NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 329

TOXICOLOGY AND CARCINOGENESIS STUDIES OF 1,2-EPOXYBUTANE

(CAS NO. 106-88-7)

IN F344/N RATS AND $B6C3F_1$ MICE

(INHALATION STUDIES)

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

NATIONAL TOXICOLOGY PROGRAM

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

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF 1,2-EPOXYBUTANE

(CAS NO. 106-88-7)

IN F344/N RATS AND B6C3F$_1$ MICE

(INHALATION STUDIES)

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P.O. Box 12233
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NCTE TO THE READER

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

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

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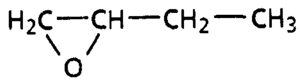

1,2-EPOXYBUTANE

CAS No. 106-88-7

C_4H_8O Molecular weight 72.1

Synonyms: 1-butene oxide; 1,2-butene oxide; butylene oxide; 1,2-butylene oxide; ethyl ethylene oxide; ethyl oxirane

ABSTRACT

1,2-Epoxybutane was selected for study because it is a short-chain epoxide that had been shown to be mutagenic and because no carcinogenicity data were available. Approximately 8 million pounds of 1,2-epoxybutane are produced annually in the United States. The chemical is used primarily as a stabilizer in chlorinated hydrocarbon solvents.

Single-Exposure, Fourteen-Day, and Thirteen-Week Studies: Single-exposure, 14-day, 13-week, and 2-year studies were conducted in F344/N rats and B6C3F$_1$ mice. The chemical was greater than 99% pure and was administered as a vapor by the inhalation route to mimic worker exposure; room air was used as the control exposure during these studies. Exposures were 6 hours per day (5 days per week), except in the single-exposure studies (4 hours). Additional studies were performed to evaluate the potential for genetic damage in bacteria and in mammalian cells. In the single-exposure studies, the chemical was administered at exposure concentrations of 400-6,550 ppm in rats and 400-2,050 ppm in mice. In the 14-day studies, rats and mice were exposed at 400-6,400 ppm, and in the 13-week studies, rats and mice were exposed at 50-800 ppm.

All rats in the single-exposure studies at 6,550 ppm died; compound-related deaths were not seen in other dosed groups. All mice at 2,050 ppm and 4/5 mice of each sex at 1,420 ppm died; compound-related mortality was not seen in other dosed groups.

In the 14-day studies, all rats at 3,200 and 6,400 ppm and 2/5 female rats at 1,600 ppm died; all mice at 1,600, 3,200, and 6,400 ppm and 1/5 male mice at 800 ppm died. Final mean body weights of surviving rats exposed at 800 or 1,600 ppm were 12%-33% lower than those of the controls; final mean body weights of surviving mice at 800 ppm were 10%-12% lower than those of the controls. Compound-related lesions included pulmonary hemorrhage and rhinitis in rats at 1,600 ppm and nephrosis in mice at 800 and 1,600 ppm.

In the 13-week studies, no compound-related mortality was observed in rats; all mice exposed at 800 ppm died. No compound-related clinical signs were seen in rats or in surviving mice. The final mean body weight of rats exposed at 800 ppm was 23% lower than that of controls for males and 16% lower for females. Final body weights of surviving mice were unaffected by exposure. Inflammation of the nasal turbinates was seen in rats at 800 ppm but not at lower exposure concentrations. Renal tubular necrosis was seen in mice at 800 ppm but not at lower concentrations. Inflammation of the nasal turbinates was observed in female mice at 100, 200, 400, and 800 ppm and in male mice at 200, 400, and 800 ppm. The highest exposure concentration selected for the 2-year studies in rats was 400 ppm because of body weight effects and nasal lesions observed at 800 ppm. The highest concentration selected for the 2-year studies in mice was 100 ppm because the nasal lesions seen at 200 and 400 ppm were considered to be potentially life threatening.

Two-Year Studies: The 2-year toxicology and carcinogenesis studies of 1,2-epoxybutane were conducted by exposing groups of 50 animals per species and sex to the chemical by inhalation, 6 hours per day 5 days per week. Rats were exposed at concentrations of 0, 200, or 400 ppm for 103 weeks and mice at 0, 50, or 100 ppm for 102 weeks.

Body Weight and Survival in the Two-Year Studies: The survival of all groups of dosed rats was at least 50% until week 98, but final survival was reduced in the dosed groups (final survival--male: control, 30/50; low dose, 18/50; high dose, 23/50; female: 32/50; 21/50; 22/50). Mean body weights of control and exposed male rats were similar until week 86; thereafter, mean body weights of high dose male rats were 4%-8% lower than those of controls. Mean body weights of high dose female rats were 5%-10% lower than those of controls after week 22.

Survival in male mice was comparable among groups (final survival: 41/50; 45/50; 33/50). Survival in female mice was greater than 50% in all groups at week 86 and then was reduced in high dose females toward the end of the study (final survival: 29/50; 25/50; 9/50). This decreased survival was associated with suppurative inflammation of the ovary and uterus. *Klebsiella oxytoca* was isolated from these ovarian/uterine lesions. Mean body weights of high dose male mice were 10%-14% lower than those of the controls after week 69; mean body weights of low dose male mice were 4%-8% lower than those of the controls after week 86. Mean body weights of high dose female mice were 13%-23% lower than those of the controls after week 60, and mean body weights of low dose female mice were 12%-16% lower than those of the controls after week 73.

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: Dosed rats had nonneoplastic lesions of the nasal cavity including inflammation, epithelial hyperplasia, squamous metaplasia, hyperostosis of the nasal turbinate bone, and atrophy of the olfactory epithelium. Seven papillary adenomas of the nasal cavity were seen in high dose male rats and two in high dose female rats. The historical incidences of nasal cavity adenomas in untreated male and untreated female F344/N rats are less than 0.1%. The incidences of alveolar/bronchiolar carcinomas (0/50; 1/50; 4/49) and adenomas or carcinomas (combined) (0/50; 2/50; 5/49) were increased in high dose male rats; no increased incidences of these tumors were observed in dosed female rats.

Dosed mice had increased incidences of nonneoplastic lesions of the nasal cavity but no significant increase in the incidence of neoplastic lesions of the nasal cavity. The nonneoplastic lesions included suppurative inflammation (empyema), epithelial hyperplasia, erosion, regeneration, and squamous metaplasia in the nasal cavity; atrophy of the olfactory sensory epithelium; hyperplasia of the nasal gland (Bowman's glands); and inflammation and hyperplasia of the nasolacrimal duct. A single squamous cell papilloma was seen in the incisive duct of one high dose male mouse.

Genetic Toxicology: 1,2-Epoxybutane was mutagenic in *Salmonella typhimurium* strains TA100 and TA1535 when tested with a preincubation protocol with and without rat liver S9, indicating that it is a direct-acting mutagen capable of inducing base-pair substitutions in prokaryotes; it did not cause gene reversion in strains TA1537 or TA98. 1,2-Epoxybutane induced forward mutations at the TK locus of cultured mouse L5178Y lymphoma cells with and without metabolic activation. Both chromosomal aberrations and sister chromatid exchanges were induced in cultured Chinese hamster ovary cells after exposure to 1,2-epoxybutane in the presence and absence of metabolic activation. 1,2-Epoxybutane, when fed to male Drosophila, caused significant increases in the number of sex-linked recessive lethal mutations and reciprocal translocations in the germ cells.

Data Audit: An audit of the experimental data was conducted for the 2-year studies of 1,2-epoxybutane. No data discrepancies were found that influenced the final interpretations.

Conclusions: Under the conditions of these 2-year inhalation studies, there was *clear evidence of carcinogenic activity** of 1,2-epoxybutane for male F344/N rats, as shown by an increased incidence of papillary adenomas of the nasal cavity, alveolar/bronchiolar carcinomas, and alveolar/bronchiolar adenomas or carcinomas (combined). There was *equivocal evidence of carcinogenic activity* for female F344/N rats, as shown by the presence of papillary adenomas of the nasal cavity. There was *no evidence of carcinogenic activity* for male or female B6C3F_1 mice exposed at 50 or 100 ppm. 1,2-Epoxybutane exposure was associated with adenomatous hyperplasia and inflammatory lesions of the nasal cavity in rats and inflammatory lesions of the nasal cavity in mice.

SUMMARY OF THE TWO-YEAR FEED AND GENETIC TOXICOLOGY STUDIES OF 1,2-EPOXYBUTANE

Male F344/N Rats	Female F344/N Rats	Male B6C3F_1 Mice	Female B6C3F_1 Mice
Exposure concentrations			
0, 200, or 400 ppm 1,2-epoxybutane, 6 h/d, 5 d/wk	0, 200, or 400 ppm 1,2-epoxybutane, 6 h/d, 5 d/wk	0, 50, or 100 ppm 1,2-epoxybutane, 6 h/d, 5 d/wk	0, 50, or 100 ppm 1,2-epoxybutane, 6 h/d, 5 d/wk
Body weights in the 2-year study			
Slightly reduced in exposed groups	Slightly reduced in exposed groups	Reduced in exposed groups	Reduced in exposed groups
Survival rates in the 2-year study			
30/50; 18/50; 23/50	32/50; 21/50; 22/50	41/50; 45/50; 33/50	29/50; 25/50; 9/50
Nonneoplastic effects			
Nasal cavity lesions	Nasal cavity lesions	Nasal cavity lesions	Nasal cavity lesions
Neoplastic effects			
Papillary adenomas of the nasal cavity (0/50; 0/50; 7/50), alveolar bronchiolar/ neoplasms (0/50; 2/50; 5/49)	Papillary adenomas of the nasal cavity (0/50; 0/50; 2/50)	None	None
Level of evidence of carcinogenic activity			
Clear evidence	Equivocal evidence	No evidence	No evidence

Genetic toxicology

Salmonella (gene mutation) (a)	Mouse L5178Y/TK $^{+/-}$ (gene mutation) (a)	CHO cells in vitro: SCE (a)	CHO cells in vitro: Aberration (a)	Drosophila: Sex-linked rec. lethals	Drosophila: Reciprocal translocation
Positive in strains TA100, TA1535; negative in strains TA98, TA1537	Positive	Positive	Positive	Positive	Positive

(a) With and without S9 liver enzyme fraction used for exogenous metabolic activation.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 6.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 10-11.

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

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

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

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

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

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APPENDIXES

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on 1,2-epoxybutane on August 19, 1986, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF 1,2-EPOXYBUTANE

On August 19, 1986, the draft Technical Report on the toxicology and carcinogenesis studies of 1,2-epoxybutane received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. J. Dunnick, NTP, introduced the studies by reviewing the experimental design, results, and proposed conclusions (clear evidence of carcinogenic activity for male rats; some evidence of carcinogenic activity for female rats; no evidence of carcinogenic activity for male or female mice). Dr. Dunnick pointed out that the conclusion for female rats in the draft report, equivocal evidence of carcinogenic activity, had been changed during final staff review based on the rarity of the papillary adenomas of the nasal cavity; this change was supported by increases in the same lesions in male rats and in previous NTP studies of propylene oxide.

Dr. Popp, a principal reviewer, agreed with the conclusions for male rats and male and female mice while questioning the new conclusion for female rats. He asked whether the conclusion in male rats was based on benign or malignant lung tumors or on a combination of the two. Dr. Dunnick replied that it was based on both carcinomas and combined adenomas or carcinomas. Dr. Popp commented that there should be mention in the text of the significance of the respiratory tract viruses identified by serology. Dr. Dunnick said that there were no lesions to indicate an active infection.

As a second principal reviewer, Dr. Perera agreed with the conclusions as presented, endorsing the chemical relatedness of the papillary adenomas of the nasal cavity in high dose female rats. Since 2-year studies with 1,3-butadiene and ethylene oxide were conducted in the same animal room, she asked for inclusion of a statement that the room air was not contaminated by these chemicals. [See page 60.]

As a third principal reviewer, Dr. Sivak agreed with the conclusions for male rats and male and female mice but thought the observation of two nasal cavity adenomas in high dose female rats was not enough to justify some evidence. Dr. S. Eustis, NIEHS, elaborated on the staff decision for the stronger level. Besides the rarity of the tumors and their occurrence in male rats, the occurrence of adenomatous hyperplasia, believed by some to be preneoplastic lesions, provided additional evidence.

Further discussion focused on the strength of the evidence for male rats. Dr. Purchase contended that the zero incidence of lung tumors in controls was low contrasted with the six tumors (6/249) observed in chamber controls in previous studies at the same laboratory. Considering the difficulty of distinguishing among pulmonary hyperplasia, adenomas, and carcinomas, he believed some evidence of carcinogenic activity was more appropriate. Dr. Paul Cammer, representing the Halogenated Solvents Industry Alliance, made a brief presentation supporting a lower level of evidence. Dr. Eustis responded that the progressive nature of the pulmonary tumor process and the consistency of diagnoses introduced through the NTP pathology quality assurance process eliminated inconsistent diagnoses. Dr. J. Huff, NIEHS, added that Program pathologists have no difficulty in differentiating among hyperplasia, benign tumors, and malignant tumors. Dr. J. Haseman, NIEHS, said that the statistical significance of the increased incidence of lung neoplasms in high dose male rats (5/49) would have been similar had the comparison been based on the historical control rate at the study laboratory (6/249) rather than on the observed tumor incidence in the concurrent controls (0/50). Dr. Hooper expressed concern about the identity of the reported 1% impurity in the study chemical. Dr. Dunnick said that more recent analyses indicated a purity of 99.9% or greater.

Dr. Popp moved that the Technical Report on 1,2-epoxybutane be accepted with the conclusions as originally written, clear evidence of carcinogenic activity for male rats, equivocal evidence of carcinogenic activity for female rats, and no evidence of carcinogenic activity for male and female mice. Dr. Sivak seconded the motion. Dr. Perera offered an amendment to the motion that the staff's modification to some evidence of carcinogenic activity for female rats be accepted. Dr. Hooper seconded the amendment, which was defeated by six votes to three (Dr. Hooper, Dr. Mirer, and Dr. Perera), with one abstention (Dr. Purchase). The original motion was then approved by seven votes to two (Dr. Hooper and Dr. Perera), with one abstention (Dr. Purchase).

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of 1,2-Epoxybutane is based on the 13-week studies that began in March 1981 and ended in June 1981 and on the 2-year studies that began in November 1981 and ended in November 1983 at Battelle Pacific Northwest Laboratories.

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I. INTRODUCTION

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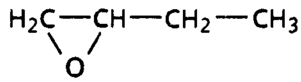


1,2-EPOXYBUTANE

CAS No. 106-88-7

C_4H_8O Molecular weight 72.1

Synonyms: 1-butene oxide; 1,2-butene oxide; butylene oxide; 1,2-butylene oxide; ethyl ethylene oxide; ethyl oxirane

Production, Use, and Exposure

1,2-Epoxybutane is used as a stabilizer in chlorinated hydrocarbon solvents (e.g., 1,1,1-trichloroethane, trichloroethylene, and dichloromethane); more than 75% of the compound produced is used for this purpose. Other uses include production of butylene glycol, butanolamines, and surface active agents (Hine et al., 1981; Fed. Regist., 1984). 1,2-Epoxybutane is a highly flammable and reactive chemical (Table 1). In 1978, production in the United States was estimated at 8 million pounds per year. Approximately 50,000 people are exposed annually to 1,2-epoxybutane (Fed. Regist., 1984). There are no National Institute for Occupational Safety and Health (NIOSH) administrative standards or standards from the American Conference of Government Industrial Hygienists. Manufacturers have established an 8-hour time-weighted-average (TWA) limit in the workplace of 40 ppm (Fed. Regist., 1984). The U.S. Environmental Protection Agency estimates that the atmospheric half-life for the oxidation of 1,2-epoxybutane is approximately 6 days; 1,2-epoxybutane could also undergo atmospheric hydrolysis.

Studies in Animals

The oral LD_{50} in male Wistar rats is 1,170 mg/kg; the dermal LD_{50} in New Zealand rabbits is 1,740 mg/kg. A 4-hour inhalation study in Wistar rats showed an LC_{100} of 8,000 ppm (6/6 dead) and a lowest lethal concentration of 4,000 ppm (1/6 dead) (Smyth et al., 1962; Weil et al., 1963). Rats, guinea pigs, and rabbits are reported to tolerate a 7-hour exposure to epoxybutane at a concentration of 400 ppm (Hine et al., 1981). Epoxybutane (10% in acetone) applied three times per week for 540 days to the clipped skin of ICR/Ha Swiss mice did not have a toxic effect (Van Duuren et al., 1967).

Two-week and 13-week inhalation studies of 1,2-epoxybutane in male and female F344 rats and $B6C3F_1$ mice were reported by Miller et al. (1981). In the 2-week studies, rats and mice were exposed to 1,2-epoxybutane at concentrations of 0, 400, 800, or 1,600 ppm, 6 hours per

TABLE 1. PHYSICAL PROPERTIES OF 1,2-EPOXYBUTANE (a)

Physical description	Water-white liquid
Specific gravity at 25° C	0.826
Freezing point	Below −60° C
Boiling point (760 mm Hg)	62.0°-64.5° C
Refractive index at 25° C	1.381
Density of saturated air (air = 1)	~0.977
Vapor density (mm Hg)	176
Solubility at 25° C (g/100 g H_2O)	~8.24
Solubility in common solvents	Miscible with common aliphatic and aromatic solvents
Flash point (closed cup)	−15° F
Flammability limits (at 25° C and 760 mm Hg)	~1 ppm (2.94 mg/m^3) to 340 ppm (1.00 g/m^3)

(a) Hine et al., 1981; NIOSH, 1982a,b

day, 5 days per week for a total of 9 exposure days. Exposure at 1,600 ppm was fatal to mice; all rats survived. Decreased body weight gain was seen at 800 and 1,600 ppm in rats and mice. In the 13-week studies, animals were exposed at 0, 75, 150, or 600 ppm, 6 hours per day, 5 days per week for 13 weeks. Histologic examination revealed compound-related lesions in the nasal mucosa (focal thickening and flattening of the respiratory epithelium and inflammatory cells in the nasal mucosa) of rats and mice exposed at 600 ppm, whereas none was found at 75 or 150 ppm. Body weight gain was lower at 600 ppm in female rats and in male and female mice; survival of dosed groups was comparable to that of controls. No data on long-term toxicity have been reported.

Teratogenicity and Reproduction Studies

Sikov et al. (1980) reported a teratogenicity study in Wistar rats and New Zealand white rabbits. Female rats were exposed by inhalation to epoxybutane 7 hours per day, 5 days per week for 3 weeks prior to mating, and from day 0 to 19 of gestation at 0, 250, or 1,000 ppm. Animals were evaluated at gestation day 21. The only maternal toxicity observed in the high dose group was a slight decrease in body weight relative to that of the controls; no teratogenic effects were seen in any exposed group. Artificially inseminated rabbits were exposed to epoxybutane at 0, 250, or 1,000 ppm 7 hours per day from gestation day 0 to 24; animals were examined at gestation day 30. Some maternal deaths occurred at both exposure concentrations, but no teratogenic effects were seen. The pregnancy rate was reduced in the high dose group.

Reproductive studies have not been reported, although Miller et al. (1981) noted no histopathologic abnormalities in the reproductive organs of male and female F344 rats or B6C3F$_1$ mice exposed to 1,2-epoxybutane at 600 ppm for 13 weeks.

Metabolism

The metabolism of 1,2-epoxybutane has not been studied extensively. Jones (1975) suggested that epoxides are detoxified in vivo by conjugation with glutathione. In one study in which 1,2-epoxybutane was administered as a single dose to rats (1.9 mmol/kg), 11% of the original dose was excreted in the urine as 2-hydroxybutyl mercapturic acid (James et al., 1968).

Genetic Toxicology

There are extensive data in the literature on the mutagenicity of 1,2-epoxybutane. In general, the compound exhibited mutagenic activity across a wide spectrum of species ranging from bacteria to mammals. 1,2-Epoxybutane induced gene mutations in *Klebsiella pneumoniae* in the absence of metabolic activation (Voogd et al., 1981; Knaap et al., 1982) and exhibited strain-specific mutagenic activity that was sometimes dependent on S9 metabolic activation in tests with *Escherichia coli* (McMahon et al., 1979; McCarroll et al., 1981; De Flora et al., 1984). In tests with *Salmonella typhimurium*, 1,2-epoxybutane induced gene reversion, usually at doses above 500 µg/plate, in strains TA100, TA100-FR1, TA1535, and TA1530, all of which indicate base-pair substitutions (McCann and Ames, 1976; Rosenkranz and Speck, 1975, 1976; Chen et al., 1975; Speck and Rosenkranz, 1976; Henschler et al., 1977; Wade et al., 1978; De Flora, 1979; Weinstein et al., 1981) but not in strains TA1536, TA1537, TA1538, TA98, C3076, or D3052, which are used to detect frame-shift mutations (Rosenkranz and Poirier, 1979; Simmon, 1979a; McMahon et al., 1979; Katz et al., 1980; De Flora, 1981; De Flora et al., 1984). Similarly, the NTP found 1,2-epoxybutane at doses of 1,000 µg and above to be mutagenic in *S. typhimurium* strains TA100 and TA1535 with a preincubation protocol with and without S9 from the livers of Aroclor 1254-induced male Sprague Dawley rats and male Syrian hamsters; the compound did not cause gene reversion in strains TA1537 and TA98 (Canter et al., 1986; Appendix E, Table E1).

1,2-Epoxybutane produced a dose-related increase in gene mutations in *Neurospora crassa* (Kolmark and Giles, 1955) and in *Schizosaccharomyces pombe* (Migliore et al., 1982; Rossi et al., 1983), as well as an increase in the frequency of mitotic recombination in *Saccharomyces cerevisiae* (Simmon, 1979b) with and without S9. Conflicting results have been reported in the Drosophila sex-linked recessive lethal assays which are probably related to differences in dose or route of administration. McGregor (1981) reported no increase in sex-linked recessive lethal mutations following inhalation of 1,2-epoxybutane at 1,000 ppm over a period of 7 hours, whereas induction of sex-linked recessive lethal mutations was observed by Knaap et al. (1982) following an injection of 117-233 mM solutions of the chemical. NTP studies showed that 1,2-epoxybutane fed for 72 hours to male Drosophila at doses of 50,000 or 60,000 ppm caused significant increases in the number of sex-linked recessive lethal mutations and reciprocal translocations in the germ cells (Yoon et al., 1985; Tables E5 and E6).

The results of assays in mouse L5178Y lymphoma cells in the absence of exogenous metabolic activation were positive for induction of gene mutations (Amacher et al., 1980; Knaap et al., 1982). The results of NTP-sponsored mouse lymphoma assays, both in the presence and absence of Aroclor 1254-induced F344 rat liver S9, confirmed the mutagenicity of 1,2-epoxybutane in these L5178Y cells (Table E2). In Chinese hamster ovary cells, 1,2-epoxybutane produced a strong, dose-related increase in the number of sister chromatid exchanges (SCEs) in the presence and absence of Aroclor 1254-induced male Sprague Dawley rat liver S9, as well as an increase in the frequency of chromosomal aberrations (Tables E3 and E4). Because the increase in chromosomal aberrations in the absence of S9 activation, although significant, occurred at doses that were severely toxic to the cells and resulted in poor chromosomal morphology, the overall results of the assay were judged to be "weakly positive." Treatment of human fibroblast cell cultures with up to 84 µg/ml 1,2-epoxybutane in the presence of S9 did not induce unscheduled DNA synthesis (UDS) (McGregor, 1981); neither was UDS induced after exposure of rat hepatocyte cultures to 1,2-epoxybutane at 10 mg/ml in the absence of S9 (Williams et al., 1982). In vivo mammalian tests for genotoxicity were also negative. No sperm abnormalities were induced in male mice after inhalation exposure at up to 1,000 ppm 1,2-epoxybutane for 7 hours per day for 5 consecutive days, and no dominant lethal mutations were observed in rats after similar exposures (McGregor, 1981).

Study Rationale

1,2-Epoxybutane was selected for toxicology and carcinogenesis studies because it was representative of the short-chain epoxides and had a relatively high volume of production and because no carcinogenicity data were available for this chemical. The inhalation route was selected to mimic the potential human exposure in the workplace.

II. MATERIALS AND METHODS

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF 1,2-EPOXYBUTANE

1,2-Epoxybutane was obtained in two lots from Dow Chemical Company (Richmond, Virginia) (Table 2). Purity and identity analyses of the bulk chemical were conducted at Midwest Research Institute (MRI) (Kansas City, Missouri). (MRI reports on the analyses performed in support of the epoxybutane studies are on file at NIEHS.) Both lots of study material were a clear, colorless liquid with a boiling point of 63° C. Each lot was identified as 1,2-epoxybutane by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. Infrared and nuclear magnetic resonance spectra were consistent with the structure and with literature spectra. (See Figures 1 through 4 for representative spectra.) The ultraviolet/visible spectrum was consistent with the structure of 1,2-epoxybutane; no absorbance was found in the visible region.

Purity of both lots used in the study was determined by elemental analysis, Karl Fischer water analysis, titration of the epoxide group by hydrogen iodide generated in situ from tetrabutylammonium iodide with perchloric acid, and gas chromatography. Gas chromatographic analysis was performed with flame ionization detection and either a Carbopack C/0.1% SP1000, 80/100, 1.8 m × 4 mm ID glass column (system 1) or a Tenax-GC, 60/80, 1.8 m × 4 mm ID glass column (system 2).

Cumulative data indicated a purity of greater than 99% for both lots used in these studies. Results of elemental analysis of both lots were consistent with theoretical values. Water content by Karl Fischer titration ranged from 0.016% to 0.03%. Nonaqueous titration of the epoxide group gave a purity of 92.4% for lot no. MM10258 and 96.5% for lot no. RR810402. These titration values are considered to be inaccurate due to the inherent difficulties in this type of titration analysis. Gas chromatographic analyses of both lots by the two systems listed above detected a single homogeneous major peak and no impurities with peak areas greater than 0.1% of that of the major peak in either lot. A retrospective analysis of both lots by gas chromatography/mass spectroscopy indicated a purity of greater than 99% and only one impurity (identified as 1,2-butanediol and found to be present at less than 0.2%) in each lot.

Stability studies of the bulk chemical were run for 2 weeks at −20° to 60° C. Analysis by gas chromatography with system 1 indicated that 1,2-epoxybutane was stable as a bulk chemical when kept for 2 weeks at temperatures up to 60° C. Further confirmation of the stability of the bulk chemical (stored at room temperature) during the toxicology and carcinogenesis studies was obtained by periodic gas chromatographic analysis with a Porapak QS, 2.3 m × 2 mm ID glass column. No degradation was seen over the course of the studies. The identity of the chemical at the study laboratory was confirmed by infrared spectroscopy.

TABLE 2. IDENTITY AND SOURCE OF LOTS USED IN THE INHALATION STUDIES OF 1,2-EPOXYBUTANE

Single-Exposure Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Lot Numbers			
MM10258	Same as single-exposure studies	Same as single-exposure studies	MM10258; RR810402
Date of Initial Use			
1/31/80	9/30/80	3/4/81	Lot no. MM10258, 11/25/81; lot no. RR810402, 5/14/82
Supplier			
Dow Chemical Co. (Richmond, Virginia)	Same as single-exposure studies	Same as single-exposure studies	Same as single-exposure studies

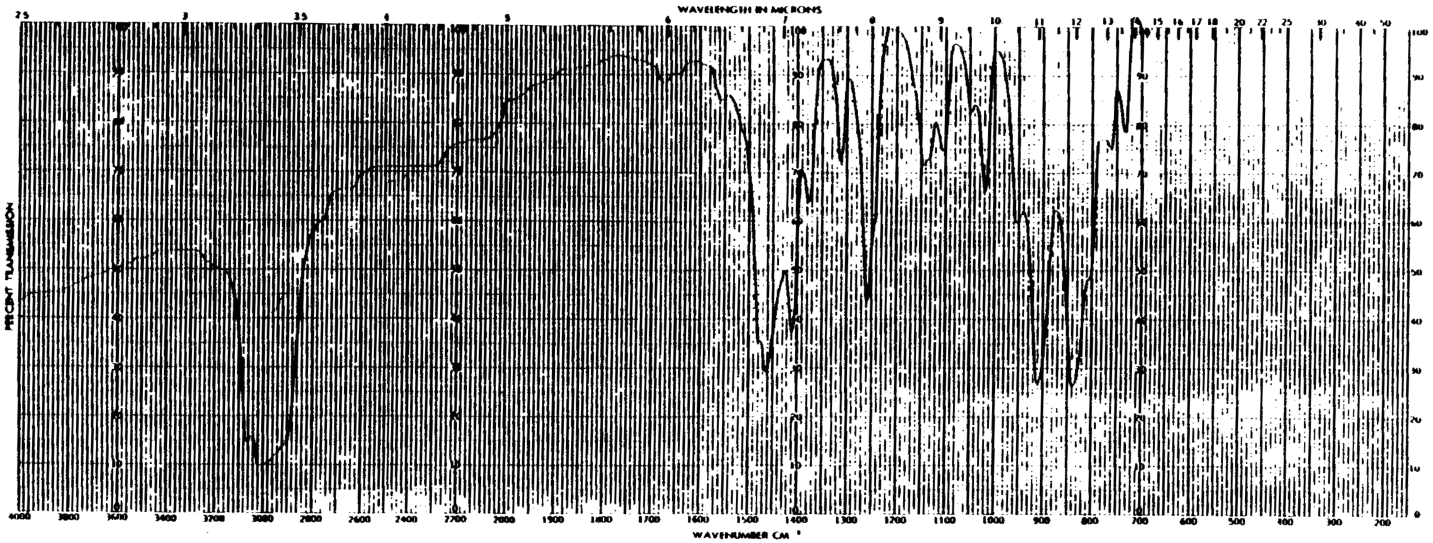


FIGURE 1. INFRARED ABSORPTION SPECTRUM OF 1,2-EPOXYBUTANE (LOT NO. MM10258)

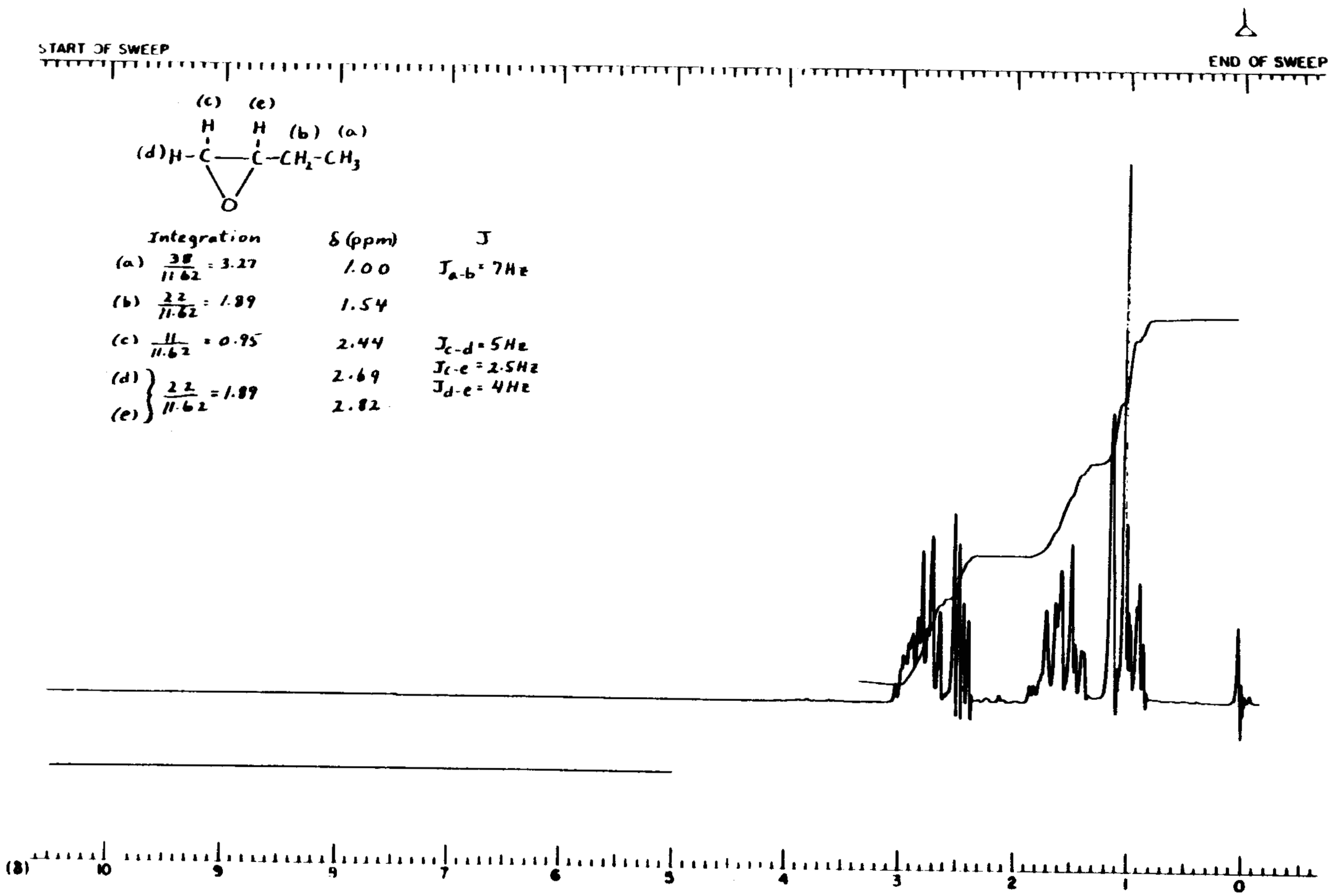


FIGURE 2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF 1,2-EPOXYBUTANE (LOT NO. MM10258)

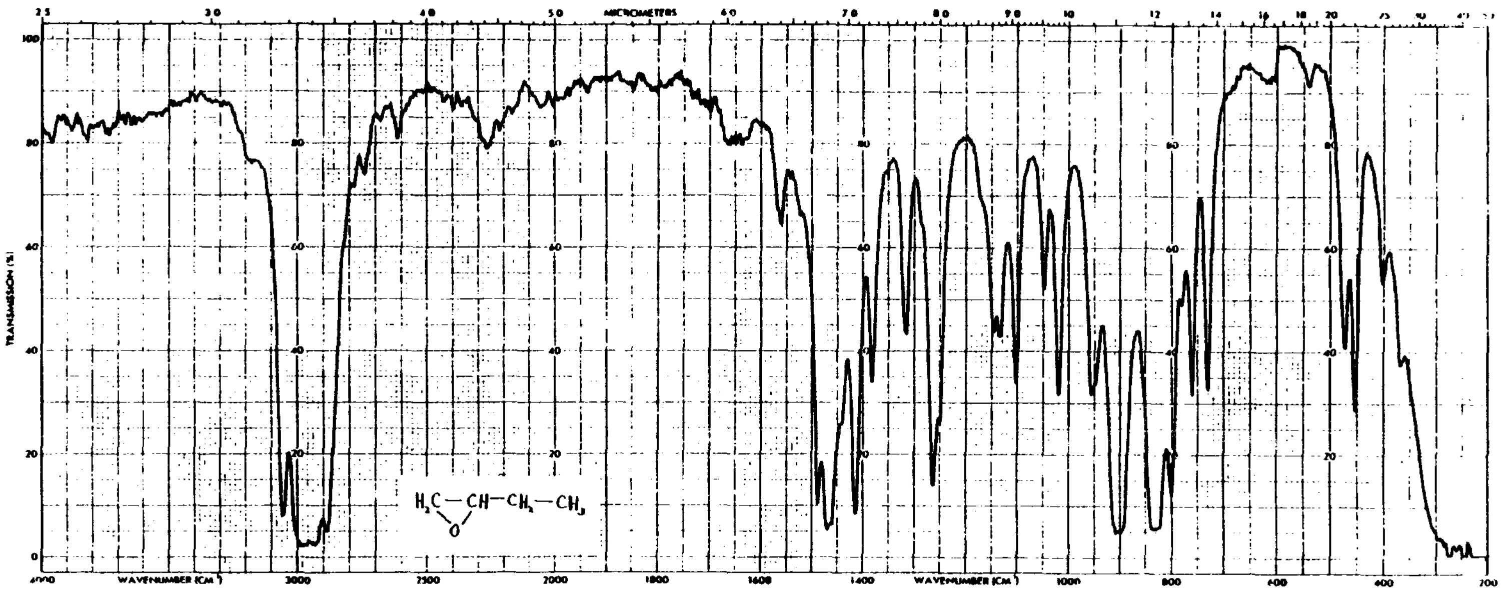


FIGURE 3. INFRARED ABSORPTION SPECTRUM OF 1,2-EPOXYBUTANE (LOT NO. RR810402)

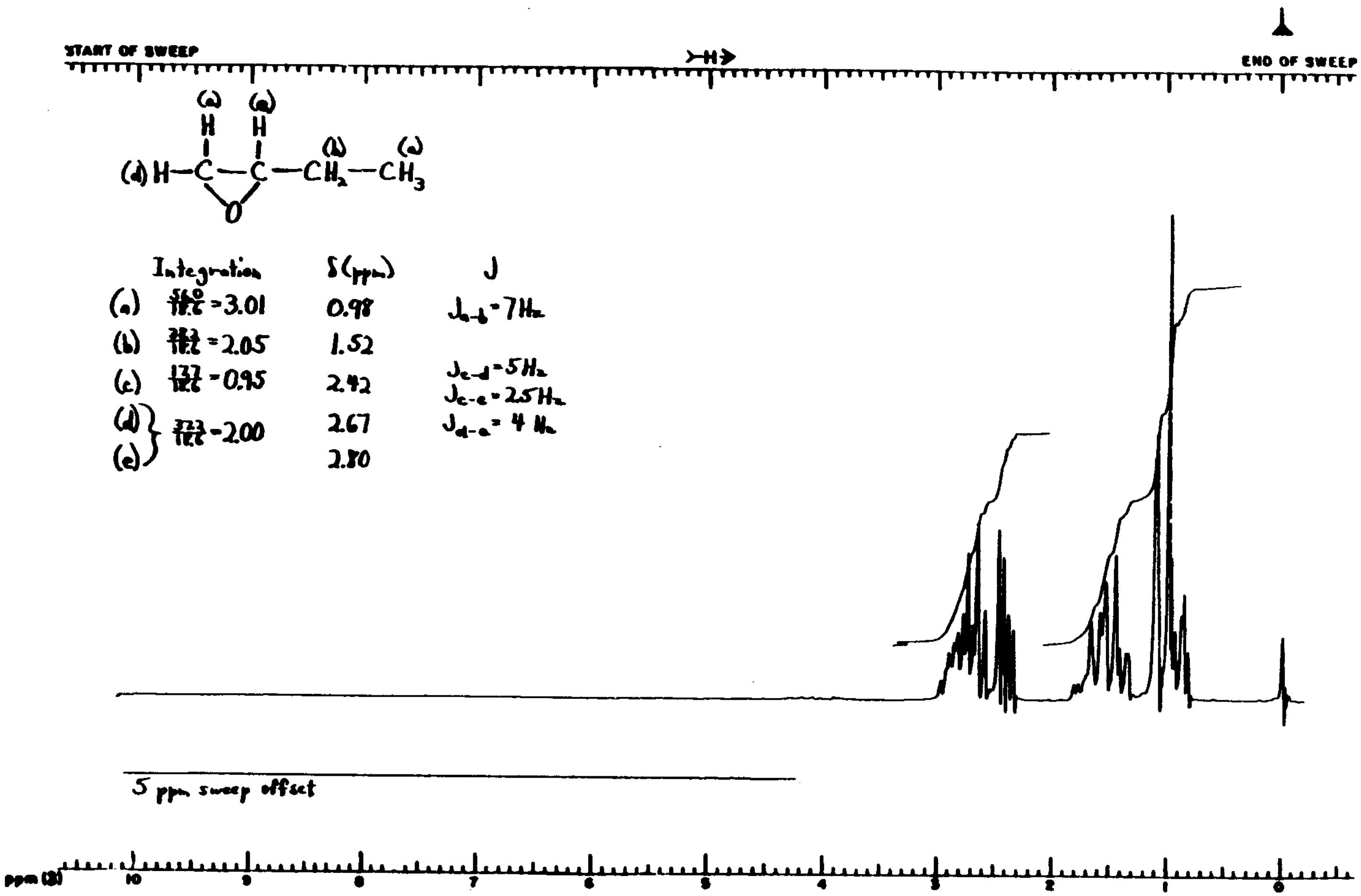


FIGURE 4. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF 1,2-EPOXYBUTANE (LOT NO. RR810402)

GENERATION AND MEASUREMENT OF CHAMBER CONCENTRATIONS

Vapor Generation System

The liquid to be vaporized was contained in a 1.6-liter stainless steel reservoir housed in a vapor hood in the exposure room (Figure 5). The liquid was pumped from this reservoir to a stainless steel cylinder covered with a glass fiber wick from which the liquid was vaporized (Decker et al., 1982) (Figure 6). An 80-watt heater and a temperature-sensing element were incorporated within the cylinder. The heater maintained the vaporizer at approximately 58° C. The surface temperature of the vaporizer was slightly lower. To minimize material loss due to condensation on duct walls, each cylindrical vaporizer was positioned in the fresh air duct leading directly into the exposure chamber.

Vapor Concentration Monitoring

Two online methods were used during the course of the 2-year studies to monitor the concentration of 1,2-epoxybutane in the chambers. A schematic diagram of the monitoring system is shown in Figure 7. Initially, a photoionization detector (model PI201, HNU Systems, Inc., Newton, Massachusetts) was used. On May 21, 1982, the photoionization detector was replaced by a gas chromatograph (HP-5710 or HP-5840) equipped with a flame ionization detector, a nickel column packed with 1% SP1000 on Carbopack B, and an automatic sampling valve. All exposure chambers and the room air were sampled approximately twice during each exposure hour. Starting December 22, 1981, a standard gas, 25 ppm propylene in air, was used to establish instrument performance. The calibration of the monitoring photoionization detector and gas chromatograph was confirmed and corrected as necessary by periodic assay of grab samples taken from the chambers and analyzed on a second gas chromatograph. Weekly mean exposure concentrations for the 2-year studies are presented in Figures 8 through 11. A summary of the chamber concentrations is presented in Table 3; Table 4 summarizes the distribution of the mean daily concentrations.

TABLE 3. SUMMARY OF CHAMBER CONCENTRATIONS IN THE TWO-YEAR INHALATION STUDIES OF 1,2-EPOXYBUTANE

Target Concentration (ppm)	Total Number of Readings	Mean Concentration (a) (ppm)
50	3,255	50 ± 5.6
100	3,315	99.6 ± 7.9
200	3,331	197.4 ± 15.2
400	3,366	399.0 ± 42.4

(a) Mean ± standard deviation

TABLE 4. DISTRIBUTION OF MEAN DAILY CONCENTRATIONS OF 1,2-EPOXYBUTANE DURING THE TWO-YEAR INHALATION STUDIES

Range of Concentration (percent of target)	Number of Days Mean Within Range			
	50 ppm	100 ppm	200 ppm	400 ppm
>150	0	0	0	0
130 - 150	13	0	0	
120 - 130	1	1	0	1
110 - 120	12	2	4	0
100 - 110	194	191	186	234
90 - 100	266	285	287	253
80 - 90	12	7	13	5
70 - 80	4	1	2	1
50 - 0	0	0	3	1
<50	0	0	0	0

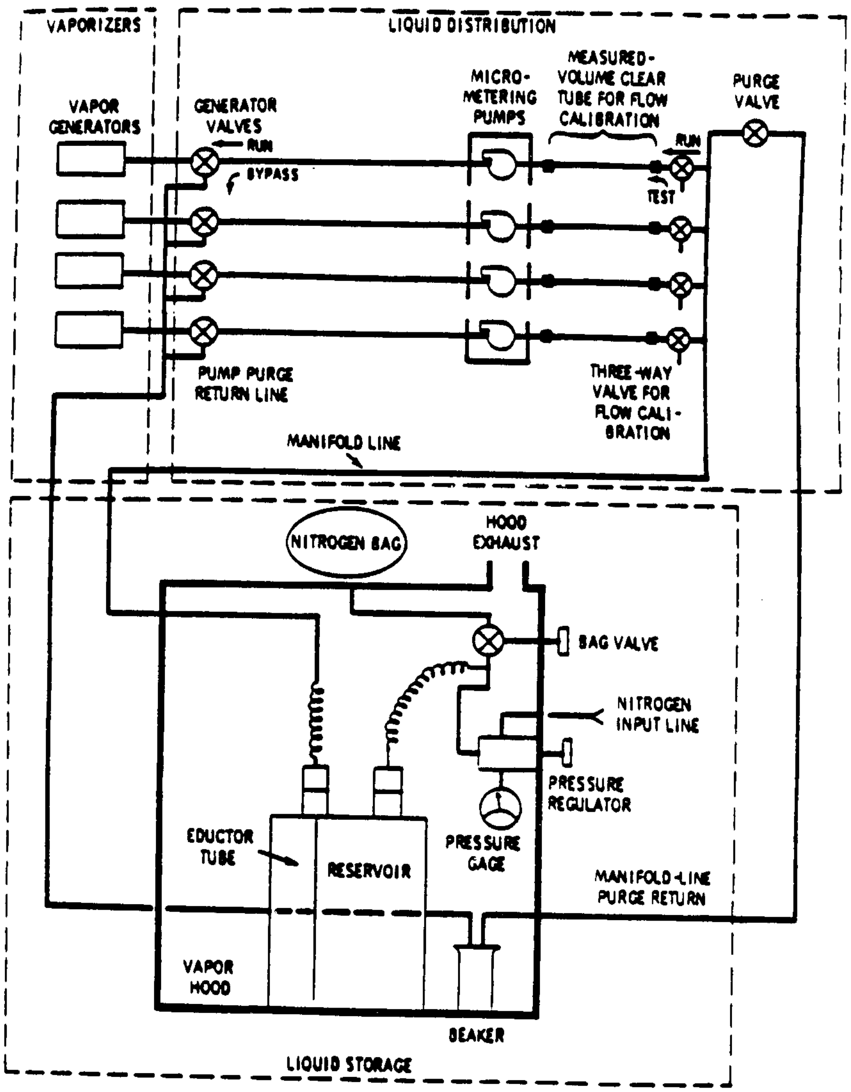


FIGURE 5. DIAGRAM OF THE 1,2-EPOXYBUTANE VAPOR GENERATION SYSTEM

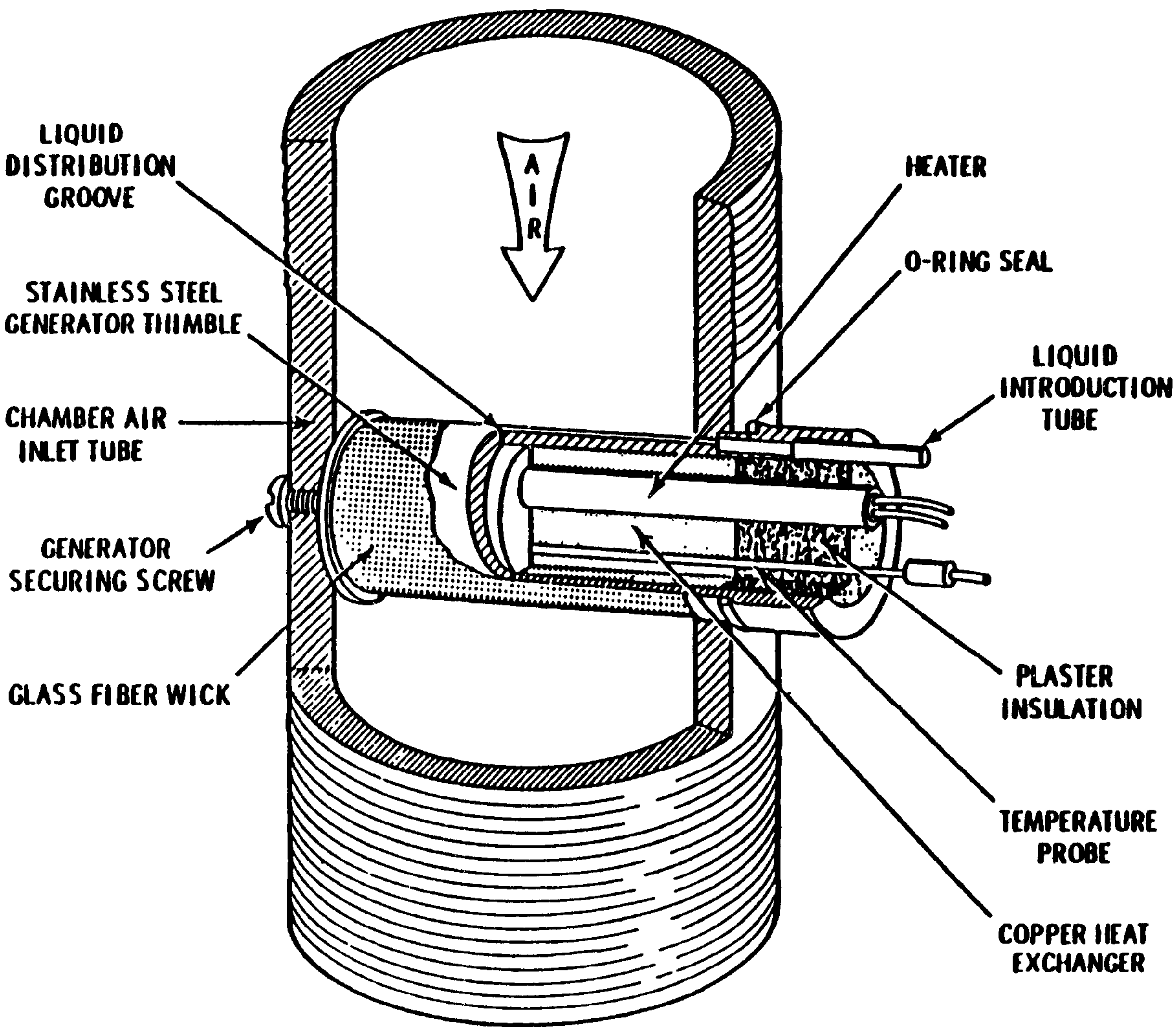


FIGURE 6. CUTAWAY DRAWING OF THE LIQUID VAPOR GENERATOR FOR 1,2-EPOXYBUTANE

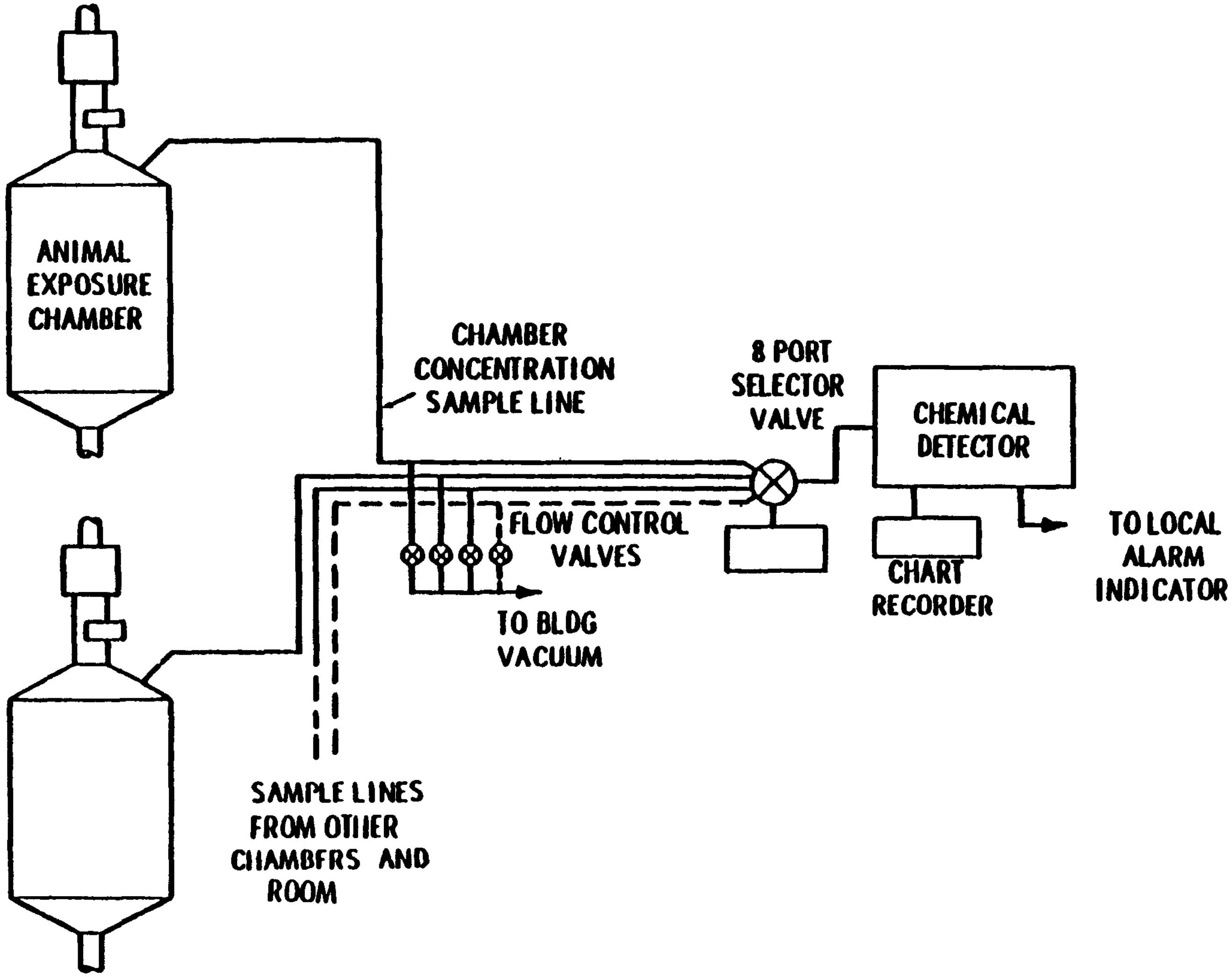


FIGURE 7. MONITORING SYSTEM FOR 1,2-EPOXYBUTANE

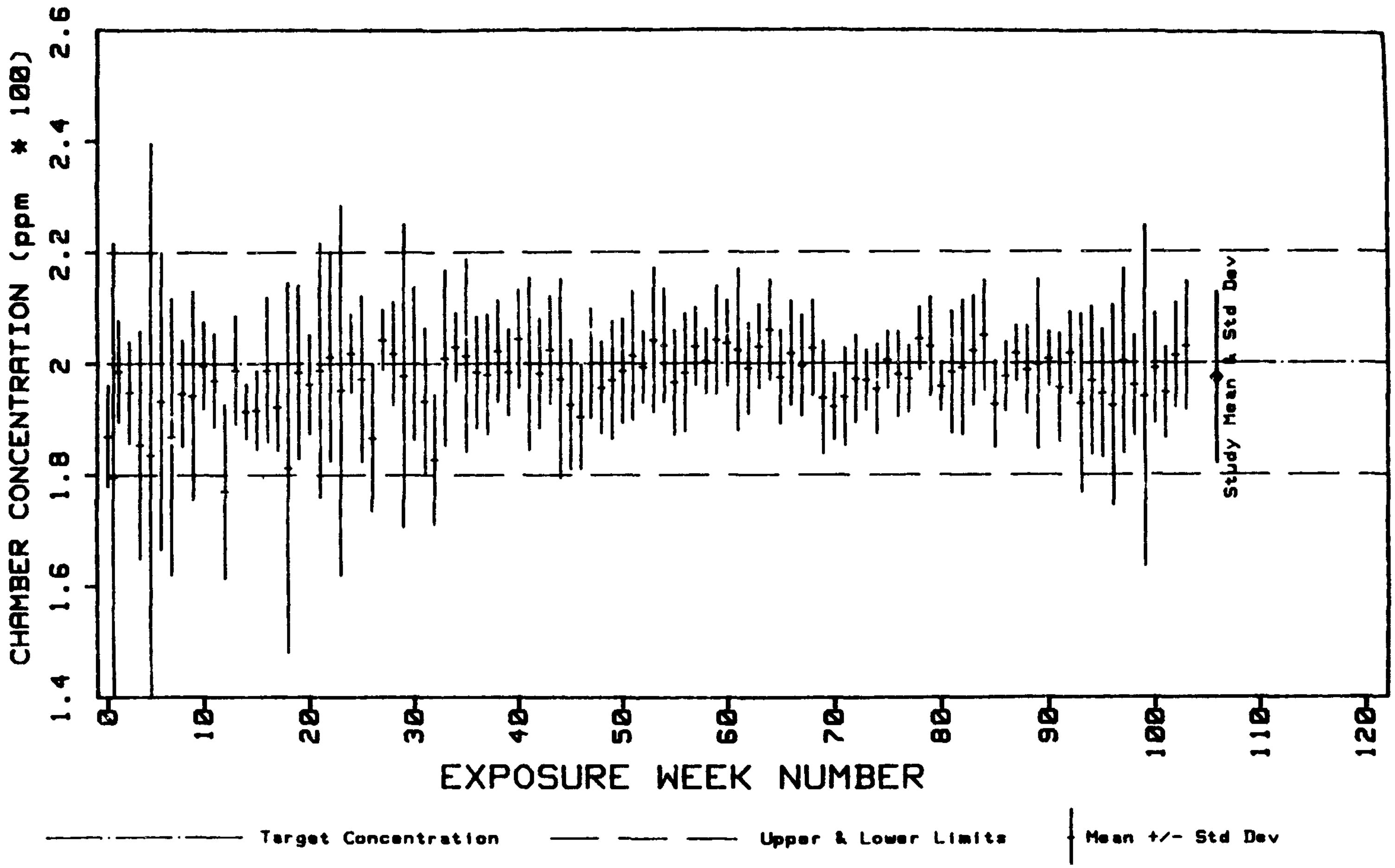


FIGURE 8. WEEKLY MEAN CONCENTRATION AND STANDARD DEVIATION IN THE 200-PPM RAT EXPOSURE CHAMBER IN THE TWO-YEAR INHALATION STUDIES OF 1,2-EPOXYBUTANE

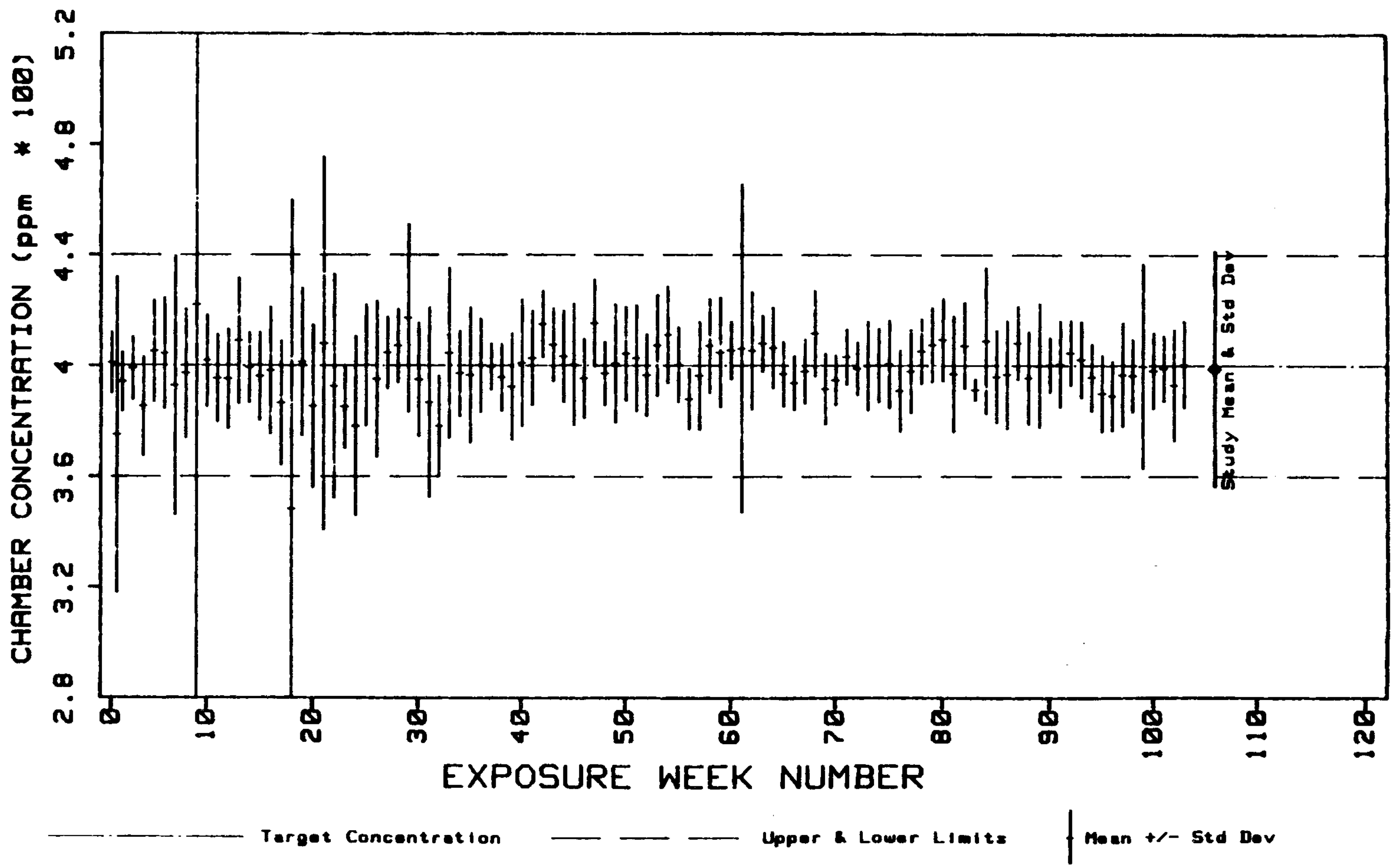


FIGURE 9. WEEKLY MEAN CONCENTRATION AND STANDARD DEVIATION IN THE 400-PPM RAT EXPOSURE CHAMBER IN THE TWO-YEAR INHALATION STUDIES OF 1,2-EPOXYBUTANE

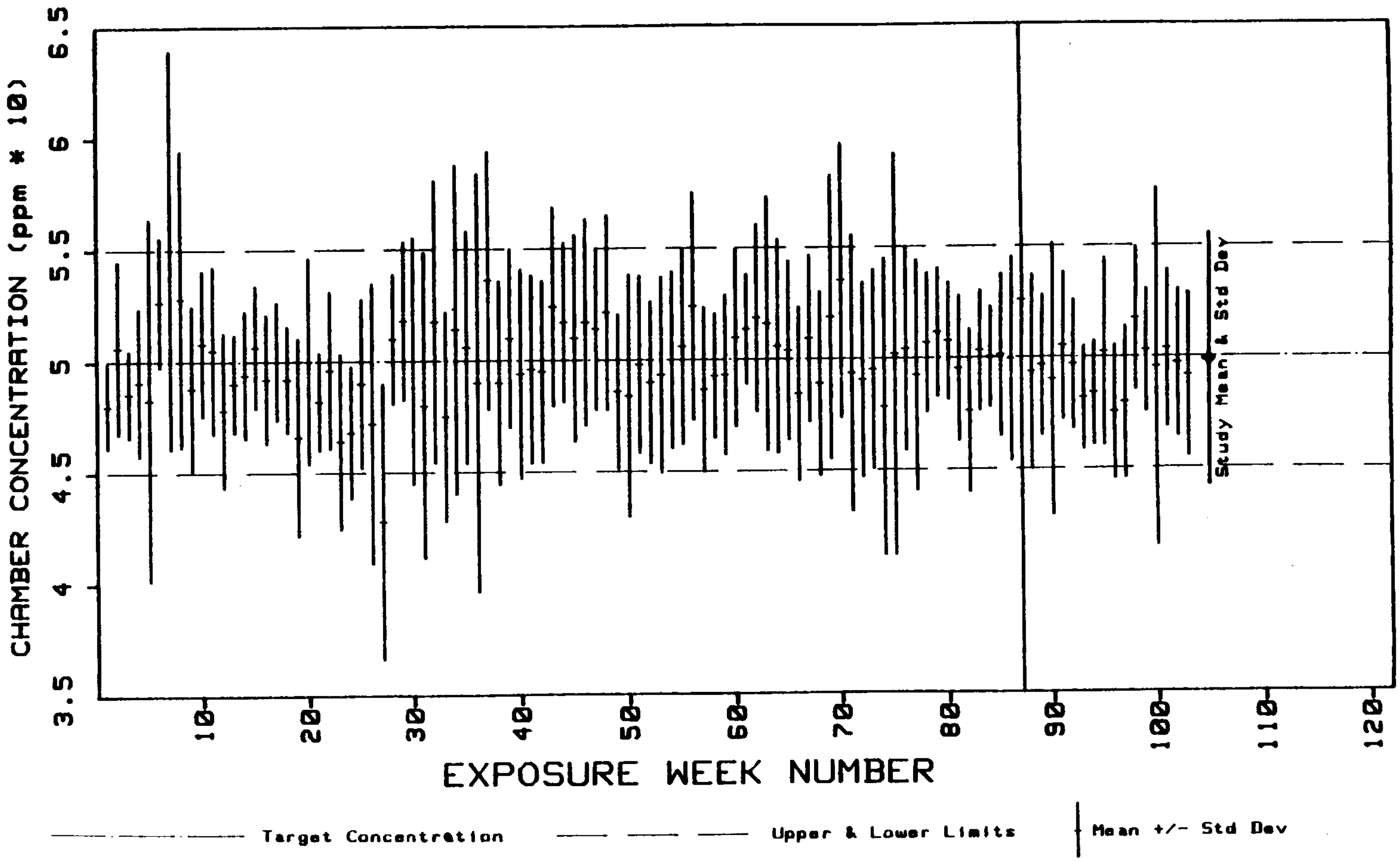


FIGURE 10. WEEKLY MEAN CONCENTRATION AND STANDARD DEVIATION IN THE 50-PPM MOUSE EXPOSURE CHAMBER IN THE TWO-YEAR INHALATION STUDIES OF 1,2-EPOXYBUTANE

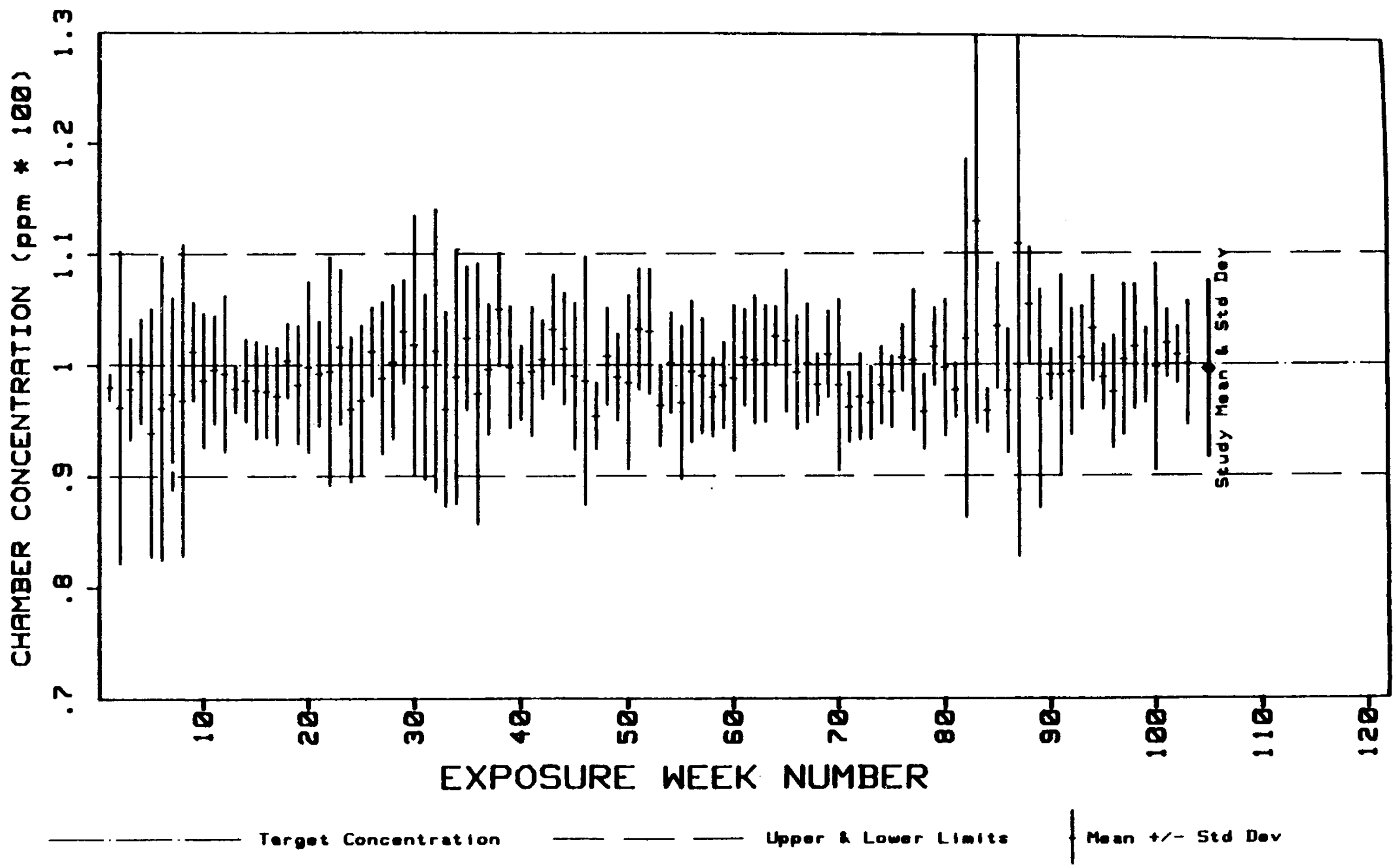


FIGURE 11. WEEKLY MEAN CONCENTRATION AND STANDARD DEVIATION IN THE 100-PPM MOUSE EXPOSURE CHAMBER IN THE TWO-YEAR INHALATION STUDIES OF 1,2-EPOXYBUTANE

Vapor Concentration Uniformity in Chamber

Uniformity of vapor concentration in each exposure chamber was measured with a portable photoionization detector periodically throughout the studies. The data showed that when expressed as a percentage of the normalized average concentration of all 12 sampling positions, the standard deviation did not exceed 5% for all but two measurements. (For those two measurements, the standard deviation was within 10%.)

Degradation Study of 1,2-Epoxybutane in Chamber

Samples of the atmosphere in the 1,2-epoxybutane exposure chamber were examined for the occurrence of potential degradation products, specifically 1,2-butandiol. Through the use of a Hewlett Packard model 5840A gas chromatograph equipped with a flame ionization detector and a 6 ft × 4 mm ID glass column packed with 10% Carbowax 20M on 80/100 Chromosorb WAW, a single homogeneous peak was observed; no evidence for any degradation was detected. It is concluded from this study that the 1,2-epoxybutane vapor generated during these studies was at least 99% pure.

SINGLE-EXPOSURE STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and observed for 22-23 days before the studies began. The animals were 7-9 weeks old when placed on study. A high exposure concentration of 8,000 ppm (target concentration) was selected based on an estimate of LC$_{100}$ of 8,000 ppm in rats (Weil et al., 1963). Mice were exposed at 4,000 ppm 1 day earlier than mice at the other exposure concentrations, and because all mice died at this concentration, mice were not included in the 8,000-ppm (target concentration) groups.

Groups of five rats and mice of each sex were exposed for 4 hours to air containing 1,2-epoxybutane concentrations of 398, 721, 1,420, 2,050, and (for rats only) 6,550 ppm. These concentrations were lower than the target concentrations of 500, 1,000, 2,000, or 4,000 ppm because of a malfunctioning detector. Controls were not used. Animals were weighed before exposure and were observed three times per day throughout the 14-day observation period. Necropsies were not performed on the animals. Details of animal maintenance are presented in Table 5.

FOURTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and observed for 27 days before being placed on study. The animals were 8-10 weeks old when the studies began.

Groups of five rats and mice of each sex were exposed to air containing 1,2-epoxybutane at target concentrations of 0, 400, 800, 1,600, 3,200, or 6,400 ppm for 6 hours per day, 5 days per week for 14 days (10 exposures). (Although the results of the single-exposure studies suggested the use of lower concentrations in the 14-day studies in mice, a decision was made to use the same exposure concentrations for both species, so that all animals could be accommodated in the same exposure chambers.) Rats and mice were observed three times daily and were weighed before exposure, after 1 week, and at necropsy. A necropsy was performed on all animals. Details of animal maintenance are presented in Table 5.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to 1,2-epoxybutane and to determine the concentrations to be used in the 2-year studies.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories, observed for 20-21 days, and assigned to groups according to tables of random numbers. Feed was available ad libitum during nonexposure periods; water was available at all times.

Groups of 10 rats and 10 mice of each sex were exposed to air containing 1,2-epoxybutane at target concentrations of 0, 50, 100, 200, 400, or 800 ppm, 6 hours per day, 5 days per week for 13 weeks (65 exposures). Further experimental details are summarized in Table 5.

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE INHALATION STUDIES OF 1,2-EPOXYBUTANE

Single-Exposure Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN			
Size of Study Groups			
5 males and 5 females of each species	5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses			
Target--500, 1,000, 2,000, or 4,000 ppm rats and mice or 8,000 ppm (rats only) 1,2-epoxybutane by inhalation	Target--0, 400, 800, 1,600, 3,200, or 6,400 ppm 1,2-epoxybutane by inhalation	0, 50, 100, 200, 400, or 800 ppm 1,2-epoxybutane by inhalation	Rats--0, 200, or 400 ppm 1,2-epoxybutane by inhalation; mice--0, 50, or 100 ppm
Date of First Dose			
2/1/80 (1/31/80 for 4,000-ppm groups)	9/30/80	3/4/81	11/25/81
Date of Last Dose			
Not applicable	10/13/80	6/1/81	Rats--11/18/83; mice--11/11/83
Duration of Dosing			
Single 4-h exposure	6 h/d, 5 d/wk for 14 d for 10 exposures	6 h/d, 5 d/wk for 13 wk for 65 exposures	6 h/d, 5 d/wk for 103 wk (rats) or 102 wk (mice)
Type and Frequency of Observation			
Observed throughout exposure period and 3 × d thereafter for 14 d; weighed before exposure	Observed 3 × d during exposure period; weighed before exposure, after 1 wk, and at necropsy	Observed 2 × d; weighed on d 1, 1 × wk thereafter, and at necropsy	Observed 2 × d; weighed 1 × wk for 13 wk and 1 × mo thereafter; clinical exam 1 × mo
Necropsy and Histologic Examination			
No necropsy or histologic exam performed	Necropsy performed on all animals; tissues for the following animals examined histologically: rats--1 male at 3,200 ppm, 2 males and 2 females at 1,600 ppm, 1 male at 800 ppm; mice--2 males at 1,600 ppm, 2 males and 1 female at 800 ppm, 1 male at 400 ppm	Necropsy performed on all animals; all controls and the two highest dose groups examined histologically. Tissues examined: adrenal glands, brain, esophagus, gallbladder (mice), heart, kidneys, larynx, liver, lungs and mainstem bronchi, mandibular and mesenteric lymph nodes, nasal cavity and nasal turbinates, pancreas, parathyroids, pituitary gland, prostate or uterus/ovaries, salivary glands, skeletal muscle, skin with mammary gland, spleen, sternebrae or femur or vertebrae including marrow, stomach, thymus, thyroid gland, trachea, and urinary bladder	Necropsy and histologic exam performed on all animals; the following tissues examined: adrenal glands, brain, clitoral or preputial gland, colon, esophagus, gallbladder (mice), gross lesions and tissue masses, heart, kidneys, lungs and mainstem bronchi, mammary gland, mandibular lymph nodes, nasal cavity and nasal turbinates, pancreas, parathyroids, pituitary gland, prostate/testes/epididymis or ovaries/uterus, rectum, regional lymph nodes, salivary glands, skin, small intestine, spleen, sternebrae including marrow, stomach, thymus, thyroid gland, trachea, tracheobronchial lymph nodes, and urinary bladder
Strain and Species			
F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice
Animal Source			
Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)
Study Laboratory			
Battelle Pacific Northwest Laboratories	Battelle Pacific Northwest Laboratories	Battelle Pacific Northwest Laboratories	Battelle Pacific Northwest Laboratories

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE INHALATION STUDIES OF 1,2-EPOXYBUTANE (Continued)

Single-Exposure Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE			
Method of Animal Identification			
By cage number; no body mark identification	Ear tags	Ear tags	Ear tags
Time Held Before Study			
22-23 d	27 d	20-21 d	21 d
Age When Placed on Study			
Rats--7-8 wk; mice--7-9 wk	Rats--8-9 wk; mice--9-10 wk	Rats--7-8 wk; mice--8-9 wk	Same as 13-wk studies
Age When Killed			
14 d	Rats--10-11 wk; mice--11-12 wk	Rats--20-21 wk; mice--21-22 wk	Rats--112-113 wk; mice--112-113 wk
Necropsy Dates			
Not performed	10/14/80	6/3/81-6/5/81	Rats--11/28/83-11/30/83; mice--11/21/83-11/23/83
Method of Animal Distribution			
Assigned to groups according to tables of random numbers	Same as single-exposure studies	Same as single-exposure studies	Same as single-exposure studies
Feed			
NIH 07 Rat and Mouse Ration (Zeigler Bros., Gardners, PA); available ad libitum	Same as single-exposure studies	Same as single-exposure studies	Same as single-exposure studies
Water			
Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as single-exposure studies	Same as single-exposure studies	Same as single-exposure studies
Cages			
Stainless steel wire cages (Hanford Metal, Inc., Aberdeen, MD)	Same as single-exposure studies	Stainless steel wire bottom cages (Hazleton Systems, Inc., Aberdeen, MD)	Same as 13-wk studies
Animals per Cage			
1	1	1	1
Other Chemicals on Study in the Same Room			
None	None	1,3-Butadiene	Ethylene oxide; 1,3-butadiene
Animal Room Environment			
Temp--70°-75° F during exposure, 72°-76° F during nonexposure period; hum--62%-65% during exposure, 40%-60% during nonexposure period; fluorescent light 12h/d; 10 room air changes/h during exposure, 20 room air changes/h during nonexposure period	Temp--71°-77° F during exposure; hum--55%-75% during exposure; light and air flow same as single-exposure studies	Temp--73°-76° F during exposure (mean of 74.8° ± 1.1° F); hum--45%-55% during exposure; light and air flow same as single-exposure studies	Temp--generally 73°-80° F for rats, 71°-79° F for mice during exposure; mean of 72.5° ± 1.7° F during nonexposure periods; hum--rats: 40%-76%, mice: 43%-69% during exposure; mean of 43% during nonexposure periods; light and air flow same as single-exposure studies

Animals were checked twice per day; moribund animals were killed. Individual animal weights were recorded weekly. At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 5.

TWO-YEAR STUDIES

Study Design

Groups of 50 rats of each sex were exposed to air containing 1,2-epoxybutane at concentrations of 0 (chamber controls), 200, or 400 ppm, 6 hours per day, 5 days per week for 103 weeks. Groups of 50 mice of each sex were exposed to 1,2-epoxybutane at concentrations of 0, 50, or 100 ppm on the same schedule for 102 weeks. Actual concentrations are summarized in Tables 3 and 4 and Figures 8 to 11.

Source and Specifications of Animals

The male and female F344/N rats and B6C3F$_1$ (C57BL/6N, female × C3H/HeN MTV$^-$, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the Carcinogenesis Program. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Animals were shipped to the study laboratory at 4-6 weeks of age and were quarantined for 3 weeks. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rodents were placed on study at 7-9 weeks of age.

Animal Maintenance

All animals were housed individually in Hazleton chambers throughout the study. Feed and water were available ad libitum except during exposure periods; water was available at all times. Details of animal maintenance are given in Table 5. Serologic analyses were performed as described in Appendix F.

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded once per month. Individual body weights were recorded once per week for the first 13 weeks of the studies and once per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals including those found dead, unless they were excessively autolyzed or cannibalized, missexed, or found missing. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study.

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissues examined microscopically are listed in Table 5.

When the pathology evaluation was completed, the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assessment pathologist. The quality assessment report and slides were submitted to the Pathology Working Group (PWG) Chairperson, who reviewed all target tissues and those for which there was a disagreement between the laboratory and quality assessment pathologists.

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

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

Statistical Methods

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

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

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

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

For studies in which compound administration has little effect on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death. Continuity-corrected tests were used in the analysis of tumor incidence, and reported P values are one-sided.

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

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

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

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

III. RESULTS

RATS

SINGLE-EXPOSURE STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs
Survival
Pathology and Statistical Analyses of Results

MICE

SINGLE-EXPOSURE STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs
Survival
Pathology and Statistical Analyses of Results

SINGLE-EXPOSURE STUDIES

All rats exposed at 6,550 ppm died during the exposure period. No other deaths occurred. Final body weights were not taken, and necropsies were not performed. Clinical signs observed in males and females at 2,050 and 6,550 ppm were ocular discharge and dyspnea. Rats had signs of eye irritation during exposure at 1,400 ppm. A top exposure concentration of 6,400 ppm was selected for the 14-day studies in order to have an exposure concentration at which target organs could be identified.

FOURTEEN-DAY STUDIES

All rats exposed at 3,200 or 6,400 ppm and 2/5 female rats exposed at 1,600 ppm died before the end of the studies (Table 6). The final mean body weight of rats exposed at 800 or 1,600 ppm was 12% or 33% lower than that of the controls for males and 12% or 17% lower for females. Erratic movements and piloerection were compound-related effects in rats exposed at 1,600 ppm. Multifocal pulmonary hemorrhage of moderate severity was observed in 2/2 males and 1/2 females exposed at 1,600 ppm. Acute suppurative rhinitis of moderate severity was observed in 2/2 males and 2/2 females exposed at 1,600 ppm. Controls were not examined microscopically. Because of body weight effects and/or mortality at 1,600 ppm and above, the highest exposure concentration selected for the 13-week studies was 800 ppm.

TABLE 6. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FOURTEEN-DAY INHALATION STUDIES OF 1,2-EPOXYBUTANE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
0	5/5	176 ± 4	226 ± 6	+50 ± 5	--
400	5/5	164 ± 2	210 ± 4	+46 ± 3	93
800	5/5	177 ± 5	199 ± 5	+22 ± 4	88
1,600	5/5	177 ± 9	151 ± 13	−26 ± 7	67
3,200	(d) 0/5	182 ± 4	(e)	(e)	(e)
6,400	(f) 0/5	173 ± 7	(e)	(e)	(e)
FEMALE					
0	5/5	132 ± 2	155 ± 2	+23 ± 1	--
400	5/5	127 ± 3	144 ± 2	+17 ± 1	93
800	5/5	129 ± 2	137 ± 4	+8 ± 2	88
1,600	(g) 3/5	131 ± 2	128 ± 4	−3 ± 2	83
3,200	(h) 0/5	122 ± 3	(e)	(e)	(e)
6,400	(f) 0/5	131 ± 5	(e)	(e)	(e)

(a) Number surviving/number initially in the group
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors of the group ± standard error of the mean
(d) Day of death: 1,1,2,2,2
(e) No data are reported due to the 100% mortality in this group.
(f) Day of death: all 1
(g) Day of death: 10,12
(h) Day of death: 2,2,2,2,3

THIRTEEN-WEEK STUDIES

No compound-related deaths occurred (Table 7). The final mean body weight of rats exposed at 800 ppm was 23% lower than that of the controls for males and 16% lower for females. No compound-related clinical signs were observed. Liver weight to body weight ratios were similar in dosed and control rats (Table 8). Inflammation of the nasal cavity was seen in all rats that received 1,2-epoxybutane at 800 ppm but not at lower concentrations. The inflammation was present primarily in the dorsal and lateral portions of the nasal cavity and affected the respiratory and olfactory epithelium. The lesion was characterized by lymphocytic and neutrophilic infiltration of the mucosa and accumulation of purulent exudate in the lumen of the nasal cavity, with focal loss of epithelial cells from the mucosa.

Dose Selection Rationale: Because of the lower body weight gain and nasal cavity inflammation at 800 ppm, 1,2-epoxybutane concentrations selected for rats for the 2-year studies were 200 and 400 ppm .

TABLE 7. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK INHALATION STUDIES OF 1,2-EPOXYBUTANE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
0	10/10	164 ± 4	362 ± 5	+198 ± 3	--
50	10/10	161 ± 3	356 ± 7	+195 ± 5	98
100	10/10	161 ± 3	348 ± 5	+187 ± 5	96
200	10/10	158 ± 4	355 ± 7	+197 ± 5	98
400	10/10	159 ± 3	344 ± 6	+185 ± 4	95
800	10/10	163 ± 3	277 ± 6	+114 ± 7	77
FEMALE					
0	10/10	127 ± 3	199 ± 4	+72 ± 2	--
50	10/10	129 ± 3	200 ± 4	+71 ± 3	101
100	(d) 9/10	128 ± 3	207 ± 3	+78 ± 2	104
200	10/10	130 ± 2	205 ± 4	+75 ± 4	103
400	10/10	127 ± 2	199 ± 4	+72 ± 3	100
800	10/10	128 ± 3	168 ± 3	+40 ± 2	84

(a) Number surviving/number initially in the group
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors of the group ± standard error of the mean
(d) Week of death: 11

TABLE 8. ABSOLUTE AND RELATIVE LIVER WEIGHTS OF RATS IN THE THIRTEEN-WEEK INHALATION STUDIES OF 1,2-EPOXYBUTANE (a)

Concentration (ppm)	No. Examined	Necropsy Body Weight (grams)	Liver Weight (mg)	Liver Weight/ Necropsy Body Weight Ratio (mg/g)
MALE				
0	10	362 ± 16	13,685 ± 1,637	37.8 ± 4.14
50	10	356 ± 21	14,446 ± 1,369	40.7 ± 3.78
100	10	348 ± 17	14,236 ± 1,360	41.0 ± 3.21
200	10	355 ± 22	14,354 ± 1,347	40.3 ± 1.78
400	10	344 ± 20	13,697 ± 1,940	39.8 ± 4.71
800	10	(b) 277 ± 20	(b) 11,400 ± 1,422	41.0 ± 3.56
FEMALE				
0	10	199 ± 12	7,300 ± 678	36.6 ± 2.81
50	10	200 ± 13	7,383 ± 891	36.9 ± 3.57
100	9	207 ± 8	7,831 ± 749	37.8 ± 3.31
200	10	205 ± 12	7,931 ± 660	38.8 ± 2.45
400	10	199 ± 12	7,370 ± 833	37.1 ± 4.13
800	10	(b) 168 ± 8	(c) 6,236 ± 682	37.1 ± 3.15

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

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of exposed and control male rats were similar until week 86; thereafter, mean body weights of high dose male rats were 4%-8% lower than those of the controls (Table 9 and Figure 12). Mean body weights of high dose female rats were 5%-10% lower than those of the controls after week 22. No compound-related clinical signs were observed in either males or females.

TABLE 9. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR INHALATION STUDIES OF 1,2-EPOXYBUTANE

Weeks on Study	Control		200 ppm			400 ppm		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE								
0	191	50	190	99	50	191	100	50
1	227	50	233	103	50	232	102	50
2	244	50	252	103	50	249	102	50
3	261	50	268	103	50	269	103	50
4	272	50	280	103	50	280	103	50
5	282	50	289	102	50	290	103	50
6	294	50	301	102	50	300	102	50
7	303	50	314	104	50	309	102	50
8	314	50	321	102	50	320	102	50
9	320	50	334	104	50	327	102	50
10	329	50	343	104	50	335	102	50
11	341	50	353	104	50	345	101	50
12	352	50	363	103	50	356	101	50
13	360	50	372	103	50	359	100	50
17	382	50	393	103	50	386	101	50
22	409	50	418	102	50	409	100	50
25	416	50	426	102	50	415	100	50
30	431	50	434	101	50	428	99	50
34	442	50	445	101	50	439	99	50
38	447	50	455	102	50	447	100	50
43	454	50	456	100	50	451	99	50
47	462	49	464	100	50	458	99	50
51	467	49	471	101	49	463	99	50
56	470	49	476	101	49	467	99	50
60	478	49	478	100	49	469	98	50
65	487	49	484	99	49	474	97	49
69	484	49	487	101	49	478	99	49
73	492	48	489	99	49	476	97	49
77	489	48	483	99	47	470	96	45
81	484	48	474	98	45	469	97	45
86	486	45	479	99	40	463	95	44
90	483	42	470	97	37	455	94	42
94	480	39	458	95	33	447	93	38
98	472	37	452	96	29	435	92	34
105	446	30	423	95	18	427	96	23
FEMALE								
0	137	50	136	99	50	134	98	50
1	151	50	157	104	49	151	100	50
2	162	50	162	100	49	157	97	50
3	170	50	168	99	49	164	96	50
4	175	50	179	102	49	172	98	50
5	179	50	181	101	49	175	98	50
6	187	50	186	99	49	180	96	50
7	185	50	191	103	49	183	99	50
8	191	50	198	104	49	189	99	50
9	196	50	202	103	49	194	99	50
10	197	50	204	104	49	197	100	50
11	203	50	208	102	49	195	96	50
12	207	50	211	102	49	202	98	50
13	208	50	213	102	49	200	96	50
17	219	50	223	102	49	213	97	50
22	233	50	232	100	49	221	95	49
25	239	50	240	100	49	226	95	49
30	249	50	247	99	49	233	94	49
34	256	50	256	100	48	243	95	49
38	264	50	263	100	48	248	94	49
43	271	50	264	97	48	254	94	49
47	284	50	278	98	48	260	92	49
51	297	50	288	97	47	272	92	49
56	298	50	301	101	47	279	94	48
60	311	50	308	99	47	285	92	48
65	323	50	315	98	47	297	92	48
69	328	50	327	100	45	305	93	48
73	335	50	333	99	42	309	92	47
77	342	49	332	97	42	308	90	43
81	345	47	333	97	42	315	91	42
86	347	44	335	97	36	320	92	40
90	347	43	331	95	34	322	93	38
94	343	40	337	98	27	315	92	36
98	345	36	325	94	25	319	92	30
105	342	32	317	93	22	311	91	22

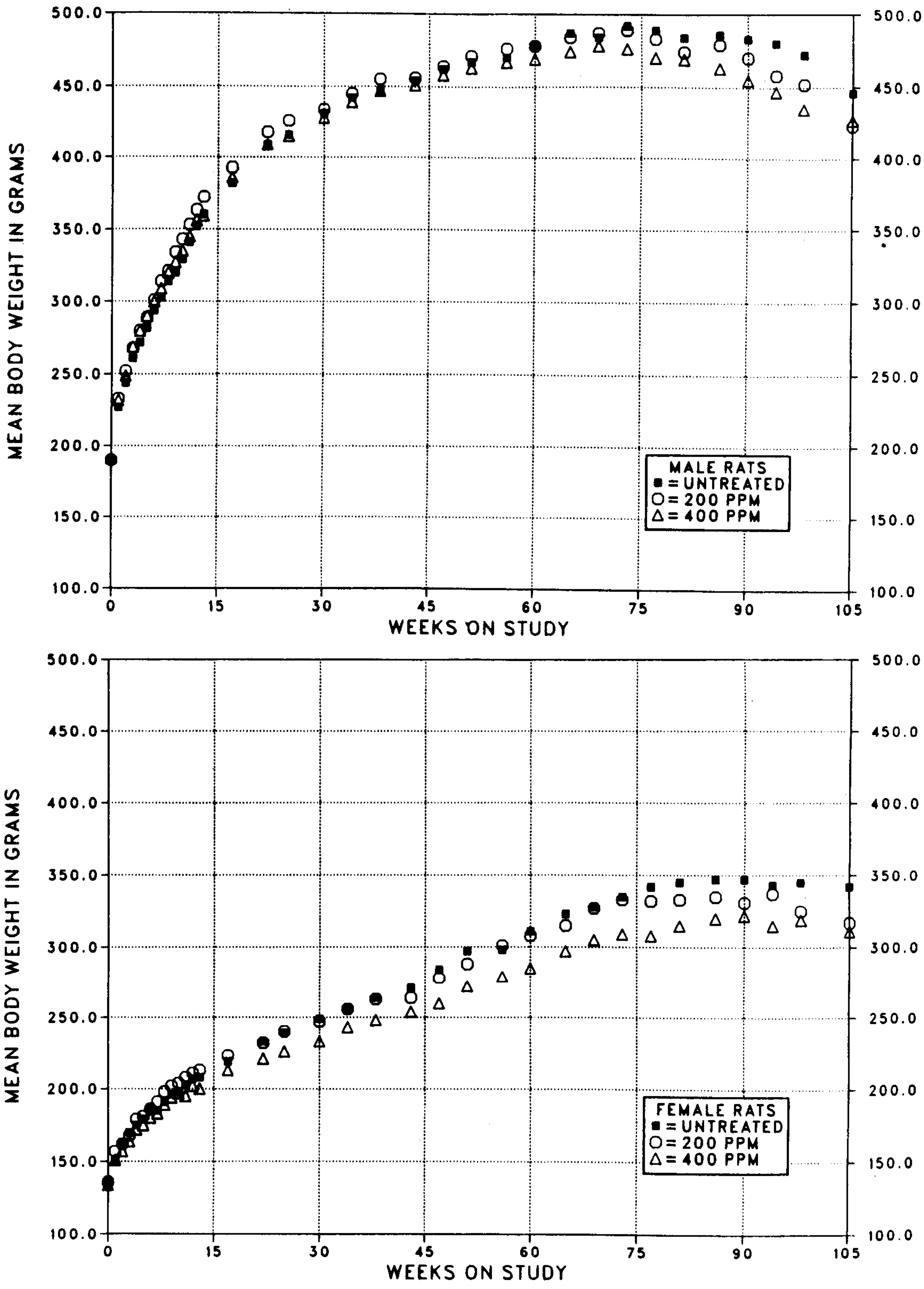


FIGURE 12. GROWTH CURVES FOR RATS EXPOSED TO 1,2-EXOPYBUTANE BY INHALATION FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats exposed to 1,2-epoxybutane by inhalation at the concentrations used in these studies and for controls are shown in Table 10 and in the Kaplan and Meier curves in Figure 13. The survival of the low dose groups of both male (after week 101) and female (after week 90) rats was significantly lower than that of the control groups.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the nasal cavity, lung, hematopoietic system, thyroid gland, anterior pituitary gland, and preputial gland.

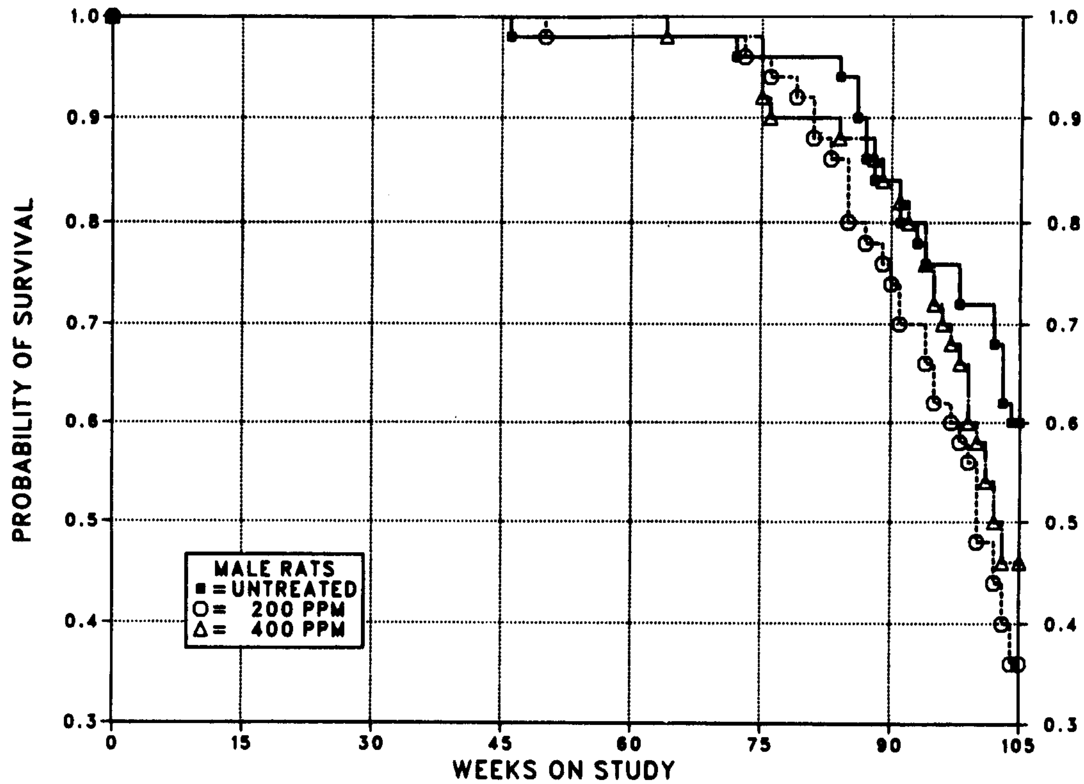
Lesions in male rats are summarized in Appendix A. Histopathologic findings on neoplasms are summarized in Table A1. Table A2 gives the survival and tumor status for individual male rats. Table A3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5%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

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

TABLE 10. SURVIVAL OF RATS IN THE TWO-YEAR INHALATION STUDIES OF 1,2-EPOXYBUTANE

	Control	200 ppm	400 ppm
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	20	32	27
Killed at termination	30	18	23
Survival P values (c)	0.207	0.024	0.225
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	18	29	27
Accidentally killed	0	0	1
Killed at termination	32	21	22
Survival P values (c)	0.098	0.019	0.092

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



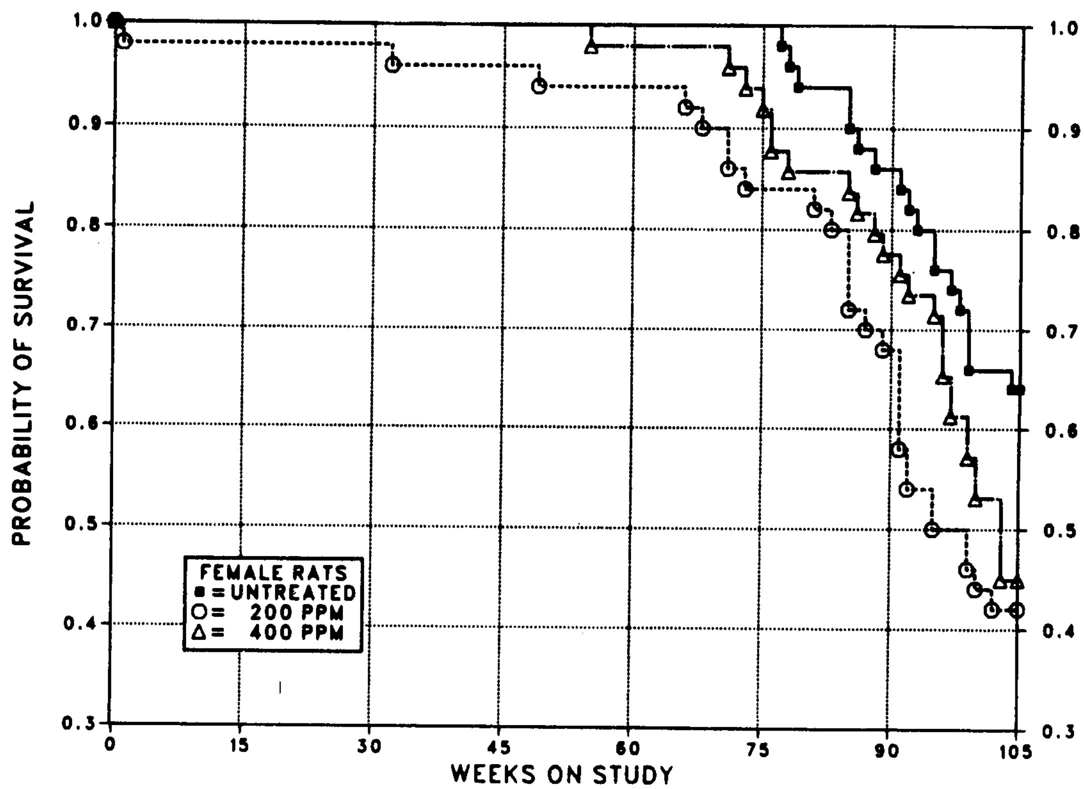


FIGURE 13. KAPLAN-MEIER SURVIVAL CURVES FOR RATS EXPOSED TO 1,2-EPOXYBUTANE BY INHALATION FOR TWO YEARS

Nasal Cavity: Suppurative and serous inflammation, hyperplasia of the respiratory epithelium, and squamous metaplasia were observed at increased incidences in exposed male and female rats (Table 11). Suppurative inflammation was characterized by the presence of neutrophils within the nasal cavity and mucosa; serous inflammation consisted of an eosinophilic proteinaceous material containing few inflammatory cells within the lumen of the nasal cavity. Other inflammatory lesions with lymphocyte and macrophage infiltrates were diagnosed as unspecified inflammation. Epithelial hyperplasia consisted of diffuse crowding of epithelial cells and increased thickness of the respiratory epithelium. In focal areas, nodular proliferation of respiratory epithelium formed glandlike structures that were diagnosed as adenomatous hyperplasia. Squamous metaplasia was a focal or multifocal lesion that occurred frequently within the respiratory epithelium, especially in the anterior section of the nasal cavity. Atrophy of the olfactory sensory epithelium was observed at increased incidences in exposed male and female rats. Hyperostosis of the nasal turbinate bone, consisting of a periosteal cell proliferation and new bone formation, was observed at increased frequency in high dose male rats.

The incidence of papillary adenomas in high dose male rats was significantly greater than that in the controls (Table 12). These tumors were exophytic papillary growths of a cuboidal to columnar nonciliated epithelium which were attached to the underlying mucosa by thin stalks or broad bases. There was no evidence of local invasive growth by these adenomas. Papillary adenomas were observed in two high dose female rats.

Lung: Alveolar/bronchiolar carcinomas and alveolar/bronchiolar adenomas or carcinomas (combined) in male rats occurred with significant positive trends; the incidences in the high dose group were significantly greater than those in the controls (Table 13). The incidences of adenomas or carcinomas (combined) in female rats were as follows: control, 2/50; low dose, 0/49; high dose, 1/50.

Hematopoietic System: The incidence of mononuclear cell leukemia was significantly greater by the life table test (P=0.011) in low dose (but not in high dose) male rats than that in the controls (control, 25/50; low dose, 31/50; high dose, 22/50).

TABLE 11. NUMBER OF RATS WITH LESIONS OF THE NASAL CAVITY OR OLFACTORY SENSORY EPITHELIUM IN THE TWO-YEAR INHALATION STUDIES OF 1,2-EPOXYBUTANE

Site/Lesion	Male 0	Male 200 ppm	Male 400 ppm	Female 0	Female 200 ppm	Female 400 ppm
Number examined	50	50	50	50	50	50
Nasal cavity						
Inflammation, NOS	9	36	42	25	32	43
Serous inflammation	2	28	36	0	18	31
Suppurative inflammation	10	37	49	6	26	45
Hyperostosis	0	2	11	0	2	16
Epithelial hyperplasia	8	38	46	5	29	40
Adenomatous hyperplasia	0	0	5	0	0	2
Squamous metaplasia	4	22	40	1	14	36
Papillary adenoma	0	0	7	0	0	2
Olfactory sensory epithelium						
Atrophy	0	18	12	0	13	8

TABLE 12. ANALYSIS OF NASAL CAVITY PAPILLARY ADENOMAS IN RATS IN THE TWO-YEAR INHALATION STUDIES OF 1,2-EPOXYBUTANE (a)

	Control	200 ppm	400 ppm
MALE (b)			
Overall Rates	0/50 (0%)	0/50 (0%)	7/50 (14%)
Adjusted Rates	0.0%	0.0%	24.2%
Terminal Rates	0/30 (0%)	0/18 (0%)	3/23 (13%)
Week of First Observation			97
Life Table Tests	P<0.001	(c)	P=0.005
Incidental Tumor Tests	P=0.002	(c)	P=0.015
FEMALE (d)			
Overall Rates	0/50 (0%)	0/50 (0%)	2/50 (4%)

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix A, Table A3 (footnotes).
(b) Historical incidence of nasal cavity neoplasms in chamber controls at study laboratory: 0/249; historical incidence in untreated controls in NTP studies: 2/1,977 (0.1%)
(c) No P value is reported because no tumors were observed in the 200-ppm and control groups.
(d) Historical incidence of nasal cavity neoplasms in chamber controls at study laboratory: 0/249; historical incidence in untreated controls in NTP studies: 1/2,021 (0.05%)

TABLE 13. ANALYSIS OF ALVEOLAR/BRONCHIOLAR LESIONS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE

	Control	200 ppm	400 ppm
Epithelial Hyperplasia			
Overall Rates	5/50 (10%)	5/50 (10%)	8/49 (16%)
Adenoma			
Overall Rates	0/50 (0%)	1/50 (2%)	1/49 (2%)
Carcinoma (a)			
Overall Rates	0/50 (0%)	1/50 (2%)	4/49 (8%)
Adjusted Rates	0.0%	5.6%	13.5%
Terminal Rates	0/30 (0%)	1/18 (6%)	2/23 (9%)
Week of First Observation		105	95
Life Table Tests	P=0.022	P=0.398	P=0.049
Incidental Tumor Tests	P=0.028	P=0.398	P=0.077
Adenoma or Carcinoma (b)			
Overall Rates	0/50 (0%)	2/50 (4%)	5/49 (10%)
Adjusted Rates	0.0%	8.9%	17.6%
Terminal Rates	0/30 (0%)	1/18 (6%)	3/23 (13%)
Week of First Observation		100	95
Life Table Tests	P=0.013	P=0.161	P=0.022
Incidental Tumor Tests	P=0.019	P=0.234	P=0.036

(a) Historical incidence in chamber controls at study laboratory (mean ± SD): 4/249 (2% ± 2%); historical incidence in untreated controls in NTP studies: 14/1,973 (0.7% ± 1%)
(b) Historical incidence in chamber controls at study laboratory (mean ± SD): 6/249 (2% ± 0.9%); historical incidence in untreated controls in NTP studies: 38/1,973 (2% ± 2%)

Thyroid Gland: Follicular cell adenomas or carcinomas (combined) in female rats occurred with a significant positive trend by the life table test (P=0.043) but not by the incidental tumor test (the more appropriate test for analysis of these nonfatal tumors); the incidences in the dosed groups were not significantly greater than that in the controls (control, 0/45; low dose, 1/48; high dose, 3/48). Follicular cell hyperplasia was not observed in either control or high dose rats.

Anterior Pituitary Gland: Adenomas in female rats occurred with a significant positive trend, and the incidence in the high dose group was significantly greater than that in the controls (Table 14). The incidences of adenomas or carcinomas (combined) are significant by the life table test but not by the incidental tumor test (the latter test is considered more appropriate for analysis of nonfatal tumors).

Preputial Gland: The incidences of adenomas, carcinomas, or squamous cell carcinomas (combined) in male rats (control, 3/50; low dose, 3/50; high dose, 8/50) were marginally significant by the life table trend test (P=0.050) but not by the incidental tumor trend test (the more appropriate test for analysis of these nonfatal tumors). The incidence in the high dose group was not significantly greater than that in the controls.

TABLE 14. ANALYSIS OF ANTERIOR PITUITARY GLAND LESIONS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE

	Control	200 ppm	400 ppm
Hyperplasia			
Overall Rates	10/49 (20%)	7/48 (15%)	4/48 (8%)
Adenoma			
Overall Rates	25/49 (51%)	26/48 (54%)	32/48 (67%)
Adjusted Rates	66.9%	77.3%	88.0%
Terminal Rates	19/31 (61%)	14/21 (67%)	17/21 (81%)
Week of First Observation	88	71	71
Life Table Tests	P=0.005	P=0.051	P=0.005
Incidental Tumor Tests	P=0.017	P=0.185	P=0.017
Carcinoma			
Overall Rates	6/49 (12%)	8/48 (17%)	3/48 (6%)
Adenoma or Carcinoma (a)			
Overall Rates	31/49 (63%)	34/48 (71%)	35/48 (73%)
Adjusted Rates	73.0%	91.3%	94.2%
Terminal Rates	20/31 (65%)	18/21 (86%)	19/21 (90%)
Week of First Observation	77	66	71
Life Table Tests	P=0.016	P=0.016	P=0.019
Incidental Tumor Tests	P=0.069	P=0.140	P=0.096

(a) Historical incidence in chamber controls at study laboratory (mean ± SD): 123/241 (51% ± 7%); historical incidence in untreated controls in NTP studies: 931/1,952 (48% ± 11%)

SINGLE-EXPOSURE STUDIES

All mice exposed at 2,050 ppm, 4/5 males and 4/5 females exposed at 1,420 ppm, and 1/5 males exposed at 398 ppm died before the end of the studies (Table 15). Final body weights were not taken, and necropsies were not performed. Dyspnea was seen in mice exposed at 2,050 ppm. During exposure, mice exposed at 1,420 ppm were restless and showed signs of eye irritation. Mice were housed in the same exposure chambers as rats.

FOURTEEN-DAY STUDIES

All mice exposed at concentrations of 1,600 ppm or higher and 1/5 males exposed at 800 ppm died before the end of the studies (Table 16). Clinical signs observed in mice at 800 ppm included dyspnea and listlessness on the first exposure day. The final mean body weights of mice exposed at 800 ppm were lower than the initial weights. Moderate nephrosis was observed in 2/2 males exposed at 1,600 ppm. Mild to slight nephrosis was observed in 2/2 males and 1/2 females exposed at 800 ppm. Controls were not examined microscopically. Because of mortality at 1,600 ppm and above, the highest exposure concentration selected for the 13-week studies was 800 ppm.

THIRTEEN-WEEK STUDIES

All mice exposed at 800 ppm died before the end of the studies (Table 17). Final mean body weights were not affected by exposure to 1,2-epoxybutane. Mice exposed at 800 ppm were listless during and after the first day of exposure; clinical signs were not seen at lower doses. The liver weight to body weight ratio of female mice that received 400 ppm was significantly lower than that of the controls (Table 18). Renal tubular necrosis was seen in 6/10 males and 8/10 females exposed at 800 ppm but not at lower exposure concentrations. Inflammation of the nasal turbinates was observed in all mice exposed at 200 ppm or higher, in 0/10 males and 7/10 females exposed at 100 ppm, and in none of the controls. Renal and upper respiratory tract changes were considered to be compound related.

TABLE 15. SURVIVAL OF MICE IN THE SINGLE-EXPOSURE INHALATION STUDIES OF 1,2-EPOXYBUTANE

Concentration (ppm)	Male (a)	Female (b)
398	(c) 4/5	5/5
721	5/5	5/5
1,420	(d) 1/5	(d) 1/5
2,050	(e) 0/5	(e) 0/5

(a) LC_{50} value by probit analysis: 944 ppm with a 95% confidence interval of 540-1,516 ppm
(b) LC_{50} value by the Spearman-Karber procedure: 1,123 ppm with a 95% confidence interval of 915-1,379 ppm
(c) Day of death: 5
(d) All deaths occurred within 2 hours of the end of exposure.
(e) All deaths occurred within 40 minutes of the end of exposure.

TABLE 16. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FOURTEEN-DAY INHALATION STUDIES OF 1,2-EPOXYBUTANE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
0	5/5	25.6 ± 0.5	27.4 ± 0.6	+1.8 ±0.4	--
400	5/5	24.2 ± 1.2	26.2 ± 1.1	+2.0 ±0.5	96.6
800	(d) 4/5	25.4 ± 0.4	24.8 ± 1.1	−1.0 ±0.9	90.5
1,600	(e) 0/5	27.4 ± 0.7	(f)	(f)	(f)
3,200	(e) 0/5	26.2 ± 0.4	(f)	(f)	(f)
6,400	(e) 0/5	22.6 ± 0.2	(f)	(f)	(f)
FEMALE					
0	5/5	21.6 ± 0.2	23.6 ± 0.2	+2.0 ±0.4	--
400	5/5	21.4 ± 0.4	22.6 ± 0.4	+1.2 ±0.8	95.8
800	5/5	21.2 ± 0.5	20.8 ± 0.7	−0.4 ±0.2	88.1
1,600	(e) 0/5	22.4 ± 0.7	(f)	(f)	(f)
3,200	(e) 0/5	19.2 ± 0.7	(f)	(f)	(f)
6,400	(e) 0/5	20.0 ± 0.0	(f)	(f)	(f)

(a) Number surviving/number initially in the group
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors of the group ± standard error of the mean
(d) Day of death: 3
(e) Day of death: all 1
(f) No data are reported due to the 100% mortality in this group.

TABLE 17. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK INHALATION STUDIES OF 1,2-EPOXYBUTANE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
0	10/10	23.8 ± 0.4	30.8 ± 0.8	+7.0 ± 0.6	--
50	(d) 8/10	22.5 ± 0.2	31.0 ± 1.1	+8.5 ± 1.1	100.6
100	10/10	24.0 ± 0.5	31.0 ± 0.4	+7.0 ± 0.4	100.6
200	10/10	24.1 ± 0.3	30.7 ± 0.9	+6.6 ± 0.7	99.7
400	10/10	22.2 ± 0.2	30.1 ± 0.3	+7.9 ± 0.2	99.7
800	(e) 0/10	22.4 ± 0.5	(f)	(f)	(f)
FEMALE					
0	10/10	19.6 ± 0.4	25.7 ± 0.5	+6.1 ± 0.6	--
50	10/10	19.9 ± 0.3	27.9 ± 0.4	+8.0 ± 0.5	108.6
100	10/10	20.0 ± 0.6	(g) 26.9 ± 0.4	+6.9 ± 0.4	104.7
200	10/10	20.1 ± 0.6	27.0 ± 0.8	+6.9 ± 0.9	105.1
400	10/10	19.7 ± 0.5	25.5 ± 0.5	+5.8 ± 0.2	99.2
800	(h) 0/10	18.2 ± 0.4	(f)	(f)	(f)

(a) Number surviving/number initially in the group
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors of the group ± standard error of the mean
(d) Week of death: 11,11
(e) Week of death: 1,1,1,1,2,2,2,2,2,11
(f) No data are reported due to the 100% mortality in this group.
(g) Final body weights were not recorded for two animals; reported final weights and weight change are based on eight animals.
(h) Week of death: 1,1,1,1,1,1,1,1,2,2

TABLE 18. ABSOLUTE AND RELATIVE LIVER WEIGHTS OF MICE IN THE THIRTEEN-WEEK INHALATION STUDIES OF 1,2-EPOXYBUTANE (a)

Concentration (ppm)	No. Examined	Necropsy Body Weight (grams)	Liver Weight (mg)	Liver Weight/ Necropsy Body Weight Ratio (mg/g)
MALE				
0	10	30.8 ± 2.6	1,808 ± 185	58.9 ± 5.79
50	8	31.0 ± 3.0	1,833 ± 170	59.5 ± 6.56
100	10	31.0 ± 1.2	1,644 ± 107	53.0 ± 2.43
200	10	30.7 ± 2.8	1,885 ± 239	61.5 ± 6.74
400	10	30.1 ± 1.0	(b) 1,503 ± 117	50.0 ± 4.24
FEMALE				
0	10	25.7 ± 1.6	1,505 ± 132	58.6 ± 3.25
50	10	(c) 27.9 ± 1.3	1,588 ± 150	56.9 ± 4.07
100	8	26.9 ± 1.1	1,482 ± 61	55.2 ± 2.13
200	10	27.0 ± 2.5	1,585 ± 157	58.9 ± 4.95
400	10	25.5 ± 1.6	(b) 1,254 ± 145	(b) 49.1 ± 3.54

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

Dose Selection Rationale: Because all mice exposed at 800 ppm died and because the respiratory tract lesions at 200 ppm and above were considered potentially life threatening, exposure concentrations selected for mice for the 2-year studies were 50 and 100 ppm 1,2-epoxybutane.

TWO-YEAR STUDIES

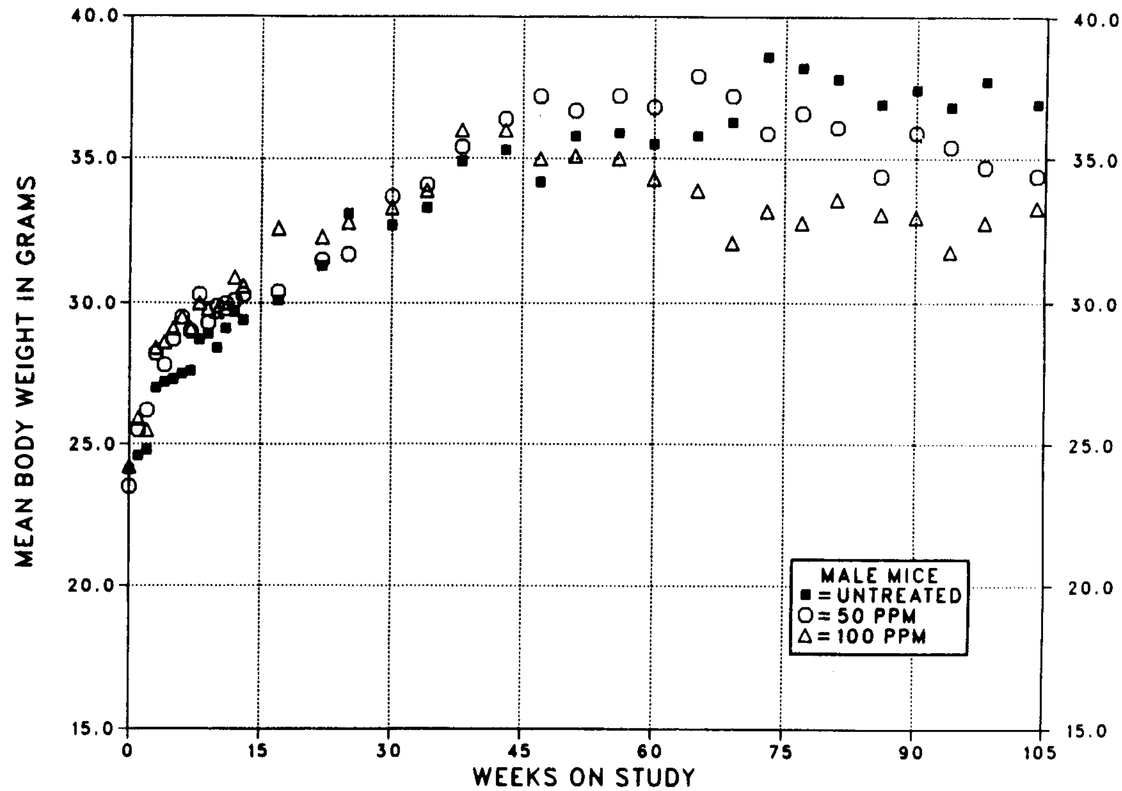
Body Weights and Clinical Signs

Mean body weights of high dose male mice were generally higher than those of the controls until week 47 and 10%-14% lower after week 69 (Table 19 and Figure 14). Mean body weights of low dose male mice were generally higher than those of the controls until week 69 and 4%-8% lower after week 86. Mean body weights of high dose female mice were 13%-23% lower than those of the controls after week 60. Mean body weights of low dose female mice were 12%-16% lower than those of the controls after week 73. Female mice at 100 ppm were inactive and listless during the last 2 months on study; no other dose-related clinical signs were observed in either males or females.

TABLE 19. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR INHALATION STUDIES OF 1,2-EPOXYBUTANE

Weeks on Study	Control Av. Wt. (grams)	Control No. of Survivors	50 ppm Av. Wt. (grams)	50 ppm Wt. (percent of controls)	50 ppm No. of Survivors	100 ppm Av. Wt. (grams)	100 ppm Wt. (percent of controls)	100 ppm No. of Survivors
MALE								
0	24.1	50	23.5	98	50	24.2	100	50
1	24.6	50	25.5	104	50	25.9	105	50
2	24.8	50	26.2	106	50	25.5	103	50
3	27.0	49	28.2	104	49	28.4	105	50
4	27.2	49	27.8	102	49	28.6	105	50
5	27.3	49	28.7	105	49	29.1	107	50
6	27.5	49	29.5	107	49	29.5	107	50
7	27.6	49	29.0	105	49	29.1	105	50
8	28.7	49	30.3	106	49	30.0	105	50
9	28.9	49	29.3	101	49	29.8	103	50
10	28.4	49	29.9	105	49	29.7	105	50
11	29.1	49	30.0	103	49	29.8	102	50
12	29.7	49	30.1	101	49	30.9	104	50
13	29.4	49	30.3	103	49	30.6	104	50
17	30.1	49	30.4	101	49	32.6	108	50
22	31.3	49	31.5	101	49	32.3	103	50
25	33.1	48	31.7	96	49	32.8	99	50
30	32.7	48	33.7	103	49	33.3	102	50
34	33.3	48	34.1	102	49	33.9	102	50
38	34.9	48	35.4	101	49	36.0	103	50
43	35.3	48	36.4	103	49	36.0	102	50
47	34.2	48	37.2	109	49	35.0	102	50
51	35.8	48	36.7	103	49	35.1	98	50
56	35.9	48	37.2	104	49	35.0	97	50
60	35.5	48	36.8	104	49	34.3	97	50
65	35.8	47	37.9	106	49	33.9	95	50
69	36.3	47	37.2	102	49	32.1	88	50
73	38.6	47	35.9	93	49	33.2	86	50
77	38.2	46	36.6	96	49	32.8	86	49
81	37.8	46	36.1	96	49	33.6	89	49
86	36.9	45	34.4	93	49	33.1	90	46
90	37.4	45	35.9	96	48	33.0	88	43
94	36.8	45	35.4	96	47	31.8	86	42
98	37.7	43	34.7	92	46	32.8	87	37
104	36.9	41	34.4	93	45	33.3	90	33
FEMALE								
0	19.7	50	20.2	103	50	19.7	100	50
1	20.2	50	20.6	102	50	22.2	110	50
2	22.1	50	21.1	95	50	20.8	94	50
3	22.2	49	22.5	101	50	23.3	105	49
4	23.7	49	23.3	98	50	24.2	102	49
5	24.1	49	25.0	104	50	25.3	105	49
6	24.8	49	25.2	102	50	25.8	104	49
7	24.2	49	24.8	102	50	25.1	104	49
8	25.3	49	26.4	104	50	26.5	105	49
9	25.9	49	26.4	102	50	26.5	102	49
10	25.8	49	26.6	103	50	26.9	104	49
11	25.8	49	26.9	104	50	26.3	102	49
12	26.3	49	26.3	100	50	26.2	100	49
13	25.6	49	26.2	102	49	26.7	104	49
17	27.3	49	27.1	99	49	27.4	100	49
22	27.2	49	28.6	105	49	28.0	103	49
25	28.6	49	28.2	99	49	28.8	101	49
30	28.7	49	29.2	102	49	29.8	104	49
34	28.8	49	30.4	106	49	29.6	103	49
38	30.0	49	30.5	102	49	29.5	98	49
43	30.3	48	30.3	100	49	30.2	100	49
47	30.4	48	30.6	101	49	29.7	98	49
51	31.6	48	31.0	98	49	28.8	91	49
56	32.1	48	30.4	95	48	28.5	89	47
60	32.2	48	30.7	95	48	28.1	87	45
65	33.2	48	30.0	90	48	27.7	83	43
69	33.1	48	31.6	95	48	28.0	85	40
73	34.2	47	30.2	88	46	28.3	83	38
77	34.6	43	30.0	87	45	28.0	81	32
81	35.8	40	30.2	84	42	28.0	78	30
86	33.6	38	29.5	88	41	28.1	84	26
90	35.4	34	31.0	88	38	27.4	77	17
94	34.7	33	29.9	86	36	27.8	80	14
98	35.1	31	29.9	85	31	27.5	78	10
104	34.3	29	29.9	87	25	29.9	87	(a) 8

(a) Nine survivors but only eight were weighed



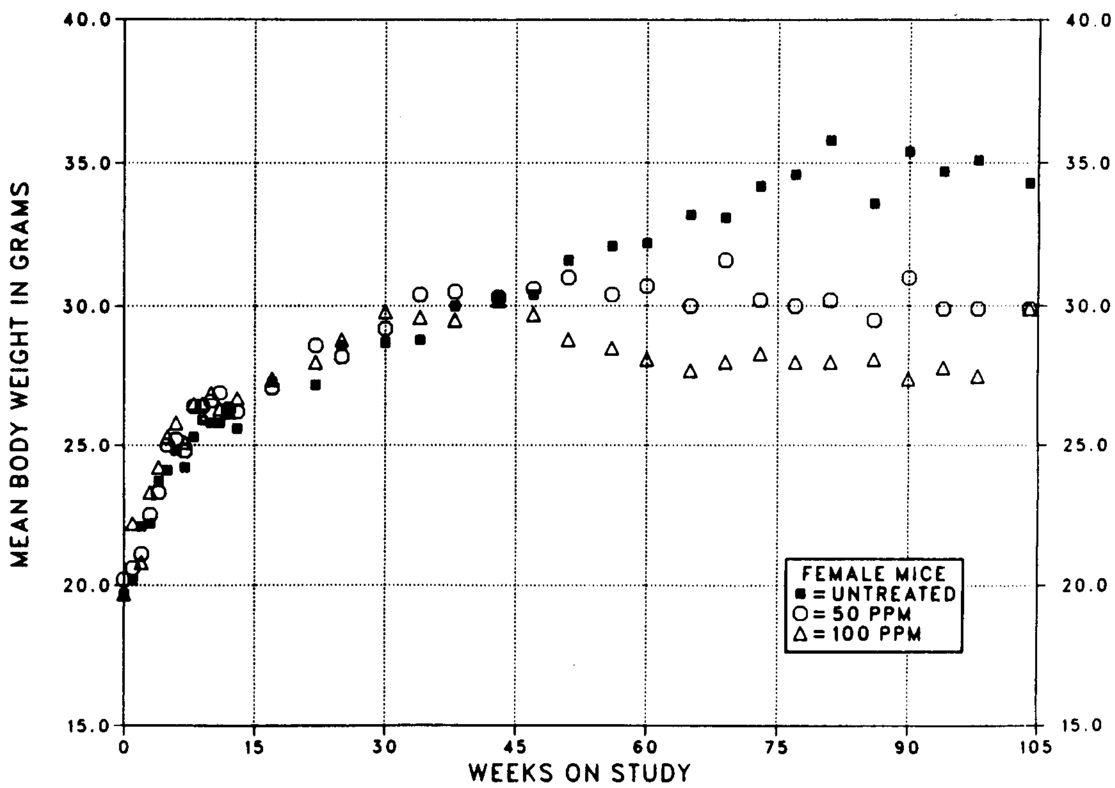


FIGURE 14. GROWTH CURVES FOR MICE EXPOSED TO 1,2-EPOXYBUTANE BY INHALATION FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice exposed to 1,2-epoxybutane by inhalation at the concentrations used in these studies and for controls are shown in Table 20 and in the Kaplan and Meier curves in Figure 15. The survival of the high dose female group was significantly lower than that of the controls after week 69. The survival of the high dose groups of males ($P=0.002$) and females ($P<0.001$) was significantly lower than that of the low dose groups.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the respiratory epithelium of the nasal cavity, nasal gland (Bowman's glands), nasolacrimal duct, olfactory sensory epithelium, ovary, uterus, and pituitary gland.

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

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

TABLE 20. SURVIVAL OF MICE IN THE TWO-YEAR INHALATION STUDIES OF 1,2-EPOXYBUTANE

	Control	50 ppm	100 ppm
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	9	3	17
Accidentally killed	0	1	0
Animals missexed	0	1	0
Killed at termination	41	45	33
Survival P values (c)	0.066	0.132	0.133
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	20	25	40
Accidentally killed	1	0	0
Animals missexed	0	0	1
Killed at termination	29	25	9
Survival P values (c)	<0.001	0.633	<0.001

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

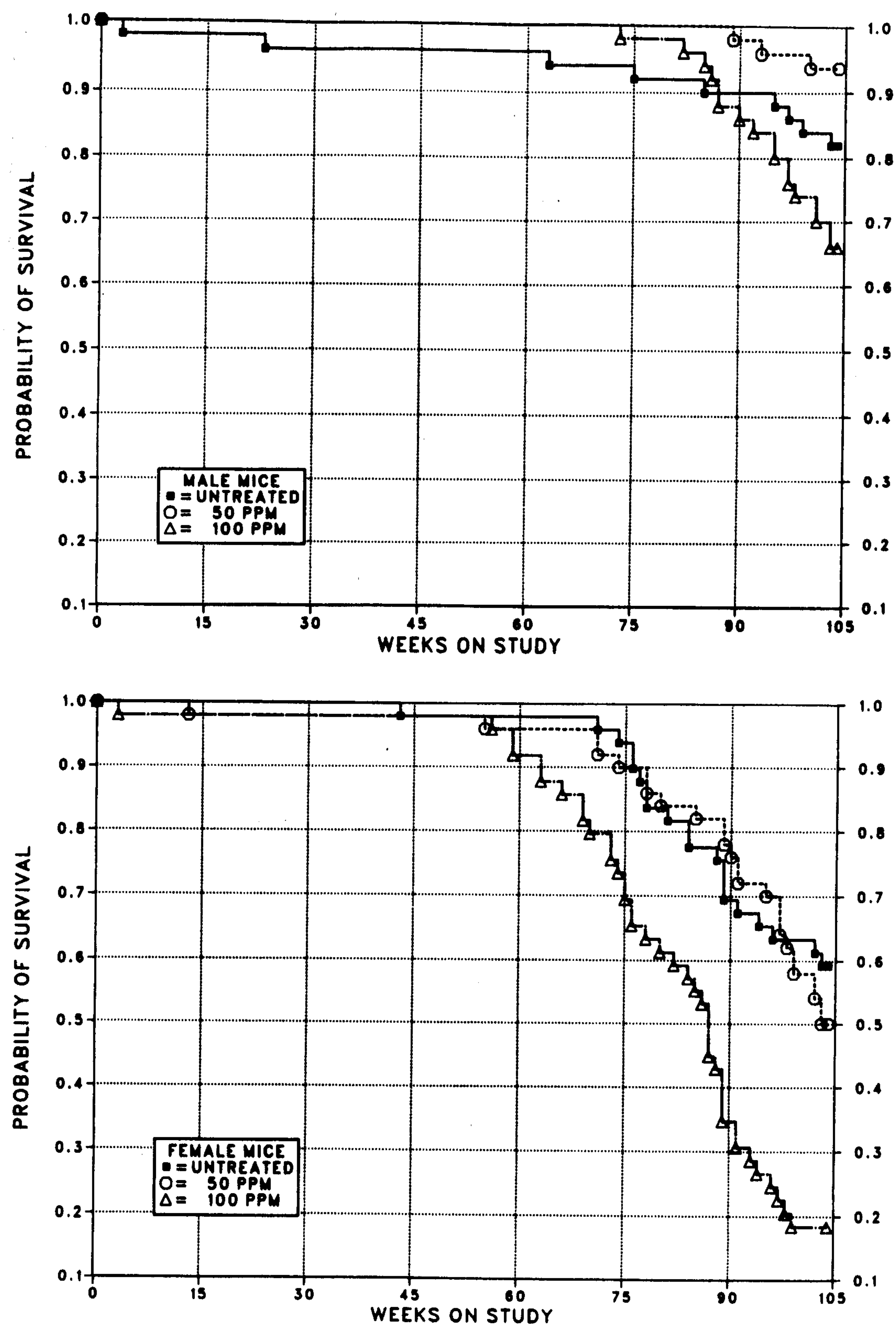


FIGURE 15. KAPLAN-MEIER SURVIVAL CURVES FOR MICE EXPOSED TO 1,2-EPOXYBUTANE BY INHALATION FOR TWO YEARS

Nasal Cavity, Nasal Gland, Nasolacrimal Duct, and Olfactory Sensory Epithelium: Empyema and chronic inflammation were diagnosed by the study pathologist to describe the presence of suppurative exudate in the nasal cavity and infiltration of the nasal mucosa with lymphocytes and macrophages. Erosion, respiratory epithelial regeneration and hyperplasia, and squamous metaplasia were observed at increased incidences in dosed male and dosed female mice (Table 21).

Cysts and hyperplasia of the nasal gland (Bowman's glands in the respiratory mucosa), suppurative and chronic inflammation and epithelial hyperplasia of the nasolacrimal duct, and atrophy of the olfactory sensory epithelium were also observed at increased incidences in dosed mice. A single squamous cell papilloma was seen in the incisive duct of one high dose male mouse.

Ovary or Uterus: Suppurative inflammation (primarily ovarian abscesses) of the uterus and/or ovary was present in all dosed groups (uterus: vehicle control, 6/50; low dose, 11/49; high dose, 7/48; ovary: 7/49; 20/47; 21/45). These lesions were cultured from one control, four low dose, and four high dose animals. *Klebsiella oxytoca* was isolated from each lesion.

Pituitary Gland: Adenomas or carcinomas (combined) in female mice occurred with a significant negative trend (P=0.018 by the incidental tumor test; control, 22/47; low dose, 12/46; high dose, 5/46).

TABLE 21. NUMBER OF MICE WITH LESIONS OF THE NASAL CAVITY, NASAL GLAND, NASOLACRIMAL DUCT, OR OLFACTORY SENSORY EPITHELIUM IN THE TWO-YEAR INHALATION STUDIES OF 1,2-EPOXYBUTANE

Site/Lesion	Male			Female		
	0	50 ppm	100 ppm	0	50 ppm	100 ppm
Number examined	49	49	50	50	50	48
Nasal cavity						
Empyema	0	32	40	0	33	40
Chronic inflammation	0	33	40	0	39	44
Erosion	0	7	17	0	16	24
Regeneration	0	15	17	0	14	15
Epithelial hyperplasia	0	32	45	1	34	35
Squamous metaplasia	1	24	41	0	34	41
Squamous cell papilloma	0	0	1	0	0	0
Nasal gland						
Cyst	0	1	6	0	9	7
Hyperplasia	0	10	24	0	23	29
Nasolacrimal duct						
Empyema	0	0	0	0	2	5
Suppurative inflammation	0	6	2	1	3	4
Chronic inflammation	0	3	4	1	5	6
Epithelial hyperplasia	0	12	21	1	18	21
Olfactory sensory epithelium						
Atrophy	0	13	32	0	25	35

IV. DISCUSSION AND CONCLUSIONS

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Study Rationale

1,2-Epoxybutane was selected for study because it was a representative of the simple short-chain epoxides, a class of compounds that was suspected to contain carcinogens because other epoxides had been shown to be carcinogens (IARC, 1976). The chemical (greater than 99% pure) was administered as a vapor to F344/N rats and $B6C3F_1$ mice in a series of short-term and 2-year studies by the inhalation route to mimic worker exposure. There is currently no threshold limit value for this chemical, although the manufacturer has established an 8-hour TWA of 40 ppm (Fed. Regist., 1984). The highest concentration used in the 2-year rat studies (400 ppm; 1,178 mg/m^3) is 10 times this TWA, and the highest concentration used in the mouse studies (100 ppm; 294 mg/m^3) is 2.5 times this TWA.

Short-Term Studies

In the single-exposure studies, compound-related mortality was seen at 6,550 ppm in rats and at 1,420 ppm and above in mice. In the 14-day studies, compound-related mortality was seen at 3,200 ppm and above in male rats, at 1,600 ppm and above in female rats, and at 1,600 ppm and above in mice of each sex. The results of the 13-week studies were similar to those published previously by Miller et al. (1981), who reported that exposure of F344 rats and $B6C3F_1$ mice to 1,2-epoxybutane at concentrations of 0, 75, 150, or 600 ppm resulted in no compound-related deaths. In the NTP 13-week studies, no deaths were seen in rats at concentrations up to 800 ppm or in mice up to 400 ppm, whereas all mice at 800 ppm died. In the Miller et al. study, compound-related nasal cavity lesions were seen in rats and mice at 600 ppm but not at 75 or 150 ppm. In the NTP studies, nasal cavity lesions were seen in rats at 800 ppm but not at lower concentrations, and nasal cavity lesions were seen in mice at 200, 400, and 800 ppm. In the NTP studies, renal necrosis was observed in mice at 800 ppm, a dose that was lethal.

Results of the 13-week studies were used to select exposure concentrations for the 2-year studies. The highest concentration selected for the 2-year rat studies was 400 ppm because at 800 ppm body weight was markedly lower than that of the controls and nasal lesions were observed. The highest concentration selected for the 2-year studies in mice was 100 ppm because the nasal lesions seen at 200 ppm and above were considered to be potentially life threatening.

Two-Year Studies in Rats

Survival of rats was at least 50% in all groups until week 98, but survival was reduced after this time in exposed groups (final survival--male: control, 30/50; low dose, 18/50; high dose, 23/50; female: 32/50; 21/50; 22/50). Mean body weights of high dose male rats were 5%-8% lower than those of controls after week 86, and mean body weights of high dose female rats were 5%-10% lower after week 22.

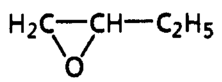
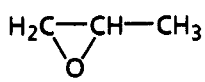
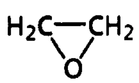
The respiratory system of rats was adversely affected after exposure to 1,2-epoxybutane for 2 years. Nonneoplastic lesions of the nasal cavity (including inflammation, epithelial and adenomatous hyperplasia, and squamous metaplasia of the respiratory epithelium), atrophy of the olfactory epithelium, and hyperostosis were observed in exposed animals. Seven papillary adenomas of the nasal cavity were seen in high dose male rats and two in high dose female rats. The incidence of alveolar/bronchiolar adenomas or carcinomas (combined) was increased in high dose male rats (control, 0/50; low dose, 2/50; high dose, 5/49) but not in high dose female rats. Although more than 60% of the animals tested had positive serologic titers for RCV/SDA virus at 17 and 24 months, there were no lesions in the salivary gland or lung to indicate active infection.

The finding of benign neoplasms of the nasal cavity (nasal cavity neoplasms have not been seen in any of the 249 chamber control male rats at this laboratory and in only 0.1% [2/1,977] of untreated control male rats in all NTP studies) and of benign and malignant neoplasms of the lung in male rats is clear evidence that this chemical is a carcinogen. The presence in female rats of two tumors in the nasal cavity, a site for tumors in male rats, is considered equivocal evidence of carcinogenicity.

The incidence of mononuclear cell leukemia was increased in low dose male rats, but because leukemia was not also increased in high dose animals, the effect is not considered to be compound related. The incidences of several nonfatal tumors, including thyroid gland follicular cell adenomas or carcinomas (combined) in female rats, adenomas or carcinomas (combined) of the pituitary gland in female rats, and preputial gland tumors in male rats, were marginally increased by the life table trend test but not by the incidental tumor trend test (the more appropriate test for analysis of nonfatal tumors), and these effects are not considered to be compound related.

Propylene oxide, a related epoxide, also was studied at the same laboratory in F344/N rats at the same inhalation exposure concentrations (0, 200, and 400 ppm) (NTP, 1985; Table 22). Inflammation, hyperplasia, and metaplasia of the nasal cavity respiratory epithelium were seen in dosed animals. Propylene oxide caused an increased incidence of papillary adenomas of the nasal cavity in male and female rats.

TABLE 22. COMPOUND-RELATED CARCINOGENIC RESPONSES IN NTP TWO-YEAR INHALATION STUDIES OF EPOXIDES AND RELATED COMPOUNDS (a)

Chemical	Strain/ Species/ Sex	Exposure Concentration (ppm)	Site or Type of Neoplasm: Nasal Cavity	Lung	Other Organ Systems
1,2-Epoxybutane (b)	F344/N rats				
	Male	0, 200, 400	+	+	–
	Female	0, 200, 400	±	–	–
	$B6C3F_1$ mice				
	Male	0, 50, 100	–	–	–
	Female	0, 50, 100	–	–	–
Propylene oxide (c)	F344/N rats				
	Male	0, 200, 400	+	–	–
	Female	0, 200, 400	+	–	–
	$B6C3F_1$ mice				
	Male	0, 200, 400	+	–	–
	Female	0, 200, 400	+	–	–
Ethylene oxide (d)	$B6C3F_1$ mice				
	Male	0, 625, 1,250	–	+	+ (Harderian gland)
	Female	0, 625, 1,250	–	+	+ (Harderian gland, lymphomas, uterus, mammary gland)
1,3-Butadiene (e)	$B6C3F_1$ mice				
$H_2C=CH-CH=CH_2$	Male	0, 625, 1,250	–	+	+ (Heart, lymphomas, forestomach)
	Female	0, 625, 1,250	–	+	+ (Heart, lymphomas, forestomach, ovary, mammary gland, liver)

(a) Carcinogenic response: +, presence of compound-related neoplasms; ±, equivocal evidence for compound-related neoplasms; –, no evidence for compound-related neoplasms.
(b) This Technical Report
(c) NTP, 1985
(d) NTP 1987--rats not studied.
(e) NTP 1984--study terminated early; rats not studied.

IV. DISCUSSION AND CONCLUSIONS

Two-Year Studies in Mice

Final survival of dosed male mice was comparable to that of controls. Survival of dosed female mice was greater than 50% at week 86 but was reduced in the high dose group toward the end of the study (final survival: control, 29/50; low dose, 25/50; high dose, 9/50). Suppurative inflammation of the ovary and uterus was seen in some female mice dying before the end of the study, and the incidences of these lesions were greater in dosed animals. Klebsiella was cultured from some of these lesions. Klebsiella infections were seen in other NTP studies conducted during this time period, and similar uterine/ovarian lesions were seen in female mice in those studies (Rao et al., 1987). Mean body weights of dosed mice were reduced during the second year of the studies.

The nasal cavity was the site primarily affected in mice. As was seen in rats, 1,2-epoxybutane caused nonneoplastic lesions of the nasal cavity in dosed mice, including suppurative (empyema) and chronic inflammation; epithelial hyperplasia, erosion, and regeneration; squamous metaplasia; atrophy of the sensory epithelium; hyperplasia of the nasal gland (Bowman's glands); and inflammation and hyperplasia of the nasolacrimal duct. The single squamous cell papilloma was seen in the incisive duct of a high dose male mouse but was not considered to be compound related. 1,2-Epoxybutane at exposure concentrations that caused nonneoplastic lesions of the nasal cavity in both rats and mice was carcinogenic in the nasal cavity of rats only. The reasons for this species difference need further investigation.

Inhalation exposure of B6C3F$_1$ mice to propylene oxide at concentrations of 200 and 400 ppm caused inflammation and hemangiomas or hemangiosarcomas (combined) of the nasal cavity (NTP, 1985; Table 22). 1,2-Epoxybutane at 50 or 100 ppm was not carcinogenic for mice, even though nonneoplastic inflammatory and hyperplastic lesions occurred. Two other related chemicals were studied in mice in the same room at this laboratory: 1,3-butadiene and ethylene oxide (NTP, 1984, 1987; Table 22). These chemicals given by the inhalation route were not carcinogenic in the nasal cavity but did cause increased incidences of neoplasms at other sites. Ethylene oxide caused increased incidences of lung and harderian gland tumors in male and female mice exposed at 50 or 100 ppm (NTP, 1987). 1,3-Butadiene, which is metabolized in vitro first to 1,2-epoxy-3-butene and then to diepoxybutane and 3,4-epoxy-1,2-butanediol (Malvoisin and Roberfroid, 1982), caused increased incidences of neoplasms of the lung, stomach, and heart and lymphomas in male mice and of neoplasms of the lung, stomach, mammary gland, ovary, and liver and lymphomas in female mice at concentrations of 625 or 1,250 ppm (NTP, 1984). Other epoxides have been shown to be carcinogenic in rodents after oral administration and inhalation exposure (IARC, 1985). In the 1,2-epoxybutane studies reported here, there was no cross-contamination in the exposure chamber with the other chemicals (1,3-butadiene or ethylene oxide) on study in the same room.

Adenomas or carcinomas (combined) of the pituitary gland occurred with a significant negative trend in female mice. This may be related in part to the increased mortality in exposed female mice.

Genetic Toxicology

1,2-Epoxybutane is clearly mutagenic. It induces gene mutations in a variety of bacterial species (Dunkel, 1979; McMahon et al., 1979; Voogd et al., 1981; De Flora et al., 1984), as well as in fungi (Kolmark and Giles, 1955; Migliore et al., 1982; Rossi et al., 1983), Drosophila (Knaap et al., 1982; Yoon et al., 1985), and mammalian cells in culture (Amacher et al., 1980; Knaap et al., 1982). It also induces sister chromatid exchanges (Table E3) but not unscheduled DNA synthesis in cultured mammalian cells (McGregor, 1981; Williams et al., 1982). Although 1,2-epoxybutane can be clastogenic, as demonstrated by the induction of chromosomal aberrations in cultured Chinese hamster ovary cells treated in the absence of metabolic activation (Table E4) and of translocations in Drosophila after feeding to adult males, it did not induce dominant lethal mutations in the germ cells of male rats exposed by inhalation (McGregor, 1981). The negative dominant lethal result and the absence of sperm-head abnormalities in germ cells of male mice that were exposed to 1,2-epoxybutane by inhalation may indicate that the chemical did not reach the testis in amounts sufficient to produce an observable effect.

The mutagenicity of ethylene oxide (NTP, 1987; Embree and Hine, 1975; Pfeiffer and Dunkleberg, 1980) and propylene oxide (NTP, 1985; Canter et al., 1986), structural analogs of 1,2-epoxybutane, appears to be similar to that of 1,2-epoxybutane in that mutations are induced in the base-pair substitution strains TA100 and TA1535 of *S. typhimurium* in both the absence and presence of metabolic activation (Bootman et al., 1979; McMahon et al., 1979; De Flora, 1981). 1,3-Butadiene induces mutations in strains TA100 and TA1535 but only in the presence of metabolic activation (Wade et al., 1978).

Data Audit

The experimental and tabulated data for the NTP Technical Report on 1,2-epoxybutane were examined for accuracy, consistency, completeness, and compliance with Good Laboratory Practice regulations. As summarized in Appendix H, the audit revealed no discrepancies that influenced the final interpretation of the results of these studies.

Conclusions: Under the conditions of these 2-year inhalation studies, there was *clear evidence of carcinogenic activity** of 1,2-epoxybutane for male F344/N rats, as shown by an increased incidence of papillary adenomas of the nasal cavity, alveolar/bronchiolar carcinomas and alveolar/bronchiolar adenomas or carcinomas (combined). There was *equivocal evidence of carcinogenic activity* for female F344/N rats, as shown by the presence of papillary adenomas of the nasal cavity. There was *no evidence of carcinogenic activity* for male or female $B6C3F_1$ mice exposed at 50 or 100 ppm. 1,2-Epoxybutane exposure was associated with adenomatous hyperplasia and inflammatory lesions of the nasal cavity in rats and inflammatory lesions of the nasal cavity in mice.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 7.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 10-11.

V. REFERENCES

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APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE

	Chamber Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell papilloma		3 (6%)	
Squamous cell carcinoma			1 (2%)
Basal cell tumor		1 (2%)	
Keratoacanthoma	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma	2 (4%)	4 (8%)	3 (6%)
Fibrosarcoma	1 (2%)		
Osteosarcoma			1 (2%)
Neurofibrosarcoma		1 (2%)	
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Papillary adenoma			7 (14%)
#Lung	(50)	(50)	(49)
Alveolar/bronchiolar adenoma		1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma		1 (2%)	4 (8%)
Sarcoma, NOS, metastatic	1 (2%)		
Osteosarcoma		1 (2%)	
Osteosarcoma, metastatic			2 (4%)
Chordoma, metastatic			2 (4%)
Neurilemoma, metastatic			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	24 (48%)	30 (60%)	21 (42%)
#Spleen	(50)	(50)	(49)
Sarcoma, NOS		1 (2%)	
Sarcoma, NOS, metastatic	1 (2%)		
Leukemia, mononuclear cell	1 (2%)	1 (2%)	1 (2%)
#Thymus	(37)	(36)	(38)
Thymoma, benign			1 (3%)
CIRCULATORY SYSTEM			
#Spleen	(50)	(50)	(49)
Hemangiosarcoma			1 (2%)
DIGESTIVE SYSTEM			
*Mouth	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)	1 (2%)	
#Liver	(50)	(50)	(49)
Neoplastic nodule	2 (4%)	2 (4%)	2 (4%)
Hepatocellular carcinoma			1 (2%)
Osteosarcoma, metastatic			1 (2%)
#Pancreas	(47)	(50)	(48)
Acinar cell adenoma			1 (2%)
#Stomach	(50)	(49)	(49)
Sarcoma, NOS			1 (2%)
Leiomyosarcoma	1 (2%)		

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Small intestine	(49)	(48)	(46)
Adenocarcinoma, NOS	1 (2%)		
Leiomyosarcoma			1 (2%)
#Cecum	(48)	(47)	(47)
Adenocarcinoma, NOS	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Tubular cell adenocarcinoma			1 (2%)
#Urinary bladder	(49)	(48)	(47)
Transitional cell papilloma	1 (2%)		
ENDOCRINE SYSTEM			
#Pituitary intermedia	(48)	(48)	(47)
Adenoma, NOS	1 (2%)		2 (4%)
#Anterior pituitary	(48)	(48)	(47)
Carcinoma, NOS	3 (6%)	5 (10%)	2 (4%)
Adenoma, NOS	23 (48%)	21 (44%)	22 (47%)
#Adrenal	(50)	(49)	(48)
Cortical adenoma	1 (2%)	1 (2%)	2 (4%)
Pheochromocytoma	16 (32%)	18 (37%)	21 (44%)
Pheochromocytoma, malignant	2 (4%)		
#Thyroid	(49)	(45)	(45)
Follicular cell adenoma		1 (2%)	
Follicular cell carcinoma	1 (2%)		
C-cell adenoma	4 (8%)	2 (4%)	3 (7%)
C-cell carcinoma		1 (2%)	
#Parathyroid	(28)	(32)	(37)
Adenoma, NOS			1 (3%)
#Pancreatic islets	(47)	(50)	(48)
Islet cell adenoma	4 (9%)	7 (14%)	4 (8%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Fibroadenoma	2 (4%)		
*Preputial gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)	2 (4%)	3 (6%)
Squamous cell carcinoma		1 (2%)	
Adenoma, NOS	2 (4%)		5 (10%)
#Prostate	(47)	(48)	(48)
Adenoma, NOS		1 (2%)	
#Testis	(50)	(50)	(49)
Interstitial cell tumor	39 (78%)	41 (82%)	43 (88%)
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Osteosarcoma		1 (2%)	
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Neurilemoma, malignant			1 (2%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	Low Dose	High Dose
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, invasive			1 (2%)
*Peritoneal cavity	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)		
Osteosarcoma			1 (2%)
*Tunica vaginalis	(50)	(50)	(50)
Mesothelioma, NOS	1 (2%)	1 (2%)	2 (4%)
Mesothelioma, malignant			1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Adenocarcinoma, NOS, metastatic	1 (2%)		
Sarcoma, NOS, metastatic			1 (2%)
Neurofibrosarcoma, metastatic		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	2	5	8
Moribund sacrifice	18	27	19
Terminal sacrifice	30	18	23
TUMOR SUMMARY			
Total animals with primary tumors**	50	49	48
Total primary tumors	137	150	161
Total animals with benign tumors	46	47	48
Total benign tumors	97	102	116
Total animals with malignant tumors	31	38	33
Total malignant tumors	37	45	41
Total animals with secondary tumors##	2	1	7
Total secondary tumors	3	1	8
Total animals with tumors uncertain-- benign or malignant	3	3	4
Total uncertain tumors	3	3	4

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

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE: CHAMBER CONTROL

ANIMAL NUMBER	029	046	020	016	047	025	033	023	032	038	027	048	002	005	001	036	028	041	044	006	003	004	007	008	009
WEEKS ON STUDY	046	072	084	086	086	087	087	088	091	091	093	094	098	098	102	102	103	103	103	104	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																					X				
Subcutaneous tissue	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma						X																			
Fibrosarcoma	X																								
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS, metastatic					X																				
Trachea	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS, metastatic					X																				
Leukemia, mononuclear cell				X																					
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	−	+	−	+	+	+	−	+	+	−	+	+	+	−	−	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																									
Salivary gland	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																X									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma														X											
Small intestine	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS										X															
Large intestine	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS		X																							
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS				X								X						X							
Adenoma, NOS			X			X		X		X	X		X	X							X		X	X	X@
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma							X																		
Pheochromocytoma			X												X	X	X			X			X	X	
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																		X							
C-cell adenoma																									X
Parathyroid	−	−	+	+	−	−	+	+	+	+	+	+	−	+	−	+	+	+	+	+	−	−	−	+	−
Pancreatic islets	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma									X						X							X			
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	+	N	N	+	+	+	N	N	N	N	+	N	+	+	N	N	+	N	N	N	N	N
Fibroadenoma																	X								
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor			X		X		X		X					X	X	X	X	X	X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Adenoma, NOS									X																
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS					X																				
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS						X																			
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS, metastatic		X																							
Leukemia, mononuclear cell						X	X		X			X	X	X	X				X	X	X		X	X	

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

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

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

ANIMAL NUMBER	010	011	012	013	014	015	017	018	019	021	022	024	026	030	031	034	035	037	039	040	042	043	045	049	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	*50
Keratoacanthoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	*50
Fibroma															X											2
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS, metastatic																										1
Leukemia, mononuclear cell																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	−	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	−	+	+	−	+	−	−	37
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma													X													1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																							X			2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma, NOS																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Transitional cell papilloma																								X		1
ENDOCRINE SYSTEM																										
Pituitary	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS																										3
Adenoma, NOS	X			X	X			X		X	X			X			X	X	X	X			X			23
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																										1
Pheochromocytoma			X	X			X	X		X		X	X					X					X			16
Pheochromocytoma, malignant							X														X					2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell carcinoma																										1
C-cell adenoma				X													X		X							4
Parathyroid	−	−	−	+	+	+	+	−	−	+	+	−	−	−	+	+	−	−	+	+	+	+	+	−	−	28
Pancreatic islets	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Islet cell adenoma																							X			4
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	+	+	N	N	+	+	+	+	N	+	N	+	+	N	N	N	N	+	+	*50
Fibroadenoma											X															2
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	39
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	−	+	+	+	+	47
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS		X																								1
Adenoma, NOS													X													2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS																										1
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenocarcinoma, NOS, metastatic																										1
Leukemia, mononuclear cell					X		X	X	X			X	X	X	X			X		X	X		X			24

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE: LOW DOSE

ANIMAL NUMBER	039	043	049	050	022	044	004	008	010	023	020	040	019	012	046	014	042	026	038	016	025	024	001	021	029
WEEKS ON STUDY	050	073	076	079	081	081	083	085	085	085	087	089	090	091	091	094	094	095	095	097	098	099	100	100	100
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma						X										X									
Basal cell tumor																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma												X													
Neurofibrosarcoma																		X							
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								X	
Alveolar/bronchiolar carcinoma																									
Osteosarcoma																									X
Trachea	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Leukemia, mononuclear cell																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Thymus	+	−	−	+	+	+	−	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS				X										X		X									
Adenoma, NOS		X	X										X								X		X	X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma							X			X			X			X	X		X			X	X		X
Thyroid	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																							X		
C-cell adenoma							X																		
C cell carcinoma																									
Parathyroid	−	+	+	−	+	−	+	−	+	+	+	+	+	+	−	+	−	+	−	+	+	+	+	−	−
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma			X																						
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	N	N	+	+	+	+	+	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor					X	X		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS															X				X						
Squamous cell carcinoma																						X			
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																								X	
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Neurofibrosarcoma, metastatic																		X							
Leukemia, mononuclear cell			X		X		X	X	X	X	X		X		X		X		X	X		X	X		X

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

ANIMAL NUMBER	037	009	045	015	032	028	033	002	003	005	006	007	011	013	017	018	027	030	031	034	035	036	041	047	048	TOTAL TISSUES TUMORS
WEEKS ON STUDY	100	102	102	103	103	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma													X													3
Basal cell tumor												X														1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma													X											X	X	4
Neurofibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma															X											1
Osteosarcoma																										1
Trachea	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS				X																						1
Leukemia, mononuclear cell								X																		1
Lymph nodes	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	−	+	+	−	+	−	+	−	−	+	−	+	+	+	+	−	+	+	+	+	+	+	−	−	36
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma															X											1
Salivary gland	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule									X																X	2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS																X			X							5
Adenoma, NOS			X		X		X		X	X	X	X	X				X			X	X	X	X	X	X	21
Adrenal	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma																						X				1
Pheochromocytoma						X	X					X	X		X	X				X				X	X	18
Thyroid	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	45
Follicular cell adenoma																										1
C-cell adenoma																		X								2
C-cell carcinoma																									X	1
Parathyroid	+	+	+	−	+	−	+	−	−	+	−	+	−	+	+	+	+	+	+	−	+	−	+	−	+	32
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma			X													X			X	X			X	X		7
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	N	N	+	+	N	+	N	+	+	N	N	N	+	+	N	+	N	+	+	+	N	+	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X	41
Prostate	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS																X										1
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										2
Squamous cell carcinoma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS				X																						1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Neurofibrosarcoma, metastatic																										1
Leukemia, mononuclear cell	X	X	X	X		X			X	X	X	X						X	X	X		X		X	X	30

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE: HIGH DOSE

ANIMAL NUMBER	024	029	030	038	011	006	045	040	016	048	037	039	026	027	050	018	013	009	010	036	004	012	034	032	043
WEEKS ON STUDY	064	075	075	075	076	084	088	089	091	092	094	094	095	095	096	097	098	099	099	099	100	101	101	102	102
INTEGUMENTARY SYSTEM																									
Skin	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																				X					
Subcutaneous tissue	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma								X																	
Osteosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma													X	X											
Osteosarcoma, metastatic																			X						
Chordoma, metastatic		X																							
Neurilemoma, metastatic													X												
Trachea	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary adenoma																X				X				X	X
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Leukemia, mononuclear cell																									
Lymph nodes	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	–	–	+	–	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+
Thymoma, benign																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Liver	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Hepatocellular carcinoma																									
Osteosarcoma, metastatic																									
Bile duct	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																X									
Esophagus	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS							X																		
Small intestine	+	+	–	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Large intestine	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma																									
Urinary bladder	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS											X														X
Adenoma, NOS	X			X		X								X	X			X				X			
Adrenal	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																		X							
Pheochromocytoma		X							X		X			X				X		X		X	X		
Thyroid	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+
C cell adenoma																X									
Parathyroid	+	+	+	–	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	–
Adenoma, NOS																				X					
Pancreatic islets	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	+	N	N	+	N	N	N	N	N	+	+	N	N	N	N	N	+	+	+	+	+	N
Testis	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor		X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prostate	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS										X										X	X				
Adenoma, NOS							X									X								X	
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Eye	N	N	N	N	+	N	N	N	N	N	+	N	+	N	N	N	N	N	N	N	N	N	N	N	N
Neurilemoma, malignant													X												
BODY CAVITIES																									
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Alveolar/bronchiolar carcinoma, invasive																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma																			X						
Tunica vaginalis	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									
Mesothelioma, malignant																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS, metastatic							X																		
Leukemia, mononuclear cell						X		X	X		X	X			X		X	X						X	

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

ANIMAL NUMBER	001	023	002	003	005	007	008	014	015	017	019	020	021	022	025	028	031	033	035	041	042	044	046	047	049	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	103	103	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell carcinoma																										1
Subcutaneous tissue	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma			X																					X		3
Osteosarcoma	X																									1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma								X																		1
Alveolar/bronchiolar carcinoma															X									X		4
Osteosarcoma, metastatic	X																									2
Chordoma, metastatic							X																			2
Neurilemoma, metastatic																										1
Trachea	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Papillary adenoma										X											X				X	7
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma										X																1
Leukemia, mononuclear cell													X													1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	−	−	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	38
Thymoma, benign																	X									1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule									X								X									2
Hepatocellular carcinoma															X											1
Osteosarcoma, metastatic	X																									1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pancreas	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Acinar cell adenoma																										1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, NOS																										1
Small intestine	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Leiomyosarcoma														X												1
Large intestine	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenocarcinoma										X																1
Urinary bladder	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma, NOS																										2
Adenoma, NOS	X		X		X@	X		X		X	X@	X					X		X		X	X	X	X	X	22
Adrenal	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cortical adenoma											X															2
Pheochromocytoma			X			X	X	X		X	X	X						X	X		X		X	X	X	21
Thyroid	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	45
C-cell adenoma							X																		X	3
Parathyroid	−	+	+	+	+	+	−	+	−	−	+	+	+	+	+	+	−	+	−	−	+	−	+	+	−	37
Adenoma, NOS																										1
Pancreatic islets	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma				X																	X	X	X			4
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	N	+	N	N	+	N	N	+	N	N	+	N	+	+	+	+	+	+	N	+	N	+	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X		X	X	X		X	X	X	X	X		X	X	X	43
Prostate	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										3
Adenoma, NOS			X										X													5
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Eye	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Neurilemoma, malignant																										1
BODY CAVITIES																										
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Alveolar/bronchiolar carcinoma, inv																								X		1
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma																										1
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS	X									X																2
Mesothelioma, malignant																				X						1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS, metastatic																										1
Leukemia, mononuclear cell	X	X		X		X		X			X			X			X		X	X	X				X	21

* Animals necropsied
@ Multiple occurrence of morphology

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE

	Chamber Control	200 ppm	400 ppm
Skin: Squamous Cell Papilloma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	0.0%	10.2%	0.0%
Terminal Rates (c)	0/30 (0%)	1/18 (6%)	0/23 (0%)
Week of First Observation		81	
Life Table Tests (d)	P=0.606	P=0.087	(e)
Incidental Tumor Tests (d)	P=0.628	P=0.144	(e)
Cochran-Armitage Trend Test (d)	P=0.640		
Fisher Exact Test (d)		P=0.121	(e)
Skin: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	0.0%	10.2%	3.0%
Terminal Rates (c)	0/30 (0%)	1/18 (6%)	0/23 (0%)
Week of First Observation		81	99
Life Table Tests (d)	P=0.351	P=0.087	P=0.483
Incidental Tumor Tests (d)	P=0.398	P=0.144	P=0.606
Cochran-Armitage Trend Test (d)	P=0.378		
Fisher Exact Test (d)		P=0.121	P=0.500
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (b)	5.5%	18.8%	10.8%
Terminal Rates (c)	1/30 (3%)	3/18 (17%)	2/23 (9%)
Week of First Observation	87	89	89
Life Table Tests (d)	P=0.331	P=0.186	P=0.429
Incidental Tumor Tests (d)	P=0.268	P=0.244	P=0.344
Cochran-Armitage Trend Test (d)	P=0.417		
Fisher Exact Test (d)		P=0.339	P=0.500
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (b)	7.4%	18.8%	10.8%
Terminal Rates (c)	1/30 (3%)	3/18 (17%)	2/23 (9%)
Week of First Observation	46	89	89
Life Table Tests (d)	P=0.487	P=0.334	P=0.599
Incidental Tumor Tests (d)	P=0.346	P=0.406	P=0.344
Cochran-Armitage Trend Test (d)	P=0.579		
Fisher Exact Test (d)		P=0.500	P=0.661N
Subcutaneous Tissue: Fibroma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (a)	3/50 (6%)	5/50 (10%)	3/50 (6%)
Adjusted Rates (b)	7.4%	21.3%	10.8%
Terminal Rates (c)	1/30 (3%)	3/18 (17%)	2/23 (9%)
Week of First Observation	46	89	89
Life Table Tests (d)	P=0.488	P=0.214	P=0.599
Incidental Tumor Tests (d)	P=0.376	P=0.309	P=0.344
Cochran-Armitage Trend Test (d)	P=0.576		
Fisher Exact Test (d)		P=0.357	P=0.661N
Nasal Cavity: Papillary Adenoma			
Overall Rates (a)	0/50 (0%)	0/50 (0%)	7/50 (14%)
Adjusted Rates (b)	0.0%	0.0%	24.2%
Terminal Rates (c)	0/30 (0%)	0/18 (0%)	3/23 (13%)
Week of First Observation			97
Life Table Tests (d)	P<0.001	(e)	P=0.005
Incidental Tumor Tests (d)	P=0.002	(e)	P=0.015
Cochran-Armitage Trend Test (d)	P=0.001		
Fisher Exact Test (d)		(e)	P=0.006

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	200 ppm	400 ppm
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	0/50 (0%)	1/50 (2%)	4/49 (8%)
Adjusted Rates (b)	0.0%	5.6%	13.5%
Terminal Rates (c)	0/30 (0%)	1/18 (6%)	2/23 (9%)
Week of First Observation		105	95
Life Table Tests (d)	P=0.022	P=0.398	P=0.049
Incidental Tumor Tests (d)	P=0.028	P=0.398	P=0.077
Cochran-Armitage Trend Test (d)	P=0.024		
Fisher Exact Test (d)		P=0.500	P=0.056
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	0/50 (0%)	2/50 (4%)	5/49 (10%)
Adjusted Rates (b)	0.0%	8.9%	17.6%
Terminal Rates (c)	0/30 (0%)	1/18 (6%)	3/23 (13%)
Week of First Observation		100	95
Life Table Tests (d)	P=0.013	P=0.161	P=0.022
Incidental Tumor Tests (d)	P=0.019	P=0.234	P=0.036
Cochran-Armitage Trend Test (d)	P=0.015		
Fisher Exact Test (d)		P=0.247	P=0.027
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	25/50 (50%)	31/50 (62%)	22/50 (44%)
Adjusted Rates (b)	61.5%	79.6%	62.5%
Terminal Rates (c)	15/30 (50%)	11/18 (61%)	11/23 (48%)
Week of First Observation	86	76	84
Life Table Tests (d)	P=0.390	P=0.011	P=0.459
Incidental Tumor Tests (d)	P=0.376N	P=0.183	P=0.452N
Cochran-Armitage Trend Test (d)	P=0.308N		
Fisher Exact Test (d)		P=0.157	P=0.345N
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Overall Rates (a)	2/50 (4%)	2/50 (4%)	3/49 (6%)
Adjusted Rates (b)	6.0%	11.1%	13.0%
Terminal Rates (c)	1/30 (3%)	2/18 (11%)	3/23 (13%)
Week of First Observation	102	105	105
Life Table Tests (d)	P=0.293	P=0.510	P=0.378
Incidental Tumor Tests (d)	P=0.333	P=0.605	P=0.450
Cochran-Armitage Trend Test (d)	P=0.398		
Fisher Exact Test (d)		P=0.691	P=0.490
Pituitary Gland: Adenoma			
Overall Rates (a)	23/48 (48%)	21/48 (44%)	22/47 (47%)
Adjusted Rates (b)	62.2%	75.8%	68.8%
Terminal Rates (c)	16/29 (55%)	12/18 (67%)	14/23 (61%)
Week of First Observation	84	73	64
Life Table Tests (d)	P=0.290	P=0.159	P=0.353
Incidental Tumor Tests (d)	P=0.518N	P=0.526	P=0.519
Cochran-Armitage Trend Test (d)	P=0.497N		
Fisher Exact Test (d)		P=0.419N	P=0.539N
Pituitary Gland: Carcinoma			
Overall Rates (a)	3/48 (6%)	5/48 (10%)	2/47 (4%)
Adjusted Rates (b)	7.5%	17.8%	6.1%
Terminal Rates (c)	0/29 (0%)	2/18 (11%)	0/23 (0%)
Week of First Observation	86	79	94
Life Table Tests (d)	P=0.487N	P=0.244	P=0.556N
Incidental Tumor Tests (d)	P=0.393N	P=0.484	P=0.376N
Cochran-Armitage Trend Test (d)	P=0.431N		
Fisher Exact Test (d)		P=0.357	P=0.510N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	200 ppm	400 ppm
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	26/48 (54%)	26/48 (54%)	24/47 (51%)
Adjusted Rates (b)	65.0%	85.1%	70.7%
Terminal Rates (c)	16/29 (55%)	14/18 (78%)	14/23 (61%)
Week of First Observation	84	73	64
Life Table Tests (d)	P=0.341	P=0.077	P=0.411
Incidental Tumor Tests (d)	P=0.422N	P=0.432	P=0.511N
Cochran-Armitage Trend Test (d)	P=0.421N		
Fisher Exact Test (d)		P=0.581N	P=0.461N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	16/50 (32%)	18/49 (37%)	21/48 (44%)
Adjusted Rates (b)	45.0%	58.1%	65.5%
Terminal Rates (c)	11/30 (37%)	7/18 (39%)	13/23 (57%)
Week of First Observation	84	83	75
Life Table Tests (d)	P=0.057	P=0.071	P=0.056
Incidental Tumor Tests (d)	P=0.136	P=0.334	P=0.155
Cochran-Armitage Trend Test (d)	P=0.137		
Fisher Exact Test (d)		P=0.388	P=0.161
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	17/50 (34%)	18/49 (37%)	21/48 (44%)
Adjusted Rates (b)	47.9%	58.1%	65.5%
Terminal Rates (c)	12/30 (40%)	7/18 (39%)	13/23 (57%)
Week of First Observation	84	83	75
Life Table Tests (d)	P=0.078	P=0.094	P=0.078
Incidental Tumor Tests (d)	P=0.183	P=0.397	P=0.204
Cochran-Armitage Trend Test (d)	P=0.188		
Fisher Exact Test (d)		P=0.470	P=0.217
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	4/49 (8%)	2/45 (4%)	3/45 (7%)
Adjusted Rates (b)	13.3%	8.0%	11.7%
Terminal Rates (c)	4/30 (13%)	1/17 (6%)	2/22 (9%)
Week of First Observation	105	83	97
Life Table Tests (d)	P=0.558N	P=0.574N	P=0.650N
Incidental Tumor Tests (d)	P=0.549N	P=0.536N	P=0.619N
Cochran-Armitage Trend Test (d)	P=0.460N		
Fisher Exact Test (d)		P=0.380N	P=0.548N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	4/49 (8%)	3/45 (7%)	3/45 (7%)
Adjusted Rates (b)	13.3%	13.8%	11.7%
Terminal Rates (c)	4/30 (13%)	2/17 (12%)	2/22 (9%)
Week of First Observation	105	83	97
Life Table Tests (d)	P=0.573N	P=0.548	P=0.650N
Incidental Tumor Tests (d)	P=0.565N	P=0.584	P=0.619N
Cochran-Armitage Trend Test (d)	P=0.466N		
Fisher Exact Test (d)		P=0.548N	P=0.548N
Pancreatic Islets: Islet Cell Adenoma			
Overall Rates (a)	4/47 (9%)	7/50 (14%)	4/48 (8%)
Adjusted Rates (b)	11.9%	32.2%	17.4%
Terminal Rates (c)	2/28 (7%)	5/18 (28%)	4/23 (17%)
Week of First Observation	91	76	105
Life Table Tests (d)	P=0.434	P=0.100	P=0.540
Incidental Tumor Tests (d)	P=0.543	P=0.216	P=0.570
Cochran-Armitage Trend Test (d)	P=0.553N		
Fisher Exact Test (d)		P=0.299	P=0.631N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	200 ppm	400 ppm
Preputial Gland: Adenoma			
Overall Rates (a)	2/50 (4%)	0/50 (0%)	5/50 (10%)
Adjusted Rates (b)	5.6%	0.0%	16.5%
Terminal Rates (c)	1/30 (3%)	0/18 (0%)	2/23 (9%)
Week of First Observation	91		88
Life Table Tests (d)	P=0.095	P=0.311N	P=0.163
Incidental Tumor Tests (d)	P=0.094	P=0.245N	P=0.177
Cochran-Armitage Trend Test (d)	P=0.118		
Fisher Exact Test (d)		P=0.247N	P=0.218
Preputial Gland: Carcinoma or Squamous Cell Carcinoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	3.3%	8.9%	8.5%
Terminal Rates (c)	1/30 (3%)	0/18 (0%)	0/23 (0%)
Week of First Observation	105	91	92
Life Table Tests (d)	P=0.220	P=0.226	P=0.265
Incidental Tumor Tests (d)	P=0.271	P=0.391	P=0.331
Cochran-Armitage Trend Test (d)	P=0.238		
Fisher Exact Test (d)		P=0.309	P=0.309
Preputial Gland: Adenoma, Carcinoma, or Squamous Cell Carcinoma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	8/50 (16%)
Adjusted Rates (b)	8.9%	8.9%	23.7%
Terminal Rates (c)	2/30 (7%)	0/18 (0%)	2/23 (9%)
Week of First Observation	91	91	88
Life Table Tests (d)	P=0.050	P=0.532	P=0.070
Incidental Tumor Tests (d)	P=0.056	P=0.598N	P=0.086
Cochran-Armitage Trend Test (d)	P=0.061		
Fisher Exact Test (d)		P=0.661	P=0.100
Testis: Interstitial Cell Tumor			
Overall Rates (a)	39/50 (78%)	41/50 (82%)	43/49 (88%)
Adjusted Rates (b)	95.1%	95.2%	93.5%
Terminal Rates (c)	28/30 (93%)	16/18 (89%)	20/23 (87%)
Week of First Observation	84	81	75
Life Table Tests (d)	P=0.033	P=0.004	P=0.031
Incidental Tumor Tests (d)	P=0.078	P=0.154	P=0.131
Cochran-Armitage Trend Test (d)	P=0.126		
Fisher Exact Test (d)		P=0.401	P=0.154
All Sites: Mesothelioma			
Overall Rates (a)	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	2.2%	4.5%	12.3%
Terminal Rates (c)	0/30 (0%)	0/18 (0%)	2/23 (9%)
Week of First Observation	87	103	103
Life Table Tests (d)	P=0.153	P=0.699	P=0.235
Incidental Tumor Tests (d)	P=0.198	P=0.653N	P=0.263
Cochran-Armitage Trend Test (d)	P=0.202		
Fisher Exact Test (d)		P=0.753N	P=0.309

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

TABLE A4a. HISTORICAL INCIDENCE OF NASAL CAVITY TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

No nasal cavity tumors have been observed in 249 chamber control male rats at Battelle Pacific Northwest Laboratories.

Overall Historical Incidence in Untreated Controls

No. Examined	No. of Tumors	Diagnosis
1,977	1	Squamous cell papilloma
	1	Squamous cell carcinoma
TOTAL	2 (0.1%)	

(a) Data as of August 30, 1985, for studies of at least 104 weeks. No more than one tumor was observed in any untreated control group

TABLE A4b. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence in Chamber Controls at Battelle Pacific Northwest Laboratories			
Propylene oxide	0/50	2/50	2/50
Methyl methacrylate	0/49	1/49	1/49
Propylene	0/50	1/50	1/50
Dichloromethane	1/50	0/50	1/50
Tetrachloroethylene	1/50	0/50	1/50
TOTAL	2/249 (0.8%)	4/249 (1.6%)	6/249 (2.4%)
SD (b)	1.10%	1.68%	0.89%
Range (c)			
High	1/50	2/50	2/50
Low	0/50	0/50	1/50
Overall Historical Incidence in Untreated Controls			
TOTAL	26/1,973 (1.3%)	14/1,973 (0.7%)	38/1,973 (1.9%)
SD (b)	1.75%	1.41%	1.99%
Range (c)			
High	3/49	3/50	3/49
Low	0/89	0/50	0/50

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

TABLE A4c. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls	
	Leukemia	Lymphoma or Leukemia
Historical Incidence in Chamber Controls at Battelle Pacific Northwest Laboratories		
Propylene oxide	20/50	22/50
Methyl methacrylate	19/50	20/50
Propylene	16/50	16/50
Dichloromethane	34/50	34/50
Tetrachloroethylene	28/50	28/50
TOTAL	117/250 (46.8%)	120/250 (48.0%)
SD (b)	14.81%	14.14%
Range (c)		
High	34/50	34/50
Low	16/50	16/50
Overall Historical Incidence in Untreated Controls		
TOTAL	583/1,977 (29.5%)	612/1,977 (31.0%)
SD (b)	11.59%	11.80%
Range (c)		
High	30/50	30/50
Low	5/50	5/50

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

TABLE A4d. HISTORICAL INCIDENCE OF PREPUTIAL GLAND TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence in Chamber Controls at Battelle Pacific Northwest Laboratories			
Propylene oxide	0/50	0/50	0/50
Methyl methacrylate	3/50	2/50	5/50
Propylene	0/50	0/50	0/50
Dichloromethane	0/50	3/50	3/50
Tetrachloroethylene	1/50	2/50	3/50
TOTAL	4/250 (1.6%)	7/250 (2.8%)	11/250 (4.4%)
SD (b)	2.61%	2.68%	4.34%
Range (c)			
High	3/50	3/50	5/50
Low	0/50	0/50	0/50
Overall Historical Incidence in Untreated Controls			
TOTAL	(d) 50/1,977 (2.5%)	(e) 65/1,977 (3.3%)	(d,e) 115/1,977 (5.8%)
SD (b)	3.61%	2.95%	4.44%
Range (c)			
High	8/50	5/50	8/50
Low	0/90	0/50	0/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes one papillary adenoma and one cystadenoma
(e) Includes two squamous cell carcinomas; eight adenocarcinomas, NOS, and two sebaceous adenocarcinomas

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE

	Chamber Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Epidermal inclusion cyst		2 (4%)	
*Subcutaneous tissue	(50)	(50)	(50)
Abscess, NOS		1 (2%)	1 (2%)
Inflammation, chronic	1 (2%)		1 (2%)
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Hemorrhage			1 (2%)
Inflammation, NOS	9 (18%)	36 (72%)	42 (84%)
Inflammation, serous	2 (4%)	28 (56%)	36 (72%)
Inflammation, suppurative	10 (20%)	37 (74%)	49 (98%)
Hyperostosis		2 (4%)	11 (22%)
Hyperplasia, epithelial	8 (16%)	38 (76%)	46 (92%)
Hyperplasia, adenomatous			5 (10%)
Metaplasia, squamous	4 (8%)	22 (44%)	40 (80%)
*Larynx	(50)	(50)	(50)
Inflammation, suppurative	15 (30%)	8 (16%)	21 (42%)
Hyperplasia, epithelial	2 (4%)		
#Trachea	(49)	(47)	(48)
Inflammation, suppurative	2 (4%)	1 (2%)	4 (8%)
Hyperplasia, epithelial	1 (2%)		2 (4%)
#Lung/bronchus	(50)	(50)	(49)
Inflammation, suppurative	1 (2%)		1 (2%)
Fibrosis	1 (2%)		
Hyperplasia, epithelial			1 (2%)
#Lung	(50)	(50)	(49)
Foreign body, NOS			1 (2%)
Congestion, NOS		3 (6%)	1 (2%)
Edema, NOS		1 (2%)	
Hemorrhage	5 (10%)	6 (12%)	4 (8%)
Inflammation, suppurative			2 (4%)
Inflammation, chronic focal	7 (14%)	7 (14%)	8 (16%)
Perivascular cuffing	19 (38%)	12 (24%)	22 (45%)
Pigmentation, NOS	1 (2%)		
Hyperplasia, alveolar epithelium	5 (10%)	5 (10%)	7 (14%)
Metaplasia, osseous	2 (4%)	1 (2%)	1 (2%)
Histiocytosis	13 (26%)	10 (20%)	9 (18%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(48)	(49)	(47)
Fibrosis		2 (4%)	1 (2%)
#Spleen	(50)	(50)	(49)
Accessory structure		1 (2%)	
Inflammation, granulomatous focal			1 (2%)
Fibrosis	7 (14%)	7 (14%)	6 (12%)
Adhesion, fibrous		1 (2%)	
Necrosis, NOS	2 (4%)	1 (2%)	
Hemosiderosis		2 (4%)	
Hyperplasia, lymphoid	1 (2%)		
Hematopoiesis			3 (6%)
#Mandibular lymph node	(49)	(48)	(49)
Inflammation, chronic			1 (2%)
Hyperplasia, NOS	2 (4%)	4 (8%)	2 (4%)
Erythrophagocytosis			1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Thoracic lymph node	(49)	(48)	(49)
Congestion, NOS			1 (2%)
Inflammation, chronic	1 (2%)		
Hemosiderosis			1 (2%)
Hyperplasia, NOS	1 (2%)	1 (2%)	
Erythrophagocytosis			1 (2%)
#Mesenteric lymph node	(49)	(48)	(49)
Hyperplasia, NOS	1 (2%)		
#Renal lymph node	(49)	(48)	(49)
Hyperplasia, NOS	1 (2%)		
#Lung	(50)	(50)	(49)
Leukocytosis, NOS	1 (2%)		
Hyperplasia, lymphoid	3 (6%)	6 (12%)	4 (8%)
#Liver	(50)	(50)	(49)
Leukocytosis, NOS	3 (6%)		
Hematopoiesis	1 (2%)		2 (4%)
#Adrenal	(50)	(49)	(48)
Leukocytosis, NOS	1 (2%)		
Hematopoiesis		2 (4%)	
CIRCULATORY SYSTEM			
*Thoracic cavity	(50)	(50)	(50)
Perivasculitis			1 (2%)
#Mandibular lymph node	(49)	(48)	(49)
Lymphangiectasis		2 (4%)	1 (2%)
#Renal lymph node	(49)	(48)	(49)
Lymphangiectasis		1 (2%)	
*Nasal cavity	(50)	(50)	(50)
Thrombosis, NOS	7 (14%)	7 (14%)	2 (4%)
#Heart	(50)	(50)	(50)
Thrombosis, NOS	5 (10%)	4 (8%)	3 (6%)
Inflammation, chronic	48 (96%)	44 (88%)	47 (94%)
Perivasculitis	1 (2%)		
Hemosiderosis	1 (2%)		
*Blood vessel	(50)	(50)	(50)
Aneurysm		1 (2%)	
Perivasculitis		1 (2%)	
Hypertrophy, NOS		2 (4%)	
#Liver	(50)	(50)	(49)
Thrombosis, NOS		1 (2%)	
#Pancreas	(47)	(50)	(48)
Perivasculitis	2 (4%)		3 (6%)
#Testis	(50)	(50)	(49)
Perivasculitis	7 (14%)	6 (12%)	4 (8%)
DIGESTIVE SYSTEM			
*Mouth	(50)	(50)	(50)
Ulcer, NOS		1 (2%)	
Inflammation, chronic		1 (2%)	
#Salivary gland	(48)	(49)	(48)
Inflammation, NOS	3 (6%)		
Focal cellular change	1 (2%)		
Atrophy, NOS	1 (2%)		1 (2%)
Hyperplasia, epithelial	1 (2%)	4 (8%)	2 (4%)
Metaplasia, squamous	1 (2%)		

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Liver	(50)	(50)	(49)
Inflammation, granulomatous focal	11 (22%)	7 (14%)	5 (10%)
Degeneration, NOS	1 (2%)	3 (6%)	2 (4%)
Degeneration, cystic	6 (12%)	3 (6%)	6 (12%)
Degeneration, lipoid	7 (14%)	4 (8%)	4 (8%)
Necrosis, NOS	3 (6%)	3 (6%)	3 (6%)
Pigmentation, NOS	3 (6%)	2 (4%)	
Cytoplasmic vacuolization	2 (4%)	3 (6%)	1 (2%)
Basophilic cyto change	25 (50%)	21 (42%)	23 (47%)
Hyperplasia, focal	8 (16%)	5 (10%)	8 (16%)
Angiectasis		6 (12%)	4 (8%)
Regeneration, NOS	1 (2%)		
#Bile duct	(50)	(50)	(49)
Hyperplasia, NOS	30 (60%)	22 (44%)	18 (37%)
#Pancreas	(47)	(50)	(48)
Inflammation, NOS	1 (2%)		
Atrophy, NOS	13 (28%)	20 (40%)	20 (42%)
#Pancreatic acinus	(47)	(50)	(48)
Hyperplasia, NOS			1 (2%)
#Glandular stomach	(50)	(49)	(49)
Hemorrhage		1 (2%)	
Inflammation, NOS		1 (2%)	1 (2%)
Ulcer, NOS		1 (2%)	
Inflammation, suppurative	3 (6%)	3 (6%)	
Erosion	5 (10%)	3 (6%)	1 (2%)
Fibrosis	1 (2%)		
#Forestomach	(50)	(49)	(49)
Inflammation, NOS	4 (8%)	4 (8%)	
Ulcer, NOS	4 (8%)	3 (6%)	1 (2%)
Inflammation, suppurative	1 (2%)		
Hyperplasia, epithelial	6 (12%)	7 (14%)	2 (4%)
Hyperkeratosis			1 (2%)
#Colon	(48)	(47)	(47)
Parasitism	6 (13%)	12 (26%)	11 (23%)
#Cecum	(48)	(47)	(47)
Parasitism		1 (2%)	
*Rectum	(50)	(50)	(50)
Parasitism	5 (10%)	5 (10%)	2 (4%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Hydronephrosis			2 (4%)
Hemorrhage	1 (2%)		
Inflammation, suppurative	3 (6%)	2 (4%)	6 (12%)
Nephropathy	48 (96%)	49 (98%)	48 (96%)
Hyperplasia, tubular cell	1 (2%)	1 (2%)	
#Kidney/pelvis	(50)	(50)	(50)
Inflammation, suppurative	3 (6%)	1 (2%)	
Hyperplasia, epithelial	6 (12%)	1 (2%)	2 (4%)
#Urinary bladder	(49)	(48)	(47)
Calculus, unknown gross or micro	1 (2%)		
Hemorrhage			1 (2%)
Inflammation, suppurative	3 (6%)		1 (2%)
Hyperplasia, epithelial	3 (6%)	2 (4%)	2 (4%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Pituitary intermedia	(48)	(48)	(47)
Degeneration, cystic			1 (2%)
#Anterior pituitary	(48)	(48)	(47)
Cyst, NOS	1 (2%)		
Degeneration, cystic	2 (4%)	3 (6%)	
Hyperplasia, NOS	10 (21%)	7 (15%)	8 (17%)
#Adrenal	(50)	(49)	(48)
Degeneration, NOS		1 (2%)	
Degeneration, lipoid	14 (28%)	14 (29%)	12 (25%)
Necrosis, NOS	1 (2%)		
Basophilic cyto change	1 (2%)		
#Adrenal cortex	(50)	(49)	(48)
Focal cellular change	1 (2%)	1 (2%)	
Hyperplasia, NOS	8 (16%)	6 (12%)	3 (6%)
#Adrenal medulla	(50)	(49)	(48)
Hyperplasia, NOS	5 (10%)	10 (20%)	6 (13%)
#Thyroid	(49)	(45)	(45)
Cyst, NOS			1 (2%)
Degeneration, cystic	3 (6%)		1 (2%)
Hyperplasia, C-cell	21 (43%)	19 (42%)	15 (33%)
#Parathyroid	(28)	(32)	(37)
Hyperplasia, NOS	4 (14%)	4 (13%)	4 (11%)
#Pancreatic islets	(47)	(50)	(48)
Hyperplasia, NOS	5 (11%)	3 (6%)	1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Galactocele	1 (2%)		
Hyperplasia, NOS	11 (22%)	20 (40%)	13 (26%)
*Preputial gland	(50)	(50)	(50)
Dilatation, NOS		2 (4%)	
Inflammation, suppurative	8 (16%)	8 (16%)	7 (14%)
Abscess, NOS	1 (2%)	3 (6%)	2 (4%)
Inflammation, chronic	1 (2%)	1 (2%)	
Hyperplasia, epithelial	2 (4%)		1 (2%)
#Prostate	(47)	(48)	(48)
Inflammation, NOS		1 (2%)	
Inflammation, suppurative	5 (11%)	11 (23%)	8 (17%)
Inflammation, chronic suppurative	1 (2%)		1 (2%)
Hyperplasia, epithelial	2 (4%)	8 (17%)	5 (10%)
*Seminal vesicle	(50)	(50)	(50)
Inflammation, suppurative	3 (6%)	2 (4%)	7 (14%)
#Testis	(50)	(50)	(49)
Atrophy, NOS	35 (70%)	43 (86%)	42 (86%)
Hyperplasia, interstitial cell	7 (14%)	4 (8%)	2 (4%)
*Epididymis	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		
Cytoplasmic change, NOS	13 (26%)	16 (32%)	10 (20%)
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Hemorrhage	2 (4%)	5 (10%)	2 (4%)
Perivascular cuffing	1 (2%)		
Necrosis, NOS		3 (6%)	
*Olfactory sensory epithelium	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)	1 (2%)	4 (8%)
Atrophy, NOS		18 (36%)	12 (24%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	Low Dose	High Dose
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Degeneration, NOS		1 (2%)	1 (2%)
*Lacrimal apparatus	(50)	(50)	(50)
Inflammation, NOS		1 (2%)	
Pigmentation, NOS		1 (2%)	
*Nasolacrimal duct	(50)	(50)	(50)
Hemorrhage			1 (2%)
Inflammation, serous		1 (2%)	
Inflammation, suppurative	11 (22%)	11 (22%)	9 (18%)
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
Fibrous osteodystrophy	3 (6%)	4 (8%)	1 (2%)
*Cartilage, NOS	(50)	(50)	(50)
Necrosis, focal	1 (2%)		
BODY CAVITIES			
*Peritoneal cavity	(50)	(50)	(50)
Mineralization		1 (2%)	
Necrosis, fat	1 (2%)	1 (2%)	
Hemosiderosis		1 (2%)	
*Pericardium	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
*Tunica vaginalis	(50)	(50)	(50)
Hyperplasia, mesothelial			1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Mineralization	3 (6%)	5 (10%)	3 (6%)
Inflammation, NOS		1 (2%)	
Abscess, NOS			1 (2%)
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX B

SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE

	Chamber Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell papilloma		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma		1 (2%)	
Fibrosarcoma			1 (2%)
Neurilemoma			1 (2%)
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Papillary adenoma			2 (4%)
#Lung	(50)	(49)	(50)
Alveolar/bronchiolar adenoma	1 (2%)		1 (2%)
Alveolar/bronchiolar carcinoma	1 (2%)		
Fibrosarcoma, metastatic			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	25 (50%)	22 (44%)	24 (48%)
#Spleen	(50)	(48)	(49)
Leukemia, mononuclear cell		2 (4%)	1 (2%)
#Liver	(50)	(49)	(50)
Leukemia, mononuclear cell	1 (2%)	1 (2%)	
#Thymus	(38)	(40)	(43)
Thymoma, malignant		1 (3%)	
CIRCULATORY SYSTEM			
#Liver	(50)	(49)	(50)
Hemangiosarcoma		1 (2%)	
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(50)
Squamous cell papilloma		1 (2%)	
#Liver	(50)	(49)	(50)
Hepatocellular carcinoma	1 (2%)		
Neurofibrosarcoma, metastatic	1 (2%)		
#Pancreas	(50)	(49)	(49)
Granulosa cell carcinoma, invasive		1 (2%)	
#Forestomach	(50)	(48)	(49)
Squamous cell papilloma			1 (2%)
Squamous cell carcinoma			1 (2%)
#Small intestine	(49)	(46)	(46)
Leiomyoma		1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(48)	(48)
Granulosa cell carcinoma, invasive		1 (2%)	
Sarcoma, NOS			1 (2%)
Endometrial stromal sarcoma, metastatic	1 (2%)		
#Urinary bladder	(49)	(47)	(47)
Transitional cell papilloma			1 (2%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Pituitary intermedia	(49)	(48)	(48)
Adenoma, NOS	1 (2%)		
#Anterior pituitary	(49)	(48)	(48)
Carcinoma, NOS	6 (12%)	8 (17%)	3 (6%)
Adenoma, NOS	25 (51%)	26 (54%)	32 (67%)
#Adrenal	(50)	(48)	(48)
Cortical adenoma	1 (2%)	2 (4%)	1 (2%)
Pheochromocytoma	4 (8%)	4 (8%)	2 (4%)
#Thyroid	(45)	(48)	(48)
Follicular cell adenoma			2 (4%)
Follicular cell carcinoma		1 (2%)	1 (2%)
C-cell adenoma	3 (7%)	4 (8%)	1 (2%)
C-cell carcinoma	2 (4%)	3 (6%)	
#Parathyroid	(24)	(34)	(31)
Adenoma, NOS		1 (3%)	
#Pancreatic islets	(50)	(49)	(49)
Islet cell adenoma		1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenoma, NOS	1 (2%)		2 (4%)
Adenocarcinoma, NOS	1 (2%)	2 (4%)	1 (2%)
Fibroadenoma	15 (30%)	12 (24%)	16 (32%)
*Clitoral gland	(50)	(50)	(50)
Carcinoma, NOS	2 (4%)	3 (6%)	2 (4%)
Papilloma, NOS			1 (2%)
Adenoma, NOS	1 (2%)	3 (6%)	
#Uterus	(49)	(48)	(49)
Sarcoma, NOS	1 (2%)		
Fibroma	1 (2%)		
Leiomyoma	1 (2%)		1 (2%)
Endometrial stromal polyp	5 (10%)	4 (8%)	8 (16%)
Endometrial stromal sarcoma	2 (4%)		
#Ovary	(49)	(48)	(50)
Adenocarcinoma, NOS		1 (2%)	
Thecoma			1 (2%)
Granulosa cell tumor			1 (2%)
Granulosa cell carcinoma		1 (2%)	1 (2%)
NERVOUS SYSTEM			
#Brain	(50)	(48)	(50)
Carcinoma, NOS, invasive	2 (4%)	3 (6%)	1 (2%)
Granular cell tumor, NOS	1 (2%)		
SPECIAL SENSE ORGANS			
None			
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Peritoneal cavity	(50)	(50)	(50)
Fibrosarcoma, invasive			1 (2%)
Mesothelioma, malignant			1 (2%)
Neurofibrosarcoma	1 (2%)		

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	Low Dose	High Dose
ALL OTHER SYSTEMS			
Perineum			
Fibroma		1	
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	2	8	4
Moribund sacrifice	16	21	23
Terminal sacrifice	32	21	22
Accidentally killed, NOS			1
TUMOR SUMMARY			
Total animals with primary tumors**	45	47	47
Total primary tumors	103	108	112
Total animals with benign tumors	32	38	42
Total benign tumors	59	62	74
Total animals with malignant tumors	34	33	34
Total malignant tumors	43	46	37
Total animals with secondary tumors##	4	4	2
Total secondary tumors	4	5	3
Total animals with tumors uncertain-- benign or malignant	1		1
Total uncertain tumors	1		1

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

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE: CHAMBER CONTROL

ANIMAL NUMBER	028	029	050	033	041	007	017	038	040	036	003	008	021	005	002	018	023	019	001	004	006	009	010	011	012
WEEKS ON STUDY	077	078	079	085	085	086	088	091	092	093	095	095	097	098	099	099	099	104	105	105	105	105	105	105	105
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X																	
Alveolar/bronchiolar carcinoma																							X		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Neurofibrosarcoma, metastatic																									
Leukemia, mononuclear cell																					X				
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal sarcoma, metastatic																					X				
Urinary bladder	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS	X	X						X		X		X											X		
Adenoma, NOS							X		X		X			X	X	X			X			X			
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma						X																			
Pheochromocytoma											X							X							
Thyroid	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+
C-cell adenoma																					X				
C-cell carcinoma																									
Parathyroid	−	+	+	+	+	+	+	+	+	−	+	+	−	−	+	−	+	−	−	−	−	−	+	−	−
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS				X																					
Adenocarcinoma, NOS																									
Fibroadenoma								X	X		X			X					X		X				
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS											X								X						
Adenoma, NOS																									
Uterus	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS		X																							
Fibroma																									
Leiomyoma																									
Endometrial stromal polyp				X										X		X									
Endometrial stromal sarcoma																					X	X			
Ovary	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive	X									X															
Granular cell tumor, NOS														X											
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Neurofibrosarcoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell			X	X	X	X			X			X	X	X	X	X	X	X	X	X			X	X	

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

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

ANIMAL NUMBER	013	014	015	016	020	022	024	025	026	027	030	031	032	034	035	037	039	042	043	044	045	046	047	048	049	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	−	−	+	−	−	−	+	+	+	−	+	+	+	+	+	+	−	−	+	−	38
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																		X								1
Neurofibrosarcoma, metastatic																		X								1
Leukemia, mononuclear cell																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal sarcoma, meta																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	49
Carcinoma, NOS																										6
Adenoma, NOS	X	X		X		X@	X			X	X	X		X	X	X	X	X				X	X	X	X	25
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																										1
Pheochromocytoma						X											X									4
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	45
C-cell adenoma																X	X									3
C-cell carcinoma				X															X							2
Parathyroid	−	−	+	−	−	+	+	+	−	+	−	−	−	+	−	+	+	−	−	+	+	+	−	−	−	24
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS																										1
Adenocarcinoma, NOS																		X								1
Fibroadenoma	X	X			X						X	X					X			X			X	X		15
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										2
Adenoma, NOS																X										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, NOS																										1
Fibroma																	X									1
Leiomyoma																							X			1
Endometrial stromal polyp	X																						X			5
Endometrial stromal sarcoma																										2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																										2
Granular cell tumor, NOS																										1
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Neurofibrosarcoma																		X								1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell					X	X	X				X						X	X		X	X		X			25

* Animals necropsied
@ Multiple occurrence of morphology

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE: LOW DOSE

ANIMAL NUMBER	012	022	036	002	028	039	048	042	014	018	010	011	016	034	008	031	003	006	019	047	050	033	041	004	026
WEEKS ON STUDY	001	032	049	066	068	071	071	073	081	083	085	085	085	085	087	089	091	091	091	091	091	092	092	095	095
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																					X				
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma							X																		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																	X								
Lymph nodes	−	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	A	A	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
Thymoma, malignant										X															
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																									
Salivary gland	−	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																						X			
Leukemia, mononuclear cell																									
Bile duct	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell carcinoma, invasive						X																			
Esophagus	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	A	A	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Leiomyoma																									
Large intestine	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+
URINARY SYSTEM																									
Kidney	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell carcinoma, invasive						X																			
Urinary bladder	+	A	A	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS				X						X							X						X		
Adenoma, NOS							X	X	X					X	X	X		X			X				X
Adrenal	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma								X				X	X									X			
Thyroid	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																									
C-cell adenoma																									
C-cell carcinoma																									
Parathyroid	−	A	A	+	+	+	+	+	−	+	−	+	−	+	−	+	+	−	+	−	+	+	+	−	+
Adenoma, NOS							X																		
Pancreatic islets	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS														X											
Fibroadenoma							X						X	X	X						X				
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																	X								X
Adenoma, NOS																								X	
Uterus	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp														X				X					X		
Ovary	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																								X	
Granulosa cell carcinoma						X																			
NERVOUS SYSTEM																									
Brain	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive										X							X						X		
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell					X			X			X		X			X			X	X				X	X
Perineum, NOS																									
Fibroma																									

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

ANIMAL NUMBER	001	025	049	021	005	007	009	013	015	017	020	023	024	027	029	030	032	035	037	038	040	043	044	045	046	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	099	099	100	102	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia, mononuclear cell																								X		2
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	−	+	+	+	+	+	−	+	+	−	−	+	+	−	+	+	+	+	+	+	40
Thymoma, malignant																										1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma											X															1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Leukemia, mononuclear cell							X																			1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granulosa cell carcinoma, invasive																										1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Leiomyoma												X														1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Granulosa cell carcinoma, invasive																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS										X			X									X		X		8
Adenoma, NOS	X		X	X	X	X	X	X	X		X			X	X	X		X		X	X		X		X	26
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cortical adenoma										X				X												2
Pheochromocytoma																										4
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell carcinoma													X													1
C-cell adenoma	X					X										X				X						4
C-cell carcinoma							X		X												X					3
Parathyroid	+	−	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	−	34
Adenoma, NOS																										1
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma																							X			1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																									X	2
Fibroadenoma								X			X		X	X					X	X				X		12
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS										X																3
Adenoma, NOS													X									X				3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Endometrial stromal polyp			X																							4
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma, NOS																										1
Granulosa cell carcinoma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS, invasive																										3
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell	X	X	X	X		X				X	X		X			X		X	X		X	X				22
Perineum, NOS																										
Fibroma																	X									1

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE: HIGH DOSE

ANIMAL NUMBER	010	019	050	024	035	006	016	001	007	009	041	036	046	039	003	018	022	044	004	038	021	028	008	026	029
WEEKS ON STUDY	021	055	071	073	075	076	076	078	085	086	088	089	091	092	095	096	096	096	097	097	099	099	100	100	103
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma				X																					
Neurilemoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X														
Fibrosarcoma, metastatic				X																					
Trachea	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary adenoma						X								X											
HEMATOPOIETIC SYSTEM																									
Bone marrow	A	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Leukemia, mononuclear cell																								X	
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Thymus	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Squamous cell carcinoma																									
Small intestine	A	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Large intestine	A	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
URINARY SYSTEM																									
Kidney	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Sarcoma, NOS																									
Urinary bladder	A	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Transitional cell papilloma																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Carcinoma, NOS																			X						
Adenoma, NOS			X		X						X	X	X		X	X	X	X		X	X			X	
Adrenal	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Cortical adenoma																							X		
Pheochromocytoma																									
Thyroid	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Follicular cell adenoma																				X					
Follicular cell carcinoma																									
C-cell adenoma																									
Parathyroid	A	−	+	−	+	+	−	+	+	+	+	+	−	−	+	−	+	+	−	+	+	+	−	+	−
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Islet cell adenoma																					X				
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adenocarcinoma, NOS																									
Fibroadenoma														X			X		X		X			X	
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS														X											
Papilloma, NOS																									
Uterus	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Endometrial stromal polyp								X			X		X	X						X					
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thecoma																									
Granulosa cell tumor																									
Granulosa cell carcinoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																			X						
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma, invasive				X																					
Mesothelioma, malignant																						X			
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell						X	X	X	X		X	X	X			X	X	X		X		X	X		X

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

ANIMAL NUMBER	034	037	049	002	005	011	012	013	014	015	017	020	023	025	027	030	031	032	033	040	042	043	045	047	048	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	103	103	103	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																										1
Neurilemoma						X																				1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Fibrosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Papillary adenoma																										2
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia, mononuclear cell																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	43
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma											X															1
Squamous cell carcinoma				X																						1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Sarcoma, NOS					X																					1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Transitional cell papilloma									X																	1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	48
Carcinoma, NOS										X												X				3
Adenoma, NOS	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X				X	X	32
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cortical adenoma																										1
Pheochromocytoma									X							X										2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma																		X								2
Follicular cell carcinoma							X																			1
C-cell adenoma																				X						1
Parathyroid	+	+	+	+	−	+	−	−	+	−	+	+	+	−	+	−	−	−	+	+	+	+	+	−	+	31
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS		X									X															2
Adenocarcinoma, NOS																	X									1
Fibroadenoma	X		X	X			X	X		X				X	X	X		X						X		16
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																				X						2
Papilloma, NOS																							X			1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyoma																						X				1
Endometrial stromal polyp													X				X				X					8
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thecoma																					X					1
Granulosa cell tumor															X											1
Granulosa cell carcinoma											X															1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																										1
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma, invasive																										1
Mesothelioma, malignant																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell	X	X		X		X	X		X									X					X	X	X	24

* Animals necropsied

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE

	Chamber Control	200 ppm	400 ppm
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	26/50 (52%)	25/50 (50%)	25/50 (50%)
Adjusted Rates (b)	58.7%	70.2%	62.3%
Terminal Rates (c)	14/32 (44%)	11/21 (52%)	8/22 (36%)
Week of First Observation	79	68	76
Life Table Tests (d)	P=0.218	P=0.129	P=0.252
Incidental Tumor Tests (d)	P=0.390N	P=0.420	P=0.449N
Cochran-Armitage Trend Test (d)	P=0.460N		
Fisher Exact Test (d)		P=0.500N	P=0.500N
Pituitary Gland: Adenoma			
Overall Rates (a)	25/49 (51%)	26/48 (54%)	32/48 (67%)
Adjusted Rates (b)	66.9%	77.3%	88.0%
Terminal Rates (c)	19/31 (61%)	14/21 (67%)	17/21 (81%)
Week of First Observation	88	71	71
Life Table Tests (d)	P=0.005	P=0.051	P=0.005
Incidental Tumor Tests (d)	P=0.017	P=0.185	P=0.017
Cochran-Armitage Trend Test (d)	P=0.073		
Fisher Exact Test (d)		P=0.457	P=0.087
Pituitary Gland: Carcinoma			
Overall Rates (a)	6/49 (12%)	8/48 (17%)	3/48 (6%)
Adjusted Rates (b)	13.7%	27.6%	12.4%
Terminal Rates (c)	1/31 (3%)	4/21 (19%)	2/21 (10%)
Week of First Observation	77	66	97
Life Table Tests (d)	P=0.372N	P=0.202	P=0.365N
Incidental Tumor Tests (d)	P=0.174N	P=0.546	P=0.138N
Cochran-Armitage Trend Test (d)	P=0.226N		
Fisher Exact Test (d)		P=0.371	P=0.254N
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	31/49 (63%)	34/48 (71%)	35/48 (73%)
Adjusted Rates (b)	73.0%	91.3%	94.2%
Terminal Rates (c)	20/31 (65%)	18/21 (86%)	19/21 (90%)
Week of First Observation	77	66	71
Life Table Tests (d)	P=0.016	P=0.016	P=0.019
Incidental Tumor Tests (d)	P=0.069	P=0.140	P=0.096
Cochran-Armitage Trend Test (d)	P=0.179		
Fisher Exact Test (d)		P=0.282	P=0.212
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	4/50 (8%)	4/48 (8%)	2/48 (4%)
Adjusted Rates (b)	11.4%	10.4%	9.1%
Terminal Rates (c)	2/32 (6%)	0/21 (0%)	2/22 (9%)
Week of First Observation	95	73	105
Life Table Tests (d)	P=0.404N	P=0.464	P=0.499N
Incidental Tumor Tests (d)	P=0.269N	P=0.545N	P=0.395N
Cochran-Armitage Trend Test (d)	P=0.293N		
Fisher Exact Test (d)		P=0.619	P=0.359N
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	0/45 (0%)	1/48 (2%)	3/48 (6%)
Adjusted Rates (b)	0.0%	4.8%	11.9%
Terminal Rates (c)	0/29 (0%)	1/21 (5%)	2/22 (9%)
Week of First Observation		105	97
Life Table Tests (d)	P=0.043	P=0.436	P=0.083
Incidental Tumor Tests (d)	P=0.059	P=0.436	P=0.115
Cochran-Armitage Trend Test (d)	P=0.066		
Fisher Exact Test (d)		P=0.516	P=0.133

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	200 ppm	400 ppm
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	3/45 (7%)	4/48 (8%)	1/48 (2%)
Adjusted Rates (b)	10.3%	17.7%	4.5%
Terminal Rates (c)	3/29 (10%)	3/21 (14%)	1/22 (5%)
Week of First Observation	105	99	105
Life Table Tests (d)	P=0.371N	P=0.326	P=0.407N
Incidental Tumor Tests (d)	P=0.330N	P=0.329	P=0.407N
Cochran-Armitage Trend Test (d)	P=0.227N		
Fisher Exact Test (d)		P=0.536	P=0.284N
Thyroid Gland: C-Cell Carcinoma			
Overall Rates (a)	2/45 (4%)	3/48 (6%)	0/48 (0%)
Adjusted Rates (b)	6.9%	14.3%	0.0%
Terminal Rates (c)	2/29 (7%)	3/21 (14%)	0/22 (0%)
Week of First Observation	105	105	
Life Table Tests (d)	P=0.288N	P=0.353	P=0.300N
Incidental Tumor Tests (d)	P=0.288N	P=0.353	P=0.300N
Cochran-Armitage Trend Test (d)	P=0.184N		
Fisher Exact Test (d)		P=0.531	P=0.231N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	5/45 (11%)	7/48 (15%)	1/48 (2%)
Adjusted Rates (b)	17.2%	31.4%	4.5%
Terminal Rates (c)	5/29 (17%)	6/21 (29%)	1/22 (5%)
Week of First Observation	105	99	105
Life Table Tests (d)	P=0.209N	P=0.171	P=0.172N
Incidental Tumor Tests (d)	P=0.184N	P=0.173	P=0.172N
Cochran-Armitage Trend Test (d)	P=0.088N		
Fisher Exact Test (d)		P=0.426	P=0.088N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	15/50 (30%)	12/50 (24%)	16/50 (32%)
Adjusted Rates (b)	40.6%	41.6%	53.4%
Terminal Rates (c)	11/32 (34%)	7/21 (33%)	9/22 (41%)
Week of First Observation	91	71	92
Life Table Tests (d)	P=0.156	P=0.425	P=0.171
Incidental Tumor Tests (d)	P=0.279	P=0.456N	P=0.312
Cochran-Armitage Trend Test (d)	P=0.456		
Fisher Exact Test (d)		P=0.326N	P=0.500
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (a)	16/50 (32%)	12/50 (24%)	18/50 (36%)
Adjusted Rates (b)	41.9%	41.6%	58.8%
Terminal Rates (c)	11/32 (34%)	7/21 (33%)	10/22 (45%)
Week of First Observation	85	71	92
Life Table Tests (d)	P=0.110	P=0.506	P=0.119
Incidental Tumor Tests (d)	P=0.213	P=0.335N	P=0.240
Cochran-Armitage Trend Test (d)	P=0.372		
Fisher Exact Test (d)		P=0.252N	P=0.417
Mammary Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	2/50 (4%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	5.2%	7.4%	12.6%
Terminal Rates (c)	1/32 (3%)	1/21 (5%)	2/22 (9%)
Week of First Observation	85	87	103
Life Table Tests (d)	P=0.293	P=0.582	P=0.369
Incidental Tumor Tests (d)	P=0.327	P=0.643N	P=0.424
Cochran-Armitage Trend Test (d)	P=0.406		
Fisher Exact Test (d)		P=0.691	P=0.500

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	200 ppm	400 ppm
Clitoral Gland: Adenoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	3.1%	12.9%	0.0%
Terminal Rates (c)	1/32 (3%)	2/21 (10%)	0/22 (0%)
Week of First Observation	105	95	
Life Table Tests (d)	P=0.485N	P=0.173	P=0.575N
Incidental Tumor Tests (d)	P=0.435N	P=0.172	P=0.575N
Cochran-Armitage Trend Test (d)	P=0.378N		
Fisher Exact Test (d)		P=0.309	P=0.500N
Clitoral Gland: Adenoma or Papilloma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	3.1%	12.9%	4.5%
Terminal Rates (c)	1/32 (3%)	2/21 (10%)	1/22 (5%)
Week of First Observation	105	95	105
Life Table Tests (d)	P=0.484	P=0.173	P=0.676
Incidental Tumor Tests (d)	P=0.530	P=0.172	P=0.676
Cochran-Armitage Trend Test (d)	P=0.610		
Fisher Exact Test (d)		P=0.309	P=0.753
Clitoral Gland: Carcinoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	5.5%	11.0%	7.1%
Terminal Rates (c)	1/32 (3%)	1/21 (5%)	1/22 (5%)
Week of First Observation	95	91	92
Life Table Tests (d)	P=0.488	P=0.337	P=0.603
Incidental Tumor Tests (d)	P=0.571	P=0.416	P=0.653
Cochran-Armitage Trend Test (d)	P=0.594		
Fisher Exact Test (d)		P=0.500	P=0.691
Clitoral Gland: Adenoma, Papilloma, or Carcinoma			
Overall Rates (a)	3/50 (6%)	6/50 (12%)	3/50 (6%)
Adjusted Rates (b)	8.6%	23.0%	11.5%
Terminal Rates (c)	2/32 (6%)	3/21 (14%)	2/22 (9%)
Week of First Observation	95	91	92
Life Table Tests (d)	P=0.411	P=0.096	P=0.524
Incidental Tumor Tests (d)	P=0.502	P=0.120	P=0.567
Cochran-Armitage Trend Test (d)	P=0.573		
Fisher Exact Test (d)		P=0.243	P=0.661
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	5/49 (10%)	4/48 (8%)	8/49 (16%)
Adjusted Rates (b)	13.2%	12.6%	24.5%
Terminal Rates (c)	2/32 (6%)	0/21 (0%)	3/22 (14%)
Week of First Observation	85	85	78
Life Table Tests (d)	P=0.138	P=0.578	P=0.161
Incidental Tumor Tests (d)	P=0.239	P=0.397N	P=0.299
Cochran-Armitage Trend Test (d)	P=0.216		
Fisher Exact Test (d)		P=0.513N	P=0.276
Ovary: Thecoma, Granulosa Cell Tumor, or Carcinoma			
Overall Rates (a)	0/49 (0%)	1/48 (2%)	3/50 (6%)
Adjusted Rates (b)	0.0%	2.2%	13.6%
Terminal Rates (c)	0/32 (0%)	0/21 (0%)	3/22 (14%)
Week of First Observation		71	105
Life Table Tests (d)	P=0.039	P=0.479	P=0.063
Incidental Tumor Tests (d)	P=0.056	P=0.682	P=0.063
Cochran-Armitage Trend Test (d)	P=0.063		
Fisher Exact Test (d)		P=0.495	P=0.125

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

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

TABLE B4a. HISTORICAL INCIDENCE OF NASAL CAVITY TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

No nasal cavity tumors have been observed in 247 chamber control fem. .ats at Battelle Pacific Northwest Laboratories.

Overall Historical Incidence in Untreated Controls

No. Examined	No. of Tumors	Diagnosis
2,021	1	Papilloma, NOS
TOTAL	1 (0.05%)	

(a) Data as of August 30, 1985, for studies of at least 104 weeks. No more than one tumor was observed in any untreated control group.

TABLE B4b. HISTORICAL INCIDENCE OF PITUITARY GLAND TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence in Chamber Controls at Battelle Pacific Northwest Laboratories			
Propylene oxide	25/48	0/48	25/48
Methyl methacrylate	30/50	1/50	31/50
Propylene	18/44	1/44	19/44
Dichloromethane	24/49	1/49	25/49
Tetrachloroethylene	19/50	4/50	23/50
TOTAL	116/241 (48.1%)	7/241 (2.9%)	123/241 (51.0%)
SD (b)	8.83%	3.01%	7.21%
Range (c)			
High	30/50	4/50	31/50
Low	19/50	0/48	19/44
Overall Historical Incidence in Untreated Controls			
TOTAL	(d) 862/1,952 (44.2%)	(e) 71/1,952 (3.6%)	(d,e) 931/1,952 (47.7%)
SD (b)	11.56%	3.97%	11.02%
Range (c)			
High	33/47	8/49	33/47
Low	7/39	0/50	9/39

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes 150 chromophobe adenomas
(e) Includes 2 adenocarcinomas, NOS, and 11 chromophobe carcinomas

TABLE B4c. HISTORICAL INCIDENCE OF THYROID GLAND FOLLICULAR CELL TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls: Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence in Chamber Controls at Battelle Pacific Northwest Laboratories			
Propylene oxide	0/45	0/45	0/45
Methyl methacrylate	1/48	1/48	2/48
Propylene	0/39	1/39	1/39
Dichloromethane	0/47	0/47	0/47
Tetrachloroethylene	0/46	0/46	0/46
TOTAL	1/225 (0.4%)	2/225 (0.9%)	3/225 (1.3%)
SD (b)	0.93%	1.28%	1.93%
Range (c)			
High	1/48	1/39	2/48
Low	0/47	0/47	0/47
Overall Historical Incidence in Untreated Controls			
TOTAL	(d) 13/1,952 (0.7%)	(e) 7/1,952 (0.4%)	(d,e) 20/1,952 (1.0%)
SD (b)	1.11%	0.78%	1.34%
Range (c)			
High	2/42	1/47	2/42
Low	0/50	0/86	0/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes one papillary adenoma, one cystadenoma, and one papillary cystadenoma
(e) Includes one papillary carcinoma and one papillary cystadenocarcinoma

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE

	Chamber Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Ulcer, NOS		2 (4%)	2 (4%)
Inflammation, suppurative	1 (2%)	4 (8%)	2 (4%)
Acanthosis			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
Metaplasia, osseous	1 (2%)		
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Inflammation, NOS	25 (50%)	32 (64%)	43 (86%)
Inflammation, serous		18 (36%)	31 (62%)
Inflammation, suppurative	6 (12%)	26 (52%)	45 (90%)
Hyperostosis		2 (4%)	16 (32%)
Hyperplasia, epithelial	5 (10%)	29 (58%)	40 (80%)
Hyperplasia, adenomatous			2 (4%)
Metaplasia, squamous	1 (2%)	14 (28%)	36 (72%)
*Nose	(50)	(50)	(50)
Inflammation, NOS	1 (2%)		
*Larynx	(50)	(50)	(50)
Inflammation, NOS		1 (2%)	
Inflammation, suppurative	8 (16%)	14 (28%)	18 (36%)
Hyperplasia, epithelial	3 (6%)	3 (6%)	
Metaplasia, squamous			2 (4%)
#Trachea	(50)	(48)	(49)
Inflammation, NOS		1 (2%)	1 (2%)
Inflammation, suppurative		1 (2%)	3 (6%)
Hyperplasia, epithelial		2 (4%)	4 (8%)
#Lung/bronchus	(50)	(49)	(50)
Inflammation, suppurative			1 (2%)
Hyperplasia, epithelial		1 (2%)	
#Lung	(50)	(49)	(50)
Foreign body, NOS			1 (2%)
Congestion, NOS		2 (4%)	
Hemorrhage	3 (6%)	4 (8%)	4 (8%)
Inflammation, interstitial	1 (2%)		
Inflammation, suppurative			2 (4%)
Inflammation, chronic focal	4 (8%)	2 (4%)	2 (4%)
Inflammation, granulomatous			1 (2%)
Fibrosis		1 (2%)	
Perivascular cuffing	22 (44%)	20 (41%)	21 (42%)
Hemosiderosis		1 (2%)	
Hyperplasia, alveolar epithelium	2 (4%)	5 (10%)	7 (14%)
Histiocytosis	3 (6%)	9 (18%)	8 (16%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(49)	(48)	(46)
Fibrosis		2 (4%)	
#Spleen	(50)	(48)	(49)
Hematoma, NOS		1 (2%)	1 (2%)
Inflammation granulomatous focal	1 (2%)		
Fibrosis		5 (10%)	2 (4%)
Adhesion, fibrous	1 (2%)		3 (6%)
Hemosiderosis	1 (2%)	3 (6%)	2 (4%)
Hematopoiesis	1 (2%)	1 (2%)	

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Mandibular lymph node	(49)	(48)	(49)
Inflammation, chronic			1 (2%)
Hyperplasia, NOS	1 (2%)		
#Thoracic lymph node	(49)	(48)	(49)
Congestion, NOS	1 (2%)	1 (2%)	2 (4%)
Inflammation, chronic	1 (2%)	1 (2%)	
Hemosiderosis			1 (2%)
Hyperplasia, NOS		1 (2%)	
#Renal lymph node	(49)	(48)	(49)
Congestion, NOS			1 (2%)
Inflammation, granulomatous focal		1 (2%)	
Pigmentation, NOS	2 (4%)	2 (4%)	
Hyperplasia, NOS		1 (2%)	
#Lung	(50)	(49)	(50)
Leukocytosis, NOS	1 (2%)		
Erythrophagocytosis	1 (2%)		
Hyperplasia, lymphoid	1 (2%)	1 (2%)	1 (2%)
#Liver	(50)	(49)	(50)
Hematopoiesis	1 (2%)	1 (2%)	
#Cecum	(49)	(46)	(46)
Hyperplasia, lymphoid		1 (2%)	
#Adrenal	(50)	(48)	(48)
Hematopoiesis			1 (2%)
#Thymus	(38)	(40)	(43)
Hyperplasia, epithelial	2 (5%)		
CIRCULATORY SYSTEM			
#Brain	(50)	(48)	(50)
Thrombosis, NOS		1 (2%)	
*Nasal cavity	(50)	(50)	(50)
Thrombosis, NOS	3 (6%)	2 (4%)	3 (6%)
#Heart	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)	4 (8%)	3 (6%)
Inflammation, NOS			1 (2%)
Inflammation, chronic	40 (80%)	39 (78%)	34 (68%)
*Blood vessel	(50)	(50)	(50)
Aneurysm		1 (2%)	
Perivasculitis		1 (2%)	
#Liver	(50)	(49)	(50)
Thrombosis, NOS	1 (2%)	1 (2%)	1 (2%)
#Pancreas	(50)	(49)	(49)
Perivasculitis		1 (2%)	
#Kidney	(50)	(48)	(48)
Thrombosis, NOS			1 (2%)
#Uterus	(49)	(48)	(49)
Perivasculitis		1 (2%)	
#Adrenal	(50)	(48)	(48)
Thrombosis, NOS			1 (2%)
DIGESTIVE SYSTEM			
*Mouth	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	1 (2%)
*Tongue	(50)	(50)	(50)
Epidermal inclusion cyst	1 (2%)		
*Tooth	(50)	(50)	(50)
Congenital malformation, NOS		1 (2%)	
#Salivary gland	(50)	(48)	(50)
Hyperplasia, NOS	1 (2%)		
Hyperplasia, epithelial			1 (2%)
Metaplasia, squamous		1 (2%)	

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Liver	(50)	(49)	(50)
Congestion, NOS	1 (2%)		
Hemorrhage	1 (2%)		
Inflammation, chronic		1 (2%)	
Inflammation, granulomatous focal	27 (54%)	20 (41%)	12 (24%)
Degeneration, NOS		1 (2%)	4 (8%)
Degeneration, lipoid	8 (16%)	11 (22%)	9 (18%)
Necrosis, NOS	4 (8%)	3 (6%)	1 (2%)
Pigmentation, NOS	2 (4%)	1 (2%)	1 (2%)
Cytoplasmic vacuolization	1 (2%)	1 (2%)	1 (2%)
Basophilic cyto change	33 (66%)	27 (55%)	21 (42%)
Hyperplasia, focal	3 (6%)		2 (4%)
Angiectasis	1 (2%)	1 (2%)	4 (8%)
Regeneration, NOS		1 (2%)	
#Liver/periportal	(50)	(49)	(50)
Inflammation, NOS	1 (2%)	1 (2%)	
#Bile duct	(50)	(49)	(50)
Hyperplasia, NOS	7 (14%)	11 (22%)	9 (18%)
#Pancreas	(50)	(49)	(49)
Pigmentation, NOS	1 (2%)		
Focal cellular change	2 (4%)	2 (4%)	
Atrophy, NOS	14 (28%)	12 (24%)	12 (24%)
#Glandular stomach	(50)	(48)	(49)
Epidermal inclusion cyst		1 (2%)	
Hemorrhage			1 (2%)
Inflammation, NOS			1 (2%)
Ulcer, NOS	1 (2%)	2 (4%)	1 (2%)
Inflammation, suppurative	2 (4%)	3 (6%)	2 (4%)
Erosion	3 (6%)	1 (2%)	2 (4%)
#Forestomach	(50)	(48)	(49)
Edema, NOS			1 (2%)
Hemorrhage			1 (2%)
Inflammation, NOS	2 (4%)	4 (8%)	1 (2%)
Ulcer, NOS	2 (4%)	3 (6%)	2 (4%)
Inflammation, suppurative	1 (2%)		1 (2%)
Hyperplasia, epithelial	6 (12%)	5 (10%)	3 (6%)
#Jejunum	(49)	(46)	(46)
Parasitism			1 (2%)
#Colon	(49)	(46)	(46)
Parasitism	6 (12%)	4 (9%)	9 (20%)
*Rectum	(50)	(50)	(50)
Parasitism	5 (10%)		5 (10%)
URINARY SYSTEM			
#Kidney	(50)	(48)	(48)
Hydronephrosis			1 (2%)
Nephropathy	48 (96%)	46 (96%)	43 (90%)
Infarct, NOS			1 (2%)
Hyperplasia, tubular cell		1 (2%)	
#Kidney/pelvis	(50)	(48)	(48)
Hyperplasia, epithelial		1 (2%)	
#Urinary bladder	(49)	(47)	(47)
Calculus, microscopic examination			1 (2%)
Hyperplasia, epithelial			2 (4%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(48)	(48)
Cyst, NOS	1 (2%)	1 (2%)	
Degeneration, cystic	16 (33%)	9 (19%)	10 (21%)
Hyperplasia, NOS	10 (20%)	7 (15%)	4 (8%)
#Adrenal	(50)	(48)	(48)
Inflammation, granulomatous focal	2 (4%)		
Degeneration, cystic			1 (2%)
Degeneration, lipoid	22 (44%)	24 (50%)	28 (58%)
Necrosis, NOS	1 (2%)	1 (2%)	1 (2%)
Pigmentation, NOS	1 (2%)		
#Adrenal cortex	(50)	(48)	(48)
Focal cellular change		1 (2%)	
Hyperplasia, NOS	9 (18%)	9 (19%)	8 (17%)
Angiectasis	1 (2%)		
#Adrenal medulla	(50)	(48)	(48)
Hyperplasia, NOS	5 (10%)	7 (15%)	6 (13%)
#Thyroid	(45)	(48)	(48)
Inflammation, NOS		1 (2%)	
Hyperplasia, C-cell	24 (53%)	25 (52%)	24 (50%)
#Parathyroid	(24)	(34)	(31)
Hyperplasia, NOS	1 (4%)	1 (3%)	3 (10%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Galactocele	2 (4%)	1 (2%)	
Inflammation, suppurative	2 (4%)		
Inflammation, chronic	2 (4%)		
Inflammation, granulomatous focal	1 (2%)	3 (6%)	
Hyperplasia, NOS	45 (90%)	40 (80%)	48 (96%)
*Clitoral gland	(50)	(50)	(50)
Cyst, NOS	1 (2%)		
Inflammation, suppurative	7 (14%)	6 (12%)	3 (6%)
Abscess, NOS	3 (6%)	3 (6%)	5 (10%)
Inflammation, chronic	1 (2%)	3 (6%)	
Hyperplasia, epithelial		1 (2%)	2 (4%)
#Uterus	(49)	(48)	(49)
Dilatation, NOS	1 (2%)	1 (2%)	
Hemorrhage	1 (2%)		1 (2%)
Inflammation, suppurative	3 (6%)		1 (2%)
#Uterus/endometrium	(49)	(48)	(49)
Hyperplasia, NOS	2 (4%)		
Hyperplasia, cystic	1 (2%)	1 (2%)	3 (6%)
#Ovary	(49)	(48)	(50)
Cyst, NOS	2 (4%)	3 (6%)	1 (2%)
Atrophy, NOS	5 (10%)	7 (15%)	6 (12%)
NERVOUS SYSTEM			
#Brain	(50)	(48)	(50)
Hemorrhage	2 (4%)	1 (2%)	2 (4%)
Inflammation, NOS		1 (2%)	
Necrosis, NOS	1 (2%)		
*Olfactory sensory epithelium	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)	4 (8%)	1 (2%)
Atrophy, NOS		13 (26%)	8 (16%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	Low Dose	High Dose
SPECIAL SENSE ORGANS			
*Eyeball, tunica fibrosa	(50)	(50)	(50)
Mineralization			1 (2%)
*Eye/retina	(50)	(50)	(50)
Atrophy, NOS	3 (6%)	1 (2%)	
*Eye/crystalline lens	(50)	(50)	(50)
Mineralization	2 (4%)		
Degeneration, NOS	3 (6%)	1 (2%)	
*Lacrimal apparatus	(50)	(50)	(50)
Inflammation, NOS	1 (2%)	2 (4%)	1 (2%)
Inflammation, chronic		1 (2%)	
Pigmentation, NOS		2 (4%)	
Metaplasia, squamous		1 (2%)	
*Nasolacrimal duct	(50)	(50)	(50)
Inflammation, suppurative	7 (14%)	10 (20%)	6 (12%)
*Ear	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Epidermal inclusion cyst	1 (2%)		
Inflammation, NOS	1 (2%)		
Inflammation, chronic	1 (2%)		
Fibrous osteodystrophy	1 (2%)	3 (6%)	
Hyperostosis	1 (2%)		1 (2%)
*Sternum	(50)	(50)	(50)
Inflammation, NOS		1 (2%)	
BODY CAVITIES			
*Peritoneal cavity	(50)	(50)	(50)
Necrosis, fat			1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Mineralization		3 (6%)	
Hyperplasia, mesothelial		1 (2%)	
Foot			
Hemorrhage		1	
Inflammation, acute/chronic		1	
Adipose tissue			
Inflammation, suppurative	1		
Fibrosis	1		1
SPECIAL MORPHOLOGY SUMMARY			
Auto/necropsy/histo performed		2	1

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

APPENDIX C

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE

	Chamber Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	49	50
INTEGUMENTARY SYSTEM			
None			
RESPIRATORY SYSTEM			
*Nasal cavity	(49)	(49)	(50)
Squamous cell papilloma			1 (2%)
#Lung	(49)	(49)	(50)
Hepatocellular carcinoma, metastatic	1 (2%)	1 (2%)	2 (4%)
Alveolar/bronchiolar adenoma	7 (14%)	2 (4%)	3 (6%)
Alveolar/bronchiolar carcinoma	5 (10%)	7 (14%)	4 (8%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(49)	(49)	(50)
Malignant lymphoma, NOS		2 (4%)	
Malignant lymphoma, histiocytic type	2 (4%)		1 (2%)
Malignant lymphoma, mixed type	3 (6%)		
#Spleen	(49)	(49)	(50)
Hepatocellular carcinoma, metastatic		1 (2%)	
#Lymph node	(40)	(49)	(49)
Malignant lymphoma, NOS			1 (2%)
#Mandibular lymph node	(40)	(49)	(49)
Malignant lymphoma, mixed type		1 (2%)	
CIRCULATORY SYSTEM			
*Subcutaneous tissue	(49)	(49)	(50)
Hemangiosarcoma			1 (2%)
#Mesenteric lymph node	(40)	(49)	(49)
Hemangioma	1 (3%)		
#Liver	(49)	(49)	(50)
Hemangiosarcoma		2 (4%)	
#Urinary bladder	(49)	(49)	(49)
Hemangioma		1 (2%)	
DIGESTIVE SYSTEM			
*Tooth	(49)	(49)	(50)
Odontoma, NOS			1 (2%)
#Liver	(49)	(49)	(50)
Hepatocellular adenoma	4 (8%)	8 (16%)	7 (14%)
Hepatocellular carcinoma	11 (22%)	7 (14%)	6 (12%)
#Forestomach	(49)	(49)	(50)
Squamous cell papilloma	1 (2%)		1 (2%)
#Ileum	(49)	(49)	(50)
Adenocarcinoma, NOS	1 (2%)		
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Adrenal	(49)	(48)	(50)
Cortical carcinoma			1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Thyroid	(48)	(48)	(49)
Follicular cell adenoma	1 (2%)	3 (6%)	
C-cell carcinoma	1 (2%)		
#Pancreatic islets	(49)	(49)	(50)
Islet cell adenoma		1 (2%)	
REPRODUCTIVE SYSTEM			
None			
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(49)	(49)	(50)
Adenoma, NOS	2 (4%)		
Papillary adenoma	1 (2%)	3 (6%)	2 (4%)
*Left ear	(49)	(49)	(50)
Sarcoma, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	5	2	5
Moribund sacrifice	4	1	12
Terminal sacrifice	41	45	33
Accidentally killed, nda		1	
Animal missexed		1	
TUMOR SUMMARY			
Total animals with primary tumors**	28	26	24
Total primary tumors	40	37	30
Total animals with benign tumors	16	16	13
Total benign tumors	17	18	14
Total animals with malignant tumors	18	17	14
Total malignant tumors	23	19	15
Total animals with secondary tumors##	1	1	2
Total secondary tumors	1	2	2
Total animals with tumors uncertain-- benign or malignant			1
Total uncertain tumors			1

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

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE: CHAMBER CONTROL

ANIMAL NUMBER	032	001	041	043	008	024	003	026	018	002	004	005	006	007	009	010	011	012	013	014	015	016	017	019	020
WEEKS ON STUDY	003	023	063	075	085	095	097	099	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104
RESPIRATORY SYSTEM																									
Lungs and bronchi	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																						X			
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma					X	X						X													
Trachea	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	A	+	−	−	−	+	+	+	+	−	−	−	−	+	−	+	+	+	+	+	+	+	+	+	+
Hemangioma																			X						
Thymus	A	−	+	+	−	−	−	−	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma					X	X	X		X							X		X		X		X			
Bile duct	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	A	+	+	+	N	N	+	+	N	N	N	+	+	+	+	N	N	N	+	+	+	N	+	+	+
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	A	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Stomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Large intestine	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−
Adrenal	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	A	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
C-cell carcinoma																									
Parathyroid	A	+	−	−	+	−	−	−	−	+	−	−	+	−	+	−	+	−	+	−	−	−	−	−	−
REPRODUCTIVE SYSTEM																									
Mammary gland	A	N	N	N	N	+	+	+	N	+	N	N	N	N	+	+	+	N	N	N	N	N	+	N	N
Testis	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	A	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
Papillary adenoma																X									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, histiocytic type								X																	
Malignant lymphoma, mixed type																									

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

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

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

ANIMAL NUMBER	021	022	023	025	027	028	029	030	031	033	034	035	036	037	038	039	040	042	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma							X	X		X						X	X					X	X			7
Alveolar/bronchiolar carcinoma				X						X																5
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Hemangioma																										1
Thymus	+	–	–	+	+	+	–	–	–	+	+	+	–	–	+	–	+	–	+	–	+	–	+	+	+	31
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma	X							X	X						X											4
Hepatocellular carcinoma								X								X								X		11
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	N	+	+	+	+	+	+	N	+	N	+	+	N	N	+	+	+	N	+	+	+	+	+	+	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	44
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma														X												1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS		X																								1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma												X														1
C-cell carcinoma		X																								1
Parathyroid	+	–	+	–	+	–	–	–	+	–	–	–	–	+	+	–	–	+	+	–	+	+	+	–	+	19
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	+	+	N	+	+	N	N	+	+	+	N	N	N	N	+	N	+	N	N	N	N	N	*49
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Adenoma, NOS			X	X																						2
Papillary adenoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Malignant lymphoma, histiocytic type													X													2
Malignant lymphoma, mixed type								X		X		X														3

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE: LOW DOSE

ANIMAL NUMBER	001	050	028	048	022	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021
WEEKS ON STUDY	003	089	093	098	100	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic					X																				
Alveolar/bronchiolar adenoma							X										X								
Alveolar/bronchiolar carcinoma																						X			
Trachea	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic					X																				
Lymph nodes	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type														X											
Thymus	+	+	+	S	+	+	+	+	–	–	+	+	–	–	+	+	–	+	+	+	–	–	–	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma													X	X		X								X	
Hepatocellular carcinoma					X		X							X	X	X			X						
Hemangiosarcoma			X																						
Bile duct	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	S	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	+	N	+	+
Pancreas	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																		X							
ENDOCRINE SYSTEM																									
Pituitary	+	+	–	S	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Follicular cell adenoma							X					X													
Parathyroid	+	–	–	S	+	–	–	–	–	–	+	+	–	–	+	–	+	+	+	–	–	–	–	–	–
Pancreatic islets	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma															X										
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	S	N	+	N	+	N	+	N	+	+	N	N	N	N	N	N	+	N	N	N	N	N
Testis	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary adenoma															X										
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS					X																				

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

ANIMAL NUMBER	023	024	025	026	027	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	049	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metas																										1
Alveolar/bronchiolar adenoma																										2
Alveolar/bronchiolar carcinoma	X						X				X		X	X				X								7
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, mixed type																										1
Thymus	+	–	+	–	–	+	–	+	+	+	+	–	+	+	–	+	–	+	+	+	+	–	+	+	–	32
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma																		X	X	X			X			8
Hepatocellular carcinoma												X														7
Hemangiosarcoma									X																	2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	N	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	N	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma																										1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	46
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	48
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma												X														3
Parathyroid	–	–	–	+	+	+	+	–	–	+	–	+	+	–	+	–	–	–	+	–	+	–	+	–	+	20
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	+	N	N	+	+	N	+	+	N	N	N	+	N	+	+	+	+	+	+	+	+	+	N	*49
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Papillary adenoma											X											X				3
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Malignant lymphoma, NOS			X																							2

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE: HIGH DOSE

ANIMAL NUMBER	015	026	014	009	028	046	012	047	039	049	010	027	036	007	033	002	018	001	003	004	005	006	008	011	013
WEEKS ON STUDY	073	082	085	086	087	087	090	092	095	095	097	097	098	101	101	103	103	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic					X											X									
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma													X												
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS																						X			
Thymus	−	−	+	−	+	−	+	+	−	+	−	−	−	−	−	+	−	+	+	−	+	−	−	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Odontoma, NOS	X																								
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																								X	
Hepatocellular carcinoma					X			X				X	X			X									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	N	+	N	+	N	+	+	N	+	+	+	+	+	+	N	N	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	−	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																				X					
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical carcinoma																									
Thyroid	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	−	−	−	−	−	+	+	+	+	+	−	+	−	−	−	+	+	−	−	+	+	−	+	+	−
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	+	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary adenoma																						X			
Ear	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, histiocytic type									X																

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

ANIMAL NUMBER	016	017	019	020	021	022	023	024	025	029	030	031	032	034	035	037	038	040	041	042	043	044	045	048	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Hemangiosarcoma							X																			1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										2
Alveolar/bronchiolar adenoma	X	X																						X		3
Alveolar/bronchiolar carcinoma		X				X									X											4
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma												X														1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, NOS																										1
Thymus	−	+	+	−	+	+	−	+	+	+	−	−	+	+	+	−	+	+	−	+	−	+	+	+	−	27
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Odontoma, NOS																										1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X				X			X					X				X						X			7
Hepatocellular carcinoma					X																					6
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	46
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical carcinoma									X																	1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid	−	+	−	−	+	−	−	−	+	+	−	+	+	−	+	−	+	−	−	−	−	−	−	+	−	21
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	N	N	N	N	+	N	N	N	N	N	N	N	+	N	N	+	N	+	N	+	+	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papillary adenoma																X										2
Ear	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS								X																		1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, histiocytic type																										1

* Animals necropsied

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE

	Chamber Control	50 ppm	100 ppm
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	7/49 (14%)	2/49 (4%)	3/50 (6%)
Adjusted Rates (b)	17.1%	4.4%	9.1%
Terminal Rates (c)	7/41 (17%)	2/45 (4%)	3/33 (9%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.149N	P=0.061N	P=0.257N
Incidental Tumor Tests (d)	P=0.149N	P=0.061N	P=0.257N
Cochran-Armitage Trend Test (d)	P=0.094N		
Fisher Exact Test (d)		P=0.080N	P=0.151N
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	5/49 (10%)	7/49 (14%)	4/50 (8%)
Adjusted Rates (b)	11.3%	15.6%	11.5%
Terminal Rates (c)	3/41 (7%)	7/45 (16%)	3/33 (9%)
Week of First Observation	85	104	98
Life Table Tests (d)	P=0.555N	P=0.440	P=0.598N
Incidental Tumor Tests (d)	P=0.375N	P=0.396	P=0.375N
Cochran-Armitage Trend Test (d)	P=0.422N		
Fisher Exact Test (d)		P=0.380	P=0.487N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	11/49 (22%)	9/49 (18%)	6/50 (12%)
Adjusted Rates (b)	25.3%	20.0%	17.4%
Terminal Rates (c)	9/41 (22%)	9/45 (20%)	5/33 (15%)
Week of First Observation	85	104	98
Life Table Tests (d)	P=0.215N	P=0.322N	P=0.262N
Incidental Tumor Tests (d)	P=0.121N	P=0.355N	P=0.137N
Cochran-Armitage Trend Test (d)	P=0.108N		
Fisher Exact Test (d)		P=0.401N	P=0.133N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	3/49 (6%)	1/49 (2%)	0/50 (0%)
Adjusted Rates (b)	7.3%	2.2%	0.0%
Terminal Rates (c)	3/41 (7%)	1/45 (2%)	0/33 (0%)
Week of First Observation	104	104	
Life Table Tests (d)	P=0.075N	P=0.273N	P=0.162N
Incidental Tumor Tests (d)	P=0.075N	P=0.273N	P=0.162N
Cochran-Armitage Trend Test (d)	P=0.059N		
Fisher Exact Test (d)		P=0.309N	P=0.117N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	5/49 (10%)	3/49 (6%)	2/50 (4%)
Adjusted Rates (b)	11.9%	6.5%	5.3%
Terminal Rates (c)	4/41 (10%)	2/45 (4%)	1/33 (3%)
Week of First Observation	99	100	95
Life Table Tests (d)	P=0.217N	P=0.311N	P=0.301N
Incidental Tumor Tests (d)	P=0.109N	P=0.409N	P=0.186N
Cochran-Armitage Trend Test (d)	P=0.152N		
Fisher Exact Test (d)		P=0.357N	P=0.210N
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	1/49 (2%)	3/49 (6%)	1/50 (2%)
Adjusted Rates (b)	2.4%	6.5%	3.0%
Terminal Rates (c)	1/41 (2%)	2/45 (4%)	1/33 (3%)
Week of First Observation	104	93	104
Life Table Tests (d)	P=0.548	P=0.336	P=0.713
Incidental Tumor Tests (d)	P=0.597N	P=0.270	P=0.713
Cochran-Armitage Trend Test (d)	P=0.602N		
Fisher Exact Test (d)		P=0.309	P=0.747N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	50 ppm	100 ppm
Liver: Hepatocellular Adenoma			
Overall Rates (a)	4/49 (8%)	8/49 (16%)	7/50 (14%)
Adjusted Rates (b)	9.8%	17.8%	21.2%
Terminal Rates (c)	4/41 (10%)	8/45 (18%)	7/33 (21%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.115	P=0.225	P=0.149
Incidental Tumor Tests (d)	P=0.115	P=0.225	P=0.149
Cochran-Armitage Trend Test (d)	P=0.238		
Fisher Exact Test (d)		P=0.178	P=0.274
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	11/49 (22%)	7/49 (14%)	6/50 (12%)
Adjusted Rates (b)	24.3%	15.2%	14.6%
Terminal Rates (c)	7/41 (17%)	6/45 (13%)	1/33 (3%)
Week of First Observation	85	100	87
Life Table Tests (d)	P=0.191N	P=0.176N	P=0.245N
Incidental Tumor Tests (d)	P=0.011N	P=0.269N	P=0.010N
Cochran-Armitage Trend Test (d)	P=0.102N		
Fisher Exact Test (d)		P=0.217N	P=0.133N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	14/49 (29%)	13/49 (27%)	12/50 (24%)
Adjusted Rates (b)	31.0%	28.3%	30.6%
Terminal Rates (c)	10/41 (24%)	12/45 (27%)	7/33 (21%)
Week of First Observation	85	100	87
Life Table Tests (d)	P=0.525	P=0.401N	P=0.568
Incidental Tumor Tests (d)	P=0.178N	P=0.528N	P=0.184N
Cochran-Armitage Trend Test (d)	P=0.344N		
Fisher Exact Test (d)		P=0.500N	P=0.387N
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	1/48 (2%)	3/48 (6%)	0/49 (0%)
Adjusted Rates (b)	2.5%	6.8%	0.0%
Terminal Rates (c)	1/40 (3%)	3/44 (7%)	0/33 (0%)
Week of First Observation	104	104	
Life Table Tests (d)	P=0.433N	P=0.340	P=0.538N
Incidental Tumor Tests (d)	P=0.433N	P=0.340	P=0.538N
Cochran-Armitage Trend Test (d)	P=0.372N		
Fisher Exact Test (d)		P=0.308	P=0.495N
Harderian Gland: Papillary Adenoma			
Overall Rates (a)	1/49 (2%)	3/49 (6%)	2/50 (4%)
Adjusted Rates (b)	2.4%	6.7%	6.1%
Terminal Rates (c)	1/41 (2%)	3/45 (7%)	2/33 (6%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.316	P=0.339	P=0.424
Incidental Tumor Tests (d)	P=0.316	P=0.339	P=0.424
Cochran-Armitage Trend Test (d)	P=0.407		
Fisher Exact Test (d)		P=0.309	P=0.508
Harderian Gland: Adenoma or Papillary Adenoma			
Overall Rates (a)	3/49 (6%)	3/49 (6%)	2/50 (4%)
Adjusted Rates (b)	7.3%	6.7%	6.1%
Terminal Rates (c)	3/41 (7%)	3/45 (7%)	2/33 (6%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.507N	P=0.619N	P=0.599N
Incidental Tumor Tests (d)	P=0.507N	P=0.619N	P=0.599N
Cochran-Armitage Trend Test (d)	P=0.403N		
Fisher Exact Test (d)		P=0.661	P=0.490N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

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

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE

	Chamber Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	49	50
INTEGUMENTARY SYSTEM			
*Skin	(49)	(49)	(50)
Epidermal inclusion cyst			1 (2%)
Inflammation, chronic			1 (2%)
Atrophy, NOS	11 (22%)	12 (24%)	6 (12%)
*Subcutaneous tissue	(49)	(49)	(50)
Inflammation, chronic	2 (4%)		1 (2%)
RESPIRATORY SYSTEM			
*Nasal cavity	(49)	(49)	(50)
Empyema		32 (65%)	40 (80%)
Inflammation, chronic		33 (67%)	40 (80%)
Granulation tissue			1 (2%)
Erosion		7 (14%)	17 (34%)
Multinucleate giant cell			1 (2%)
Hyperplasia, epithelial		32 (65%)	45 (90%)
Metaplasia, squamous	1 (2%)	24 (49%)	41 (82%)
Regeneration, NOS		15 (31%)	17 (34%)
*Nasal gland	(49)	(49)	(50)
Cyst, NOS		1 (2%)	6 (12%)
Hyperplasia, NOS		10 (20%)	24 (48%)
*Larynx	(49)	(49)	(50)
Inflammation, NOS			1 (2%)
Hyperplasia, epithelial			3 (6%)
*Laryngeal submucosa	(49)	(49)	(50)
Cyst, NOS	1 (2%)	4 (8%)	2 (4%)
Inflammation, NOS		3 (6%)	2 (4%)
Hyperplasia, NOS			1 (2%)
#Trachea	(49)	(49)	(50)
Hyperplasia, epithelial	1 (2%)		3 (6%)
Metaplasia, squamous			1 (2%)
#Tracheal submucosa	(49)	(49)	(50)
Cyst, NOS	29 (59%)	36 (73%)	33 (66%)
Inflammation, focal		1 (2%)	
#Bronchial submucosa	(49)	(49)	(50)
Cyst, NOS	11 (22%)	17 (35%)	8 (16%)
#Lung/bronchiole	(49)	(49)	(50)
Inflammation, chronic	1 (2%)		
#Lung	(49)	(49)	(50)
Mineralization			1 (2%)
Emphysema, NOS	6 (12%)		2 (4%)
Congestion, acute passive	2 (4%)	1 (2%)	4 (8%)
Inflammation, necrotizing			3 (6%)
Inflammation, acute diffuse			1 (2%)
Inflammation, chronic	6 (12%)	8 (16%)	4 (8%)
Histiocytosis	1 (2%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
#Bone marrow	(49)	(49)	(50)
Hyperplasia, NOS			1 (2%)
#Spleen	(49)	(49)	(50)
Congestion, acute passive	1 (2%)		1 (2%)
Hematopoiesis	5 (10%)		8 (16%)
#Splenic follicles	(49)	(49)	(50)
Atrophy, NOS	1 (2%)		

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Lymph node	(40)	(49)	(49)
Hyperplasia, NOS	4 (10%)		
Plasmacytosis	1 (3%)		
#Mandibular lymph node	(40)	(49)	(49)
Cyst, NOS			3 (6%)
Edema, NOS			1 (2%)
Inflammation, suppurative			1 (2%)
Hemosiderosis	2 (5%)		1 (2%)
Hyperplasia, NOS		4 (8%)	5 (10%)
Histiocytosis	1 (3%)	1 (2%)	4 (8%)
Plasmacytosis	1 (3%)		
#Bronchial lymph node	(40)	(49)	(49)
Abscess, NOS		1 (2%)	
Hemosiderosis	1 (3%)		
Hyperplasia, NOS	1 (3%)		
Histiocytosis		1 (2%)	
#Mediastinal lymph node	(40)	(49)	(49)
Histiocytosis		1 (2%)	
#Mesenteric lymph node	(40)	(49)	(49)
Edema, NOS		2 (4%)	
Hemorrhage		1 (2%)	1 (2%)
Hyperplasia, NOS	1 (3%)	2 (4%)	
Histiocytosis	1 (3%)		
Hematopoiesis	1 (3%)	3 (6%)	
#Renal lymph node	(40)	(49)	(49)
Histiocytosis	1 (3%)		
#Lung	(49)	(49)	(50)
Hyperplasia, lymphoid		1 (2%)	2 (4%)
#Liver	(49)	(49)	(50)
Hematopoiesis	2 (4%)	3 (6%)	3 (6%)
#Kidney	(49)	(49)	(50)
Hematopoiesis	1 (2%)	1 (2%)	
#Thymus	(31)	(32)	(27)
Atrophy, NOS	1 (3%)		
CIRCULATORY SYSTEM			
#Brain	(49)	(49)	(50)
Periarteritis	1 (2%)		
*Larynx	(49)	(49)	(50)
Perivasculitis		1 (2%)	1 (2%)
#Lung	(49)	(49)	(50)
Thrombosis, NOS	1 (2%)		
Perivasculitis			2 (4%)
#Heart	(49)	(49)	(50)
Thrombosis, NOS	2 (4%)		
Abscess, NOS			1 (2%)
Inflammation, chronic	1 (2%)		
Perivasculitis	1 (2%)		
#Heart/atrium	(49)	(49)	(50)
Thrombosis, NOS	1 (2%)		
#Cardiac valve	(49)	(49)	(50)
Degeneration, mucoid	8 (16%)	12 (24%)	12 (24%)
Endocardiosis	1 (2%)	1 (2%)	
Hemosiderosis			1 (2%)
*Aorta	(49)	(49)	(50)
Inflammation, chronic	1 (2%)		6 (12%)
*Coronary artery	(49)	(49)	(50)
Periarteritis		1 (2%)	2 (4%)
Hyperplasia, NOS	1 (2%)		

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	Low Dose	High Dose
CIRCULATORY SYSTEM (Continued)			
*Cerebral artery	(49)	(49)	(50)
Necrosis, fibrinoid	1 (2%)		
Hyperplasia, NOS	1 (2%)		
*Renal artery	(49)	(49)	(50)
Inflammation, NOS		1 (2%)	
DIGESTIVE SYSTEM			
*Tooth	(49)	(49)	(50)
Deformity, NOS			1 (2%)
Inflammation, NOS		1 (2%)	2 (4%)
Dysplasia, NOS		1 (2%)	2 (4%)
*Pulp of tooth	(49)	(49)	(50)
Inflammation, suppurative	1 (2%)		
Abscess, NOS	2 (4%)	2 (4%)	1 (2%)
Inflammation, chronic	4 (8%)		
Necrosis, NOS	1 (2%)		
*Periodontal tissues	(49)	(49)	(50)
Inflammation, suppurative		1 (2%)	
Inflammation, chronic		1 (2%)	1 (2%)
#Salivary gland	(49)	(49)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)	2 (4%)	1 (2%)
#Liver	(49)	(49)	(50)
Mineralization			1 (2%)
Multiple cysts		1 (2%)	
Congestion, acute passive	1 (2%)		
Lymphocytic inflammatory infiltrate			1 (2%)
Abscess, NOS	1 (2%)		
Inflammation, chronic focal			1 (2%)
Necrosis, NOS	4 (8%)	1 (2%)	4 (8%)
Focal cellular change	1 (2%)		
Eosinophilic cyto change	1 (2%)	1 (2%)	
Angiectasis	1 (2%)		
#Bile duct	(49)	(49)	(50)
Hyperplasia, NOS		1 (2%)	
#Pancreas	(49)	(49)	(50)
Inflammation, suppurative			1 (2%)
Inflammation, chronic focal			1 (2%)
#Pancreatic duct	(49)	(49)	(50)
Mineralization	1 (2%)		
#Glandular stomach	(49)	(49)	(50)
Cyst, NOS	2 (4%)	3 (6%)	2 (4%)
Metaplasia, squamous	1 (2%)		
#Gastric submucosa	(49)	(49)	(50)
Inflammation, chronic		1 (2%)	
#Forestomach	(49)	(49)	(50)
Hyperplasia, epithelial	2 (4%)	1 (2%)	1 (2%)
Hyperkeratosis	2 (4%)	2 (4%)	4 (8%)
#Peyer's patch	(49)	(49)	(50)
Hyperplasia, NOS		4 (8%)	1 (2%)
#Ileum	(49)	(49)	(50)
Inflammation, chronic focal		1 (2%)	
Fibrosis	1 (2%)		1 (2%)
#Colon	(48)	(49)	(48)
Parasitism		1 (2%)	

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	Low Dose	High Dose
URINARY SYSTEM			
#Kidney	(49)	(49)	(50)
Ectopia			1 (2%)
Hydronephrosis	1 (2%)		
Congestion, acute passive	1 (2%)		
Hemorrhage	1 (2%)		1 (2%)
Pyelonephritis, NOS	1 (2%)		2 (4%)
Lymphocytic inflammatory infiltrate	6 (12%)	8 (16%)	2 (4%)
Fibrosis, multifocal			1 (2%)
Nephrosis, NOS	6 (12%)	2 (4%)	2 (4%)
Hyperplasia, tubular cell	1 (2%)	1 (2%)	2 (4%)
#Kidney/tubule	(49)	(49)	(50)
Dilatation, NOS			1 (2%)
Degeneration, hydropic	1 (2%)		
Crystals, NOS		2 (4%)	3 (6%)
Cytoplasmic vacuolization		1 (2%)	
#Kidney/pelvis	(49)	(49)	(50)
Inflammation, suppurative		1 (2%)	
*Ureter	(49)	(49)	(50)
Inflammation, chronic			1 (2%)
#Urinary bladder	(49)	(49)	(49)
Calculus, unknown gross or microscopic		1 (2%)	
Inflammation, NOS	4 (8%)	1 (2%)	
Erosion	1 (2%)	1 (2%)	
Hyperplasia, epithelial	2 (4%)		
ENDOCRINE SYSTEM			
#Pituitary	(46)	(46)	(47)
Cyst, NOS			2 (4%)
Congestion, acute passive	1 (2%)		
Cytoplasmic vacuolization			1 (2%)
#Adrenal/capsule	(49)	(48)	(50)
Hyperplasia, NOS	26 (53%)	30 (63%)	26 (52%)
#Adrenal cortex	(49)	(48)	(50)
Cyst, NOS		1 (2%)	
Degeneration, NOS	4 (8%)	3 (6%)	
Hyperplasia, focal	4 (8%)	5 (10%)	6 (12%)
#Adrenal medulla	(49)	(48)	(50)
Congestion, acute passive	1 (2%)		
#Thyroid	(48)	(48)	(49)
Cyst, NOS		1 (2%)	
Hyperplasia, follicular cell		2 (4%)	4 (8%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(49)	(49)	(50)
Dilatation/ducts		1 (2%)	
*Prepuce	(49)	(49)	(50)
Ulcer, NOS	1 (2%)		
Inflammation, acute focal	1 (2%)		
Abscess, NOS	1 (2%)	1 (2%)	
Inflammation, chronic	3 (6%)		
*Preputial gland	(49)	(49)	(50)
Cyst, NOS	4 (8%)		2 (4%)
Inflammation, suppurative			1 (2%)
Abscess, NOS	1 (2%)	1 (2%)	
#Prostate	(47)	(49)	(47)
Inflammation, suppurative	1 (2%)		1 (2%)
*Seminal vesicle	(49)	(49)	(50)
Mineralization	1 (2%)		
Dilatation, NOS	2 (4%)	1 (2%)	

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM			
*Seminal vesicle (Continued)	(49)	(49)	(50)
Inflammation, suppurative			1 (2%)
Inflammation, necrotizing		1 (2%)	
#Testis	(49)	(49)	(50)
Inflammation, necrotizing	1 (2%)		
Fibrosis, focal			1 (2%)
Atrophy, NOS	18 (37%)	7 (14%)	11 (22%)
Hyperplasia, interstitial cell			1 (2%)
*Scrotum	(49)	(49)	(50)
Abscess, NOS		1 (2%)	
NERVOUS SYSTEM			
#Brain/meninges	(49)	(49)	(50)
Inflammation, acute			1 (2%)
#Leptomeninges	(49)	(49)	(50)
Perivascular cuffing		1 (2%)	
#Lateral ventricle	(49)	(49)	(50)
Inflammation, suppurative			1 (2%)
*Choroid plexus	(49)	(49)	(50)
Inflammation, acute			1 (2%)
#Brain	(49)	(49)	(50)
Congestion, acute passive	1 (2%)		1 (2%)
#Brain/thalamus	(49)	(49)	(50)
Mineralization	11 (22%)	9 (18%)	8 (16%)
*Olfactory sensory epithelium	(49)	(49)	(50)
Atrophy, NOS		13 (27%)	32 (64%)
SPECIAL SENSE ORGANS			
*Eye/sclera	(49)	(49)	(50)
Inflammation, chronic	1 (2%)		
*Eye/cornea	(49)	(49)	(50)
Metaplasia, squamous	1 (2%)		
*Eye/lacrimal gland	(49)	(49)	(50)
Lymphocytic inflammatory infiltrate			1 (2%)
*Nasolacrimal duct	(49)	(49)	(50)
Inflammation, suppurative		6 (12%)	2 (4%)
Inflammation, chronic		3 (6%)	4 (8%)
Erosion		1 (2%)	2 (4%)
Hyperplasia, epithelial		12 (24%)	21 (42%)
MUSCULOSKELETAL SYSTEM			
*Maxilla	(49)	(49)	(50)
Deformity, NOS		1 (2%)	
BODY CAVITIES			
*Mediastinum	(49)	(49)	(50)
Inflammation, chronic	1 (2%)		
*Peritoneum	(49)	(49)	(50)
Hematoma, NOS			1 (2%)
Inflammation, suppurative			1 (2%)
Inflammation, chronic focal			1 (2%)
*Epicardium	(49)	(49)	(50)
Inflammation, suppurative			1 (2%)
*Tunica vaginalis	(49)	(49)	(50)
Inflammation, suppurative			1 (2%)

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	Low Dose	High Dose
ALL OTHER SYSTEMS			
*Multiple organs	(49)	(49)	(50)
Angiectasis	1 (2%)		
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported		1	
Animal missexed/no necropsy		1	
Autolysis/no necropsy	1		

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

APPENDIX D

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE

	Chamber Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	48
INTEGUMENTARY SYSTEM			
None			
RESPIRATORY SYSTEM			
#Lung	(50)	(49)	(48)
Squamous cell carcinoma		1 (2%)	
Hepatocellular carcinoma, metastatic			1 (2%)
Alveolar/bronchiolar adenoma	2 (4%)	2 (4%)	1 (2%)
Alveolar/bronchiolar carcinoma	2 (4%)	1 (2%)	2 (4%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(48)
Malignant lymphoma, NOS	7 (14%)	4 (8%)	2 (4%)
Malignant lymphoma, undiffer type			1 (2%)
Malignant lymphoma, lymphocytic type		1 (2%)	
Malignant lymphoma, histiocytic type	2 (4%)	1 (2%)	
Malignant lymphoma, mixed type	4 (8%)	2 (4%)	1 (2%)
#Spleen	(50)	(49)	(48)
Malignant lymphoma, undiffer type			1 (2%)
Malignant lymphoma, mixed type		1 (2%)	
#Liver	(50)	(49)	(48)
Malignant lymphoma, histiocytic type			1 (2%)
#Kidney	(50)	(49)	(48)
Malignant lymphoma, lymphocytic type			1 (2%)
#Uterus	(50)	(49)	(48)
Malignant lymphoma, histiocytic type			1 (2%)
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(48)
Hemangiosarcoma	1 (2%)		
#Spleen	(50)	(49)	(48)
Hemangiosarcoma			2 (4%)
*Muscle hip/thigh	(50)	(50)	(48)
Hemangiosarcoma		1 (2%)	
#Uterus	(50)	(49)	(48)
Hemangiosarcoma			1 (2%)
#Ovary	(49)	(47)	(45)
Hemangioma	1 (2%)		
DIGESTIVE SYSTEM			
#Liver	(50)	(49)	(48)
Hepatocellular adenoma	2 (4%)	2 (4%)	3 (6%)
Hepatocellular carcinoma	2 (4%)	1 (2%)	2 (4%)
#Pancreas	(50)	(49)	(48)
Acinar cell carcinoma		1 (2%)	
#Forestomach	(50)	(49)	(48)
Squamous cell papilloma	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(49)	(48)
Sarcoma, NOS, metastatic	1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Pituitary	(47)	(46)	(46)
Carcinoma, NOS	3 (6%)	5 (11%)	
Adenoma, NOS	19 (40%)	7 (15%)	5 (11%)
#Adrenal	(49)	(47)	(47)
Adenoma, NOS	1 (2%)		
Cortical adenoma		1 (2%)	
#Adrenal medulla	(49)	(47)	(47)
Pheochromocytoma	1 (2%)		
#Thyroid	(48)	(47)	(47)
Follicular cell adenoma		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(48)
Adenocarcinoma, NOS	2 (4%)	1 (2%)	2 (4%)
#Uterus	(50)	(49)	(48)
Adenocarcinoma, NOS		2 (4%)	
Sarcoma, NOS		1 (2%)	
Leiomyosarcoma		1 (2%)	
Endometrial stromal polyp		2 (4%)	
#Ovary	(49)	(47)	(45)
Papillary cystadenoma, NOS	1 (2%)		
Granulosa cell tumor	1 (2%)		2 (4%)
Mixed tumor, benign	2 (4%)		
Teratoma, NOS	1 (2%)	1 (2%)	
NERVOUS SYSTEM			
#Brain/thalamus	(50)	(49)	(48)
Carcinoma, NOS, metastatic	1 (2%)		
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(48)
Papillary carcinoma			1 (2%)
Adenoma, NOS	1 (2%)		
Papillary adenoma	1 (2%)	3 (6%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Abdominal cavity	(50)	(50)	(48)
Sarcoma, NOS			1 (2%)
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	11	19	22
Moribund sacrifice	9	6	18
Terminal sacrifice	29	25	9
Accidentally killed, nda	1		
Animal missexed			1

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	35	29	20
Total primary tumors	57	43	31
Total animals with benign tumors	27	14	9
Total benign tumors	32	18	10
Total animals with malignant tumors	18	19	15
Total malignant tumors	23	24	19
Total animals with secondary tumors##	2		1
Total secondary tumors	2		1
Total animals with tumors uncertain-- benign or malignant	2	1	2
Total uncertain tumors	2	1	2

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

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE: CHAMBER CONTROL

ANIMAL NUMBER	033	016	020	003	021	028	044	013	026	030	009	037	045	005	048	049	006	001	038	019	022	002	004	007	008
WEEKS ON STUDY	003	043	071	074	076	076	077	078	078	081	084	084	088	089	089	089	091	094	096	102	103	104	104	104	104
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																					X				
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Thymus	+	−	+	−	+	+	+	−	+	−	−	−	+	+	+	−	+	+	+	+	+	+	+	−	+
CIRCULATORY SYSTEM																									
Heart	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma																					X		X		
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	+	+	+	N	N	N	+	+	+	+	N	+	+	+	N	+	+	N	+	+	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS, metastatic																		X							
Urinary bladder	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																			X		X				
Adenoma, NOS																		X							X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	−	+	−	+	−	−	−	−	−	+	+	−	−	−	+	−	−	−	−	−	−	−	−	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	N	N	+	+	N	+	+	+	+	N	N	+	+	+	+	+	+	N	+	+	+	+
Adenocarcinoma, NOS																X									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Papillary cystadenoma, NOS																									
Granulosa cell tumor																X									
Mixed tumor, benign															X										
Teratoma, NOS																		X							
Hemangioma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic																									
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																							X		
Papillary adenoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangiosarcoma																									
Malignant lymphoma, NOS			X				X							X	X		X								X
Malignant lymphoma, histiocytic type																				X			X		
Malignant lymphoma, mixed type									X										X						

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

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

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

ANIMAL NUMBER	010	011	012	014	015	017	018	023	024	025	027	029	031	032	034	035	036	039	040	041	042	043	046	047	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																	X									2
Alveolar/bronchiolar carcinoma																		X			X					2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma										X														X		2
Hepatocellular carcinoma																										2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	+	+	+	+	+	+	+	N	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																							X			1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS, metastatic																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	47
Carcinoma, NOS																	X									3
Adenoma, NOS		X			X	X	X		X	X	X	X	X	X		X		X	X	X	X	X	X			19
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS																									X	1
Pheochromocytoma			X																							1
Thyroid	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid	–	–	–	+	–	–	–	–	–	+	+	–	+	+	+	+	–	–	+	+	–	–	+	+	+	19
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																									X	2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papillary cystadenoma, NOS														X												1
Granulosa cell tumor																										1
Mixed tumor, benign																									X	2
Teratoma, NOS																										1
Hemangioma															X											1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, metastatic																	X									1
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																										1
Papillary adenoma															X											1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangiosarcoma																					X					1
Malignant lymphoma, NOS										X																7
Malignant lymphoma, histiocytic type																										2
Malignant lymphoma, mixed type									X									X								4

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE: LOW DOSE

ANIMAL NUMBER	050	048	012	036	023	013	044	011	009	015	042	014	037	046	017	006	010	038	028	007	020	003	031	002	004
WEEKS ON STUDY	013	055	071	071	074	078	078	080	085	089	089	090	091	091	095	097	097	097	098	099	099	102	102	103	103
RESPIRATORY SYSTEM																									
Lungs and bronchi	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Alveolar/bronchiolar adenoma													X												
Alveolar/bronchiolar carcinoma																									
Trachea	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Lymph nodes	A	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	A	−	−	+	+	−	+	+	−	+	−	+	+	+	−	+	+	+	+	−	+	−	+	+	+
CIRCULATORY SYSTEM																									
Heart	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma					X																				
Hepatocellular carcinoma				X																					
Bile duct	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	+	N	+	+	+	+	N	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell carcinoma							X																		
Esophagus	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	A	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	A	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																							X		
Adenoma, NOS																			X						
Adrenal	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Thyroid	A	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
Follicular cell adenoma																									
Parathyroid	A	−	−	−	−	−	−	−	−	−	−	−	+	−	+	−	+	−	−	+	−	−	−	−	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Uterus	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																	X			X					
Sarcoma, NOS																					X				
Leiomyosarcoma																									
Endometrial stromal polyp																									
Ovary	A	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Teratoma, NOS																									
NERVOUS SYSTEM																									
Brain	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary adenoma					X																X				
MUSCULOSKELETAL SYSTEM																									
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N
Hemangiosarcoma																			X						
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS																							X		
Malignant lymphoma, lymphocytic type		X																							
Malignant lymphoma, histiocytic type																									
Malignant lymphoma, mixed type																									

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

ANIMAL NUMBER	001	005	008	016	018	019	021	022	024	025	026	027	029	030	032	033	034	035	039	040	041	043	045	047	049	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma														X												1
Alveolar/bronchiolar adenoma															X											2
Alveolar/bronchiolar carcinoma												X														1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, mixed type																X										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	−	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	37
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma									X																	2
Hepatocellular carcinoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	N	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinar cell carcinoma																										1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Carcinoma, NOS						X								X				X				X				5
Adenoma, NOS	X	X		X	X				X						X											7
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	47
Cortical adenoma											X															1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Follicular cell adenoma							X																			1
Parathyroid	−	+	+	−	−	−	+	−	−	+	+	−	−	+	−	+	−	−	+	−	−	−	+	−	−	14
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	N	+	+	N	*50
Adenocarcinoma, NOS																		X								1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS																										2
Sarcoma, NOS																										1
Leiomyosarcoma													X													1
Endometrial stromal polyp								X							X											2
Ovary	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Teratoma, NOS																					X					1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papillary adenoma						X																				3
MUSCULOSKELETAL SYSTEM																										
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangiosarcoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS			X			X															X					4
Malignant lymphoma, lymphocytic type																										1
Malignant lymphoma, histiocytic type													X													1
Malignant lymphoma, mixed type	X																							X		2

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE: HIGH DOSE

ANIMAL NUMBER	003	012	007	008	024	020	034	033	004	018	001	006	025	046	005	021	013	045	023	036	048	050	040	019	026
WEEKS ON STUDY	003	055	056	059	059	063	063	066	069	069	070	073	073	074	075	075	076	076	078	080	082	084	085	086	087
RESPIRATORY SYSTEM																									
Lungs and bronchi	A	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																					X				
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma															X										
Trachea	A	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	A	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Spleen	A	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																X									
Malignant lymphoma, undifferentiated type																									
Lymph nodes	A	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	A	S	−	−	+	+	+	+	+	+	+	−	−	−	−	−	−	+	−	−	−	−	−	+	−
CIRCULATORY SYSTEM																									
Heart	A	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	A	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	A	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																	X								
Hepatocellular carcinoma																					X				
Malignant lymphoma, histiocytic type																									
Bile duct	A	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	A	S	N	+	+	+	+	+	+	+	+	+	+	N	+	+	N	N	+	N	N	+	+	+	+
Pancreas	A	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	A	S	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	−
Stomach	A	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	A	S	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Large intestine	A	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	A	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, lymphocytic type																									
Urinary bladder	A	S	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	A	S	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Adenoma, NOS																									
Adrenal	A	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	A	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	A	S	+	+	−	−	−	+	−	+	−	−	−	−	+	+	−	−	−	−	−	+	−	−	−
REPRODUCTIVE SYSTEM																									
Mammary gland	A	S	N	+	+	N	+	N	N	N	+	+	+	N	+	+	+	+	+	N	+	+	+	+	N
Adenocarcinoma, NOS					X																				
Uterus	A	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Malignant lymphoma, histiocytic type																X									
Ovary	A	S	−	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Granulosa cell tumor																						X			
NERVOUS SYSTEM																									
Brain	A	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	A	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary carcinoma																									
Papillary adenoma																									
BODY CAVITIES																									
Peritoneum	A	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	A	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS																									
Malignant lymphoma, undifferentiated type																									
Malignant lymphoma, mixed type																									

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

ANIMAL NUMBER	029	039	049	032	002	014	031	044	015	027	035	041	042	038	037	011	009	010	016	017	022	028	030	043	047	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	087	087	087	088	089	089	089	089	091	091	093	094	096	097	098	099	104	104	104	104	104	104	104	104	104	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma				X																						1
Alveolar/bronchiolar carcinoma																									X	2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma												X														2
Malignant lymphoma, undiffer type																						X				1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	–	+	–	–	–	+	+	+	–	+	–	+	+	+	+	+	+	+	+	–	27
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular adenoma																						X	X			3
Hepatocellular carcinoma					X																					2
Malignant lymphoma, histiocytic type																			X							1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder & common bile duct	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	*48
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Malignant lymphoma, lymphocytic type																							X			1
Urinary bladder	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma, NOS														X			X			X		X			X	5
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	47
Thyroid	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid	+	+	+	–	+	–	–	–	–	–	–	+	+	+	+	–	+	–	+	+	–	–	–	–	+	19
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	*48
Adenocarcinoma, NOS															X											2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																						X				1
Malignant lymphoma, histiocytic type																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Granulosa cell tumor															X											2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*48
Papillary carcinoma																X										1
Papillary adenoma																X										1
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*48
Sarcoma, NOS									X																	1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*48
Malignant lymphoma, NOS									X					X												2
Malignant lymphoma, undiffer type													X													1
Malignant lymphoma, mixed type															X											1

* Animals necropsied

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE

	Chamber Control	50 ppm	100 ppm
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	3/49 (6%)	3/48 (6%)
Adjusted Rates (b)	13.3%	10.4%	17.5%
Terminal Rates (c)	3/29 (10%)	2/25 (8%)	1/9 (11%)
Week of First Observation	103	91	75
Life Table Tests (d)	P=0.303	P=0.557N	P=0.327
Incidental Tumor Tests (d)	P=0.579N	P=0.495N	P=0.643
Cochran-Armitage Trend Test (d)	P=0.442N		
Fisher Exact Test (d)		P=0.511N	P=0.523N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	4/50 (8%)	3/50 (6%)	1/48 (2%)
Adjusted Rates (b)	11.9%	12.0%	9.1%
Terminal Rates (c)	2/29 (7%)	3/25 (12%)	0/9 (0%)
Week of First Observation	78	104	98
Life Table Tests (d)	P=0.438N	P=0.547N	P=0.520N
Incidental Tumor Tests (d)	P=0.234N	P=0.497N	P=0.187N
Cochran-Armitage Trend Test (d)	P=0.143N		
Fisher Exact Test (d)		P=0.500N	P=0.194N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	13/50 (26%)	9/50 (18%)	8/48 (17%)
Adjusted Rates (b)	33.4%	31.9%	53.1%
Terminal Rates (c)	5/29 (17%)	7/25 (28%)	3/9 (33%)
Week of First Observation	71	55	75
Life Table Tests (d)	P=0.304	P=0.301N	P=0.285
Incidental Tumor Tests (d)	P=0.206N	P=0.233N	P=0.150N
Cochran-Armitage Trend Test (d)	P=0.152N		
Fisher Exact Test (d)		P=0.235N	P=0.190N
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	1/50 (2%)	1/50 (2%)	3/48 (6%)
Adjusted Rates (b)	3.4%	3.1%	19.8%
Terminal Rates (c)	1/29 (3%)	0/25 (0%)	1/9 (11%)
Week of First Observation	104	98	75
Life Table Tests (d)	P=0.047	P=0.748	P=0.076
Incidental Tumor Tests (d)	P=0.157	P=0.676N	P=0.211
Cochran-Armitage Trend Test (d)	P=0.190		
Fisher Exact Test (d)		P=0.753	P=0.293
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	2/50 (4%)	1/50 (2%)	3/48 (6%)
Adjusted Rates (b)	6.9%	3.1%	19.8%
Terminal Rates (c)	2/29 (7%)	0/25 (0%)	1/9 (11%)
Week of First Observation	104	98	75
Life Table Tests (d)	P=0.125	P=0.531N	P=0.142
Incidental Tumor Tests (d)	P=0.297	P=0.424N	P=0.312
Cochran-Armitage Trend Test (d)	P=0.383		
Fisher Exact Test (d)		P=0.500N	P=0.480
Liver: Hepatocellular Adenoma			
Overall Rates (a)	2/50 (4%)	2/49 (4%)	3/48 (6%)
Adjusted Rates (b)	6.9%	6.1%	24.5%
Terminal Rates (c)	2/29 (7%)	1/25 (4%)	2/9 (22%)
Week of First Observation	104	74	76
Life Table Tests (d)	P=0.117	P=0.652	P=0.118
Incidental Tumor Tests (d)	P=0.229	P=0.639	P=0.183
Cochran-Armitage Trend Test (d)	P=0.389		
Fisher Exact Test (d)		P=0.684	P=0.480

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	50 ppm	100 ppm
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	3/49 (6%)	5/48 (10%)
Adjusted Rates (b)	13.3%	8.0%	30.5%
Terminal Rates (c)	3/29 (10%)	1/25 (4%)	2/9 (22%)
Week of First Observation	103	71	76
Life Table Tests (d)	P=0.101	P=0.555N	P=0.076
Incidental Tumor Tests (d)	P=0.378	P=0.497N	P=0.301
Cochran-Armitage Trend Test (d)	P=0.403		
Fisher Exact Test (d)		P=0.511N	P=0.474
Pituitary Gland: Adenoma			
Overall Rates (a)	19/47 (40%)	7/46 (15%)	5/46 (11%)
Adjusted Rates (b)	65.4%	28.4%	49.1%
Terminal Rates (c)	18/28 (64%)	6/23 (26%)	4/9 (44%)
Week of First Observation	94	98	97
Life Table Tests (d)	P=0.102N	P=0.012N	P=0.384N
Incidental Tumor Tests (d)	P=0.052N	P=0.006N	P=0.235N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.006N	P=0.001N
Pituitary Gland: Carcinoma			
Overall Rates (a)	3/47 (6%)	5/46 (11%)	0/46 (0%)
Adjusted Rates (b)	9.7%	20.2%	0.0%
Terminal Rates (c)	1/28 (4%)	4/23 (17%)	0/9 (0%)
Week of First Observation	96	102	
Life Table Tests (d)	P=0.491N	P=0.289	P=0.363N
Incidental Tumor Tests (d)	P=0.265N	P=0.486	P=0.114N
Cochran-Armitage Trend Test (d)	P=0.138N		
Fisher Exact Test (d)		P=0.345	P=0.125N
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	22/47 (47%)	12/46 (26%)	5/46 (11%)
Adjusted Rates (b)	70.8%	47.1%	49.1%
Terminal Rates (c)	19/28 (68%)	10/23 (43%)	4/9 (44%)
Week of First Observation	94	98	97
Life Table Tests (d)	P=0.088N	P=0.071N	P=0.223N
Incidental Tumor Tests (d)	P=0.018N	P=0.015N	P=0.049N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.031N	P<0.001N
Harderian Gland: Papillary Adenoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	1/48 (2%)
Adjusted Rates (b)	3.4%	9.1%	10.0%
Terminal Rates (c)	1/29 (3%)	1/25 (4%)	0/9 (0%)
Week of First Observation	104	74	99
Life Table Tests (d)	P=0.310	P=0.280	P=0.487
Incidental Tumor Tests (d)	P=0.596	P=0.347	P=0.698
Cochran-Armitage Trend Test (d)	P=0.596		
Fisher Exact Test (d)		P=0.309	P=0.742
Harderian Gland: Adenoma or Papillary Adenoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	(e) 1/48 (2%)
Adjusted Rates (b)	6.9%	9.1%	10.0%
Terminal Rates (c)	2/29 (7%)	1/25 (4%)	0/9 (0%)
Week of First Observation	104	74	99
Life Table Tests (d)	P=0.474	P=0.458	P=0.617
Incidental Tumor Tests (d)	P=0.484N	P=0.531	P=0.710N
Cochran-Armitage Trend Test (d)	P=0.415N		
Fisher Exact Test (d)		P=0.500	P=0.515N

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

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

TABLE D4. HISTORICAL INCIDENCE OF PITUITARY GLAND TUMORS IN FEMALE $B6C3F_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls: Adenoma (b)	Carcinoma (c)	Adenoma or Carcinoma (b,c)
Historical Incidence at Battelle Pacific Northwest Laboratories			
Propylene oxide	8/46	1/46	9/46
Methyl methacrylate	12/49	0/49	12/49
Propylene	13/41	0/41	13/41
Dichloromethane	4/46	0/46	4/46
Tetrachloroethylene	2/45	5/45	7/45
TOTAL	39/227 (17.2%)	6/227 (2.6%)	45/227 (19.8%)
SD (d)	11.16%	4.82%	8.73%
Range (e)			
High	13/41	5/45	13/41
Low	2/45	0/49	4/46
Overall Historical Incidence			
TOTAL	177/1,815 (9.8%)	13/1,815 (0.7%)	190/1,815 (10.5%)
SD (d)	9.39%	1.44%	9.61%
Range (e)			
High	12/40	3/50	16/50
Low	0/48	0/49	0/48

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Includes adenoma, NOS, and chromophobe adenoma
(c) Includes carcinoma, NOS, adenocarcinoma, and chromophobe carcinoma
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE

	Chamber Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	48
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(48)
Inflammation, NOS	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(48)
Inflammation, suppurative		1 (2%)	
Inflammation, chronic	1 (2%)		
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(48)
Edema, NOS			1 (2%)
Empyema		33 (66%)	40 (83%)
Inflammation, chronic		39 (78%)	44 (92%)
Erosion		16 (32%)	24 (50%)
Hyperplasia, epithelial	1 (2%)	34 (68%)	35 (73%)
Metaplasia, squamous		34 (68%)	41 (85%)
Regeneration, NOS		14 (28%)	15 (31%)
*Nasal gland	(50)	(50)	(48)
Cyst, NOS		9 (18%)	7 (15%)
Inflammation, chronic			1 (2%)
Atrophy, NOS		1 (2%)	
Hyperplasia, NOS		23 (46%)	29 (60%)
*Larynx	(50)	(50)	(48)
Hyperplasia, epithelial		2 (4%)	1 (2%)
*Laryngeal submucosa	(50)	(50)	(48)
Cyst, NOS		2 (4%)	1 (2%)
Inflammation, chronic focal			1 (2%)
#Trachea	(50)	(49)	(48)
Cyst, NOS	19 (38%)	23 (47%)	25 (52%)
Inflammation, acute			1 (2%)
Hyperplasia, epithelial			4 (8%)
Metaplasia, squamous			2 (4%)
#Bronchial submucosa	(50)	(49)	(48)
Cyst, NOS	3 (6%)	5 (10%)	4 (8%)
#Lung/bronchiole	(50)	(49)	(48)
Hyperplasia, epithelial			2 (4%)
#Lung	(50)	(49)	(48)
Mineralization	2 (4%)	1 (2%)	
Emphysema, alveolar	1 (2%)		4 (8%)
Congestion, acute passive	2 (4%)	1 (2%)	2 (4%)
Hemorrhage		1 (2%)	
Lymphocytic inflammatory infiltrate	1 (2%)		1 (2%)
Inflammation, suppurative	2 (4%)	1 (2%)	4 (8%)
Inflammation, acute	2 (4%)	1 (2%)	6 (13%)
Inflammation, chronic	10 (20%)	15 (31%)	8 (17%)
Hyperplasia, alveolar epithelium	2 (4%)	1 (2%)	1 (2%)
Bronchiolization	1 (2%)	1 (2%)	
Histiocytosis		1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(48)
Hyperplasia, lymphoid		1 (2%)	
Hematopoiesis			1 (2%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Bone marrow	(50)	(49)	(46)
Hemorrhage	1 (2%)		
Hyperplasia, NOS		2 (4%)	3 (7%)
Granulocytic hyperplasia	10 (20%)	26 (53%)	42 (88%)
#Spleen	(50)	(49)	(48)
Accessory structure		1 (2%)	
Congestion, NOS		1 (2%)	1 (2%)
Necrosis, focal			2 (4%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	1 (2%)
Hematopoiesis	9 (18%)	19 (39%)	22 (46%)
#Splenic capsule	(50)	(49)	(48)
Inflammation, suppurative	2 (4%)	1 (2%)	1 (2%)
Inflammation, chronic			1 (2%)
#Lymph node	(48)	(48)	(48)
Hyperplasia, NOS			1 (2%)
#Mandibular lymph node	(48)	(48)	(48)
Cyst, NOS			1 (2%)
Hemorrhage			2 (4%)
Inflammation, acute focal			2 (4%)
Inflammation, chronic			4 (8%)
Necrosis, focal			1 (2%)
Hyperplasia, NOS	2 (4%)	22 (46%)	30 (63%)
Plasmacytosis	1 (2%)	1 (2%)	1 (2%)
Mastocytosis			1 (2%)
Hematopoiesis			2 (4%)
#Bronchial lymph node	(48)	(48)	(48)
Inflammation, suppurative	1 (2%)		2 (4%)
Abscess, NOS		2 (4%)	
Necrosis, focal			1 (2%)
Hyperplasia, NOS	5 (10%)	2 (4%)	2 (4%)
Hematopoiesis	1 (2%)		
#Mediastinal lymph node	(48)	(48)	(48)
Inflammation, acute		1 (2%)	2 (4%)
Abscess, NOS		1 (2%)	
Necrosis, focal	1 (2%)		1 (2%)
Histiocytosis		1 (2%)	1 (2%)
Plasmacytosis			2 (4%)
#Mesenteric lymph node	(48)	(48)	(48)
Hemorrhage	1 (2%)	1 (2%)	
Inflammation, suppurative		1 (2%)	
Hyperplasia, NOS			2 (4%)
Hematopoiesis		1 (2%)	
#Renal lymph node	(48)	(48)	(48)
Inflammation, chronic			1 (2%)
Necrosis, focal			2 (4%)
Hyperplasia, NOS	1 (2%)	1 (2%)	
#Lung	(50)	(49)	(48)
Hyperplasia, lymphoid	15 (30%)	8 (16%)	8 (17%)
#Salivary gland	(50)	(49)	(48)
Hematopoiesis		1 (2%)	
#Liver	(50)	(49)	(48)
Leukemoid reaction		1 (2%)	
Hematopoiesis	6 (12%)	4 (8%)	10 (21%)
#Kidney	(50)	(49)	(48)
Hematopoiesis		1 (2%)	4 (8%)
#Urinary bladder/muscularis	(48)	(49)	(45)
Hyperplasia, lymphoid			1 (2%)
#Ovary	(49)	(47)	(45)
Hematopoiesis	1 (2%)		

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Adrenal	(49)	(47)	(47)
Hematopoiesis		2 (4%)	1 (2%)
#Thymus	(41)	(37)	(27)
Cyst, NOS			1 (4%)
Inflammation, suppurative		1 (3%)	2 (7%)
Abscess, NOS			1 (4%)
Necrosis, focal			1 (4%)
Hyperplasia, NOS	1 (2%)		
CIRCULATORY SYSTEM			
*Mediastinum	(50)	(50)	(48)
Periarteritis			1 (2%)
*Skin	(50)	(50)	(48)
Periarteritis			1 (2%)
#Lung	(50)	(49)	(48)
Perivasculitis	1 (2%)		
#Heart	(49)	(49)	(48)
Mineralization	1 (2%)		
Thrombosis, NOS			1 (2%)
Inflammation, multifocal	1 (2%)		
Inflammation, suppurative	1 (2%)		1 (2%)
Inflammation, chronic			2 (4%)
Periarteritis			1 (2%)
Degeneration, NOS			1 (2%)
#Cardiac valve	(49)	(49)	(48)
Mineralization			1 (2%)
Sclerosis		1 (2%)	
Degeneration, mucoid	8 (16%)	8 (16%)	8 (17%)
Hemosiderosis			1 (2%)
*Aorta	(50)	(50)	(48)
Periarteritis			1 (2%)
*Aortic tunica intima	(50)	(50)	(48)
Inflammation, suppurative			1 (2%)
*Coronary artery	(50)	(50)	(48)
Periarteritis		1 (2%)	
*Pulmonary artery	(50)	(50)	(48)
Periarteritis			1 (2%)
*Pulmonary trunk	(50)	(50)	(48)
Inflammation, acute diffuse			1 (2%)
*Renal artery	(50)	(50)	(48)
Necrosis, fibrinoid			1 (2%)
#Salivary gland	(50)	(49)	(48)
Perivasculitis			1 (2%)
#Pancreas	(50)	(49)	(48)
Perivasculitis	1 (2%)		
#Kidney	(50)	(49)	(48)
Perivasculitis			2 (4%)
DIGESTIVE SYSTEM			
*Tooth	(50)	(50)	(48)
Deformity, NOS			1 (2%)
Inflammation, NOS		2 (4%)	1 (2%)
Dysplasia, NOS		2 (4%)	
*Root of tooth	(50)	(50)	(48)
Abscess, NOS			1 (2%)
Necrosis, focal			1 (2%)
*Periodontal tissues	(50)	(50)	(48)
Cyst, NOS		1 (2%)	
Abscess, NOS			1 (2%)
Inflammation, chronic		1 (2%)	1 (2%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Salivary gland	(50)	(49)	(48)
Cystic ducts			1 (2%)
Lymphocytic inflammatory infiltrate	2 (4%)		3 (6%)
Inflammation, suppurative			2 (4%)
#Liver	(50)	(49)	(48)
Cyst, NOS			1 (2%)
Hemorrhagic cyst			1 (2%)
Inflammation, NOS	1 (2%)		
Inflammation, acute diffuse	2 (4%)		
Necrosis, NOS	1 (2%)	1 (2%)	4 (8%)
Hemosiderosis	1 (2%)		
Cytoplasmic vacuolization	1 (2%)		
Focal cellular change		1 (2%)	2 (4%)
Histiocytosis			1 (2%)
#Hepatic capsule	(50)	(49)	(48)
Inflammation, NOS	2 (4%)		3 (6%)
*Gallbladder	(50)	(50)	(48)
Inflammation, NOS	1 (2%)	1 (2%)	2 (4%)
Necrosis, NOS		1 (2%)	
*Gallbladder/serosa	(50)	(50)	(48)
Inflammation, NOS	1 (2%)	2 (4%)	2 (4%)
#Pancreas	(50)	(49)	(48)
Inflammation, NOS	2 (4%)	5 (10%)	4 (8%)
Focal cellular change			1 (2%)
Atrophy, NOS		1 (2%)	
Hyperplasia, diffuse	1 (2%)	1 (2%)	1 (2%)
#Pancreatic duct	(50)	(49)	(48)
Inflammation, chronic		1 (2%)	
#Glandular stomach	(50)	(49)	(48)
Cyst, NOS	3 (6%)	1 (2%)	1 (2%)
Necrosis, focal			1 (2%)
Atrophy, NOS		2 (4%)	
Hyperplasia, focal	1 (2%)		
Metaplasia, squamous			1 (2%)
#Gastric submucosa	(50)	(49)	(48)
Inflammation, NOS			1 (2%)
#Forestomach	(50)	(49)	(48)
Hyperplasia, epithelial		1 (2%)	
Hyperkeratosis	4 (8%)	4 (8%)	4 (8%)
#Peyer's patch	(50)	(48)	(47)
Hyperplasia, NOS		1 (2%)	
#Ileum	(50)	(48)	(47)
Inflammation, suppurative			1 (2%)
Inflammation, chronic			1 (2%)
#Large intestine	(50)	(49)	(47)
Inflammation, acute diffuse			1 (2%)
#Colon	(50)	(49)	(47)
Fibrosis			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(49)	(48)
Hemorrhage	1 (2%)	3 (6%)	5 (10%)
Pyelonephritis, NOS	1 (2%)	1 (2%)	
Lymphocytic inflammatory infiltrate	14 (28%)	9 (18%)	14 (29%)
Inflammation, active chronic		1 (2%)	
Nephrosis, NOS	2 (4%)	2 (4%)	6 (13%)
Necrosis, NOS			1 (2%)
#Kidney/capsule	(50)	(49)	(48)
Inflammation, suppurative			2 (4%)
#Renal papilla	(50)	(49)	(48)
Necrosis, NOS	1 (2%)		

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	Low Dose	High Dose
URINARY SYSTEM (Continued)			
#Kidney/tubule	(50)	(49)	(48)
Cytoplasmic aggregate, NOS	2 (4%)		1 (2%)
#Urinary bladder	(48)	(49)	(45)
Degeneration, NOS			1 (2%)
#Urinary bladder/submucosa	(48)	(49)	(45)
Inflammation, chronic	15 (31%)	9 (18%)	5 (11%)
ENDOCRINE SYSTEM			
#Pituitary	(47)	(46)	(46)
Cyst, NOS			1 (2%)
Congestion, acute passive	1 (2%)		
Hyperplasia, NOS	6 (13%)	5 (11%)	6 (13%)
#Adrenal/capsule	(49)	(47)	(47)
Inflammation, NOS	1 (2%)	1 (2%)	3 (6%)
Inflammation, suppurative		1 (2%)	
Degeneration, NOS			1 (2%)
Hyperplasia, NOS	47 (96%)	41 (87%)	47 (100%)
#Adrenal cortex	(49)	(47)	(47)
Cyst, NOS	1 (2%)		1 (2%)
Hemorrhage			1 (2%)
Inflammation, acute			1 (2%)
Fibrosis	29 (59%)	25 (53%)	19 (40%)
Degeneration, NOS	31 (63%)	29 (62%)	19 (40%)
Amyloidosis			1 (2%)
Atrophy, NOS			1 (2%)
Hyperplasia, focal	1 (2%)		
#Adrenal medulla	(49)	(47)	(47)
Cyst, NOS			1 (2%)
Hemorrhage		1 (2%)	
#Thyroid	(48)	(47)	(47)
Cyst, NOS	1 (2%)	3 (6%)	
Cystic follicles		1 (2%)	1 (2%)
Degeneration, NOS			3 (6%)
Hyperplasia, C-cell			1 (2%)
Hyperplasia, follicular cell	5 (10%)	1 (2%)	1 (2%)
#Parathyroid	(19)	(14)	(19)
Cyst, NOS		1 (7%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(48)
Dilatation/ducts	7 (14%)	2 (4%)	3 (6%)
Inflammation, chronic diffuse			1 (2%)
Hyperplasia, NOS			1 (2%)
*Clitoral gland	(50)	(50)	(48)
Cyst, NOS			1 (2%)
Inflammation, necrotizing	1 (2%)		
#Uterus	(50)	(49)	(48)
Inflammation, suppurative	6 (12%)	11 (22%)	7 (15%)
Inflammation, chronic diffuse		1 (2%)	
#Uterine serosa	(50)	(49)	(48)
Inflammation, chronic diffuse			1 (2%)
#Uterus/endometrium	(50)	(49)	(48)
Inflammation, acute		1 (2%)	
Hyperplasia, NOS	1 (2%)		1 (2%)
Hyperplasia, cystic	32 (64%)	27 (55%)	21 (44%)
Metaplasia, squamous		1 (2%)	
#Uterus/myometrium	(50)	(49)	(48)
Fibrosis		1 (2%)	

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM (Continued)			
#Ovary	(49)	(47)	(45)
Mineralization			1 (2%)
Cyst, NOS	13 (27%)	12 (26%)	4 (9%)
Hemorrhagic cyst		1 (2%)	1 (2%)
Inflammation, suppurative	7 (14%)	20 (43%)	21 (45%)
Inflammation, chronic	3 (6%)	1 (2%)	2 (4%)
Hyperplasia, stromal		1 (2%)	
#Mesovarium	(49)	(47)	(45)
Inflammation, suppurative			1 (2%)
Inflammation, chronic		6 (13%)	2 (4%)
NERVOUS SYSTEM			
#Brain/meninges	(50)	(49)	(48)
Inflammation, suppurative			1 (2%)
Perivascular cuffing		1 (2%)	
#Cerebrum	(50)	(49)	(48)
Perivascular cuffing	1 (2%)		
#Brain	(50)	(49)	(48)
Congestion, acute passive		1 (2%)	1 (2%)
Perivascular cuffing	2 (4%)	3 (6%)	1 (2%)
#Brain/thalamus	(50)	(49)	(48)
Mineralization	9 (18%)	2 (4%)	8 (17%)
Deformity, NOS	6 (12%)	2 (4%)	3 (6%)
Inflammation, suppurative			1 (2%)
*Olfactory sensory epithelium	(50)	(50)	(48)
Atrophy, NOS		25 (50%)	35 (73%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(48)
Microphthalmia	1 (2%)		
*Eye/cornea	(50)	(50)	(48)
Hyperplasia, epithelial	1 (2%)		
*Nasolacrimal duct	(50)	(50)	(48)
Cyst, NOS			1 (2%)
Inflammation, suppurative	1 (2%)	3 (6%)	4 (8%)
Empyema		2 (4%)	5 (10%)
Inflammation, chronic	1 (2%)	5 (10%)	6 (13%)
Erosion			3 (6%)
Hyperplasia, epithelial	1 (2%)	18 (36%)	21 (44%)
Hyperkeratosis		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Skull	(50)	(50)	(48)
Hyperostosis		1 (2%)	
*Maxilla	(50)	(50)	(48)
Necrosis, focal			1 (2%)
*Sternum	(50)	(50)	(48)
Abscess, NOS		1 (2%)	
*Rib	(50)	(50)	(48)
Chondrodystrophy	1 (2%)		
*Skeletal muscle	(50)	(50)	(48)
Inflammation, acute	1 (2%)		
*Intercostal muscle	(50)	(50)	(48)
Inflammation, suppurative	1 (2%)	1 (2%)	

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF 1,2-EPOXYBUTANE (Continued)

	Chamber Control	Low Dose	High Dose
BODY CAVITIES			
*Mediastinum	(50)	(50)	(48)
Inflammation, suppurative	2 (4%)	4 (8%)	4 (8%)
Inflammation, necrotizing			1 (2%)
Inflammation, chronic	2 (4%)	1 (2%)	
*Peritoneum	(50)	(50)	(48)
Inflammation, NOS	5 (10%)	14 (28%)	11 (23%)
Abscess, NOS			2 (4%)
Granulation tissue			1 (2%)
*Pleura	(50)	(50)	(48)
Inflammation, suppurative	2 (4%)	2 (4%)	6 (13%)
*Epicardium	(50)	(50)	(48)
Inflammation, suppurative			2 (4%)
*Mesentery	(50)	(50)	(48)
Inflammation, NOS			5 (10%)
ALL OTHER SYSTEMS			
None			
SPECIAL MORPHOLOGY SUMMARY			
Animal missexed/no necropsy			1
Auto/necropsy/no histo		1	
Autolysis/no necropsy			1

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

APPENDIX E

GENETIC TOXICOLOGY OF

1,2-EPOXYBUTANE

TABLE E1. MUTAGENICITY OF 1,2-EPOXYBUTANE IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/plate (b)					
		−S9		+S9 (hamster)		+S9 (rat)	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
TA100	0	137 ± 5.9	100 ± 6.7	127 ± 6.6	94 ± 4.2	122 ± 5.8	118 ± 6.7
	100	164 ± 6.1	106 ± 9.1	132 ± 10.1	121 ± 9.3	141 ± 4.5	123 ± 3.7
	333	191 ± 27.2	123 ± 4.2	146 ± 12.9	123 ± 7.2	125 ± 13.7	130 ± 9.0
	1,000	349 ± 12.9	178 ± 4.9	176 ± 1.0	198 ± 13.6	200 ± 6.7	230 ± 27.0
	3,333	721 ± 9.4	346 ± 46.6	353 ± 15.1	420 ± 55.4	427 ± 15.1	353 ± 6.0
	10,000	1,228 ± 23.1	976 ± 43.3	650 ± 63.5	717 ± 123.2	809 ± 100.8	811 ± 18.9
	Summary	Positive	Positive	Positive	Positive	Positive	Positive
	Positive control (c)	540 ± 17.5	630 ± 160.3	2,374 ± 52.6	2,176 ± 25.0	1,565 ± 145.8	697 ± 67.4
TA1535	0	23 ± 3.5	20 ± 1.2	9 ± 1.7	10 ± 1.5	12 ± 2.0	58 ± 44.3
	100	27 ± 3.7	19 ± 0.7	8 ± 2.5	13 ± 2.6	12 ± 3.4	12 ± 2.4
	333	40 ± 2.0	25 ± 2.8	8 ± 0.7	16 ± 2.3	19 ± 3.7	15 ± 1.8
	1,000	62 ± 8.5	39 ± 6.1	32 ± 4.4	26 ± 0.9	32 ± 1.0	37 ± 2.0
	3,333	130 ± 8.7	89 ± 5.0	77 ± 9.2	89 ± 2.3	87 ± 7.2	93 ± 7.7
	10,000	273 ± 25.5	189 ± 23.8	213 ± 24.1	220 ± 9.9	397 ± 99.9	162 ± 41.8
	Summary	Positive	Positive	Positive	Positive	Positive	Positive
	Positive control (c)	550 ± 11.3	714 ± 141.8	574 ± 24.2	585 ± 24.7	104 ± 9.2	387 ± 22.4
TA1537	0	6 ± 0.3		10 ± 2.7		7 ± 0.3	
	100	10 ± 2.4		8 ± 0.3		11 ± 1.8	
	333	12 ± 1.9		10 ± 3.3		10 ± 2.7	
	1,000	10 ± 1.3		6 ± 0.9		7 ± 0.6	
	3,333	11 ± 2.2		6 ± 0.0		6 ± 1.5	
	10,000	13 ± 5.5		6 ± 0.9		9 ± 1.5	
	Summary	Negative		Negative		Negative	
	Positive control (c)	373 ± 48.8		435 ± 24.6		40 ± 0.3	
TA98	0	29 ± 4.6		55 ± 6.4		40 ± 1.3	
	100	25 ± 2.1		52 ± 6.1		45 ± 4.7	
	333	26 ± 6.2		42 ± 1.7		39 ± 3.8	
	1,000	23 ± 2.9		44 ± 4.4		38 ± 4.0	
	3,333	26 ± 3.3		47 ± 3.3		48 ± 2.5	
	10,000	23 ± 3.7		34 ± 5.5		42 ± 3.5	
	Summary	Negative		Negative		Negative	
	Positive control (c)	900 ± 17.3		2,081 ± 34.5		1,192 ± 104.2	

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

TABLE E2. MUTAGENICITY OF 1,2-EPOXYBUTANE IN MOUSE L5178Y LYMPHOMA CELLS (a,b)

Compound	Concentration (µg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutant Count	Mutant Fraction (c)
Inveresk Research International Study					
-S9					
Trial 1					
Distilled water		75.5 ± 3.9	100.0 ± 9.2	67.3 ± 7.5	30.3 ± 4.8
1,2-Epoxybutane	50	73.0 ± 13.0	91.5 ± 3.5	81.5 ± 1.5	38.0 ± 6.0
	100	72.0 ± 13.0	81.5 ± 10.5	76.0 ± 1.0	36.0 ± 7.0
	200	86.0 ± 1.0	81.0 ± 2.0	105.0 ± 15.0	40.5 ± 5.5
	400	51.5 ± 30.5	54.0 ± 26.0	174.5 ± 92.5	(d) 120.5 ± 11.5
	800	28	10	455	545
Ethyl methanesulfonate	250	66.0 ± 8.0	60.0 ± 6.0	341.5 ± 24.5	(d) 173.0 ± 8.0
Trial 2					
Distilled water		60.8 ± 3.9	100.0 ± 6.0	124.0 ± 15.3	69.3 ± 10.2
1,2-Epoxybutane	50	63.5 ± 1.5	101.0 ± 4.0	123.5 ± 11.5	65.5 ± 4.5
	100	52.0 ± 9.0	94.0 ± 21.0	96.5 ± 6.5	64.5 ± 15.5
	200	66.0 ± 2.0	104.0 ± 2.0	163.5 ± 7.5	83.0 ± 6.0
	400	63.5 ± 5.5	93.0 ± 9.0	209.0 ± 21.0	(d) 109.5 ± 1.5
	800	41.0 ± 7.0	47.5 ± 1.5	614.0 ± 161.0	(d) 492.0 ± 52.0
	1,600	Lethal			
Ethyl methanesulfonate	250	51.0 ± 3.0	70.0 ± 6.0	470.0 ± 27.0	(d) 311.0 ± 38.0
+S9					
Trial 1					
Distilled water		83.8 ± 1.3	100.0 ± 7.2	86.5 ± 12.3	34.5 ± 4.8
1,2-Epoxybutane	50	70.5 ± 9.5	99.5 ± 8.5	45.5 ± 13.5	21.0 ± 4.0
	100	71.0 ± 5.0	98.5 ± 4.5	78.5 ± 18.5	37.5 ± 11.5
	200	40.0 ± 14.0	51.5 ± 12.5	67.0 ± 19.0	(d) 57.5 ± 4.5
	400	56.0 ± 13.0	58.5 ± 8.5	102.5 ± 4.5	(d) 65.0 ± 18.0
	800	20.5 ± 7.5	14.5 ± 6.5	176.5 ± 16.5	(d) 347.5 ± 153.5
	1,600	Lethal			
Methylcholanthrene	2.5	41.5 ± 1.5	22.0 ± 3.0	455.0 ± 13.0	(d) 368.0 ± 2.0
Trial 2					
Distilled water		99.0 ± 3.1	100.0 ± 6.1	200.3 ± 11.0	68.0 ± 4.8
1,2-Epoxybutane	50	91.5 ± 5.5	69.5 ± 6.5	134.0 ± 27.0	48.0 ± 7.0
	100	81.5 ± 5.5	75.5 ± 2.5	133.0 ± 4.0	55.0 ± 2.0
	200	86.5 ± 0.5	64.5 ± 6.5	205.0 ± 0.0	79.0 ± 0.0
	400	76.0 ± 5.0	47.0 ± 1.0	365.5 ± 14.5	(d) 161.5 ± 4.5
	800	41.0 ± 7.0	9.0 ± 1.0	663.5 ± 8.5	(d) 558.5 ± 106.5
	1,600	Lethal			
Methylcholanthrene	2.5	76.5 ± 6.5	49.5 ± 11.5	679.5 ± 95.5	303.0 ± 68.0

TABLE E2. MUTAGENICITY OF 1,2-EPOXYBUTANE IN MOUSE L5178Y LYMPHOMA CELLS (Continued)

Compound	Concentration (μl/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutant Count	Mutant Fraction (c)
Litton Bionetics, Inc., Study					
−S9					
Trial 1					
Distilled water		86.3 ± 3.7	100.3 ± 3.5	69.3 ± 6.5	26.5 ± 1.5
1,2-Epoxybutane	0.0313	72.0 ± 4.0	101.5 ± 8.5	93.0 ± 15.0	(d) 43.5 ± 9.5
	0.0625	89.0 ± 10.0	98.0 ± 6.0	103.5 ± 6.5	40.0 ± 7.0
	0.125	82.0 ± 3.0	77.5 ± 12.5	108.5 ± 20.5	(d) 45.0 ± 10.0
	0.25	83.0 ± 5.0	74.5 ± 3.5	200.0 ± 8.0	(d) 81.0 ± 2.0
	0.5	74.0 ± 7.0	23.0 ± 2.0	580.0 ± 45.0	(d) 261.0 ± 4.0
Ethyl methanesulfonate	500 μg/ml	42.0 ± 4.0	25.0 ± 2.0	981.0 ± 59.0	(d) 787.0 ± 29.0
Trial 2					
Distilled water		98.3 ± 5.2	100.3 ± 5.3	104.3 ± 5.9	35.8 ± 2.8
1,2-Epoxybutane	0.0313	94.5 ± 0.5	98.0 ± 3.0	85.5 ± 1.5	30.0 ± 1.0
	0.0625	94.5 ± 3.5	95.5 ± 6.5	86.5 ± 7.5	30.5 ± 3.5
	0.125	90.5 ± 12.5	97.0 ± 3.0	156.0 ± 14.0	(d) 58.0 ± 3.0
	0.25	85.5 ± 7.5	80.0 ± 2.0	230.5 ± 12.5	(d) 90.5 ± 3.5
	0.5	64.0 ± 8.0	22.0 ± 2.0	698.0 ± 63.0	(d) 366.0 ± 13.0
	1	Lethal			
Ethyl methanesulfonate	500 μg/ml	66.0 ± 5.0	40.5 ± 5.5	1,361.0 ± 73.0	(d) 695.0 ± 86.0
+S9					
Trial 1					
Distilled water		86.5 ± 1.6	100.0 ± 8.4	186.0 ± 9.2	71.8 ± 2.3
1,2-Epoxybutane	0.0156	68.5 ± 3.5	88.5 ± 13.5	206.5 ± 1.5	101.0 ± 4.0
	0.0313	83.0 ± 9.0	86.5 ± 3.5	315.0 ± 31.0	(d) 126.5 ± 0.5
	0.0625	74.0 ± 14.0	30.0 ± 0.0	411.5 ± 40.5	(d) 189.0 ± 17.0
	0.125	73.5 ± 12.5	21.5 ± 0.5	546.5 ± 39.5	(d) 258.0 ± 61.0
	0.25	51.0 ± 9.0	10.0 ± 4.0	629.5 ± 29.5	(d) 421.5 ± 54.5
	0.5	Lethal			
Methylcholanthrene	5 μg/ml	36.5 ± 2.5	11.0 ± 2.0	637.5 ± 20.5	(d) 592.5 ± 58.5
Trial 2					
Distilled water		100.0 ± 8.0	100.0 ± 1.0	135.5 ± 11.5	45.0 ± 0.0
1,2-Epoxybutane	0.0313	105.5 ± 3.5	74.5 ± 2.5	162.5 ± 2.5	51.5 ± 2.5
	0.0625	85.5 ± 8.5	41.5 ± 1.5	214.5 ± 25.5	(d) 84.0 ± 2.0
	0.125	85.0 ± 1.0	33.5 ± 2.5	240.5 ± 16.5	(d) 95.0 ± 8.0
	0.25	72.0 ± 0.0	22.0 ± 1.0	433.5 ± 25.5	(d) 201.0 ± 11.0
	0.5	33.5 ± 2.5	4.0 ± 0.0	520.0 ± 65.0	(d) 518.5 ± 23.5
Methylcholanthrene	5 μg/ml	55.5 ± 2.5	20.0 ± 1.0	710.0 ± 11.0	(d) 424.5 ± 13.5

TABLE E2. MUTAGENICITY OF 1,2-EPOXYBUTANE IN MOUSE L5178Y LYMPHOMA CELLS (Continued)

Compound	Concentration (µl/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutant Count	Mutant Fraction (c)
SRI International Study					
−S9					
Dimethyl sulfoxide		84.0 ± 1.0	100.0 ± 1.0	119.0 ± 30.0	47.5 ± 12.5
1,2-Epoxybutane	0.174	90.5 ± 2.5	87.0 ± 1.0	226.0 ± 5.0	(d) 83.5 ± 4.5
	0.204	86.5 ± 7.5	72.0 ± 7.0	282.0 ± 6.0	(d) 109.5 ± 11.5
	0.24	83.5 ± 1.5	67.0 ± 0.0	288.0 ± 2.0	(d) 115.5 ± 3.5
	0.283	83.0 ± 1.0	62.5 ± 2.5	361.5 ± 3.5	(d) 145.0 ± 3.0
	0.333	79.0 ± 5.0	51.5 ± 3.5	392.0 ± 14.0	(d) 166.0 ± 5.0
	0.392	64.5 ± 0.5	39.0 ± 1.0	445.0 ± 9.0	(d) 229.5 ± 6.5
	0.461	60.5 ± 2.5	29.0 ± 1.0	475.5 ± 20.5	(d) 262.0 ± 1.0
	0.542	43.0 ± 2.0	15.5 ± 0.5	464.0 ± 19.0	(d) 363.0 ± 31.0
	0.638	31.0 ± 2.0	7.5 ± 0.5	407.0 ± 11.0	(d) 441.0 ± 37.0
	0.75	21.0 ± 1.0	4.0 ± 0.0	320.5 ± 10.5	(d) 511.0 ± 6.0
Ethyl methanesulfonate	500 µg/ml	51.5 ± 2.5	40.0 ± 0.0	900.5 ± 3.5	(d) 584.0 ± 28.0
+S9					
Trial 1					
Dimethyl sulfoxide		93.0 ± 3.0	100.0 ± 1.0	310.0 ± 6.0	111.0 ± 1.0
1,2-Epoxybutane	0.066	66.0 ± 0.0	40.0 ± 0.0	470.0 ± 19.0	(d) 237.5 ± 9.5
	0.077	57.0 ± 3.0	30.5 ± 1.5	586.5 ± 25.5	(d) 346.5 ± 32.5
	0.091	43.0 ± 2.0	15.5 ± 0.5	544.5 ± 30.5	(d) 424.0 ± 43.0
	0.107	31.0 ± 2.0	7.5 ± 0.5	489.0 ± 10.0	(d) 534.5 ± 25.5
	0.126	24.5 ± 1.5	4.5 ± 0.5	430.5 ± 2.5	(d) 579.5 ± 31.5
	0.148	21	3	321	518
	0.174	Lethal			
Methylcholanthrene	5 µg/ml	76.0 ± 10.0	58.0 ± 6.0	539.0 ± 1.0	(d) 239.0 ± 31.0
Trial 2					
Dimethyl sulfoxide		106.8 ± 6.1	100.8 ± 5.4	191.8 ± 6.8	60.3 ± 4.3
1,2-Epoxybutane	0.037	89.0 ± 5.0	77.0 ± 0.0	262.0 ± 12.0	(d) 98.0 ± 1.0
	0.044	101.0 ± 5.0	87.0 ± 1.0	298.5 ± 38.5	98.0 ± 8.0
	0.051	94.0 ± 0.0	79.0 ± 1.0	298.5 ± 62.5	(d) 106.0 ± 22.0
	0.06	97.5 ± 10.5	84.5 ± 8.5	237.0 ± 29.0	81.0 ± 1.0
	0.071	94.5 ± 1.5	68.5 ± 2.5	336.5 ± 14.5	(d) 119.0 ± 7.0
	0.084	90.0 ± 13.0	61.5 ± 7.5	389.5 ± 15.5	(d) 146.5 ± 14.5
	0.098	82.0 ± 2.0	49.0 ± 0.0	459.0 ± 9.0	(d) 186.0 ± 1.0
	0.116	76.0 ± 2.0	33.0 ± 1.0	519.5 ± 22.5	(d) 229.0 ± 4.0
	0.136	60.0 ± 5.0	15.0 ± 2.0	638.0 ± 29.0	(d) 356.5 ± 15.5
	0.16	39.5 ± 3.5	5.5 ± 0.5	597.0 ± 22.0	(d) 510.0 ± 25.0
Methylcholanthrene	5 µg/ml	73.0 ± 2.9	39.7 ± 3.9	702.7 ± 11.7	(d) 321.0 ± 9.6

TABLE E2. MUTAGENICITY OF 1,2-EPOXYBUTANE IN MOUSE L5178Y LYMPHOMA CELLS (Continued)

(a) The experimental protocol is presented in detail by Myhr et al. (1985) and follows the basic format of Clive et al. (1979). The highest dose of study compound is determined by solubility or toxicity and may not exceed 5 mg/ml. Cells (6×10^5/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency.

(b) Mean ± standard error of replicate trials for approximately 3×10^6 cells each. All data are evaluated statistically for both trend and peak response. Both responses must be significantly ($P<0.05$) positive for a chemical to be considered mutagenic. If only one of these responses is significant, the call is "questionable"; the absence of both trend and peak response results in a "negative" call.

(c) Mutant fraction (frequency) is a ratio of the mutant count to the cloning efficiency, divided by 3 (to arrive at MF per 1×10^6 cells treated); MF = mutant fraction.

(d) Significant positive response; occurs when the relative mutant fraction (average MF of treated culture/average MF of solvent control) is greater than or equal to 1.6.

(e) Tests conducted with metabolic activation were performed as described in (a) except that S9, prepared from the liver of Aroclor 1254-induced F344 rats, was added at the same time as the study chemical and/or solvent.

TABLE E3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY 1,2-EPOXYBUTANE (a)

Compound	Dose (µg/ml)	Total Cells	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-some	SCEs/ Cell	Hours in BrdU	Relative SCEs/cell (percent) (b)
−S9 (c)								
Trial 1--Summary: Positive								
Dimethyl sulfoxide		50	1,045	416	0.40	8.3	26.5	
1,2-Epoxybutane	1.6	50	1,041	497	0.48	9.9	26.5	119.3
	5	50	1,034	531	0.51	10.6	26.5	127.7
	16	50	1,035	735	0.71	14.7	26.5	177.1
	50	50	1,044	1,572	1.51	31.4	26.5	378.3
	160	0						
Mitomycin C	0.001	50	1,043	470	0.45	9.4	26.5	113.3
	0.010	50	1,046	2,571	2.46	51.4	26.5	619.3
Trial 2--Summary: Positive								
Dimethyl sulfoxide		50	1,047	453	0.43	9.1	26.0	
1,2-Epoxybutane	16	50	1,030	636	0.62	12.7	26.0	139.6
	50	50	1,037	1,185	1.14	23.7	26.0	260.4
	100	50	1,045	1,739	1.66	34.8	26.0	382.4
	160	50	1,033	2,460	2.38	49.2	26.0	540.7
Mitomycin C	0.001	50	1,040	1,208	1.16	24.2	26.0	265.9
	0.010	25	509	1,652	3.25	66.1	26.0	726.4
+S9 (d)								
Trial 1--Summary: Positive								
Dimethyl sulfoxide		50	1,046	470	0.45	9.4	26.0	
1,2-Epoxybutane	16	50	1,030	501	0.49	10.0	26.0	106.4
	50	50	1,043	632	0.61	12.6	26.0	134.0
	160	50	1,045	1,090	1.04	21.8	26.0	231.9
	500	50	1,049	2,151	2.05	43.0	26.0	457.4
	1,600	0						
Cyclophosphamide	0.3	50	1,046	790	0.76	15.8	26.0	168.1
	2	50	1,050	2,006	1.91	40.1	26.0	426.6
Trial 2--Summary: Positive								
Dimethyl sulfoxide		50	1,040	461	0.44	9.2	26.0	
1,2-Epoxybutane	16	50	1,046	466	0.45	9.3	26.0	101.1
	50	50	1,045	564	0.54	11.3	26.0	122.8
	160	50	1,043	775	0.74	15.5	26.0	168.5
	500	50	1,042	1,631	1.57	32.6	26.0	354.3
Cyclophosphamide	0.3	50	1,036	678	0.65	13.6	26.0	147.8
	2	10	207	430	2.08	43.0	26.0	467.4

TABLE E3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY 1,2-EPOXYBUTANE (Continued)

(a) Study performed at Environmental Health Research and Testing Laboratory. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine; a detailed description of the SCE protocol is presented by Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as described in (c) or (d) below and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air-dried, and stained.
(b) SCEs/cell of culture exposed to study chemical relative to those of culture exposed to solvent
(c) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then BrdU was added, and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and colcemid was added, and incubation was continued for 2-3 hours. Cells were then collected by mitotic shake-off, fixed, dropped onto slides, air-dried, and stained (Galloway et al., 1985).
(d) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Then cells were washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with colcemid present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

TABLE E4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY 1,2-EPOXYBUTANE (a)

Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
– S9 (b)				
Trial 1--Harvest time: 13.0 hours				
Dimethyl sulfoxide				
	100	2	0.02	2
1,2-Epoxybutane				
16	100	4	0.04	4
50	100	3	0.03	3
160	100	13	0.13	7
500	56	10	0.18	16
1,600	0			
Summary: Weakly positive				
Mitomycin C				
0.25	100	33	0.33	30
1	50	18	0.36	26
+ S9 (c)				
Trial 1--Harvest time: 14.0 hours				
Dimethyl sulfoxide				
	100	3	0.03	3
1,2-Epoxybutane				
16	100	4	0.04	4
50	100	6	0.06	3
160	100	8	0.08	7
500	100	3	0.03	3
500	100	9	0.09	9
Summary: Weakly positive				
Cyclophosphamide				
15	100	14	0.14	13
50	50	28	0.56	42
Trial 3--Harvest time: 12.0 hours				
Dimethyl sulfoxide				
	100	1	0.01	1
1,2-Epoxybutane				
50	100	3	0.03	3
160	100	2	0.02	2
500	100	2	0.02	2
750	100	14	0.14	13
Summary: Positive				
Cyclophosphamide				
15	100	16	0.16	13
50	50	25	0.50	38
– S9 (b)				
Trial 2--Harvest time: 12.0 hours				
Dimethyl sulfoxide				
	100	0	0.000	0
1,2-Epoxybutane				
16	100	4	0.04	4
50	100	0	0.00	0
160	100	1	0.01	1
500	40	8	0.20	18
Summary: Questionable				
Mitomycin C				
0.25	100	24	0.24	21
1	50	19	0.38	34
+ S9 (c)				
Trial 2--Harvest time: 12.0 hours				
Dimethyl sulfoxide				
	100	3	0.03	3
1,2-Epoxybutane				
16	100	5	0.05	5
50	100	0	0.00	0
160	100	0	0.00	0
500	100	9	0.09	6
750	0			
Summary: Negative				
Cyclophosphamide				
15	100	25	0.25	21
50	50	27	0.54	40

TABLE E4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY 1,2-EPOXYBUTANE (Continued)

(a) Study performed at Environmental Health Research and Testing Laboratory. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent as indicated in (b) or (c). Cells were arrested in first metaphase by addition of colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.
(b) In the absence of S9, cells were incubated with study compound or solvent for 8-10 hours at 37° C. Cells were then washed and fresh medium containing colcemid was added for an additional 2-3 hours followed by harvest.
(c) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8-10 hours. Colcemid was added for the last 2-3 hours of incubation prior to harvest. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

TABLE E5. INDUCTION OF SEX-LINKED RECESSIVE LETHAL MUTATIONS IN DROSOPHILA BY 1,2-EPOXYBUTANE (a,b)

Route of Exposure	Dose (ppm)	Incidence of Lethality (percent)	Incidence of Sterility (percent)	No. of Lethals/No. of X Chromosomes Tested Mating 1	Mating 2	Mating 3	Overall Total (b)
Feeding	50,000	24	5	7/1,902	5/1,661	4/1,788	16/5,310 (0.3%)
	0			2/2,154	1/2,113	1/2,002	4/6,269 (0.06%)

(a) Study performed at University of Wisconsin, Madison
(b) A detailed protocol of the sex-linked recessive lethal assay is presented in Zimmering et al. (1985). Exposure by feeding was done by allowing 24-hour-old Canton-S males to feed for 3 days on a solution of the study chemical dissolved in 5% sucrose. 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; none was found. After 17 days, presumptive lethal mutations were identified as vials containing no wild-type males; these were retested. Results were significant at the 5% level (Margolin et al., 1983).

TABLE E6. INDUCTION OF RECIPROCAL TRANSLOCATIONS IN DROSOPHILA BY 1,2-EPOXYBUTANE (a,b)

Route of Exposure	Dose (ppm)	Transfers (translocations/total F_1 tested) 1	2	3	4	5	6	Total No. of Tests	Total No. of Trans-locations	Total Trans-locations (percent)
Feeding	50,000	0/1,681	0/1,532	0/1,433	0/1,298	1/374	0/116	6,434	1	0.01
	60,000	0/430	0/418	1/426	0/319	0/202	0/148	1,943	1	0.05
Historical control	0							104,844	2	0.0019

(a) Study performed at University of Wisconsin, Madison
(b) A detailed protocol of the reciprocal translocation assay is presented in Zimmering et al. (1985). Exposed males were mated to three bw;e females for 3 days and discarded. The females were transferred to fresh medium every 3-4 days to produce a total of six cultures, and then they were discarded. In this manner, successive cultures sample sperm that were stored for increasing lengths of time. Individual F_1 males were backcrossed to bw;e 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 significant at the 5% level (Kastenbaum and Bowman, 1970).

APPENDIX F

RESULTS OF SEROLOGIC ANALYSIS

APPENDIX F. RESULTS OF SEROLOGIC ANALYSIS

I. Methods

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results.

A few F344/N rats from each exposure group were bled from the tail during months 2 and 17. Blood was taken from 10 $B6C3F_1$ mice killed in a moribund state between months 20 and 22. Data from animals surviving 24 months were collected from 5/50 randomly selected control animals of each sex and species. The blood from each animal was collected and clotted, and the serum 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:

	Hemagglutination Inhibition	Complement Fixation	ELISA
Mice	PVM (pneumonia virus of mice) Reo 3 (reovirus type 3) GDVII (Theiler's encephalomyelitis virus) Poly (polyoma virus) MVM (minute virus of mice) Ectro (infectious ectromelia) Sendai	M. Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus)	MHV (mouse hepatitis virus) *M. pul.* (*Mycoplasma pulmonis*) (24 mo)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai	RCV (rat coronavirus) (2,17 mo) SDAV (Sialodacryoadenitis virus)	RCV (24 mo)

II. Results

TABLE F1. MURINE ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR INHALATION STUDIES OF 1,2-EPOXYBUTANE (a)

	Interval (months)	No. of Animals	Positive Serologic Reaction for
RATS			
	2	--	None positive
	17	3/5 males, 3/5 females	RCV/SDAV
	24	5/5 males, 5/5 females	RCV/SDAV
MICE			
	20-22	--	None positive
	24	--	None positive

(a) Samples were sent to Microbiological Associates (Bethesda, MD) for determination of antibody titers.

APPENDIX G

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

Pellet Diet: October 1981 to October 1983

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

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

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

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

TABLE G2. VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION (a)

	Amount	Source
Vitamin		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D_3	4,600,000 IU	D-activated animal sterol
K_3	2.8 g	Menadione activity
d-α-Tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	*d*-Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B_{12}	4,000 μg	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	*d*-Biotin
Mineral		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

(a) Per ton (2,000 lb) of finished product

TABLE G3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION (a)

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	23.5 ± 0.73	22.2-24.9	25
Crude fat (percent by weight)	4.9 ± 0.54	3.3-5.7	25
Crude fiber (percent by weight)	3.30 ± 0.25	2.9-3.8	25
Ash (percent by weight)	6.5 ± 0.46	5.7-7.31	25
Essential Amino Acid (percent of total diet)			
Arginine	1.323 ± 0.830	1.21-1.39	4
Cystine	0.310 ± 0.099	0.218-0.400	4
Glycine	1.155 ± 0.069	1.06-1.21	4
Histidine	0.572 ± 0.030	0.530-0.603	4
Isoleucine	0.910 ± 0.033	0.881-0.944	4
Leucine	1.949 ± 0.065	1.85-1.99	4
Lysine	1.279 ± 0.075	1.20-1.37	4
Methionine	0.422 ± 0.187	0.306-0.699	4
Phenylalanine	0.909 ± 0.167	0.665-1.04	4
Threonine	0.844 ± 0.029	0.824-0.886	4
Tryptophan	0.187	0.171-0.211	3
Tyrosine	0.631 ± 0.094	0.566-0.769	4
Valine	1.11 ± 0.050	1.05-1.17	4
Essential Fatty Acid (percent of total diet)			
Linoleic	2.44	2.37-2.52	3
Linolenic	0.274	0.256-0.308	3
Arachidonic	0.008		1
Vitamin			
Vitamin A (IU/kg)	12,052 ± 4,522	4,100-24,000	25
Vitamin D (IU/kg)	3,650	3,000-6,300	2
α-Tocopherol (ppm)	41.53 ± 7.52	31.1-48.9	4
Thiamine (ppm)	16.4 ± 2.17	13.0-21.0	25
Riboflavin (ppm)	7.5 ± 0.96	6.1-8.2	4
Niacin (ppm)	85.0 ± 14.2	65.0-97.0	4
Pantothenic acid (ppm)	29.3 ± 4.6	23.0-34.0	4
Pyridoxine (ppm)	7.6 ± 1.5	5.6-8.8	4
Folic acid (ppm)	2.8 ± 0.88	1.8-3.7	4
Biotin (ppm)	0.27 ± 0.05	0.21-0.32	4
Vitamin B_{12} (ppb)	21.0 ± 11.9	11.0-38.0	4
Choline (ppm)	3,302.0 ± 120.0	3,200-3,430	4
Mineral			
Calcium (percent)	1.27 ± 0.11	1.11-1.44	25
Phosphorus (percent)	0.98 ± 0.05	0.88-1.11	25
Potassium (percent)	0.862 ± 0.10	0.772-0.970	3
Chloride (percent)	0.546 ± 0.10	0.442-0.635	4
Sodium (percent)	0.311 ± 0.038	0.258-0.350	4
Magnesium (percent)	0.169 ± 0.133	0.151-0.181	4
Sulfur (percent)	0.316 ± 0.070	0.270-0.420	4
Iron (ppm)	447.0 ± 57.3	409-523	4
Manganese (ppm)	90.6 ± 8.20	81.7-95.5	4
Zinc (ppm)	53.6 ± 5.27	46.1-58.6	4
Copper (ppm)	10.77 ± 3.19	8.09-15.39	4
Iodine (ppm)	2.95 ± 1.05	1.52-3.82	4
Chromium (ppm)	1.81 ± 0.28	1.44-2.09	4
Cobalt (ppm)	0.68 ± 0.14	0.49-0.80	4

(a) One to four batches of feed analyzed for nutrients reported in this table were manufactured from 1983 through 1985.

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

Contaminant	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.53 ± 0.13	0.27-0.77	25
Cadmium (ppm) (a)	<0.1	<0.1-0.1	25
Lead (ppm)	0.80 ± 0.64	0.33-3.37	25
Mercury (ppm)	<0.05		25
Selenium	0.29 ± 0.06	0.14-0.38	25
Aflatoxins (ppb) (a)	<5	<5	25
Nitrate nitrogen (ppm) (b)	9.2 ± 4.7	<0.1-22.0	25
Nitrite nitrogen (ppm) (b)	2.3 ± 1.92	<0.1-7.2	25
BHA (ppm) (c)	5.1 ± 4.9	<2.0-17.0	25
BHT (ppm) (c)	2.9 ± 2.7	<1.0-12.0	25
Aerobic plate count (CFU/g) (d)	44,180 ± 35,870	5,500-130,000	25
Coliform (MPN/g) (e)	11.5 ± 20.1	<3-93	24
Coliform (MPN/g) (f)	32.8 ± 91.7	<3-460	25
E. coli (MPN/g) (g)	<3		25
Total nitrosamines (ppb) (h)	4.0 ± 2.6	0.8-9.3	25
N-Nitrosodimethylamine (ppb) (h)	3.1 ± 2.5	0.8-8.3	25
N-Nitrosopyrrolidine (ppb)	1.14 ± 0.47	<0.9-2.9	25
Pesticide (ppm) (b)			
α-BHC (a, i)	<0.01		25
β-BHC (a)	<0.02		25
γ-BHC-Lindane (a)	<0.01		25
δ-BHC (a)	<0.01		25
Heptachlor (a)	<0.01		25
Aldrin (a)	<0.01		25
Heptachlor epoxide (a)	<0.01		25
DDE (a)	<0.01		25
DDD (a)	<0.01		25
DDT (a)	<0.01		25
HCB (a)	<0.01		25
Mirex (a)	<0.01		25
Methoxychlor (j)	<0.05	0.06 (7/26/83)	25
Dieldrin (a)	<0.01		25
Endrin (a)	<0.01		25
Telodrin (a)	<0.01		25
Chlordane (a)	<0.05		25
Toxaphene (a)	<0.1		25
Estimated PCBs (a)	<0.2		25
Ronnel (a)	<0.01		25
Ethion (a)	<0.02		25
Trithion (a)	<0.05		25
Diazinon (a)	<0.1		25
Methyl parathion (a)	<0.02		25
Ethyl parathion (a)	<0.02		25
Malathion (k)	0.10 ± 0.10	<0.05-0.45	25
Endosulfan I (l)	<0.01		23
Endosulfan II (l)	<0.01		23
Endosulfan sulfate (l)	<0.03		23

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

(a) All values were less than the detection limit. The detection limit is given as the mean.
(b) Sources of contamination: alfalfa, grains, and fish meal
(c) Sources of contamination: soy oil and fish meal
(d) CFU = colony forming unit
(e) MPN = most probable number; mean, standard deviation, and range exclude one very high value of 460 MPN/g obtained for the batch produced on 9/23/82.
(f) Mean, standard deviation, and range include the high value given in footnote d.
(g) All values were less than 3 MPN/g.
(h) All values were corrected for percent recovery.
(i) BHC = hexachlorocyclohexane or benzene hexachloride
(j) There was one observation above the detection limit. The value and the date it was obtained are given under the range.
(k) Twelve batches contained more than 0.05 ppm.
(l) Four batches (10/26/81-11/25/81) were not analyzed for endosulfan I, endosulfan II, or endosulfan sulfate.

APPENDIX H

DATA AUDIT SUMMARY

APPENDIX H. DATA AUDIT SUMMARY

The experimental data, documents, pathology materials, and draft NTP Technical Report for the 2-year toxicology and carcinogenesis studies of 1,2-epoxybutane in rats and mice were audited for accuracy, consistency, completeness, and compliance with Good Laboratory Practice regulations (implemented by the NTP beginning October 1, 1981). The studies were conducted for the NTP by Battelle Pacific Northwest Laboratories, Richland, Washington, under a subcontract with Tracor Jitco, Inc., until 1982 and then under contract with NIEHS. Animal exposures to 1,2-epoxybutane began in November 1981 and ended in November 1983. The retrospective audit was conducted at the NTP Archives in April and May 1986 by the following personnel from Argus Research Laboratories: Paul A. Wennerberg, D.V.M., M.S. (Principal Investigator); Lynn E. Blalok, M.S.; Betty L. Brandau, Ph.D.; and Sharon H. Srebro, B.S; and the following personnel from Pathology Associates, Inc.: Kathleen M. Walsh, D.V.M., Diplomate A.C.V.P.; Stephanie M. Taulbee; and Trella S. Cooper, B.A.

The audit report is on file at the NIEHS, Research Triangle Park, North Carolina. The audit included a review of the following material:

(1) All records concerning animal receipt, quarantine, randomization, and disposition before start of studies.
(2) Chemistry data for a random 10% of the exposure days and all other chemistry records.
(3) Body weights and clinical observation data from a random 10% sample of the study animals.
(4) All inlife records concerning environmental conditions, palpable masses, mortality, and animal identification.
(5) All postmortem records for individual animals concerning identification, disposition codes, and condition codes and correlation between gross observations and microscopic diagnoses.
(6) Wet tissues from a random 10% of the study animals to verify animal identification and to examine for untrimmed potential lesions.
(7) Slides and blocks of tissues from all control and high dose animals to examine for proper match and inventory.
(8) Tabulated pathology diagnoses for a random 10% of study animals to verify computer data entry.

The audit showed that the data in the Technical Report (including inlife observations, chemistry, and pathology data) correspond to the data at the NTP Archives. Clinical observations were not always consistent from month to month. Some animals were able to escape from their individual cages within the exposure chamber (a total of 41 instances during the 2 years); the animals were returned to the appropriate cage unit according to standard operating procedures. Missing ear tags were replaced according to standard operating procedures, and animal identification in the wet tissue bags agreed with the assigned study-specific number and animal number. A few untrimmed potential lesions were found in the wet tissues (predominantly in the stomach and spleen), but none was found in the target organs associated with carcinogenic effect (i.e., nose or lungs of rats). Additional diagnoses were not performed, since they would not have altered the interpretations of the study.

The NIEHS/NTP concludes that the data at the NTP Archives support the results presented in this Technical Report.

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NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS PUBLISHED AS OF JANUARY 1988

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

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