NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 326

TOXICOLOGY AND CARCINOGENESIS STUDIES OF ETHYLENE OXIDE

(CAS NO. 75-21-8)

IN 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 ETHYLENE OXIDE

(CAS NO. 75-21-8)

IN B6C3F$_1$ MICE

(INHALATION STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

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

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

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

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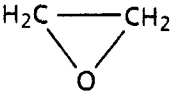
CONTENTS

CONTENTS (Continued)

APPENDIXES



ETHYLENE OXIDE

CAS No. 75-21-8

C_2H_4O Molecular weight 44.05

Synonyms: oxirane; EO; ETO; dihydrooxirene; dimethylene oxide; 1,2-epoxyethane; oxane; α,β-oxidoethane

ABSTRACT

Ethylene oxide is a major industrial chemical used primarily as an intermediate in the manufacture of other chemicals; e.g., ethylene glycol, a major component of automotive and other antifreeze products. Exposure to ethylene oxide is greatest in the health care industry, where an estimated 75,000 workers are potentially exposed. Ethylene oxide was nominated for toxicology and carcinogenesis studies in B6C3F$_1$ mice because of its extensive production; the potential for human exposure in the workplace, from medical devices, or from food; the positive results of genetic toxicology assays; and the previous use of only F344/N rats in inhalation carcinogenicity studies.

Two inhalation studies reported in 1984 by Snellings et al. and by Lynch et al. demonstrated carcinogenic responses in F344 rats. Results were similar in both studies and consisted of increased incidences of mononuclear cell leukemia, peritoneal mesotheliomas, and primary brain tumors.

Experimental Design: Toxicology and carcinogenesis studies of ethylene oxide (greater than 99% pure) were conducted by exposing groups of 50 B6C3F$_1$ mice of each sex to air containing 0, 50, or 100 ppm ethylene oxide, 6 hours per day, 5 days per week for 102 weeks. These doses were selected because, in 14-week studies, all mice exposed at 600 ppm died within 1 week, and all mice exposed at 400 ppm died by week 4. Rhinitis was observed in both sexes exposed at 200, 400, and 600 ppm as was renal tubular degeneration in both sexes at 100, 200, and 400 ppm. The latter effects observed at 100 ppm were slight and deemed not to be life threatening in 2-year studies.

Two-Year Studies: Survival of exposed and control mice was comparable in the 2-year studies (male: control, 28/50; low dose, 31/50; high dose, 34/50; female: 25/50; 24/50; 31/50). Final mean body weights in exposed mice were 95%-102% of those of the controls. No compound-related clinical signs were observed.

Those neoplastic lesions that occurred at elevated incidences in mice exposed to ethylene oxide are reported in the following table. In male mice, alveolar/bronchiolar carcinomas, alveolar/bronchiolar adenomas, and papillary cystadenomas of the harderian gland occurred with positive trends. In female mice, alveolar/bronchiolar adenomas, alveolar/bronchiolar carcinomas, papillary cystadenomas of the harderian gland, malignant lymphomas, and uterine adenocarcinomas occurred with positive trends. Mammary gland tumors also were increased in exposed female mice.

Data Audit: An audit of the experimental data was conducted for the 2-year studies of ethylene oxide. 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** for B6C3F$_1$ mice as indicated by dose-related increased incidences of benign or malignant neoplasms of the lung and benign neoplasms of the harderian gland in both male and female B6C3F$_1$ mice following exposure to ethylene oxide vapors at 50 and 100 ppm. In female mice, ethylene oxide caused additional malignant neoplasms of the uterus, mammary gland, and hematopoietic system (lymphoma).

NEOPLASTIC LESIONS RELATED TO ETHYLENE OXIDE EXPOSURE IN B6C3F$_1$ MICE

	Chamber Control	50 ppm	100 ppm
MALE			
Alveolar/bronchiolar adenoma	5/50 (10%)	11/50 (22%)	11/50 (22%)
Alveolar/bronchiolar carcinoma	6/50 (12%)	10/50 (20%)	16/50 (32%)
Harderian gland papillary cystadenoma	1/43 (2%)	9/44 (20%)	8/42 (19%)
Harderian gland papillary cystadenocarcinoma	0/43 (0%)	0/44 (0%)	1/42 (2%)
FEMALE			
Alveolar/bronchiolar adenoma	2/49 (4%)	4/48 (8%)	17/49 (35%)
Alveolar/bronchiolar carcinoma	0/49 (0%)	1/48 (2%)	7/49 (14%)
Harderian gland papillary cystadenoma	1/46 (2%)	6/46 (13%)	8/47 (17%)
Harderian gland papillary cystadenocarcinoma	0/46 (0%)	1/46 (2%)	0/47 (0%)
Malignant lymphoma	9/49 (18%)	6/48 (13%)	22/49 (45%)
Uterine adenocarcinoma	0/49 (0%)	1/47 (2%)	5/49 (10%)
Mammary gland adenocarcinoma or adenosquamous carcinoma	1/49 (2%)	8/48 (17%)	6/49 (12%)

SUMMARY OF THE TWO-YEAR INHALATION STUDIES OF ETHYLENE OXIDE

Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Exposure concentrations 0, 50, or 100 ppm ethylene oxide	0, 50, or 100 ppm ethylene oxide
Survival rates 28/50; 31/50; 34/50	25/50; 24/50; 31/50
Nonneoplastic effects None	None
Neoplastic effects Neoplasms of the lung and harderian gland	Neoplasms of the lung and harderian gland
Level of evidence of carcinogenic activity Clear evidence	Clear evidence

*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 page 9.

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.

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on ethylene oxide 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 ETHYLENE OXIDE

On August 19, 1986, the draft Technical Report on the toxicology and carcinogenesis studies of ethylene oxide 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. Trent R. Lewis, NIOSH/NTP, introduced the studies by reviewing the experimental design, results, and proposed conclusions (clear evidence of carcinogenic activity).

Dr. Mirer, a principal reviewer, agreed with the conclusions as written. He felt that higher doses could have been used, since there were no declines in weight gain, increases in mortality, or increases in nontumor pathology; thus, there may have been a reduction in sensitivity for detecting tumor-induction potential at other organ sites. Dr. Lewis said that ethylene oxide has a moderately steep dose-response curve so that increasing the top dose might have resulted in inadequate survival.

As a second principal reviewer, Dr. Capen agreed with the conclusions as written.

As a third principal reviewer, Dr. Hooper also agreed with the conclusions. He asked that more exposure information and dose levels from various studies be cited, including a number of genetic toxicology studies. This would allow the reader to compare exposure levels with those in the current study as well as with allowable workplace exposure concentrations. Dr. Lewis replied that such detailed information could be included, although since so much has been reported previously, perhaps inclusion of references to pertinent review articles would be appropriate.

In other discussion, Dr. Purchase commented on the metabolic conversion of ethylene to ethylene oxide in mammals and the fact that ethylene oxide can be detected in exhaled air in untreated mammals. Dr. Scala said that since lesions were observed in several organs in the short-term studies, a simple statement should be made that these lesions were not seen in the 2-year studies.

Dr. Mirer moved that the Technical Report on ethylene oxide be accepted with the conclusions as written for male and female mice, clear evidence of carcinogenic activity. Dr. Capen seconded the motion, and it was approved by 10 affirmative votes with 1 abstention (Dr. Purchase).

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Ethylene Oxide is based on the 14-week studies that began in June 1980 and ended in September 1980 and on the 2-year studies that began in August 1981 and ended in July 1983 at Battelle Pacific Northwest Laboratories.

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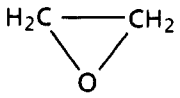
I. INTRODUCTION

Chemical Identification
Production and Use
Regulation
Toxicity
Pharmacokinetics
Metabolism
Genotoxicity
Teratogenicity and Reproductive Toxicity
Neurotoxicity
Carcinogenicity
Study Rationale

I. INTRODUCTION



ETHYLENE OXIDE

CAS No. 75-21-8

C_2H_4O Molecular weight 44.05

Synonyms: oxirane; EO; ETO; dihydrooxirene; dimethylene oxide; 1,2-epoxyethane; oxane; α,β-oxidoethane

Chemical Identification

At room temperature, ethylene oxide is a flammable and reactive gas; the flash point is 18° C (open cup), and the upper and lower explosive limits are 100% and 3% by volume in air. The saturated vapor pressure at 20° C is 1,095 torr. Ethylene oxide is miscible with water and most organic solvents. Its odor, which has been described as etherlike, is detectable at about 700 ppm or higher (NIOSH, 1981).

Production and Use

Ethylene oxide is produced chiefly by the oxidation of ethylene in the presence of a silver oxide catalyst (WHO, 1985). Because of its reactivity and use in the synthesis of many organic compounds, in particular ethylene glycol, ethylene oxide is a major industrial chemical. It is among the 25 chemical compounds with the greatest annual production (approximately 6 billion pounds--2.7 billion kg) in the United States. It is used primarily as a chemical intermediate in the manufacture of antifreeze, polyester resins, nonionic surfactants, and specialty solvents (NIOSH, 1981). Most ethylene oxide is consumed in the chemical plants where it is produced. Approximately 0.24% of the ethylene oxide produced annually in the United States (approximately 7 million kg) is used in the manufacture of medical products, and about 0.02% (540,000 kg) is used as a gaseous sterilant in hospitals (Glaser, 1979). Less than 1% is used as an insecticidal fumigant (USEPA, 1985). As a sterilant, it is usually diluted about 90% with an inert gas to reduce explosion hazards. Occupational exposure to ethylene oxide tends to be greater in health instrument manufacturing plants and in hospitals than in the chemical process industry, although such exposure is usually short term and intermittent (Glaser, 1979). An estimated 75,000 health care workers in the United States are potentially exposed to ethylene oxide (NIOSH, 1981).

Regulation

Over the past decade, the toxicity of ethylene oxide has been investigated extensively, and several reviews on the chemical have been published (ECETOC, 1982, 1984; USEPA, 1985; IARC, 1985; WHO, 1985; Kolman et al., 1986). Taking into account the available toxicologic and epidemiologic data, both the International Agency for Research on Cancer (IARC) and the World Health Organization (WHO) have taken the position that ethylene oxide should be considered a probable human carcinogen, and that its level in the environment should be kept as low as possible. Until 1984, the permissible exposure limit for ethylene oxide enforced by the Occupational Safety and Health Administration (OSHA) was 50 ppm. Based on reports of mutagenic, reproductive, and tumorigenic effects, the standard was lowered to 1 ppm (1.8 mg/m^3); no short-term exposure limit was adopted (USCFR, 1984). The threshold limit value (TLV) suggested by the American Conference of Governmental Industrial Hygienists (ACGIH) is the same as the OSHA standard except that the excursion limit for short-term exposures is three times the TLV-time-weighted average (TWA) for no more than a total of 30 minutes during the workday. Under no circumstances should exposure exceed five times the TLV-TWA (ACGIH, 1985-1986).

Toxicity

The effects of ethylene oxide exposure in humans and animals vary with vapor concentrations and duration of exposure; i.e., with total body dose and peak blood levels. Ethylene oxide is an irritant and a systemic poison; at concentrations higher than 1,000 ppm, it produces central nervous system depression (USCFR, 1984). The most commonly observed effects in humans have been headache, nausea, vomiting, dyspnea, and respiratory irritation (Thiess, 1963). Ethylene oxide is moderately toxic for animals; e.g., the rat oral LD_{50} value is 330 mg/kg body weight (Smyth et al., 1941); the male rat 4-hour LC_{50} value is 1,460 ppm, and the female mouse 4-hour LC_{50} value is 835 ppm (Jacobson et al., 1956). Death of laboratory animals exposed to ethylene oxide at high concentrations is usually due to pulmonary edema or secondary lung infections; clinical signs include convulsions and paralysis (Jacobson et al., 1956; Waite et al., 1930).

Aqueous solutions of ethylene oxide can be extremely irritating to the skin of both laboratory animals and humans, with erythema, edema, and vesiculation occasionally accompanied by bleb formation appearing 1-5 hours after exposure (Sexton and Henson, 1950). Evaporation of liquid ethylene oxide from the skin may cause sufficient cooling to produce a lesion similar to that caused by frostbite (Hine and Rowe, 1981). Ethylene oxide vapors at high concentrations are irritating to the eyes of humans and animals; ocular contact with liquid ethylene oxide can cause corneal injury (McLaughlin, 1946; Thiess, 1963; McDonald et al., 1973).

Pharmacokinetics

Information on the pharmacokinetics, tissue distribution, and elimination of ethylene oxide is scant. Data on the distribution and retention of radiolabeled ethylene oxide have been derived from three studies. In the first, Ehrenberg et al. (1974) found that five male CBA mice exposed to static atmospheres of tritiated ethylene oxide in sealed glass vessels excreted an average of 78% of the estimated dose within 48 hours. Two mice were exposed for 75 minutes to an atmosphere containing 1.15 ppm, two mice for 60 minutes to an atmosphere containing 7.4 ppm, and one mouse for 75 minutes to an atmosphere containing 33 ppm. The biologic half-life of ethylene oxide in mice was 0.15 hours as compared with a half-life in water of 76 hours at 37° C and 6 months at 4° C. In the second study, Appelgren et al. (1977) injected mice with [^{14}C]ethylene oxide (dose not reported) and used whole-body radiography to follow the distribution. Ethylene oxide was rapidly distributed to all parts of the body during the 4 hours after injection. Twenty-four hours after injection, radioactivity remained in the liver, intestinal mucosa, epididymis, cerebellum, bronchi, and bone marrow. Tyler and McKelvey (1983) exposed groups of four male F344 rats to ^{14}C-labeled ethylene oxide at 10, 100, or 1,000 ppm for one 6-hour exposure. Rats exposed at 1,000 ppm excreted proportionately less urinary radioactivity and exhaled more [^{14}C]carbon dioxide and [^{14}C]ethylene oxide than did the other groups. These data suggest that metabolism and excretion of ethylene oxide in rats involve saturable processes.

Metabolism

No data on the metabolism of ethylene oxide in humans have been reported in the literature. Limited data from animal studies indicate two possible pathways for the metabolism of ethylene oxide: hydrolysis and glutathione conjugation. The hydrolytic product, 1,2-ethanediol (ethylene glycol), has been identified in the plasma and urine of four male beagle dogs 1 hour after intravenous injections of 25 or 75 mg ethylene oxide/kg body weight (Martis et al., 1982). Ethylene glycol was the major metabolite of ethylene oxide in the dogs; between 7% and 24% of the administered dose was eliminated in the urine within 24 hours. No other compound-related metabolites were identified. Jones and Wells (1981) demonstrated involvement of glutathione in the detoxification of ethylene oxide. Sprague Dawley rats were given a single intraperitoneal injection of radiolabeled ethylene oxide at 2 mg/kg body weight. Urinary metabolites identified were *S*-(2-hydroxyethyl)cysteine (9% of the administered radioactivity) and *N*-acetyl-*S*-(2-hydroxyethyl)cysteine (33% of the administered radioactivity). Approximately 43% of the administered radioactive dose was excreted in the urine within 50 hours of dosing.

In rabbits, no effect on glutathione levels in liver or blood was noted after 12 weeks of exposure to ethylene oxide at 0, 10, 50, or 250 ppm for 6 hours per day, 5 days per week (Yager and Benz, 1982).

Genotoxicity

There is substantial evidence from studies on prokaryotic and eukaryotic organisms that ethylene oxide is both a point mutagen and a clastogen. Ethylene oxide alkylates DNA and RNA in vitro. Sites of the in vitro reactions include the N7 position of guanine (Brookes and Lawley, 1961), the N1 position of adenosine (Windmueller and Kaplan, 1962), and the N3 position of uridine (Ukita et al., 1963). To date, N7-(2-hydroxyethyl)guanine is the only DNA alkylation product found in vivo (Ehrenberg et al., 1974; Segerback, 1983). Ethylene oxide also interacts with nucleophilic centers in proteins (Ehrenberg et al., 1974; Segerback, 1983).

Ethylene oxide is mutagenic to plants, micro-organisms, insects, and mammals. Mutagenic responses were observed in barley (Ehrenberg et al., 1959), wheat (Mac Key, 1968), rice (Jana and Roy, 1975), and *Tradescantia paludosa* (Smith and Lotfy, 1954) after exposure to ethylene oxide. It is a direct-acting mutagen causing base-pair substitution in Salmonella (Embree and Hine, 1975; Pfeiffer and Dunkelberg, 1980) and is mutagenic to Neurospora (Kilbey and Kolmark, 1968; Kolmark and Giles, 1955) and to Drosophila (Bird, 1952; Fahmy and Fahmy, 1956). Test results for ethylene oxide were negative after a single intravenous injection of up to 50 mg/kg in a dominant lethal study in mice (Appelgren et al., 1977), but results were positive after intraperitoneal administration of 60 mg/kg per day, 5 days per week for 5 weeks (Generoso et al., 1980). In addition, inhalation of ethylene oxide at 225 ppm for 2 or 11 weeks, 6 hours per day, 5 days per week, resulted in a significant dose-related increase in dominant lethal mutations in male mice (Generoso et al., 1983).

Generoso et al. (1986) compared the effects of different dose rates (contributions of different concentrations and durations of exposure, with constant total exposure [concentration × time]) on the dominant-lethal response in male (C3H × 101)F_1 mice. The dose-response curve was nonlinear; the highest airborne concentration (1,200 ppm for 1.5 hours) resulted in the greatest embryonic mortality (64%). The 600-ppm concentration (3 hours) produced 32% embryonic mortality, and the lowest airborne concentration (300 ppm for 6 hours) produced 11% embryonic mortality.

Induction of heritable translocations in male mice also was reported after a single intraperitoneal injection of 150 mg/kg ethylene oxide (Generoso et al., 1980). Intravenous injection of ethylene oxide induced a dose-dependent increase in the number of micronuclei in the bone marrow of mice (Appelgren et al., 1978). Micronuclei in the erythroblasts and polychromatic erythrocytes were elevated in workers exposed to ethylene oxide vapor (Hogstedt et al., 1983). Sister chromatid exchanges (SCEs) were increased in peripheral lymphocytes of rats (Kligerman et al., 1983), rabbits (Yager and Benz, 1982), monkeys (Lynch et al., 1984a), and humans (Ehrenberg and Hallstrom, 1967; Garry et al., 1979; Abrahams, 1980; Laurent et al., 1984) exposed to air containing ethylene oxide.

Stolley et al. (1984) found a significant increase in the number of SCEs in peripheral blood lymphocytes from workers exposed to relatively high atmospheric levels of ethylene oxide (5-20 to 50-200 ppm, 8-hour TWA). The SCE rates in workers exposed to ethylene oxide at more moderate levels (5-10 ppm, 8-hour TWA) were also significantly increased over those in nonexposed controls. These elevated SCE rates persisted through a 24-month followup period during which no exposure occurred. Workers at an occupational site that had low levels of atmospheric ethylene oxide (0.5 ppm, 8-hour TWA) showed no significant elevation in SCE rates.

Sarto et al. (1984) also investigated cytogenic damage in hospital workers exposed to atmospheric ethylene oxide and found that at doses as low as 0.35 ppm, SCEs in peripheral blood lymphocytes were significantly increased; these effects persisted through an 18-month followup period.

Inhalation of ethylene oxide increased the incidence of chromosomal aberrations in bone marrow cells of rats (Fomenko and Strekalova, 1973;

Strekalova et al., 1975; Embree et al., 1977). The incidence of chromosomal aberrations was increased in circulating lymphocytes of monkeys (Lynch et al., 1984a) and of workers exposed to air containing ethylene oxide (Hogstedt et al., 1983; Sarto et al., 1984).

Teratogenicity and Reproductive Toxicity

Groups of 22 female F344 rats were exposed to ethylene oxide at 0, 10, 33, or 100 ppm on days 6-15 of gestation. No maternal toxicity was observed, and a 5%-8% decrease in fetal weight was observed only in the rats exposed at 100 ppm (Snellings et al., 1982a). In a second inhalation study of teratologic effects, groups of 32-45 female Sprague Dawley rats were exposed to ethylene oxide at 0 or 150 ppm on days 7-16 of gestation (group 1), on days 1-16 of gestation (group 2), or during 3 weeks before mating and on days 1-16 of gestation (group 3) (Hackett et al., 1982). No dams died, but body weights were decreased in group 3. Significant increases in resorptions per litter and in resorptions per implantation site were observed in group 3. In all exposed groups, weights and lengths of the fetuses were decreased, and reduced ossification of the sternebra and primary skull was observed.

Groups of 24-37 female CD-1 mice were administered intravenous doses of 0, 75, or 150 mg ethylene oxide/kg body weight in an aqueous dextrose solution on days 4-6, 6-8, 8-10, or 10-12 of gestation (LaBorde and Kimmel, 1980). Signs of maternal toxicity (weakness, labored breathing, tremors, and death) were observed in mice injected with 150 mg/kg ethylene oxide on days 4-6, 8-10, or 10-12 of gestation. Fetotoxicity in the form of a 20% reduction in mean fetal weight was observed in mice administered the highest dose. Fetal malformations, consisting primarily of fused cervical arches, were found in 19% of fetuses in exposed litters as compared with 2% of fetuses in control groups.

In a second intravenous study, New Zealand White rabbits were injected with 0, 9, 18, or 36 mg/kg ethylene oxide on days 6-14 of gestation or with 0, 18, or 36 mg/kg on days 6-9 of gestation (Jones-Price et al., 1982). Significant decreases in maternal weight gain were observed at the 18 and 36 mg/kg doses. No embryotoxic effects were observed in the groups exposed on days 6-9; however, significant dose-related trends for decreased numbers of live fetuses per litter and increased resorptions per litter were observed in groups exposed on days 6-14.

Groups of 30 male and female F344 rats were exposed to ethylene oxide at concentrations of 0, 10, 33, or 100 ppm, 6 hours per day, 5 days per week for 12 weeks, in a one-generation study of reproduction (Snellings et al., 1982b). The male and female rats were housed together for up to 2 weeks; pregnant rats were exposed for 6 hours per day, 7 days per week from day 1 through day 19 of gestation. The pregnant females were allowed to deliver and 5 days after parturition were exposed again to ethylene oxide for 6 hours per day, 7 days per week until day 21 post partum. Significantly more females in the 100-ppm group had lengthened gestation periods compared with the other groups of rats. The number of pups per litter as well as the number of implantation sites per female were decreased at the 100-ppm concentration. There were no effects on survival or parturition. There were no effects on body weights or organs in the parental generation.

Hollingsworth et al. (1956) reported degeneration of testicular tubules in guinea pigs exposed to ethylene oxide at 356 ppm for 7 hours per day, 5 days per week for up to 32 weeks. Sperm motility and sperm counts were decreased in male Cynomolgus monkeys exposed to ethylene oxide at 50 or 100 ppm for 7 hours per day, 5 days per week for 2 years (Lynch et al., 1983). The magnitude of the decreases was similar at both concentrations. The incidence of abnormal sperm heads did not change.

One epidemiologic study suggested that ethylene oxide exposure may be associated with spontaneous abortions in female workers who used ethylene oxide and other chemicals to sterilize instruments (Hemminki et al., 1982).

Neurotoxicity

Exposure of humans and animals to ethylene oxide vapor at concentrations in excess of 200 ppm impairs sensory and motor functions and results in peripheral neuropathy and muscle

atrophy (Hollingsworth et al., 1956; Jacobson et al., 1956; Gross et al., 1979; Finelli et al., 1983). Kuzuhara et al. (1983) reported axonal degeneration and typical denervation atrophy of muscle in two workers exposed to ethylene oxide at more than 700 ppm for several months. Male Wistar rats exposed to ethylene oxide at 500 ppm for 6 hours per day, 3 days per week for 13 weeks, developed hindleg ataxia (Ohnishi et al., 1985). Axonal degeneration of the myelinated fibers in the hindleg nerves was also observed. Axonal dystrophy of the nucleus gracilis and demyelination of the terminal axons of the fasciculus gracilis were observed in the medulla oblongata of monkeys after intermittent exposure at 50 or 100 ppm for 2 years (Sprinz et al., 1982).

Carcinogenicity

Ethylene oxide has been evaluated for carcinogenicity in animals when administered by the dermal, intragastric, subcutaneous, or inhalation routes of exposure. No skin tumors were observed in thirty 8-week-old female ICR/Ha Swiss mice painted on the clipped dorsal skin three times weekly for life with 0.1 ml of a 10% solution of ethylene oxide in acetone (Van Duuren et al., 1965). The median survival time for the dosed mice was 493 days, and no tumor incidences at other sites were reported.

Dunkelberg (1982) administered ethylene oxide by gavage at doses of 0, 7.5, or 30 mg/kg body weight to groups of 50 female Sprague Dawley rats. Fasted rats were dosed twice weekly for 107 weeks, and the experiment was terminated after 150 weeks. "Salad oil" was used as the vehicle. A positive control group received β-propiolactone. At the 7.5 mg/kg dose, 8/50 (16%) of the animals developed tumors, and at 30 mg/kg, 31/50 (62%) developed tumors; the first tumors appeared after 79 weeks. These local tumors were primarily squamous cell carcinomas of the forestomach. Carcinomas in situ, papillomas, and reactive changes of the squamous epithelium of the forestomach were observed in other animals administered ethylene oxide. No tumors of the stomach were reported in the controls. The incidences of tumors in other organs were similar in dosed and control rats.

The carcinogenic potential of ethylene oxide in mice was also evaluated by the subcutaneous route of administration (Dunkelberg, 1981). Groups of 100 female NMRI mice were injected subcutaneously once per week for a maximum of 95 weeks with 0.1 ml tricaprylin containing 0, 0.1, 0.3, or 1.0 mg ethylene oxide. A control group of 200 mice was included, and the experiment was terminated after 106 weeks. The groups of mice receiving total ethylene oxide doses of 9.1, 27.3, or 91.0 mg had 5, 8, or 11 local sarcomas, respectively. The group administered tricaprylin alone had four sarcomas. No increased incidences of tumors at remote sites were reported. In a second subcutaneous injection study, Walpole (1958) injected 12 rats (sex and strain unspecified) with a total ethylene oxide dose of 1 g/kg body weight. Ethylene oxide was dissolved in arachis oil and administered over 94 days (dosing schedule not specified). Rats were observed for their lifetimes following dosing, and no tumors were observed. Since important details of the study were not specified and small numbers of animals were used, it is difficult to evaluate this negative result.

Two long-term inhalation studies were conducted. Male and female F344 rats were exposed to ethylene oxide at concentrations of 10, 33, or 100 ppm 6 hours per day, 5 days per week for 2 years (Snellings et al., 1984). Two groups of rats served as controls. Each group consisted initially of 120 animals of each sex. The incidence of mononuclear cell leukemia was significantly increased in a dose-related fashion in females killed at 24 months (control, 11/115; 10 ppm, 11/54; 33 ppm, 14/48; 100 ppm, 15/26). A dose-related increase in peritoneal mesotheliomas was reported in male rats that died or were killed in a moribund condition. Dose-related increased incidences of primary brain tumors in rats of each sex were also found in the study by Snellings et al. (1984) and were reported by Garman et al. (1985) (male: 0 ppm, 0/236 [pooled]; 10 ppm, 1/119; 33 ppm, 5/118; 100 ppm, 7/119; female: 0 ppm, 0/234 [pooled]; 10 ppm, 1/115; 33 ppm, 3/119; 100 ppm, 4/119). The primary brain tumors included 6 granular cell tumors, 12 astrocytomas, 1 oligodendroglioma, 2 mixed cell gliomas, and 2 malignant sarcomas.

The number of female rats with multiple neoplasms and with at least one malignant neoplasm was greater in exposed groups than in the controls.

Another inhalation study was conducted in which groups of 80 male F344 rats were exposed to ethylene oxide for 7 hours per day, 5 days per week for 2 years, at concentrations of 0, 50, or 100 ppm (Lynch et al., 1983, 1984b). A significantly increased incidence of mononuclear cell leukemia occurred only in rats exposed at the 50-ppm concentration (control, 24/77; 50 ppm, 38/79; 100 ppm, 30/76); the absence of a dose-response relationship was attributed to increased mortality at the 100-ppm concentration. Dose-related increased incidences of peritoneal mesotheliomas (control, 3/78; 50 ppm, 9/79; 100 ppm, 21/79) and mixed cell gliomas in the brain (0/76; 2/77; 5/79) were observed in the rats. The increased incidences of both tumors were significant at the 100-ppm concentration.

Epidemiologic studies show an association between ethylene oxide exposure and an excess risk of cancer in humans. Hogstedt et al. (1979a, 1984) reported statistically significant incidences of leukemia and cancer of all sites and deaths attributed to leukemia in workers exposed to ethylene oxide used as a sterilant. In a followup cohort mortality study, Hogstedt et al. (1979b, 1984) examined the incidence of cancer in production workers at an ethylene oxide manufacturing plant. Significantly increased mortality from stomach cancer and leukemia was found. In these studies, the increased mortality and incidence of leukemia were not limited to a particular type of leukemia. In addition, the workers were reportedly exposed to other chemicals. Recently, in an expanded cohort mortality study encompassing workers from three exposure sites, Hogstedt et al. (1986) reported eight cases of leukemia vs. 0.8 cases expected and six cases of stomach cancer compared with 0.65 cases expected. The latter publication was a followup of their investigation reported in 1979 and 1984, with the addition of one case of leukemia found in a production worker at a third worksite. In a study reported by Morgan et al. (1981) as negative, there was increased mortality from pancreatic cancer and Hodgkin's disease which was statistically significant by the Poisson test (USEPA, 1985).

Study Rationale

Ethylene oxide was studied in $B6C3F_1$ mice because of its extensive production; the potential for human exposure in the workplace, from medical devices, or from food; the positive results of genetic assays; and the previous use of only F344 rats in inhalation studies.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF ETHYLENE OXIDE

GENERATION AND MEASUREMENT OF CHAMBER CONCENTRATIONS

- Vapor Generation System
- Vapor Concentration Monitoring
- Degradation Study of Ethylene Oxide in Chamber
- Vapor Concentration Uniformity in Chamber

SINGLE-EXPOSURE STUDIES

FOURTEEN-DAY STUDIES

FOURTEEN-WEEK STUDIES

TWO-YEAR STUDIES

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

PROCUREMENT AND CHARACTERIZATION OF ETHYLENE OXIDE

Ethylene oxide was obtained from Union Carbide, Linde Division (Torrance, California, and Somerset, New Jersey), in eight different lots (Table 1). The liquefied ethylene oxide was stored at room temperature in its original cylinder and was analyzed periodically at the study laboratory by infrared spectroscopy (Figure 1) and gas chromatography with a flame ionization detector and Porapak QS 80/100 mesh column. The identity and purity of the ethylene oxide was confirmed in all cases, and all results of bulk lot analyses indicated purity of greater than 99%. No degradation of the bulk chemical was observed over the course of the studies.

GENERATION AND MEASUREMENT OF CHAMBER CONCENTRATIONS

Vapor Generation System

Liquefied ethylene oxide was dispensed through an eductor tube from the 175-pound cylinder to a coiled-tube hot water boiler by pressurizing the tankhead space with nitrogen (regulated at 20 psi). The vapor was generated in a stainless steel coiled tube boiler located in a 55° ± 10° C water bath. From the boiler, ethylene oxide vapor was routed through a manifold to dual gas metering valves that controlled the gas flow to each chamber. The manifold and valves were heated to about 55° C with a heat tape and a small heater.

After passing through the metering valves, vapor could be routed by means of three-way ball valves either to the exposure chambers or through a flowmeter to the exhaust. This procedure allowed for periodic measurement of the vapor flow from the metering valves. Ethylene oxide vapor could not be continuously routed through the flowmeter because buildup of polymer would cause a slight change in calibration. Vapor to each chamber was routed through a three-way purge/expose valve into a pipe at the chamber inlet, where the gas was mixed with 0.28 ± 0.04 m^3/min of diluent air. The purge/expose valves allowed the vapor generation and distribution system to be purged with nitrogen after each exposure period. Liquid purged from the system was collected in a 500-ml flask in the vapor hood from which it vaporized between exposure periods (Figure 2). The liquid appeared to be unpolymerized and undegraded ethylene oxide that had condensed daily in the generation system; no evidence was found that this liquid contained degradation products that were identifiable in the chamber atmospheres.

TABLE 1. IDENTITY AND SOURCE OF ETHYLENE OXIDE USED IN THE INHALATION STUDIES

Single-Exposure Studies	Fourteen-Day Studies	Fourteen-Week Studies	Two-Year Studies
Lot Numbers			
0018-1	0018-1	0018-1	0190-1, 2050-1, 2061-1, 2131-1, E10-13-82, E1-21-83, E3-28-83
Date of Initial Use			
2/8/80	3/5/80	6/2/80	0190-1, 8/6/81; 2050-1, 3/4/82; 2061-1, 3/11/82; 2131-1,9/13/82; E10-13-82, 10/25/82; E1-21-83, 2/16/83; E3-28-83, 4/1/83
Supplier			
Union Carbide, Inc. (Torrance, CA)	Same as single-exposure studies	Same as single-exposure studies	Union Carbide Corp. (Somerset, NJ)

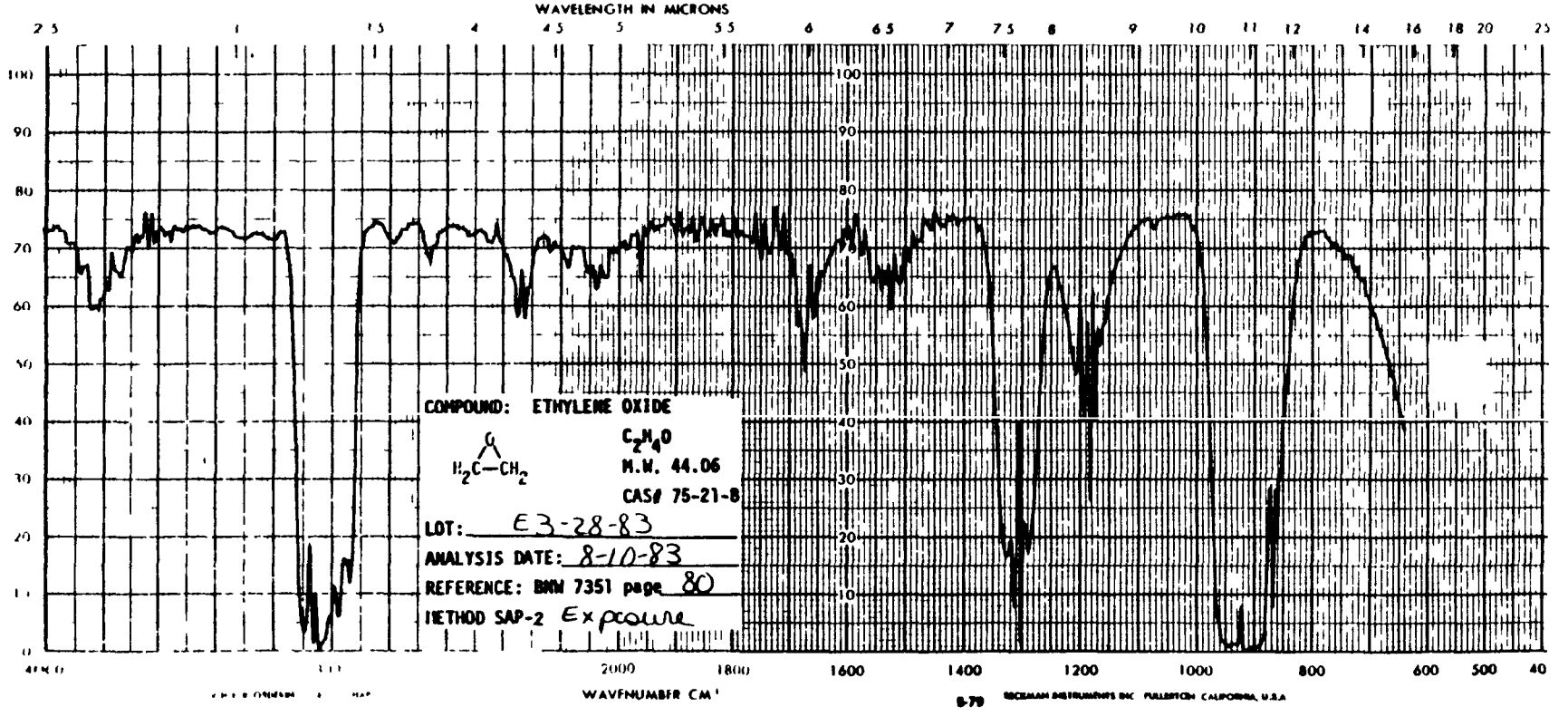


FIGURE 1. INFRARED SPECTRUM OF THE VAPOR PHASE OF ETHYLENE OXIDE (LOT E3-28-83)

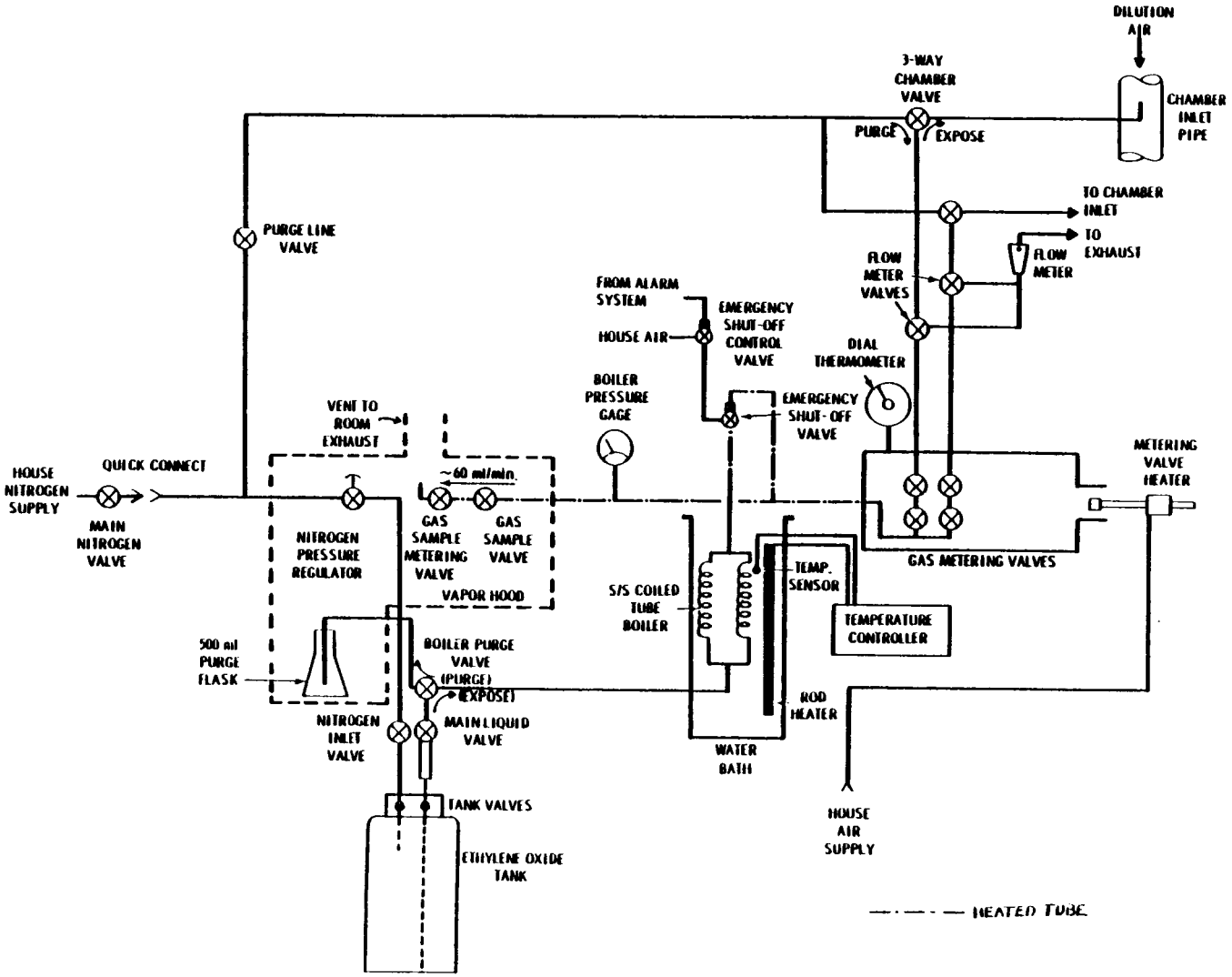


FIGURE 2. BLOCK DIAGRAM OF THE ETHYLENE OXIDE VAPOR GENERATION SYSTEM

Vapor Concentration Monitoring

Two online methods were used during the course of the 2-year studies to monitor the concentration of ethylene oxide in the chambers. A schematic diagram of the monitoring system is shown in Figure 3. Initially, a photoionization detector (PID) (model PI201, HNU Systems, Inc., Newton, Massachusetts) was used. After 79 exposure days, the photoionization detector was replaced by a Hewlett-Packard Model 5840 gas chromatograph equipped with a flame ionization detector, a glass column packed with Porapak QS 80/100, and an automatic sampling valve. A change in method was made to permit the use of one gas chromatograph to monitor the ethylene oxide study as well as the ongoing 1,3-butadiene study. All chambers and the room air were sampled approximately twice during each exposure hour. The calibration of the monitoring photoionization detector and gas chromatograph was confirmed and corrected at least once every month with a calibration gas consisting of a measured volume of ethylene oxide in a known volume of room air. Weekly mean exposure concentrations for the 2-year studies are presented in Figures 4 and 5. A summary of the chamber concentrations is presented in Table 2; Table 3 summarizes the distribution of mean daily concentrations. Standard deviations for the weekly mean exposures were largest during the first 8 months of the study and resulted from difficulties in regulating the flow rate of the ethylene oxide. These variations were corrected by the installation of a new flow meter.

When the ethylene oxide studies began, 1,3-butadiene was already on study in the same exposure room. Both chemicals were monitored by the same instruments, initially the photoionization detector and later the gas chromatograph. The PID was zeroed with the detection lamp off to avoid "null out" of any chemicals detected during the zeroing process. A 500-ppm propylene-in-air online standard was used to calibrate the gas chromatograph. The gas chromatograph (or the PID) was connected to an eight-port sample valve that allowed sampling of each station (three 1,3-butadiene chambers, three ethylene oxide chambers, a propylene standard, and room air). To prevent possible retention of a study chemical within the gas chromatograph (or PID), the propylene standard was sampled after the three 1,3-butadiene chambers and the room air was sampled after the three ethylene oxide chambers.

TABLE 2. SUMMARY OF CHAMBER CONCENTRATIONS IN THE TWO-YEAR INHALATION STUDIES OF ETHYLENE OXIDE

Target Concentration (ppm)	Total Number of Readings	Mean Concentration (ppm) (a)
50	7,771	49.7 ± 3.6
100	7,773	99.3 ± 7.8

(a) Mean ± standard deviation

TABLE 3. DISTRIBUTION OF MEAN DAILY CONCENTRATIONS OF ETHYLENE OXIDE DURING THE TWO-YEAR INHALATION STUDIES

Range of Concentration (percent of target)	Number of Days Mean Within Range	
	50 ppm	100 ppm
>130	0	1
120-130	2	1
110-120	2	5
100-110	188	182
90-100	281	282
80-90	12	13
70-80	2	3
<70	0	0

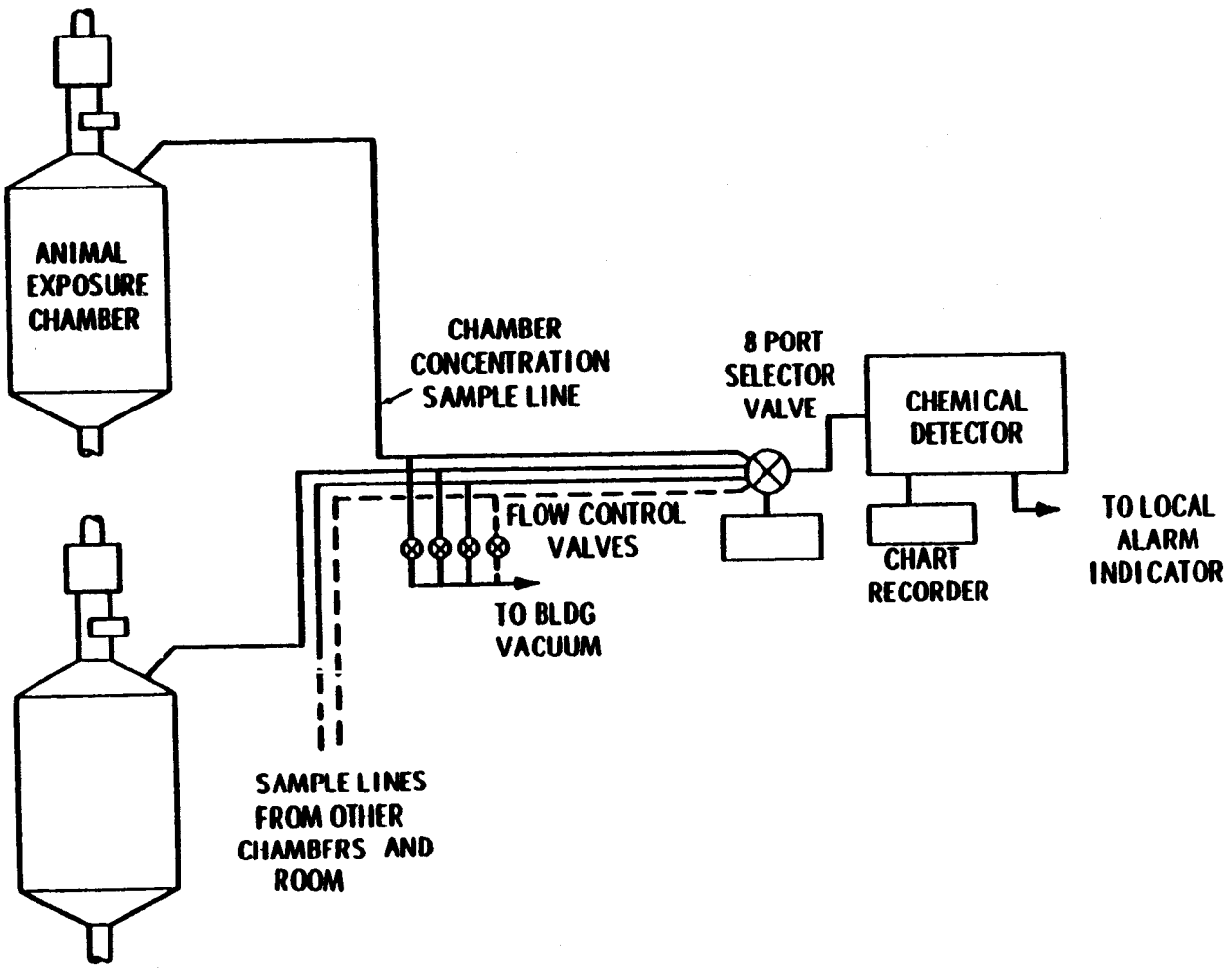


FIGURE 3. CHAMBER CONCENTRATION MONITORING SYSTEM

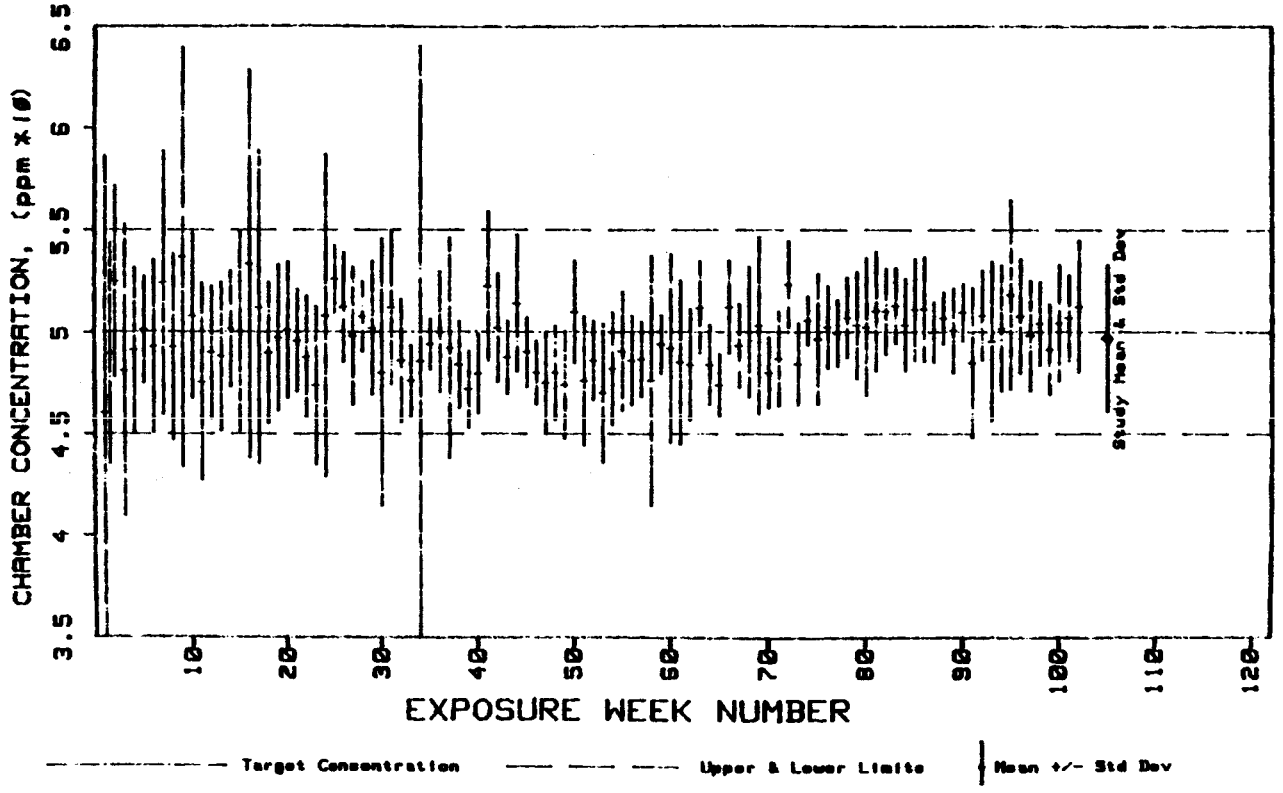


FIGURE 4. WEEKLY MEAN CONCENTRATION AND STANDARD DEVIATION IN THE 50-ppm ETHYLENE OXIDE EXPOSURE CHAMBER FOR ENTIRE 102-WEEK STUDIES

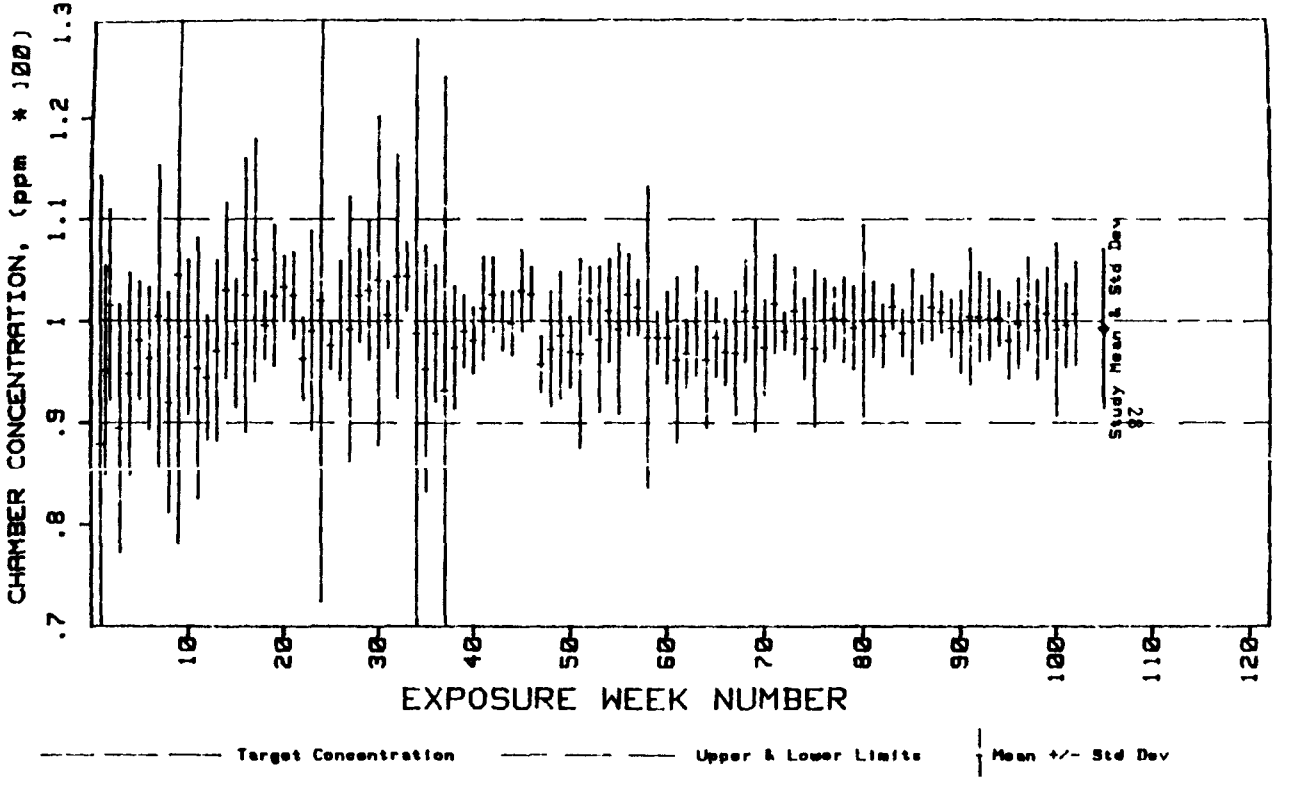


FIGURE 5. WEEKLY MEAN CONCENTRATION AND STANDARD DEVIATION IN THE 100-ppm ETHYLENE OXIDE EXPOSURE CHAMBER FOR ENTIRE 102-WEEK STUDIES

There was no analytical interference between ethylene oxide and 1,3-butadiene. Under the conditions of operation of the gas chromatographic method, the specific retention times were 1.0 minute for propylene, 1.9 minutes for ethylene oxide, and 2.6 minutes for 1,3-butadiene.

Degradation Study of Ethylene Oxide in Chamber

Samples of ethylene oxide exposure chamber atmospheres were examined for the occurrence of potential degradation products, specifically ethylene glycol and acetaldehyde, by a Hewlett-Packard Model 5830 gas chromatograph equipped with a flame ionization detector and a glass column packed with Porapak PS 80/100. No evidence for any degradation was detected.

Vapor Concentration Uniformity in Chamber

Uniformity of vapor concentration in each exposure chamber was measured periodically throughout the studies with a portable photoionization detector. The data showed that when expressed as percentages of the normalized average concentration of all 12 sampling positions, the standard deviation did not exceed 3%.

SINGLE-EXPOSURE STUDIES

Male and female B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and observed for 28 days before being placed on study. Groups of five mice of each sex were exposed for 4 hours to air containing ethylene oxide at target concentrations of 100, 200, 400, 800, or 1,600 ppm. No controls were used. Mice were observed continuously during the exposure period and three times per day during nonexposure periods. They were weighed only before exposure. Necropsies were not performed. Details of animal maintenance are presented in Table 4.

FOURTEEN-DAY STUDIES

Male and female B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and observed for 20 days before being placed on study. The animals were 7-9 weeks old when the studies began. Groups of five mice of each sex were exposed to air containing ethylene oxide at target concentrations of 0, 50, 100, 200, 400, or 800 ppm for 6 hours per day, 5 days per week for 14 days (10 exposures). Mice were observed three times per day and were weighed on days 1 and 8 and at necropsy. A necropsy was performed on all animals. Tissues and groups examined are listed in Table 4.

FOURTEEN-WEEK STUDIES

Fourteen-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to ethylene oxide and to determine the concentrations to be used in the 2-year studies.

Five- to six-week-old male and female B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for 19 days before being placed on study. Groups of 10 mice of each sex were exposed to air containing ethylene oxide at target concentrations of 0, 50, 100, 200, 400, or 600 ppm, 6 hours per day, 5 days per week for 14 weeks (65 exposures).

Animals were observed two times per day; moribund animals were killed. Individual animal weights were recorded weekly. At the end of the 14-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Further experimental details are presented in Table 4.

TWO-YEAR STUDIES

Study Design

Two-year studies were conducted at Battelle Pacific Northwest Laboratories. Groups of 50 mice of each sex were exposed to air containing ethylene oxide at target concentrations of 0 (chamber control), 50, or 100 ppm, 6 hours per day, 5 days per week for 102 weeks. Actual concentrations are summarized in Table 3.

Source and Specifications of Animals

The male and female B6C3F$_1$ (C57BL/6N, female $\times$ C3H/HeN MTV$^-$, male) mice used in

TABLE 4. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE INHALATION STUDIES OF ETHYLENE OXIDE

Single-Exposure Studies	Fourteen-Day Studies	Fourteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN			
Size of Study Groups			
5 male and 5 female mice	5 male and 5 female mice	10 male and 10 female mice	50 male and 50 female mice
Target Concentrations			
100, 200, 400, 800, or 1,600 ppm ethylene oxide by inhalation	0, 50, 100, 200, 400, or 800 ppm ethylene oxide by inhalation	0, 50, 100, 200, 400, or 600 ppm ethylene oxide by inhalation	0, 50, or 100 ppm ethylene oxide by inhalation
Date of First Exposure			
2/8/80	3/5/80	6/2/80	8/6/81
Date of Last Exposure			
N/A	3/18/80	9/4/80	7/22/83
Duration of Exposure			
4 h	6 h/d, 5 d/wk for 2 wk	6 h/d, 5 d/wk (except d 4) for 65 exposures	6 h/d, 5 d/wk for 102 wk (except 25 d) for 487 exposures
Type and Frequency of Observation			
Observed continuously during exposure and 3 × d during nonexposure periods; weighed before exposure	Observed 3 × d; weighed on d 1 and 8 and at necropsy	Observed 2 × d; weighed before exposure, 1 × wk thereafter, and at necropsy	Same as 13-wk studies except weighed 1 × 4 wk after week 13
Necropsy and Histologic Examination			
Necropsy not performed	Necropsy performed on all animals. Tissues from 8 mice that lived to the end of the studies were examined histologically. Tissues examined in 6 exposed mice: skin, mandibular lymph nodes, salivary glands, larynx, trachea, lungs and bronchi, heart, thyroid gland, esophagus, stomach, duodenum, colon, liver, gallbladder, pancreas, spleen, kidneys, adrenal glands, urinary bladder, seminal vesicles/prostate/testis or ovaries/uterus, nasal cavity, brain, pituitary gland, and eyes. The eyes of 2 female controls were examined microscopically	Necropsy performed on all animals; histologic exam performed on all controls and the 2 highest dose groups. Tissues examined: gross lesions and tissue masses, skin, liver, ovaries/uterus, lungs, bronchi, heart, thymus, trachea, spleen, kidneys, adrenal glands, urinary bladder, sternebrae including marrow, and nasal cavity	Necropsy and histologic exam performed on all animals. Tissues examined: gross lesions and tissue masses, mandibular lymph nodes, mammary gland, skin, salivary glands, sternebrae, thyroid gland, parathyroids, small intestine (3 sections), colon, liver, prostate/testis or ovaries/uterus, gallbladder, lungs, bronchi, heart, esophagus, stomach, brain (3 sections), thymus, trachea, pancreas, spleen, kidneys, adrenal glands, urinary bladder, pituitary gland, nasal cavity, and nasal turbinates (3 sections)
ANIMALS AND ANIMAL MAINTENANCE			
Strain and Species			
$B6C3F_1$ mice	$B6C3F_1$ mice	$B6C3F_1$ mice	$B6C3F_1$ mice
Animal Source			
Charles River Breeding Laboratories (Portage, MI)	Same as single-exposure studies	Same as single-exposure studies	Frederick Cancer Research Center (Frederick, MD)

TABLE 4. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE INHALATION STUDIES OF ETHYLENE OXIDE (Continued)

Single-Exposure Studies	Fourteen-Day Studies	Fourteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)			
Study Laboratory			
Battelle Pacific Northwest Laboratories (Richland, WA)	Battelle Pacific Northwest Laboratories (Richland, WA)	Battelle Pacific Northwest Laboratories (Richland, WA)	Battelle Pacific Northwest Laboratories (Richland, WA)
Method of Animal Identification			
None	Ear tags	Ear tags	Ear tags
Time Held Before Study			
28 d	20 d	19 d	21 d
Age When Placed on Study			
8-10 wk	7-9 wk	8-9 wk	8 wk
Age When Killed			
10-12 wk	9-11 wk	22-23 wk	112-113 wk
Necropsy Dates			
2/21/80	3/19/80	9/5/80	8/1/83-8/3/83
Method of Animal Distribution			
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 except during exposure	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 (Harford Metal, Inc., Aberdeen, MD) placed within the exposure chamber	Same as single-exposure studies	Same as single-exposure studies	Same as single-exposure studies
Animals per Cage			
1	1	1	1
Other Chemicals on Study in the Same Room			
None	None	None	1,2-epoxybutane; 1,3-butadiene
Animal Room Environment			
Temp--70°-72° F during exposure, 72°-76° F at other times; humidity--40%-60%; fluorescent light 12 h/d; 10 chamber air changes/h during exposure, 20 air changes/h at all other times	Temp--72°-78° F; humidity--42%-63%; fluorescent light 12 h/d; chamber air changes same as single-exposure studies	Temp--72°-76° F during exposure, 73.4° ± 1.6° F at other times; humidity--40%-60%; fluorescent light 12 h/d; chamber air changes same as single-exposure studies	Temp--room, 72.5° ± 1.7° F, chamber, 72°-86° F; humidity--room, 43% ± 4%; fluorescent light 12 h/d; chamber air changes same as single-exposure studies

these studies were produced under strict barrier conditions at Frederick Cancer Research Center under a contract to the Carcinogenesis Program. Breeding stock for the foundation colony 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. The mice were shipped to the study laboratory at 5 weeks of age, quarantined for 21 days, and then placed on study at 8 weeks of age. Thereafter, a complete necropsy was performed on five animals per sex to assess their health status.

Animal Maintenance

Mice were housed continuously in the exposure chambers from approximately 1 week before exposure started until they were killed at the end of the studies. During nonexposure periods, the front doors of the exposure chambers were open while air continued to be exhausted through the chambers. All animals were housed individually. Feed and water were available ad libitum except during exposure periods, when only water was available. Details of animal maintenance are given in Table 4. Serologic analyses were performed as described in Appendix C.

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded once per week. 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 4.

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 dead of other than natural causes or were found to be missing; 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 are used in the analysis of tumor incidence, and reported P values are one-sided.

Life Table Analysis--The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the 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 chamber 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

SINGLE-EXPOSURE STUDIES

FOURTEEN-DAY STUDIES

FOURTEEN-WEEK STUDIES

TWO-YEAR STUDIES

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

SINGLE-EXPOSURE STUDIES

All mice exposed at 1,600 ppm and 5/5 males and 4/5 females exposed at 800 ppm died before the end of the studies (Table 5). At 800 ppm, lacrimation was observed after 3 hours; dyspnea was observed after 4 hours. At 1,600 ppm, dyspnea, lacrimation, and incoordination were observed after 3 hours; semiconsciousness, severe dyspnea, and diarrhea were observed after 3.5 hours.

FOURTEEN-DAY STUDIES

All mice exposed at 800 ppm died before the end of the studies (Table 6). Other deaths were not clearly compound related. Final mean body weights of dosed and control mice showed no consistent dose-related changes. Mice exposed at 800 ppm were hunched and listless during and immediately after exposure.

FOURTEEN-WEEK STUDIES

All mice exposed at 400 or 600 ppm died before the end of the studies (Table 7). Final mean body weights of dosed and control mice were comparable. All mice exposed at 600 ppm had anorexia, dyspnea, and decreased activity and were bloated and listless.

TABLE 5. SURVIVAL OF MICE IN THE SINGLE-EXPOSURE INHALATION STUDIES OF ETHYLENE OXIDE

	Target Concentration (ppm)	Measured Concentration (ppm)	Survival (a)
MALE			
	100	96	5/5
	200	201	5/5
	400	409	5/5
	800	816	(b) 0/5
	1,600	1,542	(c) 0/5
FEMALE (d)			
	100	96	5/5
	200	201	5/5
	400	409	5/5
	800	816	(e) 1/5
	1,600	1,542	(c) 0/5

(a) Number surviving/number initially in group
(b) Day of death: 2,2,2,2,6
(c) All deaths occurred within 4 hours of the end of exposure.
(d) LC_{50} value by the Spearman-Karber method: 660 ppm with a 95% confidence interval of 509-856 ppm
(e) Day of death: 1,2,2,3

TABLE 6. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FOURTEEN-DAY INHALATION STUDIES OF ETHYLENE OXIDE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
0	5/5	29.0 ± 0.8	30.2 ± 0.8	+1.2 ± 1.0	--
50	5/5	26.6 ± 0.5	28.4 ± 0.5	+1.8 ± 0.6	94.0
100	5/5	25.0 ± 1.1	27.6 ± 1.4	+2.6 ± 0.9	91.4
200	5/5	26.6 ± 1.2	27.6 ± 0.8	+1.0 ± 0.5	91.4
400	5/5	26.8 ± 0.4	29.4 ± 0.5	+2.6 ± 0.7	97.4
800	(d) 0/5	27.2 ± 0.9	(e)	(e)	(e)
FEMALE					
0	5/5	22.0 ± 0.5	24.8 ± 0.4	+2.8 ± 0.5	--
50	5/5	20.6 ± 1.4	21.8 ± 1.4	+1.2 ± 0.2	87.9
100	5/5	22.0 ± 0.3	24.0 ± 0.7	+2.0 ± 0.6	96.8
200	(f) 3/5	19.2 ± 1.0	21.0 ± 1.7	+2.3 ± 2.2	84.7
400	5/5	21.6 ± 0.2	24.0 ± 0.6	+2.4 ± 0.6	96.8
800	(d) 0/5	21.2 ± 0.2	(e)	(e)	(e)

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Day of death: 1,1,1,1,2
(e) No data are reported due to 100% mortality in this group.
(f) Day of death: 7,11

TABLE 7. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FOURTEEN-WEEK INHALATION STUDIES OF ETHYLENE OXIDE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
0	10/10	23.7 ± 0.4	30.5 ± 1.1	+ 6.8 ± 1.3	--
50	(d) 9/10	23.9 ± 0.5	31.0 ± 0.8	+ 7.3 ± 1.1	101.6
100	(e) 9/10	24.4 ± 0.4	32.4 ± 0.7	+ 8.0 ± 0.8	106.2
200	(f) 9/10	25.6 ± 0.6	31.0 ± 0.7	+ 5.2 ± 0.4	101.6
400	(g) 0/10	24.7 ± 0.5	(h)	(h)	(h)
600	(f) 0/10	25.3 ± 0.5	(h)	(h)	(h)
FEMALE					
0	10/10	20.8 ± 0.5	27.1 ± 0.6	+ 6.3 ± 0.7	--
50	10/10	20.8 ± 0.2	26.9 ± 0.8	+ 6.1 ± 0.9	99.3
100	10/10	21.5 ± 0.3	27.2 ± 0.6	+ 5.7 ± 0.7	100.4
200	10/10	20.5 ± 0.5	26.4 ± 0.5	+ 5.9 ± 0.7	97.4
400	(i) 0/10	21.1 ± 0.5	(h)	(h)	(h)
600	(f) 0/10	20.1 ± 0.5	(h)	(h)	(h)

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Week of death: 5
(e) Week of death: 3
(f) Week of death: all 1
(g) Week of death: 1,1,1,1,2,2,2,2,3,4
(h) No data are reported due to 100% mortality in this group.
(i) Week of death: 2,2,2,2,2,2,2,2,2,3

Thymic lymphocytic necrosis was observed in males and females at 600 ppm; lymphocytic necrosis of the spleen was found in males at 600 ppm; renal tubular necrosis was seen in males and females at 600 ppm; renal tubular degeneration was observed in males and females at 100, 200, and 400 ppm; and rhinitis of the nasal cavity was observed in males and females at 200, 400, and 600 ppm (Table 8). Loss of polarity of olfactory and respiratory epithelial cells, necrosis of epithelium, loss of cilia, and transmigration of inflammatory cells with accumulation of purulent exudate in some mice were the most frequent alterations found in the nasal portion of the respiratory tract. These dose-related lesions appeared most pronounced in the dorsal turbinate areas.

The relative liver weight of female mice exposed at 50 ppm was significantly lower than that of the controls (Table 9).

TABLE 8. INCIDENCES AND SEVERITY OF LESIONS IN MICE IN THE FOURTEEN-WEEK INHALATION STUDIES OF ETHYLENE OXIDE (a)

Site/Lesion	Chamber Control	100 ppm	200 ppm	400 ppm	600 ppm
MALE					
Thymus					
Necrosis, lymphocytic	0/10	0/9	1/10 (0.2)	0/4	10/10 (3.8)
Hypoplasia, lymphocytic	0/10	1/9 (0.1)	3/10 (0.4)	3/4 (2.8)	0/10
Spleen					
Necrosis, lymphocytic	0/10	0/1	0/9	0/10	5/10 (1.4)
Kidney					
Necrosis, tubular	0/10	1/10 (0.2)	1/10 (0.1)	5/10 (1.4)	8/10 (2.3)
Degeneration, tubular	0/10	5/10 (0.7)	6/10 (0.7)	4/10 (1.5)	0/10
Glomerulopathy, fibroid	0/10	0/10	0/10	0/10	1/10 (0.4)
Congestion	0/10	0/10	0/10	0/10	1/10 (0.2)
Nasal cavity					
Rhinitis	0/10	0/10	4/10 (0.4)	10/10 (2.8)	10/10 (3.3)
FEMALE					
Thymus					
Necrosis, lymphocytic	0/10	0/10	0/10	0/5	6/10 (2.4)
Hypoplasia, lymphocytic	0/10	0/10	1/10 (0.1)	5/5 (3.6)	4/10 (1.4)
Spleen					
Necrosis, lymphocytic	0/10	--	0/10	0/10	1/10 (0.3)
Kidney					
Necrosis, tubular	0/10	0/10	0/10	5/10 (1.8)	5/10 (1.6)
Degeneration, tubular	2/10 (0.2)	0/10	8/10 (1.0)	6/10 (2.3)	4/10 (1.1)
Nasal cavity					
Rhinitis	0/9	0/9	8/10 (1.2)	9/9 (2.8)	10/10 (3.4)

(a) Number of observations/number examined. Severity ranked on a subjective scale of from 0 (normal) to 4 (most severe); values in parentheses are mean severity values.

TABLE 9. ANALYSIS OF LIVER WEIGHT TO BODY WEIGHT RATIOS FOR MICE IN THE FOURTEEN-WEEK INHALATION STUDIES OF ETHYLENE OXIDE (a)

Concentration (ppm)	No. Examined	Final Body Weight (grams)	Liver Weight (mg)	Liver Weight/Body Weight (mg/g)
MALE				
0	10	30.5 ± 3.63	1,911 ± 353	62.4 ± 6.05
50	9	31.0 ± 2.45	1,794 ± 271	57.8 ± 6.28
100	9	32.4 ± 2.24	1,996 ± 253	61.5 ± 5.73
200	9	31.0 ± 2.06	1,858 ± 256	59.8 ± 5.14
FEMALE				
0	10	27.1 ± 1.79	1,653 ± 144	61.1 ± 4.35
50	10	26.9 ± 2.51	1,508 ± 220	(b) 56.0 ± 5.66
100	10	27.2 ± 1.75	1,614 ± 121	59.4 ± 4.16
200	10	26.4 ± 1.51	1,735 ± 174	65.6 ± 3.79

(a) Mean ± standard deviation
(b) $P<0.05$ vs the controls by Dunnett's test (Dunnett, 1955)

Dose Selection Rationale: Histopathologic examinations of mice in the 14-week studies revealed a dose-related incidence and severity of nasal, thymic, and renal lesions in the exposed animals. Because only minimal renal tubular degeneration was found in male mice exposed at 100 ppm ethylene oxide, concentrations of 50 and 100 ppm were selected for the 2-year studies.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed mice were not adversely affected by exposure to ethylene oxide (Table 10 and Figure 6). No compound-related clinical signs were observed.

TABLE 10. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR INHALATION STUDIES OF ETHYLENE OXIDE

Weeks on Study	Chamber Control		50 ppm			100 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	23.6	50	24.5	104	50	24.8	105	50
1	25.6	50	25.6	100	50	26.2	102	50
2	26.9	50	27.3	101	50	27.0	100	50
3	27.8	50	28.0	101	50	28.4	102	50
4	28.5	50	28.3	99	50	28.4	100	50
5	28.8	50	29.0	101	50	29.3	102	50
6	29.2	50	30.0	103	50	30.2	103	50
7	30.1	50	29.5	98	50	30.0	100	50
8	30.1	50	30.6	102	50	30.4	101	50
9	31.0	50	31.0	100	49	31.5	102	50
10	31.5	50	31.8	101	49	31.8	101	50
11	31.0	50	31.9	103	49	31.9	103	50
12	31.7	50	32.4	102	49	32.6	103	50
13	32.0	49	32.3	101	49	32.7	102	50
18	32.6	49	31.2	96	49	32.4	99	50
22	32.4	49	33.8	104	49	33.2	102	50
26	33.5	49	35.2	105	49	35.1	105	50
30	34.3	49	35.0	102	49	35.4	103	50
35	35.0	49	36.3	104	49	36.6	105	50
39	36.8	49	37.0	101	49	37.9	103	49
45	36.9	49	40.3	109	49	39.3	107	49
49	37.4	49	39.9	107	49	39.1	105	49
53	38.7	49	39.8	103	49	39.6	102	49
58	39.0	48	40.6	104	48	41.0	105	49
63	40.2	46	42.8	106	47	42.1	105	47
67	41.8	46	41.8	100	47	41.7	100	45
72	40.1	45	41.2	103	47	42.5	106	45
76	39.9	42	39.0	98	45	42.3	106	43
81	40.3	42	41.0	102	42	40.8	101	43
86	40.4	41	40.0	99	41	40.9	101	41
90	40.3	37	38.9	97	39	38.2	95	39
94	39.4	34	38.9	99	35	39.5	100	39
99	38.0	30	38.8	102	33	37.8	99	38
103	37.4	29	36.2	97	31	38.3	102	34
FEMALE								
0	19.7	50	19.6	99	50	20.2	103	50
1	21.4	50	20.6	96	50	20.5	96	50
2	22.4	48	22.3	100	49	21.6	96	50
3	22.6	48	23.4	104	48	22.3	99	50
4	22.5	47	24.4	108	48	22.9	102	50
5	23.7	46	24.3	103	48	23.2	98	50
6	24.6	46	24.6	100	48	24.8	101	50
7	24.9	46	24.9	100	48	24.3	98	50
8	24.4	46	24.4	100	48	25.1	103	50
9	25.0	46	26.2	105	48	25.8	103	50
10	25.9	46	25.7	99	47	25.5	98	50
11	26.4	46	26.4	100	47	26.9	102	50
12	27.4	46	27.1	99	47	26.0	95	50
13	27.1	46	27.2	100	46	25.7	95	50
18	27.2	46	26.4	97	45	26.9	99	50
22	27.5	45	27.2	99	45	27.4	100	50
26	29.0	45	29.0	100	45	28.5	98	50
30	29.7	45	28.2	95	45	28.2	95	50
35	30.1	45	29.4	98	45	28.2	94	50
39	31.3	45	30.2	96	45	30.7	98	50
45	32.5	45	31.9	98	45	30.8	95	50
49	31.9	45	32.3	101	44	33.3	104	50
53	33.2	45	32.6	98	44	31.7	95	50
58	34.2	44	33.4	98	43	33.3	97	50
63	35.2	44	33.9	96	43	32.9	93	50
67	36.0	44	33.9	94	43	34.3	95	48
72	35.3	43	34.9	99	42	34.7	98	48
76	35.2	41	34.1	97	42	36.1	103	48
81	34.9	41	33.6	96	36	32.9	94	48
86	35.7	37	32.9	92	32	34.3	96	47
90	35.5	36	31.8	90	30	34.0	96	44
94	34.7	35	31.8	92	29	33.0	95	41
99	33.1	28	31.9	96	25	33.8	102	37
103	33.7	27	32.1	95	24	33.3	99	32

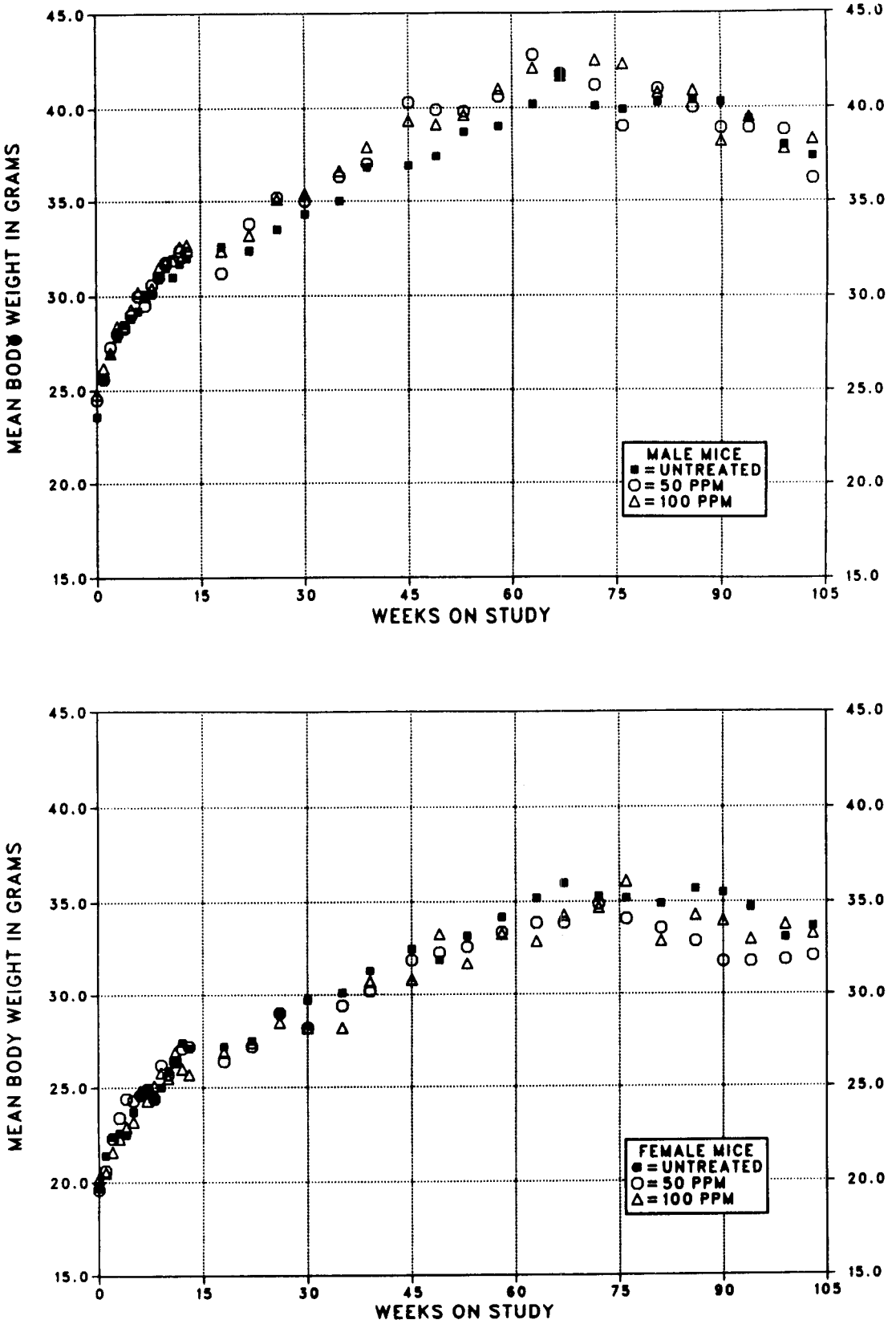


FIGURE 6. GROWTH CURVES FOR MICE EXPOSED TO ETHYLENE OXIDE BY INHALATION FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice exposed to ethylene oxide at the concentrations used in these studies and for controls are shown in Table 11 and in the Kaplan and Meier curves in Figure 7. No significant differences in survival were observed between any groups of either sex.

TABLE 11. SURVIVAL OF MICE IN THE TWO-YEAR INHALATION STUDIES OF ETHYLENE OXIDE

	Chamber Control	50 ppm	100 ppm
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	22	18	16
Accidentally killed	0	1	0
Killed at termination	27	31	34
Died during termination period	1	0	0
Survival P values (c)	0.264	0.562	0.308
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	23	22	18
Accidentally killed	1	3	0
Animals missing	0	1	0
Animals missexed	1	0	1
Killed at termination	25	24	30
Died during termination period	0	0	1
Survival P values (c)	0.197	0.985	0.232

(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 chamber control column, and the results of the life table pairwise comparisons with the chamber controls are in the dosed columns.

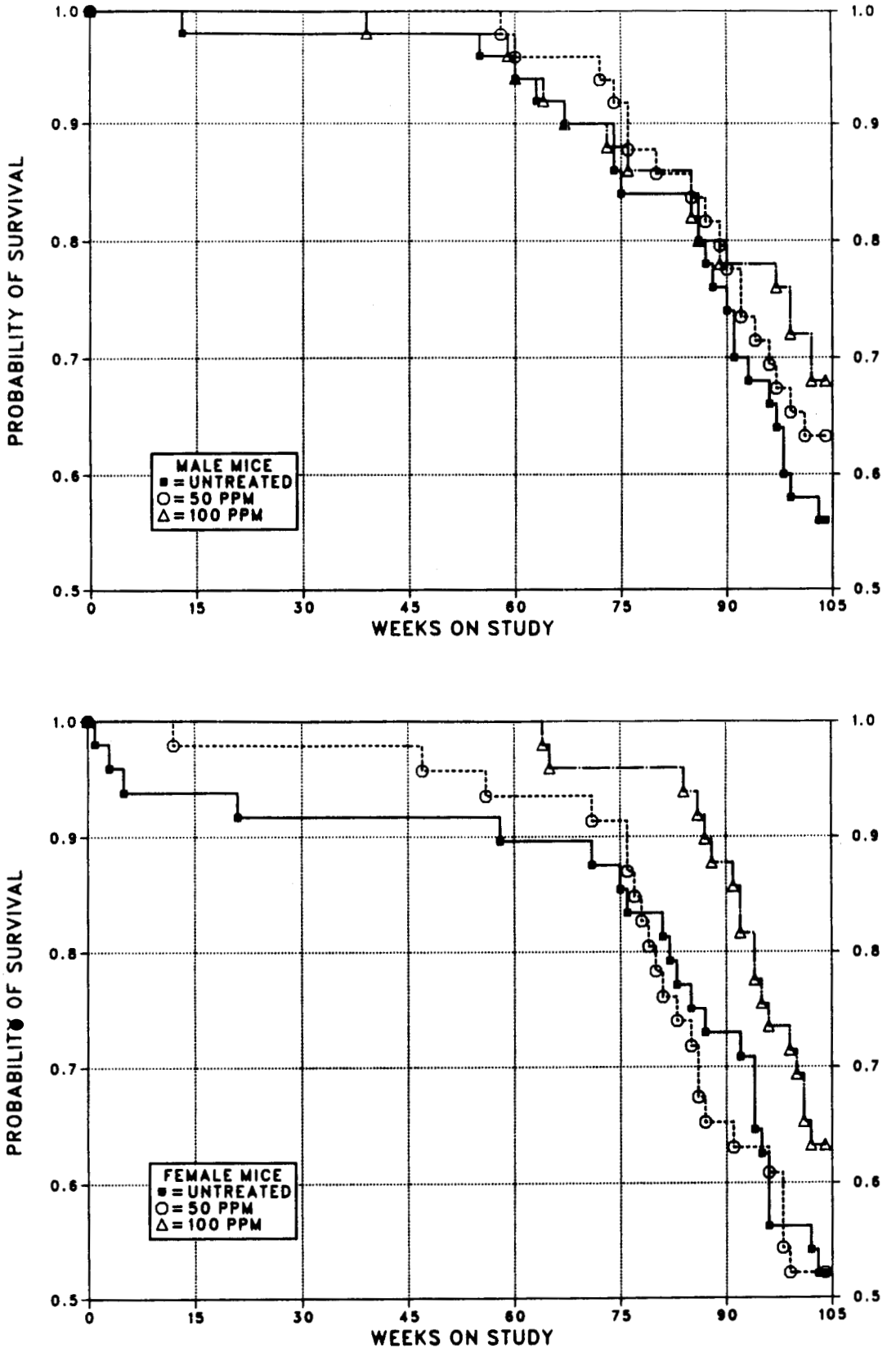


FIGURE 7. KAPLAN-MEIER SURVIVAL CURVES FOR MICE EXPOSED TO ETHYLENE OXIDE BY INHALATION FOR TWO YEARS

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 lung, harderian gland, hematopoietic system, uterus, mammary gland, and liver.

Lesions in male mice 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 mice. 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 mice are listed in Table A4. Findings on nonneoplastic lesions are summarized in Table A5.

Lesions in female mice 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 mice. 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 mice are listed in Table B4. Findings on nonneoplastic lesions are summarized in Table B5.

Lung: Alveolar/bronchiolar carcinomas in male and female mice and alveolar/bronchiolar adenomas in female mice occurred with significant positive trends (Table 12). The combined incidences of the benign and malignant lung tumors occurred with positive trends in both male and female mice (male: control, 11/50; low dose, 19/50; high dose, 26/50; female: 2/49; 5/48; 22/49). The combined incidences in the 100-ppm exposure groups were significantly greater than those in the controls. The incidences of adenomas and carcinomas in the high dose groups, except for adenomas in male mice, were significantly greater than those in the controls.

Harderian Gland: Papillary cystadenomas in dosed male and female mice occurred with significant positive trends, and the incidences in dosed males and dosed females were significantly greater than those in the controls (Table 13). In addition, one papillary cystadenocarcinoma was observed in a high dose male mouse and one in a low dose female mouse.

Hematopoietic System: Malignant lymphomas occurred with a positive trend in female mice, and the incidence in the high dose group was greater than that in the controls (Table 14). The incidence in the low dose group was slightly lower than that in the controls.

TABLE 12. ANALYSIS OF LUNG LESIONS IN MICE IN THE TWO-YEAR INHALATION STUDIES OF ETHYLENE OXIDE (a)

	Chamber Control	50 ppm	100 ppm
MALE			
Alveolar Epithelial Hyperplasia			
Overall Rates	3/50 (6%)	6/50 (12%)	8/50 (16%)
Alveolar/Bronchiolar Adenoma			
Overall Rates	5/50 (10%)	11/50 (22%)	11/50 (22%)
Adjusted Rates	16.5%	31.6%	31.3%
Terminal Rates	4/28 (14%)	8/31 (26%)	10/34 (29%)
Week of First Observation	88	60	99
Life Table Tests	P=0.155	P=0.122	P=0.164
Incidental Tumor Tests	P=0.110	P=0.095	P=0.127
Alveolar/Bronchiolar Carcinoma			
Overall Rates	6/50 (12%)	10/50 (20%)	16/50 (32%)
Adjusted Rates	18.3%	32.3%	43.0%
Terminal Rates	3/28 (11%)	10/31 (32%)	13/34 (38%)
Week of First Observation	87	104	76
Life Table Tests	P=0.032	P=0.267	P=0.048
Incidental Tumor Tests	P=0.017	P=0.230	P=0.019
Alveolar/Bronchiolar Adenoma or Carcinoma (b)			
Overall Rates	11/50 (22%)	19/50 (38%)	26/50 (52%)
Adjusted Rates	33.2%	55.4%	68.3%
Terminal Rates	7/28 (25%)	16/31 (52%)	22/34 (65%)
Week of First Observation	87	60	76
Life Table Tests	P=0.010	P=0.109	P=0.014
Incidental Tumor Tests	P=0.002	P=0.070	P=0.003
FEMALE			
Alveolar Epithelial Hyperplasia			
Overall Rates	2/49 (4%)	0/48 (0%)	3/49 (6%)
Alveolar/Bronchiolar Adenoma			
Overall Rates	2/49 (4%)	4/48 (8%)	17/49 (35%)
Adjusted Rates	7.7%	16.7%	46.2%
Terminal Rates	1/25 (4%)	4/24 (17%)	12/31 (39%)
Week of First Observation	103	104	87
Life Table Tests	P<0.001	P=0.314	P=0.001
Incidental Tumor Tests	P<0.001	P=0.277	P<0.001
Alveolar/Bronchiolar Carcinoma			
Overall Rates	0/49 (0%)	1/48 (2%)	7/49 (14%)
Adjusted Rates	0.0%	4.2%	21.5%
Terminal Rates	0/25 (0%)	1/24 (4%)	6/31 (19%)
Week of First Observation		104	95
Life Table Tests	P=0.005	P=0.492	P=0.019
Incidental Tumor Tests	P=0.005	P=0.492	P=0.017
Alveolar/Bronchiolar Adenoma or Carcinoma (c)			
Overall Rates	2/49 (4%)	5/48 (10%)	22/49 (45%)
Adjusted Rates	7.7%	20.8%	58.6%
Terminal Rates	1/25 (4%)	5/24 (21%)	16/31 (52%)
Week of First Observation	103	104	87
Life Table Tests	P<0.001	P=0.196	P<0.001
Incidental Tumor Tests	P<0.001	P=0.168	P<0.001

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix A, Table A3 (footnotes).
(b) Historical incidence in chamber controls at study laboratory (mean ± SD): 53/249 (21% ± 10%); historical incidence in untreated controls in NTP studies: 351/2,080 (17% ± 8%)
(c) Historical incidence in chamber controls at study laboratory (mean ± SD): 21/247 (9% ± 4%); historical incidence in untreated controls in NTP studies: 135/2,076 (7% ± 4%)

TABLE 13. ANALYSIS OF HARDERIAN GLAND LESIONS IN MICE IN THE TWO-YEAR INHALATION STUDIES OF ETHYLENE OXIDE

	Chamber Control	50 ppm	100 ppm
MALE			
Focal Hyperplasia			
Overall Rates	2/43 (5%)	3/44 (7%)	0/42 (0%)
Papillary Cystadenoma (a)			
Overall Rates	1/43 (2%)	9/44 (20%)	(b) 8/42 (19%)
Adjusted Rates	4.0%	30.7%	27.6%
Terminal Rates	1/25 (4%)	8/28 (29%)	7/27(26%)
Week of First Observation	104	97	73
Life Table Tests	P=0.026	P=0.014	P=0.021
Incidental Tumor Tests	P=0.024	P=0.012	P=0.021
FEMALE			
Focal Hyperplasia			
Overall Rates	3/46 (7%)	3/46 (7%)	4/47 (9%)
Papillary Cystadenoma (c)			
Overall Rates	1/46 (2%)	(b) 6/46 (13%)	8/47 (17%)
Adjusted Rates	4.3%	26.1%	24.8%
Terminal Rates	1/23 (4%)	6/23 (26%)	6/29 (21%)
Week of First Observation	104	104	94
Life Table Tests	P=0.037	P=0.052	P=0.039
Incidental Tumor Tests	P=0.034	P=0.052	P=0.033

(a) Historical incidence in chamber controls of adenomas at study laboratory (mean ± SD): 7/249 (3% ± 4%); historical incidence in untreated controls in NTP studies: 63/2,091 (3% ± 3%)
(b) A papillary cystadenocarcinoma was also present in an animal with a papillary cystadenoma.
(c) Historical incidence in chamber controls of adenomas at study laboratory (mean ± SD): 1/249 (0.4% ± 1%); historical incidence in untreated controls in NTP studies: 35/2,090 (2% ± 2%)

TABLE 14. ANALYSIS OF MALIGNANT LYMPHOMAS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE (a)

	Chamber Control	50 ppm	100 ppm
Overall Rates	9/49 (18%)	6/48 (13%)	22/49 (45%)
Adjusted Rates	26.4%	19.0%	48.3%
Terminal Rates	3/25 (12%)	2/24 (8%)	8/31 (26%)
Week of First Observation	82	56	64
Life Table Tests	P=0.023	P=0.343N	P=0.049
Incidental Tumor Tests	P=0.002	P=0.334N	P=0.005

(a) Historical incidence in chamber controls at study laboratory (mean ± SD): 51/249 (20% ± 7%); historical incidence in untreated controls in NTP studies: 595/2,090 (28% ± 12%)

Uterus: Adenocarcinomas occurred in female mice with a positive trend, and the incidence in high dose female mice was marginally increased compared with that in the controls (Table 15).

Mammary Gland: The incidences of adenocarcinomas and adenocarcinomas or adenosquamous carcinomas (combined) in low dose female mice were greater than those in the controls (Table 16).

Liver: The incidence of hepatocellular adenomas in low dose female mice was greater than that in the controls (control, 1/49; low dose, 8/48; high dose, 3/49; P=0.021). Hepatocellular carcinomas occurred with a negative trend (5/49; 1/48; 0/49; P<0.01). The incidence of adenomas or carcinomas (combined) in dosed female mice was not significantly different from that in the controls (6/49; 9/48; 3/49).

TABLE 15. ANALYSIS OF UTERINE TUMORS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE

	Chamber Control	50 ppm	100 ppm
Adenocarcinoma			
Overall Rates	0/49 (0%)	1/47 (2%)	5/49 (10%)
Adjusted Rates	0.0%	3.6%	14.3%
Terminal Rates	0/25 (0%)	0/24 (0%)	3/31 (10%)
Week of First Observation		98	91
Life Table Tests	P=0.024	P=0.507	P=0.058
Incidental Tumor Tests	P=0.019	P=0.383	P=0.051
Adenoma			
Overall Rates	0/49 (0%)	1/47 (2%)	0/49 (0%)
Adenoma or Adenocarcinoma (a)			
Overall Rates	0/49 (0%)	2/47 (4%)	5/49 (10%)
Adjusted Rates	0.0%	7.6%	14.3%
Terminal Rates	0/25 (0%)	1/24 (4%)	3/31 (10%)
Week of First Observation		98	91
Life Table Tests	P=0.036	P=0.239	P=0.058
Incidental Tumor Tests	P=0.028	P=0.173	P=0.051

(a) Historical incidence of uterine glandular tumors in chamber controls at study laboratory (mean): 4/236 (2%); historical incidence in untreated controls in NTP studies: 8/2,055 (0.4%)

TABLE 16. ANALYSIS OF MAMMARY GLAND TUMORS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE

	Chamber Control	50 ppm	100 ppm
Adenocarcinoma			
Overall Rates	1/49 (2%)	6/48 (13%)	4/49 (8%)
Adjusted Rates	2.9%	18.9%	11.8%
Terminal Rates	0/25 (0%)	2/24 (8%)	3/31 (10%)
Week of First Observation	94	76	92
Life Table Tests	P=0.265	P=0.061	P=0.247
Incidental Tumor Tests	P=0.179	P=0.033	P=0.234
Adenosquamous Carcinoma			
Overall Rates	0/49 (0%)	2/48 (4%)	2/49 (4%)
Adenocarcinoma or Adenosquamous Carcinoma (a)			
Overall Rates	1/49 (2%)	8/48 (17%)	6/49 (12%)
Adjusted Rates	2.9%	24.8%	17.1%
Terminal Rates	0/25 (0%)	3/24 (13%)	4/31 (13%)
Week of First Observation	94	76	92
Life Table Tests	P=0.139	P=0.020	P=0.100
Incidental Tumor Tests	P=0.082	P=0.012	P=0.087

(a) Historical incidence in chamber controls at study laboratory (mean): 6/249 (2%); historical incidence in untreated controls in NTP studies: 51/2,090 (2%)

IV. DISCUSSION AND CONCLUSIONS

Short-Term Studies
Survival and Body Weight in the Two-Year Studies
Pathologic Findings in the Two-Year Studies
Mutagenicity
Carcinogenicity
Data Audit
Conclusions

IV. DISCUSSION AND CONCLUSIONS

Short-Term Studies

A series of short-term inhalation toxicity studies (4-hour, 14-day, and 14-week) were conducted to assess the toxicity of ethylene oxide in B6C3F$_1$ mice. Histopathologic examinations in the 14-week studies revealed dose-related increases in incidence and severity of nasal, thymic, and renal lesions in the exposed mice. One hundred-percent mortality and severe clinical signs occurred in mice of each sex exposed at 400 or 600 ppm. Final mean body weights of 50-, 100-, and 200-ppm and control groups were comparable. Based on the deaths and lesions observed in the 14-week studies, the concentrations of ethylene oxide selected for the 2-year studies were 0, 50, and 100 ppm.

Survival and Body Weight in the Two-Year Studies

Survival rates of exposed and control male and female mice were comparable (see Table 11). Mean body weights were not adversely affected by exposure to ethylene oxide (see Table 10 and Figure 6). Haseman et al. (1985) reported that in recent 2-year NTP carcinogenesis studies, the overall survival rates were 74% and 73%, respectively, for untreated male and female B6C3F$_1$ mice and 67% and 61% for corn oil gavage control male and female B6C3F$_1$ mice. Historical survival rates of control B6C3F$_1$ mice based on five previously completed NTP inhalation studies were 86% (215/250) and 64% (159/250), respectively, for chamber-housed untreated male and female mice. In the present studies, the survival rates of chamber control male and female mice were 56% and 50%, respectively. Since the occurrence of nonaccidental deaths before termination of the studies was greatest in both male and female control mice, the slightly lower survival among all groups in the present studies may be attributed to the general health status of the mice. One health problem was the presence of infections of the urogenital tract. Klebsiella was cultured from ovarian abscesses at week 93; in males, ulcerative skin lesions on and around the prepuce were observed and attributed to a variety of bacterial strains. Serologic analyses for murine viruses and *Mycoplasma pulmonis* showed no positive titers in the serum of mice collected before the start of the studies, after 17-19 months, or after 24 months (Appendix C). Most of the deaths occurred during the last 30 weeks of the studies (see Table 10 and Figure 7). Survival of both sexes of mice in all dose groups was adequate and did not affect the sensitivity of the study to determine the carcinogenic potential of ethylene oxide.

On three occasions, high dose mice were exposed to ethylene oxide at concentrations of 200, 245, and 289 ppm for less than 1 hour; low dose mice were exposed at concentrations of 81, 82, and 100 ppm for less than 1 hour. These deviations occurred early in the exposure phase (five of the six in the first 5 months of the studies); survival was 90%-100% at this time and was similar in the exposed and control mice. Thus, these deviations did not increase mortality or influence the findings in these studies.

Pathologic Findings in the Two-Year Studies

In the 2-year studies, only 1/50 male B6C3F$_1$ mice exposed at 100 ppm exhibited renal tubular degeneration; no other males or females were diagnosed as having this lesion. In contrast, renal tubular degeneration was observed in 5/10 males exposed at 100 ppm for 14 weeks. The disparity between the incidences of this lesion in male mice in the 14-week and 2-year studies may lie with the confounding influence of subtle lesions detected in the presence of age-related changes in B6C3F$_1$ mice. Thymic, splenic, and nasal lesions observed in the 14-week studies were not seen in the 2-year studies. These lesions were observed in the 14-week studies at higher exposure concentrations of ethylene oxide than were employed in the 2-year studies and therefore are attributed to the difference in exposure levels.

Inhalation of ethylene oxide produced increased incidences of alveolar/bronchiolar adenomas and alveolar/bronchiolar carcinomas in both male and female B6C3F$_1$ mice (see Table 12). Alveolar/bronchiolar adenomas and carcinomas develop spontaneously in male and female B6C3F$_1$ mice (Ward et al., 1979); however, the incidences of the combined lung tumors in males at both exposure concentrations and in females at 100 ppm exceed the upper ranges for historical controls

(Appendix A, Table A4a; Appendix B, Table B4a). No other studies of ethylene oxide either in other species or by other routes of exposure have reported an increased incidence of lung tumors. Incidences of alveolar/bronchiolar adenomas and carcinomas in the two rat inhalation studies (Snellings et al., 1984; Lynch et al., 1984b) were 2% or lower and did not differ between control and exposed F344 rats.

Positive trends in the incidences of papillary cystadenomas of the harderian gland were also observed in male and female mice (see Table 13); the incidences in exposed males and females were significantly greater than those in the controls. The incidence of this tumor in the present studies was 2% in both the male and female chamber controls, similar to the historical incidences at the study laboratory and in untreated controls in NTP studies overall (Tables A4b and B4c). The incidences in the four exposed groups ranged from 13% to 20%, each being slightly greater than the reported historical upper range. This increase in papillary cystadenomas in both sexes at both exposure concentrations is considered biologically significant, since the results of the trend tests were significant and the incidences in dosed males and females were greater than those in the controls. There was no evidence of an increased incidence of tumors of the harderian gland in F344 rats exposed by inhalation to ethylene oxide.

Malignant lymphomas occurred at an increased incidence in the high dose female group (control, 9/49; low dose, 6/48; high dose, 22/49; $P<0.05$). The incidences of malignant lymphomas in male mice were dose related but not significantly increased. Increased incidences of lymphomas were not observed in the rat inhalation studies (Snellings et al., 1984; Lynch et al., 1984b).

Uterine glandular tumors were increased in the high dose females (see Table 15). The incidence of 5/49 (10%) exceeded the overall mean historical incidence in untreated control female $B6C3F_1$ mice (8/2,055; 0.4%) and the historical incidence at the study laboratory (4/236; 1.7%). Due to the low historical incidence of uterine glandular tumors and the absence of these tumors in the control group, the increased incidence in the 100-ppm group was considered to be due to exposure to ethylene oxide. No compound-related uterine glandular tumors have been observed in previous carcinogenesis studies of ethylene oxide.

The incidences of adenocarcinomas and adenocarcinomas or adenosquamous carcinomas (combined) of the mammary gland were increased in exposed females compared with those in controls (see Table 16). The combined incidences of 8/48 and 6/49 for the 50- and 100-ppm groups exceed the historical incidences of 2% for the NTP studies and those of the study laboratory (Table B4f). Statistical significance for differences in the incidences of mammary gland tumors was observed only between controls and the low dose group. The sixfold to eightfold increases in incidences of mammary gland tumors in exposed female $B6C3F_1$ mice were considered to be due to exposure to ethylene oxide.

One feature of inhalation exposure of animals to ethylene oxide is the absence of neoplasms of the nasal cavity. Although ethylene oxide is a potent direct-acting alkylating agent for DNA throughout the various body tissues of an organism (Ehrenberg et al., 1974; Segerback, 1983; Brookes and Lawley, 1961), the tissue that came into initial direct contact with the chemical did not exhibit an increase in neoplasms. In some cases, nasal tumors in animals and humans may be dependent on chronic irritation induced by the chemical as well as by the ability of the chemical to react with DNA. Suggestive evidence for this hypothesis are the nasal tumors in animals induced by formaldehyde (Swenberg et al., 1980) and the low incidence of nasal tumors induced in rats and mice exposed to propylene oxide at 300-400 ppm in air but not at lower concentrations (NTP, 1985a; Lynch et al., 1984b).

Mutagenicity

The available data demonstrate that ethylene oxide is a direct-acting mutagen and clastogen with activity noted both in vivo and in vitro in biologic systems varying from micro-organisms to higher plants and animals, including humans. Exposure of mice to ethylene oxide results in increased frequencies of inherited dominant visible mutations and gene mutations detected by changes in electrophoretic mobility of

proteins (Lewis et al., 1986) as well as inherited translocations and dominant lethality (Generoso et al., 1980, 1986). Although Russell et al. (1984) reported no increase in mutation rates at morphologic specific loci in male (101 × C3H)F_1 mice after total accumulated inhalation exposure to ethylene oxide of 101,000 or 150,000 ppm·hours over a 16-23 week period, positive results in dominant lethal and translocation tests indicate that exposure to ethylene oxide represents a potential reproductive hazard. Dose-rate studies have demonstrated that, although overall long-term cumulative exposure is an important parameter for risk assessment, exposure to short bursts of ethylene oxide at relatively high concentrations, such as occurs frequently in the workplace, may represent an even greater risk in terms of germ cell damage (Generoso et al., 1986).

Carcinogenicity

There was prior strong evidence that ethylene oxide is a carcinogen in animals and suggestive evidence in humans. Exposure to ethylene oxide produced peritoneal mesotheliomas in male F344 rats and mononuclear cell leukemia in female F344 rats after inhalation exposure at concentrations up to 100 ppm for 2 years (Snellings et al., 1984). Increased incidences of primary brain tumors in rats of each sex were also observed (Snellings et al., 1984; Garman et al., 1985). In a second inhalation study, male F344 rats exposed to ethylene oxide at concentrations up to 100 ppm developed mononuclear cell leukemia, peritoneal mesotheliomas, and mixed cell brain gliomas (Lynch et al., 1984b). Gavage administration of ethylene oxide to female Sprague Dawley rats produced squamous cell carcinomas of the forestomach (Dunkelberg, 1982). Sarcomas were produced in female NMRI mice that received subcutaneous injections of ethylene oxide once weekly for 90 weeks (Dunkelberg, 1981). Thus, ethylene oxide induces tumors both at the site of administration and distally.

The results of three epidemiologic studies in humans have suggested an association between exposure to ethylene oxide and a higher incidence of cancer. The incidences of leukemia and cancer of all sites and deaths attributed to leukemia were increased in workers exposed to ethylene oxide used as a sterilant (Hogstedt et al., 1979a, 1984). Increased mortality from stomach cancer and leukemia was reported by these same investigators in a cohort mortality study of ethylene oxide production workers (Hogstedt et al., 1979b, 1984). The U.S. Environmental Protection Agency reanalyzed data reported as negative by Morgan et al. (1981) and stated that there was increased mortality from pancreatic cancer and Hodgkin's disease (USEPA, 1985). In the three studies, the higher mortality rates and incidence of cancer were not limited to a particular type of malignancy, and the workers in the cohort study were exposed to other chemicals in addition to ethylene oxide.

Compounds structurally related to ethylene oxide have been tested for carcinogenicity, but results indicate a lower tumorigenic activity. Propylene oxide, a homolog of ethylene oxide, was studied by both Lynch et al. (1984b) and the NTP (1985a). In the former study, adenomas were detected in the nasal passages of 2/50 F344 male rats exposed at 300 ppm propylene oxide. Propylene oxide was found to produce papillary adenomas of the nasal turbinates in F344/N rats and hemangiomas or hemangiosarcomas (combined) of the same tissue site in mice exposed at 400 ppm in the NTP study. Thus, propylene oxide produces tumors in the nasal cavity, whereas ethylene oxide produces tumors at sites other than the nasal cavity. The role of differing air concentrations in tests for tumorigenic responses cannot be discounted.

Ethylene, which is reported to be metabolized to ethylene oxide (Segerback, 1983; Filser and Bolt, 1983), has also been tested for carcinogenicity. No carcinogenic responses were reported in male and female F344 rats exposed by inhalation to ethylene at concentrations up to 3,000 ppm for 24 months (Hamm et al., 1984). Similarly, no evidence of carcinogenicity was reported in F344/N rats or B6C3F_1 mice of either sex exposed to propylene at concentrations up to 10,000 ppm for 2 years (NTP, 1985b). Ethylene and propylene do not appear to pose the same degree of carcinogenic hazard to humans as do their respective monoepoxides.

Data Audit

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

Conclusions

Under the conditions of these 2-year inhalation studies, there was *clear evidence of carcinogenic activity** for B6C3F$_1$ mice as indicated by dose-related increased incidences of benign or malignant neoplasms of the lung and benign neoplasms of the harderian gland in both male and female B6C3F$_1$ mice following exposure to ethylene oxide vapors at 50 and 100 ppm. In female mice, ethylene oxide caused additional malignant neoplasms of the uterus, mammary gland, and hematopoietic system (lymphoma).

*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 page 9.

V. REFERENCES

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1. Abrahams, R. (1980) Recent studies with workers exposed to ethylene oxide. Jorkasky, J., Ed.: The Safe Use of Ethylene Oxide: Proceedings of the Educational Seminar. Washington, DC: Health Industry Manufacturers, pp. 27-38, 211-220.

2. American Conference of Governmental Industrial Hygienists (ACGIH) (1985-1986) Threshold Limit Values and Biological Exposure Indices for 1985-1986. Cincinnati: ACGIH, p. 19.

3. Appelgren, L.-E.; Eneroth, G.; Grant, C. (1977) Studies on ethylene oxide: Whole body autoradiography and dominant lethal test in mice. Proc. Eur. Soc. Toxicol. 18:315-317.

4. Appelgren, L.-E.; Eneroth, G.; Grant, C.; Landstrom, L.-E.; Tenghagen, K. (1978) Testing of ethylene oxide for mutagenicity using the micronucleus test in mice and rats. Acta Pharmacol. Toxicol. 43:69-71.

5. Armitage, P. (1971) Statistical Methods in Medical Research. New York: John Wiley & Sons Inc., pp. 362-365.

6. Berenblum, I., Ed. (1969) Carcinogenicity Testing: A Report of the Panel on Carcinogenicity of the Cancer Research Commission of UICC, Vol. 2. Geneva: International Union Against Cancer.

7. Bird, M. (1952) Chemical production of mutagens in *Drosophila*: Comparison of techniques. J. Genet. 50:480-485.

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

9. Brookes, P.; Lawley, P. (1961) The alkylation of guanosine and guanylic acid. J. Chem. Soc., pp. 3923-3928.

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

11. Dunkelberg, H. (1981) Carcinogenic activity of ethylene oxide and its reaction products 2-chloroethanol, 2-bromoethanol, ethylene glycol and diethylene glycol. I. Carcinogenicity of ethylene oxide in comparison with 1,2-propylene oxide after subcutaneous administration in mice. Zbl. Bakt. Hyg. I. Abt. Orig. B. 174:384-404.

12. Dunkelberg, H. (1982) Carcinogenicity of ethylene oxide and 1,2-propylene oxide upon intragastric administration to rats. Br. J. Cancer 46:924-933.

13. Dunnett, C. (1955) A multiple comparison procedure for comparing several treatments with a control. J. Am. Stat. Assoc. 50:1096-1122.

14. Ehrenberg, L.; Hallstrom, T. (1967) Haematologic Studies on Persons Occupationally Exposed to Ethylene Oxide. International Atomic Energy Report SM 92/96, pp. 327-334.

15. Ehrenberg, L.; Gustafsson, A.; Lundqvist, U. (1959) The mutagenic effects of ionizing radiation and reactive ethylene derivatives in barley. Hereditas 45:351-368.

16. Ehrenberg, L.; Hiesche, K.; Osterman-Golkar, S.; Wennberg, I. (1974) Evaluation of genetic risks of alkylating agents. Tissue doses in the mouse from air contaminated with ethylene oxide. Mutat. Res. 24:83-103.

17. Embree, J.; Hine, C. (1975) Mutagenicity of ethylene oxide. Toxicol. Appl. Pharmacol. 33:172-173.

18. Embree, J.; Lyon, J.; Hine, C. (1977) The mutagenic potential of ethylene oxide using the dominant-lethal assay in rats. Toxicol. Appl. Pharmacol. 40:261-267.

19. European Chemical Industry Ecology and Toxicology Centre (ECETOC) (1982) Technical Report No. 5: Toxicity of Ethylene Oxide and its Relevance to Man.

20. European Chemical Industry Ecology and Toxicology Centre (ECETOC) (1984) Technical Report No. 11: Ethylene Oxide Toxicology and its Relevance to Man: An Up-Dating of ECETOC Technical Report No. 5.

21. Fahmy, O.; Fahmy, M. (1956) Cytogenetic analysis of the action of carcinogens and tumor inhibitors in *Drosophila melanogaster*: V. Differential genetic response to the alkylating mutagens and x-radiation. J. Genet. 54:146-164.

22. Filser, J.; Bolt, H. (1983) Exhalation of ethylene oxide by rats on exposure to ethylene. Mutat. Res. 120:57-60.

23. Finelli, P.; Morgan, T.; Yaar, I.; Granger, C. (1983) Ethylene oxide-induced polyneuropathy: A clinical and electrophysiologic study. Arch. Neurol. 40:419-421.

24. Fomenko, V.; Strekalova, E. (1973) The mutagenic effects of some industrial toxins as a function of concentration and exposure time. Toksikol. Nov. Prom. Khim. Vesh. 7:51-57.

25. Garman, R.; Snellings, W.; Maronpot, R. (1985) Brain tumors in F344 rats associated with chronic inhalation exposure to ethylene oxide. Neurotoxicology 6:117-138.

26. Garry, V.; Hozier, J.; Jacobs, D.; Wade, R.; Gray, D. (1979) Ethylene oxide: Evidence of human chromosomal effects. Environ. Mutagen. 1:375-382.

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

28. Generoso, W.; Cain, K.; Krishna, M.; Sheu, C.; Gryder, R. (1980) Heritable translocation and dominant-lethal mutation induction with ethylene oxide in mice. Mutat. Res. 73:133-142.

29. Generoso, W.; Cumming, R.; Bandy, J.; Cain, K. (1983) Increased dominant-lethal effects due to prolonged exposure of mice to inhaled ethylene oxide. Mutat. Res. 119:377-379.

30. Generoso, W.; Cain, K.; Hughes, L.; Sega, G.; Braden, P.; Gosslee, D.; Shelby, M. (1986) Ethylene oxide dose and dose-rate effects in the mouse dominant-lethal test. Environ. Mutagen. 8:1-8.

31. Glaser, Z. (1979) Ethylene oxide: Toxicology review and field study results of hospital use. J. Environ. Pathol. Toxicol. 2:173-208.

32. Gross, J.; Haas, M.; Swift, T. (1979) Ethylene oxide neurotoxicity: Report of four cases and review of the literature. Neurology 29:978-983.

33. Hackett, P.; Brown, M.; Buschbom, R.; Clark, M.; Miller, R.; Music, R.; Rowe, S.; Schirmer, R.; Sikov, M. (1982) Teratogenic Study of Ethylene and Propylene Oxide and n-Butyl Acetate. NIOSH Contract No. 210-80-0013. Richland, WA: Battelle Pacific Northwest Laboratories.

34. Hamm, T., Jr.; Guest, D.; Dent, J. (1984) Chronic toxicity and oncogenicity bioassay of inhaled ethylene in Fischer-344 rats. Fundam. Appl. Toxicol. 4:473-478.

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

36. Haseman, J.; Huff, J.; Boorman, G. (1984) Use of historical control data in carcinogenicity studies in rodents. Toxicol. Pathol. 12:126-135.

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

38. Hemminki, K.; Mutanen, P.; Saloniemi, I.; Niemi, M.-L.; Vainio, H. (1982) Spontaneous abortions in hospital staff engaged in sterilising instruments with chemical agents. Br. Med. J. 285:1461-1463.

39. Hine, C.; Rowe, V. (1981) Epoxy compounds. Patty, F., Ed.: Industrial Hygiene and Toxicology, Vol. IIA, 3rd ed. New York/London: Interscience Publishers, p. 2141.

40. Hogstedt, C.; Malmqvist, N.; Wadman, B. (1979a) Leukemia in workers exposed to ethylene oxide. J. Am. Med. Assoc. 241:1132-1133.

41. Hogstedt, C.; Rohlen, O.; Berndtsson, B.; Axelson, O.; Ehrenberg, L. (1979b) A cohort study of mortality and cancer incidents in ethylene oxide production workers. Br. J. Ind. Med. 26:276-280.

V. REFERENCES

42. Hogstedt, B.; Gullberg, B.; Hedner, K.; Kolnig, A.-M.; Mitelman, F.; Skerfving, S.; Widegren, B. (1983) Chromosome aberrations and micronuclei in bone marrow cells and peripheral blood lymphocytes in humans exposed to ethylene oxide. Hereditas 98:105-113.

43. Hogstedt, C.; Aringer, L.; Gustavsson, A. (1984) Ethylene oxide and cancer: Review of the literature and follow-up of 2 studies. Arb. Halsa 49:1-32.

44. Hogstedt, C.; Aringer, L.; Gustavsson, A. (1986) Epidemiologic support for ethylene oxide as a cancer-causing agent. J. Am. Med. Assoc. 255:1575-1578.

45. Hollingsworth, R.; Rowe, V.; Oyen, F.; McCollister, D.; Spencer, H. (1956) Toxicity of ethylene oxide determined on experimental animals. Arch. Ind. Health 13:217-227.

46. International Agency for Research on Cancer (IARC) (1985) Ethylene oxide. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Allyl Compounds, Aldehydes, Epoxides and Peroxides, Vol. 36. Lyon, France: IARC, pp. 189-226.

47. Jacobson, K.; Hackley, E.; Feinsilver, L. (1956) The toxicity of inhaled ethylene oxide and propylene oxide vapors. Arch. Ind. Health 13:237-244.

48. Jana, M.; Roy, K. (1975) Effectiveness and efficiency of ethyl methanesulphonate and ethylene oxide in mice. Mutat. Res. 28:211-215.

49. Jones, A.; Wells, G. (1981) The comparative metabolism of 2-bromoethanol and ethylene oxide in the rat. Xenobiotica 11:763-770.

50. Jones-Price, C.; Kimmel, C.; Marks, T.; LeDoux, T.; Reel, J.; Fisher, P.; Langhoff-Paschke, L.; Marr, M. (1982) Final Report: Teratologic Evaluation of Ethylene Oxide in New Zealand White Rabbits. NIEHS Contract No. N01-ES-2127. Research Triangle Park, NC: Research Triangle Institute.

51. Kaplan, E.; Meier, P. (1958) Nonparametric estimation of incomplete observations. J. Am. Stat. Assoc. 53:457-481.

52. Kilbey, B.; Kolmark, H. (1968) A mutagenic after-effect associated with ethylene oxide in *Neurospora crassa*. Molec. Gen. Genet. 101:185-188.

53. Kligerman, A.; Erexson, G.; Phelps, M.; Wilmer, J. (1983) Sister-chromatid exchange induction in peripheral blood lymphocytes of rats exposed to ethylene oxide by inhalation. Mutat. Res. 120:37-44.

54. Kolman, A.; Naslund, M.; Calleman, C. (1986) Genotoxic effects of ethylene oxide and their relevance to human cancer. Carcinogenesis 7:1245-1250.

55. Kolmark, G.; Giles, N. (1955) Comparative studies of monoepoxides as inducers of reverse mutations in Neurospora. Genetics 40:890-902.

56. Kuzuhara, S.; Kanazawa, I.; Nakanishi, T.; Egashira, T. (1983) Ethylene oxide polyneuropathy. Neurology 33:377-380.

57. LaBorde, J.; Kimmel, C. (1980) The teratogenicity of ethylene oxide administered intravenously to mice. Toxicol. Appl. Pharmacol. 56:16-22.

58. Laurent, C.; Frederic, J.; Leonard, A. (1984) Sister chromatid exchange frequency in workers exposed to high levels of ethylene oxide, in a hospital sterilization service. Int. Arch. Occup. Environ. Health 54:33-43.

59. Lewis, S.; Barnett, L.; Felton, C.; Johnson, F.; Skow, L.; Cachiero, N.; Shelby, M. (1986) Dominant visible and electrophoretically expressed mutations induced in male mice exposed to ethylene oxide by inhalation. Environ. Mutagen. 8:867-872.

60. Linhart, M.; Cooper, J.; Martin, R.; Page, N.; Peters, J. (1974) Carcinogenesis Bioassay Data System. Comput. Biomed. Res. 7:230-248.

61. Lynch, D.; Lewis, T.; Moorman, W.; Sabharwal, P. (1983) Toxic and mutagenic effects of ethylene oxide and propylene oxide on spermatogenic functions in Cynomolgus monkeys. Toxicologist 3:60.

62. Lynch, D.; Lewis, T.; Moorman, W.; Burg, J.; Gulati, D.; Kaur, P.; Sabharwal, P. (1984a) Sister-chromatid exchanges and chromosome aberrations in lymphocytes from monkeys exposed to ethylene oxide and propylene oxide by inhalation. Toxicol. Appl. Pharmacol. 76:85-95.

63. Lynch, D.; Lewis, T.; Moorman, W.; Burg, J.; Groth, D.; Khan, A.; Ackerman, L.; Cockrell, B. (1984b) Carcinogenic and toxicologic effects of inhaled ethylene oxide and propylene oxide in F344 rats. Toxicol. Appl. Pharmacol. 76:69-84.

64. Mac Key, J. (1968) Mutagenesis in Volgare wheat. Hereditas 59:505-517.

65. Mantel, N.; Haenszel, W. (1959) Statistical aspects of the analysis of data from retrospective studies of disease. J. Natl. Cancer Inst. 22:719-748.

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

67. Martis, L.; Kroes, R.; Darby, T.; Woods, E. (1982) Disposition kinetics of ethylene oxide, ethylene glycol and 2-chlorethanol in the dog. J. Toxicol. Environ. Health 10:847-856.

68. McConnell, E.; Solleveld, H.; Swenberg, J.; Boorman, G. (1986) Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. J. Natl. Cancer Inst. 76:283-289.

69. McDonald, T.; Kasten, K.; Hervey, R.; Gregg, S.; Borgmann, A.; Murchison, T. (1973) Acute ocular toxicity of ethylene oxide, ethylene glycol, and ethylene chlorohydrin. Bull. Parenter. Drug Assoc. 27:153-164.

70. McLaughlin, R. (1946) Chemical burns of the human cornea. Am. J. Ophthalmol. 29:1355-1362.

71. Morgan, R.; Claxton, K.; Divine, B.; Kaplan, S.; Harris, V. (1981) Mortality among ethylene oxide workers. J. Occup. Med. 23:767-770.

72. National Cancer Institute (NCI) (1976) Guidelines for Carcinogen Bioassay in Small Rodents. NCI Technical Report No. 1. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health.

73. National Institute for Occupational Safety and Health (NIOSH) (1981) Current Intelligence Bulletin: Ethylene Oxide (EtO). Publication No. 81-130. Cincinnati: U.S. Department of Health and Human Services, NIOSH.

74. National Institutes of Health (NIH) (1978) NIH Specification, NIH-11-133f, November 1.

75. National Toxicology Program (NTP) (1985a) Toxicology and Carcinogenesis Studies of Propylene Oxide in F344/N Rats and B6C3F$_1$ Mice. NTP TR 267. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. 168 p.

76. National Toxicology Program (NTP) (1985b) Toxicology and Carcinogenesis Studies of Propylene in F344/N Rats and B6C3F$_1$ Mice. NTP TR 272. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. 146 p.

77. Ohnishi, A.; Inoue, N.; Yamamoto, T.; Murai, Y.; Hori, H.; Koga, M.; Tanaka, I.; Akiyama, T. (1985) Ethylene oxide induces central-peripheral distal axonal degeneration of the lumbar primary neurones in rats. Br. J. Ind. Med. 42:373-379.

78. Pfeiffer, E.; Dunkelberg, H. (1980) Mutagenicity of ethylene oxide and propylene oxide and of the glycols and halohydrins formed from them during the fumigation of foodstuffs. Food Cosmet. Toxicol. 18:115-118.

79. Russell, L.; Cumming, R.; Hunsicker, P. (1984) Specific-locus mutation rates in the mouse following inhalation of ethylene oxide, and application of the results to estimation of human genetic risk. Mutat. Res. 129:381-388.

V. REFERENCES

80. Sarto, F.; Cominato, I.; Pinton, A.; Brovedani, P.; Faccioli, C.; Bianchi, V.; Levis, A. (1984) Cytogenetic damage in workers exposed to ethylene oxide. Mutat. Res. 138:185-195.

81. Segerback, D. (1983) Alkylation of DNA and hemoglobin in the mouse following exposure to ethene and ethene oxide. Chem. Biol. Interact. 45:139-151.

82. Sexton, R.; Henson, E. (1950) Experimental ethylene oxide human skin injuries. AMA Arch. Ind. Hyg. Occup. Med. 2:549-564.

83. Smith, H.; Lotfy, T. (1954) Comparative effects of certain chemicals on Tradescantia chromosomes as observed at pollen tuber mitosis. Am. J. Bot. 41:589-593.

84. Smyth, H.; Seaton, J.; Fischer, L. (1941) Single dose toxicity of some glycols and their derivatives. J. Ind. Hyg. Toxicol. 23:259-268.

85. Snellings, W.; Maronpot, R.; Zelenak, J.; Laffoon, C. (1982a) Teratology study in Fischer 344 rats exposed to ethylene oxide by inhalation. Toxicol. Appl. Pharmacol. 64:476-481.

86. Snellings, W.; Zelenak, J.; Weil, C. (1982b) Effects on reproduction in Fischer 344 rats exposed to ethylene oxide by inhalation for one generation. Toxicol. Appl. Pharmacol. 63:382-388.

87. Snellings, W.; Weil, C.; Maronpot, R. (1984) A two-year inhalation study of the carcinogenic potential of ethylene oxide in Fischer 344 rats. Toxicol. Appl. Pharmacol. 75:105-117.

88. Sprinz, H.; Matzke, H.; Carter, J. (1982) Neuropathological Evaluation of Monkeys Exposed to Ethylene and Propylene Oxide. PB 83-134817. Kansas City, MO: Midwest Research Institute, prepared for NIOSH.

89. Stolley, P.; Soper, K.; Galloway, S.; Nichols, W.; Norman, S.; Wolman, S. (1984) Sister-chromatid exchanges in association with occupational exposure to ethylene oxide. Mutat. Res. 129:89-102.

90. Strekalova, E.; Chirkova, Y.; Golubovich, Y. (1975) The mutagenic effects of ethylene oxide on sex and somatic cells in male white rats. Toksikol. Nov. Prom. Khim. Veshchestr. 6:11-16.

91. Swenberg, J.; Kerns, W.; Mitchell, R.; Gralla, E.; Pakov, K. (1980) Induction of squamous cell carcinomas of the rat nasal cavity by inhalation exposure to formaldehyde vapor. Cancer Res. 40:3398-3402.

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

93. Thiess, A. (1963) Observations on the hazards of ethylene oxide. Arch. Toxikol. 20:127-140.

94. Tyler, T.; McKelvey, J. (1983) Dose Dependent Disposition of ^{14}C Labeled Ethylene Oxide in Rats. Intramural Report 45-190. Export, PA: Bushy Run Research Center. 18 p.

95. Ukita, T.; Okuyama, H.; Hayatsu, H. (1963) Modification of nucleosides and nucleotides: I. Reaction of ethylene oxide with uridine and uridylic acid. Chem. Pharm. Bull. 11:1399-1404.

96. U.S. Code of Federal Regulations (USCFR) (1984) 29 CFR 1910, Vol. 49, No. 122, June 22.

97. U.S. Environmental Protection Agency (USEPA) (1985) Health Assessment Document for Ethylene Oxide. Final Report. EPA-600/8-84/009F. Research Triangle Park, NC, pp. 9-128.

98. Van Duuren, B.; Orris, L.; Nelson, N. (1965) Carcinogenicity of epoxides, lactones, and peroxy compounds. Part II. J. Natl. Cancer Inst. 35:707-717.

99. Waite, C.; Patty, F.; Yant, W. (1930) Acute responses of guinea pigs to vapors of some new commercial organic compounds. IV. Ethylene oxide. Public Health Rep. 45:1832-1843.

100. Walpole, A. (1958) Carcinogenic action of alkylating agents. Ann. N.Y. Acad. Sci. 68:750-761.

101. Ward, J.; Goodman, D.; Squire, R.; Chu, K.; Linhart, M. (1979) Neoplastic and nonneoplastic lesions in aging (C57BL/6N × C3H/HeN)F_1 (B6C3F_1) mice. J. Natl. Cancer Inst. 63:849-854.

102. Windmueller, H.; Kaplan, N. (1962) The preparation and properties of *N*-hydroxyethyl derivatives of adenosine, adenosine triphosphate and nicotinamide dinucleotide. J. Biol. Chem. 236:2716-2726.

103. World Health Organization (WHO) (1985) Environmental Health Criteria. Ethylene Oxide. Geneva: World Health Organization. Vol. 55. 79 p.

104. Yager, J.; Benz, R. (1982) Sister chromatid exchanges induced in rabbit lymphocytes by ethylene oxide after inhalation exposure. Environ. Mutagen. 4:121-134.

APPENDIX A

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE

	CHAMBER CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
None			
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Squamous cell carcinoma, metastatic		1 (2%)	
Hepatocellular carcinoma, metastatic	4 (8%)	3 (6%)	4 (8%)
Alveolar/bronchiolar adenoma	5 (10%)	11 (22%)	11 (22%)
Alveolar/bronchiolar carcinoma	6 (12%)	10 (20%)	16 (32%)
Cortical carcinoma, metastatic		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS	1 (2%)	1 (2%)	1 (2%)
Malignant lymphoma, histiocytic type			1 (2%)
Malignant lymphoma, mixed type			1 (2%)
#Spleen	(49)	(48)	(48)
Malignant lymphoma, mixed type		1 (2%)	
#Mandibular lymph node	(13)	(21)	(12)
Squamous cell carcinoma, metastatic		1 (5%)	
#Bronchial lymph node	(13)	(21)	(12)
Squamous cell carcinoma, metastatic		1 (5%)	
#Ileum	(45)	(45)	(46)
Malignant lymphoma, NOS		1 (2%)	
CIRCULATORY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Hemangioma			1 (2%)
#Myocardium	(50)	(50)	(50)
Cortical carcinoma, metastatic		1 (2%)	
#Liver	(49)	(50)	(50)
Hemangiosarcoma	1 (2%)		1 (2%)
DIGESTIVE SYSTEM			
#Liver	(49)	(50)	(50)
Hepatocellular adenoma	6 (12%)	8 (16%)	11 (22%)
Hepatocellular carcinoma	9 (18%)	9 (18%)	11 (22%)
#Forestomach	(47)	(48)	(48)
Squamous cell papilloma	2 (4%)	2 (4%)	3 (6%)
Squamous cell carcinoma		1 (2%)	
#Duodenum	(45)	(45)	(46)
Carcinoma, NOS	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(49)	(50)
Tubular cell adenoma			1 (2%)
Cortical carcinoma, metastatic		1 (2%)	
ENDOCRINE SYSTEM			
#Pituitary	(44)	(43)	(48)
Carcinoma, NOS		1 (2%)	
#Adrenal	(49)	(50)	(48)
Cortical adenoma	1 (2%)		

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE (Continued)

	CHAMBER CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Adrenal (Continued)	(49)	(50)	(48)
Cortical carcinoma		1 (2%)	
#Adrenal/capsule	(49)	(50)	(48)
Adenoma, NOS	2 (4%)	1 (2%)	3 (6%)
#Adrenal medulla	(49)	(50)	(48)
Pheochromocytoma		1 (2%)	
#Thyroid	(47)	(47)	(49)
Follicular cell adenoma		2 (4%)	2 (4%)
REPRODUCTIVE SYSTEM			
#Testis	(50)	(50)	(50)
Interstitial cell tumor		1 (2%)	1 (2%)
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
#Harderian gland	(43)	(44)	(42)
Papillary cystadenoma, NOS	1 (2%)	9 (20%)	8 (19%)
Papillary cystadenocarcinoma NOS			1 (2%)
*Ear	(50)	(50)	(50)
Squamous cell carcinoma		1 (2%)	
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic			1 (2%)
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	12	8	10
Moribund sacrifice	11	10	6
Terminal sacrifice	27	31	34
Accidentally killed, nda		1	
TUMOR SUMMARY			
Total animals with primary tumors**	29	38	41
Total primary tumors	35	61	73
Total animals with benign tumors	15	26	27
Total benign tumors	17	35	41
Total animals with malignant tumors	18	22	26
Total malignant tumors	18	26	32
Total animals with secondary tumors##	4	5	5
Total secondary tumors	4	9	5

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

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE: CHAMBER CONTROL

ANIMAL NUMBER	00091	00211	00244	00466	00611	00717	00848	00747	00833	00836	00919	00840	00813	00925	00941	00963	00965	00970	00973	00985	00996	01015	01035	01044	01044
WEEKS ON STUDY	01353	05550	06600	06633	06767	07744	07744	07755	08866	08866	08877	08888	09090	09091	09191	09193	09396	09497	09698	09898	09999	10003	10004	10044	10044
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic			X					X	X								X								
Alveolar/bronchiolar adenoma												X												X	X
Alveolar/bronchiolar carcinoma											X					X				X					
Trachea	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	A	+	−	+	+	−	−	−	−	−	+	−	+	−	−	+	−	−	−	−	−	−	−	−
Thymus	−	A	−	+	−	−	−	−	+	−	+	+	+	+	+	+	−	+	−	−	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																			X						X
Hepatocellular carcinoma			X	X		X		X	X	X		X	X					X							
Hemangiosarcoma																									
Bile duct	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	N	N	N	N	N	N	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+
Pancreas	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
Stomach	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																					X				
Small intestine	+	A	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Carcinoma, NOS																									
Large intestine	−	A	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	A	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																	X								
Cortical adenoma																									
Thyroid	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	−	+	+	+	−	+	−	+	+	−	−	−	−	−	−	−	+	−	+	−	−	−	−	+	−
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	N	N	+	N	N	N	+	N	+	+	N	N	N	+	+	N	+	N	+	N	+	+	+
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	A	+	+	+	+	+	+	−	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	−	A	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−
Papillary cystadenoma, 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, NOS					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 A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: CHAMBER CONTROL (Continued)

ANIMAL NUMBER	00005	00007	00008	00010	00012	00014	00016	00018	00020	00022	00023	00027	00028	00029	00031	00032	00034	00037	00038	00039	00042	00043	00044	00049	00050	TOTAL:
WEEKS ON STUDY	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										4
Alveolar/bronchiolar adenoma												X											X			5
Alveolar/bronchiolar carcinoma										X	X													X		6
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	−	−	−	−	+	−	−	−	−	−	−	+	−	−	−	+	−	+	−	+	−	−	−	−	+	13
Thymus	−	−	+	+	+	+	+	+	−	−	+	−	+	−	+	−	−	+	−	+	+	+	+	−	+	29
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma	X					X		X														X				6
Hepatocellular carcinoma																										9
Hemangiosarcoma							X																			1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	N	+	+	+	N	+	+	+	+	N	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell papilloma							X																			2
Small intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Carcinoma, NOS									X																	1
Large intestine	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	44
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS															X											2
Cortical adenoma															X											1
Thyroid	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid	−	−	+	−	−	+	−	+	−	−	−	−	−	−	−	−	+	−	−	+	−	−	−	−	+	15
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	+	+	N	+	N	+	+	N	+	+	N	+	N	+	+	N	N	+	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	43
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Papillary cystadenoma, 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, NOS																										1

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE: LOW DOSE

ANIMAL NUMBER	021	008	005	036	027	007	031	037	032	018	038	046	010	044	035	006	014	002	013	001	003	004	009	011	012
WEEKS ON STUDY	009	058	060	072	074	076	076	080	085	087	089	090	092	092	094	096	097	099	101	104	104	104	104	104	104
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic																									
Hepatocellular carcinoma, metastatic					X					X							X								
Alveolar/bronchiolar adenoma			X													X			X			X		X	
Alveolar/bronchiolar carcinoma																					X				X
Cortical carcinoma, metastatic								X																	
Trachea	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																							X		
Lymph nodes	−	+	+	−	+	+	−	+	−	−	+	−	−	+	−	+	+	−	+	−	−	+	+	−	−
Squamous cell carcinoma, metastatic																									
Thymus	+	+	−	−	+	+	−	−	−	+	+	−	+	−	+	+	−	+	−	−	+	+	−	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical carcinoma, metastatic								X																	
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																X			X		X				X
Hepatocellular carcinoma			X		X	X		X	X	X	X			X			X								
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	N	N	N	+	+	+	+	+	N	+	+	+	+	+	+	+	N	N	+	+	+	+	+
Pancreas	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Stomach	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Squamous cell carcinoma																									
Small intestine	+	−	−	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Malignant lymphoma, NOS																									
Large intestine	+	+	−	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical carcinoma, metastatic								X																	
Urinary bladder	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	−	+	−	+	−	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Cortical carcinoma								X																	
Pheochromocytoma													X												
Thyroid	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Follicular cell adenoma															X										
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
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor																									
Prostate	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	−	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary cystadenoma, NOS																	X							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
Squamous cell carcinoma																									
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																									

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

ANIMAL NUMBER	0 1 5	0 1 6	0 1 7	0 1 9	0 2 0	0 2 2	0 2 3	0 2 4	0 2 5	0 2 6	0 2 8	0 2 9	0 3 0	0 3 3	0 3 4	0 3 9	0 4 0	0 4 1	0 4 2	0 4 3	0 4 5	0 4 7	0 4 8	0 4 9	0 5 0	TOTAL TISSUES TUMORS
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic				X																						1
Hepatocellular carcinoma, metastatic																										3
Alveolar/bronchiolar adenoma	X				X		X		X			X										X				11
Alveolar/bronchiolar carcinoma		X	X		X							X		X			X		X					X		10
Cortical carcinoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Malignant lymphoma, mixed type																										1
Lymph nodes	−	−	−	+	−	−	−	+	−	−	−	−	−	−	+	−	+	+	+	−	−	+	+	−	−	21
Squamous cell carcinoma, metastatic				X@																						1
Thymus	+	+	−	+	+	+	−	+	+	+	+	−	+	+	+	+	+	−	−	+	+	−	−	+	+	32
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical carcinoma, metastatic																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma								X	X					X				X								8
Hepatocellular carcinoma																										9
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	45
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell papilloma														X					X							2
Squamous cell carcinoma											X															1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Malignant lymphoma, NOS																			X							1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical carcinoma, metastatic																										1
Urinary bladder	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	43
Carcinoma, NOS												X														1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS														X												1
Cortical carcinoma																										1
Pheochromocytoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	47
Follicular cell adenoma												X														2
Parathyroid	−	+	+	+	+	−	+	−	+	−	−	+	−	+	+	−	−	−	−	−	−	+	+	−	−	20
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	+	N	+	+	N	N	N	N	N	N	N	N	+	N	+	N	+	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor			X																							1
Prostate	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	44
Papillary cystadenoma, NOS							X			X	X				X	X		X		X						9
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
Squamous cell carcinoma				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, NOS																								X		1

* Animals necropsied
@ Multiple occurrence of morphology

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE: HIGH DOSE

ANIMAL NUMBER	04 47	04 46	03 35	05 50	03 36	03 33	03 39	00 09	01 15	02 29	01 11	02 28	01 14	03 37	01 10	03 34	00 01	00 02	00 03	00 04	00 05	00 06	00 07	00 08	01 12
WEEKS ON STUDY	03 39	05 59	06 00	06 64	06 67	07 73	07 76	08 85	08 85	08 86	08 89	09 97	09 99	09 99	10 02	10 02	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic							X	X		X					X										
Alveolar/bronchiolar adenoma														X				X	X						
Alveolar/bronchiolar carcinoma							X								X	X	X	X					X	X	
Trachea	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	−	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	−	−	A	−	+	−	+	+	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	+
Thymus	+	−	+	−	−	+	+	−	+	+	−	+	−	−	+	+	−	+	+	−	−	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																X		X	X	X			X		
Hepatocellular carcinoma						X	X	X		X	X			X	X							X			
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	N	N	N	N	+	+	+	N	N	N	+	N	+	+	+	+	+	N	+	+	+	+	+
Pancreas	+	−	A	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Stomach	−	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	−	−	A	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	−	−	A	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									X
Urinary bladder	−	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	−	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																					X				
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Follicular cell adenoma																									
Parathyroid	−	−	+	+	+	−	+	−	+	−	−	−	−	−	−	−	−	−	−	+	−	−	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	+	N	N	N	N	+	N	+	N	+	+	+	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor																									
Prostate	−	+	A	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+
Papillary cystadenoma, NOS						X													X						
Papillary cystadenocarcinoma, NOS																									
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, metastatic																									
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, histiocytic type													X												
Malignant lymphoma, mixed type																									

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

ANIMAL NUMBER	013	016	017	018	019	020	021	022	023	024	025	026	027	030	031	032	038	040	041	042	043	044	045	048	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	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Hemangioma								X																		1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										4
Alveolar/bronchiolar adenoma	X			X		X	X					X			X	X								X		11
Alveolar/bronchiolar carcinoma					X			X	X	X			X				X	X		X					X	16
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph nodes	−	−	−	−	−	+	−	−	−	−	+	−	+	−	−	+	−	+	−	−	+	−	+	−	−	12
Thymus	+	+	−	+	−	+	−	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	−	+	+	34
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma					X		X		X							X					X				X	11
Hepatocellular carcinoma		X			X							X														11
Hemangiosarcoma										X																1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	N	N	+	N	N	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	46
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	45
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell papilloma						X												X					X			3
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS																X						X				3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma								X														X				2
Parathyroid	−	−	−	+	−	−	+	−	−	−	+	−	+	+	−	−	−	−	−	−	−	−	−	−	+	15
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	+	N	+	N	N	+	+	+	+	+	+	N	N	+	N	N	N	+	N	N	N	+	+	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor																							X			1
Prostate	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	+	+	+	+	+	−	+	+	−	+	+	+	−	+	+	+	−	+	+	+	+	−	+	+	+	42
Papillary cystadenoma, NOS	X	X		X											X	X			X							8
Papillary cystadenocarcinoma, NOS		X																								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, metast																	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, NOS																										1
Malignant lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type			X																							1

* Animals necropsied

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE

	Chamber Control	50 ppm	100 ppm
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	5/50 (10%)	11/50 (22%)	11/50 (22%)
Adjusted Rates (b)	16.5%	31.6%	31.3%
Terminal Rates (c)	4/28 (14%)	8/31 (26%)	10/34 (29%)
Week of First Observation	88	60	99
Life Table Tests (d)	P=0.155	P=0.122	P=0.164
Incidental Tumor Tests (d)	P=0.110	P=0.095	P=0.127
Cochran-Armitage Trend Test (d)	P=0.076		
Fisher Exact Test (d)		P=0.086	P=0.086
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	6/50 (12%)	10/50 (20%)	16/50 (32%)
Adjusted Rates (b)	18.3%	32.3%	43.0%
Terminal Rates (c)	3/28 (11%)	10/31 (32%)	13/34 (38%)
Week of First Observation	87	104	76
Life Table Tests (d)	P=0.032	P=0.267	P=0.048
Incidental Tumor Tests (d)	P=0.017	P=0.230	P=0.019
Cochran-Armitage Trend Test (d)	P=0.010		
Fisher Exact Test (d)		P=0.207	P=0.014
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	11/50 (22%)	19/50 (38%)	26/50 (52%)
Adjusted Rates (b)	33.2%	55.4%	68.3%
Terminal Rates (c)	7/28 (25%)	16/31 (52%)	22/34 (65%)
Week of First Observation	87	60	76
Life Table Tests (d)	P=0.010	P=0.109	P=0.014
Incidental Tumor Tests (d)	P=0.002	P=0.070	P=0.003
Cochran-Armitage Trend Test (d)	P=0.001		
Fisher Exact Test (d)		P=0.063	P=0.002
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	2.2%	9.7%	8.1%
Terminal Rates (c)	0/28 (0%)	3/31 (10%)	1/34 (3%)
Week of First Observation	67	104	99
Life Table Tests (d)	P=0.305	P=0.336	P=0.367
Incidental Tumor Tests (d)	P=0.236	P=0.320	P=0.249
Cochran-Armitage Trend Test (d)	P=0.238		
Fisher Exact Test (d)		P=0.309	P=0.309
Liver: Hepatocellular Adenoma			
Overall Rates (a)	6/49 (12%)	8/50 (16%)	11/50 (22%)
Adjusted Rates (b)	20.4%	24.1%	31.4%
Terminal Rates (c)	5/28 (18%)	6/31 (19%)	10/34 (29%)
Week of First Observation	98	96	102
Life Table Tests (d)	P=0.216	P=0.459	P=0.260
Incidental Tumor Tests (d)	P=0.159	P=0.391	P=0.214
Cochran-Armitage Trend Test (d)	P=0.122		
Fisher Exact Test (d)		P=0.403	P=0.154
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	9/49 (18%)	9/50 (18%)	11/50 (22%)
Adjusted Rates (b)	19.8%	19.7%	25.8%
Terminal Rates (c)	0/28 (0%)	0/31 (0%)	4/34 (12%)
Week of First Observation	60	60	73
Life Table Tests (d)	P=0.421	P=0.575N	P=0.477
Incidental Tumor Tests (d)	P=0.126	P=0.591	P=0.192
Cochran-Armitage Trend Test (d)	P=0.370		
Fisher Exact Test (d)		P=0.584N	P=0.421

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE (Continued)

	Chamber Control	50 ppm	100 ppm
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	15/49 (31%)	17/50 (34%)	21/50 (42%)
Adjusted Rates (b)	36.2%	39.1%	49.6%
Terminal Rates (c)	5/28 (18%)	6/31 (19%)	13/34 (38%)
Week of First Observation	60	60	73
Life Table Tests (d)	P=0.275	P=0.488	P=0.313
Incidental Tumor Tests (d)	P=0.065	P=0.384	P=0.099
Cochran-Armitage Trend Test (d)	P=0.140		
Fisher Exact Test (d)		P=0.442	P=0.166
Forestomach: Squamous Cell Papilloma			
Overall Rates (a)	2/47 (4%)	2/48 (4%)	3/48 (6%)
Adjusted Rates (b)	6.9%	6.5%	8.8%
Terminal Rates (c)	1/27 (4%)	2/31 (6%)	3/34 (9%)
Week of First Observation	99	104	104
Life Table Tests (d)	P=0.507	P=0.647N	P=0.604
Incidental Tumor Tests (d)	P=0.469	P=0.688N	P=0.554
Cochran-Armitage Trend Test (d)	P=0.415		
Fisher Exact Test (d)		P=0.684N	P=0.510
Forestomach: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	2/47 (4%)	3/48 (6%)	3/48 (6%)
Adjusted Rates (b)	6.9%	9.7%	8.8%
Terminal Rates (c)	1/27 (4%)	3/31 (10%)	3/34 (9%)
Week of First Observation	99	104	104
Life Table Tests (d)	P=0.520	P=0.559	P=0.604
Incidental Tumor Tests (d)	P=0.485	P=0.520	P=0.554
Cochran-Armitage Trend Test (d)	P=0.421		
Fisher Exact Test (d)		P=0.510	P=0.510
Adrenal Gland Capsule: Adenoma			
Overall Rates (a)	2/49 (4%)	1/50 (2%)	3/48 (6%)
Adjusted Rates (b)	6.4%	3.2%	8.8%
Terminal Rates (c)	1/28 (4%)	1/31 (3%)	3/34 (9%)
Week of First Observation	96	104	104
Life Table Tests (d)	P=0.473	P=0.473N	P=0.583
Incidental Tumor Tests (d)	P=0.440	P=0.515N	P=0.540
Cochran-Armitage Trend Test (d)	P=0.391		
Fisher Exact Test (d)		P=0.492N	P=0.490
Harderian Gland: Papillary Cystadenoma			
Overall Rates (a)	1/43 (2%)	9/44 (20%)	(e) 8/42 (19%)
Adjusted Rates (b)	4.0%	30.7%	27.6%
Terminal Rates (c)	1/25 (4%)	8/28 (29%)	7/27 (26%)
Week of First Observation	104	97	73
Life Table Tests (d)	P=0.026	P=0.014	P=0.021
Incidental Tumor Tests (d)	P=0.024	P=0.012	P=0.021
Cochran-Armitage Trend Test (d)	P=0.019		
Fisher Exact Test (d)		P=0.008	P=0.013

(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 cystadenocarcinoma was also present in an animal with a papillary cystadenoma.

TABLE A4a. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence for Chamber Controls at Battelle Pacific Northwest Laboratories			
Propylene oxide	14/50	2/50	15/50
Methyl methacrylate	10/50	3/50	11/50
Propylene	7/50	9/50	16/50
Dichloromethane	3/50	2/50	5/50
Tetrachloroethylene	3/49	4/49	6/49
TOTAL	37/249 (14.9%)	20/249 (8.0%)	53/249 (21.3%)
SD (b)	9.42%	5.83%	10.00%
Range (c)			
High	14/50	9/50	16/50
Low	3/50	2/50	5/50
Overall Historical Incidence for Untreated Controls in NTP Studies			
TOTAL	255/2,080 (12.3%)	105/2,080 (5.0%)	351/2,080 (16.9%)
SD (b)	6.74%	3.95%	8.07%
Range (c)			
High	14/50	8/48	17/50
Low	1/50	0/50	1/49

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

TABLE A4b. HISTORICAL INCIDENCE OF HARDERIAN GLAND TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Adenocarcinoma	Adenoma or Adenocarcinoma
Historical Incidence for Chamber Controls at Battelle Pacific Northwest Laboratories			
Propylene oxide	(b) 1/50	0/50	(b) 1/50
Methyl methacrylate	4/50	2/50	6/50
Propylene	(b) 2/50	0/50	(b) 2/50
Dichloromethane	0/50	0/50	0/50
Tetrachloroethylene	0/49	(c) 1/49	(c) 1/49
TOTAL	7/249 (2.8%)	3/249 (1.2%)	10/249 (4.0%)
SD (d)	3.55%	1.79%	4.69%
Range (e)			
High	4/50	2/50	6/50
Low	0/50	0/50	0/50
Overall Historical Incidence for Untreated Controls in NTP Studies			
TOTAL	(f) 63/2,091 (3.0%)	(g) 4/2,091 (0.2%)	67/2,091 (3.2%)
SD (d)	3.23%	0.59%	3.25%
Range (e)			
High	6/50	1/50	6/50
Low	0/50	0/50	0/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Papillary cystadenoma
(c) Papillary cystadenocarcinoma
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.
(f) Includes 50 adenomas, NOS; 5 papillary adenomas; 5 cystadenomas; and 3 papillary cystadenomas
(g) Includes one adenocarcinoma, NOS, and three carcinomas, NOS

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE

	CHAMBER CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Ulcer, NOS		1 (2%)	
Inflammation, chronic focal		1 (2%)	
Atrophy, NOS		1 (2%)	1 (2%)
Hyperkeratosis		1 (2%)	
Acanthosis		1 (2%)	1 (2%)
Parakeratosis		1 (2%)	
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Edema, NOS		1 (2%)	
Hemorrhage		1 (2%)	
Inflammation, suppurative	1 (2%)		1 (2%)
Hyperplasia, epithelial			1 (2%)
Metaplasia, squamous			1 (2%)
*Nasal gland	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
Hyperplasia, focal		1 (2%)	
*Laryngeal submucosa	(50)	(50)	(50)
Cyst, NOS	2 (4%)	7 (14%)	1 (2%)
#Trachea	(49)	(49)	(49)
Metaplasia, squamous			1 (2%)
#Tracheal submucosa	(49)	(49)	(49)
Cyst, NOS	39 (80%)	41 (84%)	26 (53%)
Inflammation, chronic diffuse		1 (2%)	
#Tracheal gland	(49)	(49)	(49)
Hyperplasia, NOS		4 (8%)	
#Lung/bronchus	(50)	(50)	(50)
Cytoplasmic aggregate, NOS		1 (2%)	1 (2%)
#Bronchial submucosa	(50)	(50)	(50)
Cyst, NOS	18 (36%)	21 (42%)	10 (20%)
#Lung	(50)	(50)	(50)
Congestion, acute passive	4 (8%)	1 (2%)	
Inflammation, chronic focal		1 (2%)	1 (2%)
Hyperplasia, alveolar epithelium	3 (6%)	6 (12%)	8 (16%)
#Lung/alveoli	(50)	(50)	(50)
Inflammation, acute diffuse		1 (2%)	
Histiocytosis	1 (2%)	2 (4%)	3 (6%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(49)	(50)	(50)
Hypoplasia, NOS			1 (2%)
#Spleen	(49)	(48)	(48)
Atrophy, NOS		1 (2%)	
Hyperplasia, lymphoid		1 (2%)	1 (2%)
Hematopoiesis	2 (4%)	2 (4%)	3 (6%)
#Bronchial lymph node	(13)	(21)	(12)
Edema, NOS		1 (5%)	
Hyperplasia, NOS		1 (5%)	

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE (Continued)

	CHAMBER CONTROL	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Mesenteric lymph node	(13)	(21)	(12)
Hyperplasia, NOS		1 (5%)	
Hematopoiesis		1 (5%)	
#Lung	(50)	(50)	(50)
Hyperplasia, lymphoid	**1 (2%)**	**3 (6%)**	
#Peyer's patch	(45)	(45)	(46)
Hyperplasia, lymphoid			**1 (2%)**
#Duodenum	(45)	(45)	(46)
Hyperplasia, lymphoid	1 (2%)		
#Thymus	(29)	(32)	(34)
Mineralization		1 (3%)	
Cyst, NOS	2 (7%)	3 (9%)	
Necrosis, diffuse		1 (3%)	
CIRCULATORY SYSTEM			
#Lung	(50)	(50)	(50)
Perivasculitis	1 (2%)		**1 (2%)**
#Myocardium	(50)	(50)	(50)
Mineralization		1 (2%)	
Inflammation, suppurative		1 (2%)	
Inflammation, chronic	1 (2%)	2 (4%)	
Degeneration, NOS	1 (2%)		
#Endocardium	(50)	(50)	(50)
Inflammation, NOS			**1 (2%)**
#Cardiac valve	(50)	(50)	(50)
Inflammation, acute suppurative		1 (2%)	
Infection, bacterial		1 (2%)	
Degeneration, mucoid	27 (54%)	9 (18%)	18 (36%)
Hemosiderosis	4 (8%)	2 (4%)	4 (8%)
*Sup. pancreaticoduodenal artery	(50)	(50)	(50)
Inflammation, chronic	**1 (2%)**		
#Thyroid	(47)	(47)	(49)
Perivasculitis	1 (2%)		
DIGESTIVE SYSTEM			
*Pulp of tooth	(50)	(50)	(50)
Abscess, NOS		2 (4%)	
Inflammation, chronic focal	1 (2%)	2 (4%)	
#Salivary gland	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)	3 (6%)	
#Liver	(49)	(50)	(50)
Torsion	2 (4%)	1 (2%)	
Necrosis, focal		2 (4%)	1 (2%)
Necrosis, diffuse	9 (18%)	3 (6%)	4 (8%)
Infarct, NOS	2 (4%)		
Focal cellular change	4 (8%)	3 (6%)	3 (6%)
#Liver/hepatocytes	(49)	(50)	(50)
Cytoplasmic vacuolization			1 (2%)
#Pancreas	(48)	(48)	(46)
Inflammation, chronic focal		1 (2%)	1 (2%)
Atrophy, NOS			1 (2%)
#Esophagus	(48)	(45)	(45)
Hyperplasia, epithelial			1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE (Continued)

	CHAMBER CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Gastric mucosa	(47)	(48)	(48)
Dilatation, NOS		2 (4%)	1 (2%)
Cyst, NOS			3 (6%)
Inflammation, suppurative			1 (2%)
Necrosis, NOS		1 (2%)	
Atrophy, NOS			2 (4%)
Hyperplasia, focal		4 (8%)	
Metaplasia, squamous	2 (4%)	2 (4%)	
#Gastric submucosa	(47)	(48)	(48)
Inflammation, chronic focal		2 (4%)	
#Forestomach	(47)	(48)	(48)
Atypia, NOS			1 (2%)
Hyperplasia, epithelial		2 (4%)	3 (6%)
Hyperkeratosis		3 (6%)	2 (4%)
#Intestinal villus	(45)	(45)	(46)
Atrophy, NOS		1 (2%)	1 (2%)
#Peyer's patch	(45)	(45)	(46)
Hyperplasia, NOS	1 (2%)		
#Colon	(45)	(47)	(46)
Parasitism			1 (2%)
#Colonic submucosa	(45)	(47)	(46)
Lymphocytic inflammatory infiltrate		1 (2%)	
*Perirectal tissue	(50)	(50)	(50)
Inflammation, necrotizing	1 (2%)		
*Anus	(50)	(50)	(50)
Inflammation, chronic focal		1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(49)	(50)
Mineralization	3 (6%)	4 (8%)	
Cyst, NOS	4 (8%)	7 (14%)	2 (4%)
Hemorrhage		5 (10%)	
Inflammation, suppurative	2 (4%)	7 (14%)	4 (8%)
Inflammation, chronic	3 (6%)	7 (14%)	3 (6%)
Glomerulosclerosis, NOS	1 (2%)	1 (2%)	1 (2%)
#Kidney/tubule	(50)	(49)	(50)
Dilatation, NOS	6 (12%)	3 (6%)	1 (2%)
Cast, NOS	1 (2%)	3 (6%)	1 (2%)
Degeneration, NOS		2 (4%)	
Necrosis, focal			1 (2%)
Nuclear enlargement		3 (6%)	3 (6%)
Cytoplasmic vacuolization	1 (2%)	1 (2%)	4 (8%)
Cytoplasmic aggregate, NOS			1 (2%)
#Kidney/pelvis	(50)	(49)	(50)
Hyperplasia, epithelial		1 (2%)	1 (2%)
#Urinary bladder	(46)	(47)	(48)
Calculus, unknown gross or micro	1 (2%)	1 (2%)	
Inflammation, suppurative	1 (2%)		1 (2%)
Inflammation, acute			1 (2%)
Inflammation, chronic	1 (2%)		2 (4%)
Hyperplasia, epithelial	1 (2%)	1 (2%)	1 (2%)
#Urinary bladder/mucosa	(46)	(47)	(48)
Hemorrhage			1 (2%)
Erosion			1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE (Continued)

	CHAMBER CONTROL	LOW DOSE	HIGH DOSE
URINARY SYSTEM (Continued)			
*Urethra	(50)	(50)	(50)
Calculus, unknown gross or micro	1 (2%)		
Ulcer, NOS			1 (2%)
Inflammation, suppurative			1 (2%)
Erosion	1 (2%)		
ENDOCRINE SYSTEM			
#Pituitary	(44)	(43)	(48)
Cyst, NOS		5 (12%)	
Inclusion, nuclear		1 (2%)	
Hyperplasia, focal			1 (2%)
#Adrenal	(49)	(50)	(48)
Accessory structure	1 (2%)		1 (2%)
#Adrenal/capsule	(49)	(50)	(48)
Hyperplasia, diffuse	32 (65%)	35 (70%)	28 (58%)
#Adrenal cortex	(49)	(50)	(48)
Cyst, NOS		2 (4%)	
Inflammation, acute suppurative		1 (2%)	
Infection, bacterial		1 (2%)	
Degeneration, lipoid	1 (2%)	2 (4%)	
Necrosis, focal		1 (2%)	
Hypertrophy, NOS	1 (2%)		1 (2%)
Hyperplasia, focal	3 (6%)	5 (10%)	3 (6%)
Hyperplasia, diffuse			1 (2%)
#Adrenal medulla	(49)	(50)	(48)
Cyst, NOS			1 (2%)
#Thyroid	(47)	(47)	(49)
Cystic follicles		1 (2%)	1 (2%)
Hyperplasia, follicular cell	2 (4%)		
#Thyroid colloid	(47)	(47)	(49)
Degeneration, NOS			1 (2%)
#Parathyroid	(15)	(20)	(15)
Cyst, NOS			1 (7%)
#Pancreatic islets	(48)	(48)	(46)
Hyperplasia, focal			1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Dilatation/ducts			1 (2%)
Hyperplasia, NOS	1 (2%)		1 (2%)
*Penis	(50)	(50)	(50)
Ulcer, NOS			1 (2%)
Inflammation, suppurative	1 (2%)		
Inflammation, chronic			1 (2%)
*Prepuce	(50)	(50)	(50)
Cyst, NOS			1 (2%)
Ulcer, NOS	3 (6%)	4 (8%)	6 (12%)
Inflammation, suppurative	1 (2%)	3 (6%)	1 (2%)
Inflammation, chronic focal	1 (2%)		
Inflammation, chronic diffuse		1 (2%)	2 (4%)
Acanthosis			1 (2%)
*Preputial gland	(50)	(50)	(50)
Cyst, NOS	11 (22%)	10 (20%)	12 (24%)
Inflammation, suppurative	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic	1 (2%)	3 (6%)	2 (4%)
Hyperplasia, NOS			2 (4%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE (Continued)

	CHAMBER CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)			
#Prostate	(43)	(47)	(46)
Inflammation, suppurative	6 (14%)	3 (6%)	5 (11%)
*Seminal vesicle	(50)	(50)	(50)
Dilatation, NOS	9 (18%)	2 (4%)	6 (12%)
Inflammation, suppurative	3 (6%)	2 (4%)	4 (8%)
Inflammation, chronic			1 (2%)
Hyperplasia, epithelial			1 (2%)
#Testis	(50)	(50)	(50)
Mineralization			1 (2%)
Atrophy, NOS	21 (42%)	21 (42%)	33 (66%)
*Epididymis	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	
NERVOUS SYSTEM			
#Brain/thalamus	(50)	(50)	(50)
Mineralization	12 (24%)	19 (38%)	18 (36%)
SPECIAL SENSE ORGANS			
*Eye/cornea	(50)	(50)	(50)
Pannus			1 (2%)
*Nasolacrimal duct	(50)	(50)	(50)
Inflammation, suppurative		3 (6%)	
#Harderian gland	(43)	(44)	(42)
Cyst, NOS	1 (2%)		1 (2%)
Hyperplasia, focal	2 (5%)	3 (7%)	
MUSCULOSKELETAL SYSTEM			
*Costochondral synchondrosis	(50)	(50)	(50)
Inflammation, NOS		1 (2%)	
Fibrous osteodystrophy		1 (2%)	
*Muscle of thorax	(50)	(50)	(50)
Degeneration, NOS	1 (2%)		
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Hemorrhage		1 (2%)	
Inflammation, chronic		2 (4%)	
*Abdominal cavity	(50)	(50)	(50)
Hemorrhage	1 (2%)		
ALL OTHER SYSTEMS			
Perineum			
Inflammation, suppurative		1	
SPECIAL MORPHOLOGY SUMMARY			
Auto/necropsy/histo perf	1		1

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

APPENDIX B

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE

	CHAMBER CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	49	48	49
ANIMALS EXAMINED HISTOLOGICALLY	49	48	49
INTEGUMENTARY SYSTEM			
*Skin	(49)	(48)	(49)
Sebaceous adenoma			1 (2%)
*Subcutaneous tissue	(49)	(48)	(49)
Sarcoma, NOS	1 (2%)	1 (2%)	3 (6%)
Myxosarcoma	1 (2%)		
Neurilemoma, malignant	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(49)	(48)	(49)
Adenocarcinoma, NOS, metastatic	1 (2%)		1 (2%)
Hepatocellular carcinoma, metastatic	1 (2%)		
Alveolar/bronchiolar adenoma	2 (4%)	4 (8%)	17 (35%)
Alveolar/bronchiolar carcinoma		1 (2%)	7 (14%)
Adenosquamous carcinoma, metastatic		1 (2%)	
Pheochromocytoma, metastatic		1 (2%)	
Osteosarcoma, metastatic	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(49)	(48)	(49)
Malignant lymphoma, NOS	7 (14%)	3 (6%)	19 (39%)
Malignant lymphoma, histiocytic type	1 (2%)		
*Mediastinum	(49)	(48)	(49)
Malignant lymphoma, NOS		1 (2%)	
#Spleen	(49)	(46)	(49)
Malignant lymphoma, NOS			1 (2%)
#Mesenteric lymph node	(23)	(26)	(35)
Malignant lymphoma, NOS			1 (3%)
#Renal lymph node	(23)	(26)	(35)
Adenocarcinoma, NOS, metastatic			1 (3%)
#Duodenum	(48)	(43)	(49)
Malignant lymphoma, NOS		1 (2%)	
#Kidney	(49)	(48)	(49)
Malignant lymphoma, NOS	1 (2%)	1 (2%)	
#Uterus	(49)	(47)	(49)
Malignant lymphoma, NOS			1 (2%)
CIRCULATORY SYSTEM			
*Skin	(49)	(48)	(49)
Hemangioma			1 (2%)
DIGESTIVE SYSTEM			
#Liver	(49)	(48)	(49)
Hepatocellular adenoma	1 (2%)	8 (17%)	3 (6%)
Hepatocellular carcinoma	5 (10%)	1 (2%)	
#Forestomach	(48)	(46)	(48)
Squamous cell papilloma	2 (4%)	5 (11%)	6 (13%)
#Duodenum	(48)	(43)	(49)
Adenomatous polyp, NOS		1 (2%)	
*Rectum	(49)	(48)	(49)
Endometrial stromal sarcoma, invasive			1 (2%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE (Continued)

	CHAMBER CONTROL	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Pituitary	(48)	(45)	(48)
Carcinoma, NOS	1 (2%)	3 (7%)	2 (4%)
Adenoma, NOS	4 (8%)	4 (9%)	4 (8%)
#Adrenal medulla	(48)	(47)	(49)
Pheochromocytoma	2 (4%)	1 (2%)	
Pheochromocytoma, malignant		1 (2%)	
#Thyroid	(45)	(46)	(47)
Follicular cell adenoma	2 (4%)	1 (2%)	
#Pancreatic islets	(49)	(46)	(48)
Islet cell adenoma		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(49)	(48)	(49)
Adenocarcinoma, NOS	1 (2%)	6 (13%)	4 (8%)
Adenosquamous carcinoma		2 (4%)	2 (4%)
#Uterus	(49)	(47)	(49)
Adenoma, NOS		1 (2%)	
Adenocarcinoma, NOS		1 (2%)	5 (10%)
Endometrial stromal polyp	1 (2%)	1 (2%)	1 (2%)
Endometrial stromal sarcoma			1 (2%)
#Ovary	(48)	(47)	(49)
Papillary cystadenoma, NOS			1 (2%)
Granulosa cell tumor	1 (2%)		
NERVOUS SYSTEM			
#Brain	(49)	(47)	(49)
Carcinoma, NOS, invasive			1 (2%)
SPECIAL SENSE ORGANS			
#Harderian gland	(46)	(46)	(47)
Papillary cystadenoma, NOS	1 (2%)	6 (13%)	8 (17%)
Papillary cystadenocarcinoma NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Skull	(49)	(48)	(49)
Osteoma			1 (2%)
Osteosarcoma	2 (4%)		
*Sternum	(49)	(48)	(49)
Osteosarcoma			1 (2%)
BODY CAVITIES			
*Pelvis	(49)	(48)	(49)
Adenocarcinoma, NOS, metastatic			1 (2%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE (Continued)

	CHAMBER CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*Multiple organs	(49)	(48)	(49)
Sarcoma, NOS	1 (2%)		
Lower leg			
Osteosarcoma	1		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	8	7	6
Moribund sacrifice	15	15	13
Terminal sacrifice	25	24	30
Accidentally killed, nda	1	3	
Animal missing		1	
Animal missexed	1		1
TUMOR SUMMARY			
Total animals with primary tumors**	30	33	46
Total primary tumors	39	56	90
Total animals with benign tumors	13	21	29
Total benign tumors	15	33	43
Total animals with malignant tumors	23	21	35
Total malignant tumors	23	23	47
Total animals with secondary tumors##	3	2	3
Total secondary tumors	3	2	5
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 B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE: CHAMBER CONTROL

ANIMAL NUMBER	01210	02101	00909	00505	03101	02707	03303	00006	01707	00404	00803	01505	04202	03808	03309	02303	02209	03306	01108	03300	03302	04401	04403	04505	00101
WEEKS ON STUDY	00101	00101	00303	00505	02101	05808	07101	07505	07606	08101	08802	08303	08505	08707	09002	09404	09404	09404	09505	09606	09606	09902	10102	10303	10404
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																X									
Myxosarcoma										X															
Neurilemoma, malignant									X																
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic																	X								
Hepatocellular carcinoma, metastatic																									
Alveolar/bronchiolar adenoma																								X	
Osteosarcoma, metastatic														X											
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	−	−	−	−	−	−	+	+	+	−	+	+	−	−	+	+	+	+	+	+	−	+	+	−	−
Thymus	+	+	+	−	+	+	+	−	+	+	+	+	−	−	+	−	+	+	+	+	−	+	+	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma																						X			
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	N	N	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																	X								
Small intestine	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS													X												
Urinary bladder	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS																		X							X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	−	−	−	−	+	+	−	−	−	+	+	−	−	−	+	−	−	−	−	+	−	+	−	−	−
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	N	N	N	N	N	+	+	N	N	+	+	N	+	+	+	+	+	N	N	+	+	+	+
Adenocarcinoma, NOS																	X								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Granulosa cell tumor																		X							
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary cystadenoma, NOS																									
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma														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
Sarcoma, NOS								X																	
Malignant lymphoma, NOS											X				X			X		X					
Malignant lymphoma, histiocytic type																			X						
Lower leg, NOS																									
Osteosarcoma																									

+: 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 MICE: CHAMBER CONTROL (Continued)

ANIMAL NUMBER	0002	0005	0007	0008	0011	0012	0013	0014	0016	0019	0020	0022	0024	0025	0026	0028	0034	0035	0037	0040	0044	0046	0047	0048	0049	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Sarcoma, NOS																										1
Myxosarcoma																										1
Neurilemoma, malignant																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS, metastatic																										1
Hepatocellular carcinoma, metastatic							X																			1
Alveolar/bronchiolar adenoma	X																									2
Osteosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	−	+	−	−	+	+	−	+	S	−	−	+	−	+	−	+	+	−	+	−	−	+	−	−	−	23
Thymus	+	+	+	−	+	+	+	+	S	+	+	+	−	+	−	+	+	+	+	+	+	−	+	+	+	38
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma												X														1
Hepatocellular carcinoma							X								X				X				X			5
Bile duct	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	*49
Pancreas	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	48
Stomach	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell papilloma	X																									2
Small intestine	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, NOS																										1
Urinary bladder	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS																		X								1
Adenoma, NOS				X															X							4
Adrenal	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	48
Pheochromocytoma																		X				X				2
Thyroid	+	+	−	+	+	+	−	−	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Follicular cell adenoma				X		X																				2
Parathyroid	−	−	−	−	+	−	−	−	S	−	+	+	+	+	+	−	+	−	+	−	−	−	+	−	−	16
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	+	+	+	+	+	S	N	+	+	+	+	+	+	+	+	+	N	+	+	N	N	N	*49
Adenocarcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endometrial stromal polyp			X																							1
Ovary	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Granulosa cell tumor																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	+	+	+	+	+	+	−	−	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Papillary cystadenoma, NOS											X															1
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Osteosarcoma																										2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Sarcoma, NOS																										1
Malignant lymphoma, NOS												X				X				X						7
Malignant lymphoma, histiocytic type																										1
Lower leg, NOS																										
Osteosarcoma				X																						1

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE: LOW DOSE

ANIMAL NUMBER	0039	0046	0008	0112	0111	0227	0005	0004	0440	0445	0443	0118	0225	0221	0119	0117	0448	0002	0003	0224	0331	0501	0115	0226	0336
WEEKS ON STUDY	0002	0003	0009	0122	0115	0447	0556	0771	0776	0766	0777	0778	0779	0800	0801	0833	0855	0866	0866	0877	0911	0966	0988	0998	0998
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	M	B	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	
Sarcoma, NOS																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	M	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Adenosquamous carcinoma, metastatic																X									
Pheochromocytoma, metastatic														X											
Trachea	M	B	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	
HEMATOPOIETIC SYSTEM																									
Bone marrow	M	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Spleen	M	B	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	
Lymph nodes	M	B	+	+	−	−	−	−	+	−	−	+	+	−	+	−	+	−	+	−	+	+	+	−	
Thymus	M	B	+	+	−	+	−	+	+	−	+	−	+	−	+	−	+	+	+	+	−	+	+	+	
CIRCULATORY SYSTEM																									
Heart	M	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
DIGESTIVE SYSTEM																									
Salivary gland	M	B	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	
Liver	M	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hepatocellular adenoma						X						X				X	X						X		
Hepatocellular carcinoma													X												
Bile duct	M	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Gallbladder & common bile duct	M	B	N	N	+	+	N	+	+	+	N	+	N	N	+	+	+	N	+	N	+	+	+	+	
Pancreas	M	B	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	
Esophagus	M	B	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	−	+	+	+	+	+	+	
Stomach	M	B	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	
Squamous cell papilloma																							X		X
Small intestine	M	B	−	−	−	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	
Adenomatous polyp, NOS																									
Malignant lymphoma, NOS																									
Large intestine	M	B	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	
URINARY SYSTEM																									
Kidney	M	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Malignant lymphoma, NOS																									
Urinary bladder	M	B	+	+	−	+	−	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	
ENDOCRINE SYSTEM																									
Pituitary	M	B	+	−	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Carcinoma, NOS															X										
Adenoma, NOS																	X						X		
Adrenal	M	B	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Pheochromocytoma													X												
Pheochromocytoma, malignant														X											
Thyroid	M	B	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	
Follicular cell adenoma						X																			
Parathyroid	M	B	+	−	−	−	−	−	+	−	+	−	+	−	−	+	+	−	−	−	+	+	+	+	−
Pancreatic islets	M	B	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Islet cell adenoma												X													
REPRODUCTIVE SYSTEM																									
Mammary gland	M	B	N	N	N	+	N	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS									X	X													X	X	
Adenosquamous carcinoma																X									
Uterus	M	B	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adenocarcinoma, NOS																								X	
Endometrial stromal polyp																									X
Ovary	M	B	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	
NERVOUS SYSTEM																									
Brain	M	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	
SPECIAL SENSE ORGANS																									
Harderian gland	M	B	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Papillary cystadenoma, NOS																									
Papillary cystadenocarcinoma, NOS																									
BODY CAVITIES																									
Mediastinum	M	B	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
ALL OTHER SYSTEMS																									
Multiple organs, NOS	M	B	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										X					X			

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

ANIMAL NUMBER	023	001	006	007	009	010	013	014	016	020	022	028	029	030	031	032	034	035	037	038	041	042	044	047	049	TOTAL:
WEEKS ON STUDY	099	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*48
Sarcoma, NOS															X											1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar adenoma						X			X		X													X		4
Alveolar/bronchiolar carcinoma							X																			1
Adenosquamous carcinoma, metastatic																										1
Pheochromocytoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph nodes	−	+	+	−	−	+	−	+	+	+	−	−	+	−	−	−	+	+	+	−	+	+	−	+	+	26
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	39
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular adenoma							X	X	X																	8
Hepatocellular carcinoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	*48
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	43
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Squamous cell papilloma											X						X	X								5
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Adenomatous polyp, NOS		X																								1
Malignant lymphoma, NOS				X																						1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Malignant lymphoma, NOS						X																				1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Carcinoma, NOS			X										X													3
Adenoma, NOS																		X				X				4
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pheochromocytoma																										1
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Follicular cell adenoma																										1
Parathyroid	−	+	−	+	+	+	+	−	−	−	+	+	−	−	−	−	−	−	−	+	−	+	−	−	+	20
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	N	N	+	N	+	+	*48
Adenocarcinoma, NOS					X																				X	6
Adenosquamous carcinoma													X													2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS				X																						1
Adenocarcinoma, NOS																										1
Endometrial stromal polyp																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SPECIAL SENSE ORGANS																										
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	46
Papillary cystadenoma, NOS						X			X							X	X	X				X				6
Papillary cystadenocarcinoma, NOS																		X								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	*48
Malignant lymphoma, 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	*48
Malignant lymphoma, NOS																										3

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE: HIGH DOSE

ANIMAL NUMBER	0231	0116	0115	0220	0550	0225	0448	0007	0333	0002	0224	0226	0339	0227	0117	0111	0114	0445	0001	0003	0004	0005	0006	0008	0009
WEEKS ON STUDY	0644	0655	0844	0866	0877	0888	0911	0992	0992	0994	0994	0995	0996	0999	1000	1011	1011	1022	1044	1044	1044	1044	1044	1044	1044
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous adenoma																									
Hemangioma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																	X							X	
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic																									
Alveolar/bronchiolar adenoma					X	X					X		X					X							
Alveolar/bronchiolar carcinoma												X									X				
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS																									
Lymph nodes	+	+	+	−	−	+	+	+	+	+	−	+	+	+	−	+	+	+	−	+	+	+	+	−	+
Adenocarcinoma, NOS, metastatic																									
Malignant lymphoma, NOS																									
Thymus	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																					X				
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	+	N	+	+	+	N	+	N	+	+	+	+	+	+	+	+	N	+	N	N	+	+	N
Pancreas	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma												X				X						X	X		X
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rectum	N	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal sarcoma, invasive					X																				
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																X								X	
Adenoma, NOS																							X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	−	+	−	−	−	−	−	+	−	−	+	+	−	−	−	−	+	+	−	+	−	−	−	−
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS								X											X	X					
Adenosquamous carcinoma											X														
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS							X								X									X	
Endometrial stromal polyp																					X				
Endometrial stromal sarcoma					X																				
Malignant lymphoma, NOS				X																					
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary cystadenoma, NOS																					X				
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																X									
SPECIAL SENSE ORGANS																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−
Papillary cystadenoma, NOS											X		X						X						
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteoma																									X
Osteosarcoma																									
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
Adenocarcinoma, NOS, metastatic																									
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	X	X			X			X	X	X		X	X	X	X	X	X	X		X				X

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

ANIMAL NUMBER	0010	0012	0013	0018	0019	0021	0022	0028	0029	0030	0031	0032	0034	0035	0036	0037	0038	0040	0041	0042	0043	0044	0046	0047	0049	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES / TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Sebaceous adenoma									X																	1
Hemangioma																							X			1
Subcutaneous tissue	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Sarcoma, NOS	X																									3
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS, metastatic																			X							1
Alveolar/bronchiolar adenoma		X		X		X				X	X		X		X		X		X	X		X	X			17
Alveolar/bronchiolar carcinoma					X						X			X									X		X	7
Trachea	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, NOS															X											1
Lymph nodes	+	+	S	+	+	+	–	+	+	–	–	+	–	+	+	–	+	+	+	+	–	+	–	–	+	35
Adenocarcinoma, NOS, metastatic																			X							1
Malignant lymphoma, NOS					X																					1
Thymus	+	+	S	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
CIRCULATORY SYSTEM																										
Heart	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	48
DIGESTIVE SYSTEM																										
Salivary gland	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma		X																X								3
Bile duct	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	S	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	N	N	+	*49
Pancreas	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	S	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	S	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell papilloma																X										6
Small intestine	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Rectum	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Endometrial stromal sarcoma, invasive																										1
URINARY SYSTEM																										
Kidney	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS																										2
Adenoma, NOS											X							X		X						4
Adrenal	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid	+	+	S	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid	+	–	S	+	–	–	+	+	–	+	–	–	–	–	–	+	–	–	–	–	+	–	–	–	+	16
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	*49
Adenocarcinoma, NOS											X															4
Adenosquamous carcinoma																						X				2
Uterus	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS															X				X							5
Endometrial stromal polyp																										1
Endometrial stromal sarcoma																										1
Malignant lymphoma, NOS																										1
Ovary	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papillary cystadenoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS, invasive																										1
SPECIAL SENSE ORGANS																										
Harderian gland	+	+	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Papillary cystadenoma, NOS				X			X				X	X				X										8
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Osteoma																										1
Osteosarcoma																				X						1
BODY CAVITIES																										
Peritoneum	N	N	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Adenocarcinoma, NOS, metastatic																			X							1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	S	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	X																X								19

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE

	Chamber Control	50 ppm	100 ppm
Subcutaneous Tissue: Sarcoma or Myxosarcoma			
Overall Rates (a)	2/49 (4%)	1/48 (2%)	3/49 (6%)
Adjusted Rates (b)	5.4%	4.2%	9.2%
Terminal Rates (c)	0/25 (0%)	1/24 (4%)	2/31 (6%)
Week of First Observation	81	104	101
Life Table Tests (d)	P=0.485	P=0.535N	P=0.588
Incidental Tumor Tests (d)	P=0.455	P=0.525N	P=0.553
Cochran-Armitage Trend Test (d)	P=0.400		
Fisher Exact Test (d)		P=0.508N	P=0.500
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	2/49 (4%)	4/48 (8%)	17/49 (35%)
Adjusted Rates (b)	7.7%	16.7%	46.2%
Terminal Rates (c)	1/25 (4%)	4/24 (17%)	12/31 (39%)
Week of First Observation	103	104	87
Life Table Tests (d)	P<0.001	P=0.314	P=0.001
Incidental Tumor Tests (d)	P<0.001	P=0.277	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.329	P<0.001
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	0/49 (0%)	1/48 (2%)	7/49 (14%)
Adjusted Rates (b)	0.0%	4.2%	21.5%
Terminal Rates (c)	0/25 (0%)	1/24 (4%)	6/31 (19%)
Week of First Observation		104	95
Life Table Tests (d)	P=0.005	P=0.492	P=0.019
Incidental Tumor Tests (d)	P=0.005	P=0.492	P=0.017
Cochran-Armitage Trend Test (d)	P=0.002		
Fisher Exact Test (d)		P=0.495	P=0.006
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	2/49 (4%)	5/48 (10%)	22/49 (45%)
Adjusted Rates (b)	7.7%	20.8%	58.6%
Terminal Rates (c)	1/25 (4%)	5/24 (21%)	16/31 (52%)
Week of First Observation	103	104	87
Life Table Tests (d)	P<0.001	P=0.196	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.168	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.209	P<0.001
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	9/49 (18%)	6/48 (13%)	22/49 (45%)
Adjusted Rates (b)	26.4%	19.0%	48.3%
Terminal Rates (c)	3/25 (12%)	2/24 (8%)	8/31 (26%)
Week of First Observation	82	56	64
Life Table Tests (d)	P=0.023	P=0.343N	P=0.049
Incidental Tumor Tests (d)	P=0.002	P=0.334N	P=0.005
Cochran-Armitage Trend Test (d)	P=0.002		
Fisher Exact Test (d)		P=0.303N	P=0.004
Liver: Hepatocellular Adenoma			
Overall Rates (a)	1/49 (2%)	8/48 (17%)	3/49 (6%)
Adjusted Rates (b)	4.0%	24.2%	9.7%
Terminal Rates (c)	1/25 (4%)	3/24 (13%)	3/31 (10%)
Week of First Observation	104	47	104
Life Table Tests (d)	P=0.411	P=0.019	P=0.384
Incidental Tumor Tests (d)	P=0.274	P=0.021	P=0.384
Cochran-Armitage Trend Test (d)	P=0.291		
Fisher Exact Test (d)		P=0.014	P=0.309

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE (Continued)

	Chamber Control	50 ppm	100 ppm
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	5/49 (10%)	1/48 (2%)	0/49 (0%)
Adjusted Rates (b)	18.8%	2.6%	0.0%
Terminal Rates (c)	4/25 (16%)	0/24 (0%)	0/31 (0%)
Week of First Observation	96	79	
Life Table Tests (d)	P=0.007N	P=0.115N	P=0.019N
Incidental Tumor Tests (d)	P=0.008N	P=0.116N	P=0.021N
Cochran-Armitage Trend Test (d)	P=0.011N		
Fisher Exact Test (d)		P=0.107N	P=0.028N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	6/49 (12%)	9/48 (19%)	3/49 (6%)
Adjusted Rates (b)	22.7%	26.2%	9.7%
Terminal Rates (c)	5/25 (20%)	3/24 (13%)	3/31 (10%)
Week of First Observation	96	47	104
Life Table Tests (d)	P=0.132N	P=0.271	P=0.146N
Incidental Tumor Tests (d)	P=0.199N	P=0.285	P=0.155N
Cochran-Armitage Trend Test (d)	P=0.221N		
Fisher Exact Test (d)		P=0.273	P=0.243N
Forestomach: Squamous Cell Papilloma			
Overall Rates (a)	2/48 (4%)	5/46 (11%)	6/48 (13%)
Adjusted Rates (b)	6.8%	18.8%	18.1%
Terminal Rates (c)	1/25 (4%)	3/24 (13%)	4/30 (13%)
Week of First Observation	94	98	95
Life Table Tests (d)	P=0.188	P=0.206	P=0.207
Incidental Tumor Tests (d)	P=0.149	P=0.117	P=0.172
Cochran-Armitage Trend Test (d)	P=0.108		
Fisher Exact Test (d)		P=0.200	P=0.134
Pituitary Gland: Adenoma			
Overall Rates (a)	4/48 (8%)	4/45 (9%)	4/48 (8%)
Adjusted Rates (b)	14.6%	14.2%	12.9%
Terminal Rates (c)	3/25 (12%)	2/24 (8%)	4/31 (13%)
Week of First Observation	94	85	104
Life Table Tests (d)	P=0.443N	P=0.614	P=0.527N
Incidental Tumor Tests (d)	P=0.481N	P=0.578	P=0.546N
Cochran-Armitage Trend Test (d)	P=0.573		
Fisher Exact Test (d)		P=0.606	P=0.643
Pituitary Gland: Carcinoma			
Overall Rates (a)	1/48 (2%)	3/45 (7%)	2/48 (4%)
Adjusted Rates (b)	4.0%	10.9%	6.1%
Terminal Rates (c)	1/25 (4%)	2/24 (8%)	1/31 (3%)
Week of First Observation	104	81	101
Life Table Tests (d)	P=0.488	P=0.286	P=0.576
Incidental Tumor Tests (d)	P=0.460	P=0.330	P=0.536
Cochran-Armitage Trend Test (d)	P=0.400		
Fisher Exact Test (d)		P=0.284	P=0.500
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	5/48 (10%)	7/45 (16%)	6/48 (13%)
Adjusted Rates (b)	18.5%	24.2%	18.6%
Terminal Rates (c)	4/25 (16%)	4/24 (17%)	5/31 (16%)
Week of First Observation	94	81	101
Life Table Tests (d)	P=0.519N	P=0.344	P=0.608N
Incidental Tumor Tests (d)	P=0.552	P=0.339	P=0.608
Cochran-Armitage Trend Test (d)	P=0.439		
Fisher Exact Test (d)		P=0.334	P=0.500

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE (Continued)

	Chamber Control	50 ppm	100 ppm
Mammary Gland: Adenocarcinoma			
Overall Rates (a)	1/49 (2%)	6/48 (13%)	4/49 (8%)
Adjusted Rates (b)	2.9%	18.9%	11.8%
Terminal Rates (c)	0/25 (0%)	2/24 (8%)	3/31 (10%)
Week of First Observation	94	76	92
Life Table Tests (d)	P=0.265	P=0.061	P=0.247
Incidental Tumor Tests (d)	P=0.179	P=0.033	P=0.234
Cochran-Armitage Trend Test (d)	P=0.169		
Fisher Exact Test (d)		P=0.053	P=0.181
Mammary Gland: Adenocarcinoma or Adenosquamous Carcinoma			
Overall Rates (a)	1/49 (2%)	8/48 (17%)	6/49 (12%)
Adjusted Rates (b)	2.9%	24.8%	17.1%
Terminal Rates (c)	0/25 (0%)	3/24 (13%)	4/31 (13%)
Week of First Observation	94	76	92
Life Table Tests (d)	P=0.139	P=0.020	P=0.100
Incidental Tumor Tests (d)	P=0.082	P=0.012	P=0.087
Cochran-Armitage Trend Test (d)	P=0.067		
Fisher Exact Test (d)		P=0.014	P=0.056
Uterus: Adenocarcinoma			
Overall Rates (a)	0/49 (0%)	1/47 (2%)	5/49 (10%)
Adjusted Rates (b)	0.0%	3.6%	14.3%
Terminal Rates (c)	0/25 (0%)	0/24 (0%)	3/31 (10%)
Week of First Observation		98	91
Life Table Tests (d)	P=0.024	P=0.507	P=0.058
Incidental Tumor Tests (d)	P=0.019	P=0.383	P=0.051
Cochran-Armitage Trend Test (d)	P=0.011		
Fisher Exact Test (d)		P=0.490	P=0.028
Uterus: Adenoma or Adenocarcinoma			
Overall Rates (a)	0/49 (0%)	2/47 (4%)	5/49 (10%)
Adjusted Rates (b)	0.0%	7.6%	14.3%
Terminal Rates (c)	0/25 (0%)	1/24 (4%)	3/31 (10%)
Week of First Observation		98	91
Life Table Tests (d)	P=0.036	P=0.239	P=0.058
Incidental Tumor Tests (d)	P=0.028	P=0.173	P=0.051
Cochran-Armitage Trend Test (d)	P=0.017		
Fisher Exact Test (d)		P=0.237	P=0.028
Harderian Gland: Papillary Cystadenoma			
Overall Rates (a)	1/46 (2%)	(e) 6/46 (13%)	8/47 (17%)
Adjusted Rates (b)	4.3%	26.1%	24.8%
Terminal Rates (c)	1/23 (4%)	6/23 (26%)	6/29 (21%)
Week of First Observation	104	104	94
Life Table Tests (d)	P=0.037	P=0.052	P=0.039
Incidental Tumor Tests (d)	P=0.034	P=0.052	P=0.033
Cochran-Armitage Trend Test (d)	P=0.016		
Fisher Exact Test (d)		P=0.055	P=0.016

(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 cystadenocarcinoma was observed in an animal with a papillary cystadenoma.

TABLE B4a. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence for Chamber Controls at Battelle Pacific Northwest Laboratories			
Propylene oxide	4/50	0/50	4/50
Methyl methacrylate	1/49	1/49	2/49
Propylene	6/50	0/50	6/50
Dichloromethane	2/50	1/50	3/50
Tetrachloroethylene	4/48	2/48	6/48
TOTAL	17/247 (6.9%)	4/247 (1.6%)	21/247 (8.5%)
SD (b)	3.91%	1.74%	3.68%
Range (c)			
High	6/50	2/48	6/48
Low	1/49	0/50	2/49
Overall Historical Incidence for Untreated Controls in NTP Studies			
TOTAL	97/2,076 (4.7%)	39/2,076 (1.9%)	135/2,076 (6.5%)
SD (b)	3.76%	1.95%	4.44%
Range (c)			
High	7/50	3/50	8/50
Low	0/50	0/50	0/50

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

TABLE B4b. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls	
	Lymphoma	Lymphoma or Leukemia
Historical Incidence for Chamber Controls at Battelle Pacific Northwest Laboratories		
Propylene oxide	12/50	12/50
Methyl methacrylate	8/50	8/50
Propylene	16/50	16/50
Dichloromethane	7/50	7/50
Tetrachloroethylene	8/49	8/49
TOTAL	51/249 (20.5%)	51/249 (20.5%)
SD (b)	7.49%	7.49%
Range (c)		
High	16/50	16/50
Low	7/50	7/50
Overall Historical Incidence for Untreated Controls in NTP Studies		
TOTAL	595/2,090 (28.5%)	622/2,090 (29.8%)
SD (b)	11.98%	11.72%
Range (c)		
High	(d) 37/50	(d) 38/50
Low	5/50	6/50

(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) Second highest, 31/50; third highest, 23/50

TABLE B4c. HISTORICAL INCIDENCE OF HARDERIAN GLAND TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Adenocarcinoma	Adenoma or Adenocarcinoma
Historical Incidence for Chamber Controls at Battelle Pacific Northwest Laboratories			
Propylene oxide	0/50	0/50	0/50
Methyl methacrylate	0/50	0/50	0/50
Propylene	0/50	0/50	0/50
Dichloromethane	0/50	1/50	1/50
Tetrachloroethylene	1/49	0/49	1/49
TOTAL	1/249 (0.4%)	1/249 (0.4%)	2/249 (0.8%)
SD (b)	0.91%	0.89%	1.11%
Range (c)			
High	1/49	1/50	1/49
Low	0/50	0/50	0/50
Overall Historical Incidence for Untreated Controls in NTP Studies			
TOTAL	(d) 35/2,090 (1.7%)	(e) 4/2,090 (0.2%)	(d,e) 39/2,090 (1.9%)
SD (b)	1.99%	0.74%	2.15%
Range (c)			
High	4/50	2/50	4/50
Low	0/50	0/50	0/50

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

TABLE B4d. HISTORICAL INCIDENCE OF UTERINE GLANDULAR TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	No. Examined	No. of Tumors	Diagnosis
Historical Incidence for Chamber Controls at Battelle Pacific Northwest Laboratories			
Propylene oxide	48	0	
Methyl methacrylate	48	3	Adenocarcinoma, NOS
Propylene	47	0	
Dichloromethane	50	1	Adenocarcinoma, NOS
Tetrachloroethylene	43	0	
TOTAL	236	4 (1.7%)	
Overall Historical Incidence for Untreated Controls in NTP Studies			
		1	Adenoma, NOS
		1	Papillary cystadenoma
		1	Carcinoma, NOS
		1	Squamous cell carcinoma
		4	Adenocarcinoma, NOS
TOTAL	2,055	(b) 8 (0.4%)	

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

TABLE B4e. HISTORICAL INCIDENCE OF MAMMARY GLAND TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	No. Examined	No. of Tumors	Diagnosis
Historical Incidence for Chamber Controls at Battelle Pacific Northwest Laboratories			
Propylene oxide	50	0	
Methyl methacrylate	50	1	Acinar cell carcinoma
		1	Adenosquamous carcinoma
Propylene	50	2	Adenocarcinoma, NOS
Dichloromethane	50	2	Adenocarcinoma, NOS
Tetrachloroethylene	49	0	
TOTAL	249	6 (2.4%)	
Overall Historical Incidence for Untreated Controls in NTP Studies			
		5	Adenoma, NOS
		1	Acinar cell adenoma
		1	Intraductal carcinoma
		27	Adenocarcinoma, NOS
		1	Papillary adenocarcinoma
		3	Acinar cell carcinoma
		(b) 3	Adenosquamous carcinoma
		1	Adenocarcinoma/squamous metaplasia
		9	Mixed tumor, malignant
TOTAL	2,090	(c) 51 (2.4%)	

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) No more than one adenosquamous carcinoma was observed in any untreated control group.
(c) No more than three benign, six malignant, or six benign or malignant (combined) tumors (excluding mixed tumor, malignant) were observed in any untreated control group.

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE

	CHAMBER CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	49	48	49
ANIMALS EXAMINED HISTOLOGICALLY	49	48	49
INTEGUMENTARY SYSTEM			
*Skin	(49)	(48)	(49)
Edema, NOS	1 (2%)	1 (2%)	
Scar		1 (2%)	
Atrophy, NOS		1 (2%)	
RESPIRATORY SYSTEM			
*Nasal cavity	(49)	(48)	(49)
Deformity, NOS		1 (2%)	
Inflammation, suppurative	3 (6%)		5 (10%)
Inflammation, chronic diffuse			2 (4%)
Erosion			1 (2%)
Hyperplasia, epithelial			4 (8%)
Angiectasis		1 (2%)	
Metaplasia, squamous	1 (2%)		3 (6%)
*Nasal gland	(49)	(48)	(49)
Cyst, NOS			2 (4%)
Hyperplasia, NOS			1 (2%)
*Larynx	(49)	(48)	(49)
Hyperplasia, epithelial		1 (2%)	
*Laryngeal submucosa	(49)	(48)	(49)
Cyst, NOS		1 (2%)	
#Tracheal submucosa	(49)	(46)	(49)
Cyst, NOS	19 (39%)	20 (43%)	28 (57%)
#Lung/bronchus	(49)	(48)	(49)
Inflammation, chronic			1 (2%)
#Bronchial submucosa	(49)	(48)	(49)
Cyst, NOS	8 (16%)	9 (19%)	7 (14%)
#Lung/bronchiole	(49)	(48)	(49)
Hyperplasia, epithelial			1 (2%)
#Lung	(49)	(48)	(49)
Emphysema, NOS	1 (2%)	1 (2%)	
Congestion, acute passive	5 (10%)	1 (2%)	
Hyperplasia, alveolar epithelium	2 (4%)		3 (6%)
#Lung/alveoli	(49)	(48)	(49)
Histiocytosis			3 (6%)
HEMATOPOIETIC SYSTEM			
*Mediastinum	(49)	(48)	(49)
Hematopoiesis		1 (2%)	
#Bone marrow	(49)	(48)	(49)
Hyperplasia, focal			1 (2%)
Myelofibrosis	30 (61%)	31 (65%)	33 (67%)
#Spleen	(49)	(46)	(49)
Hematoma, NOS			1 (2%)
Atrophy, NOS	1 (2%)	1 (2%)	1 (2%)
Erythrophagocytosis		3 (7%)	
Hyperplasia, lymphoid	5 (10%)	2 (4%)	2 (4%)
Hematopoiesis	7 (14%)	13 (28%)	10 (20%)
#Splenic follicles	(49)	(46)	(49)
Necrosis, diffuse		1 (2%)	

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE (Continued)

	CHAMBER CONTROL	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Mandibular lymph node	(23)	(26)	(35)
Edema, NOS		1 (4%)	
Hyperplasia, NOS			1 (3%)
Histiocytosis		1 (4%)	
Erythrophagocytosis			3 (9%)
#Bronchial lymph node	(23)	(26)	(35)
Necrosis, diffuse		1 (4%)	
#Mediastinal lymph node	(23)	(26)	(35)
Hyperplasia, NOS		1 (4%)	
#Mesenteric lymph node	(23)	(26)	(35)
Hyperplasia, NOS	1 (4%)		1 (3%)
#Axillary lymph node	(23)	(26)	(35)
Histiocytosis			1 (3%)
*Skull	(49)	(48)	(49)
Myelofibrosis	1 (2%)		2 (4%)
*Sternum	(49)	(48)	(49)
Myelofibrosis		1 (2%)	
#Lung	(49)	(48)	(49)
Hyperplasia, lymphoid	10 (20%)	10 (21%)	5 (10%)
#Liver	(49)	(48)	(49)
Erythrophagocytosis		1 (2%)	
Hematopoiesis	2 (4%)	2 (4%)	4 (8%)
#Pancreas	(49)	(46)	(48)
Hyperplasia, lymphoid			1 (2%)
#Gastric submucosa	(48)	(46)	(48)
Mastocytosis		1 (2%)	
#Kidney	(49)	(48)	(49)
Hematopoiesis	2 (4%)		
#Urinary bladder/submucosa	(47)	(44)	(48)
Hyperplasia, lymphoid	1 (2%)		
#Thymus	(38)	(39)	(46)
Cyst, NOS			2 (4%)
Necrosis, NOS		1 (3%)	
CIRCULATORY SYSTEM			
*Mammary gland	(49)	(48)	(49)
Thrombosis, NOS	1 (2%)		
#Lung	(49)	(48)	(49)
Perivasculitis			1 (2%)
#Myocardium	(49)	(48)	(48)
Inflammation, suppurative	1 (2%)		
#Endocardium	(49)	(48)	(48)
Inflammation, NOS		1 (2%)	
#Cardiac valve	(49)	(48)	(48)
Hemorrhage		1 (2%)	
Degeneration, mucoid	16 (33%)	10 (21%)	22 (46%)
Hemosiderosis	3 (6%)	6 (13%)	2 (4%)
*Aorta	(49)	(48)	(49)
Perivasculitis		1 (2%)	
*Coronary artery	(49)	(48)	(49)
Inflammation, chronic		1 (2%)	

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE (Continued)

	CHAMBER CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#Salivary gland	(49)	(46)	(49)
Lymphocytic inflammatory infiltrate	1 (2%)	2 (4%)	
Fibrosis, focal		1 (2%)	
#Liver	(49)	(48)	(49)
Mineralization	1 (2%)		
Multiple cysts			1 (2%)
Necrosis, focal	1 (2%)		2 (4%)
Necrosis, diffuse	5 (10%)		3 (6%)
Focal cellular change	1 (2%)	1 (2%)	1 (2%)
Angiectasis		1 (2%)	
#Liver/Kupffer cell	(49)	(48)	(49)
Hyperplasia, NOS			1 (2%)
*Gallbladder	(49)	(48)	(49)
Inflammation, suppurative		1 (2%)	
#Pancreas	(49)	(46)	(48)
Inflammation, chronic		1 (2%)	
#Gastric mucosa	(48)	(46)	(48)
Mineralization		1 (2%)	2 (4%)
Cyst, NOS	1 (2%)	1 (2%)	4 (8%)
Atrophy, NOS		1 (2%)	
Hyperplasia, diffuse			1 (2%)
Metaplasia, squamous			2 (4%)
#Gastric submucosa	(48)	(46)	(48)
Inflammation, chronic			3 (6%)
#Forestomach	(48)	(46)	(48)
Cyst, NOS	1 (2%)		
Ulcer, NOS			1 (2%)
Necrosis, focal			1 (2%)
Hyperplasia, epithelial	4 (8%)	9 (20%)	10 (21%)
Hyperkeratosis	3 (6%)	6 (13%)	5 (10%)
#Colon	(49)	(45)	(49)
Parasitism			1 (2%)
*Rectum	(49)	(48)	(49)
Granulation tissue			1 (2%)
URINARY SYSTEM			
#Kidney	(49)	(48)	(49)
Cyst, NOS		2 (4%)	
Hemorrhage	1 (2%)	2 (4%)	
Lymphocytic inflammatory infiltrate	6 (12%)	5 (10%)	1 (2%)
Glomerulosclerosis, NOS	1 (2%)		
#Kidney/cortex	(49)	(48)	(49)
Fibrosis, focal		1 (2%)	
Metaplasia, osseous	1 (2%)		
#Renal papilla	(49)	(48)	(49)
Inflammation, suppurative	1 (2%)		
#Kidney/glomerulus	(49)	(48)	(49)
Amyloidosis	1 (2%)	1 (2%)	
Atrophy, NOS		2 (4%)	
#Kidney/tubule	(49)	(48)	(49)
Dilatation, NOS	3 (6%)	4 (8%)	1 (2%)
Cast, NOS	1 (2%)	2 (4%)	1 (2%)
Nephrosis, NOS	1 (2%)		
Cytoplasmic aggregate, NOS	1 (2%)		2 (4%)
Atrophy, NOS	1 (2%)		

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE (Continued)

	CHAMBER CONTROL	LOW DOSE	HIGH DOSE
URINARY SYSTEM (Continued)			
#Kidney/pelvis	(49)	(48)	(49)
Mineralization	1 (2%)		
#Urinary bladder/submucosa	(47)	(44)	(48)
Lymphocytic inflammatory infiltrate	1 (2%)		2 (4%)
Inflammation, chronic	2 (4%)	2 (5%)	1 (2%)
ENDOCRINE SYSTEM			
#Pituitary	(48)	(45)	(48)
Cyst, NOS		1 (2%)	1 (2%)
Hemorrhagic cyst		1 (2%)	
Inclusion, nuclear		1 (2%)	1 (2%)
Cytoplasmic vacuolization		3 (7%)	
Cytoplasmic aggregate, NOS		1 (2%)	
Hyperplasia, focal	2 (4%)	8 (18%)	10 (21%)
Hyperplasia, diffuse	4 (8%)	3 (7%)	4 (8%)
#Adrenal	(48)	(47)	(49)
Accessory structure			1 (2%)
#Adrenal/capsule	(48)	(47)	(49)
Hyperplasia, diffuse	43 (90%)	41 (87%)	43 (88%)
#Adrenal cortex	(48)	(47)	(49)
Cyst, NOS			1 (2%)
Fibrosis	26 (54%)	34 (72%)	25 (51%)
Degeneration, lipoid	27 (56%)	34 (72%)	30 (61%)
Hyperplasia, focal	1 (2%)	1 (2%)	
#Adrenal medulla	(48)	(47)	(49)
Cyst, NOS		1 (2%)	
Hemorrhage	1 (2%)		
Hyperplasia, focal	1 (2%)		
#Thyroid	(45)	(46)	(47)
Cystic follicles		1 (2%)	
Involution, NOS		1 (2%)	1 (2%)
Hyperplasia, cystic	1 (2%)		
#Thyroid colloid	(45)	(46)	(47)
Degeneration, NOS	2 (4%)	3 (7%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(49)	(48)	(49)
Dilatation/ducts	3 (6%)	2 (4%)	3 (6%)
*Vagina	(49)	(48)	(49)
Inflammation, suppurative	1 (2%)		
#Uterus	(49)	(47)	(49)
Mucocele		1 (2%)	
Hydrometra	4 (8%)		
Cyst, NOS			1 (2%)
Hemorrhage		1 (2%)	
Hematoma, NOS	1 (2%)	1 (2%)	
Inflammation, suppurative	1 (2%)	2 (4%)	
Amyloidosis		1 (2%)	
Atrophy, NOS		1 (2%)	
#Uterus/endometrium	(49)	(47)	(49)
Fibrosis			1 (2%)
Hyperplasia, NOS		1 (2%)	
Hyperplasia, cystic	37 (76%)	33 (70%)	36 (73%)
#Uterus/myometrium	(49)	(47)	(49)
Fibrosis		1 (2%)	

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE (Continued)

	CHAMBER CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)			
#Ovary	(48)	(47)	(49)
Cyst, NOS	6 (13%)	14 (30%)	13 (27%)
Parovarian cyst		1 (2%)	
Abscess, NOS		3 (6%)	
#Mesovarium	(48)	(47)	(49)
Inflammation, chronic	5 (10%)		
Inflammation, chronic focal		1 (2%)	1 (2%)
NERVOUS SYSTEM			
#Cerebral ventricle	(49)	(47)	(49)
Fibrosis, focal		1 (2%)	
#Cerebrum	(49)	(47)	(49)
Mineralization		1 (2%)	1 (2%)
Atrophy, focal		1 (2%)	
#Brain	(49)	(47)	(49)
Hemorrhage		1 (2%)	
Hematoma, NOS	1 (2%)		
#Brain/thalamus	(49)	(47)	(49)
Mineralization	11 (22%)	14 (30%)	13 (27%)
Atrophy, NOS		1 (2%)	
SPECIAL SENSE ORGANS			
*Eye	(49)	(48)	(49)
Microphthalmia	2 (4%)	1 (2%)	2 (4%)
Mineralization			1 (2%)
*Eye/cornea	(49)	(48)	(49)
Ulcer, NOS		1 (2%)	
Pannus		1 (2%)	
*Eye/crystalline lens	(49)	(48)	(49)
Cataract			1 (2%)
*Nasolacrimal duct	(49)	(48)	(49)
Cyst, NOS			1 (2%)
Inflammation, suppurative	1 (2%)	1 (2%)	4 (8%)
Inflammation, chronic	1 (2%)	1 (2%)	1 (2%)
Erosion			1 (2%)
Hyperplasia, epithelial		1 (2%)	1 (2%)
#Harderian gland	(46)	(46)	(47)
Cyst, NOS		1 (2%)	
Inflammation, suppurative		1 (2%)	
Atrophy, NOS		1 (2%)	1 (2%)
Hyperplasia, focal	3 (7%)	3 (7%)	4 (9%)
Metaplasia, squamous			1 (2%)
MUSCULOSKELETAL SYSTEM			
*Skull	(49)	(48)	(49)
Fibrous osteodystrophy	1 (2%)	1 (2%)	
BODY CAVITIES			
*Mediastinum	(49)	(48)	(49)
Inflammation, suppurative		1 (2%)	
*Peritoneum	(49)	(48)	(49)
Inflammation, suppurative		1 (2%)	1 (2%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF ETHYLENE OXIDE (Continued)

	CHAMBER CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
Site unknown			
Inflammation, suppurative		1	
SPECIAL MORPHOLOGY SUMMARY			
Animal missexed/no necropsy	1		1
Animal missing/no necropsy		1	
Accidental death/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 C

RESULTS OF SEROLOGIC ANALYSIS

APPENDIX C. 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.

Data were collected from animals killed in a moribund condition between month 17 and 19 and from 5/50 randomly selected control animals of each sex and species that lived to the end of the studies. The blood from each animal was collected and clotted, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the antibody titers. The following tests were performed:

	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)	M. Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus) Sendai	MHV (mouse hepatitis virus) *M. pul.* (*Mycoplasma pulmonis*)

II. Results

No positive titers were observed in any animal killed at 17-19 months or at 24 months.

APPENDIX D

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

Pellet Diet: July 1981 to July 1983

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

TABLE D1. 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 D2. VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION (a)

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

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

TABLE D3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION (a)

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

(a) One to four batches of feed analyzed for nutrients reported in this table were manufactured from 1983 through1985.
(b) One batch (7/22/81) not analyzed for thiamine.

TABLE D4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminant	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.50 ± 0.13	0.29-0.77	25
Cadmium (ppm) (a)	<0.10		25
Lead (ppm) (b)	0.74 ± 0.42	0.33-1.97	23
Lead (ppm) (c)	0.92 ± 0.75	0.33-3.37	25
Mercury (ppm) (a)	<0.05		25
Selenium (ppm)	0.29 ± 0.07	0.14-0.40	25
Aflatoxins (ppb)	<10	<5.0-<10.0	25
Nitrate nitrogen (ppm) (d)	9.22 ± 4.39	1.9-17.0	25
Nitrite nitrogen (ppm) (d)	2.19 ± 1.55	0.6-6.9	25
BHA (ppm) (e)	5.86 ± 4.87	2.0-17.0	25
BHT (ppm) (e)	3.0 ± 2.7	<1.0-12.0	25
Aerobic plate count (CFU/g) (f)	43,936 ± 31,267	4,900-110,000	25
Coliform (MPN/g) (g)	14.96 ± 22.36	<3-93	24
Coliform (MPN/g) (h)	32.76 ± 91.66	<3-460	25
E. coli (MPN/g) (i)	<3		25
Total nitrosamines (ppb)	3.42 ± 2.72	0.8-9.3	25
N-Nitrosodimethylamine (ppb)	2.68 ± 2.37	0.8-8.3	25
N-Nitrosopyrrolidine (ppb)	1.14 ± 0.48	<0.5-2.9	25
Pesticides (ppm) (d)			
α-BHC (a, j)	<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 (k)	<0.05	0.09 (8/26/81); 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 (l)	0.09 ± 0.06	<0.05-0.42	25
Endosulfan I (m)	<0.01		20
Endosulfan II (m)	<0.01		20
Endosulfan sulfate (m)	<0.03		20

TABLE D4. 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) Mean, standard deviation, and range exclude two high values of 2.65 ppm and 3.37 ppm obtained for batches produced on 8/26/81 and on 7/21/82.
(c) Mean, standard deviation, and range include the high values given in footnote b.
(d) Sources of contamination: alfalfa, grains, and fish meal
(e) Sources of contamination: soy oil and fish meal
(f) CFU = colony forming unit
(g) MPN = most probable number; mean, standard deviation, and range exclude one very high value of 460 MPN/g obtained for the batch produced on 9/23/82.
(h) Mean, standard deviation, and range include the high value given in footnote g.
(i) All values were less than 3 MPN/g.
(j) BHC = hexachlorocyclohexane or benzene hexachloride
(k) There were two observations above the detection limit. The values and the dates they were obtained are given under the range.
(l) Eleven batches contained more than 0.05 ppm.
(m) Four batches (7/22/81-11/25/81) were not analyzed for endosulfan I, endosulfan II, and endosulfan sulfate.

APPENDIX E

DATA AUDIT SUMMARY

APPENDIX E. DATA AUDIT SUMMARY

The experimental data, documents, pathology materials, and draft NTP Technical Report for the 2-year toxicology and carcinogenesis studies of ethylene oxide in mice were audited for accuracy, consistency, completeness, and compliance with Good Laboratory Practice requirements of the Food and Drug Administration (implemented by the NTP beginning October 1, 1981). The laboratory experiments were conducted for the NTP by Battelle Pacific Northwest Laboratories, Richland, Washington, under a subcontract with Tracor Jitco, Inc., until November 28, 1982, and then under contract with the NIEHS. Animal exposures to ethylene oxide began August 6, 1981, and ended August 3, 1983. The retrospective audit was conducted at the NTP Archives in April and May 1986 by Argus Research Laboratories. The following individuals were involved with the audit: Paul A. Wennerberg, D.V.M., M.S.; Lynn E. Blalock, M.S.; Elizabeth L. Feussner, V.M.D., D.A.B.T.; Betty L. Brandau, Ph.D.; Sharon H. Srebro, B.S.; and Carol L. Veigle, HTL. Pathology Associates, Inc., personnel consisted of Kirby N. Smith, D.V.M.; Kathleen M. Walsh, D.V.M., Diplomate A.C.V.P. (reviewer); Patricia D. Hall; Bonnie Jo Johnson; and James McCloud, Jr.

The full report of the audit is on file at the NIEHS. The audit included, as minimum requirements, a review of:

(1) All records concerning animal receipt, quarantine, randomization, and disposition prior to study start.
(2) All chemistry records, including chromatograms and exposure sheets for a random 10% of the exposure days.
(3) Clinical observations recorded during the last 6 months of life and all body weights for a random 10% sample of the study animals.
(4) All inlife records concerning environmental conditions, palpable masses, mortality, animal identification, and correlation of final inlife observation of masses, date of death, and disposition with necropsy records.
(5) All postmortem records for individual animals concerning identification, disposition codes, condition codes, correct data entry, and correlation between gross observations and microscopic diagnoses.
(6) Inventory and labeling for all wet tissue bags.
(7) Wet tissues from a random 10% sample of the study animals and from animals that had a gross observation without a corresponding microscopic diagnosis to verify animal identification and to examine for untrimmed lesions.
(8) Slides and blocks of tissues from all control and high dose animals to examine for proper match and inventory.
(9) All information presented in the draft Technical Report.

The audit showed that all required data were present with the exception of records documenting the disposition of extra animals, clinical observations for October 1981, and gas chromatograms for chamber concentration measurements made between August 6, 1981, and November 25, 1981. Clinical observations for individual animals were not always consistent from month to month. Over the course of the study, animals escaped from individual cages within a chamber on 17 occasions but were identified and returned to the appropriate cage. After the first 9 months of the study, missing eartags were replaced following a standard operating procedure, and animal identification in the wet tissue bags agreed with the assigned study-specific number and individual animal number. Miscellaneous untrimmed potential lesions (12) and gross observations without a corresponding microscopic diagnosis (24) were found. These were distributed across study groups and did not involve any particular organ.

The audit findings were reviewed by NTP staff. In conclusion, the documents and materials at the NTP Archives support the data and conclusions presented in this Technical Report.

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NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS PUBLISHED AS OF OCTOBER 1987

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
252	Geranyl Acetate
251	Toluene Diisocyanate
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
324	Boric Acid
325	Pentachloronitrobenzene
327	Xylenes (Mixed)

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