0.131N	P=0.376	P=0.247	P<0.001	P=0.002

(T)Terminal sacrifice

[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.

[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality

[c] Observed incidence at terminal kill

[d] Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

[e] Not applicable; no tumors in animal group

TABLE D4
Statistical Analysis of Selected Primary Tumors in Male Mice in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 330:0, 330:330, and 330:1,000 ppm Groups

F_0 Concentration F_1 Concentration	330 ppm 0 ppm	330 ppm 330 ppm	330 ppm 1,000 ppm
Liver: Hepatocellular Adenoma			
Overall rates[a]	6/49 (12%)	20/49 (41%)	15/49 (31%)
Life table tests[b]	P=0.088	P=0.008	P=0.047
Logistic regression tests[b]	P=0.141	P=0.007	P=0.037
Cochran-Armitage test[b]	P=0.085		
Fisher exact test[b]		P=0.001	P=0.024
Liver: Hepatocellular Carcinoma			
Overall rates	8/49 (16%)	19/49 (39%)	45/49 (92%)
Life table tests	P<0.001	P=0.030	P<0.001
Logtistic Regression	P<0.001	P=0.040	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.011	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rates	13/49 (27%)	34/49 (69%)	47/49 (96%)
Life table tests	P<0.001	P<0.001	P<0.001
Logistic regression tests	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001
Pituitary Gland, Pars Distalis: Adenoma			
Overall rates	0/42 (0%)	0/45 (0%)	4/39 (10%)
Life table tests	P=0.006	-	P=0.054
Logistic regression tests	P=0.009	-	P=0.072
Cochran-Armitage test	P=0.007		
Fisher exact test		-	P=0.049
Thyroid Gland: Follicular Cell Adenoma			
Overall rates	1/46 (2%)	2/48 (4%)	33/49 (67%)
Life table tests	P<0.001	P=0.590	P<0.001
Logistic regression tests	P<0.001	P=0.590	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.516	P<0.001
Thyroid Gland: Follicular Cell Carcinoma			
Overall rates	0/46 (0%)	0/48 (0%)	9/49 (18%)
Life table tests	P<0.001	-[c]	P=0.004
Logistic regression tests	P<0.001	-	P=0.007
Cochran-Armitage test	P<0.001		
Fisher exact test		-	P=0.002

TABLE D4
Statistical Analysis of Selected Primary Tumors in Male Mice in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 330:0, 330:330, and 330:1,000 ppm Groups (continued)

F_0 Concentration	330 ppm	330 ppm	330 ppm
F_1 Concentration	0 ppm	330 ppm	1,000 ppm
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall rates	1/46 (2%)	2/48 (4%)	35/49 (71%)
Life table tests	P<0.001	P=0.590	P<0.001
Logistic regression tests	P<0.001	P=0.590	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.516	P<0.001

[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.

[b] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates.

[c] Not applicable; no tumors in animal group

TABLE D5
Statistical Analysis of Selected Primary Tumors in Male Mice in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:330, 110:330, and 330:330 ppm Groups

F_0 Concentration F_1 Concentration	0 ppm 330 ppm	110 ppm 330 ppm	330 ppm 330 ppm
Liver: Hepatocellular Adenoma			
Overall rates[a]	16/50 (32%)	15/47 (32%)	20/49 (41%)
Life table tests[b]	P=0.178	P=0.530N	P=0.229
Logistic regression tests[b]	P=0.199	P=0.578	P=0.240
Cochran-Armitage test[b]	P=0.194		
Fisher exact test[b]		P=0.583N	P=0.241
Liver: Hepatocellular Carcinoma			
Overall rates	19/50 (38%)	15/47 (32%)	19/49 (39%)
Life table tests	P=0.428	P=0.279N	P=0.524
Logtistic Regression	P=0.433	P=0.357N	P=0.522
Cochran-Armitage test	P=0.469		
Fisher exact test		P=0.340N	P=0.551
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rates	32/50 (64%)	26/47 (55%)	34/49 (69%)
Life table tests	P=0.224	P=0.193N	P=0.333
Logistic regression tests	P=0.236	P=0.268N	P=0.321
Cochran-Armitage test	P=0.258		
Fisher exact test		P=0.253N	P=0.361
Pituitary Gland, Pars Distalis: Adenoma			
Overall rates	0/42 (0%)	0/41 (0%)	0/45 (0%)
Thyroid Gland: Follicular Cell Adenoma			
Overall rates	1/49 (2%)	1/47 (2%)	2/48 (4%)
Life table tests	P=0.382	P=0.762	P=0.489
Logistic regression tests	P=0.382	P=0.762	P=0.489
Cochran-Armitage test	P=0.389		
Fisher exact test		P=0.742	P=0.492
Thyroid Gland: Follicular Cell Carcinoma			
Overall rates	0/49 (0%)	0/47 (0%)	0/48 (0%)

[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.

[b] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

TABLE D6
Statistical Analysis of Selected Primary Tumors in Male Mice in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:1,000 and 330:1,000 ppm Groups

F_0 Concentration F_1 Concentration	0 ppm 1,000 ppm	330 ppm 1,000 ppm
Liver: Hepatocellular Adenoma		
Overall rates[a]	9/50 (18%)	15/49 (31%)
Life table tests[b]		P=0.177
Logistic regression tests[b]		P=0.115
Fisher exact test[b]		P=0.109
Liver: Hepatocellular Carcinoma		
Overall rates	45/50 (90%)	45/49 (92%)
Life table tests		P=0.395N
Logistic regression tests		P=0.695N
Fisher exact test		P=0.513
Liver: Hepatocellular Adenoma or Carcinoma		
Overall rates	46/50 (92%)	47/49 (96%)
Life table tests		P=0.453N
Logistic regression tests		-[c]
Fisher exact test		P=0.349
Pituitary Gland, Pars Distalis: Adenoma		
Overall rates	8/41 (20%)	4/39 (10%)
Life table tests		P=0.175N
Logistic regression tests		P=0.162N
Fisher exact test		P=0.200N
Thyroid Gland: Follicular Cell Adenoma		
Overall rates	26/50 (52%)	33/49 (67%)
Life table tests		P=0.262
Logistic regression tests		P=0.105
Fisher exact test		P=0.088
Thyroid Gland: Follicular Cell Carcinoma		
Overall rates	5/50 (10%)	9/49 (18%)
Life table tests		P=0.247
Logistic regression tests		P=0.200
Fisher exact test		P=0.183
Thyroid Gland: Follicular Cell Adenoma or Carcinoma		
Overall rates	29/50 (58%)	35/49 (71%)
Life table tests		P=0.323
Logistic regression tests		P=0.136
Fisher exact test		P=0.117

[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.

[b] Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

[c] Value of statistic cannot be computed

TABLE D7a
Historical Incidence of Adenomas and Carcinomas of the Pituitary Gland Pars Distalis in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Untreated Controls
Historical Incidence at Battelle Columbus Laboratories	
Chlorobenzene	0/39
N-Phenyl-2-Naphthylamine	0/43
Rotenone	0/44
l-Ascorbic Acid	0/43
Overall Historical Incidence	
Total	11/1495 (0.7%)
Standard deviation	1.6%
Range	
High	2/35
Low	0/50

[a] Data as of 1 March 1989 for studies of at least 104 weeks. Standard deviation and range are presented for groups of 35 or more animals.

TABLE D7b
Historical Incidence of Lung Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	5/50	1/50	5/50
N-Phenyl-2-Naphthylamine	6/49	5/49	11/49
Rotenone	5/47	1/47	6/47
l-Ascorbic Acid	3/49	2/49	5/49
Total	19/195 (9.7%)	9/195 (4.6%)	27/195 (13.8%)
Standard deviation	2.6%	3.8%	5.9%
Range			
High	6/49	5/49	11/49
Low	3/49	1/50	5/50
Overall Historical Incidence			
Total	204/1684 (12.1%)	80/1684 (4.8%)	277/1684 (16.4%)
Standard deviation	6.2%	2.7%	6.9%
Range			
High	14/50	5/50	17/50
Low	1/50	0/49	4/50

[a] Data as of 1 March 1989 for studies of at least 104 weeks. Standard deviation and range are presented for groups of 35 or more animals.

TABLE D7c
Historical Incidence of Hepatocellular Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	7/50	14/50	19/50
N-Phenyl-2-Naphthylamine	6/47	6/47	11/47
Rotenone	7/47	6/47	12/47
l-Ascorbic Acid	6/50	10/50	16/50
Total	26/194 (13.4%)	36/194 (18.6%)	58/194 (29.9%)
Standard deviation	1.3%	7.2%	6.6%
Range			
High	7/47	14/50	19/50
Low	6/50	6/47	11/47
Overall Historical Incidence			
Total	233/1678 (13.9%)	285/1678 (17.0%)	494/1678 (29.4%)
Standard deviation	7.5%	6.3%	8.0%
Range			
High	22/50	15/50	29/50
Low	2/45	4/50	7/48

[a] Data as of 1 March 1989 for studies of at least 104 weeks. Standard deviation and range are presented for groups of 35 or more animals.

TABLE D7d
Historical Incidence of Thyroid Follicular Cell Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	3/42	0/42	3/42
N-Phenyl-2-Naphthylamine	0/48	0/48	0/48
Rotenone	0/46	0/46	0/46
l-Ascorbic Acid	1/48	0/48	1/48
Total	4/184 (2.2%)	0/184 (0.0%)	4/184 (2.2%)
Standard deviation	3.3%	0.0%	3.3%
Range			
High	3/42	---	3/42
Low	0/48	---	0/48
Overall Historical Incidence			
Total	30/1630 (1.8%)	2/1630 (0.1%)	32/1630 (2.0%)
Standard deviation	2.2%	0.5%	2.2%
Range			
High	3/42	1/47	3/42
Low	0/50	0/50	0/50

[a] Data as of 1 March 1989 for studies of at least 104 weeks. Standard deviation and range are presented for groups of 35 or more animals.

TABLE D8
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Ethylene Thiourea

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	330 ppm 0 ppm	33 ppm 100 ppm	0 ppm 330 ppm	110 ppm 330 ppm	330 ppm 330 ppm
Disposition Summary						
Animals initially in study	50	50	34	50	50	50
Animals removed	50	50	34	50	50	50
Animals examined histopathologically	50	49	33	50	50	49
Alimentary System						
Gallbladder	(40)	(12)	(6)	(10)	(13)	(11)
Inflammation, chronic active	1 (3%)					
Intestine large, cecum	(45)	(19)	(7)	(17)	(14)	(13)
Inflammation, acute					1 (7%)	
Parasite metazoan			1 (14%)			
Intestine large, colon	(50)	(21)	(8)	(17)	(16)	(16)
Parasite metazoan	5 (10%)			3 (18%)		1 (6%)
Intestine large, rectum	(48)	(19)	(8)	(17)	(15)	(16)
Parasite metazoan					1 (7%)	
Intestine small, ileum	(44)	(18)	(7)	(16)	(14)	(13)
Parasite metazoan			1 (14%)			
Intestine small, jejunum	(45)	(20)	(10)	(18)	(16)	(18)
Inflammation, chronic active	1 (2%)					
Liver	(49)	(49)	(33)	(50)	(47)	(49)
Basophilic focus	3 (6%)	5 (10%)	3 (9%)	5 (10%)	4 (9%)	3 (6%)
Clear cell focus	1 (2%)		1 (3%)	3 (6%)	1 (2%)	5 (10%)
Eosinophilic focus	2 (4%)			8 (16%)	3 (6%)	3 (6%)
Fatty change, focal	1 (2%)					
Fibrosis						1 (2%)
Hematopoietic cell proliferation	3 (6%)			1 (2%)	3 (6%)	4 (8%)
Infarct	14 (29%)	4 (8%)	2 (6%)	7 (14%)	3 (6%)	2 (4%)
Inflammation, chronic active	5 (10%)	1 (2%)		1 (2%)		
Mixed cell focus						2 (4%)
Necrosis		2 (4%)				
Bile duct, cyst		3 (6%)				2 (4%)
Bile duct, hyperplasia				2 (4%)		
Central vein, thrombus				1 (2%)		1 (2%)
Centrilobular, cytomegaly		1 (2%)	6 (18%)	36 (72%)	33 (70%)	29 (59%)
Centrilobular, necrosis						1 (2%)
Centrilobular, necrosis, acute			1 (3%)	2 (4%)		
Mesentery	(6)	(1)			(1)	(1)
Angiectasis	1 (17%)					
Inflammation, chronic active	2 (33%)					1 (100%)
Pancreas	(48)	(20)	(7)	(17)	(15)	(17)
Inflammation, chronic active					1 (7%)	
Acinus, atrophy	5 (10%)				1 (7%)	
Acinus, focal cellular change	1 (2%)					
Acinus, inflammation, chronic active				1 (6%)		1 (6%)
Duct, cyst	1 (2%)			1 (6%)		
Salivary glands	(50)	(21)	(8)	(19)	(15)	(17)
Inflammation, acute	1 (2%)					
Acinus, atrophy	1 (2%)					

TABLE D8
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 1,000 ppm	330 ppm 1,000 ppm
Disposition Summary		
Animals initially in study	50	50
Animals removed	50	50
Animals examined histopathologically	50	50
Alimentary System		
Gallbladder	(33)	(27)
Epithelium, hypertrophy, focal		1 (4%)
Intestine large, cecum	(42)	(40)
Parasite metazoan		3 (8%)
Intestine large, colon	(49)	(45)
Inflammation, necrotizing, acute	1 (2%)	
Parasite metazoan	8 (16%)	9 (20%)
Intestine large, rectum	(46)	(41)
Parasite metazoan	4 (9%)	4 (10%)
Intestine small, ileum	(43)	(40)
Parasite metazoan	4 (9%)	1 (3%)
Intestine small, jejunum	(44)	(40)
Inflammation, chronic active	1 (2%)	
Lymphatic, ectasia		1 (3%)
Liver	(50)	(49)
Basophilic focus		1 (2%)
Eosinophilic focus	2 (4%)	11 (22%)
Hematopoietic cell proliferation	1 (2%)	
Infarct	33 (66%)	34 (69%)
Centrilobular, cytomegaly	25 (50%)	40 (82%)
Oval cell, hyperplasia		2 (4%)
Mesentery	(5)	(3)
Angiectasis	1 (20%)	
Inflammation, chronic active	1 (20%)	
Inflammation, necrotizing, acute	1 (20%)	
Pancreas	(45)	(47)
Acinus, atrophy	4 (9%)	2 (4%)
Duct, ectasia		1 (2%)
Perivascular, inflammation, chronic active	1 (2%)	
Salivary glands	(50)	(49)
Acinus, atrophy	1 (2%)	
Perivascular, inflammation, suppurative	1 (2%)	

TABLE D8
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	330 ppm 0 ppm	33 ppm 100 ppm	0 ppm 330 ppm	110 ppm 330 ppm	330 ppm 330 ppm
Alimentary System (continued)						
Stomach, forestomach	(49)	(24)	(7)	(17)	(16)	(22)
Acanthosis	1 (2%)	1 (4%)			1 (6%)	1 (5%)
Cyst epithelial inclusion						1 (5%)
Inflammation, acute	1 (2%)					
Ulcer						1 (5%)
Stomach, glandular	(48)	(21)	(7)	(17)	(15)	(18)
Infiltration cellular, lymphocytic			1 (14%)			
Tooth	(5)					
Incisor, upper, dysplasia	3 (60%)					
Peridontal tissue, infiltration cellular, mast cell	1 (20%)					
Peridontal tissue, inflammation, suppurative	1 (20%)					
Cardiovascular System						
Heart	(50)	(23)	(8)	(19)	(15)	(19)
Bacterium, acute, multiple	1 (2%)					
Degeneration, chronic			1 (13%)			
Mineralization	1 (2%)					
Thrombus		1 (4%)				
Valve, inflammation, suppurative	1 (2%)					
Endocrine System						
Adrenal gland	(50)	(21)	(8)	(18)	(15)	(18)
Corticomedullary junction, cyst	1 (2%)					
Adrenal gland, cortex	(50)	(21)	(8)	(18)	(15)	(18)
Hyperplasia	6 (12%)					1 (6%)
Hypertrophy	8 (16%)		1 (13%)			1 (6%)
Adrenal gland, medulla	(50)	(21)	(8)	(18)	(15)	(18)
Hyperplasia	3 (6%)					
Pituitary gland	(44)	(42)	(28)	(42)	(41)	(45)
Ectasia				1 (2%)		
Craniopharyngeal duct, inflammation, chronic active				1 (2%)		
Pars distalis, cyst		2 (5%)	1 (4%)	1 (2%)	1 (2%)	
Pars distalis, hyperplasia			1 (4%)	2 (5%)	2 (5%)	1 (2%)
Thyroid gland	(50)	(46)	(33)	(49)	(47)	(48)
Artery, inflammation, chronic active						1 (2%)
Follicular cell, hyperplasia		2 (4%)	1 (3%)		3 (6%)	7 (15%)
Follicular cell, vacuolization cytoplasmic			25 (76%)	46 (94%)	43 (91%)	46 (96%)
General Body System						
None						

TABLE D8
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 1,000 ppm	330 ppm 1,000 ppm
Alimentary System (continued)		
Stomach, forestomach	(49)	(45)
Acanthosis	1 (2%)	
Inflammation, acute	1 (2%)	
Stomach, glandular	(48)	(44)
Dysplasia	1 (2%)	
Infiltration cellular, mast cell		1 (2%)
Inflammation, acute		1 (2%)
Inflammation, chronic	2 (4%)	
Tooth	(4)	(1)
Incisor, upper, dysplasia	1 (25%)	
Peridontal tissue, inflammation, suppurative	2 (50%)	1 (100%)
Cardiovascular System		
Heart	(50)	(50)
Bacterium, acute, multiple	1 (2%)	
Degeneration, chronic		1 (2%)
Mineralization		1 (2%)
Thrombus		1 (2%)
Artery, inflammation, chronic active	1 (2%)	
Valve, bacterium		1 (2%)
Valve, inflammation, suppurative	1 (2%)	1 (2%)
Endocrine System		
Adrenal gland, cortex	(50)	(49)
Hyperplasia	3 (6%)	3 (6%)
Hypertrophy	10 (20%)	7 (14%)
Adrenal gland, medulla	(50)	(49)
Hyperplasia	2 (4%)	4 (8%)
Pituitary gland	(41)	(39)
Pars distalis, hyperplasia	32 (78%)	25 (64%)
Thyroid gland	(50)	(49)
Follicular cell, hyperplasia	44 (88%)	47 (96%)
Follicular cell, vacuolization cytoplasmic	47 (94%)	46 (94%)
General Body System		
None		

TABLE D8
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	330 ppm 0 ppm	33 ppm 100 ppm	0 ppm 330 ppm	110 ppm 330 ppm	330 ppm 330 ppm
Genital System						
Epididymis	(49)	(22)	(8)	(18)	(15)	(19)
Inflammation, acute				1 (6%)		
Inflammation, chronic active						2 (11%)
Preputial gland	(2)	(2)	(1)	(2)	(4)	(3)
Inflammation, chronic active	1 (50%)		1 (100%)	2 (100%)	2 (50%)	2 (67%)
Inflammation, suppurative	1 (50%)	1 (50%)				
Duct, dilatation	1 (50%)			2 (100%)	2 (50%)	2 (67%)
Prostate	(50)	(22)	(8)	(18)	(15)	(19)
Inflammation, chronic active				2 (11%)	1 (7%)	3 (16%)
Inflammation, suppurative	3 (6%)	3 (14%)		2 (11%)		
Seminal vesicle	(4)	(2)		(1)	(1)	(1)
Dilatation	2 (50%)	2 (100%)		1 (100%)	1 (100%)	1 (100%)
Inflammation, suppurative	1 (25%)					
Testes	(50)	(22)	(8)	(20)	(14)	(19)
Seminiferous tubule, degeneration	1 (2%)	1 (5%)		2 (10%)		
Seminiferous tubule, mineralization				1 (5%)		
Hematopoietic System						
Bone marrow	(49)	(21)	(8)	(18)	(13)	(19)
Femoral, hyperplasia, neutrophil	1 (2%)	1 (5%)		1 (6%)		2 (11%)
Lymph node	(48)	(25)	(15)	(22)	(20)	(22)
Lumbar, hyperplasia, lymphoid		1 (4%)				
Mandibular, hyperplasia, lymphoid				2 (9%)		1 (5%)
Mandibular, infiltration cellular, histiocytic		1 (4%)	1 (7%)			
Lymph node, mesenteric	(14)	(11)	(7)	(4)	(8)	(6)
Hematopoietic cell proliferation	11 (79%)	7 (64%)	1 (14%)	2 (50%)	3 (38%)	
Hemorrhage						1 (17%)
Hyperplasia, lymphoid		2 (18%)	1 (14%)			
Infiltration cellular, plasma cell			1 (14%)			
Inflammation, chronic active					1 (13%)	1 (17%)
Thrombus	1 (7%)					
Spleen	(49)	(25)	(12)	(21)	(24)	(24)
Depletion lymphoid	4 (8%)	1 (4%)			2 (8%)	
Hematopoietic cell proliferation	3 (6%)	2 (8%)	2 (17%)	4 (19%)	5 (21%)	8 (33%)
Hyperplasia, lymphoid		1 (4%)		1 (5%)	1 (4%)	1 (4%)
Thymus	(29)	(11)	(4)	(11)	(11)	(11)
Depletion lymphoid		1 (9%)		1 (9%)	2 (18%)	1 (9%)
Necrosis, diffuse	1 (3%)	1 (9%)		1 (9%)		
Integumentary System						
Skin	(50)	(26)	(14)	(23)	(25)	(26)
Acanthosis		3 (12%)	4 (29%)	4 (17%)	3 (12%)	2 (8%)
Alopecia			1 (7%)			
Hyperplasia, basal cell			1 (7%)			
Parasite external	1 (2%)	4 (15%)	6 (43%)	5 (22%)	4 (16%)	5 (19%)
Ulcer	1 (2%)	3 (12%)		3 (13%)	5 (20%)	3 (12%)
Prepuce, inflammation, acute				1 (4%)		
Prepuce, subcutaneous tissue, foreign body				1 (4%)		

TABLE D8
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 1,000 ppm	330 ppm 1,000 ppm
Genital System		
Epididymis	(49)	(49)
Inflammation, chronic active		1 (2%)
Arteriole, inflammation, chronic active	1 (2%)	
Preputial gland	(2)	(1)
Inflammation, chronic active	1 (50%)	
Inflammation, suppurative	1 (50%)	
Duct, dilatation	1 (50%)	1 (100%)
Prostate	(47)	(49)
Inflammation, suppurative	1 (2%)	2 (4%)
Arteriole, inflammation, chronic active	1 (2%)	
Seminal vesicle	(2)	
Dilatation	1 (50%)	
Testes	(50)	(49)
Arteriole, inflammation, chronic active	1 (2%)	
Seminiferous tubule, degeneration	1 (2%)	1 (2%)
Hematopoietic System		
Bone marrow	(49)	(47)
Femoral, hyperplasia, neutrophil	1 (2%)	
Lymph node	(47)	(48)
Lumbar, necrosis		1 (2%)
Pancreatic, necrosis		1 (2%)
Lymph node, mesenteric	(7)	(5)
Hematopoietic cell proliferation	3 (43%)	2 (40%)
Spleen	(48)	(47)
Hematopoietic cell proliferation	3 (6%)	1 (2%)
Thymus	(16)	(16)
Necrosis, diffuse	2 (13%)	
Integumentary System		
Skin	(49)	(50)
Acanthosis		1 (2%)
Parasite external	28 (57%)	6 (12%)

TABLE D8
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	330 ppm 0 ppm	33 ppm 100 ppm	0 ppm 330 ppm	110 ppm 330 ppm	330 ppm 330 ppm
Integumentary System (continued)						
Skin (continued)	(50)	(26)	(14)	(23)	(25)	(26)
Subcutaneous tissue, edema		1 (4%)				
Subcutaneous tissue, fibrosis	1 (2%)	1 (4%)	1 (7%)	2 (9%)	1 (4%)	1 (4%)
Subcutaneous tissue, granuloma			1 (7%)			
Subcutaneous tissue, inflammation, acute	1 (2%)	1 (4%)				
Subcutaneous tissue, inflammation, chronic active		2 (8%)		1 (4%)	2 (8%)	
Subcutaneous tissue, metaplasia, osseous					1 (4%)	
Subcutaneous tissue, sebaceous gland, hyperplasia				1 (4%)		
Musculoskeletal System						
Bone	(50)	(44)	(25)	(42)	(39)	(38)
Femur, hyperostosis		1 (2%)				
Tarsal, hyperostosis	22 (44%)	24 (55%)	18 (72%)	28 (67%)	29 (74%)	29 (76%)
Nervous System						
Brain	(50)	(21)	(8)	(19)	(15)	(19)
Infarct	1 (2%)					
Respiratory System						
Lung	(50)	(49)	(33)	(50)	(47)	(49)
Inflammation, chronic, diffuse					1 (2%)	
Metaplasia, squamous	1 (2%)					
Alveolar epithelium, hyperplasia	2 (4%)	2 (4%)	3 (9%)	2 (4%)	5 (11%)	3 (6%)
Alveolus, hyperplasia, macrophage					1 (2%)	1 (2%)
Artery, embolus		1 (2%)				
Mediastinum, inflammation			1 (3%)			
Peribronchial, inflammation, chronic active					2 (4%)	1 (2%)
Peribronchiolar, inflammation, chronic active	26 (52%)	6 (12%)	5 (15%)	17 (34%)	16 (34%)	7 (14%)
Perivascular, inflammation, chronic active					2 (4%)	1 (2%)
Nose	(50)	(21)	(8)	(19)	(16)	(18)
Mucosa, inflammation, acute	2 (4%)					1 (6%)
Special Senses System						
Eye		(2)	(1)			
Atrophy			1 (100%)			
Cornea, inflammation, chronic active		1 (50%)				
Harderian gland	(4)	(1)	(3)	(3)	(1)	(3)
Hyperplasia	1 (25%)					

TABLE D8
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 1,000 ppm	330 ppm 1,000 ppm
Integumentary System (continued)		
Skin (continued)	(49)	(50)
Subcutaneous tissue, edema	1 (2%)	
Subcutaneous tissue, fibrosis	1 (2%)	1 (2%)
Subcutaneous tissue, inflammation, chronic active	5 (10%)	
Musculoskeletal System		
Bone	(50)	(50)
Tarsal, hyperostosis	15 (30%)	24 (48%)
Nervous System		
Brain	(50)	(49)
Infarct	1 (2%)	
Respiratory System		
Lung	(50)	(49)
Inflammation, chronic, diffuse	1 (2%)	
Alveolar epithelium, hyperplasia	2 (4%)	4 (8%)
Alveolus, hyperplasia, macrophage	1 (2%)	
Arteriole, capillary, inflammation, suppurative	1 (2%)	
Artery, mediastinum, inflammation, suppurative	1 (2%)	
Peribronchiolar, inflammation, chronic active	21 (42%)	18 (37%)
Peribronchiolar, inflammation, necrotizing, acute	1 (2%)	
Perivascular, inflammation, chronic active	1 (2%)	
Nose	(50)	(49)
Mucosa, inflammation, acute	1 (2%)	1 (2%)
Special Senses System		
Eye	(6)	(2)
Atrophy	5 (83%)	2 (100%)
Inflammation	1 (17%)	
Inflammation, suppurative	1 (17%)	
Harderian gland	(18)	(6)
Inflammation, chronic active	10 (56%)	2 (33%)
Inflammation, suppurative	5 (28%)	1 (17%)
Necrosis		1 (17%)

TABLE D8
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	330 ppm 0 ppm	33 ppm 100 ppm	0 ppm 330 ppm	110 ppm 330 ppm	330 ppm 330 ppm
Urinary System						
Kidney	(49)	(23)	(11)	(21)	(17)	(19)
Hydronephrosis	1 (2%)	2 (9%)				
Inflammation, chronic active		1 (4%)				
Metaplasia, osseous	1 (2%)					
Nephropathy, chronic	32 (65%)	3 (13%)		3 (14%)		2 (11%)
Capsule, fibrosis, focal		1 (4%)	1 (9%)			
Cortex, cyst			2 (18%)		1 (6%)	
Cortex, infiltration cellular, histiocytic, focal					1 (6%)	
Pelvis, bacterium	1 (2%)					
Pelvis, inflammation, suppurative	2 (4%)			1 (5%)		
Renal tubule, mineralization						1 (5%)
Renal tubule, necrosis	1 (2%)	1 (4%)				
Urethra	(2)	(2)		(1)		
Inflammation, chronic active				1 (100%)		
Inflammation, suppurative	2 (100%)	1 (50%)				
Bulbourethral gland, dilatation		1 (50%)				
Urinary bladder	(49)	(20)	(8)	(17)	(15)	(16)
Calculus gross observation		2 (10%)				
Dilatation	2 (4%)	3 (15%)	2 (25%)	2 (12%)		2 (13%)
Inflammation, chronic active	3 (6%)	2 (10%)		1 (6%)		
Mineralization	2 (4%)					
Mucosa, hyperplasia				1 (6%)		

TABLE D8
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 1,000 ppm	330 ppm 1,000 ppm
Urinary System		
Kidney	(50)	(49)
Infarct		1 (2%)
Nephropathy, chronic	22 (44%)	17 (35%)
Pelvis, inflammation, suppurative	1 (2%)	
Renal tubule, necrosis	1 (2%)	1 (2%)
Urethra	(3)	(1)
Inflammation, suppurative	3 (100%)	1 (100%)
Urinary bladder	(48)	(48)
Inflammation, chronic active	1 (2%)	
Arteriole, inflammation, chronic active	1 (2%)	

APPENDIX E
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR FEED STUDY OF ETHYLENE THIOUREA

TABLE E1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Ethylene Thiourea[a]

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	330 ppm 0 ppm	33 ppm 100 ppm	0 ppm 330 ppm	110 ppm 330 ppm	330 ppm 330 ppm
Disposition Summary						
Animals initially in study	50	50	29	50	50	50
Early deaths						
Natural death	7	9	2	2	5	4
Moribund sacrifice	9	4	6	6	11	10
Survivors						
Terminal sacrifice	34	37	21	42	34	36
Animals examined microscopically	50	50	29	50	50	50
Alimentary System						
Esophagus	(49)	(13)	(8)	(8)	(16)	(14)
Squamous cell carcinoma	1 (2%)					
Gallbladder	(41)	(7)	(8)	(7)	(12)	(8)
Intestine large, cecum	(44)	(10)	(8)	(7)	(14)	(11)
Leiomyosarcoma	1 (2%)					
Intestine large, colon	(49)	(12)	(8)	(9)	(16)	(12)
Leiomyosarcoma				1 (11%)		
Intestine small, jejunum	(46)	(12)	(10)	(8)	(19)	(13)
Liver	(50)	(49)	(28)	(50)	(50)	(50)
Carcinoma, metastatic, islets, pancreatic			1 (2%)			
Fibrosarcoma, metastatic, skin	1 (2%)					
Hemangioma		1 (2%)				
Hemangiosarcoma		1 (2%)		4 (8%)	2 (4%)	1 (2%)
Hemangiosarcoma, multiple	1 (2%)				1 (2%)	
Hepatoblastoma					1 (2%)	1 (2%)
Hepatocellular carcinoma	2 (4%)	5 (10%)	2 (7%)	14 (28%)	11 (22%)	9 (18%)
Hepatocellular carcinoma, multiple				15 (30%)	20 (40%)	14 (28%)
Hepatocellular adenoma	2 (4%)	1 (2%)	2 (7%)	19 (38%)	17 (34%)	14 (28%)
Hepatocellular adenoma, multiple				14 (28%)	17 (34%)	21 (42%)
Histiocytic sarcoma, single			1 (4%)	2 (4%)	1 (2%)	2 (4%)
Mesentery	(6)	(2)	(1)	(1)	(1)	
Fibrosarcoma, metastatic, skin						1 (100%)
Hemangiosarcoma	1 (17%)					
Lipoma	1 (17%)					
Pancreas	(50)	(11)	(8)	(7)	(16)	(13)
Salivary glands	(50)	(13)	(8)	(8)	(15)	(14)
Stomach, forestomach	(48)	(15)	(10)	(11)	(17)	(14)
Papilloma squamous	1 (2%)	1 (7%)		1 (9%)	1 (6%)	
Stomach, glandular	(48)	(11)	(8)	(8)	(15)	(13)
Cardiovascular System						
Heart	(50)	(13)	(8)	(8)	(16)	(14)

TABLE E1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 1,000 ppm	330 ppm 1,000 ppm
Disposition Summary		
Animals initially in study	50	50
Early deaths		
Natural death	10	7
Moribund sacrifice	10	14
Survivors		
Terminal sacrifice	30	29
Animals examined microscopically	50	50
Alimentary System		
Gallbladder	(39)	(39)
Intestine small, jejunum	(50)	(48)
Liver	(50)	(50)
Hemangiosarcoma	2 (4%)	
Hepatoblastoma	2 (4%)	8 (16%)
Hepatoblastoma, multiple		1 (2%)
Hepatocellular carcinoma	3 (6%)	3 (6%)
Hepatocellular carcinoma, multiple	44 (88%)	45 (90%)
Hepatocellular adenoma	11 (22%)	10 (20%)
Hepatocellular adenoma, multiple	3 (6%)	7 (14%)
Histiocytic sarcoma, single	1 (2%)	2 (4%)
Mesentery	(2)	(1)
Pancreas	(50)	(50)
Salivary glands	(49)	(50)
Histiocytic sarcoma, single		1 (2%)
Stomach, forestomach	(49)	(50)
Stomach, glandular	(49)	(50)
Cardiovascular System		
Heart	(50)	(50)

TABLE E1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	330 ppm 0 ppm	33 ppm 100 ppm	0 ppm 330 ppm	110 ppm 330 ppm	330 ppm 330 ppm
Endocrine System						
Adrenal gland	(49)	(13)	(8)	(8)	(16)	(12)
Capsule, adenoma					1 (6%)	
Adrenal gland, cortex	(49)	(13)	(8)	(8)	(16)	(11)
Adrenal gland, medulla	(48)	(13)	(8)	(8)	(16)	(11)
Pheochromocytoma benign	1 (2%)					
Islets, pancreatic	(49)	(13)	(8)	(7)	(15)	(12)
Carcinoma		1 (8%)				
Pituitary gland	(47)	(48)	(28)	(49)	(48)	(47)
Pars distalis, adenoma	10 (21%)	11 (23%)	6 (21%)	19 (39%)	14 (29%)	26 (55%)
Pars distalis, carcinoma	1 (2%)		1 (4%)			
Pars intermedia, adenoma			2 (7%)		1 (2%)	1 (2%)
Thyroid gland	(50)	(49)	(29)	(50)	(50)	(49)
Follicular cell, adenoma		1 (2%)	1 (3%)	1 (2%)	3 (6%)	1 (2%)
Follicular cell, adenoma, multiple				1 (2%)	2 (4%)	9 (18%)
Follicular cell, carcinoma						1 (2%)
General Body System						
None						
Genital System						
Ovary	(49)	(26)	(20)	(15)	(24)	(25)
Cystadenoma	1 (2%)					
Cystadenoma, papillary				1 (7%)		2 (8%)
Hemangioma		1 (4%)				
Luteoma		1 (4%)				
Uterus	(48)	(33)	(13)	(19)	(20)	(20)
Hemangiosarcoma					1 (5%)	
Histiocytic sarcoma, single						1 (5%)
Leiomyosarcoma				1 (5%)		
Hematopoietic System						
Bone marrow	(49)	(13)	(8)	(8)	(16)	(13)
Femoral, hemangiosarcoma	1 (2%)					
Femoral, histiocytic sarcoma, single			1 (13%)	1 (13%)		
Lymph node	(49)	(18)	(15)	(19)	(25)	(19)
Mandibular, hemangiosarcoma, metastatic, liver					1 (4%)	
Mandibular, histiocytic sarcoma, single			1 (7%)	2 (11%)	1 (5%)	
Mandibular, sarcoma, metastatic, uncertain primary site				1 (5%)		
Pancreatic, leiomyosarcoma, metastatic, intestine large				1 (5%)		
Lymph node, mesenteric	(14)	(10)	(8)	(12)	(14)	(9)
Histiocytic sarcoma, single			1 (13%)	1 (8%)		1 (11%)
Lymph node, thoracic	(2)					
Spleen	(50)	(23)	(13)	(28)	(31)	(34)
Hemangiosarcoma	1 (2%)	1 (4%)		3 (11%)	1 (3%)	1 (3%)
Histiocytic sarcoma, single			1 (8%)	1 (4%)		2 (6%)
Thymus	(39)	(7)	(4)	(6)	(12)	(5)

TABLE E1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 1,000 ppm	330 ppm 1,000 ppm
Endocrine System		
Adrenal gland, cortex	(48)	(50)
Histiocytic sarcoma, single	1 (2%)	
Adrenal gland, medulla	(50)	(50)
Pheochromocytoma benign	1 (2%)	1 (2%)
Pituitary gland	(49)	(47)
Pars distalis, adenoma	26 (53%)	24 (51%)
Thyroid gland	(50)	(50)
Follicular cell, adenoma	4 (8%)	12 (24%)
Follicular cell, adenoma, multiple	31 (62%)	26 (52%)
Follicular cell, carcinoma	8 (16%)	4 (8%)
General Body System		
Tissue NOS	(1)	
Hepatocellular carcinoma, metastatic, liver	1 (100%)	
Genital System		
Ovary	(50)	(48)
Cystadenoma	2 (4%)	
Cystadenoma, papillary		1 (2%)
Granulosa cell tumor benign	1 (2%)	
Yolk sac carcinoma		1 (2%)
Uterus	(48)	(48)
Histiocytic sarcoma, single	1 (2%)	
Polyp stromal		1 (2%)
Hematopoietic System		
Bone marrow	(49)	(49)
Femoral, histiocytic sarcoma, single	1 (2%)	
Lymph node	(47)	(49)
Mandibular, histiocytic sarcoma, single	1 (2%)	2 (4%)
Mediastinal, histiocytic sarcoma, single		2 (4%)
Renal, histiocytic sarcoma, single		1 (2%)
Lymph node, mesenteric	(4)	(9)
Hepatocellular carcinoma, metastatic, liver		1 (11%)
Histiocytic sarcoma, single		2 (22%)
Spleen	(49)	(50)
Hemangiosarcoma	1 (2%)	1 (2%)
Histiocytic sarcoma, single	1 (2%)	2 (4%)
Thymus	(23)	(33)

TABLE E1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	330 ppm 0 ppm	33 ppm 100 ppm	0 ppm 330 ppm	110 ppm 330 ppm	330 ppm 330 ppm
Integumentary System						
Mammary gland	(35)	(13)	(8)	(8)	(16)	(11)
Adenocarcinoma	1 (3%)		1 (13%)	2 (25%)	2 (13%)	3 (27%)
Fibroadenoma	1 (3%)	1 (8%)				
Skin	(50)	(13)	(8)	(8)	(16)	(15)
Subcutaneous tissue, fibrosarcoma	1 (2%)	1 (8%)				1 (7%)
Subcutaneous tissue, hemangiosarcoma		1 (2%)	1 (8%)			
Subcutaneous tissue, sarcoma						1 (7%)
Musculoskeletal System						
Bone	(50)	(13)	(9)	(9)	(16)	(14)
Cranium, osteosarcoma	1 (2%)	1 (8%)				
Lumbar, osteosarcoma						1 (7%)
Nervous System						
Brain	(50)	(13)	(8)	(8)	(16)	(14)
Carcinoma, metastatic, pituitary gland		1 (2%)				
Histiocytic sarcoma, single				1 (13%)		1 (7%)
Osteosarcoma, metastatic, bone		1 (8%)				
Respiratory System						
Lung	(50)	(50)	(29)	(50)	(50)	(50)
Adenocarcinoma, metastatic, harderian gland			1 (3%)			
Alveolar/bronchiolar adenoma	2 (4%)	3 (6%)	1 (3%)	7 (14%)	2 (4%)	5 (10%)
Alveolar/bronchiolar adenoma, multiple						1 (2%)
Alveolar/bronchiolar carcinoma	3 (6%)	2 (4%)		1 (2%)	1 (2%)	2 (4%)
Fibrosarcoma, metastatic, skin						1 (2%)
Hepatocellular carcinoma, metastatic, liver				1 (2%)		
Histiocytic sarcoma, single			1 (3%)	2 (4%)	1 (2%)	2 (4%)
Osteosarcoma, metastatic, bone		1 (2%)				
Special Senses System						
Harderian gland	(3)	(3)	(1)	(4)	(1)	(1)
Adenocarcinoma		1 (33%)	1 (100%)	2 (50%)		
Adenoma	2 (67%)	2 (67%)		1 (25%)	1 (100%)	1 (100%)
Bilateral, adenoma				1 (25%)		
Urinary System						
Kidney	(50)	(12)	(8)	(11)	(16)	(15)
Histiocytic sarcoma, single				1 (9%)		
Renal tubule, adenoma, multiple	1 (2%)					
Urinary bladder	(48)	(12)	(8)	(9)	(13)	(11)

TABLE E1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 1,000 ppm	330 ppm 1,000 ppm
Integumentary System		
Mammary gland	(33)	(37)
Adenocarcinoma		1 (3%)
Fibroadenoma		1 (3%)
Skin	(49)	(50)
Papilloma squamous	1 (2%)	
Subcutaneous tissue, fibrosarcoma		1 (2%)
Subcutaneous tissue, mast cell tumor benign	1 (2%)	
Respiratory System		
Lung	(50)	(50)
Alveolar/bronchiolar adenoma		4 (8%)
Alveolar/bronchiolar carcinoma		1 (2%)
Carcinoma, metastatic, thyroid gland	1 (2%)	
Carcinoma, metastatic, uncertain primary site	1 (2%)	
Hepatoblastoma, metastatic, liver		4 (8%)
Hepatocellular carcinoma, metastatic, liver	7 (14%)	5 (10%)
Hepatocellular carcinoma, metastatic, multiple		1 (2%)
Histiocytic sarcoma, single	1 (2%)	2 (4%)
Special Senses System		
Harderian gland	(4)	(3)
Adenocarcinoma		1 (33%)
Adenoma	1 (25%)	1 (33%)
Histiocytic sarcoma, single		1 (33%)
Urinary System		
Kidney	(50)	(50)
Renal tubule, adenocarcinoma		1 (2%)
Urinary bladder	(49)	(49)

TABLE E1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	330 ppm 0 ppm	33 ppm 100 ppm	0 ppm 330 ppm	110 ppm 330 ppm	330 ppm 330 ppm
Systemic Lesions						
Multiple organs[b]	(50)	(50)	(29)	(50)	(50)	(50)
Histiocytic sarcoma			1 (3%)	2 (4%)	1 (2%)	2 (4%)
Lymphoma malignant				1 (2%)	1 (2%)	
Lymphoma malignant, histiocytic	1 (2%)	1 (2%)	1 (3%)	1 (2%)		
Lymphoma malignant, lymphocytic	5 (10%)	2 (4%)	2 (7%)	2 (4%)	6 (12%)	3 (6%)
Lymphoma malignant, mixed	14 (28%)	11 (22%)	5 (17%)	10 (20%)	17 (34%)	7 (14%)
Lymphoma malignant, undifferentiated cell	1 (2%)	2 (4%)			2 (4%)	3 (6%)
Tumor Summary						
Total animals with primary neoplasms[c]	36	33	20	49	49	50
Total primary neoplasms	59	53	26	124	126	131
Total animals with benign neoplasms	17	19	9	42	40	44
Total benign neoplasms	22	23	12	65	59	81
Total animals with malignant neoplasms	30	25	13	44	44	38
Total malignant neoplasms	37	30	14	59	67	50
Total animals with secondary neoplasms[d]	2	2	1	3	1	1
Total secondary neoplasms	2	3	1	3	1	2
Total animals with malignant neoplasms of uncertain primary site				1		

TABLE E1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 1,000 ppm	330 ppm 1,000 ppm
Systemic Lesions		
Multiple organs[b]	(50)	(50)
Histiocytic sarcoma	2 (4%)	2 (4%)
Lymphoma malignant histiocytic		1 (2%)
Lymphoma malignant lymphocytic	6 (12%)	5 (10%)
Lymphoma malignant mixed	5 (10%)	8 (16%)
Lymphoma malignant undifferentiated cell	3 (6%)	1 (2%)
Tumor Summary		
Total animals with primary neoplasms	48	50
Total primary neoplasms	158	173
Total animals with benign neoplasms	41	43
Total benign neoplasms	82	88
Total animals with malignant neoplasms	48	50
Total malignant neoplasms	76	85
Total animals with secondary neoplasms	10	9
Total secondary neoplasms	10	11
Total animals with malignant neoplasms of uncertain primary site	1	

[a] Effects on rats exposed to ethylene thiourea perinatally through 8 weeks of age (F_0 concentration) and for 2 years postnatally (F_1 concentration)
[b] The number in parentheses is the number of animals with any tissue examined microscopically.
[c] Primary tumors: all tumors except metastatic tumors
[d] Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

TABLE E2
Statistical Analysis of Primary Tumors in Female Mice in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 0:330, and 0:1,000 ppm Groups

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	0 ppm 330 ppm	0 ppm 1,000 ppm
Harderian Gland: Adenoma or Adenocarcinoma			
Overall rates[a]	2/50 (4%)	4/50 (8%)	1/50 (2%)
Adjusted rates[b]	5.4%	9.3%	3.2%
Terminal rates[c]	1/35 (3%)	4/43 (9%)	1/31 (3%)
First incidence (days)	701	740 (T)	740 (T)
Life table tests[d]	P=0.404N	P=0.429	P=0.541N
Logistic regression tests[d]	P=0.358N	P=0.388	P=0.503N
Cochran-Armitage test[d]	P=0.339N		
Fisher exact test[d]		P=0.339	P=0.500N
Liver: Hepatocellular Adenoma			
Overall rates	2/50 (4%)	33/50 (66%)	14/50 (28%)
Adjusted rates	5.7%	70.2%	41.9%
Terminal rates	2/35 (6%)	29/43 (67%)	12/31 (39%)
First incidence (days)	740 (T)	503	674
Life table tests	P=0.033	P<0.001	P<0.001
Logistic regression tests	P=0.092	P<0.001	P<0.001
Cochran-Armitage test	P=0.114		
Fisher exact test		P<0.001	P<0.001
Liver: Hepatocellular Carcinoma			
Overall rates	2/50 (4%)	29/50 (58%)	47/50 (94%)
Adjusted rates	5.7%	64.4%	97.9%
Terminal rates	2/35 (6%)	27/43 (63%)	30/31 (97%)
First incidence (days)	740 (T)	667	499
Life table tests	P<0.001	P<0.001	P<0.001
Logistic regression tests	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rates	4/50 (8%)	44/50 (88%)	48/50 (96%)
Adjusted rates	11.4%	93.6%	100.0%
Terminal rates	4/35 (11%)	40/43 (93%)	31/31 (100%)
First incidence (days)	740 (T)	503	499
Life table tests	P<0.001	P<0.001	P<0.001
Logistic regression tests	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001
Lung: Alveolar/bronchiolar Adenoma			
Overall rates	2/50 (4%)	7/50 (14%)	0/50 (0%)
Adjusted rates	5.5%	16.3%	0.0%
Terminal rates	1/35 (3%)	7/43 (16%)	0/31 (0%)
First incidence (days)	705	740 (T)	-[e]
Life table tests	P=0.173N	P=0.139	P=0.263N
Logistic regression tests	P=0.146N	P=0.114	P=0.238N
Cochran-Armitage test	P=0.135N		
Fisher exact test		P=0.080	P=0.247N

TABLE E2
Statistical Analysis of Primary Tumors in Female Mice in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 0:330, and 0:1,000 ppm Groups (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	0 ppm 330 ppm	0 ppm 1,000 ppm
Lung: Alveolar/bronchiolar Carcinoma			
Overall rates	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted rates	8.6%	2.3%	0.0%
Terminal rates	3/35 (9%)	1/43 (2%)	0/31 (0%)
First incidence (days)	740 (T)	740 (T)	-
Life table tests	P=0.100N	P=0.235N	P=0.143N
Logistic regression tests	P=0.100N	P=0.235N	P=0.143N
Cochran-Armitage test	P=0.088N		
Fisher exact test		P=0.309N	P=0.121N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rates	5/50 (10%)	8/50 (16%)	0/50 (0%)
Adjusted rates	13.8%	18.6%	0.0%
Terminal rates	4/35 (11%)	8/43 (19%)	0/31 (0%)
First incidence (days)	705	740 (T)	-
Life table tests	P=0.037N	P=0.418	P=0.045N
Logistic regression tests	P=0.029N	P=0.374	P=0.035N
Cochran-Armitage test	P=0.026N		
Fisher exact test		P=0.277	P=0.028N
Pituitary Gland, Pars Distalis: Adenoma			
Overall rates	10/47 (21%)	19/49 (39%)	26/49 (53%)
Adjusted rates	28.2%	44.0%	62.6%
Terminal rates	9/34 (26%)	18/42 (43%)	16/31 (52%)
First incidence (days)	667	569	611
Life table tests	P<0.001	P=0.125	P<0.001
Logistic regression tests	P=0.001	P=0.084	P=0.001
Cochran-Armitage test	P=0.001		
Fisher exact test		P=0.050	P=0.001
Pituitary Gland, Pars Distalis: Adenoma or Carcinoma			
Overall rates	11/47 (23%)	19/49 (39%)	26/49 (53%)
Adjusted rates	31.1%	44.0%	62.6%
Terminal rates	10/34 (29%)	18/42 (43%)	16/31 (52%)
First incidence (days)	667	569	611
Life table tests	P<0.001	P=0.186	P=0.002
Logistic regression tests	P=0.002	P=0.130	P=0.003
Cochran-Armitage test	P=0.003		
Fisher exact test		P=0.080	P=0.003
Thyroid Gland: Follicular Cell Adenoma			
Overall rates	0/50 (0%)	2/50 (4%)	35/50 (70%)
Adjusted rates	0.0%	4.7%	85.0%
Terminal rates	0/35 (0%)	2/43 (5%)	25/31 (81%)
First incidence (days)	-	740 (T)	611
Life table tests	P<0.001	P=0.285	P<0.001
Logistic regression tests	P<0.001	P=0.285	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.247	P<0.001

TABLE E2
Statistical Analysis of Primary Tumors in Female Mice in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 0:330, and 0:1,000 ppm Groups (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	0 ppm 330 ppm	0 ppm 1,000 ppm
Thyroid Gland: Follicular Cell Carcinoma			
Overall rates	0/50 (0%)	0/50 (0%)	8/50 (16%)
Adjusted rates	0.0%	0.0%	21.7%
Terminal rates	0/35 (0%)	0/43 (0%)	4/31 (13%)
First incidence (days)	-	-	674
Life table tests	P<0.001	-	P=0.005
Logistic regression tests	P<0.001	-	P=0.005
Cochran-Armitage test	P<0.001		
Fisher exact test		-	P=0.003
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall rates	0/50 (0%)	2/50 (4%)	38/50 (76%)
Adjusted rates	0.0%	4.7%	90.3%
Terminal rates	0/35 (0%)	2/43 (5%)	27/31 (87%)
First incidence (days)	-	740 (T)	611
Life table tests	P<0.001	P=0.285	P<0.001
Logistic regression tests	P<0.001	P=0.285	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.247	P<0.001
All Organs: Hemangiosarcoma			
Overall rates	3/50 (6%)	6/50 (12%)	3/50 (6%)
Adjusted rates	8.1%	14.0%	9.7%
Terminal rates	2/35 (6%)	6/43 (14%)	3/31 (10%)
First incidence (days)	670	740 (T)	740 (T)
Life table tests	P=0.596N	P=0.346	P=0.615
Logistic regression tests	P=0.533N	P=0.293	P=0.659
Cochran-Armitage test	P=0.500N		
Fisher exact test		P=0.243	P=0.661N
All Organs: Malignant Lymphoma (all types)			
Overall rates	21/50 (42%)	14/50 (28%)	14/50 (28%)
Adjusted rates	49.3%	31.1%	38.5%
Terminal rates	14/35 (40%)	12/43 (28%)	10/31 (32%)
First incidence (days)	327	668	614
Life table tests	P=0.250N	P=0.038N	P=0.198N
Logistic regression tests	P=0.124N	P=0.110N	P=0.104N
Cochran-Armitage test	P=0.122N		
Fisher exact test		P=0.104N	P=0.104N
All Organs: Benign Tumors			
Overall rates	17/50 (34%)	42/50 (84%)	41/50 (82%)
Adjusted rates	44.5%	87.5%	97.6%
Terminal rates	14/35 (40%)	37/43 (86%)	30/31 (97%)
First incidence (days)	667	503	611
Life table tests	P<0.001	P<0.001	P<0.001
Logistic regression tests	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001

TABLE E2
Statistical Analysis of Primary Tumors in Female Mice in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 0:330, and 0:1,000 ppm Groups (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	0 ppm 330 ppm	0 ppm 1,000 ppm
All Organs: Malignant Tumors			
Overall rates	30/50 (60%)	44/50 (88%)	48/50 (96%)
Adjusted rates	67.8%	89.8%	100.0%
Terminal rates	21/35 (60%)	38/43 (88%)	31/31 (100%)
First incidence (days)	327	503	499
Life table tests	P<0.001	P=0.123	P<0.001
Logistic regression tests	P<0.001	P=0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.001	P<0.001
All Organs: Benign or Malignant Tumors			
Overall rates	36/50 (72%)	49/50 (98%)	48/50 (96%)
Adjusted rates	79.8%	100.0%	100.0%
Terminal rates	26/35 (74%)	43/43 (100%)	31/31 (100%)
First incidence (days)	327	503	499
Life table tests	P=0.001	P=0.196	P=0.006
Logistic regression tests	P<0.001	P<0.001	P=0.001
Cochran-Armitage test	P=0.001		
Fisher exact test		P<0.001	P<0.001

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

TABLE E3
Statistical Analysis of Primary Tumors in Female Mice in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 330:0, 33:100, 110:330, 330:330, and 330:1,000 ppm Groups

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	330 ppm 0 ppm	33 ppm 100 ppm	110 ppm 330 ppm	330 ppm 330 ppm	330 ppm 1,000 ppm
Harderian Gland: Adenoma or Carcinoma						
Overall rates[a]	2/50 (4%)	3/50 (6%)	1/29 (3%)	1/50 (2%)	1/50 (2%)	2/50 (4%)
Adjusted rates[b]	5.4%	7.5%	3.8%	2.8%	2.6%	6.9%
Terminal rates[c]	1/35 (3%)	2/38 (5%)	0/21 (0%)	1/36 (3%)	0/36 (0%)	2/29 (7%)
First incidence (days)	701	698	562	740 (T)	738	740 (T)
Life table tests[d]		P=0.536	P=0.681N	P=0.493N	P=0.473N	P=0.632
Logistic regression tests[d]		P=0.516	P=0.687N	P=0.481N	P=0.477N	P=0.671
Fisher exact test[d]		P=0.500	P=0.697N	P=0.500N	P=0.500N	P=0.691N
Liver: Hepatocellular Adenoma						
Overall rates	2/50 (4%)	1/49 (2%)	2/28 (7%)	34/50 (68%)	35/50 (70%)	17/50 (34%)
Adjusted rates	5.7%	2.6%	10.0%	73.7%	81.1%	45.5%
Terminal rates	2/35 (6%)	1/38 (3%)	2/20 (10%)	24/36 (67%)	28/36 (78%)	10/29 (34%)
First incidence (days)	740 (T)	740 (T)	740 (T)	621	619	443
Life table tests		P=0.471N	P=0.481	P<0.001	P<0.001	P<0.001
Logistic regression tests		P=0.471N	P=0.481	P<0.001	P<0.001	P<0.001
Fisher exact test		P=0.508N	P=0.454	P<0.001	P<0.001	P<0.001
Liver: Hepatocellular Carcinoma						
Overall rates	2/50 (4%)	5/49 (10%)	2/28 (7%)	31/50 (62%)	23/50 (46%)	48/50 (96%)
Adjusted rates	5.7%	11.7%	8.0%	71.8%	57.2%	100.0%
Terminal rates	2/35 (6%)	3/38 (8%)	0/20 (0%)	24/36 (67%)	19/36 (53%)	29/29 (100%)
First incidence (days)	740 (T)	523	529	621	653	443
Life table tests		P=0.253	P=0.493	P<0.001	P<0.001	P<0.001
Logistic regression tests		P=0.170	P=0.475	P<0.001	P<0.001	P<0.001
Fisher exact test		P=0.210	P=0.454	P<0.001	P<0.001	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma						
Overall rates	4/50 (8%)	5/49 (10%)	4/28 (14%)	46/50 (92%)	46/50 (92%)	49/50 (98%)
Adjusted rates	11.4%	11.7%	17.2%	95.8%	100.0%	100.0%
Terminal rates	4/35 (11%)	3/38 (8%)	2/20 (10%)	34/36 (94%)	36/36 (100%)	29/29 (100%)
First incidence (days)	740 (T)	523	529	621	619	443
Life table tests		P=0.550	P=0.335	P<0.001	P<0.001	P<0.001
Logistic regression tests		P=0.461	P=0.309	P<0.001	P<0.001	P<0.001
Fisher exact test		P=0.487	P=0.306	P<0.001	P<0.001	P<0.001
Lung: Alveolar/bronchiolar Adenoma						
Overall rates	2/50 (4%)	3/50 (6%)	1/29 (3%)	2/50 (4%)	6/50 (12%)	4/50 (8%)
Adjusted rates	5.5%	7.2%	4.8%	5.6%	16.1%	13.8%
Terminal rates	1/35 (3%)	2/38 (5%)	1/21 (5%)	2/36 (6%)	5/36 (14%)	4/29 (14%)
First incidence (days)	705	491	740 (T)	740 (T)	738	740 (T)
Life table tests		P=0.537	P=0.675N	P=0.683N	P=0.153	P=0.260
Logistic regression tests		P=0.476	P=0.691N	P=0.677N	P=0.165	P=0.291
Fisher exact test		P=0.500	P=0.697N	P=0.691N	P=0.134	P=0.339
Lung: Alveolar/bronchiolar Carcinoma						
Overall rates	3/50 (6%)	2/50 (4%)	0/29 (0%)	1/50 (2%)	2/50 (4%)	1/50 (2%)
Adjusted rates	8.6%	5.3%	0.0%	2.1%	5.6%	3.4%
Terminal rates	3/35 (9%)	2/38 (5%)	0/21 (0%)	0/36 (0%)	2/36 (6%)	1/29 (3%)
First incidence (days)	740 (T)	740 (T)	-[e]	647	740 (T)	740 (T)
Life table tests		P=0.462N	P=0.224N	P=0.292N	P=0.487N	P=0.374N
Logistic regression tests		P=0.462N	P=0.224N	P=0.292N	P=0.487N	P=0.374N
Fisher exact test		P=0.500N	P=0.248N	P=0.309N	P=0.500N	P=0.309N

TABLE E3
Statistical Analysis of Primary Tumors in Female Mice in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 330:0, 33:100, 110:330, 330:330, and 330:1,000 ppm Groups (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	330 ppm 0 ppm	33 ppm 100 ppm	110 ppm 330 ppm	330 ppm 330 ppm	330 ppm 1,000 ppm
Lung: Alveolar/bronchiolar Adenoma or Carcinoma						
Overall rates	5/50 (10%)	5/50 (10%)	1/29 (3%)	3/50 (6%)	8/50 (16%)	5/50 (10%)
Adjusted rates	13.8%	12.3%	4.8%	7.5%	21.5%	17.2%
Terminal rates	4/35 (11%)	4/38 (11%)	1/21 (5%)	2/36 (6%)	7/36 (19%)	5/29 (17%)
First incidence (days)	705	491	740 (T)	647	738	740 (T)
Life table tests		P=0.577N	P=0.258N	P=0.339N	P=0.303	P=0.513
Logistic regression tests		P=0.622N	P=0.270N	P=0.327N	P=0.343	P=0.557
Fisher exact test		P=0.630N	P=0.278N	P=0.357N	P=0.277	P=0.630N
Mammary Gland: Adenocarcinoma						
Overall rates	1/50 (2%)	0/50 (0%)	1/29 (3%)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted rates	2.9%	0.0%	4.8%	5.0%	6.7%	2.5%
Terminal rates	1/35 (3%)	0/38 (0%)	1/21 (5%)	1/36 (3%)	0/36 (0%)	0/29 (0%)
First incidence (days)	740 (T)	-	740 (T)	663	440	677
Life table tests		P=0.484N	P=0.644	P=0.509	P=0.335	P=0.743
Logistic regression tests		P=0.484N	P=0.644	P=0.508	P=0.214	P=0.760
Fisher exact test		P=0.500N	P=0.602	P=0.500	P=0.309	P=0.753N
Mammary Gland: Adenoma or Adenocarcinoma						
Overall rates	2/50 (4%)	1/50 (2%)	1/29 (3%)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted rates	5.7%	2.6%	4.8%	5.0%	6.7%	5.9%
Terminal rates	2/35 (6%)	1/38 (3%)	1/21 (5%)	1/36 (3%)	0/36 (0%)	1/29 (3%)
First incidence (days)	740 (T)	740 (T)	740 (T)	663	440	677
Life table tests		P=0.471N	P=0.676N	P=0.684N	P=0.529	P=0.645
Logistic regression tests		P=0.471N	P=0.676N	P=0.679N	P=0.424	P=0.680
Fisher exact test		P=0.500N	P=0.697N	P=0.691N	P=0.500	P=0.691N
Pituitary Gland, Pars Distalis: Adenoma						
Overall rates	10/47 (21%)	11/48 (23%)	6/28 (21%)	14/48 (29%)	26/47 (55%)	24/47 (51%)
Adjusted rates	28.2%	26.5%	28.6%	35.7%	66.6%	70.2%
Terminal rates	9/34 (26%)	8/38 (21%)	6/21 (29%)	11/35 (31%)	22/35 (63%)	19/29 (66%)
First incidence (days)	667	587	740 (T)	605	710	677
Life table tests		P=0.587N	P=0.598N	P=0.276	P=0.001	P<0.001
Logistic regression tests		P=0.585	P=0.609N	P=0.317	P=0.001	P<0.001
Fisher exact test		P=0.522	P=0.603	P=0.259	P<0.001	P=0.002
Pituitary Gland, Pars Distalis: Adenoma or Carcinoma						
Overall rates	11/47 (23%)	11/48 (23%)	7/28 (25%)	14/48 (29%)	26/47 (55%)	24/47 (51%)
Adjusted rates	31.1%	26.5%	31.0%	35.7%	66.6%	70.2%
Terminal rates	10/34 (29%)	8/38 (21%)	6/21 (29%)	11/35 (31%)	22/35 (63%)	19/29 (66%)
First incidence (days)	667	587	359	605	710	677
Life table tests		P=0.486N	P=0.574	P=0.361	P=0.002	P<0.001
Logistic regression tests		P=0.508N	P=0.558	P=0.413	P=0.003	P=0.002
Fisher exact test		P=0.574N	P=0.544	P=0.343	P=0.001	P=0.005
Thyroid Gland: Follicular Cell Adenoma						
Overall rates	0/50 (0%)	1/49 (2%)	1/29 (3%)	5/50 (10%)	10/49 (20%)	38/50 (76%)
Adjusted rates	0.0%	2.7%	4.8%	13.9%	26.8%	90.4%
Terminal rates	0/35 (0%)	1/37 (3%)	1/21 (5%)	5/36 (14%)	9/36 (25%)	25/29 (86%)
First incidence (days)	-	740 (T)	740 (T)	740 (T)	710	598
Life table tests		P=0.511	P=0.398	P=0.035	P=0.002	P<0.001
Logistic regression tests		P=0.511	P=0.398	P=0.035	P=0.002	P<0.001
Fisher exact test		P=0.495	P=0.367	P=0.028	P<0.001	P<0.001

TABLE E3
Statistical Analysis of Primary Tumors in Female Mice in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 330:0, 33:100, 110:330, 330:330, and 330:1,000 ppm Groups (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	330 ppm 0 ppm	33 ppm 100 ppm	110 ppm 330 ppm	330 ppm 330 ppm	330 ppm 1,000 ppm
Thyroid Gland: Follicular Cell Carcinoma						
Overall rates	0/50 (0%)	0/49 (0%)	0/29 (0%)	0/50 (0%)	1/49 (2%)	4/50 (8%)
Adjusted rates	0.0%	0.0%	0.0%	0.0%	2.8%	13.8%
Terminal rates	0/35 (0%)	0/37 (0%)	0/21 (0%)	0/36 (0%)	1/36 (3%)	4/29 (14%)
First incidence (days)	-	-	-	-	740 (T)	740 (T)
Life table tests		-	-	-	P=0.506	P=0.041
Logistic regression tests		-	-	-	P=0.506	P=0.041
Fisher exact test		-	-	-	P=0.495	P=0.059
Thyroid Gland: Follicular Cell Adenoma or Carcinoma						
Overall rates	0/50 (0%)	1/49 (2%)	1/29 (3%)	5/50 (10%)	10/49 (20%)	38/50 (76%)
Adjusted rates	0.0%	2.7%	4.8%	13.9%	26.8%	90.4%
Terminal rates	0/35 (0%)	1/37 (3%)	1/21 (5%)	5/36 (14%)	9/36 (25%)	25/29 (86%)
First incidence (days)	-	740 (T)	740 (T)	740 (T)	710	598
Life table tests		P=0.511	P=0.398	P=0.035	P=0.002	P<0.001
Logistic regression tests		P=0.511	P=0.398	P=0.035	P=0.002	P<0.001
Fisher exact test		P=0.495	P=0.367	P=0.028	P<0.001	P<0.001
All Organs: Hemangiosarcoma						
Overall rates	3/50 (6%)	2/50 (4%)	0/29 (0%)	4/50 (8%)	1/50 (2%)	1/50 (2%)
Adjusted rates	8.1%	4.8%	0.0%	8.9%	2.6%	3.0%
Terminal rates	2/35 (6%)	1/38 (3%)	0/21 (0%)	1/36 (3%)	0/36 (0%)	0/29 (0%)
First incidence (days)	670	609	-	605	738	709
Life table tests		P=0.473N	P=0.233N	P=0.530	P=0.287N	P=0.349N
Logistic regression tests		P=0.505N	P=0.233N	P=0.437	P=0.286N	P=0.313N
Fisher exact test		P=0.500N	P=0.248N	P=0.500	P=0.309N	P=0.309N
All Organs: Hemangioma or Hemangiosarcoma						
Overall rates	3/50 (6%)	4/50 (8%)	0/29 (0%)	4/50 (8%)	1/50 (2%)	1/50 (2%)
Adjusted rates	8.1%	9.9%	0.0%	8.9%	2.6%	3.0%
Terminal rates	2/35 (6%)	3/38 (8%)	0/21 (0%)	1/36 (3%)	0/36 (0%)	0/29 (0%)
First incidence (days)	670	609	-	605	738	709
Life table tests		P=0.535	P=0.233N	P=0.530	P=0.287N	P=0.349N
Logistic regression tests		P=0.508	P=0.233N	P=0.437	P=0.286N	P=0.313N
Fisher exact test		P=0.500	P=0.248N	P=0.500	P=0.309N	P=0.309N
All Organs: Malignant Lymphoma (all types)						
Overall rates	21/50 (42%)	16/50 (32%)	8/29 (28%)	26/50 (52%)	13/50 (26%)	14/50 (28%)
Adjusted rates	49.3%	36.0%	32.5%	57.3%	31.0%	39.8%
Terminal rates	14/35 (40%)	10/38 (26%)	5/21 (24%)	17/36 (47%)	8/36 (22%)	9/29 (31%)
First incidence (days)	327	523	552	647	653	443
Life table tests		P=0.164N	P=0.164N	P=0.288	P=0.070N	P=0.253N
Logistic regression tests		P=0.219N	P=0.148N	P=0.188	P=0.079N	P=0.104N
Fisher exact test		P=0.204N	P=0.149N	P=0.212	P=0.069N	P=0.104N
All Organs: Benign Tumors						
Overall rates	17/50 (34%)	19/50 (38%)	9/29 (31%)	40/50 (80%)	44/50 (88%)	43/50 (86%)
Adjusted rates	44.5%	43.8%	42.9%	83.2%	97.8%	95.5%
Terminal rates	14/35 (40%)	14/38 (37%)	9/21 (43%)	28/36 (78%)	35/36 (97%)	27/29 (93%)
First incidence (days)	667	491	740 (T)	605	619	443
Life table tests		P=0.536	P=0.456N	P<0.001	P<0.001	P<0.001
Logistic regression tests		P=0.465	P=0.508N	P<0.001	P<0.001	P<0.001
Fisher exact test		P=0.418	P=0.494N	P<0.001	P<0.001	P<0.001

TABLE E3
Statistical Analysis of Primary Tumors in Female Mice in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:0, 330:0, 33:100, 110:330, 330:330, and 330:1,000 ppm Groups (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	330 ppm 0 ppm	33 ppm 100 ppm	110 ppm 330 ppm	330 ppm 330 ppm	330 ppm 1,000 ppm
All Organs: Malignant Tumors						
Overall rates	30/50 (60%)	25/50 (50%)	13/29 (45%)	44/50 (88%)	38/50 (76%)	50/50 (100%)
Adjusted rates	67.8%	53.1%	44.8%	88.0%	77.5%	100.0%
Terminal rates	21/35 (60%)	16/38 (42%)	5/21 (24%)	30/36 (83%)	25/36 (69%)	29/29 (100%)
First incidence (days)	327	523	359	605	440	275
Life table tests		P=0.161N	P=0.181N	P=0.027	P=0.186	P<0.001
Logistic regression tests		P=0.227N	P=0.129N	P=0.001	P=0.059	P<0.001
Fisher exact test		P=0.211N	P=0.142N	P=0.001	P=0.066	P<0.001
All Organs: Benign or Malignant Tumors						
Overall rates	36/50 (72%)	33/50 (66%)	20/29 (69%)	49/50 (98%)	50/50 (100%)	50/50 (100%)
Adjusted rates	79.8%	68.6%	69.0%	98.0%	100.0%	100.0%
Terminal rates	26/35 (74%)	23/38 (61%)	12/21 (57%)	35/36 (97%)	36/36 (100%)	29/29 (100%)
First incidence (days)	327	491	359	605	440	275
Life table tests		P=0.227N	P=0.453N	P=0.032	P=0.023	P=0.001
Logistic regression tests		P=0.341N	P=0.484N	P<0.001	P<0.001	P<0.001
Fisher exact test		P=0.333N	P=0.484N	P<0.001	P<0.001	P<0.001

(T)Terminal sacrifice

[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.

[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality

[c] Observed incidence at terminal kill

[d] Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

[e] Not applicable; no tumors in animal group

TABLE E4
Statistical Analysis of Selected Primary Tumors in Female Mice in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 330:0, 330:330, and 330:1,000 ppm Groups

F_0 Concentration F_1 Concentration	330 ppm 0 ppm	330 ppm 330 ppm	330 ppm 1,000 ppm
Liver: Hepatocellular Adenoma			
Overall rates[a]	1/49 (2%)	35/50 (70%)	17/50 (34%)
Life table tests[b]	P=0.003	P<0.001	P<0.001
Logistic regression tests[b]	P=0.017	P<0.001	P<0.001
Cochran-Armitage test[b]	P=0.029		
Fisher exact test[b]		P<0.001	P<0.001
Liver: Hepatocellular Carcinoma			
Overall rates	5/49 (10%)	23/50 (46%)	48/50 (96%)
Life table tests	P<0.001	P<0.001	P<0.001
Logtistic Regression	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rates	5/49 (10%)	46/50 (92%)	49/50 (98%)
Life table tests	P<0.001	P<0.001	P<0.001
Logistic regression tests	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001
Pituitary Gland, Pars Distalis: Adenoma			
Overall rates	11/48 (23%)	26/47 (55%)	24/47 (51%)
Life table tests	P<0.001	P=0.001	P<0.001
Logistic regression tests	P=0.002	P=0.001	P=0.001
Cochran-Armitage test	P=0.014		
Fisher exact test		P=0.001	P=0.004
Thyroid Gland: Follicular Cell Adenoma			
Overall rates	1/49 (2%)	10/49 (20%)	38/50 (76%)
Life table tests	P<0.001	P=0.005	P<0.001
Logistic regression tests	P<0.001	P=0.006	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.004	P<0.001
Thyroid Gland: Follicular Cell Carcinoma			
Overall rates	0/49 (0%)	1/49 (2%)	4/50 (8%)
Life table tests	P=0.012	P=0.495	P=0.036
Logistic regression tests	P=0.012	P=0.495	P=0.036
Cochran-Armitage test	P=0.027		
Fisher exact test		P=0.500	P=0.061
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall rates	1/49 (2%)	10/49 (20%)	38/50 (76%)
Life table tests	P<0.001	P=0.005	P<0.001
Logistic regression tests	P<0.001	P=0.006	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.004	P<0.001

TABLE E4
Statistical Analysis of Selected Primary Tumors in Female Mice in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 330:0, 330:330, and 330:1,000 ppm Groups (continued)

(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates.

TABLE E5
Statistical Analysis of Selected Primary Tumors in Female Mice in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:330, 110:330, and 330:330 ppm Groups

F_0 Concentration F_1 Concentration	0 ppm 330 ppm	110 ppm 330 ppm	330 ppm 330 ppm
Liver: Hepatocellular Adenoma			
Overall rates[a]	33/50 (66%)	34/50 (68%)	35/50 (70%)
Life table tests[b]	P=0.150	P=0.188	P=0.114
Logistic regression tests[b]	P=0.382	P=0.495	P=0.405
Cochran-Armitage test[b]	P=0.389		
Fisher exact test[b]		P=0.500	P=0.415
Liver: Hepatocellular Carcinoma			
Overall rates	29/50 (58%)	31/50 (62%)	23/50 (46%)
Life table tests	P=0.316N	P=0.136	P=0.441N
Logtistic Regression	P=0.100N	P=0.365	P=0.175N
Cochran-Armitage test	P=0.102N		
Fisher exact test		P=0.419	P=0.158N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rates	44/50 (88%)	46/50 (92%)	46/50 (92%)
Life table tests	P=0.060	P=0.041	P=0.026
Logistic regression tests	P=0.350	P=0.419	P=0.376
Cochran-Armitage test	P=0.354		
Fisher exact test		P=0.370	P=0.370
Pituitary Gland, Pars Distalis: Adenoma			
Overall rates	19/49 (39%)	14/48 (29%)	26/47 (55%)
Life table tests	P=0.013	P=0.381N	P=0.023
Logistic regression tests	P=0.029	P=0.220N	P=0.062
Cochran-Armitage test	P=0.032		
Fisher exact test		P=0.217N	P=0.078
Thyroid Gland: Follicular Cell Adenoma			
Overall rates	2/50 (4%)	5/50 (10%)	10/49 (20%)
Life table tests	P=0.004	P=0.150	P=0.007
Logistic regression tests	P=0.007	P=0.150	P=0.011
Cochran-Armitage test	P=0.008		
Fisher exact test		P=0.218	P=0.013
Thyroid Gland: Follicular Cell Carcinoma			
Overall rates	0/50 (0%)	0/50 (0%)	0/49 (0%)

[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.

[b] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

TABLE E6
Statistical Analysis of Selected Primary Tumors in Female Mice in the 2-Year Feed Study of Ethylene Thiourea: Comparison of the 0:1,000 and 330:1,000 ppm Groups

F_0 Concentration F_1 Concentration	0 ppm 1,000 ppm	330 ppm 1,000 ppm
Liver: Hepatocellular Adenoma		
Overall rates[a]	14/50 (28%)	17/50 (34%)
Life table tests[b]		P=0.282
Logistic regression tests[b]		P=0.305
Fisher exact test[b]		P=0.333
Liver: Hepatocellular Carcinoma		
Overall rates	47/50 (94%)	48/50 (96%)
Life table tests		P=0.331
Logistic regression tests		P=0.511
Fisher exact test		P=0.500
Liver: Hepatocellular Adenoma or Carcinoma		
Overall rates	48/50 (96%)	49/50 (98%)
Life table tests		P=0.327
Logistic regression tests		P=0.518
Fisher exact test		P=0.500
Pituitary Gland, Pars Distalis: Adenoma		
Overall rates	26/49 (53%)	24/47 (51%)
Life table tests		P=0.535N
Logistic regression tests		P=0.563N
Fisher exact test		P=0.503N
Thyroid Gland: Follicular Cell Adenoma		
Overall rates	35/50 (70%)	38/50 (76%)
Life table tests		P=0.228
Logistic regression tests		P=0.194
Fisher exact test		P=0.326
Thyroid Gland: Follicular Cell Carcinoma		
Overall rates	8/50 (16%)	4/50 (8%)
Life table tests		P=0.212N
Logistic regression tests		P=0.196N
Fisher exact test		P=0.178N
Thyroid Gland: Follicular Cell Adenoma or Carcinoma		
Overall rates	38/50 (76%)	38/50 (76%)
Life table tests		P=0.412
Logistic regression tests		P=0.449
Fisher exact test		P=0.592N

[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.

[b] Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

TABLE E7a
Historical Incidence of Adenomas and Carcinomas of the Pituitary Gland Pars Distalis in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Untreated Controls
Historical Incidence at Battelle Columbus Laboratories	
Chlorobenzene	5/41
N-Phenyl-2-Naphthylamine	7/44
Rotenone	3/43
l-Ascorbic Acid	3/43
Total	18/171 (10.5%)
Standard deviation	4.4%
Range	
High	7/44
Low	3/43
Overall Historical Incidence	
Total	256/1,528 (16.8%)
Standard deviation	11.1%
Range	
High	19/49
Low	0/48

[a] Data as of 1 March 1989 for studies of at least 104 weeks. Standard deviation and range are presented for groups of 35 or more animals.

TABLE E7b
Historical Incidence of Hepatocellular Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	4/48	4/48	8/48
N-Phenyl-2-Naphthylamine	3/50	1/50	4/50
Rotenone	3/49	1/49	4/49
l-Ascorbic Acid	2/50	1/50	3/50
Total	12/197 (6.1%)	7/197 (3.6%)	19/197 (9.6%)
Standard deviation	1.8%	3.1%	4.8%
Range			
High	4/48	4/48	8/48
Low	2/50	1/50	3/50
Overall Historical Incidence			
Total	100/1,683 (5.9%)	67/1,683 (4.0%)	162/1,683 (9.6%)
Standard deviation	3.8%	2.3%	4.3%
Range			
High	8/49	4/48	10/49
Low	0/50	0/49	2/50

[a] Data as of 1 March 1989 for studies of at least 104 weeks. Standard deviation and range are presented for groups of 35 or more animals.

TABLE E7c
Historical Incidence of Thyroid Follicular Cell Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	0/40	0/40	0/40
N-Phenyl-2-Naphthylamine	1/50	1/50	2/50
Rotenone	2/48	0/48	2/48
l-Ascorbic Acid	0/44	1/44	1/44
Total	3/182 (1.6%)	2/182 (1.1%)	5/182 (2.7%)
Standard deviation	2.0%	1.2%	1.9%
Range			
High	2/48	1/44	2/48
Low	0/44	0/48	0/40
Overall Historical Incidence			
Total	35/1,614 (2.2%)	9/1,614 (0.6%)	44/1,614 (2.7%)
Standard deviation	2.8%	1.4%	3.5%
Range			
High	4/48	3/48	7/48
Low	0/50	0/50	0/50

[a] Data as of 1 March 1989 for studies of at least 104 weeks. Standard deviation and range are presented for groups of 35 or more animals.

TABLE E8
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Ethylene Thiourea

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	330 ppm 0 ppm	33 ppm 100 ppm	0 ppm 330 ppm	110 ppm 330 ppm	330 ppm 330 ppm
Disposition Summary						
Animals initially in study	50	50	29	50	50	50
Animals removed	50	50	29	50	50	50
Animals examined histopathologically	50	50	29	50	50	50
Alimentary System						
Intestine large, colon	(49)	(12)	(8)	(9)	(16)	(12)
Parasite metazoan					1 (6%)	
Intestine small, jejunum	(46)	(12)	(10)	(8)	(19)	(13)
Inflammation, chronic active		1 (8%)				
Necrosis						1 (8%)
Peyer's patch, hyperplasia, lymphoid			1 (10%)			
Liver	(50)	(49)	(28)	(50)	(50)	(50)
Basophilic focus	2 (4%)	1 (2%)		3 (6%)	2 (4%)	1 (2%)
Clear cell focus		2 (4%)		1 (2%)		1 (2%)
Eosinophilic focus			2 (7%)	11 (22%)	4 (8%)	14 (28%)
Fatty change, focal					1 (2%)	
Hematopoietic cell proliferation	8 (16%)	2 (4%)	1 (4%)	1 (2%)	4 (8%)	2 (4%)
Hyperplasia, lymphoid	1 (2%)					
Infarct	3 (6%)	2 (4%)	2 (7%)	5 (10%)	6 (12%)	4 (8%)
Inflammation, acute	1 (2%)					1 (2%)
Inflammation, chronic active	2 (4%)				1 (2%)	1 (2%)
Necrosis	2 (4%)			1 (2%)		
Vacuolization cytoplasmic				1 (2%)		
Bile duct, mineralization, multifocal				1 (2%)		
Centrilobular, cytomegaly			2 (7%)	11 (22%)	8 (16%)	9 (18%)
Centrilobular, necrosis				1 (2%)		
Centrilobular, necrosis, acute					1 (2%)	
Centrilobular, vacuolization cytoplasmic	2 (4%)			1 (2%)		
Oval cell, hyperplasia				1 (2%)		
Mesentery	(6)	(2)		(1)	(1)	(1)
Inflammation, chronic active	2 (33%)			1 (100%)	1 (100%)	
Pancreas	(50)	(11)	(8)	(7)	(16)	(13)
Acinus, atrophy	2 (4%)		1 (13%)	1 (14%)	1 (6%)	2 (15%)
Acinus, inflammation, chronic active				1 (14%)		
Duct, ectasia	2 (4%)				1 (6%)	2 (15%)
Salivary glands	(50)	(13)	(8)	(8)	(15)	(14)
Perivascular, inflammation, chronic active, multifocal	1 (2%)					
Stomach, forestomach	(48)	(15)	(10)	(11)	(17)	(14)
Acanthosis				2 (18%)		
Cyst epithelial inclusion		2 (13%)	1 (10%)			
Diverticulum					1 (6%)	
Hyperkeratosis, focal		1 (7%)				
Hyperplasia, squamous			1 (10%)		3 (18%)	
Inflammation, chronic active		2 (13%)				
Stomach, glandular	(48)	(11)	(8)	(8)	(15)	(13)
Dysplasia	1 (2%)					
Subserosa, inflammation, chronic				1 (13%)		

TABLE E8
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Ethylene Thiourea

F_0 Concentration F_1 Concentration	0 ppm 1,000 ppm	330 ppm 1,000 ppm
Disposition Summary		
Animals initially in study	50	50
Animals removed	50	50
Animals examined histopathologically	50	50
Alimentary System		
Intestine large, cecum	(50)	(48)
Inflammation, chronic active	1 (2%)	
Intestine large, colon	(50)	(49)
Parasite metazoan	3 (6%)	
Liver	(50)	(50)
Angiectasis	1 (2%)	
Eosinophilic focus	3 (6%)	2 (4%)
Hematopoietic cell proliferation	1 (2%)	2 (4%)
Hyperplasia, lymphoid	1 (2%)	
Infarct	13 (26%)	22 (44%)
Infiltration cellular, histiocytic, multifocal		1 (2%)
Inflammation, chronic active		1 (2%)
Mixed cell focus	1 (2%)	
Centrilobular, cytomegaly		8 (16%)
Centrilobular, vacuolization cytoplasmic	1 (2%)	
Mesentery	(2)	(1)
Inflammation, chronic active		1 (100%)
Pancreas	(50)	(50)
Acinus, atrophy	1 (2%)	1 (2%)
Duct, ectasia	1 (2%)	1 (2%)
Perivascular, inflammation, chronic active		1 (2%)
Salivary glands	(49)	(50)
Hyperplasia, lymphoid	1 (2%)	
Perivascular, inflammation, chronic active, multifocal		1 (2%)
Stomach, forestomach	(49)	(50)
Acanthosis	1 (2%)	1 (2%)
Diverticulum	1 (2%)	

TABLE E8
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	330 ppm 0 ppm	33 ppm 100 ppm	0 ppm 330 ppm	110 ppm 330 ppm	330 ppm 330 ppm
Cardiovascular System						
Heart	(50)	(13)	(8)	(8)	(16)	(14)
Bacterium, acute, multiple	1 (2%)				2 (13%)	
Degeneration, chronic					1 (6%)	
Inflammation, acute					2 (13%)	
Inflammation, chronic						1 (7%)
Mineralization			1 (13%)	1 (13%)		
Thrombus	1 (2%)			1 (13%)		
Interstitium, hyperplasia, diffuse						1 (7%)
Endocrine System						
Adrenal gland, cortex	(49)	(13)	(8)	(8)	(16)	(11)
Degeneration, fatty	4 (8%)					
Hematopoietic cell proliferation		1 (8%)				
Hyperplasia	1 (2%)					
Hypertrophy	3 (6%)				1 (6%)	1 (9%)
Adrenal gland, medulla	(48)	(13)	(8)	(8)	(16)	(11)
Hyperplasia				1 (13%)	1 (6%)	
Islets, pancreatic	(49)	(13)	(8)	(7)	(15)	(12)
Hyperplasia, focal	1 (2%)					
Pituitary gland	(47)	(48)	(28)	(49)	(48)	(47)
Pars distalis, angiectasis		1 (2%)				
Pars distalis, hyperplasia	19 (40%)	19 (40%)	8 (29%)	22 (45%)	23 (48%)	18 (38%)
Thyroid gland	(50)	(49)	(29)	(50)	(50)	(49)
Follicular cell, hyperplasia	2 (4%)	8 (16%)		13 (26%)	17 (34%)	22 (45%)
Follicular cell, vacuolization cytoplasmic	3 (6%)	1 (2%)	19 (66%)	49 (98%)	49 (98%)	44 (90%)
General Body System						
None						
Genital System						
Clitoral gland	(1)				(1)	
Dilatation	1 (100%)				1 (100%)	
Ovary	(49)	(26)	(20)	(15)	(24)	(25)
Angiectasis			2 (10%)			
Hemorrhage						1 (4%)
Inflammation, suppurative	1 (2%)					2 (8%)
Thrombus			1 (5%)			
Follicle, cyst	16 (33%)	8 (31%)	8 (40%)	6 (40%)	11 (46%)	8 (32%)
Periovarian tissue, cyst	3 (6%)	9 (35%)		2 (13%)	3 (13%)	4 (16%)
Uterus	(48)	(33)	(13)	(19)	(20)	(20)
Angiectasis						2 (10%)
Dilatation	2 (4%)					2 (10%)
Endometrium, hyperplasia, cystic, glandular	39 (81%)	28 (85%)	7 (54%)	13 (68%)	8 (40%)	9 (45%)

TABLE E8
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 1,000 ppm	330 ppm 1,000 ppm
Cardiovascular System		
Heart	(50)	(50)
Degeneration, chronic		1 (2%)
Inflammation, chronic	1 (2%)	
Mineralization	1 (2%)	
Endocrine System		
Adrenal gland	(50)	(50)
Accessory adrenal cortical nodule	1 (2%)	
Adrenal gland, cortex	(48)	(50)
Hematopoietic cell proliferation	1 (2%)	
Hypertrophy	1 (2%)	1 (2%)
Adrenal gland, medulla	(50)	(50)
Hemorrhage, chronic	1 (2%)	
Hyperplasia	1 (2%)	
Pituitary gland	(49)	(47)
Pars distalis, cyst		1 (2%)
Pars distalis, hyperplasia	27 (55%)	28 (60%)
Pars distalis, vacuolization cytoplasmic		2 (4%)
Thyroid gland	(50)	(50)
Follicular cell, hyperplasia	46 (92%)	46 (92%)
Follicular cell, vacuolization cytoplasmic	47 (94%)	48 (96%)
General Body System		
None		
Genital System		
Ovary	(50)	(48)
Hyperplasia, tubular	1 (2%)	
Inflammation, suppurative		1 (2%)
Follicle, cyst	8 (16%)	7 (15%)
Periovarian tissue, cyst	2 (4%)	2 (4%)
Periovarian tissue, hyperplasia, lymphoid	1 (2%)	
Uterus	(48)	(48)
Angiectasis		2 (4%)
Dilatation	2 (4%)	5 (10%)
Hyperplasia, lymphoid		1 (2%)
Inflammation, chronic active		2 (4%)
Endometrium, hyperplasia, cystic, glandular	8 (17%)	11 (23%)

TABLE E8
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	330 ppm 0 ppm	33 ppm 100 ppm	0 ppm 330 ppm	110 ppm 330 ppm	330 ppm 330 ppm
Hematopoietic System						
Bone marrow	(49)	(13)	(8)	(8)	(16)	(13)
Angiectasis				1 (13%)		
Femoral, hyperplasia, neutrophil						1 (8%)
Femoral, necrosis, acute		1 (8%)				
Lymph node	(49)	(18)	(15)	(19)	(25)	(19)
Lumbar, sinus, lymphatic, ectasia	1 (2%)					
Mandibular, angiectasis		1 (6%)				
Mandibular, hyperplasia, lymphoid	2 (4%)	1 (6%)				1 (5%)
Mandibular, hyperplasia, reticulum cell						1 (5%)
Mandibular, infiltration cellular, plasma cell	1 (2%)					
Mediastinal, hyperplasia, lymphoid	1 (2%)					
Lymph node, mesenteric	(14)	(10)	(8)	(12)	(14)	(9)
Hematopoietic cell proliferation	2 (14%)	1 (10%)	2 (25%)	2 (17%)	1 (7%)	1 (11%)
Hemorrhage	1 (7%)					
Hyperplasia, lymphoid	1 (7%)					
Inflammation, chronic active						1 (11%)
Spleen	(50)	(23)	(13)	(28)	(31)	(34)
Fibrosis	1 (2%)					1 (3%)
Hematopoietic cell proliferation	5 (10%)	3 (13%)		6 (21%)	6 (19%)	5 (15%)
Hyperplasia, lymphoid	3 (6%)	1 (4%)		2 (7%)	3 (10%)	3 (9%)
Necrosis, acute					1 (3%)	
Thymus	(39)	(7)	(4)	(6)	(12)	(5)
Depletion lymphoid					1 (8%)	1 (20%)
Integumentary System						
Mammary gland	(35)	(13)	(8)	(8)	(16)	(11)
Hyperplasia, cystic	1 (3%)					
Skin	(50)	(13)	(8)	(8)	(16)	(15)
Acanthosis	5 (10%)		4 (50%)		8 (50%)	
Parasite external	6 (12%)		6 (75%)		11 (69%)	1 (7%)
Ulcer	1 (2%)					
Subcutaneous tissue, fibrosis	1 (2%)					
Subcutaneous tissue, inflammation, chronic active					1 (6%)	
Musculoskeletal System						
Bone	(50)	(13)	(9)	(9)	(16)	(14)
Tarsal, hyperostosis			2 (22%)	1 (11%)		
Nervous System						
Brain	(50)	(13)	(8)	(8)	(16)	(14)
Compression	2 (4%)	1 (8%)	1 (13%)			
Hemorrhage	2 (4%)		1 (13%)			
Hydrocephalus	2 (4%)					
Perivascular, inflammation, chronic active	1 (2%)					

TABLE E8
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 1,000 ppm	330 ppm 1,000 ppm
Hematopoietic System		
Bone marrow	(49)	(49)
Femoral, hyperplasia, neutrophil	1 (2%)	1 (2%)
Femoral, hyperplasia, reticulum cell		1 (2%)
Lymph node	(47)	(49)
Mandibular, hyperplasia		1 (2%)
Mandibular, hyperplasia, lymphoid	4 (9%)	2 (4%)
Mediastinal, hyperplasia, lymphoid	1 (2%)	3 (6%)
Lymph node, mesenteric	(4)	(9)
Inflammation, chronic active	1 (25%)	
Spleen	(49)	(50)
Hematopoietic cell proliferation		1 (2%)
Hyperplasia, lymphoid	6 (12%)	2 (4%)
Integumentary System		
Skin	(49)	(50)
Acanthosis	17 (35%)	7 (14%)
Cyst epithelial inclusion		1 (2%)
Parasite external	22 (45%)	7 (14%)
Lip, inflammation, chronic	1 (2%)	
Subcutaneous tissue, inflammation, chronic active	2 (4%)	
Musculoskeletal System		
None		
Nervous System		
Brain	(50)	(50)
Compression	2 (4%)	2 (4%)
Hydrocephalus		2 (4%)
Perivascular, inflammation, chronic active		1 (2%)

TABLE E8
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 0 ppm	330 ppm 0 ppm	33 ppm 100 ppm	0 ppm 330 ppm	110 ppm 330 ppm	330 ppm 330 ppm
Respiratory System						
Lung	(50)	(50)	(29)	(50)	(50)	(50)
Alveolar epithelium, hyperplasia	1 (2%)	1 (2%)			1 (2%)	1 (2%)
Artery, embolus		1 (2%)				
Interstitium, inflammation, acute	1 (2%)					
Mediastinum, hyperplasia, lymphoid	1 (2%)					
Peribronchiolar, inflammation, chronic active	13 (26%)	5 (10%)	2 (7%)	7 (14%)	1 (2%)	2 (4%)
Nose	(47)	(12)	(8)	(8)	(16)	(13)
Nasolacrimal duct, inflammation, acute		1 (8%)				
Special Senses System						
Eye		(2)		(2)	(1)	
Atrophy		1 (50%)		2 (100%)	1 (100%)	
Lens, cataract		1 (50%)				
Retina, degeneration		1 (50%)				
Harderian gland	(3)	(3)	(1)	(4)	(1)	(1)
Inflammation, chronic active					1 (100%)	
Lacrimal gland	(1)					
Inflammation, chronic active	1 (100%)					
Urinary System						
Kidney	(50)	(12)	(8)	(11)	(16)	(15)
Hemorrhage			1 (13%)			
Infarct	1 (2%)					
Nephropathy, chronic			1 (13%)	1 (9%)		
Glomerulus, dilatation		1 (8%)				
Glomerulus, inflammation, acute						1 (7%)
Glomerulus, inflammation, chronic						1 (7%)
Pelvis, inflammation, suppurative	1 (2%)					
Renal tubule, cyst	1 (2%)					
Renal tubule, dilatation					1 (6%)	
Urinary bladder	(48)	(12)	(8)	(9)	(13)	(11)
Inflammation, acute	1 (2%)					
Inflammation, chronic active					1 (8%)	

TABLE E8
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Ethylene Thiourea (continued)

F_0 Concentration F_1 Concentration	0 ppm 1,000 ppm	330 ppm 1,000 ppm
Respiratory System		
Lung	(50)	(50)
Hyperplasia, lymphoid	5 (10%)	2 (4%)
Alveolar epithelium, hyperplasia	1 (2%)	1 (2%)
Peribronchiolar, inflammation, chronic active	9 (18%)	6 (12%)
Nose	(49)	(50)
Mucosa, inflammation, acute	1 (2%)	
Special Senses System		
Eye	(1)	(2)
Atrophy	1 (100%)	2 (100%)
Harderian gland	(4)	(3)
Inflammation, chronic active	1 (25%)	
Acinus, dilatation	2 (50%)	
Urinary System		
Kidney	(50)	(50)
Hyperplasia, lymphoid		2 (4%)
Nephropathy, chronic	1 (2%)	1 (2%)
Urinary bladder	(49)	(49)
Hyperplasia, lymphoid	4 (8%)	

APPENDIX F
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

Methods

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

Thirty B6C3F$_1$ mice and 30 F344/N rats of each sex were selected at the time of randomization and allocation of the animals to the various study groups. Ten animals of each designated sentinel group were killed at 6, 12, and 18 months on study. Data from animals surviving 24 months were collected from 10 randomly selected control animals of each sex and species. The blood from each animal was collected and clotted, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the antibody titers. The following tests were performed. The serology results for the sentinel animal program are presented in Table F1.

Test and Method	Time of Analysis
Rats	
Hemagglutination Inhibition:	
PVM (pneumonia virus of mice)	6, 12, and 18 months
KRV (Kilham rat virus)	6, 12, and 18 months
H-1 (Toolan's H-1 virus)	6, 12, and 18 months
Sendai virus	6, 12, and 18 months
ELISA:	
RCV/SDA (rat corona virus/sialodacryoadenitis virus)	6 and 12 months
Mycoplasma arthritidis	24 months
Mycoplasma pulmonis	24 months
Immunofluorescent Assay:	
RCV/SDA	18 months
Mice	
Complement Fixation:	
Mouse adenoma virus	6, 12, and 18 months
LCM (lymphocytic choriomeningitis virus)	6, 12, 18, and 24 months
Hemagglutination Inhibition:	
PVM	6, 12, and 18 months
Reovirus 3	6, 12, and 18 months
GDVII (mouse encephalomyelitis virus)	6 and 12 months
Polyoma virus	6, 12, 18, and 24 months
MVM (minute virus of mice)	6, 12, 18, and 24 months
Ectromelia virus	6 and 18 months
Sendai virus	6, 12, and 18 months
Vaccinia virus	12 months

Test and Method (continued)	Time of Analysis
Mice (continued)	
ELISA:	
MHV (mouse hepatitis virus)	6, 12, 18, and 24 months
PVM	24 months
Reovirus 3	24 months
Ectromelia virus	24 months
Sendai virus	24 months
GDVII	18 and 24 months
Mouse adenoma virus	24 months
Mycoplasma arthritidis	24 months
Mycoplasma pulmonis	6 and 24 months
Immunofluorescent Antibody:	
EDIM (epizootic diarrhea of infant mice)	24 months

TABLE F1
Murine Virus Antibody Determinations for Rats and Mice in the 2-Year Feed Studies of Ethylene Thiourea

Interval (months)	No. of Animals	Positive Serologic Reaction for
Rats		
6	20/20	Sendai
12	8/19	Sendai
18	8/19	Sendai
24	4/20	*M. arthriditis*
Mice		
6	12/20	PVM
	1/20	Reovirus 3
	19/20	Sendai
	4/20	MHV
	1/20	*M. pulmonis*[a]
12	1/19	PVM
	4/19	Sendai
	15/19	MHV
18	6/20	PVM
	7/20	Sendai
	17/20	MHV
	18/20	GDVII
24	10/20	PVM
	19/20	Sendai
	13/20	MHV
	3/20	GDVII
	1/20	MVM
	6/20	EDIM

[a] Further evaluation of this assay indicated that it was not specific for *M. pulmonis*, and these results were considered to be false positive.

APPENDIX G
MAXIMUM PERINATAL DOSE DETERMINATION FEED STUDIES OF ETHYLENE THIOUREA

TABLE G1
Prenatal Day 18 Litter Data for Rats in the Maximum Perinatal Dose Determination Feed Study of Ethylene Thiourea

	0 ppm	8 ppm	25 ppm	83 ppm	250 ppm
Litters	3	3	2	4	4
Implantations	28	28	16	38	35
Live fetuses	27	28	15	35	33
Fetus/litter[a]	9.0 ± 1.73	9.3 ± 2.08	7.5 ± 4.95	8.8 ± 1.26	8.2 ± 1.71
Fetal weight (gm)[a]	1.23 ± 0.18	1.39 ± 0.13	1.41 ± 0.11	1.39 ± 0.10	1.39 ± 0.08
Placental weight (gm)[a]	0.40 ± 0.09	0.40 ± 0.05	0.37 ± 0.05	0.38 ± 0.05	0.46 ± 0.09

[a] Mean ± standard deviation

TABLE G2
Survival and Mean Body Weights of Rat Pups in the Maximum Perinatal Dose Determination Feed Study of Ethylene Thiourea

	0 ppm	8 ppm	25 ppm	83 ppm	250 ppm
Precull					
Pups on day 0	128	89	140	135	101
Pups on day 4	123	86	134	134	82
Pups dead, days 0-4	5	3	6	1	19
Postcull					
Pups on day 4	79	46	76	74	39
Pups on day 28	79	46	76	73	38
Pups dead, days 4-28	0	0	0	1	1
Body Weights[a]					
Day 4	7.14 ± 0.60	7.56 ± 0.47	7.34 ± 0.80	7.26 ± 0.61	6.96 ± 0.68
Day 28	52.86 ± 5.47	55.11 ± 3.79	51.77 ± 4.94	53.23 ± 4.00	52.62 ± 4.03

[a] Mean body weight in grams ± standard deviation for postcull pups; dead pups not included in statistic calculations

TABLE G3
Prenatal Day 17 Litter Data for Mice in the Maximum Perinatal Dose Determination Feed Study of Ethylene Thiourea

	0 ppm	33 ppm	100 ppm	330 ppm	1,000 ppm
Litters	4	4	3	4	0
Implantations	31	36	26	28	0
Live Fetuses	30	36	24	24	0
Fetus/litter[a]	7.5 ± 1.73	9.0 ± 1.15	8.0 ± 1.73	6.0 ± 3.16	
Fetal weight (gm)[a]	0.96 ± 0.08	0.86 ± 0.09	0.85 ± 0.09	0.91 ± 0.08	
Placental weight (gm)[a]	0.11 ± 0.01	0.12 ± 0.02	0.13 ± 0.02	0.13 ± 0.03	

[a] Mean ± standard deviation

TABLE G4
Survival and Mean Body Weights of Mouse Pups in the Maximum Perinatal Dose Determination Feed Study of Ethylene Thiourea

	0 ppm	33 ppm	100 ppm	330 ppm	1,000 ppm
Precull					
Pups on day 0	143	100	104	89	86
Pups on day 7	143	100	104	89	86
Pups dead days 0-7	0	0	0	0	0
Postcull					
Pups on day 7	102	72	75	60	59
Pups on day 28	101	69	70	57	45
Pups dead days 7-28	1	3	5	3	14
Body Weights[a]					
Day 7	3.75 ± 0.81	3.48 ± 0.75	2.95 ± 0.73	3.30 ± 0.83	2.58 ± 0.52
Day 28	12.61 ± 1.84	11.47 ± 2.03	9.86 ± 2.14	10.62 ± 2.25	10.88 ± 2.24

[a] Mean body weight in grams ± standard deviation for postcull pups; dead pups not included in statistic calculations

APPENDIX H
THYROID FUNCTION DATA FOR RATS IN THE 2-YEAR FEED STUDIES OF ETHYLENE THIOUREA

TABLE H1
Thyroid Gland Function Data for Rats Not Exposed *in utero* in the 2-Year Feed Studies of Ethylene Thiourea[a]

	F_0:F_1 Concentration (ppm)		
	0:0	0:83	0:250
Male			
9-month interim evaluation			
Triiodothyronine (ng/dL)	100.7 ± 9.04	88.1 ± 6.13[b]	97.3 ± 4.30
Thyroxine (μg/dL)	5.0 ± 0.27	3.3 ± 0.15**[b]	3.2 ± 0.14**
Thyrotropin (ng/mL)	211.1 ± 23.6	260.7 ± 36.3[b]	340.3 ± 64.5
2-year study			
Triiodothyronine (ng/dL)	74.6 ± 4.40	93.0 ± 6.80	75.4 ± 9.58
Thyroxine (μg/dL)	3.1 ± 0.32	2.4 ± 0.23	1.8 ± 0.15**
Thyrotropin (ng/dL)	241.6 ± 23.0	307.7 ± 55.4	2,873.5 ± 729**
Female			
9-month interim evaluation			
Triiodothyronine (ng/dL)	150.3 ± 6.4	111.4 ± 5.9*	150.0 ± 5.2
Thyroxine (μg/dL)	4.1 ± 0.15	2.0 ± 0.17**	2.5 ± 0.16**
Thyrotropin (ng/mL)	161.7 ± 8.2	259.9 ± 27.3**	240.7 ± 22.3**
2-year study			
Triiodothyronine (ng/dL)	108.6 ± 6.64	137.1 ± 9.04	71.8 ± 13.12**
Thyroxine (μg/dL)	2.9 ± 0.17	2.7 ± 0.13	2.5 ± 0.17
Thyrotropin (ng/mL)	337.5 ± 48.1	515.9 ± 78.4	768.9 ± 104**

* Statistically different ($P \leq 0.05$) from the 0:0 ppm group
** $P \leq 0.01$
[a] Mean ± standard error for animals exposed to F_0 concentrations *in utero* and through 8 weeks of age and F_1 concentrations thereafter; n=10 unless otherwise specified.
[b] n=9

TABLE H2
Thyroid Gland Function Data for Rats Exposed to a Constant F_0 Concentration and Increasing F_1 Concentrations in the 2-Year Feed Studies of Ethylene Thiourea[a]

	F_0:F_1 Concentration (ppm)		
	90:0	90:83	90:250
Male			
9-month interim evaluation			
Triiodothyronine (ng/dL)	103.6 ± 4.73	64.7 ± 6.93**	94.6 ± 4.36
Thyroxine (μg/dL)	5.1 ± 0.29	3.3 ± 0.23**	2.7 ± 0.17**
Thyrotropin (ng/mL)	220.6 ± 26.8	325.2 ± 70.2	331.0 ± 32.5
2-year study			
Triiodothyronine (ng/dL)	80.5 ± 5.09	86.5 ± 7.27	51.1 ± 6.15*[b]
Thyroxine (μg/dL)	3.0 ± 0.21	2.1 ± 0.33*	1.8 ± 0.33**[b]
Thyrotropin (ng/dL)	240.4 ± 29.6	984.2 ± 234**	1,542.6 ± 826**[b]
Female			
9-month interim evaluation			
Triiodothyronine (ng/dL)	166.8 ± 7.9	120.1 ± 4.9**	117.4 ± 8.2**
Thyroxine (μg/dL)	4.1 ± 0.19	2.5 ± 0.14**	2.2 ± 0.22**
Thyrotropin (ng/mL)	177.9 ± 8.5	396.0 ± 53.8**	421.2 ± 54.7**
2-year study			
Triiodothyronine (ng/dL)	145.0 ± 14.48	124.2 ± 3.79	120.6 ± 9.42
Thyroxine (μg/dL)	2.9 ± 0.23	2.6 ± 0.18	1.7 ± 0.06**
Thyrotropin (ng/mL)	236.0 ± 34.2	628.9 ± 142**	1,370.5 ± 345**

* Statistically different ($P \leq 0.05$) from the 0:0 ppm group
** $P \leq 0.01$
[a] Mean ± standard error for animals exposed to F_0 concentrations *in utero* and through 8 weeks of age and F_1 concentrations thereafter; n=10 unless otherwise specified.
[b] n=4

TABLE H3
Thyroid Gland Function Data for Rats Exposed to Increasing F_0 and F_1 Concentrations in the 2-Year Feed Studies of Ethylene Thiourea[a]

	F_0:F_1 Concentration (ppm)				
	0:0	90:0	30:83	90:83	90:250
Male					
9-month interim evaluation					
Triiodothyronine (ng/dL)	100.7 ± 9.04	103.6 ± 4.73	69.5 ± 3.89**	64.7 ± 6.93**	94.6 ± 4.36
Thyroxine (μg/dL)	5.0 ± 0.27	5.1 ± 0.29	3.4 ± 0.19**	3.3 ± 0.23**	2.7 ± 0.17**
Thyrotropin (ng/mL)	211.1 ± 23.6	220.6 ± 26.8	307.6 ± 31.3	325.2 ± 70.2	331.0 ± 32.5*
2-year study					
Triiodothyronine (ng/dL)	74.6 ± 4.40	80.5 ± 5.09	83.5 ± 8.66	86.5 ± 7.27	51.1 ± 6.15*[b]
Thyroxine (μg/dL)	3.1 ± 0.32	3.0 ± 0.21	1.9 ± 0.21*	2.1 ± 0.33*	1.8 ± 0.33**[b]
Thyrotropin (ng/dL)	241.6 ± 23.0	240.4 ± 29.6	744.1 ± 148**	984.2 ± 234**	1,542.6 ± 826**[b]
Female					
9-month interim evaluation					
Triiodothyronine (ng/dL)	150.3 ± 6.4	166.8 ± 7.9	107.2 ± 6.8**	120.1 ± 4.9**	117.4 ± 8.2**
Thyroxine (μg/dL)	4.1 ± 0.15	4.1 ± 0.19	1.9 ± 0.15**	2.5 ± 0.14**	2.2 ± 0.22**
Thyrotropin (ng/mL)	161.7 ± 8.2	177.9 ± 8.5	288.3 ± 26.3**	396.0 ± 53.8**	421.2 ± 54.7**
2-year study					
Triiodothyronine (ng/dL)	108.6 ± 6.64	145.0 ± 14.48	113.2 ± 8.73	124.2 ± 3.79	120.6 ± 9.42
Thyroxine (μg/dL)	2.9 ± 0.17	2.9 ± 0.23	2.5 ± 0.15	2.6 ± 0.18	1.7 ± 0.06**
Thyrotropin (ng/mL)	337.5 ± 48.1	236.0 ± 34.2*	510.5 ± 26.9*	628.9 ± 142*	1,370.5 ± 345**

* Statistically different ($P \leq 0.05$) from the 0:0 ppm group
** $P \leq 0.01$
[a] Mean ± standard error for animals exposed to F_0 concentrations *in utero* and through 8 weeks of age and F_1 concentrations thereafter; n=10 unless otherwise specified.
[b] n=4

TABLE H4a
Thyroid Gland Function Data for Rats Exposed to Increasing F_0 Concentrations and a Constant F_1 Concentration of 83 ppm in the 2-Year Feed Studies of Ethylene Thiourea[a]

	F_0:F_1 Concentration (ppm)		
	0:83	30:83	90:83
Male			
9-month interim evaluation			
Triiodothyronine (ng/dL)	88.1 ± 6.13[b]	69.5 ± 3.89*	64.7 ± 6.93**
Thyroxine (μg/dL)	3.3 ± 0.15[b]	3.4 ± 0.19	3.3 ± 0.23
Thyrotropin (ng/mL)	260.7 ± 36.3[b]	307.6 ± 31.3	325.2 ± 70.2
2-year study			
Triiodothyronine (ng/dL)	93.0 ± 6.80	83.5 ± 8.66	86.5 ± 7.27
Thyroxine (μg/dL)	2.4 ± 0.23	1.9 ± 0.21	2.1 ± 0.33
Thyrotropin (ng/dL)	307.7 ± 55.4	744.1 ± 148**	984.2 ± 234**
Female			
9-month interim evaluation			
Triiodothyronine (ng/dL)	111.4 ± 5.9	107.2 ± 6.8	120.1 ± 4.9
Thyroxine (μg/dL)	2.0 ± 0.17	1.9 ± 0.15	2.5 ± 0.14
Thyrotropin (ng/mL)	295.9 ± 27.3	288.3 ± 28.3	396.0 ± 53.8
2-year study			
Triiodothyronine (ng/dL)	137.1 ± 9.04	113.2 ± 8.73	124.2 ± 3.79
Thyroxine (μg/dL)	2.7 ± 0.13	2.5 ± 0.15	2.6 ± 0.18
Thyrotropin (ng/mL)	515.9 ± 78.4	510.5 ± 26.9	628.9 ± 142

* Statistically different ($P \leq 0.05$) from the 0:0 ppm group
** $P \leq 0.01$
[a] Mean ± standard error for animals exposed to F_0 concentrations *in utero* and through 8 weeks of age and F_1 concentrations thereafter; n=10 unless otherwise specified.
[b] n=9

TABLE H4b
Thyroid Gland Function Data for Rats Exposed to Increasing F_0 Concentrations and a Constant F_1 Concentration of 250 ppm in the 2-Year Feed Studies of Ethylene Thiourea[a]

	F_0:F_1 Concentration (ppm)	
	0:250	90:250
Male		
9-month interim evaluation		
Triiodothyronine (ng/dL)	97.3 ± 4.30	94.6 ± 4.36
Thyroxine (μg/dL)	3.2 ± 0.14	2.7 ± 0.17
Thyrotropin (ng/mL)	340.3 ± 64.5	331.0 ± 32.5
2-year study		
Triiodothyronine (ng/dL)	75.4 ± 9.58	51.1 ± 6.15*[c]
Thyroxine (μg/dL)	1.8 ± 0.15	1.8 ± 0.33[c]
Thyrotropin (ng/mL)	2,873.5 ± 729[b]	1,542.6 ± 826[c]
Female		
9-month interim evaluation		
Triiodothyronine (ng/dL)	150.0 ± 5.2	117.4 ± 8.2**
Thyroxine (μg/dL)	2.5 ± 0.16	2.2 ± 0.22
Thyrotropin (ng/mL)	240.7 ± 22.3	421.2 ± 54.7**
2-year study		
Triiodothyronine (ng/dL)	71.8 ± 13.12	120.6 ± 9.42**
Thyroxine (μg/dL)	2.5 ± 0.17	1.7 ± 0.06**
Thyrotropin (ng/mL)	768.9 ± 104	1,370.5 ± 345

* Statistically different ($P \leq 0.05$) from the 0:0 ppm group
** $P \leq 0.01$
[a] Mean ± standard error for animals exposed to F_0 concentrations *in utero* and through 8 weeks of age and F_1 concentrations thereafter; n=10 unless otherwise specified.
[b] n=9
[c] n=4

APPENDIX I
THYROID FUNCTION DATA FOR MICE IN THE 2-YEAR FEED STUDIES OF ETHYLENE THIOUREA

TABLE I1
Thyroid Gland Function Data for Mice Not Exposed *in utero* in the 2-Year Feed Studies of Ethylene Thiourea[a]

	F_0:F_1 Concentration (ppm)		
	0:0	0:330	0:1000
Male			
9-month interim evaluation			
Triiodothyronine (ng/dL)	74.5 ± 4.70	88.1 ± 6.58	88.9 ± 8.51
Thyrotropin (ng/mL)	102.7 ± 3.83	111.4 ± 4.24	111.4 ± 6.48
2-year study			
Triiodothyronine (ng/dL)	103.3 ± 5.63	114.6 ± 17.55	114.8 ± 11.61
Thyrotropin (ng/dL)	118.0 ± 16.8	178.2 ± 24.5*	936.8 ± 84.3**
Female			
9-month interim evaluation			
Triiodothyronine (ng/dL)	64.6 ± 2.62	63.8 ± 3.76	90.4 ± 4.43**
Thyrotropin (ng/mL)	84.0 ± 4.40	88.0 ± 2.85	94.7 ± 3.76
2-year study			
Triiodothyronine (ng/dL)	120.1 ± 13.3	117.8 ± 14.3	131.4 ± 24.3
Thyrotropin (ng/mL)	149.0 ± 12.9	219.5 ± 24.7*	1,647.3 ± 3.78**

* Statistically different ($P \leq 0.05$) from the 0:0 ppm group
** $P \leq 0.01$
[a] Mean ± standard error for animals exposed to F_0 concentrations *in utero* and through 8 weeks of age and F_1 concentrations thereafter; n=10 unless otherwise specified.

TABLE I2
Thyroid Gland Function Data for Mice Exposed to a Constant F_0 Concentration and Increasing F_1 Concentrations in the 2-Year Feed Studies of Ethylene Thiourea[a]

	F_0:F_1 Concentration (ppm)		
	330:0	330:330	330:1,000
Male			
9-month interim evaluation			
Triiodothyronine (ng/dL)	67.7 ± 3.26	78.1 ± 4.2	91.7 ± 4.52**
Thyrotropin (ng/mL)	98.1 ± 2.97	131.7 ± 6.13**	141.6 ± 9.39**
2-year study			
Triiodothyronine (ng/dL)	99.4 ± 13.63	172.0 ± 32.29*	151.6 ± 19.64
Thyrotropin (ng/dL)	159.7 ± 29.6	210.0 ± 35.4	1,132.8 ± 226**
Female			
9-month interim evaluation			
Triiodothyronine (ng/dL)	65.1 ± 4.93	53.6 ± 4.33	86.3 ± 3.86**
Thyrotropin (ng/mL)	82.2 ± 3.98	81.6 ± 6.58	83.3 ± 6.2
2-year study			
Triiodothyronine (ng/dL)	144.3 ± 28.8	146.8 ± 13.6	125.8 ± 13.7
Thyrotropin (ng/mL)	184.6 ± 23.1	323.3 ± 88.4*	1,288 ± 186**

* Statistically different ($P \leq 0.05$) from the 0:0 ppm group
** $P \leq 0.01$
[a] Mean ± standard error for animals exposed to F_0 concentrations *in utero* and through 8 weeks of age and F_1 concentrations thereafter; n=10 unless otherwise specified.

TABLE I3
Thyroid Gland Function Data for Mice Exposed to Increasing F_0 and F_1 Concentrations and Differing F_1 Concentrations in the 2-Year Feed Studies of Ethylene Thiourea[a]

	F_0:F_1 Concentration (ppm)				
	0:0	330:0	110:330	330:330	330:1,000
Male					
9-month interim evaluation					
Triiodothyronine (ng/dL)	74.5 ± 4.70	67.7 ± 3.26	66.6 ± 5.91	78.1 ± 4.2	91.7 ± 4.52*
Thyrotropin (ng/mL)	102.7 ± 3.83	98.12 ± 2.97	117.8 ± 6.86	131.7 ± 6.13**	141.6 ± 9.39**
2-year study					
Triiodothyronine (ng/dL)	103.3 ± 5.63	99.4 ± 13.63	126.3 ± 11.67	172.0 ± 32.29	151.6 ± 19.64
Thyrotropin (ng/dL)	118.0± 16.8	159.7 ± 29.6	168.2 ± 29.7	210.0 ± 35.4*	1,132.8 ± 226**
Female					
9-month interim evaluation					
Triiodothyronine (ng/dL)	64.6 ± 2.62	65.1 ± 4.93	63.7 ± 2.09	53.6 ± 4.33	86.3 ± 3.86**
Thyrotropin (ng/mL)	84.0 ± 4.40	82.2 ± 3.98	70.2 ± 2.37	81.6 ± 6.58	83.3 ± 6.2
2-year study					
Triiodothyronine (ng/dL)	120.1 ± 13.3	144.3 ± 28.8	119.3 ± 11.3	146.8 ± 13.6	125.8 ± 13.7
Thyrotropin (ng/mL)	149.0 ± 12.9	184.6 ± 23.1	285.7 ± 45.1**	323.3 ± 88.4**	1,288 ± 186**

* Statistically different ($P \leq 0.05$) from the 0:0 ppm group
** $P \leq 0.01$
[a] Mean ± standard error for animals exposed to F_0 concentrations *in utero* and through 8 weeks of age and F_1 concentrations thereafter; n=10 unless otherwise specified.

TABLE I4a
Thyroid Gland Function Data for Mice Exposed to Increasing F_0 Concentrations and a Constant F_1 Concentration of 330 ppm in the 2-Year Feed Studies of Ethylene Thiourea[a]

	F_0:F_1 Concentration (ppm)		
	0:330	110:330	330:330
Male			
9-month interim evaluation			
Triiodothyronine (ng/dL)	88.1 ± 6.58	66.6 ± 5.91*	78.1 ± 4.2
Thyrotropin (ng/mL)	111.4 ± 4.24	117.8 ± 6.86	131.7 ± 6.13
2-year study			
Triiodothyronine (ng/dL)	114.6 ± 17.55	126.3 ± 11.67	172.0 ± 32.29
Thyrotropin (ng/dL)	178.2 ± 24.5	168.2 ± 29.7	210.0 ± 35.4
Female			
9-month interim evaluation			
Triiodothyronine (ng/dL)	63.8 ± 3.76	63.7 ± 2.09	53.6 ± 4.33
Thyrotropin (ng/mL)	88.0 ± 2.85	70.2 ± 2.37*	81.6 ± 6.58
2-year study			
Triiodothyronine (ng/dL)	117.8 ± 14.3	119.3 ± 11.3	146.8 ± 13.6
Thyrotropin (ng/mL)	219.5 ± 24.7	285.7 ± 45.1	323.3 ± 88.4

* Statistically different ($P \leq 0.05$) from the 0:0 ppm group
** $P \leq 0.01$
[a] Mean ± standard error for animals exposed to F_0 concentrations *in utero* and through 8 weeks of age and F_1 concentrations thereafter; n=10 unless otherwise specified.

TABLE I4b
Thyroid Gland Function Data for Mice Exposed to Increasing F_0 Concentrations and a Constant F_1 Concentration of 1,000 ppm in the 2-Year Feed Studies of Ethylene Thiourea[a]

	F_0:F_1 Concentration (ppm)	
	0:1,000	330:1,000
Male		
9-month interim evaluation		
Triiodothyronine (ng/dL)	88.9 ± 8.51	91.7 ± 4.52
Thyrotropin (ng/mL)	111.4 ± 6.48	141.6 ± 9.36**
2-year study		
Triiodothyronine (ng/dL)	114.8 ± 11.61	151.6 ± 19.64
Thyrotropin (ng/dL)	936.8 ± 84.3	1,132.8 ± 226
Female		
9-month interim evaluation		
Triiodothyronine (ng/dL)	90.4 ± 4.43	86.3 ± 3.86
Thyrotropin (ng/mL)	94.7 ± 3.76	83.3 ± 6.2
2-year study		
Triiodothyronine (ng/dL)	131.4 ± 24.3	125.8 ± 13.7
Thyrotropin (ng/mL)	1,647.3 ± 3.78	1,288 ± 186

* Statistically different ($P \leq 0.05$) from the 0:0 ppm group
** $P \leq 0.01$
[a] Mean ± standard error for animals exposed to F_0 concentrations *in utero* and through 8 weeks of age and F_1 concentrations thereafter; n=10 unless otherwise specified.

APPENDIX J
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

Salmonella Protocol

Testing was performed as reported by Mortelmans *et al.* (1986). Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, TX). The study chemical was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, and TA1537) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C before the addition of soft agar supplemented with *l*-histidine and *d*-biotin and subsequent plating on minimal glucose agar plates. Incubation was continued for an additional 48 hours.

Each test consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of the study chemical. The high dose was limited by toxicity or solubility but did not exceed 10 mg/plate. All negative assays were repeated, and all positive assays were repeated under the conditions that elicited the positive response.

A positive response was defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response was defined as an increase in revertants which was not dose related, not reproducible, or of insufficient magnitude to support a determination of mutagenicity. A response was considered negative when no increase in revertant colonies was observed after chemical treatment. Results are presented in Table J1.

Mouse Lymphoma Protocol

The experimental protocol is presented in detail by McGregor *et al.* (1988) and follows the basic format of Clive *et al.* (1979). All study chemicals were supplied as coded aliquots from Radian Corporation. The highest dose of the study compound was determined by solubility or toxicity and did not exceed 5 mg/mL. Mouse L5178Y lymphoma cells were maintained at 37° C as suspension cultures in Fischer's medium supplemented with 2 mM *l*-glutamine, 110 μg/mL sodium pyruvate, 0.05% pluronic F68, antibiotics, and heat-inactivated horse serum; normal cycling time was about 10 hours. To reduce the number of spontaneously occurring trifluorothymidine (TFT)-resistant cells, subcultures were exposed once to medium containing thymidine, hypoxanthine, methotrexate, and glycine for 1 day, to thymidine, hypoxanthine, and glycine for 1 day, and to normal medium for 3 to 5 days. For cloning, horse serum content was increased and Noble agar was added. Freshly prepared S9 metabolic activation factors were obtained from the liver of either Aroclor 1254-induced or noninduced male F344/N rats.

All doses within an experiment, including concurrent positive and solvent controls, were replicated. Treated cultures contained 6 x 10^6 cells in 10 mL of medium. This volume included the S9 fraction in those experiments performed with metabolic activation. Incubation with the study chemical continued for 4 hours, after which time the medium plus chemical was removed and the cells were resuspended in 20 mL of fresh medium and incubated for an additional 2 days to express the mutant phenotype. Cell density was monitored so that log phase growth was maintained. After the 48-hour expression period, 3 x 10^6 cells were plated in medium and soft agar supplemented with TFT for selection of TFT-resistant cells ($TK^{-/-}$), and 600 cells were plated in nonselective medium and soft agar to determine cloning efficiency. Plates were incubated at 37° C under 5% carbon dioxide for 10 to 12 days. All data were evaluated statistically for both trend and peak response. Both responses had to be significant ($P<0.05$) for a chemical to be considered capable of inducing TFT resistance; a single significant response led to an "equivocal" conclusion, and the absence of both a trend and a peak response resulted in a "negative" call.

Minimum criteria for accepting an experiment as valid and a detailed description of the statistical analysis and data evaluation are presented in Myhr *et al.* (1985). This assay was initially performed without S9; if

a clearly positive response was not obtained, the experiment was repeated with induced S9. Results are presented in Table J2.

Chinese Hamster Ovary Cell Cytogenetics Assays

Testing was performed as reported by Galloway *et al.* (1985) and is described briefly below. Chemicals were sent to the laboratories as coded aliquots from Radian Corporation. Chemicals were tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine (BrdU)-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of the study chemical; the high dose was limited by toxicity or solubility but did not exceed 5 mg/mL.

In the SCE test without S9, CHO cells were incubated for 26 hours with the study chemical in McCoy's 5A medium supplemented with 10% fetal bovine serum, *l*-glutamine (2 mM), and antibiotics. BrdU was added 2 hours after culture initiation. After 26 hours, the medium containing the study chemical was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 more hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with the chemical, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing BrdU and no study chemical; incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. Results are presented in Table J3.

In the chromosomal aberration test without S9, cells were incubated in McCoy's 5A medium with the study chemical for 8 hours; Colcemid was added, and incubation was continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the chromosomal aberration test with S9, cells were treated with the study chemical and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 10 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9.

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

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

Statistical analyses were conducted on both the slopes of the dose-response curves and the individual dose points. An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. Chromosomal aberration data are presented as percentage of cells with aberrations. As with SCEs, both the dose-response curve and individual dose points were statistically analyzed. For a single trial, a statistically significant ($P<0.05$) difference for one dose point and a significant trend ($P<0.015$) was considered weak evidence for a positive response (+w); significant differences for two or more doses indicated the trial was positive (+) (Galloway *et al.*, 1987). Results are presented in Table J4.

Drosophila Protocol

The assays for gene mutation and chromosomal translocation induction were performed as described by Zimmering *et al.* (1985). Study chemicals were supplied as coded aliquots from Radian Corporation (Austin, TX). Initially, study chemicals were assayed in the sex-linked recessive lethal (SLRL) test by feeding to adult Canton-S wild-type males that were no more than 24 hours old. If no response was obtained, the chemical was retested by injection into adult males. If either route of administration produced a positive result, the chemical was assayed for induction of reciprocal translocations (RTs) by using the same method of exposure. If, because of the physical nature of the chemical, feeding experiments were not possible, injection was selected as the method of study chemical administration, and a positive result was followed by an RT test.

To administer a chemical by injection, a glass Pasteur pipette is drawn out in a flame to a microfine filament and the tip is broken off to allow delivery of the test solution. Injection is performed either manually, by attaching a rubber bulb to the other end of the pipette and forcing through sufficient solution to slightly distend the abdomen of the fly (0.2-0.3 μL), or by attaching the pipette to a microinjector that automatically delivers a calibrated volume. Flies are anesthetized with ether and immobilized on a strip of double-stick tape; injection into the thorax under the wing is performed with the aid of a dissecting microscope.

Toxicity tests were performed to set concentrations of study chemical at a level that would produce 30% mortality after 72 hours of feeding or 24 hours after injection, while keeping induced sterility at an acceptable level. For the SLRL test, oral exposure was achieved by allowing Canton-S males (10-20 flies per vial) to feed for 72 hours on a solution of the study chemical in 5% sucrose. In the injection experiments, 24- to 72-hour-old Canton-S males were given a solution of the chemical dissolved in 0.7% saline or peanut oil and were allowed to recover for 24 hours. Exposed males were mated to three *Basc* females for 3 days and given fresh females at 2-day intervals to produce three matings of 3, 2, and 2 days; sample sperm from successive matings were treated at successively earlier postmeiotic stages. F_1 heterozygous females were allowed to mate with their siblings and were then placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters. (A cluster occurs when a number of mutants from a given male result from a single spontaneous premeiotic mutation event and is identified when the number of mutants from that male exceeds the number predicted by a Poisson distribution.) If a cluster was identified, all data from the male in question were discarded. Presumptive lethal mutations were identified as occurring in vials containing no wild-type males after 17 days; these were retested. At least two experiments were performed for the study chemical, resulting in the testing of approximately 5,000 treated and 5,000 control chromosomes. The only exceptions occurred when the results of the first experiment were clearly positive (induced frequency of recessive lethal mutations equal to or greater than 1%); then, the second trial was not run.

Recessive lethal data were analyzed by the normal test (Margolin *et al.*, 1983). A test result was considered to be positive if the P value was less than 0.01 and the mutation frequency in the tested group was greater than 0.10% or if the P value was less than 0.05 and the frequency in the treatment group was greater than 0.15%. A test was considered to be inconclusive if (a) the P value was between 0.05 and 0.01 but the frequency in the treatment group was between 0.10% and 0.15% or (b) the P value was between 0.10 and 0.05 but the frequency in the treatment group was greater than 0.10%. A result was considered to be negative if the P value was greater than 0.10 or if the frequency in the treatment group was less than 0.10%. Results are presented in Table J5.

For the RT test, the exposure regimen was the same as that for the SLRL test except that small mass matings were used (10 males and 20 females). Exposed males were mated to X,Y,y;bw;st females for 3 days and discarded. The females were transferred to fresh medium every 3 to 4 days for a period of about 3 weeks to produce a total of five broods. The results of the SLRL test were used to narrow the germ-

cell stage most likely to be affected by the chemical; for example, if earlier germ-cell stages seemed to exhibit increased sensitivity, mating of the males was continued and translocation tests were carried out from the offspring derived from these earlier germ cell stages. F_1 males were mated individually to X,Y,y;bw;st females and the progeny were examined for missing classes, which indicate the occurrence of a translocation in the parental male. Suspected RTs were retested. The translocation data were analyzed according to the conditional binomial (Kastenbaum and Bowman, 1970). Results are presented in Table J6.

TABLE J1
Mutagenicity of Ethylene Thiourea in *Salmonella typhimurium*

Strain	Dose (μg/plate)	Revertants/plate[a] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA100[b]	0	133 ± 1.5	126 ± 4.1	218 ± 10.2	183 ± 17.7	132 ± 8.7	144 ± 9.9
	1	125 ± 7.1	118 ± 6.6	214 ± 4.4	158 ± 16.5	146 ± 32.3	167 ± 6.9
	3.3	138 ± 6.2	130 ± 2.9	222 ± 2.9	178 ± 8.5	228 ± 9.6	171 ± 21.7
	10	124 ± 6.4	125 ± 4.6	169 ± 6.4	159 ± 8.7	239 ± 20.3	173 ± 23.7
	33	128 ± 5.9	124 ± 1.8	179 ± 15.0	152 ± 0.9	219 ± 3.5	173 ± 14.7
	100	120 ± 4.3	119 ± 3.6	200 ± 14.0	156 ± 6.5	195 ± 17.6	154 ± 12.9
Trial summary		Negative	Negative	Negative	Negative	Equivocal	Negative
Positive control[c]		481 ± 16.7	445 ± 25.7	870 ± 53.1	947 ± 46.2	509 ± 35.9	469 ± 22.9
TA1535	0	14 ± 0.7	14 ± 0.6	25 ± 1.2	24 ± 0.7	21 ± 1.7	22 ± 2.2
	1	13 ± 0.7	11 ± 0.9	22 ± 3.2	22 ± 4.4	29 ± 2.9	20 ± 2.4
	3.3	14 ± 2.1	18 ± 2.0	23 ± 3.6	23 ± 3.5	28 ± 1.7	22 ± 1.0
	10	18 ± 2.1	18 ± 2.0	25 ± 0.9	23 ± 3.8	33 ± 2.9	21 ± 2.1
	33	17 ± 2.1	14 ± 1.7	32 ± 4.9	23 ± 4.0	34 ± 3.8	21 ± 2.7
	100	17 ± 0.9	16 ± 1.0	34 ± 6.2	24 ± 4.4	35 ± 3.7	20 ± 3.7
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		745 ± 12.5	584 ±106.8	46 ± 2.3	66 ± 15.0	37 ± 2.9	39 ± 7.1
TA1537	0	8 ± 0.3	7 ± 0.6	12 ± 2.8	9 ± 1.7	9 ± 0.7	7 ± 1.5
	1	3 ± 1.8	3 ± 0.6	9 ± 0.6	8 ± 1.2	8 ± 3.1	7 ± 0.7
	3.3	9 ± 0.6	5 ± 1.8	12 ± 0.6	8 ± 1.0	10 ± 0.9	10 ± 1.5
	10	5 ± 1.5	4 ± 0.0	9 ± 0.7	6 ± 1.2	14 ± 2.4	11 ± 0.3
	33	5 ± 0.9	4 ± 1.5	14 ± 2.3	7 ± 2.0	9 ± 0.9	6 ± 0.6
	100	5 ± 0.9	5 ± 2.1	10 ± 1.3	8 ± 0.3	10 ± 1.5	8 ± 0.3
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		186 ± 34.2	187 ± 30.3	52 ± 13.9	75 ± 5.2	20 ± 3.3	38 ± 3.5
TA98	0	16 ± 1.7	15 ± 0.3	40 ± 8.1	34 ± 0.9	53 ± 20.4	27 ± 4.3
	1	11 ± 5.0	10 ± 2.5	28 ± 10.0	34 ± 4.5	21 ± 5.8	17 ± 3.0
	3.3	23 ± 0.7	16 ± 3.3	32 ± 0.9	32 ± 0.9	30 ± 3.8	30 ± 3.9
	10	22 ± 0.7	18 ± 1.7	39 ± 1.9	42 ± 2.7	31 ± 2.6	30 ± 2.6
	33	18 ± 6.1	15 ± 0.9	40 ± 0.3	37 ± 3.3	39 ± 2.9	31 ± 0.7
	100	18 ± 0.7	19 ± 0.9	35 ± 2.7	40 ± 2.4	33 ± 5.3	35 ± 4.1
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		424 ± 12.2	280 ± 23.2	704 ± 80.8	778 ± 18.0	264 ± 11.9	350 ± 40.6
TA100[d]	0	130 ± 4.9	123 ± 6.3	119 ± 10.5	84 ± 5.8	132 ± 3.0	84 ± 5.8
	100	113 ± 8.2	97 ± 12.5	106 ± 7.0	104 ± 1.3	121 ± 3.7	110 ± 8.2
	333	124 ± 1.2	106 ± 8.5	115 ± 4.4	110 ± 7.5	121 ± 2.9	99 ± 5.9
	1,000	116 ± 0.3	96 ± 4.7	126 ± 6.4	119 ± 7.5	118 ± 7.8	99 ± 4.0
	1,666						
	3,333	108 ± 2.1	102 ± 11.7	118 ± 11.9	115 ± 5.9	119 ± 3.8	96 ± 5.5
	6,666						
	10,000	121 ± 8.7	116 ± 4.4	117 ± 6.4	134 ± 7.0	120 ± 9.4	107 ± 12.2
Trial summary		Negative	Negative	Negative	Equivocal	Negative	Negative
Positive control		277 ± 18.4	336 ± 7.9	1100 ± 18.7	991 ± 7.8	688 ± 39.0	593 ±196.2

TABLE J1
Mutagenicity of Ethylene Thiourea in *Salmonella typhimurium* (continued)

Strain	Dose (μg/plate)	Revertants/plate -S9 Trial 1	-S9 Trial 2	-S9 Trial 3
TA1535	0	27 ± 3.5	19 ± 4.0	20 ± 2.3
	100	32 ± 2.3	29 ± 1.3	
	333	33 ± 7.5	30 ± 1.2	
	1,000	37 ± 2.9	30 ± 7.4	26 ± 5.2
	1,666			33 ± 2.0
	3,333	49 ± 2.5	42 ± 5.7	37 ± 5.2
	6,666			36 ± 2.8
	10,000	57 ± 3.0	46 ± 3.5	53 ± 8.5
Trial summary		Equivocal	Positive	Positive
Positive control		315 ± 14.6	334 ± 14.3	288 ± 25.5

		+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% hamster S9 Trial 3	+10% rat S9 Trial 1	+10% rat S9 Trial 2	+10% rat S9 Trial 3
TA1535	0	13 ± 2.7	8 ± 0.6	8 ± 0.7	9 ± 3.2	12 ± 3.7	10 ± 2.5
	100	15 ± 0.6	11 ± 3.1		11 ± 1.2	13 ± 2.3	
	333	13 ± 2.6	7 ± 3.2		11 ± 2.3	18 ± 2.8	
	1,000	9 ± 4.8	11 ± 2.0	17 ± 2.0	18 ± 2.0	16 ± 1.2	
	1,666			11 ± 1.2			16 ± 1.8
	3,333	16 ± 0.6	17 ± 4.0	20 ± 2.6	24 ± 1.5	23 ± 3.8	17 ± 0.9
	6,666			30 ± 2.0			17 ± 2.1
	10,000	20 ± 3.5	28 ± 6.2	27 ± 2.7	37 ± 4.9	37 ± 0.7	28 ± 3.5
Trial summary		Negative	Equivocal	Positive	Positive	Positive	Equivocal
Positive control		357 ± 17.6	337 ± 24.8	270 ± 11.2	260 ± 7.7	232 ± 8.0	148 ± 14.7

		-S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA1537	0	4 ± 0.7	5 ± 0.9	10 ± 2.7	8 ± 2.3	8 ± 0.9	12 ± 0.3
	100	5 ± 0.6	6 ± 0.7	5 ± 1.5	8 ± 2.6	12 ± 2.3	10 ± 2.1
	333	5 ± 0.9	8 ± 2.9	8 ± 3.2	11 ± 3.3	10 ± 2.6	10 ± 3.8
	1,000	4 ± 1.8	4 ± 1.5	6 ± 0.9	11 ± 1.8	13 ± 2.9	15 ± 1.8
	1,666						
	3,333	3 ± 1.2	5 ± 1.5	6 ± 0.9	5 ± 1.5	8 ± 2.3	11 ± 3.9
	6,666						
	10,000	3 ± 0.3	7 ± 1.2	10 ± 2.3	6 ± 0.7	8 ± 2.2	12 ± 1.3
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		110 ± 6.9	177 ± 7.0	446 ± 16.1	248 ± 2.3	217 ± 5.3	121 ± 12.5

TABLE J1
Mutagenicity of Ethylene Thiourea in *Salmonella typhimurium* (continued)

Strain	Dose (μg/plate)	Revertants/plate -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA98	0	15 ± 1.5	13 ± 0.6	24 ± 3.0	30 ± 0.9	33 ± 2.7	36 ± 1.5
	100	22 ± 1.8	11 ± 2.2	28 ± 1.5	28 ± 1.5	30 ± 0.9	38 ± 2.9
	333	16 ± 1.2	18 ± 0.9	27 ± 2.0	29 ± 1.2	28 ± 2.0	47 ± 2.7
	1,000	13 ± 3.3	16 ± 2.2	27 ± 2.3	34 ± 4.8	33 ± 4.7	39 ± 3.5
	1,666						
	3,333	13 ± 2.5	13 ± 3.0	32 ± 3.0	28 ± 1.9	24 ± 2.3	36 ± 4.9
	6,666						
	10,000	18 ± 1.5	17 ± 5.2	22 ± 1.0	33 ± 3.5	30 ± 0.9	39 ± 3.9
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		654 ± 54.9	693 ± 16.6	926 ± 12.5	858 ± 48.1	462 ± 37.8	236 ± 16.8

[a] Revertants are presented as mean ± standard error from three plates.
[b] Study performed at Case Western Reserve University. The detailed protocol is presented in Mortelmans *et al.* (1986). Cells and ethylene thiourea or solvent (water) 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.
[c] 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was tested on TA98, sodium azide was tested on TA100 and TA1535, and 9-aminoacridine was tested on TA1537 OR TA97.
[d] Study performed at SRI, International. Solvent was dimethylsulfoxide; protocol same as in [b].

TABLE J2
Induction of Trifluorothymidine Resistance in Mouse L5178Y Lymphoma Cells by Ethylene Thiourea[a]

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction[b]	Average Mutant Fraction[c]
-S9						
Trial 1						
Dimethylsulfoxide						
		99	103	157	53	
		86	96	83	32	
		86	102	78	30	
		83	100	79	32	37
Methylmethanesulfonate						
		35	24	132	126	
	15	36	21	196	181	154*
Ethylene Thiourea						
	225	102	108	99	33	
		92	99	93	34	33
	450	94	107	58	21	
		95	96	101	36	28
	900	73	85	72	33	
	1,800	71	67	86	40	
		63	80	97	51	46
	3,600	64	74	85	44	
		92	89	76	28	36
Trial 2						
Dimethylsulfoxide						
		79	99	69	29	
		69	93	65	31	
		69	92	40	19	
		80	116	54	23	26
Methylmethanesulfonate						
		44	35	172	130	
	15	43	37	157	122	126*
Ethylene Thiourea						
	225	90	104	71	26	
		83	111	38	15	21
	450	82	109	48	20	
		90	114	49	18	19
	900	102	96	55	18	
		86	102	44	17	17
	1,800	86	96	41	16	
		90	98	36	13	15
	3,600	78	98	42	18	
		84	104	35	14	16

TABLE J2
Induction of Trifluorothymidine Resistance in Mouse L5178Y Lymphoma Cells by Ethylene Thiourea
(continued)

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
+S9						
Trial 1						
Dimethylsulfoxide						
		63	107	28	15	
		77	101	46	20	
		61	81	36	20	
		71	111	27	13	17
3-Methylcholanthrene						
		56	32	223	132	
	2.5	51	32	195	128	130*
Ethylene Thiourea						
	225	61	87	53	29	
		63	97	39	21	25
	450	73	109	35	16	
		65	104	37	19	17
	900	68	68	51	25	
		82	92	66	27	26
	1,800	91	118	98	36	
		73	97	73	33	35*
	3,600	83	102	81	33	
		85	98	94	37	35*
Trial 2						
Dimethylsulfoxide						
		69	96	45	22	
		86	104	71	28	
		82	106	47	19	
		72	95	51	24	23
3-Methylcholanthrene						
		69	29	490	238	
	2.5	47	25	418	300	269*
Ethylene Thiourea						
	1,200	72	95	48	22	
		84	109	72	29	25
	1,800	87	87	103	40	
		84	89	88	35	37*
	2,400	75	77	97	43	
		65	69	73	38	40*
	3,000	78	71	103	44	
		73	92	104	47	46*
	3,600	73	80	124	56	
		70	68	113	54	55*

TABLE J2
Induction of Trifluorothymidine Resistance in Mouse L5178Y Lymphoma Cells by Ethylene Thiourea
(continued)

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* Significant positive response (P≤0.05); occurs when the relative mutant fraction (average MF of treated culture/average MF of solvent control is approximately equal to 1.6. MF = mutant fraction.

[a] Study performed at Inveresk Research International. The experimental protocol is presented in detail by McGregor *et al.* (1988) and follows the basic format of Clive *et al.* (1979). The highest dose of ethylene thiourea is determined by solubility or toxicity and may not exceed 5 mg/mL. All doses are tested in triplicate; the average of 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] Mutant fraction (frequency) is a ratio of the mutant count to the cloning efficiency, divided by 3 (to arrive at MF/1 x 10^6 cells treated).

[c] Mean from three replicate plates of approximately 1/3 (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 positive (P≤0.05) by the dose trend test 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.

TABLE J3
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Ethylene Thiourea[a]

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative SCEs/Chromosome (%)[b]
-S9[c]								
Trial 1 Summary: Negative								
Dimethylsulfoxide		50	1,049	472	0.44	9.4	25.5	
Mitomycin-C	0.0010	50	1,044	655	0.62	13.1	25.5	39.44
	0.0100	5	105	251	2.39	50.2	25.5	431.27
Ethylene Thiourea	500	50	1,036	476	0.45	9.5	25.5	2.11
	1,667	50	1,047	446	0.42	8.9	25.5	-5.33
	5,000	50	1,040	557	0.53	11.1	33.8	19.03
								P=0.011[d]
+S9[e]								
Trial 1 Summary: Negative								
Dimethylsulfoxide		50	1,045	509	0.48	10.2	25.5	
Cyclophosphamide	0.3500	50	1,044	716	0.68	14.3	25.5	40.80
	2.0000	5	103	174	1.68	34.8	25.5	246.83
Ethylene Thiourea	500	50	1,040	474	0.45	9.5	25.5	-6.43
	1,667	50	1,037	460	0.44	9.2	25.5	-8.93
	5,000	50	1,039	422	0.40	8.4	25.5	-16.62
								P=0.997
Trial 2 Summary: Negative								
Dimethylsulfoxide		50	1,046	569	0.54	11.4	25.5	
Cyclophosphamide	0.3500	50	1,042	853	0.81	17.1	25.5	50.49
	2.0000	5	103	200	1.94	40.0	25.5	256.96
Ethylene Thiourea	8,000	50	1,048	617	0.58	12.3	25.5	8.23
	9,000	50	1,041	571	0.54	11.4	25.5	0.83
	10,000	50	1,043	593	0.56	11.9	25.5	4.52
								P=0.380

TABLE J3
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Ethylene Thiourea
(continued)

[a] Study performed at Litton Bionetics, Incorporated. 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 ethylene thiourea or solvent (dimethylsulfoxide) as described in [c] and [e] 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] Percent increase in SCEs/chromosome of culture exposed to study chemical relative to those of culture exposed to solvent.

[c] In the absence of S9, cells were incubated with ethylene thiourea 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 to 3 hours.

[d] Significance of relative SCEs/chromosome tested by the linear regression trend test vs. log of the dose

[e] In the presence of S9, cells were incubated with ethylene thiourea or solvent for 2 hours at 37° C. The cells were then washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with Colcemid present for the final 2 to 3 hours. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats.

TABLE J4
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Ethylene Thiourea[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: 22.7 hours Summary: Negative					**Trial 1** – Harvest time: 10.5 hours Summary: Negative				
Dimethylsulfoxide					Dimethylsulfoxide				
	100	6	0.06	6.0		100	5	0.05	4.0
	100	7	0.07	6.0		100	4	0.04	4.0
Mitomycin-C					Cyclophosphamide				
0.0500	50	49	0.98	50.0	50	50	21	0.42	30.0
Ethylene Thiourea					Ethylene Thiourea				
6,000	100	3	0.03	3.0	8,000	100	5	0.05	5.0
7,000	100	4	0.04	3.0	9,000	100	8	0.08	7.0
8,000	100	7	0.07	7.0	10,000	100	8	0.08	8.0
9,000	100	11	0.11	9.0					
				P=0.092[d]					P=0.093

[a] Study performed at Litton Bionetics, Incorporated. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway *et al.* (1985). Briefly, in Chinese hamster ovary cells were incubated with ethylene thiourea or solvent (dimethylsulfoxide) as indicated in [b] and [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, cells were incubated with ethylene thiourea or solvent for 8 to 10 hours at 37° C. Cells were then washed and fresh medium containing Colcemid was added for an additional 2 to 3 hours followed by harvest.

[c] In the presence of S9, cells were incubated with ethylene thiourea or solvent for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8 to 10 hours. Colcemid was added for the last 2 to 3 hours of incubation before harvest. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats.

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

TABLE J5
Induction of Sex-Linked Recessive Lethal Mutations in *Drosophila melanogaster* by Ethylene Thiourea

Route of Exposure	Dose (ppm)	Incidence of Deaths (percent)	Incidence of Sterility (percent)	No. of Lethals/No. of X Chromosomes Tested			
				Mating 1	Mating 2	Mating 3	Total[a]
Feeding[b]	5,020	9	48	2/995	0/941	0/240	2/2,176 (0.09%)
	0			1/870	0/946	1/985	2/2,801 (0.07%)
Feeding	5,170	9	48	3/1,539	2/1,445	1/537	6/3,521 (0.17%)
	0			0/2,009	1/1,980	0/725	1/4,714 (0.02%)
Injection[c]	4,900	2	0	2/2,522	3/2,256	0/1,750	5/6,528 (0.08%)
	0			2/1,603	1/1,360	0/1,129	3/4,092 (0.07%)
Feeding	12,500	14	7	2/1,961	2/1,670	1/1,519	5/5,150 (0.10%
	0			0/1,897	0/1,771	1/1,787	1/5,455 (0.02%)

[a] Combined total number of lethal mutations/number of X chromosomes tested for three mating trials.

[b] Study performed at Brown University. A detailed protocol of the sex-linked recessive lethal assay is presented in Zimmering *et al.* (1985). In feed exposure experiments, 24-hr-old Canton-S males were allowed to feed for 3 days on a solution of the study chemical dissolved in 5% sucrose. In the injection experiments, 24-hr-old Canton-S males were treated with a solution of the chemical dissolved in 0.7% saline and allowed to recover for 24 hours. Exposed males were mated to three *Basc* females for 3 days and given fresh females at 2-day intervals to produce three broods of 3, 2, and 2 days; sample sperm from successive matings were treated as spermatozoa (mating 1), spermatids (mating 2), and spermatocytes (mating 3). F_1 heterozygous females were crossed to their siblings and placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters; no clusters were found. Presumptive lethal mutations were identified as vials containing no wild-type males after 17 days; these were retested. Results were considered to be equivocal by normal approximation to the binomial test (Margolin *et al.*, 1983).

[c] Study performed at University of Wisconsin - Madison. Protocol same as in [b]. Results were negative by normal approximation to the binomial test (Margolin *et al.*, 1983).

TABLE J6
Induction of Reciprocal Translocations in *Drosophila melanogaster* by Ethylene Thiourea[a]

Route of Exposure	Dose (ppm)	Transfers Translocations/Total F_1 Tested					No. of Tests	Total No. of Translocations	Total Translocations (%)
		1	2	3	4	5			
Feeding	500	0/2,308	0/1,654	0/927	0/891	0/202	5,982	0	0.00
Historical control	0						116,163	2	0.00

[a] Study performed at Brown University. A detailed protocol of the translocation assay is presented by Zimmering *et al.* (1985). Exposed males were mated to three X,Y,y;bs;st females for 3 days and discarded. The females were transferred to fresh medium every 3 to 4 days to produce a total of five cultures, and then they were discarded. In this manner, sample sperm from successive cultures were stored for increasing lengths of time. Individual F_1 males were backcrossed to X,Y,y;bw;st females, and the F_2 were screened for pseudolinkage. This procedure allows the recovery of translocations involving the Y, second, or third chromosomes in any combination. Presumptive translocations were retested. Results were not significant at the 5% level (Kastenbaum and Bowman, 1970).

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TR No.	CHEMICAL
201	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Dermal)
206	1,2-Dibromo-3-chloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butyl Benzyl Phthalate
214	Caprolactam
215	Bisphenol A
216	11-Aminoundecanoic Acid
217	Di(2-ethylhexyl)phthalate
219	2,6-Dichloro-p-phenylenediamine
220	C.I. Acid Red 14
221	Locust Bean Gum
222	C.I. Disperse Yellow 3
223	Eugenol
224	Tara Gum
225	D & C Red No. 9
226	C.I. Solvent Yellow 14
227	Gum Arabic
228	Vinylidene Chloride
229	Guar Gum
230	Agar
231	Stannous Chloride
232	Pentachloroethane
233	2-Biphenylamine Hydrochloride
234	Allyl Isothiocyanate
235	Zearalenone
236	*D*-Mannitol
237	1,1,1,2-Tetrachloroethane
238	Ziram
239	Bis(2-chloro-1-methylethyl)ether
240	Propyl Gallate
242	Diallyl Phthalate (Mice)
243	Trichloroethylene (Rats and Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
246	Chrysotile Asbestos (Hamsters)
247	L-Ascorbic Acid
248	4,4'-Methylenedianiline Dihydrochloride
249	Amosite Asbestos (Hamsters)
250	Benzyl Acetate
251	2,4- & 2,6-Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
254	Dichloromethane (Methylene Chloride)
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
266	Monuron
267	1,2-Propylene Oxide
269	Telone II® (1,3-Dichloropropene)
271	HC Blue No. 1
272	Propylene
273	Trichloroethylene (Four Rat Strains)
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
277	Tremolite
278	2,6-Xylidine
279	Amosite Asbestos
280	Crocidolite Asbestos
281	HC Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No. 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethyl) phosphonium Sulfate & Tetrakis(hydroxymethyl) phosphonium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	*o*-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane (Methylene Chloride)
307	Ephedrine Sulfate
308	Chlorinated Paraffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	*n*-Butyl Chloride
313	Mirex
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
320	Rotenone
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
323	Dimethyl Methylphosphonate
324	Boric Acid
325	Pentachloronitrobenzene
326	Ethylene Oxide
327	Xylenes (Mixed)
328	Methyl Carbamate
329	1,2-Epoxybutane
330	4-Hexylresorcinol
331	Malonaldehyde, Sodium Salt
332	2-Mercaptobenzothiazole
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol
335	C.I. Acid Orange 3
336	Penicillin VK
337	Nitrofurazone

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TR No.	CHEMICAL
338	Erythromycin Stearate
339	2-Amino-4-nitrophenol
340	Iodinated Glycerol
341	Nitrofurantoin
342	Dichlorvos
343	Benzyl Alcohol
344	Tetracycline Hydrochloride
345	Roxarsone
346	Chloroethane
347	D-Limonene
348	*a*-Methyldopa Sesquihydrate
349	Pentachlorophenol
350	Tribromomethane
351	*p*-Chloroaniline Hydrochloride
352	N-Methylolacrylamide
353	2,4-Dichlorophenol
354	Dimethoxane
355	Diphenhydramine Hydrochloride
356	Furosemide
357	Hydrochlorothiazide
358	Ochratoxin A
359	8-Methoxypsoralen
360	N,N-Dimethylaniline
361	Hexachloroethane
362	4-Vinyl-1-Cyclohexene Diepoxide
363	Bromoethane (Ethyl Bromide)
364	Rhodamine 6G (C.I. Basic Red 1)
365	Pentaerythritol Tetranitrate
366	Hydroquinone
367	Phenylbutazone
368	Nalidixic Acid
369	Alpha-Methylbenzyl Alcohol
370	Benzofuran
371	Toluene
372	3,3'-Dimethoxybenzidine Dihydrochloride
373	Succinic Anhydride
374	Glycidol
375	Vinyl Toluene
376	Allyl Glycidyl Ether
377	*o*-Chlorobenzalmalononitrile
378	Benzaldehyde
379	2-Chloroacetophenone
380	Epinephrine Hydrochloride
381	*d*-Carvone
382	Furfural
386	Tetranitromethane
387	Amphetamine Sulfate
389	Sodium Azide
390	3,3'-Dimethylbenzidine Dihydrochloride
391	Tris(2-chloroethyl) Phosphate
393	Sodium Fluoride
395	Probenecid
396	Monochloroacetic Acid
399	Titanocene Dichloride
405	C.I. Acid Red 114
415	Polysorbate 80

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