NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 328

TOXICOLOGY AND CARCINOGENESIS STUDIES OF METHYL CARBAMATE

(CAS NO. 598-55-0)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

NATIONAL TOXICOLOGY PROGRAM

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

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF METHYL CARBAMATE

(CAS NO. 598-55-0)

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(GAVAGE STUDIES)

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

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Public Health Service
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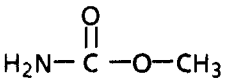
NOTE TO THE READER

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).

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Technical Report are available without charge (and while supplies last) from the NTP Public Information Office, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709.



METHYL CARBAMATE

$C_2H_5NO_2$ Molecular Weight 75.1

CAS No. 598-55-0

Synonyms:

Carbamic acid, methyl ester	Methylurethane
Methylurethan	Urethylane

ABSTRACT

Methyl carbamate is used as a chemical intermediate by the textile industry for the manufacture of dimethylol methyl carbamate-based resins that are applied on polyester/cotton blend fabrics as durable-press finishes.

Experimental Design: Toxicology and carcinogenesis studies of methyl carbamate (98% pure) were conducted by exposing groups of F344/N rats and B6C3F$_1$ mice by gavage in water in a single dose and by repeated administration for 16 days, 13 weeks, 6 months, 12 months, 18 months, and 2 years. In addition, short-term mutagenicity studies in bacteria, mammalian cells, and Drosophila and of unscheduled DNA synthesis in rat liver cells were conducted.

Single-Administration Studies: In the single-administration studies, 5/5 male and 5/5 female rats that received 8,000 mg/kg methyl carbamate and 2/5 males and 5/5 females that received 4,000 mg/kg died before the end of the 15-day observation period. Five of five male and 5/5 female mice that received 8,000 mg/kg and 1/5 males and 1/5 females that received 4,000 mg/kg died before the end of the 15-day observation period. No compound-related morphologic effects were observed in rats or mice that received 2,000 mg/kg.

Sixteen-Day Studies: In the 16-day studies, all rats dosed at 2,000 or 4,000 mg/kg died, and 3/5 male rats that received 1,000 mg/kg died. Male mice that received 2,000 or 4,000 mg/kg, female mice that received 4,000 mg/kg, and 1/5 female mice that received 2,000 mg/kg died. No compound-related gross pathologic or histopathologic effects were seen in male or female rats (groups of five each) that received 500 mg/kg or in mice that received 1,000 mg/kg.

Thirteen-Week Studies: In the 13-week studies, groups of 10 male and 10 female rats and mice received up to 800 mg/kg (male rats), 1,000 mg/kg (female rats), 1,500 mg/kg (male mice), or 2,000 mg/kg (female mice). Four of 10 male rats that received 800 mg/kg and 1/10 female rats that received 1,000 mg/kg died of compound-related causes before the end of the studies. Toxic hepatitis, splenic pigmentation, bone marrow atrophy, and testicular atrophy were observed in the two highest dose groups of rats. One of the female mice that received 2,000 mg/kg died. The dosed female mice had significantly greater relative liver weights than did the vehicle controls.

Experimental Design of Six-, Twelve-, and Eighteen-Month and Two-Year Studies: Based on the findings in the short-term studies, 2-year studies of methyl carbamate were conducted by administering 0, 100, or 200 mg/kg methyl carbamate in distilled water by gavage, 5 days per week for 103 weeks, to groups of 50 F344/N rats of each sex for 103 weeks. Groups of 50 B6C3F$_1$ mice of each sex were

administered 0, 500, or 1,000 mg/kg methyl carbamate on the same schedule. Additional groups of 30 rats of each sex were administered 0 or 400 mg/kg methyl carbamate, and additional groups of 30 mice of each sex were administered 0 or 1,000 mg/kg methyl carbamate in distilled water by gavage, 5 days per week. Ten animals from each group were killed at 6, 12, or 18 months so that the progression of lesions could be followed.

Results of Six-, Twelve-, and Eighteen-Month and Two-Year Studies: In the 6-month studies, all vehicle control and dosed (400 mg/kg) rats survived. Cytologic alterations and atypical proliferative changes were observed in the liver of all dosed male and female rats, and neoplastic nodules of the liver were observed in 6/10 dosed male and 5/10 dosed female rats. In the 12-month studies, all vehicle control male and female rats and dosed female rats survived. One of 10 dosed male rats died. Neoplastic nodules of the liver were observed in 7/10 dosed male and 9/10 dosed female rats, and hepatocellular carcinomas were observed in 8/10 dosed male and 6/10 dosed female rats. In the 18-month studies, 1/10 dosed male and 8/10 dosed female and all vehicle control rats survived. Hepatocellular carcinomas were observed in 9/10 dosed male and 8/10 dosed female rats. Compound-related neoplastic changes were not observed in mice in the 6-, 12-, or 18-month studies.

In the 2-year studies, mean body weights of high dose (200 mg/kg) male rats were generally 5%-9% lower than those of the vehicle controls after week 20. Mean body weights of high dose female rats were 5%-8% lower than those of the vehicle controls after week 56. Survival of dosed and vehicle control rats was similar (male: vehicle control, 19/50; low dose, 26/50; high dose, 29/50; female: 29/50; 36/50; 35/50). The mean body weights of high dose (1,000 mg/kg) male mice were about 8%-18% lower than those of the vehicle controls after week 24. The mean body weights of high dose (1,000 mg/kg) female mice were about 16% lower than those of the vehicle controls after week 16 and 30% lower after week 64. Survival of dosed and vehicle control mice was similar (male: 28/50; 35/50; 28/50; female: 38/50; 36/50; 32/50).

Chronic focal inflammation and cytologic alteration of the liver were observed at increased incidences in high dose rats of each sex. Hyperplasia of hepatocytes was observed at increased incidences in dosed male and high dose female rats. Neoplastic nodules or hepatocellular carcinomas (combined) in female rats occurred with a significant positive trend (0/50; 0/50; 6/49; $P<0.01$); the incidence of neoplastic nodules or hepatocellular carcinomas (combined) in high dose female rats was greater ($P<0.03$) than that in the vehicle controls. Incidences of liver neoplasms in dosed male rats were not significantly increased (4/50; 0/50; 7/49). Inflammation of the harderian gland was observed at increased incidences in dosed rats (male: 4/50; 11/50; 16/50; female: 7/50; 16/50; 30/50). The lesions were considered to be chemically related. In the 2-year studies in rats, significant decreases in tumor incidences included the following: leukemia (both sexes), pituitary gland (male), adrenal gland (male), and mammary gland (female).

In the 2-year mouse studies, multinucleate giant cells in the liver were observed at increased incidences in dosed male mice (14/50; 31/50; 31/49). Adenomatous hyperplasia and histiocytosis of the lung were observed at increased incidences in high dose mice (adenomatous hyperplasia--male: 13/50; 19/50; 24/49; female: 7/49; 10/50; 18/50; histiocytosis--male: 11/50; 7/50; 21/49; female: 9/49; 10/50; 21/50).

Genetic Toxicology: Methyl carbamate was not mutagenic in *Salmonella typhimurium* strains TA97, TA98, TA100, or TA1535 when tested with or without metabolic activation in a preincubation protocol at doses up to 10 mg/plate. Methyl carbamate did not induce forward mutations in the mouse L5178Y/TK$^{+/-}$ lymphoma assay with or without metabolic activation at doses up to 5 mg/ml. Unscheduled DNA synthesis was not detected in rat hepatocytes after in vitro treatment with methyl carbamate at concentrations of 1.0-1,000 µg/ml. When tested in Drosophila at doses of 25,000-50,000 ppm, methyl carbamate did not induce sex-linked recessive lethal mutations. Results of tests for

induction of chromosomal aberrations and sister chromatid exchanges by methyl carbamate in cultured Chinese hamster ovary cells were also negative at doses up to 5 mg/ml.

Data Audit: An audit of the experimental data was conducted for the 6-, 12-, and 18-month and 2-year studies of methyl carbamate. No data discrepancies were found that influenced the final interpretation.

Conclusions: Under the conditions of these 6-, 12-, and 18-month and 2-year gavage studies, there was *clear evidence of carcinogenic activity** for male and female F344/N rats given methyl carbamate as indicated by increased incidences of hepatocellular neoplastic nodules and hepatocellular carcinomas. There was *no evidence of carcinogenic activity* for male and female B6C3F$_1$ mice given methyl carbamate at doses of 500 or 1,000 mg/kg. Methyl carbamate also induced inflammation of the harderian gland in male and female rats and adenomatous hyperplasia and histiocytosis of the lung in male and female mice.

SUMMARY OF THE SIX-, TWELVE-, AND EIGHTEEN-MONTH AND TWO-YEAR GAVAGE STUDIES AND GENETIC TOXICOLOGY OF METHYL CARBAMATE

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Doses			
0 or 400 mg/kg methyl carbamate in water, 5 d/wk for 6, 12, or 18 mo; 0, 100, or 200 mg/kg for 2 years	0 or 400 mg/kg methyl carbamate in water, 5 d/wk for 6, 12, or 18 mo; 0, 100, or 200 mg/kg for 2 years	0 or 1,000 mg/kg methyl carbamate in water, 5 d/wk for 6, 12, or 18 mo; 0, 500, or 1,000 mg/kg for 2 years	0 or 1,000 mg/kg methyl carbamate in water, 5 d/wk for 6, 12, or 18 mo; 0, 500, or 1,000 mg/kg for 2 years
Survival in 2-year study			
19/50; 26/50; 29/50	29/50; 36/50; 35/50	28/50; 35/50; 28/50	38/50; 36/50; 32/50
Nonneoplastic effects			
Inflammation of harderian gland	Inflammation of harderian gland	Adenomatous hyperplasia and histiocytosis of the lung	Adenomatous hyperplasia and histiocytosis of the lung
Neoplastic effects			
Hepatocellular neoplastic nodules and carcinomas	Hepatocellular neoplastic nodules and carcinomas	None	None
Level of evidence of carcinogenic activity			
Clear evidence	Clear evidence	No evidence	No evidence
Genetic toxicology			
Not mutagenic in Salmonella; not mutagenic in mouse lymphoma L5178Y cells; did not induce unscheduled DNA synthesis in rat hepatocytes; did not induce sex-linked recessive lethal mutations in Drosophila; did not induce chromosomal aberrations or sister chromatid exchanges in Chinese hamster ovary cells			

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

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

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

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

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

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

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APPENDIXES

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on methyl carbamate 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 METHYL CARBAMATE

On August 19, 1986, the draft Technical Report on the toxicology and carcinogenesis studies of methyl carbamate 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. P. Chan, NIEHS/NTP, introduced the studies by reviewing the experimental design, results, and proposed conclusions (clear evidence of carcinogenic activity for rats, no evidence of carcinogenic activity for mice).

Dr. Purchase, a principal reviewer, began a discussion on the significance of the neoplastic lesions in the liver of rats. He suggested that the high incidence of necrosis and other extensive tissue damage in the liver of animals from the 12- and 18-month studies diluted and confounded the significance of the neoplastic effects. This, along with the small numbers of carcinomas in dosed male and female rats in the 2-year studies, made the designation of clear evidence of carcinogenic activity less certain. Dr. Purchase also noted some statistically significant decreases in incidences of tumors compared with those of the vehicle controls. Dr. Chan emphasized that the conclusions for rats were based on the composite findings from animals in the 6-, 12-, and 18-month studies as well as from the 2-year studies. Dr. J. Huff, NIEHS, noted that the top dose for rats in the 24-month studies was only one-half the dose used in the shorter term studies.

As a second principal reviewer, Dr. Gallo agreed with the conclusions as written. He thought that more appropriate routes of exposure would have been inhalation or dermal contact. He suggested that the studies were good examples of dose-time responses compared with tissue burden, which indicated that tissue concentration and metabolism often play a major role in comparative toxicity between species.

Dr. Scala read the review from Dr. Hughes, the third principal reviewer, who was absent due to illness. Dr. Hughes did not agree with the conclusions for rats. He said that the data from the 2-year studies alone were insufficient to support a conclusion of clear evidence of carcinogenic activity, whereas exposure of rats for 6, 12, or 18 months at higher doses than those used in the 2-year studies resulted in a cumulative toxic response as well as in a progressive carcinogenic response in rat liver. Dr. S. Eustis, NIEHS, disagreed that toxic effects of the chemical diminished the significance of the carcinogenic effects in the same organ. Dr. Eustis said that one must consider the specific type of histologic changes and that the toxicity in the liver consisted of foci of cellular alteration and atypical proliferative changes that experimentalists usually find with other potent liver carcinogens.

Further discussion focused on the 6-, 12-, and 18-month studies as they related to the level of evidence chosen for rats. Dr. Popp agreed that the tumor data from the 2-year studies alone were insufficient to justify the conclusion; rather, the conclusion was drawn from the shorter term results. Dr. Hooper argued that the increases in cytologic alterations in the liver of vehicle control rats from 6 to 12 to 18 months with no corresponding appearance of neoplasia indicated that the alterations were lesions associated with aging and were unrelated to the neoplastic process. Dr. Huff stated that it was highly unusual to observe neoplastic nodules of such a magnitude at 6 months or likewise carcinomas at 12 and 18 months. He acknowledged that it might have been useful to have another 400 mg/kg group carried to 24 months for comparison; however, mortality due to tumors was already extensive after 18 months in rats receiving 400 mg/kg.

Regarding species differences in chemical metabolism, Dr. B. Schwetz, NIEHS, reported on recent chemical disposition studies. Using a wide range of doses, the studies confirmed a longer half-life in rats (about 3 days) than in mice (about 4 hours). He said that these findings with appropriate discussion would be added to the report [see page 59].

Dr. J. Hixson, Mobay Corporation, stated that the toxicity to the liver in animals exposed at 400 mg/kg was so severe as to preclude use of the data, and assessment of carcinogenicity should be based strictly on the 2-year studies in rats. Dr. Huff noted that virtually all rats, vehicle control and exposed alike, showed evidence of cytologic alteration at 18 months. Dr. R. Lorentzen, Food and Drug Administration, observed that among the most significant findings were the anticarcinogenic effects on the pituitary gland in male rats and female mice and on the adrenal glands in male rats. Dr. Huff said that these findings would be given more emphasis; however, he wondered how relevant this was compared with the carcinogenic effects observed in the liver of rats.

Dr. Purchase moved that the Technical Report on methyl carbamate be accepted with the conclusions as written for male and female mice, no evidence of carcinogenic activity. Dr. Gallo seconded the motion, and it was approved unanimously with 10 affirmative votes. Dr. Purchase moved that the conclusions for male rats be changed to some evidence of carcinogenic activity. As there was no second, Dr. Purchase then moved to accept the conclusions as written, clear evidence of carcinogenic activity. Dr. Mirer seconded the motion, and it was approved unanimously with 10 affirmative votes. Dr. Purchase moved that the conclusions for female rats be accepted as written, clear evidence of carcinogenic activity. Dr. Perera seconded the motion, and it was approved unanimously with 10 affirmative votes.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Methyl Carbamate is based on the 13-week studies that began in July 1980 and ended in September 1980 and on the 2-year studies that began in June 1981 and ended in June 1983 at Microbiological Associates.

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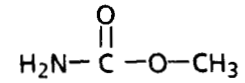
I. INTRODUCTION

Production, Use, and Exposure
Metabolism
Immunotoxicity
Genetic Toxicology
Carcinogenicity
Study Rationale

I. INTRODUCTION



METHYL CARBAMATE

$C_2H_5NO_2$ Molecular Weight 75.1

CAS No. 598-55-0

Synonyms:

Carbamic acid, methyl ester	Methylurethane
Methylurethan	Urethylane

Methyl carbamate is the methyl ester of carbamic acid; when pure, it takes the form of white, crystalline flakes or needles. Commercially, methyl carbamate is produced by reacting ammonia with methyl chloroformate. The compound is stable at room temperature and has a boiling point of 177° C at 760 mm Hg and a melting point of 54° C. The specific gravity of methyl carbamate is 1.136, and its refractive index is 1.4125. Methyl carbamate is soluble in water (2 g/ml), ethanol (1 g/ml), chloroform (0.4 g/ml), and diethyl ether and is insoluble in naphtha, xylene, hexane, and carbon tetrachloride (IARC, 1976).

Production, Use, and Exposure

Methyl carbamate is used primarily in the textile and polymer industries as a reactive intermediate. In the textile industry, it is used in the manufacture of dimethylol methyl carbamate-based resins that are applied on polyester/cotton blend fabrics as durable-press finishes. The treated fabrics have good crease-angle retention, resist acid souring in commercial laundries, do not retain chlorine (Hill, 1967), and have flame-retardant properties. Methyl carbamate also is used in the manufacture of pharmaceuticals, insecticides, and urethane (IARC, 1976).

Methyl carbamate has been produced in the United States for at least 25 years (USTC, 1960). Although current production figures are not available, it has been estimated that up to 1 million pounds (454,000 kg) of methyl carbamate may have been produced by a single firm in 1977 (USEPA, 1977). European production is estimated to be about 2 million pounds (900,000 kg) per year.

Methyl carbamate has been detected in four species of plants of the genus Salsola grown in Egypt (Karawya et al., 1972) and in Burley tobacco leaves (Schmeltz et al., 1978). No information on persistence of methyl carbamate in the environment was found in the literature.

No information on human exposure to methyl carbamate was available, but such exposure might be significant in view of the compound's wide use. The primary routes of human exposure are inhalation and dermal contact.

Metabolism

Although specific information on the metabolism of methyl carbamate is not available, it is expected that the ester linkage can be hydrolyzed in vivo to yield carbamic acid and methanol. Williams (1959) speculated that carbamic acid then may be converted to urea, and methanol may be oxidized to formaldehyde or formic acid or may be conjugated with glucuronic acid and excreted. However, rats receiving [^{14}C]methyl carbamate eliminated about 50% of an oral dose in expired air as [^{14}C]carbon dioxide and the remainder in urine and feces as unchanged methyl carbamate. Mice metabolized most of an oral dose of [carbonyl-^{14}C]methyl carbamate to [^{14}C]carbon dioxide and eliminated it via expired air (Ioannou and Matthews, 1984). These results indicate that when methyl carbamate is hydrolyzed, the carbamic acid moiety may be metabolized or spontaneously degraded to carbon dioxide.

Methyl carbamate administered orally was eliminated much more slowly by rats than by

mice; the parent compound was predominant in the tissues and urine of both species (Ioannou and Matthews, 1984). In another study, about 5%-10% of intraperitoneally administered methyl carbamate (500 mg/kg) was excreted unchanged by rats in the urine within 24 hours, and methyl carbamate was detected in the blood, liver, and lungs for up to 5 days (Boyland and Papadopoulos, 1952). Traces of *N*-hydroxycarbamate were detected in the urine of rats 24-48 hours after an intraperitoneal injection of methyl carbamate (1 g/kg) (Boyland and Nery, 1965).

Intraperitoneally administered methyl carbamate was bound to dermal and epidermal DNA in mice, with maximum binding occurring between 6 and 12 hours after dosing. Binding was greater in the dermis than in the epidermis (Pound and Lawson, 1976). A very low level of binding was detected in mouse liver and kidney DNA (Lawson and Pound, 1973). However, [^{3}H]methyl carbamate was readily incorporated into newly synthesized mouse liver RNA. The administered methyl carbamate caused a rapid breakdown of RNA and an increase in RNA synthesis in mouse liver (Williams et al., 1971).

Immunotoxicity

Methyl carbamate given intraperitoneally to B6C3F$_1$ mice (4.0 mg/kg, daily for 14 days) did not cause alterations in the immune functions, which were analyzed by bone marrow cellularity and progenitor assays; macrophage phagocytosis; lysing of sheep erythrocytes by lymphocytes; lymphoproliferative response to phytohemagglutinin, Concanavalin A, or lipopolysaccharide; delayed hypersensitivity response; natural killer-cell activity; and tumor-cell challenges (Luster et al., 1982). The effects of methyl carbamate on the immune functions of F344 rats have not been reported.

Genetic Toxicology

Methyl carbamate has been tested extensively for genotoxicity in bacterial systems. Except for one report of a "slight mutagenic effect" at the pro-1 locus of *Escherichia coli* strain WP-14 (Hemmerly and Demerec, 1955), all available reports in the literature indicate that methyl carbamate is not mutagenic in *E. coli* or *Bacillus subtilis* (Demerec et al., 1950, 1951; De Giovanni-Donnelly et al., 1967; Pai et al., 1978; Rosenkranz and Poirier, 1979; Rosenkranz and Leifer, 1980; Leifer et al., 1981; McCarroll et al., 1981a,b; Suter and Jaeger, 1982). Results of tests with methyl carbamate in the Salmonella/microsome assay were uniformly negative in a variety of *Salmonella typhimurium* strains both with or without metabolic activation (McCann et al., 1975; Commoner, 1976; Simmon, 1979a; Rosenkranz and Poirier, 1979; Dunkel et al., 1981). These results were corroborated by those of NTP-sponsored *S. typhimurium* assays in which methyl carbamate was not mutagenic in a preincubation protocol with strains TA97, TA98, TA100, or TA1535 at doses up to 10 mg/plate with or without S9 from the liver of Aroclor 1254-induced male Sprague Dawley rats or Syrian hamsters (Appendix E, Table E1).

The available evidence indicates that methyl carbamate is not genotoxic in eukaryotes, either in vitro or in vivo. Tests for mitotic recombination in yeast cultures exposed to methyl carbamate were negative (Simmon, 1979b), as were tests for nondisjunction in cultures of *Aspergillus nidulans* exposed to the chemical at doses of up to 0.4 mg/ml (Morpurgo et al., 1979). Methyl carbamate did not increase the number of forward mutations in the mouse L5178Y/TK$^{+/-}$ lymphoma assay in the presence of metabolic activation (Amacher and Turner, 1982). When tested by the NTP in this same assay, methyl carbamate was not mutagenic at doses up to 5 mg/ml with or without Aroclor 1254-induced, as well as with noninduced, male F344 rat liver S9 (Table E2). Methyl carbamate did not induce unscheduled DNA synthesis (UDS) in primary male F344 rat liver cells treated in vitro at concentrations of 1.0-1,000 µg/ml (Table E6). Exposure of cultured Chinese hamster ovary cells to methyl carbamate at doses of up to 5 mg/ml did not increase the frequency of chromosomal aberrations or induce sister chromatid exchanges (SCEs) in either the presence or absence of S9 from Aroclor 1254-induced male Sprague Dawley rat liver (Tables E3 and E4).

In in vivo studies, Cheng et al. (1981) reported no induction of SCEs in alveolar macrophages, bone marrow cells, or regenerating liver cells of hepatectomized male mice after intraperitoneal

administration of up to 6.6 mmol/kg methyl carbamate. No significant increase in the number of sex-linked recessive lethal mutations was detected after exposure of Drosophila to methyl carbamate at doses of 25,000 ppm (administered by injection) or up to 50,000 ppm (administered by feeding) (Table E5). In a dominant lethal mutation study (Epstein et al., 1972) in which male mice were given methyl carbamate intraperitoneally at 1,000 mg/kg and caged with three new female mice each week for the 8 weeks immediately following dosing, no increases in the frequency of early fetal death or preimplantation losses were observed in females mated with the dosed group relative to that in the control group. There are no reports of in vivo mutagenicity studies of methyl carbamate conducted with rats.

Carcinogenicity

Methyl carbamate has been tested in mice for carcinogenicity. Methyl carbamate injected intraperitoneally (up to 2 mg/g) once a week for 13 weeks (Shimkin et al., 1969; Larsen, 1947) or subcutaneously (5 mg) 3 days per week for 4 weeks (Yagubov and Suvalova, 1973) did not increase incidences of lung adenomas in mice at the end of a 5- to 6-month observation period. Tumor incidences in mice given a single subcutaneous injection of methyl carbamate (40 mg or 27 meq/kg) followed by weekly topical applications of croton oil were similar to those of the controls (Pound, 1967; Pound and Lawson, 1976). Mice given 15 weekly topical applications of methyl carbamate (25% in acetone) followed by applications of croton oil (0.5% in acetone) for 18 weeks did not have higher tumor incidences compared with the controls (Roe and Salaman, 1955). No carcinogenicity studies of methyl carbamate in rats have been reported in the literature.

Study Rationale

Methyl carbamate was nominated for study by the National Cancer Institute because there is a potential for long-term human exposure through commercial use and its presence in tobacco and because it is a close structural analog of urethane (ethyl carbamate), a known carcinogen in rats and mice (Mirvish, 1968; IARC, 1974). The gavage route of administration was selected for the studies because methyl carbamate sublimes freely at room temperature (Merck, 1983).

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF METHYL CARBAMATE

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

SINGLE-ADMINISTRATION STUDIES

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

SIX-, TWELVE-, AND EIGHTEEN-MONTH AND TWO-YEAR STUDIES

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

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF METHYL CARBAMATE

Methyl carbamate was obtained in a single lot (lot no. EV-8090) from Millmaster Chemical Co. (New York, New York) which was used for all studies. The study material was white, crystalline flakes with a melting point of 53°-55° C. The infrared, ultraviolet, and nuclear magnetic resonance spectra were consistent with those found in the literature (Figures 1 and 2).

Cumulative data indicated that this lot of study material was at least 98% pure. Results of elemental analysis for carbon, hydrogen, and nitrogen agreed with theoretical values. Karl Fischer titration indicated a 0.09% water content. Treatment of the study material with sodium methoxide and back titration with benzoic acid indicated a purity of 97.7%. Thin-layer chromatography with a silica gel 60 F-254 plate and furfural-sulfuric acid spray reagent showed a single spot with either acetone:chloroform (50:50) or cyclohexane:ethanol (75:25) as the solvent. Gas chromatographic analysis was conducted with flame ionization detection and a nitrogen carrier at 70 ml/min. Two impurity peaks with combined areas totaling 1.4% that of the major peak were separated on a 10% Carbowax 20M TPA column; a 20% SP2100/0.1% Carbowax 1500 column separated two impurities with peak areas of 0.01% and 1.2% of the major peak area. The larger impurity was isolated by preparative gas chromatography on a 20% SP2100/0.1% Carbowax 1500 column and was identified by mass spectroscopy and Fourier transform nuclear magnetic resonance spectroscopy as (*N*-methoxymethyl)methyl carbamate.

Methyl carbamate was stable on storage for 2 weeks at temperatures up to 60° C. The bulk material was stored at room temperature, and the reference sample was stored at −70° C. Periodic analysis by infrared spectroscopy and gas chromatography on a 10% Carbowax 20M TPA column indicated that no deterioration of the study material occurred over the course of the studies.

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

The stability of aqueous solutions of methyl carbamate at room temperature was determined in separate studies by the study laboratory and by the analytical chemistry laboratory. At the study laboratory, 9.38 mg/ml and 100 mg/ml samples of methyl carbamate in water were stored at room temperature for 14 days and then diluted with methanol and analyzed by gas chromatography on a 10% Carbowax 20M TPA column. No notable difference was observed between the 14-day samples and a reference sample stored at −70° C. In addition, the study laboratory demonstrated that a 50 mg/ml methyl carbamate/water solution was stable when stored for 21 days at 5° C. At the analytical chemistry laboratory, the 120 mg/ml samples of methyl carbamate in water were analyzed after 0, 1, 2, 5, or 7 days at room or refrigeration temperatures by high-performance liquid chromatography on a μBondapak C_{18} column with water as the solvent. No notable difference in concentration was observed at any time. For all studies except the single-administration studies, methyl carbamate was mixed with commercial-grade distilled water to yield the desired concentration (Table 1). Dose mixtures were stored at 5° C for no longer than 3 weeks.

Periodic analysis of methyl carbamate/water solutions was conducted at the study laboratory and the analytical chemistry laboratory. Water samples were diluted with methanol and analyzed by gas chromatography with a flame ionization detector and a 10% Carbowax 20M TPA column. Dose mixtures were analyzed once during the 13-week studies. The results ranged from 97% to 102% of the target concentrations (Table 2). During the 2-year studies, the dose preparations were analyzed at approximately 8-week intervals. All 62 mixes analyzed were formulated within ±10% of the target concentrations (Table 3). Referee analysis was periodically performed by the analytical chemistry laboratory. Generally good agreement was found between the samples at the two laboratories (Table 4).

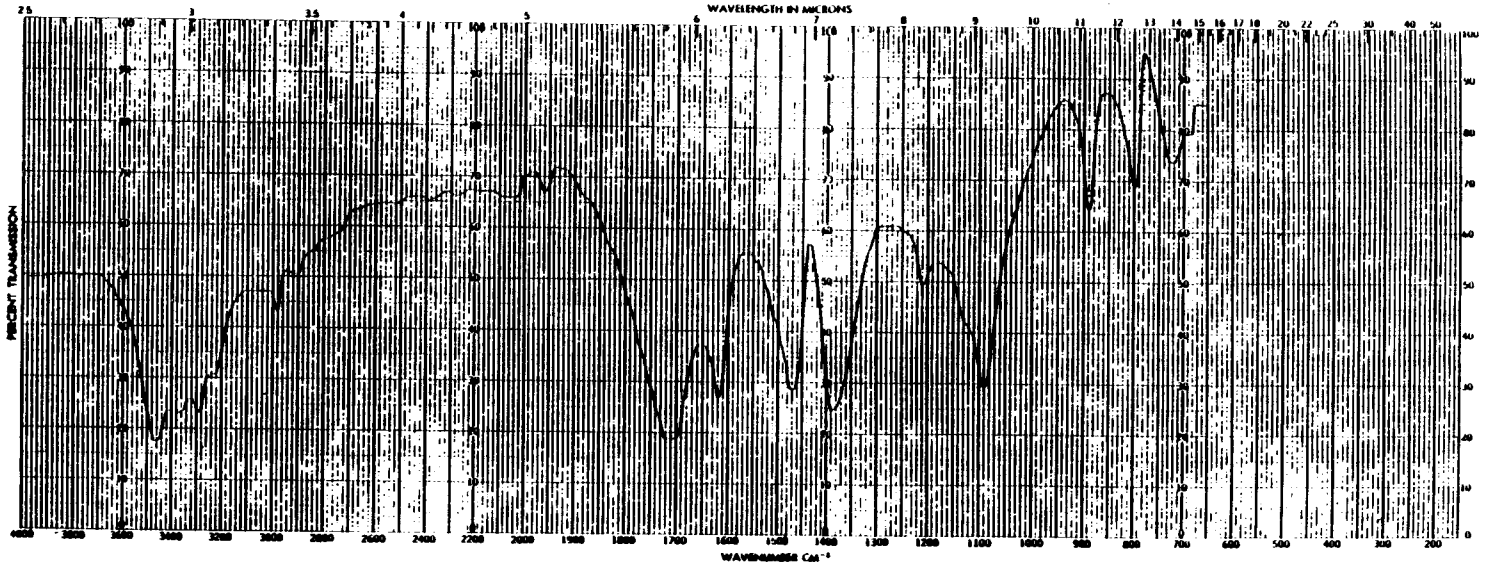


FIGURE 1. INFRARED ABSORPTION SPECTRUM OF METHYL CARBAMATE (LOT NO. EV-8090)

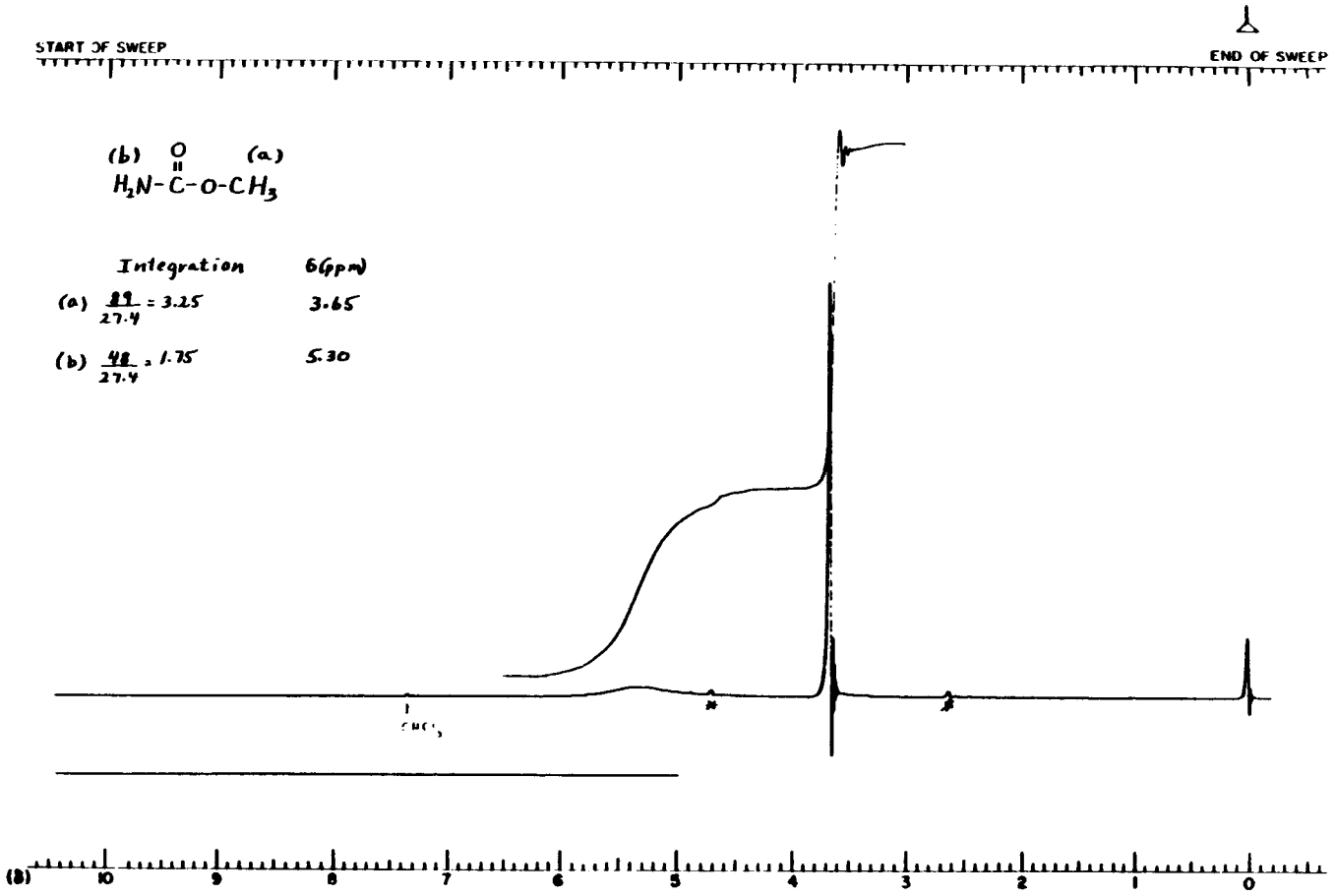


FIGURE 2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF METHYL CARBAMATE (LOT NO. EV-8090)

TABLE 1. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF METHYL CARBAMATE

Single-Administration Studies	Sixteen-Day Studies	Thirteen-Week Studies	Six-, Twelve-, and Eighteen-Month Studies	Two-Year Studies
Preparation				
Methyl carbamate weighed into a 100-ml volumetric flask, deionized water added to the mark, and the flask shaken until the solution thoroughly mixed	Same as single-administration studies except distilled water used	Same as 16-d studies	Same as 16-d studies	Same as 16-d studies
Maximum Storage Time				
Not available	8 d	15 d	3 wk	3 wk
Storage Conditions				
Room temperature	Room temperature	4° C	5° C	5° C ± 2° C in the dark

TABLE 2. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK GAVAGE STUDIES OF METHYL CARBAMATE

Date Mixed	Concentration (a) of Methyl Carbamate in Distilled Water (mg/ml)		Determined as a Percent of Target
	Target	Determined	
Before 7/4/80 (b)	9.38	9.38	100.0
	10	9.99	99.9
	12.5	12.66	101.3
	18.75	18.87	100.6
	20	19.86	99.3
	25	24.98	99.9
	37.5	36.58	97.6
	40	40.83	102.1
	50	50.01	100.0
	75	74.69	99.6
	80	80.46	100.6
	100	100.12	100.1
	150	151.54	101.0
	160	161.04	100.7
	200	200.58	100.3

(a) Results of duplicate analysis of samples prepared in duplicate
(b) Specific mix date not given

TABLE 3. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF METHYL CARBAMATE

Date Mixed	Concentration of Methyl Carbamate in Distilled Water for Target Concentrations (mg/ml) (a)				
	20	40	50	80	100
06/17/81	--	--	51.3	--	103.4
06/24/81	21.1	41.3	--	88.2	--
08/05/81	20.2	41.3	50.9	80.2	91.2
09/30/81	19.8	40.5	51.2	84.7	103.9
12/09/81	18.0	38.6	48.3	79.4	98.8
02/03/82	18.8	38.7	47.0	79.0	95.7
03/31/82	20.7	39.6	48.2	76.7	93.0
05/26/82	21.4	42.1	51.2	78.5	92.6
07/21/82	21.6	43.4	52.8	82.8	101.9
09/15/82	21.1	42.0	53.9	84.6	107.6
11/10/82	20.1	39.2	48.7	79.8	99.7
01/05/83	21.6	42.3	52.1	--	101.9
03/02/83	20.7	42.5	51.0	--	101.4
04/27/83	19.3	37.2	46.3	--	91.7
Mean (mg/ml)	20.3	40.7	50.2	81.4	98.7
Standard deviation	1.12	1.86	2.30	3.55	5.33
Coefficient of variation (percent)	5.5	4.6	4.6	4.4	5.4
Range (mg/ml)	18.0-21.6	37.2-43.4	46.3-53.9	76.7-88.2	91.2-107.6
Number of samples	13	13	13	10	13

(a) Results of duplicate analysis of samples prepared in duplicate

TABLE 4. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF METHYL CARBAMATE

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (mg/ml)	
		Study Laboratory (a)	Referee Laboratory (b)
06/17/81	50	51.3	49.3
12/09/81	40	38.6	40.7
05/26/82	20	21.4	20.2
11/10/82	100	99.7	99.8

(a) Results of duplicate analysis of samples prepared in duplicate
(b) Results of triplicate analysis

SINGLE-ADMINISTRATION STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for 3 weeks before the studies began. Rats were 8-9 weeks old and mice were 8-10 weeks old when placed on study. Rats were fasted overnight and mice were fasted for 4 hours before they were dosed. Groups of five males and five females were administered a single dose of 0, 500, 1,000, 2,000, 4,000, or 8,000 mg/kg methyl carbamate in deionized water by gavage. The selection of doses was based on the published oral LD_{50} value of 6.2 g/kg for mice (IARC, 1976). Rats and mice were observed twice per day and were weighed on day 0 and 15. A necropsy was performed on all animals. Details of animal maintenance are presented in Table 5.

SIXTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF METHYL CARBAMATE

Single-Administration Studies	Sixteen-Day Studies	Thirteen-Week Studies	Six-, Twelve-, and Eighteen-Month Studies	Two-Year Studies
EXPERIMENTAL DESIGN				
Size of Study Groups				
5 males and 5 females of each species	5 males and 5 females of each species	10 males and 10 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses				
0, 500, 1,000, 2,000, 4,000, or 8,000 mg/kg methyl carbamate in deionized water by gavage; dose vol--10 ml/kg for high dose rats and all mice; 5 ml/kg for the other rats	0, 250, 500, 1,000, 2,000, or 4,000 mg/kg methyl carbamate in distilled water by gavage; dose vol--rats: 5 ml/kg; mice: 10 ml/kg	Rats--male: 0, 50, 100, 200, 400, or 800 mg/kg methyl carbamate in distilled water by gavage; female: 0, 62.5, 125, 250, 500, or 1,000 mg/kg; dose vol--5 ml/kg; mice--male: 0, 93.75, 187.5, 375, 750, or 1,500 mg/kg; female: 0, 125, 250, 500, 1,000, or 2,000 mg/kg; dose vol--10 ml/kg	Rats--0 or 400 mg/kg methyl carbamate in distilled water by gavage; dose vol--5 ml/kg; mice--0 or 1,000 mg/kg methyl carbamate in distilled water by gavage; dose vol--10 ml/kg	Rats--0, 100, or 200 mg/kg methyl carbamate in distilled water by gavage; dose vol--5 ml/kg; mice--0, 500, or 1,000 mg/kg methyl carbamate in distilled water by gavage; dose vol--10 ml/kg
Date of First Dose				
10/5/79	Rats--1/15/80; mice--1/14/80	6/2/80	Rats--6/29/81; mice--6/22/81	Rats--6/29/81; mice--6/22/81
Date of Last Dose				
Not applicable	Rats--1/30/80; mice--1/29/80	8/29/80	Rats--6-mo studies, 1/4/82; 12-mo studies, 7/18/82; 18-mo studies, 1/11/83; mice--6-mo studies, 1/4/82; 12-mo studies, 7/19/82; 18-mo studies, 1/10/83	Rats--6/17/83; mice--6/10/83
Duration of Dosing				
Single dose	Consecutive weekdays for 12 doses over 16 d	5 d/wk for 13 wk	5 d/wk for 6, 12, or 18 mo	5 d/wk for 103 wk
Type and Frequency of Observation				
Weighed on d 0 and 15	Observed 2 × d; weighed on d 1, 8, and 15	Observed 2 × d; weighed initially and before they were killed	Observed 2 × d; weighed 1 × wk for 13 wk, 1 × 4 wk thereafter	Observed 2 × d; weighed 1 × wk for 12 wk, 1 × 4 wk until wk 100, and then 1 × wk
Necropsy and Histologic Examination				
Necropsy performed on all animals	Necropsy performed on vehicle controls and male rats that received 1,000, 2,000, or 4,000 mg/kg, all female rats, and all mice; histologic exam performed on rats that received 500 mg/kg and mice that received 1,000 mg/kg	Necropsy performed on all animals. Liver of all animals weighed. Histologic exam performed on vehicle control and high dose rats and mice. Tissues examined: spleen, heart, mesenteric fat, kidneys, lung, liver, thyroid gland, pancreas, uterus, testes, bone marrow, coronary artery, thymus, parotid gland, salivary glands, pituitary gland, and adrenal glands.	6-mo studies--necropsy and histologic exam performed on all animals; liver and adrenal glands weighed at necropsy for all animals. Tissues examined: liver in mice; liver, spleen, salivary glands, pancreas, testes, adrenal glands, and bone marrow in rats. 12-mo studies--necropsy performed on all animals; tissues examined histologically: liver in mice; liver, salivary glands,	Necropsy performed on all animals; histologic exam performed on all vehicle control and high dose animals; tissues examined: salivary glands, lung, heart, thyroid gland, pancreas, mesenteric lymph nodes, spleen, kidneys, brain, pituitary gland, aorta, coronary, cerebral, and mesenteric arteries, liver,

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF METHYL CARBAMATE (Continued)

Single-Administration Studies	Sixteen-Day Studies	Thirteen-Week Studies	Six-, Twelve-, and Eighteen-Month Studies	Two-Year Studies
Necropsy and Histologic Examination (Continued)				
		Tissues of lower dose groups examined: 400 mg/kg rats--spleen, liver, thymus, parotid gland, salivary gland, pancreas, bone marrow, and testes; 200 mg/kg rats--liver, bone marrow, and testes; mice--liver of all males, thyroid gland of 750 mg/kg dose group	and testes in rats; grossly abnormal lesions in all animals. 18-mo studies--necropsy performed on all animals; histologic exam performed on liver, testes, kidneys, lungs, bone marrow, spleen, heart, eyes, and gross lesions in rats; liver in mice	trachea, esophagus, stomach, duodenum, ileum, jejunum, cecum, nasal cavity, eyes, preputial gland, hip/thigh muscle, mediastinal lymph node, thymus, adrenal glands, urinary bladder, seminal vesicles, prostate/testes/epididymis or ovaries/uterus, inguinal lymph node, gallbladder (mice), urethra, skin, intervertebral disc, penis, bone marrow. Tissues examined histologically in low dose rats: liver, spleen, adrenal glands, eye, pituitary gland, and uterus. Tissues examined histologically in low dose mice: lung, liver, kidney, and pituitary gland (female only)
ANIMALS AND ANIMAL MAINTENANCE				
Strain and Species				
F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice
Animal Source				
Charles River Breeding Laboratories (Portage, MI)	Same as single-administration studies	Charles River Breeding Laboratories (Kingston, NY)	Frederick Cancer Research Center (Frederick, MD)	Same as 6-, 12-, and 18-month studies
Study Laboratory				
Microbiological Associates (Bethesda, MD)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Method of Animal Identification				
Ear tag	Ear punch	Ear punch	Ear tag	Ear tag
Time Held Before Study				
21 d	19 d	19 d	19 d	19 d
Age When Placed on Study				
Rats--8-9 wk; mice--8-10 wk	Rats--7-8 wk; mice--6-8 wk	Rats--7-8 wk; mice--8-9 wk	Rats--8-10 wk; mice--8 wk	8 wk
Age When Killed				
Rats--10-11 wk; mice--10-12 wk	Rats--9-10 wk; mice--8-10 wk	Rats--21-22 wk; mice--22-23 wk	Rats--6-mo studies, 34-36 wk; 12-mo studies, 62-64 wk; 18-mo studies, 89-91 wk; mice--6-mo studies, 34 wk; 12-mo studies, 62 wk; 18-mo studies, 89 wk	113 wk

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF METHYL CARBAMATE (Continued)

Single-Administration Studies	Sixteen-Day Studies	Thirteen-Week Studies	Six-, Twelve-, and Eighteen-Month Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)				
Necropsy Dates				
10/19/79	Rats--1/31/80; mice--1/30/80	Rats--9/2/80-9/3/80; mice--9/3/80-9/4/80	Rats--6-mo studies, 1/5/82-1/6/82; 12-mo studies, 7/19/82; 18-mo studies, 1/11/83; mice--6-mo studies, 1/5/82-1/6/82; 12-mo studies, 7/20/82; 18-mo studies, 1/10/83	Rats--6/27/83-7/1/83; mice--6/20/83-6/22/83
Method of Animal Distribution				
Distributed to weight classes; assigned to cages according to a table of random numbers and then assigned to groups according to a table of random numbers	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Feed				
Purina Lab Block® (Ralston Purina Co., St. Louis, MO); available ad libitum	NIH 07 Rat and Mouse Ration (Zeigler Bros., Gardners, PA); available ad libitum	Same as 16-d studies	Same as 16-d studies	Same as 16-d studies
Bedding				
Hardwood chips (P.J. Murphy Co., Moonachie, NJ)	Hardwood chips (P.J. Murphy Forest Products Corp., Rochelle Park, NJ)	Same as 16-d studies	Same as 16-d studies	Same as 16-d studies
Water				
Tap water in glass bottles; available ad libitum	Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as 16-d studies	Same as 16-d studies	Same as 16-d studies
Cages				
Polycarbonate (Lab Products, Rochelle Park, NJ, or Hazleton Systems, Aberdeen, MD)	Same as single-administration studies	Polycarbonate (Lab Products, Rochelle Park, NJ)	Same as single-administration studies	Polycarbonate (Lab Products, Rochelle Park, NJ)
Cage Filters				
Bonnet (Snow Filtration, Cincinnati, OH)	Reemay spun-bonded polyester filters (Snow Filtration, Cincinnati, OH)	Same as 16-d studies	Same as 16-d studies	Same as 16-d studies
Animals per Cage				
5	5	5	5	5
Other Chemicals on Study in the Same Room				
None	None	None	None	None

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF METHYL CARBAMATE (Continued)

Single-Administration Studies	Sixteen-Day Studies	Thirteen-Week Studies	Six-, Twelve-, and Eighteen-Month Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)				
Animal Room Environment				
Temp--60°-80° F; humidity--50%-90%; fluorescent light 12 h/d; 12-15 room air changes/h	Temp--54°-81° F; humidity--55%-80%; fluorescent light 12 h/d; 12-15 room air changes/h	Temp--65°-85° F; humidity--50%-90%; fluorescent light 12 h/d; 12-15 room air changes/h	Temp--66°-84° F; humidity--23%-84%; fluorescent light 12 h/d; 12-15 room air changes/h	Same as 6-, 12-, and 18-month studies

Laboratories and held for 19 days before the studies began. Rats were 7-8 weeks old and mice were 6-8 weeks old when placed on study. Groups of five males and five females were administered 12 doses of 0, 250, 500, 1,000, 2,000, or 4,000 mg/kg methyl carbamate in water by gavage over 16 days. Rats and mice were observed two times per day and were weighed on days 1, 8, and 15. A necropsy was performed on male rats in the vehicle control, 1,000, 2,000, and 4,000 mg/kg groups; on all female rats; and on all mice.

THIRTEEN-WEEK STUDIES

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

Five- to six-week-old male and female F344/N rats and 6- to 7-week-old male and female B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories, observed for 19 days, distributed to weight classes, and assigned to cages according to a table of random numbers. The cages were assigned to dosed and vehicle control groups according to a table of random numbers. Groups of 10 male rats were administered 0, 50, 100, 200, 400, or 800 mg/kg methyl carbamate in distilled water by gavage, 5 days per week for 13 weeks. Groups of 10 female rats were administered 0, 62.5, 125, 250, 500, or 1,000 mg/kg methyl carbamate; groups of 10 male mice were administered 0, 93.75, 187.5, 375, 750, or 1,500 mg/kg; and groups of 10 female mice were administered 0, 125, 250, 500, 1,000, or 2,000 mg/kg on the same schedule. Animals were housed five per cage. Feed and water were available ad libitum. Animals were checked two times per day; moribund animals were killed. Individual animal weights were recorded at the beginning of the studies and before the animals were killed. At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 5.

SIX-, TWELVE-, AND EIGHTEEN-MONTH AND TWO-YEAR STUDIES

Study Design

Groups of 50 male and 50 female rats were administered 0, 100, or 200 mg/kg methyl carbamate in distilled water by gavage, 5 days per week for 103 weeks. Groups of 50 male and 50 female mice were administered 0, 500, or 1,000 mg/kg methyl carbamate on the same schedule. Additional groups of 30 male and 30 female rats were administered 0 or 400 mg/kg methyl carbamate, and additional groups of 30 male and 30 female mice were administered 0 or 1,000 mg/kg methyl carbamate in distilled water by gavage, 5 days per week. Groups of 10 rats and mice of each sex were killed at 6, 12, or 18 months so that the progression of lesions could be followed.

Source and Specifications of Animals

The male and female F344/N rats and B6C3F$_1$ (C57BL/6N, female × C3H/HeN MTV$^-$, male) mice used in these studies were produced under strict barrier conditions at Frederick Cancer Research Center under a contract to the

Carcinogenesis Program. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. For the 2-year studies, animals were shipped to the study laboratory at 5 weeks of age and were quarantined for 19 days. Thereafter, a complete pathologic examination was performed on five animals of each sex and species to assess their health status. The rodents were placed on study at 8 weeks of age. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix F).

Animal Maintenance

Animals were housed five per cage; feed and water were available ad libitum. Further details of animal maintenance are given in Table 5.

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded once per week. Body weights by cage were recorded once per week for the first 12 weeks of the study and at least 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. Histopathologic examination of tissues was performed according to an "inverse pyramid" design (McConnell, 1983a,b). That is, complete histopathologic examinations (Table 5) were performed on all high dose and vehicle control animals and on low dose animals dying through month 21 of the study. In addition, histopathologic examinations were performed on all grossly visible lesions in all dose groups. Potential target organs for chemically related neoplastic and nonneoplastic effects were identified from the short-term studies or the literature and were determined by examination of the pathology data; these target organs/tissues in the lower dose group were examined histopathologically. If mortality in the highest dose group exceeded that in the vehicle control group by 15%, complete histopathologic examinations were performed on all animals in the second highest dose group in addition to those in the high dose group.

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 vehicle controls and tests for overall dose-response trends.

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

Life Table Analysis--The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the 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 vehicle control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the 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 vehicle control groups were compared in each of five time intervals: weeks 0-52, weeks 53-78, weeks 79-92, week 93 to the week before the terminal-kill period, and the terminal-kill period. The denominators of these proportions were the number of animals actually examined for tumors during the time interval. The individual time interval comparisons were then combined by the previously described method to obtain a single overall result. (See Haseman, 1984, for the computational details of both methods.) Analysis of incidental tumors based on logistic regression (Dinse and Haseman, 1986) was also used as a supplemental test in some instances. This method has the advantage of not requiring time intervals in the statistical evaluation. Except where noted, this procedure gave results similar to that of the incidental tumor test.

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

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III. RESULTS: RATS

SINGLE-ADMINISTRATION STUDIES

All rats that received 8,000 mg/kg methyl carbamate, 2/5 males and 5/5 females that received 4,000 mg/kg, and 1/5 females that received 2,000 mg/kg died before the end of the studies (Table 6). The three male rats that received 4,000 mg/kg and survived to the end of the study had rough coats until day 7. On the day of dosing, male rats that received 2,000 mg/kg were uncoordinated. Male rats that received 2,000 mg/kg had rough coats until day 4. Final mean body weights of rats that received 2,000 mg/kg were similar to those of the vehicle controls. No compound-related morphologic effects were noted at necropsy. Based on mortality data, the highest dose selected for the 16-day studies was 4,000 mg/kg.

SIXTEEN-DAY STUDIES

All rats that received 2,000 or 4,000 mg/kg methyl carbamate and 3/5 males that received 1,000 mg/kg died before the end of the studies (Table 7). Surviving male rats that received 1,000 mg/kg lost weight. Final mean body weights of females that received 1,000 mg/kg and of males that received 500 mg/kg were 13%-23% lower than those of the vehicle controls. Lacrimation, rough coats, and lethargy were observed in rats that received methyl carbamate doses of 1,000 mg/kg or higher. No compound-related histopathologic lesions were observed in the 500 mg/kg groups of rats. Based on mortality data, the highest doses selected for the 13-week studies were 800 and 1,000 mg/kg for male and female rats, respectively.

TABLE 6. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF METHYL CARBAMATE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE (d)					
0	5/5	172 ± 4	214 ± 5	+42 ± 1	--
500	5/5	151 ± 3	222 ± 5	+71 ± 2	104
1,000	5/5	160 ± 4	230 ± 4	+70 ± 3	107
2,000	5/5	153 ± 3	209 ± 3	+56 ± 1	98
4,000	(e) 3/5	160 ± 3	200 ± 5	+39 ± 4	93
8,000	(f) 0/5	145 ± 6	(g)	(g)	(g)
FEMALE (h)					
0	5/5	140 ± 4	153 ± 3	+13 ± 1	--
500	5/5	124 ± 2	147 ± 2	+23 ± 2	96
1,000	5/5	127 ± 3	154 ± 4	+27 ± 2	101
2,000	(i) 4/5	126 ± 3	147 ± 1	+24 ± 1	96
4,000	(e) 0/5	122 ± 2	(g)	(g)	(g)
8,000	(f) 0/5	121 ± 2	(g)	(g)	(g)

(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) LD_{50} value by the Spearman-Karber method: 4,287 mg/kg with a 95% confidence interval of 3,074-5,980 mg/kg
(e) Day of death: all 2
(f) Day of death: 1,2,2,2,2
(g) No data are reported due to the 100% mortality in this group.
(h) LD_{50} value by the Spearman-Karber method: 2,462 mg/kg with a 95% confidence interval of 1,876-3,231 mg/kg
(i) Day of death: 8

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

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	197 ± 6	241 ± 6	+44 ± 4	--
250	5/5	204 ± 8	236 ± 8	+32 ± 4	98
500	5/5	208 ± 8	212 ± 14	+4 ± 21	88
1,000	(d) 2/5	192 ± 8	186 ± 5	−23 ± 11	77
2,000	(e) 0/5	196 ± 7	(f)	(f)	(f)
4,000	(g) 0/5	200 ± 5	(f)	(f)	(f)
FEMALE					
0	5/5	131 ± 3	150 ± 4	+19 ± 3	--
250	5/5	128 ± 3	139 ± 1	+11 ± 3	93
500	5/5	138 ± 7	146 ± 8	+8 ± 3	97
1,000	5/5	127 ± 3	131 ± 5	+4 ± 3	87
2,000	(h) 0/5	130 ± 2	(f)	(f)	(f)
4,000	(i) 0/5	132 ± 4	(f)	(f)	(f)

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Day of death: 8,9,12
(e) Day of death: 3,3,3,4,4
(f) No data are reported due to the 100% mortality in this group.
(g) Day of death: 2,2,3,3,3
(h) Day of death: 3,3,4,4,4
(i) Day of death: all 2

THIRTEEN-WEEK STUDIES

Five of 10 males that received 800 mg/kg and 4/10 females that received 1,000 mg/kg died before the end of the studies (Table 8). The deaths of one of the males and three of the females were gavage related. The final mean body weight of males that received 400 mg/kg was 14% lower than that of the vehicle controls, and the final mean body weight of males that received 800 mg/kg was 31% lower. The final mean body weight of females that received 1,000 mg/kg was 22% lower than that of the vehicle controls. Lethargy was observed in the 400 and 800 mg/kg groups of males and in the 500 and 1,000 mg/kg groups of females. Liver weight to body weight ratios in the two highest dose groups of male rats were significantly lower than those in the vehicle controls (Table 9).

Compound-related lesions of the liver, spleen, bone marrow, and testis were observed in the two highest dose groups of male and female rats (Table 10). Toxic hepatitis occurred predominantly in periportal areas but sometimes extended to encompass the entire liver lobules, and it was characterized by necrosis, hyperchromasia, atypical nuclei, and abnormal mitoses.

Dose Selection Rationale: Because of the reduction in mean body weight gain and the incidence of histopathologic lesions observed in the 13-week studies, doses selected for rats for the 2-year studies were 100 and 200 mg/kg methyl carbamate administered in water by gavage 5 days per week.

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

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	134 ± 3	353 ± 5	+219 ± 6	--
50	10/10	134 ± 3	347 ± 5	+213 ± 6	98
100	10/10	135 ± 3	337 ± 10	+202 ± 9	95
200	10/10	132 ± 3	335 ± 7	+203 ± 9	95
400	10/10	135 ± 2	304 ± 7	+169 ± 7	86
800	(d) 5/10	136 ± 3	242 ± 17	+104 ± 16	69
FEMALE					
0	10/10	108 ± 2	197 ± 3	+89 ± 3	--
62.5	10/10	114 ± 1	201 ± 3	+87 ± 3	102
125	10/10	110 ± 2	192 ± 4	+82 ± 3	97
250	10/10	113 ± 1	193 ± 3	+80 ± 3	98
500	10/10	115 ± 1	191 ± 2	+76 ± 3	97
1,000	(e) 6/10	109 ± 2	154 ± 5	+45 ± 6	78

(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: 3,4,4,9,12
(e) Week of death: 1,8,10,13

TABLE 9. ABSOLUTE AND RELATIVE LIVER WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF METHYL CARBAMATE (a)

Dose (mg/kg)	No. Examined (b)	Necropsy Body Weight (grams)	Liver Weight (mg)	Liver Weight/Necropsy Body Weight (mg/g)
MALE				
0	10	357 ± 17.3	16,568 ± 1,239	46.5 ± 3.67
50	9	351 ± 15.8	15,984 ± 2,069	45.5 ± 5.08
100	10	345 ± 24.1	15,458 ± 2,489	44.6 ± 5.02
200	10	336 ± 23.3	14,769 ± 1,690	44.0 ± 4.90
400	10	(c) 307 ± 24.8	(c) 11,530 ± 1,758	(c) 37.4 ± 3.92
800	5	(c) 257 ± 34.9	(c) 9,712 ± 1,329	(c) 38.0 ± 3.04
FEMALE				
0	10	200 ± 9.9	7,744 ± 875	38.6 ± 2.85
62.5	10	203 ± 11.6	7,838 ± 770	38.7 ± 2.95
125	10	192 ± 11.8	7,350 ± 647	38.2 ± 1.86
250	10	193 ± 9.4	7,032 ± 967	36.4 ± 4.98
500	10	193 ± 6.5	(d) 6,834 ± 418	35.3 ± 1.98
1,000	6	(c) 155 ± 20.9	(c) 5,583 ± 496	36.4 ± 4.65

(a) Mean ± standard deviation; P values vs. the vehicle controls by Dunnett's test (Dunnett, 1955).
(b) Number of animals with both liver weight and final body weight measured
(c) $P<0.01$
(d) $P<0.05$

TABLE 10. INCIDENCE OF RATS WITH LESIONS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF METHYL CARBAMATE (a)

Site/Lesion	Male				Female			
	0	200 mg/kg	400 mg/kg	800 mg/kg	0	250 mg/kg	500 mg/kg	1,000 mg/kg
Liver								
Toxic hepatitis	0/10	0/10 (1/10)	7/10 (9/10)	10/10 (8/10)	0/10	0/10	4/10 (6/10)	10/10
Spleen								
Brown isotropic pigment in macrophages	0/10	(b)	10/10	8/9	0/10	(b)	10/10	9/10
Bone marrow								
Atrophy	0/10	(b)	0/10	8/10 (9/10)	0/10	0/10	6/10 (5/10)	8/9
Testis								
Bilateral atrophy	0/10	0/10	1/10	9/10				

(a) Incidence in parentheses is that reported by Quality Assurance Pathologist.
(b) Not examined

SIX-MONTH STUDIES

None of the rats died (Table 11). The relative adrenal gland weight of dosed males and females and the relative liver weight of dosed females were significantly lower than those of the vehicle controls (Table 12). Hepatotoxicity consisting of nodular regeneration and cytologic alteration was observed in dosed groups. Neoplastic nodules of the liver were observed in 6/10 dosed males and 5/10 dosed females but not in any of the vehicle controls (Table 13).

TWELVE-MONTH STUDIES

One dosed male rat died at week 32 (Table 11). Cytologic alteration of the hepatocytes was observed in the dosed groups of each sex. Neoplastic nodules of the liver were observed in 7/10 dosed males and 9/10 dosed females but not in any of the vehicle controls (Table 13). Hepatocellular carcinomas were observed in 8/10 dosed males and 6/10 dosed females but not in any of the vehicle controls. Testicular atrophy was observed in 10/10 dosed male rats and 2/10 vehicle control male rats.

TABLE 11. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SIX-, TWELVE-, AND EIGHTEEN-MONTH GAVAGE STUDIES OF METHYL CARBAMATE

Study	Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE						
6-month	0	10/10	180 ± 3.6	444 ± 5.8	+264 ± 6.5	--
	400	10/10	173 ± 4.2	368 ± 5.9	+195 ± 7.9	82.3
12-month	0	10/10	175 ± 5.1	501 ± 7.3	+326 ± 7.5	--
	400	(d) 9/10	173 ± 4.2	431 ± 11.5	+259 ± 11.7	86.0
18-month	0	10/10	190 ± 4.5	515 ± 12.0	+325 ± 12.6	--
	400	(e) 1/10	169 ± 5.2	368	+199	71.5
FEMALE						
6-month	0	10/10	127 ± 2.7	229 ± 5.4	+102 ± 4.2	--
	400	10/10	127 ± 3.0	214 ± 3.6	+87 ± 3.9	93.4
12-month	0	10/10	127 ± 3.1	286 ± 6.3	+159 ± 4.7	--
	400	10/10	128 ± 2.8	258 ± 6.0	+130 ± 7.0	90.2
18-month	0	10/10	133 ± 2.6	331 ± 7.3	+198 ± 8.6	--
	400	(f) 9/10	128 ± 2.5	262 ± 6.0	+133 ± 7.5	79.2

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Week of death: 32
(e) Week of death: 53,60,62,66,66,67,69,70,74
(f) Week of death: 76 (one additional death occurred during observation period)

TABLE 12. ABSOLUTE AND RELATIVE ORGAN WEIGHTS OF RATS IN THE SIX-MONTH GAVAGE STUDIES OF METHYL CARBAMATE (a)

Organ	Dose (mg/kg)	No. Examined (b)	Necropsy Body Weight (grams)	Organ Weight (mg)	Organ Weight/Necropsy Body Weight (mg/g)
MALE					
Liver	0	10	452 ± 19.4	15,948 ± 966	35.3 ± 0.91
	400	10	(c) 372 ± 19.6	(c) 12,896 ± 1,135	34.7 ± 2.40
Adrenal gland	0	9	452 ± 19.4	52.8 ± 3.27	0.117 ± 0.0054
	400	10	(c) 372 ± 19.6	(c) 36.6 ± 2.67	(c) 0.099 ± 0.0084
FEMALE					
Liver	0	10	223 ± 15.1	7,259 ± 593	32.5 ± 1.44
	400	10	213 ± 10.4	(d) 6,482 ± 540	(d) 30.3 ± 1.66
Adrenal gland	0	9	223 ± 15.1	55.9 ± 3.02	0.251 ± 0.0113
	400	10	213 ± 10.4	(c) 40.8 ± 3.33	(c) 0.191 ± 0.0153

(a) Mean ± standard deviation; P values are results of *t*-test comparisons between dosed and vehicle control groups.
(b) Number of animals with both necropsy body weight and organ weight recorded
(c) $P < 0.001$
(d) $P < 0.01$

TABLE 13. INCIDENCE OF LESIONS OF THE LIVER IN RATS IN THE SIX-, TWELVE-, AND EIGHTEEN-MONTH GAVAGE STUDIES OF METHYL CARBAMATE

Lesion	Time Interval (months)	Male		Female	
		Vehicle Control	400 mg/kg	Vehicle Control	400 mg/kg
Cytologic alteration	6	0/10	(a) 10/10	0/10	(a) 10/10
	12	2/10	(a) 10/10	3/10	(a) 10/10
	18	7/10	8/10	9/10	10/10
Neoplastic nodule	6	0/10	(a) 6/10	0/10	(b) 5/10
	12	0/10	(a) 7/10	0/10	(a) 9/10
	18	0/10	2/10	0/10	(b) 5/10
Hepatocellular carcinoma	6	0/10	0/10	0/10	0/10
	12	0/10	(a) 8/10	0/10	(a) 6/10
	18	0/10	(a) 9/10	0/10	(a) 8/10

(a) $P<0.01$ vs. controls by the Fisher exact test
(b) $P<0.05$ vs. controls by the Fisher exact test

EIGHTEEN-MONTH STUDIES

Nine of 10 dosed males and 2/10 dosed females died (Table 11). Neoplastic nodules of the liver were observed in 2/10 dosed males and 5/10 dosed females but not in any of the vehicle controls. Hepatocellular carcinomas were observed in 9/10 dosed males and 8/10 dosed females but not in any vehicle controls (Table 13). Metastases were seen in 7/10 males. Bone marrow atrophy was observed in 5/10 dosed males but not in any male vehicle controls or in any females. Retinal atrophy was observed in 10/10 dosed males and 6/10 dosed females. Cataracts were observed in 6/10 dosed males and 1/10 dosed females. The severity of chronic nephropathy in dosed rats was greater than that in the vehicle controls.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male rats were generally 5%-9% lower than those of the vehicle controls after week 20 (Table 14 and Figure 3). Mean body weights of high dose female rats were 5%-8% lower than those of the vehicle controls after week 56. No compound-related clinical signs were observed.

TABLE 14. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF METHYL CARBAMATE

Weeks on Study	Vehicle Control		100 mg/kg			200 mg/kg		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors
MALE								
2	230	50	225	98	50	229	100	50
3	265	50	257	97	50	258	97	50
4	283	50	276	98	50	277	98	50
5	294	50	288	98	50	285	97	50
6	304	50	298	98	50	294	97	50
7	324	50	316	98	50	308	95	50
8	334	50	325	97	50	323	97	50
9	343	50	331	97	50	329	96	50
10	353	50	341	97	50	340	96	50
11	364	50	353	97	50	346	95	50
12	373	50	360	97	50	358	96	50
13	378	50	367	97	50	363	96	50
16	398	50	386	97	50	399	100	50
20	426	50	408	96	50	402	94	50
24	436	50	418	96	50	411	94	50
28	452	50	438	97	49	428	95	50
32	464	50	445	96	49	438	94	50
36	477	50	461	97	48	450	94	50
40	484	50	467	96	48	458	95	50
44	491	50	473	96	48	466	95	49
48	490	50	472	96	48	465	95	49
52	496	50	477	96	48	465	94	49
56	499	50	480	96	48	467	94	49
60	499	50	481	96	48	466	93	49
64	504	50	487	97	48	470	93	49
68	509	49	483	95	48	471	93	46
72	511	49	482	94	48	466	91	46
76	513	49	486	95	46	467	91	46
80	512	48	491	96	45	469	92	45
84	496	48	479	97	45	468	94	43
88	474	43	466	98	44	453	96	42
92	481	34	459	95	38	451	94	39
96	476	28	454	95	34	431	91	39
100	462	23	445	96	30	419	91	34
102	433	22	427	99	29	409	94	31
103	428	19	427	100	26	402	94	30
FEMALE								
2	151	50	154	102	50	153	101	50
3	169	50	168	99	50	167	99	50
4	175	50	175	100	50	173	99	50
5	180	50	179	99	50	177	98	50
6	187	50	185	99	50	184	98	50
7	190	50	189	99	50	187	98	50
8	194	50	185	95	50	192	99	50
9	197	50	192	97	50	194	98	50
10	198	50	--	--	--	--	--	--
11	204	50	202	99	50	196	96	50
12	204	50	206	101	50	205	100	50
13	203	50	205	101	50	206	101	50
16	213	50	215	101	50	211	99	50
20	222	50	223	100	50	222	100	50
24	225	50	224	100	49	223	99	50
28	238	50	228	96	49	230	97	50
32	241	50	240	100	49	236	98	50
36	246	50	249	101	49	242	98	50
40	253	50	258	102	49	251	99	50
44	263	50	266	101	49	260	99	50
48	266	50	271	102	49	260	98	50
52	283	49	287	101	49	273	96	50
56	291	49	294	101	49	276	95	50
60	303	48	302	100	49	286	94	50
64	313	48	310	99	48	288	92	49
68	323	48	320	99	47	300	93	47
72	328	48	327	100	47	302	92	47
76	333	46	328	98	47	311	93	46
80	337	45	340	101	43	316	94	46
84	337	43	344	102	43	321	95	46
88	338	43	332	98	43	315	93	44
92	338	38	342	101	40	319	94	40
96	341	37	337	99	39	324	95	37
100	341	30	340	100	37	320	94	35
102	341	30	338	99	37	316	93	35
103	338	29	341	101	36	320	95	35

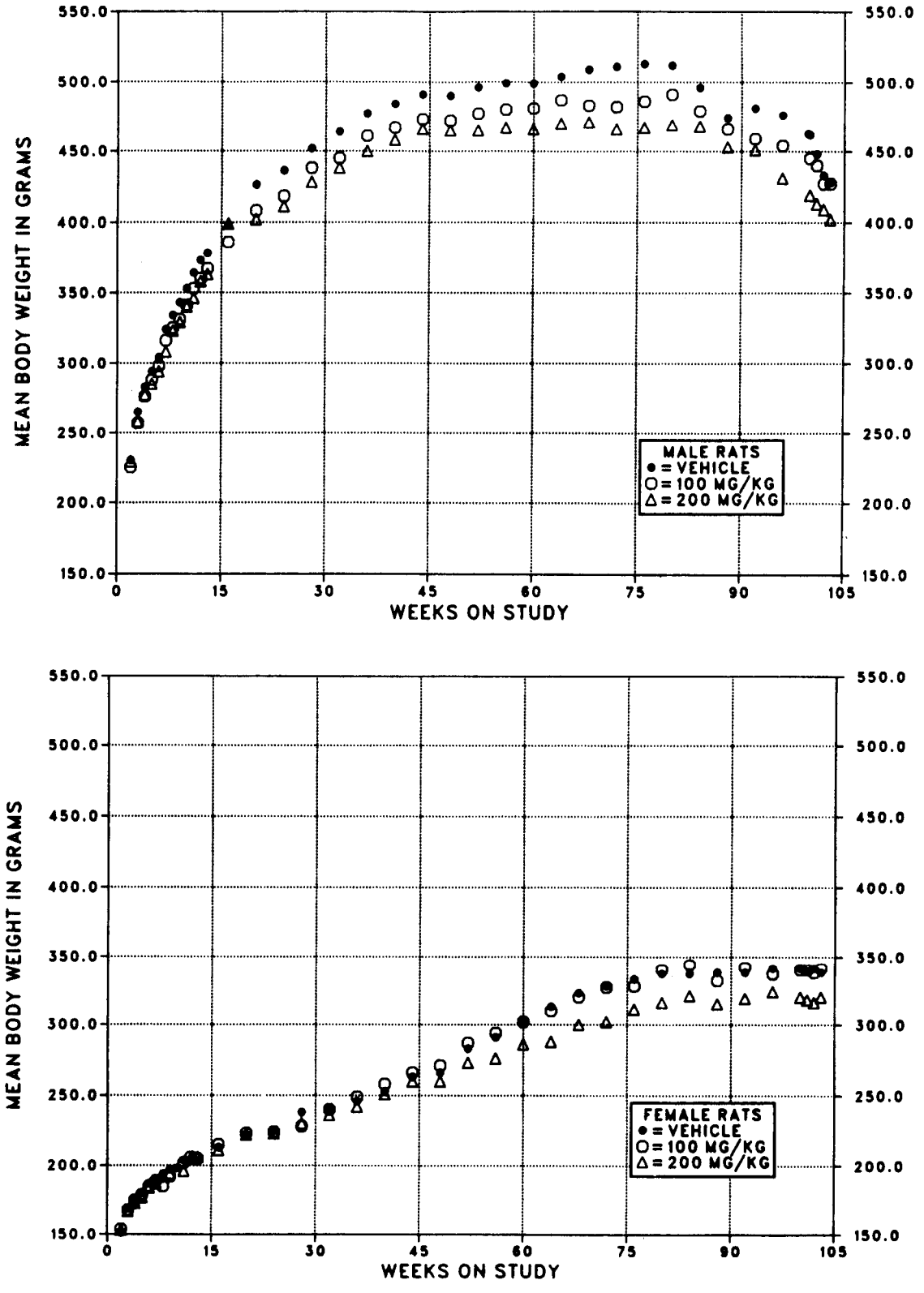

FIGURE 3. GROWTH CURVES FOR RATS ADMINISTERED METHYL CARBAMATE IN WATER BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats administered methyl carbamate by gavage at the doses used in these studies and for vehicle controls are shown in Table 15 and in the Kaplan and Meier curves in Figure 4. No significant differences in survival were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences in rats of neoplastic or nonneoplastic lesions of the liver, hematopoietic system, spleen, anterior pituitary gland, adrenal gland, mammary gland, eye, harderian gland, and heart.

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

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

TABLE 15. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF METHYL CARBAMATE

	Vehicle Control	100 mg/kg	200 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	30	24	20
Accidentally killed	1	0	1
Killed at termination	19	26	29
Survival P values (c)	0.064	0.302	0.077
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	21	14	14
Accidentally killed	0	0	1
Killed at termination	29	36	34
Died during termination period	0	0	1
Survival P values (c)	0.193	0.238	0.240

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

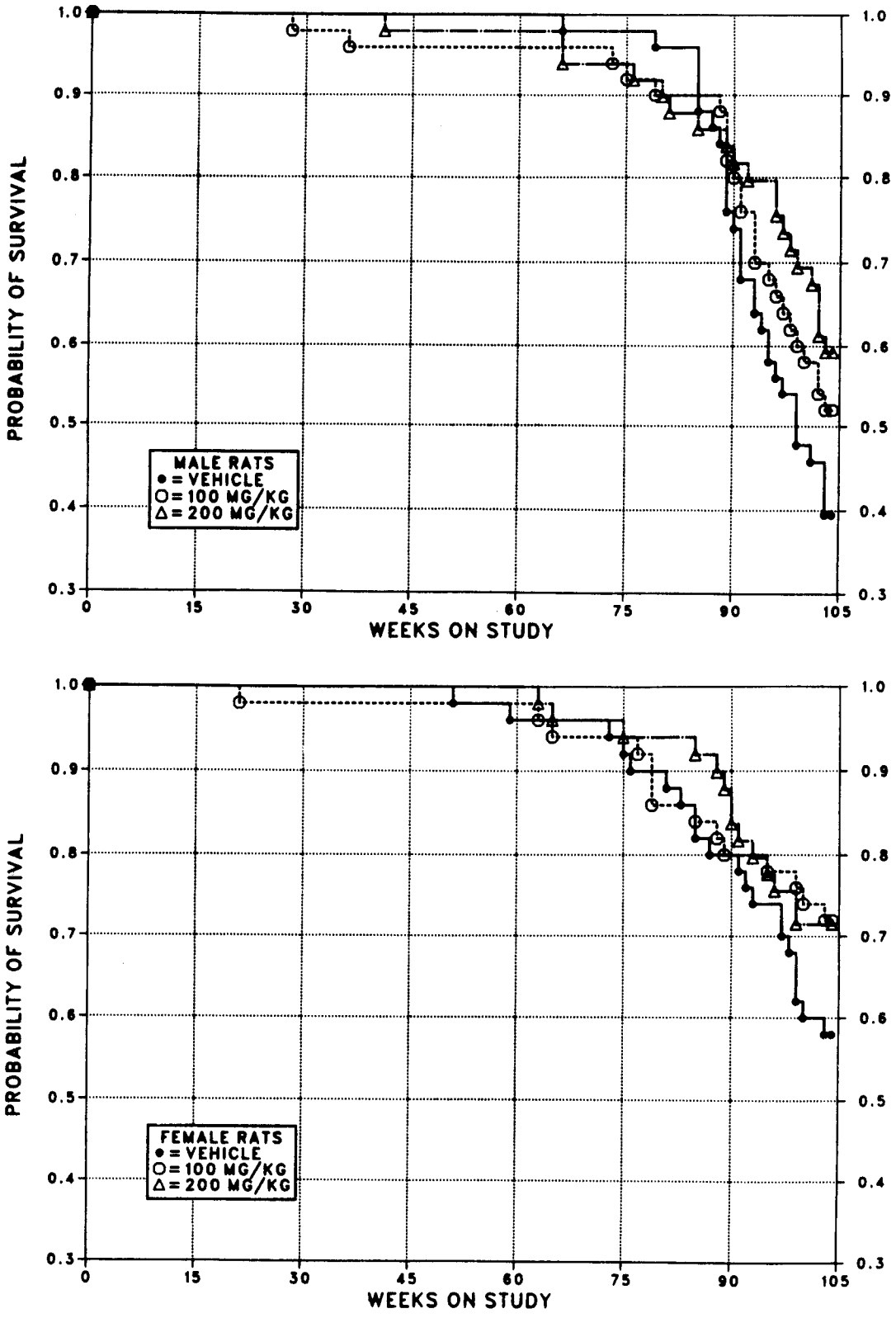

FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED METHYL CARBAMATE IN WATER BY GAVAGE FOR TWO YEARS

Liver: Chronic focal inflammation and cytologic alteration were observed at increased incidences in high dose rats of each sex (Table 16). Cytologic alteration consisted of foci or areas of hepatocytes showing increased cytoplasmic basophilic or eosinophilic staining. These staining properties are associated with increased amounts of cellular organelles including rough and smooth endoplasmic reticulum. Cytologic alteration was generally more extensive in high dose rats. Hyperplasia of hepatocytes was observed at increased incidences in dosed males and high dose females.

Hepatocellular carcinomas in male rats occurred with a significant positive trend by the incidental tumor test; the incidences in the dosed groups were not significantly different from that in the vehicle controls (Table 17). The incidence of neoplastic nodules or hepatocellular carcinomas (combined) in male rats was significantly lower in the low dose group than in the vehicle controls; the incidence in the high dose group was not significantly different from that in the vehicle controls. Neoplastic nodules and neoplastic nodules or hepatocellular carcinomas (combined) in female rats occurred with significant positive trends; the incidence of neoplastic nodules or hepatocellular carcinomas (combined) in high dose female rats was significantly greater than that in the vehicle controls.

TABLE 16. NUMBER OF RATS WITH LIVER LESIONS IN THE TWO-YEAR GAVAGE STUDIES OF METHYL CARBAMATE

Lesion	Male			Female		
	0	100 mg/kg	200 mg/kg	0	100 mg/kg	200 mg/kg
No. examined	50	50	49	50	50	49
Chronic focal inflammation	2	3	9	13	17	31
Cytologic alteration	14	11	30	25	40	46
Hyperplasia	5	11	12	6	2	16
Neoplastic nodule	3	0	3	0	0	5
Hepatocellular carcinoma	1	0	4	0	0	2

TABLE 17. ANALYSIS OF LIVER LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF METHYL CARBAMATE (a)

	Vehicle Control	100 mg/kg	200 mg/kg
MALE			
Hyperplasia			
Overall Rates	5/50 (10%)	11/50 (22%)	12/49 (24%)
Neoplastic Nodule			
Overall Rates	3/50 (6%)	0/50 (0%)	3/49 (6%)
Hepatocellular Carcinoma			
Overall Rates	1/50 (2%)	0/50 (0%)	4/49 (8%)
Adjusted Rates	4.5%	0.0%	10.4%
Terminal Rates	0/19 (0%)	0/26 (0%)	1/29 (3%)
Week of First Observation	103		89
Life Table Tests	P=0.118	P=0.459N	P=0.256
Incidental Tumor Tests	P=0.033	P=0.545N	P=0.072
Neoplastic Nodule or Hepatocellular Carcinoma (b)			
Overall Rates	4/50 (8%)	0/50 (0%)	7/49 (14%)
Adjusted Rates	19.6%	0.0%	18.7%
Terminal Rates	3/19 (16%)	0/26 (0%)	3/29 (10%)
Week of First Observation	103		80
Life Table Tests	P=0.285	P=0.033N	P=0.444
Incidental Tumor Tests	P=0.129	P=0.042N	P=0.211
FEMALE			
Hyperplasia			
Overall Rates	6/50 (12%)	2/50 (4%)	16/49 (33%)
Neoplastic Nodule			
Overall Rates	0/50 (0%)	0/50 (0%)	5/49 (10%)
Adjusted Rates	0.0%	0.0%	14.3%
Terminal Rates	0/29 (0%)	0/36 (0%)	5/35 (14%)
Week of First Observation			104
Life Table Tests	P=0.008	(c)	P=0.051
Incidental Tumor Tests	P=0.008	(c)	P=0.051
Hepatocellular Carcinoma			
Overall Rates	0/50 (0%)	0/50 (0%)	2/50 (4%)
Neoplastic Nodule or Hepatocellular Carcinoma (d)			
Overall Rates	0/50 (0%)	0/50 (0%)	6/49 (12%)
Adjusted Rates	0.0%	0.0%	16.4%
Terminal Rates	0/29 (0%)	0/36 (0%)	5/35 (14%)
Week of First Observation			91
Life Table Tests	P=0.004	(c)	P=0.029
Incidental Tumor Tests	P=0.003	(c)	P=0.026

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix A, Table A3 (footnotes).
(b) Historical incidence in water gavage controls in NTP studies (mean ± SD): 9/150 (6% ± 4%); historical incidence in untreated controls: 101/1,969 (5% ± 5%)
(c) No P value is reported because no tumors were observed in the vehicle control and 100 mg/kg groups.
(d) Historical incidence in water gavage controls in NTP studies (mean ± SD): 5/149 (3% ± 3%); historical incidence in untreated controls: 59/2,015 (3% ± 3%)

Hematopoietic System: Mononuclear cell leukemia in male and female rats occurred with significant negative trends by the life table test; the incidence of mononuclear cell leukemia in high dose male rats was significantly lower than that in the vehicle controls (Table 18).

Spleen: Pigmentation (hemosiderin) was observed at increased incidences in high dose rats of each sex (male: vehicle control, 7/50; low dose, 6/50; high dose, 13/49; female: 20/50; 25/50; 40/50).

Anterior Pituitary Gland: Cysts were observed at increased incidences in low dose male and low dose female rats (male: vehicle control, 0/50; low dose, 6/49; high dose, 1/50; female: 2/50; 13/50; 5/49). Adenomas and adenomas or carcinomas (combined) occurred with significant negative trends in male rats, and the incidences in the dosed groups were significantly lower than those in the vehicle controls (Table 19).

Adrenal Gland: Pheochromocytomas occurred in male rats with a significant negative trend, and the incidences in the dosed groups were significantly lower than that in the vehicle controls (Table 20).

TABLE 18. ANALYSIS OF MONONUCLEAR CELL LEUKEMIA IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF METHYL CARBAMATE (a)

	Vehicle Control	100 mg/kg	200 mg/kg
MALE			
Overall Rates	23/50 (46%)	30/50 (60%)	18/50 (36%)
Adjusted Rates	65.5%	76.0%	48.2%
Terminal Rates	9/19 (47%)	17/26 (65%)	11/29 (38%)
Week of First Observation	85	73	76
Life Table Tests	P=0.028N	P=0.454	P=0.047N
Incidental Tumor Tests	P=0.188N	P=0.111	P=0.301N
FEMALE			
Overall Rates	17/50 (34%)	13/50 (26%)	10/50 (20%)
Adjusted Rates	43.8%	29.8%	24.3%
Terminal Rates	9/29 (31%)	7/36 (19%)	5/35 (14%)
Week of First Observation	73	63	88
Life Table Tests	P=0.047N	P=0.159N	P=0.060N
Incidental Tumor Tests	P=0.092N	P=0.319N	P=0.116N

(a) In the low dose groups, all livers and spleens--but few lymph nodes, thymuses, small intestines or bone marrow sites--were examined.

TABLE 19. ANALYSIS OF ANTERIOR PITUITARY GLAND LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF METHYL CARBAMATE

	Vehicle Control	100 mg/kg	200 mg/kg
Hyperplasia			
Overall Rates	4/50 (8%)	8/49 (16%)	8/50 (16%)
Adenoma			
Overall Rates	26/50 (52%)	17/49 (35%)	9/50 (18%)
Adjusted Rates	77.0%	52.3%	26.5%
Terminal Rates	12/19 (63%)	11/25 (44%)	6/29 (21%)
Week of First Observation	66	88	66
Life Table Tests	P<0.001N	P=0.014N	P<0.001N
Incidental Tumor Tests	P<0.001N	P=0.058N	P<0.001N
Carcinoma			
Overall Rates	3/50 (6%)	1/49 (2%)	1/50 (2%)
Adenoma or Carcinoma (a)			
Overall Rates	29/50 (58%)	18/49 (37%)	10/50 (20%)
Adjusted Rates	81.1%	53.4%	29.7%
Terminal Rates	13/19 (68%)	11/25 (44%)	7/29 (24%)
Week of First Observation	66	88	66
Life Table Tests	P<0.001N	P=0.007N	P<0.001N
Incidental Tumor Tests	P<0.001N	P=0.035N	P<0.001N

(a) Historical incidence in water gavage controls in NTP studies (mean ± SD): 51/150 (34% ± 9%); historical incidence in untreated controls: 428/1,861 (23% ± 11%)

TABLE 20. ANALYSIS OF ADRENAL GLAND LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF METHYL CARBAMATE

	Vehicle Control	100 mg/kg	200 mg/kg
Medullary Hyperplasia			
Overall Rates	18/50 (36%)	22/49 (45%)	20/50 (40%)
Pheochromocytoma (a)			
Overall Rates	25/50 (50%)	17/49 (35%)	13/50 (26%)
Adjusted Rates	82.5%	49.9%	41.5%
Terminal Rates	14/19 (74%)	10/26 (38%)	11/29 (38%)
Week of First Observation	85	89	92
Life Table Tests	P<0.001N	P=0.013N	P<0.001N
Incidental Tumor Tests	P=0.003N	P=0.054N	P=0.002N

(a) Historical incidence in water gavage controls in NTP studies (mean ± SD): 63/149 (42% ± 4%); historical incidence in untreated controls: 452/1,950 (23% ± 12%)

Mammary Gland: Fibroadenomas in female rats occurred with a significant negative trend, and the incidence in the high dose group was significantly lower than that in the vehicle controls (Table 21).

Eye: Retinal atrophy and cataracts of the crystalline lens were observed at increased incidences in high dose rats of each sex (Table 22). Osseous metaplasia of the sclera was observed at increased incidences in dosed female rats.

Harderian Gland: Inflammation was observed at increased incidences in dosed rats of each sex (Table 22).

Heart: The incidences of chronic inflammation and multifocal fibrosis in high dose female rats were greater than those in the vehicle controls (chronic inflammation: vehicle control, 7/50; low dose, 0/10; high dose, 15/50; multifocal fibrosis: 17/50; 1/10; 29/50).

TABLE 21. ANALYSIS OF MAMMARY GLAND FIBROADENOMAS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF METHYL CARBAMATE (a)

	Vehicle Control	100 mg/kg	200 mg/kg
Overall Rates	15/50 (30%)	11/50 (22%)	6/50 (12%)
Adjusted Rates	44.3%	28.7%	17.1%
Terminal Rates	11/29 (38%)	9/36 (25%)	6/35 (17%)
Week of First Observation	83	88	104
Life Table Tests	P=0.006N	P=0.114N	P=0.008N
Incidental Tumor Tests	P=0.011N	P=0.191N	P=0.014N

(a) Historical incidence in water gavage controls in NTP studies (mean ± SD): 46/149 (31% ± 11%); historical incidence in untreated controls: 582/2,021 (29% ± 10%)

TABLE 22. NUMBER OF RATS WITH OCULAR OR HARDERIAN GLAND LESIONS IN THE TWO-YEAR GAVAGE STUDIES OF METHYL CARBAMATE

	Male			Female		
Lesion	0	100 mg/kg	200 mg/kg	0	100 mg/kg	200 mg/kg
No. examined	50	50	50	50	50	50
Eye/retina atrophy	5	11	41	10	23	43
Eye/crystalline lens cataract	8	5	27	7	9	41
Eye/sclera osseous metaplasia	31	40	35	6	24	24
Harderian gland inflammation	4	11	16	7	16	30

SINGLE-ADMINISTRATION STUDIES

All mice that received 8,000 mg/kg and 1/5 males and 1/5 females that received 4,000 mg/kg died before the end of the studies (Table 23). All male mice that received 4,000 mg/kg had rough hair coats through day 4. No compound-related clinical signs were observed in mice that received 2,000 mg/kg. Based on mortality data, the highest dose selected for the 16-day studies was 4,000 mg/kg.

SIXTEEN-DAY STUDIES

All mice that received 4,000 mg/kg and all male mice and 1/5 female mice that received 2,000 mg/kg died before the end of the studies (Table 24). Male vehicle control mice lost weight. Mean body weight gain by female vehicle control mice was less than 0.3 g. Lethargy and rough coats were observed in mice that received 2,000 mg/kg and lived to the end of the studies. No compound-related histopathologic lesions were observed in mice that received 1,000 mg/kg. Based on mortality data, the highest doses selected for the 13-week studies were 1,500 and 2,000 mg/kg for the male and female mice, respectively.

THIRTEEN-WEEK STUDIES

One of 10 female mice that received 2,000 mg/kg died before the end of the studies (Table 25). The final mean body weight of males that received 1,500 mg/kg was 6% lower than that of the vehicle controls. Final mean body weights of all groups of dosed female mice were 5%-10% lower than that of the vehicle controls. Mice that received the highest dose were lethargic and had rapid breathing after they were dosed during weeks 1 and 2 (males) and weeks 1 to 3 (females). Relative liver weights of female mice that received 500, 1,000, or 2,000 mg/kg were significantly greater than that of the vehicle controls (Table 26).

TABLE 23. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF METHYL CARBAMATE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE (d)					
0	5/5	29.6 ± 2.4	32.2 ± 1.4	+2.6 ± 2.2	--
500	5/5	28.0 ± 0.6	30.4 ± 0.7	+2.4 ± 0.4	94.4
1,000	5/5	30.8 ± 0.8	29.8 ± 0.7	−1.0 ± 1.1	92.5
2,000	5/5	31.6 ± 0.7	32.6 ± 1.0	−1.0 ± 0.8	101.2
4,000	(e) 4/5	31.6 ± 0.4	29.5 ± 0.9	−2.5 ± 0.9	91.6
8,000	(f) 0/5	29.6 ± 0.7	(g)	(g)	(g)
FEMALE (d)					
0	5/5	20.8 ± 0.5	23.0 ± 0.4	+2.2 ± 0.2	--
500	5/5	19.2 ± 0.5	21.8 ± 0.9	+2.6 ± 0.7	94.8
1,000	5/5	22.4 ± 0.7	21.8 ± 0.5	−0.6 ± 0.4	94.8
2,000	5/5	22.4 ± 0.4	21.8 ± 0.7	−0.6 ± 0.7	94.8
4,000	(f) 4/5	23.6 ± 0.4	22.8 ± 0.8	−0.8 ± 0.8	99.1
8,000	(f) 0/5	20.8 ± 0.8	(g)	(g)	(g)

(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) LD_{50} value by the Spearman-Karber method: 4,925 mg/kg with a 95% confidence interval of 3,753-6,462 mg/kg
(e) Day of death: 5
(f) Day of death: all 2
(g) No data are reported due to the 100% mortality in this group.

TABLE 24. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SIXTEEN-DAY GAVAGE STUDIES OF METHYL CARBAMATE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	25.8 ± 1.1	25.2 ± 1.3	−0.6 ± 1.4	--
250	5/5	28.0 ± 0.6	27.4 ± 1.3	−0.6 ± 1.9	108.7
500	5/5	23.4 ± 1.2	26.4 ± 1.2	+3.0 ± 2.3	104.8
1,000	5/5	27.6 ± 2.9	26.6 ± 1.3	−1.0 ± 3.0	105.6
2,000	(d) 0/5	26.4 ± 2.2	(e)	(e)	(e)
4,000	(f) 0/5	26.6 ± 1.5	(e)	(e)	(e)
FEMALE					
0	5/5	22.0 ± 0.9	22.2 ± 1.0	+0.2 ± 0.5	--
250	5/5	17.8 ± 2.4	23.0 ± 0.4	+5.2 ± 1.9	103.6
500	5/5	20.6 ± 0.7	21.0 ± 0.8	+0.4 ± 0.7	94.6
1,000	5/5	22.0 ± 0.6	21.6 ± 0.9	−0.4 ± 1.5	97.3
2,000	(g) 4/5	22.8 ± 0.8	23.0 ± 0.6	+1.0 ± 0.6	103.6
4,000	(h) 0/5	17.6 ± 3.9	(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: 3,4,5,5,6
(e) No data are reported due to the 100% mortality in this group.
(f) Day of death: 2,3,3,3,3
(g) Day of death: 6
(h) Day of death: 2,2,2,3,3

TABLE 25. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF METHYL CARBAMATE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	24.9 ± 0.2	35.5 ± 0.9	+10.6 ± 0.8	--
93.75	10/10	25.5 ± 0.3	37.7 ± 1.1	+12.2 ± 1.0	106.2
187.5	10/10	25.5 ± 0.3	38.2 ± 1.0	+12.7 ± 0.8	107.6
375	10/10	25.3 ± 0.3	36.5 ± 0.6	+11.2 ± 0.4	102.8
750	10/10	25.6 ± 0.3	36.8 ± 1.2	+11.2 ± 1.0	103.7
1,500	10/10	25.3 ± 0.5	33.3 ± 0.8	+8.0 ± 0.5	93.8
FEMALE					
0	10/10	18.8 ± 0.2	27.7 ± 0.6	+8.9 ± 0.5	--
125	10/10	18.1 ± 0.2	25.3 ± 0.3	+7.2 ± 0.3	91.3
250	10/10	18.7 ± 0.3	26.3 ± 0.8	+7.6 ± 0.6	94.9
500	10/10	18.4 ± 0.3	25.1 ± 0.6	+6.7 ± 0.5	90.6
1,000	10/10	18.8 ± 0.2	25.2 ± 0.4	+6.4 ± 0.3	91.0
2,000	(d) 9/10	19.1 ± 0.3	25.3 ± 0.5	+6.0 ± 0.5	91.3

(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: 4

TABLE 26. ABSOLUTE AND RELATIVE LIVER WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF METHYL CARBAMATE (a)

Dose (mg/kg)	No. Examined (b)	Necropsy Body Weight (grams)	Liver Weight (mg)	Liver Weight/Necropsy Body Weight (mg/g)
MALE				
0	10	36.0 ± 3.16	1,929 ± 376	53.9 ± 11.42
93.75	9	38.9 ± 3.63	2,157 ± 377	55.3 ± 7.44
187.5	10	38.6 ± 4.80	(c) 2,333 ± 376	60.4 ± 5.78
375	10	38.6 ± 2.43	2,235 ± 245	57.9 ± 5.26
750	10	38.4 ± 4.22	2,257 ± 311	58.8 ± 5.06
1,500	10	35.8 ± 2.69	2,035 ± 259	56.6 ± 4.35
FEMALE				
0	10	28.4 ± 2.27	1,441 ± 149	50.8 ± 4.35
125	10	(d) 25.4 ± 1.31	1,374 ± 73	54.2 ± 3.41
250	10	27.2 ± 2.24	1,421 ± 210	52.1 ± 4.00
500	10	26.5 ± 1.70	1,504 ± 198	(d) 56.5 ± 4.45
1,000	10	26.7 ± 1.47	1,478 ± 120	(c) 55.4 ± 2.90
2,000	9	27.2 ± 2.01	1,528 ± 193	(c) 55.9 ± 3.69

(a) Mean ± standard deviation; P values vs. the vehicle controls by Dunnett's test (Dunnett, 1955).
(b) Number of animals with both liver weight and final body weight measured
(c) $P<0.05$
(d) $P<0.01$

Minimal to mild acute multifocal hepatocellular necrosis and/or increased mitotic index were observed in the liver of dosed male mice (0/10 at 187.5 mg/kg, 3/10 at 375 mg/kg, 3/10 at 750 mg/kg, 7/10 at 1,500 mg/kg). A hepatocellular adenoma was found in one high dose male mouse.

Dose Selection Rationale: Because of lower weight gain at 1,500 mg/kg and liver lesions observed in males at 1,500 mg/kg, methyl carbamate doses selected for mice for the 2-year studies were 500 and 1,000 mg/kg administered in water by gavage 5 days per week.

SIX-MONTH STUDIES

All the mice survived to the end of the studies (Table 27). The final mean body weights of dosed male and female mice were 83% of those of the vehicle controls. No compound-related histopathologic lesions were observed. The liver weight to body weight ratios of dosed male and female mice were significantly greater than those of the vehicle controls (Table 28).

TWELVE-MONTH STUDIES

One of 10 male mice died at week 45 (Table 27). No compound-related lesions were observed.

EIGHTEEN-MONTH STUDIES

Two of 10 male vehicle controls, 3/10 dosed males, 5/10 female vehicle controls, and 3/10 dosed females died before the end of the studies (Table 27). No compound-related lesions were observed.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

The mean body weights of high dose male mice were 8%-18% lower than those of the vehicle controls after week 20 (Table 29 and Figure 5). The mean body weights of high dose female mice were more than 13% lower than those of the vehicle controls after week 16 and 30% lower after week 64. The mean body weights of low dose female mice were more than 9% lower than those of the vehicle controls after week 28 and more than 12% lower after week 68.

TABLE 27. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SIX-, TWELVE-, AND EIGHTEEN-MONTH GAVAGE STUDIES OF METHYL CARBAMATE

Study	Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE						
6-month	0	10/10	24.5 ± 0.4	39.2 ± 1.0	+14.7 ± 1.0	--
	1,000	10/10	24.3 ± 0.4	33.3 ± 0.5	+9.0 ± 0.6	84.9
12-month	0	10/10	23.6 ± 0.3	44.4 ± 0.9	+20.8 ± 0.8	--
	1,000	(d) 9/10	24.0 ± 0.6	37.8 ± 1.1	+13.8 ± 1.2	85.1
18-month	0	(e) 8/10	24.6 ± 0.6	43.3 ± 1.7	+19.0 ± 1.5	--
	1,000	(f) 7/10	24.0 ± 0.5	41.4 ± 2.0	+16.8 ± 2.3	95.6
FEMALE						
6-month	0	10/10	18.9 ± 0.1	32.0 ± 1.1	+13.1 ± 1.1	--
	1,000	10/10	19.0 ± 0.3	25.9 ± 0.5	+6.9 ± 0.5	80.9
12-month	0	10/10	19.1 ± 0.3	37.5 ± 1.7	+18.4 ± 1.8	--
	1,000	10/10	19.0 ± 0.2	30.3 ± 0.7	+11.3 ± 0.8	80.8
18-month	0	(g) 5/10	20.2 ± 0.5	42.3 ± 3.0	+22.3 ± 2.5	--
	1,000	(h) 7/10	19.6 ± 0.3	36.1 ± 1.7	+16.5 ± 1.4	85.3

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Week of death: 45
(e) Week of death: 71,80 (during observation period)
(f) Week of death: 43,65,76
(g) Week of death: 5,49,57,72,78
(h) Week of death: 51,51,67

TABLE 28. ABSOLUTE AND RELATIVE LIVER WEIGHTS OF MICE IN THE SIX-MONTH GAVAGE STUDIES OF METHYL CARBAMATE (a)

Dose (mg/kg)	Necropsy Body Weight (grams)	Liver Weight (mg)	Liver Weight/Necropsy Body Weight (mg/g)
MALE			
0	(b) 40.0 ± 3.08	1,935 ± 184	(b) 48.5 ± 4.51
1,000	(c) 33.3 ± 1.95	1,781 ± 145	(d) 53.5 ± 3.21
FEMALE			
0	32.2 ± 4.98	1,401 ± 174	43.9 ± 4.17
1,000	(e) 26.7 ± 1.16	1,439 ± 237	(e) 53.8 ± 7.89

(a) Mean ± standard deviation for 10 observations except as noted; P values are *t*-test comparisons with the vehicle controls.
(b) Nine observations
(c) $P<0.001$, relative to vehicle controls
(d) $P=0.012$, relative to vehicle controls
(e) $P<0.01$, relative to vehicle controls

TABLE 29. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF METHYL CARBAMATE

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	500 mg/kg Av. Wt. (grams)	500 mg/kg Wt. (percent of veh. controls)	500 mg/kg No. of Survivors	1,000 mg/kg Av. Wt. (grams)	1,000 mg/kg Wt. (percent of veh. controls)	1,000 mg/kg No. of Survivors
MALE								
0	25.5	50	25.5	100	50	24.3	95	50
3	29.3	50	29.7	101	50	29.7	101	50
5	30.8	50	30.9	100	50	30.4	99	50
6	31.7	50	30.2	95	50	30.7	97	50
7	33.4	50	32.6	98	50	32.5	97	50
8	34.1	50	32.7	96	50	31.8	93	50
9	34.8	50	33.6	97	50	32.6	94	50
10	35.4	50	33.8	95	50	32.8	93	49
12	36.2	50	34.5	95	50	33.3	92	49
16	36.5	49	33.6	92	49	32.0	88	49
20	38.0	49	36.4	96	49	34.6	91	49
24	40.1	49	37.9	95	49	35.7	89	49
28	41.3	49	38.7	94	49	36.4	88	49
32	42.6	49	40.3	95	49	37.4	88	49
36	43.1	49	41.3	96	49	38.5	89	48
40	43.1	49	40.7	94	49	38.2	89	45
44	44.8	49	42.7	95	49	37.8	84	45
48	46.0	49	43.2	94	48	39.4	86	45
52	43.9	49	41.4	94	48	38.1	87	42
56	44.9	48	42.6	95	48	39.5	88	41
60	46.4	47	44.9	97	47	41.7	90	41
64	46.5	44	45.0	97	47	40.5	87	38
68	45.8	41	44.4	97	44	38.1	83	38
72	45.2	39	43.4	96	43	41.5	92	35
76	45.5	39	44.9	99	43	40.8	90	34
80	45.4	38	44.6	98	42	41.8	92	34
84	44.9	38	44.0	98	42	39.5	88	33
88	45.7	37	44.3	97	42	39.1	86	32
92	45.4	35	44.1	97	42	39.0	86	31
96	45.7	32	43.7	96	41	38.6	84	28
100	46.1	29	42.7	93	40	38.4	83	28
101	45.7	29	43.1	94	37	37.8	83	28
102	45.0	28	43.3	96	37	37.9	84	28
103	45.6	28	43.0	94	36	37.5	82	28
FEMALE								
0	19.5	50	19.0	97	50	18.7	96	50
3	22.5	50	21.9	97	50	21.6	96	50
5	23.3	50	22.9	98	50	22.4	96	50
6	23.6	50	23.1	98	50	22.3	94	50
7	24.4	50	24.1	99	50	23.8	98	50
8	25.1	50	24.4	97	50	23.1	92	50
9	25.6	50	24.6	96	50	23.9	93	50
11	26.5	50	25.3	95	50	24.1	91	50
12	26.6	49	25.3	95	50	24.5	92	50
16	27.1	49	24.7	91	50	22.7	84	50
20	28.3	49	26.3	93	50	24.2	86	49
24	29.3	49	27.6	94	50	25.2	86	49
28	31.3	49	27.9	89	50	25.7	82	49
32	33.1	49	29.5	89	50	27.0	82	49
36	34.4	49	30.8	90	49	28.1	82	49
40	34.2	49	30.5	89	49	27.6	81	49
44	35.9	49	32.0	89	49	28.4	79	49
48	38.1	49	33.9	89	49	29.3	77	49
52	38.8	49	34.8	90	48	28.7	74	48
56	40.5	49	35.9	89	48	30.5	75	47
60	38.9	49	38.3	98	48	32.3	83	47
64	44.8	48	40.3	90	47	31.9	71	44
68	44.5	46	37.8	85	47	30.6	69	41
72	46.8	46	39.4	84	47	31.1	66	41
76	47.3	45	41.3	87	47	32.2	68	41
80	46.4	45	40.5	87	47	32.5	70	41
84	46.7	42	40.6	87	46	31.7	68	41
88	48.0	41	41.0	85	46	31.5	66	40
92	48.8	39	42.0	86	44	32.1	66	38
96	48.8	38	41.2	84	43	31.9	65	37
100	49.0	38	41.4	84	38	32.5	66	35
101	48.8	38	41.0	84	38	32.1	66	34
102	48.1	38	40.5	84	38	32.2	67	34
103	47.9	38	40.2	84	37	31.9	67	33

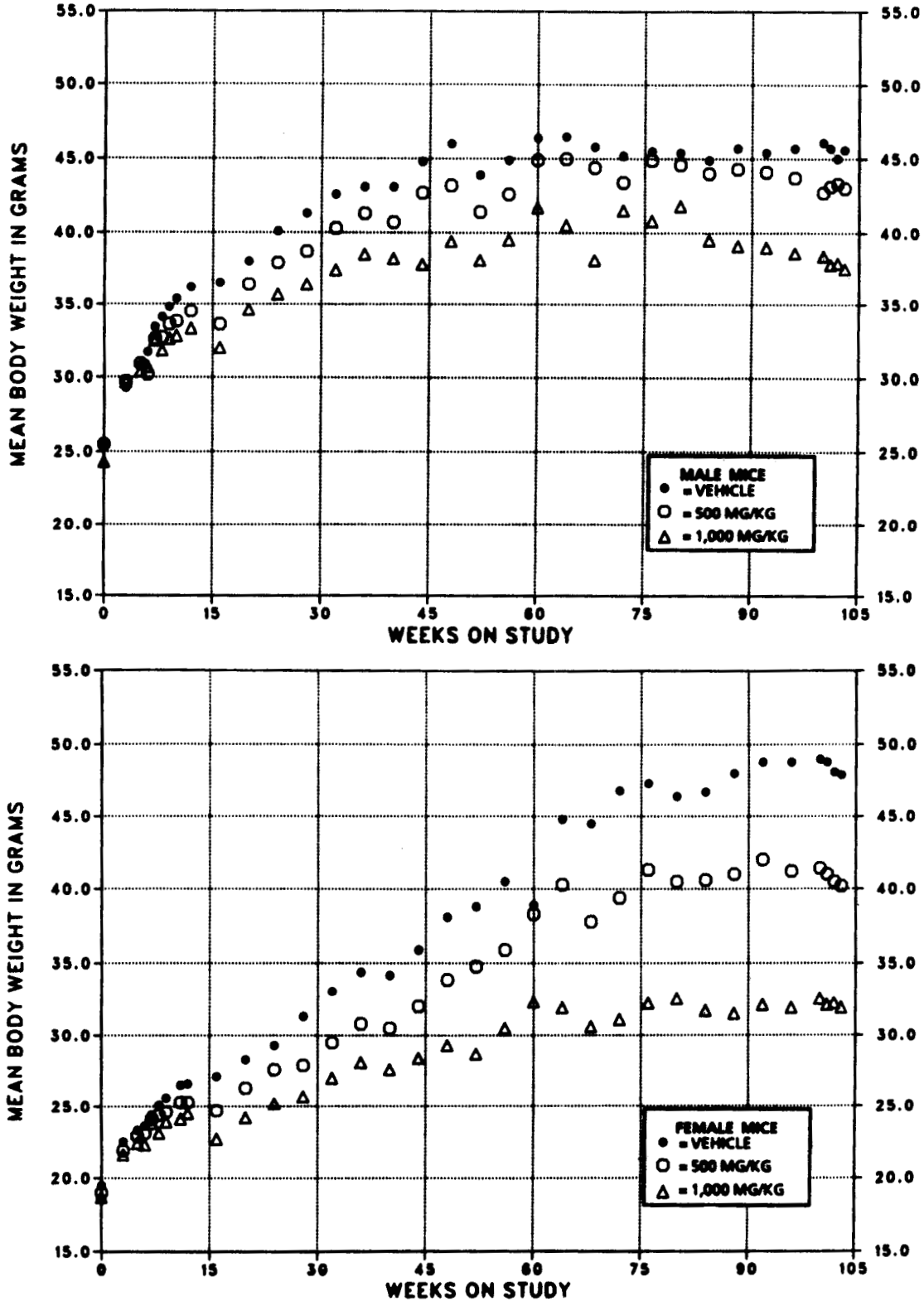

FIGURE 5. GROWTH CURVES FOR MICE ADMINISTERED METHYL CARBAMATE IN WATER BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice administered methyl carbamate by gavage at the doses used in these studies and for vehicle controls are shown in Table 30 and in the Kaplan and Meier curves in Figure 6. No significant differences in survival were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

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

Lesions in male mice are summarized in Appendix C. Histopathologic findings on neoplasms in male mice are summarized in Table C1; Table C2 gives the survival and tumor status for individual male mice. Table C3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table C3 (footnotes). Historical incidences of tumors in control male mice are listed in Table C4. Findings on nonneoplastic lesions are summarized in Table C5.

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

TABLE 30. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF METHYL CARBAMATE

	Vehicle Control	500 mg/kg	1,000 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	21	14	21
Accidentally killed	1	1	1
Killed at termination	28	35	28
Survival P values (c)	0.815	0.158	0.833
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	11	14	14
Accidentally killed	1	0	4
Killed at termination	38	36	31
Died during termination period	0	0	1
Survival P values (c)	0.535	0.795	0.599

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

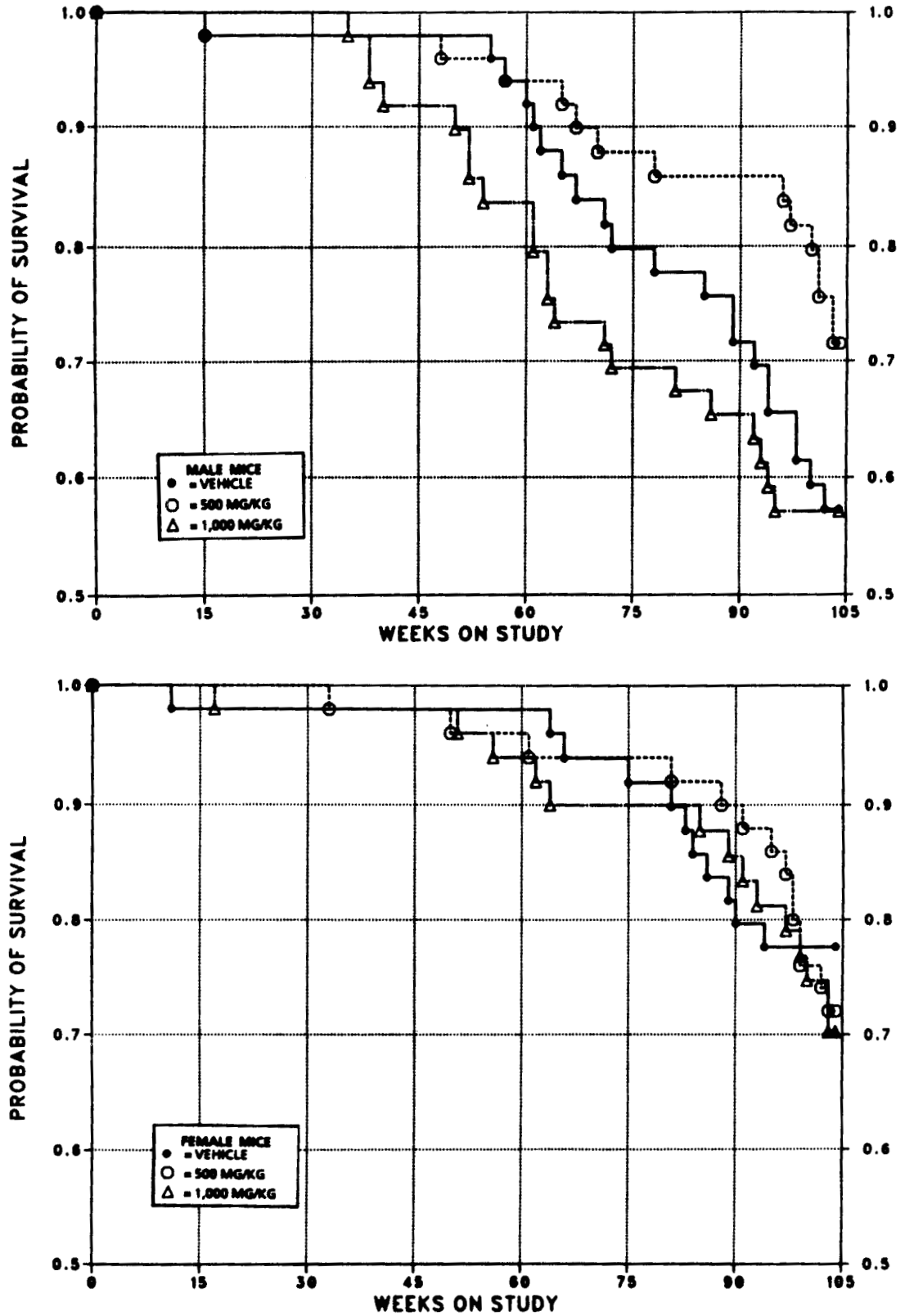

FIGURE 6. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED METHYL CARBAMATE IN WATER BY GAVAGE FOR TWO YEARS

Liver: Multinucleate giant cells were observed at increased incidences in dosed male mice (vehicle control, 14/50; low dose, 31/50; high dose, 31/49). The incidence of hepatocellular carcinomas in high dose male mice was significantly greater than that in the vehicle controls (5/50; 6/50; 10/49; P = 0.032); the incidence of hepatocellular adenomas or carcinomas (combined) in high dose male mice was not significantly greater than that in the vehicle controls (14/50; 17/50; 16/49).

Lung: Adenomatous hyperplasia and histiocytosis were observed at increased incidences in high dose mice (adenomatous hyperplasia--male: vehicle control, 13/50; low dose, 19/50; high dose, 24/49; female: 7/49; 10/50; 18/50; histiocytosis--male: 11/50; 7/50; 21/49; female: 9/49; 10/50; 21/50).

Anterior Pituitary Gland: Adenomas in female mice occurred with a significant negative trend, and the incidence in the high dose group was significantly lower than that in the vehicle controls (Table 31).

TABLE 31. ANALYSIS OF ANTERIOR PITUITARY GLAND LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF METHYL CARBAMATE (a)

	Vehicle Control	500 mg/kg	1,000 mg/kg
Hyperplasia			
Overall Rates	11/49 (22%)	1/40 (3%)	1/48 (2%)
Adenoma (b)			
Overall Rates	9/49 (18%)	3/40 (7%)	0/48 (0%)
Adjusted Rates	22.7%	9.3%	0.0%
Terminal Rates	8/38 (21%)	2/28 (7%)	0/32 (0%)
Week of First Observation	64	97	
Life Table Tests	P=0.002N	P=0.137N	P=0.005N
Incidental Tumor Tests	P=0.001N	P=0.136N	P=0.004N

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix D, Table D3 (footnotes).
(b) Historical incidence in water gavage controls in NTP studies (mean ± SD): 32/184 (17% ± 5%); historical incidence in untreated controls: 117/1,815 (10% ± 9%)

IV. DISCUSSION AND CONCLUSIONS

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The toxicity of methyl carbamate was studied by administering the chemical by gavage in a single dose or in repeated doses for 16 days, 13 weeks, 6 months, 12 months, 18 months, or 2 years to male and female F344/N rats and $B6C3F_1$ mice.

The toxicity of methyl carbamate in rats has not been reported in the literature. The results of the present single-administration studies demonstrated that the oral LD_{50} values of methyl carbamate in F344/N rats are approximately 4.3 g/kg for males and 2.5 g/kg for females. The acute toxicity of methyl carbamate in mice is low; the LD_{50} value is 6.2 g/kg after oral administration (IARC, 1976), 2 g/kg after intraperitoneal injection (Seipper et al., 1948), and from 4.5 g/kg to greater than 8 g/kg after subcutaneous injection (Pound, 1967). The oral LD_{50} values of methyl carbamate for male and female $B6C3F_1$ mice estimated from the results of the present single-administration studies are approximately 5 g/kg and are in agreement with the data reported in the literature.

In the 16-day studies, all rats that received 2,000 mg/kg or more and 3/5 male rats that received 1,000 mg/kg died. Male mice that received 2,000 or 4,000 mg/kg, female mice that received 4,000 mg/kg, and 1/5 female mice that received 2,000 mg/kg died. Compound-related gross pathologic or histopathologic changes were not seen in rats of either sex administered methyl carbamate by gavage at doses of 500 mg/kg or in mice of either sex at 1,000 mg/kg.

In the 13-week studies, male rats dosed at 400 or 800 mg/kg had lower body weights and liver weights than did the vehicle controls; their relative liver weights were also significantly lower. Female rats dosed at 1,000 mg/kg had lower body and liver weights, but the mean relative liver weight was not significantly different from that of the vehicle controls. At 400 or 500 mg/kg, methyl carbamate induced toxic hepatitis in approximately half of the dosed male and female rats, and at 800 or 1,000 mg/kg the chemical induced toxic hepatitis in all dosed male and female rats. The toxic hepatitis was predominant in periportal areas but extended to the entire liver lobules and was characterized by necrosis, hyperchromasia, atypical nuclei, and abnormal mitoses. In addition, splenic pigmentation (hemosiderin), bone marrow atrophy, and testicular atrophy (males only) were observed in male rats dosed at 400 mg/kg or above and in female rats dosed at 500 mg/kg or above.

The $B6C3F_1$ mice in the 13-week studies tolerated methyl carbamate well compared with the rats. All male mice dosed at 1,500 mg/kg or less survived, and only 1/10 female mice dosed at 2,000 mg/kg died. All female mice dosed at 1,000 mg/kg or less survived. Male mice dosed at 1,500 mg/kg and all dosed female mice had lower body weights (5%-10%) than did the vehicle controls. In contrast to the rats, the dosed male and female mice had higher relative liver weights than did the vehicle controls. The increase in relative liver weight was significant in female mice receiving 500 mg/kg or more. Multifocal hepatocellular necrosis and/or increased mitotic index were observed in the liver of male mice dosed at 375 mg/kg or above but not in the liver of dosed females. The nature of the lesion and pattern of distribution suggest that the inflammatory lesions resulted from an infection.

In the 6-month studies, male and female rats dosed at 400 mg/kg had significantly lower relative liver weights than did the vehicle controls. Cytologic alteration of the liver was observed in all dosed groups of rats, and hepatocellular neoplastic nodules were found in 6/10 males and in 5/10 females. Histopathologic changes were not found in the liver of the vehicle control rats. In the 12-month studies, hepatocellular neoplastic nodules were found in 7/10 males and 9/10 females, and hepatocellular carcinomas were observed in 8/10 males and 6/10 females. Neoplastic changes were not observed in the vehicle controls. In the 18-month studies, hepatocellular carcinomas were observed in 9/10 males and 8/10 females; hepatocellular neoplasms were not observed in the vehicle controls. In these studies, significantly lower relative adrenal gland weights were observed in dosed male and female rats at 6 months; an increased incidence of testicular atrophy was observed in dosed males in the 12-month study, and an increased incidence of bone marrow atrophy was observed in dosed males in the 18-month study.

The doses (100 and 200 mg/kg) of methyl carbamate used in the 2-year studies were one-quarter and one-half of those used in the 6-, 12-, and 18-month studies. Mean body weights of low dose male and female rats were similar to those of the vehicle controls, and those of high dose males and females were within 9% and 8% of the vehicle controls, respectively. Survival rates of dosed male and female rats were not significantly different from those of the vehicle controls.

Dose-related hepatic chronic focal inflammation and cytologic alteration were observed in male and female rats in the 2-year studies. The incidence of neoplastic nodules or hepatocellular carcinomas (combined) was significantly greater in high dose female rats (vehicle control, 0/50; low dose, 0/50; high dose, 6/49) but not in high dose male rats (4/50; 0/50; 7/49) relative to the vehicle controls. Historically, in NTP studies, neoplastic nodules or hepatocellular carcinomas (combined) were found in 6% of the male (Appendix A, Table A4a) and 3% of the female (Appendix B, Table B4a) water gavage vehicle control F344/N rats. In the present 2-year studies, neoplastic nodules or hepatocellular carcinomas (combined) were found in 8% and 0% of the vehicle control male and female rats, respectively. No neoplastic nodules or hepatocellular carcinomas were found in the vehicle control male and female rats in the 6-, 12-, and 18-month studies. The findings of the 6-, 12-, and 18-month and 2-year studies together showed that the incidences of hepatocellular neoplasms in male and female rats were dose related. Methyl carbamate at 400 mg/kg induced hepatocellular neoplasms at a greater incidence and with a shorter latency compared with methyl carbamate at 200 mg/kg in both male and female rats. At 100 mg/kg for 2 years, methyl carbamate did not induce hepatocellular neoplasms in male and female F344/N rats.

The 6-, 12-, and 18-month and 2-year studies together demonstrated a temporal relationship in hepatocarcinogenesis between hepatic cytologic alteration, growth of neoplastic nodules, and development of hepatocellular carcinomas. The studies showed that methyl carbamate induced histopathologic changes in a sequential manner; i.e., hepatic cytologic alteration and hyperplastic lesions appeared first, followed by hepatic neoplastic nodules and then hepatocellular carcinomas. Hepatocarcinogenesis has been described as a multistep process. Continued stimulation by a carcinogen or a promoter is required to complete the carcinogenesis process (Firminger, 1955; Kitigawa, 1976; Bannasch, 1976; Pitot, 1977; Hirota and Williams, 1979; Williams, 1982; Farber 1984a,b). Hepatocarcinogenesis by methyl carbamate apparently followed a pattern similar to that induced by other rat hepatocarcinogens.

Unlike the rats, male and female mice dosed with methyl carbamate in the 13-week studies and in the 6-month studies had higher liver weight to body weight ratios than did the vehicle controls. Increased incidences of hepatocellular neoplastic and nonneoplastic lesions were not found in the dosed male and female mice killed at 13 weeks, 6 months, 12 months, 18 months, and 2 years, except that a dose-related incidence of hepatic multinucleate giant cells was observed in male mice in the 2-year studies. The significance of the hepatic multinucleate giant cells was not clear.

The difference in toxicity and carcinogenicity observed between rats and mice suggests that these species respond differently to the effects of methyl carbamate. The difference may be due to varying rates of clearance. Ioannou and Matthews (1984) observed that methyl carbamate was eliminated much more slowly by rats than by mice. Absorption and tissue distribution of methyl carbamate were similar in both species and were apparently independent of dose in a range of 40-100 mg/kg in both species. However, the whole body half-life of methyl carbamate was significantly longer in rats than in mice. The products of methyl carbamate eliminated (carbon dioxide in exhaled air and parent compound in urine) were the same in both species, and only the parent compound was detected in tissues of either species. Extrapolation of their results indicates that, at the highest doses administered in the 2-year studies (200 and 1,000 mg/kg for rats and mice, respectively), the concentration in tissues of rats may have been several-fold higher than that in similar tissues of mice. Despite the higher concentrations in rat liver, methyl carbamate binding to DNA

was not detected, whereas a trace of binding to DNA was detected in mouse liver.

The higher concentration of methyl carbamate in rat tissues may account for the toxic and carcinogenic effects. As shown in the present studies, methyl carbamate caused necrosis and atypical proliferative changes in rat liver. Possibly, methyl carbamate induces DNA damage in proliferating liver cells which leads to infidelity in DNA replication. Alternatively, methyl carbamate may not interact directly with DNA but may cause changes in the methylation patterns or the tertiary structure of DNA, as has been proposed for epigenetic carcinogens (IARC, 1983). However, all the evidence available from the literature, as well as NTP-sponsored studies, demonstrates conclusively that methyl carbamate is not mutagenic. No unscheduled DNA synthesis was detected in perfused liver cells of F344 male rats exposed to methyl carbamate in vitro. The chemical did not induce gene mutations in bacteria or mammalian cells in culture, sister chromatid exchanges or chromosomal aberrations in mammalian cells in culture, or sex-linked recessive lethal mutations in Drosophila. Although in vivo mutagenicity studies conducted with mice also gave negative results, no similar in vivo mutagenicity studies have been conducted with rats, the species in which methyl carbamate shows carcinogenic activity. Further work is required to determine the mechanism of action of methyl carbamate in liver carcinogenesis in rats and the absence of carcinogenic effects in mice.

Genotoxicity data are available on three structural analogs of methyl carbamate: urethane (ethyl carbamate), *N*-methyl urethane (*N*-methylethyl carbamate), and methylurea. The results of mutagenicity tests for *N*-methyl urethane and methyl urea are negative. The third analog, ethyl carbamate (urethane), is carcinogenic, inducing tumors in different organs in a variety of laboratory rodent species. It induced lung adenomas, lymphosarcomas, hemangiomas in the liver, hepatomas, and mammary tumors in mice after oral administration. Newborn rats given ethyl carbamate intraperitoneally within 24 hours of birth developed liver, neurogenic, and embryonal kidney tumors. Older rats receiving ethyl carbamate were less sensitive to development of these tumors but did develop thyroid gland tumors (IARC, 1974). An extensive review of the mutagenicity data through 1981 for urethane was presented by Allen et al. (1982a). Urethane is most notably genotoxic in in vivo mammalian sysems. It has been shown by several investigators to induce micronuclei and sister chromatid exchanges in mice (Salamone et al., 1981; Tsuchimoto and Matter, 1981; Cheng et al., 1981; Conner and Cheng, 1983; Dragani et al., 1983; Allen et al., 1982b; Majone et al., 1983), and Nomura et al. (1983) reported somatic mutations in mice. In addition, in vitro induction of unscheduled DNA synthesis has been reported in human fibroblasts (Agrelo and Severn, 1981) and rat tracheal epithelial cells (Ide et al., 1981), and transformation has been reported in baby hamster kidney cells (Daniel and Dehnel, 1981; Styles, 1981). Knapp and Kramers (1982) reported the induction of sex-linked recessive lethal mutations in Drosophila after treatment with 112 mM urethane, and Swenberg (1981), by means of the alkaline elution assay, detected DNA damage to kidney and brain tissues of rats administered urethane at doses up to 500 mg/kg by intraperitoneal injection. Allen et al. (1982c) suggest that the stronger mutagenic activity noted for urethane in vivo might arise from the effect of a metabolite, such as vinyl carbamate, which can be converted to a reactive epoxide intermediate. No information is available on the formation of potentially mutagenic metabolites of methyl carbamate. Thus, the structural difference between a methyl and an ethyl group as the ester of carbamic acid not only influences the mutagenicity of the molecule but also exerts an organ and species specificity in carcinogenic action.

Significant negative neoplastic trends were observed in several organs in the 2-year studies; e.g., lower incidences of anterior pituitary gland adenomas and adenomas or carcinomas (combined) and adrenal gland pheochromocytomas in male rats, mononuclear cell leukemia in male and female rats, mammary gland fibroadenomas in female rats, and anterior pituitary gland adenomas in female mice. The meaning of these negative trends is not clear.

Retinal atrophy, cataracts of the crystalline lens, and osseous metaplasia of the sclera were

observed in rats in the 2-year studies as well as in rats in the 18-month studies. These eye lesions could have been caused by the fluorescent light in the study laboratory rather than by administration of methyl carbamate.

Nonneoplastic lesions associated with the administration of methyl carbamate in the 2-year studies included inflammation of the harderian gland and splenic pigmentation in male and female rats, myocardial fibrosis and inflammation in female rats, and lung adenomatous hyperplasia and histiocytosis in male and female mice.

The experimental and tabulated data for the NTP Technical Report on methyl carbamate were examined for accuracy, consistency, and compliance with Good Laboratory Practice requirements. As summarized in Appendix H, the audit revealed some discrepancies, but they were not considered to have influenced the interpretation of the studies.

Conclusions: Under the conditions of these 6-, 12-, and 18-month and 2-year gavage studies, there was *clear evidence of carcinogenic activity** for male and female F344/N rats given methyl carbamate as indicated by increased incidences of hepatocellular neoplastic nodules and hepatocellular carcinomas. There was *no evidence of carcinogenic activity* for male and female $B6C3F_1$ mice given methyl carbamate at doses of 500 or 1,000 mg/kg. Methyl carbamate also induced inflammation of the harderian gland in male and female rats and adenomatous hyperplasia and histiocytosis of the lung in male and female mice.

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

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APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF METHYL CARBAMATE

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

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)		
Basal cell tumor		1 (2%)	
Trichoepithelioma	1 (2%)		
Keratoacanthoma		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma	1 (2%)	1 (2%)	
Neurilemoma			1 (2%)
RESPIRATORY SYSTEM			
*Nares	(50)	(50)	(50)
Squamous cell papilloma		1 (2%)	
*Nasal turbinate	(50)	(50)	(50)
Adenomatous polyp, NOS			1 (2%)
#Lung	(50)	(18)	(50)
Squamous cell carcinoma	1 (2%)		
Squamous cell carcinoma, metastatic	1 (2%)		
Hepatocellular carcinoma, metastatic			1 (2%)
Alveolar/bronchiolar adenoma	3 (6%)		1 (2%)
Alveolar/bronchiolar carcinoma	1 (2%)		
Mesothelioma, NOS			1 (2%)
Osteosarcoma, metastatic		1 (6%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	20 (40%)	27 (54%)	18 (36%)
#Spleen	(50)	(50)	(49)
Fibrosarcoma	1 (2%)		
Leukemia, mononuclear cell	3 (6%)	2 (4%)	
#Mediastinal lymph node	(50)	(16)	(50)
Squamous cell carcinoma, metastatic	1 (2%)		
#Liver	(50)	(50)	(49)
Leukemia, mononuclear cell		1 (2%)	
#Thymus	(44)	(12)	(40)
Thymoma, benign			1 (3%)
CIRCULATORY SYSTEM			
#Heart	(50)	(12)	(50)
Alveolar/bronchiolar carcinoma, metastatic	1 (2%)		
Mesothelioma, NOS			1 (2%)
#Endocardium	(50)	(12)	(50)
Neurilemoma, malignant	1 (2%)		
DIGESTIVE SYSTEM			
*Periodontal tissues	(50)	(50)	(50)
Sarcoma, NOS		1 (2%)	
#Liver	(50)	(50)	(49)
Neoplastic nodule	3 (6%)		3 (6%)
Hepatocellular carcinoma	1 (2%)		4 (8%)

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

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
#Kidney	(50)	(50)	(49)
Tubular cell adenocarcinoma	1 (2%)		
#Urinary bladder	(48)	(12)	(48)
Transitional cell papilloma			1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(49)	(50)
Carcinoma, NOS	3 (6%)	1 (2%)	1 (2%)
Adenoma, NOS	26 (52%)	17 (35%)	9 (18%)
#Adrenal medulla	(50)	(49)	(50)
Pheochromocytoma	23 (46%)	11 (22%)	12 (24%)
Pheochromocytoma, malignant	4 (8%)	6 (12%)	2 (4%)
#Thyroid	(50)	(13)	(49)
Follicular cell adenoma			2 (4%)
C-cell adenoma	3 (6%)		2 (4%)
C-cell carcinoma	2 (4%)		
#Pancreatic islets	(50)	(13)	(50)
Islet cell adenoma	2 (4%)		1 (2%)
Islet cell carcinoma	1 (2%)	2 (15%)	1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Fibroadenoma	1 (2%)	1 (2%)	
*Preputial gland	(50)	(50)	(50)
Squamous cell carcinoma			1 (2%)
Adenoma, NOS	3 (6%)		4 (8%)
#Prostate	(50)	(13)	(48)
Adenoma, NOS			1 (2%)
#Testis	(50)	(41)	(48)
Interstitial cell tumor	43 (86%)	34 (83%)	38 (79%)
Mesothelioma, NOS			1 (2%)
*Epididymis	(50)	(50)	(50)
Mesothelioma, NOS			1 (2%)
NERVOUS SYSTEM			
#Cerebrum	(50)	(14)	(50)
Granular cell tumor, NOS			1 (2%)
#Brain	(50)	(14)	(50)
Carcinoma, NOS, invasive	2 (4%)		
#Brain/thalamus	(50)	(14)	(50)
Astrocytoma			1 (2%)
#Cerebellum	(50)	(14)	(50)
Granular cell tumor, NOS			1 (2%)
SPECIAL SENSE ORGANS			
*Eyeball, tunica vasculosa	(50)	(50)	(50)
Leiomyoma	1 (2%)		
*Zymbal gland	(50)	(50)	(50)
Adenoma, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*Vertebra	(50)	(50)	(50)
Osteosarcoma		1 (2%)	
*Skeletal muscle	(50)	(50)	(50)
Squamous cell carcinoma, invasive	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
Lower leg			
Sarcoma, NOS	1		
Osteosarcoma			1
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	20	15	12
Moribund sacrifice	10	9	8
Terminal sacrifice	19	26	29
Dosing accident	1		1
TUMOR SUMMARY			
Total animals with primary tumors**	50	49	47
Total primary tumors	152	108	112
Total animals with benign tumors	48	45	43
Total benign tumors	109	67	74
Total animals with malignant tumors	33	37	24
Total malignant tumors	40	41	29
Total animals with secondary tumors##	4	1	1
Total secondary tumors	6	1	1
Total animals with tumors uncertain-- benign or malignant	3		7
Total uncertain tumors	3		9

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

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

ANIMAL NUMBER	C 1 5	C 2 8	C 0 4	C 3 9	C 4 7	C 4 8	C 4 3	C 0 5	C 1 2	C 1 6	C 2 3	C 5 0	C 4 9	C 1 7	C 3 5	C 4 6	C 0 6	C 2 4	C 3 2	C 0 1	C 1 1	C 0 9	C 0 3	C 1 8	C 3 4
WEEKS ON STUDY	0 6 6	0 7 9	0 8 5	0 8 5	0 8 5	0 8 5	0 8 7	0 8 8	0 8 9	0 8 9	0 8 9	0 8 9	0 9 0	0 9 1	0 9 1	0 9 1	0 9 3	0 9 3	0 9 4	0 9 5	0 9 5	0 9 6	0 9 7	0 9 8	0 9 9
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																								X	
Trichoepithelioma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																X									
Squamous cell carcinoma, metastatic																X									
Alveolar/bronchiolar adenoma											X										X		X		
Alveolar/bronchiolar carcinoma												X													
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Leukemia, mononuclear cell								X																	
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic																X									
Thymus	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic												X													
Neurilemoma, malignant																	X								
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	–	–	–	+	+	+	+	+	+	–	–	+	+	+	–	+	+	+	+	+	+
Large intestine	+	+	+	+	–	–	–	+	+	+	+	+	+	–	–	+	+	+	–	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma												X													
Urinary bladder	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS		X				X																			
Adenoma, NOS	X				X		X			X			X		X	X							X	X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma						X	X								X						X	X			X
Pheochromocytoma, malignant																					X				
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell adenoma																									
C cell carcinoma																									
Parathyroid	–	+	–	+	+	+	+	–	+	+	–	–	+	+	+	+	–	+	+	+	–	+	+	–	–
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
Islet cell carcinoma													X												
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	N	N	N	+	N	+	N	+	+	+	+	+	+	+	+	+	+	N	N	N	N	N	+
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor			X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS															X										
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive		X				X																			
SPECIAL SENSE ORGANS																									
Eye	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
MUSCULOSKELETAL SYSTEM																									
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma, invasive																X									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell			X	X		X				X	X		X					X	X		X		X		X
Lower leg, NOS																									
Sarcoma, 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 RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	C 3 3 8	C 4 5	C 4 2	C 2 5	C 3 1	C 3 7	C 0 2	C 0 7	C 0 8	C 1 0	C 1 3	C 1 4	C 1 9	C 2 0	C 2 1	C 2 2	C 2 6	C 2 7	C 2 9	C 3 0	C 3 3	C 3 6	C 4 0	C 4 1	C 4 4	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	0 9 9	0 9 9	1 0 1	1 0 3	1 0 3	1 0 3	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																										1
Trichoepithelioma																X										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma						X																				1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Squamous cell carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma																										3
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma												X														1
Leukemia, mononuclear cell		X														X										3
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic																										1
Thymus	+	+	+	+	+	+	+	+	–	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	44
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar ca, metastatic																										1
Neurilemoma, malignant																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule								X			X	X														3
Hepatocellular carcinoma					X																					1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Large intestine	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	42
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenocarcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS											X															3
Adenoma, NOS	X	X		X	X	X			X			X	X	X	X	X	X			X		X	X	X	X	26
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma	X		X	X	X	X		X		X	X	X	X	X		X				X	X	X		X	X	23
Pheochromocytoma, malignant													X				X		X							4
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell adenoma															X									X	X	3
C-cell carcinoma						X								X												2
Parathyroid	+	+	+	+	+	+	–	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma					X																	X				2
Islet cell carcinoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	+	N	N	+	+	+	+	+	N	N	N	+	+	N	+	+	+	N	N	+	+	+	N	*50
Fibroadenoma																		X								1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	43
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS												X	X													3
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																										2
SPECIAL SENSE ORGANS																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	N	+	*50
Leiomyoma												X														1
Zymbal gland	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	*50
Adenoma, NOS	X																									1
MUSCULOSKELETAL SYSTEM																										
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma, invasive																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell					X			X	X				X	X	X						X	X			X	20
Lower leg, NOS																										
Sarcoma, NOS																										1

* Animals necropsied

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

ANIMAL NUMBER	C 3 3	C 3 5	C 3 9	C 0 8	C 0 6	C 1 3	C 0 3	C 1 7	C 4 7	C 0 7	C 2 5	C 5 0	C 0 9	C 1 5	C 2 1	C 2 8	C 3 8	C 2 6	C 4 5	C 2 9	C 4 4	C 1 8	C 2 2	C 1 0	C 0 1
WEEKS ON STUDY	0 2 8	0 3 6	0 7 3	0 7 5	0 7 9	0 8 8	0 8 9	0 8 9	0 8 9	0 9 0	0 9 1	0 9 1	0 9 3	0 9 3	0 9 3	0 9 5	0 9 6	0 9 7	0 9 8	0 9 9	1 0 0	1 0 2	1 0 2	1 0 3	1 0 4
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	N	N	N	N	N	N	N	N	N	N	N	N	N
Basal cell tumor																									
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	–	+	–	+	–	–	+	–	–
Osteosarcoma, metastatic	X																								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–
Nasal cavity	N	N	+	+	+	+	+	+	+	+	+	+	N	N	+	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma															X										
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	+	–	–	–	+	–	–	–	–	–
Thymus	+	+	+	+	+	+	–	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS											X														
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	–	+	+	+	+	+	+	+	+	–	–	+	–	–	–	–	–	–	–	–	–
Esophagus	–	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–
Stomach	+	+	–	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–
Small intestine	+	+	–	+	–	–	+	+	+	–	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–
Large intestine	+	+	–	+	–	–	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	–	+	+	+	+	+	+	+	–	–	–	+	–	–	–	–	–	–	–	–	–
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS								X																	
Adenoma, NOS						X	X				X		X	X								X			X
Adrenal	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma								X	X					X		X			X		X				
Pheochromocytoma, malignant																								X	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–
Parathyroid	+	+	–	–	–	+	+	–	+	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Pancreatic islets	+	+	+	+	–	+	+	+	+	+	+	+	+	–	–	+	–	–	–	–	–	–	–	–	–
Islet cell carcinoma										X			X												
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	N	+	+	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	+	–	+	+	+	+	+	+	+	+
Interstitial cell tumor				X		X			X	X		X				X		X	X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	+	–	–	–	–	–	–	–	–	–
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	+	–	–	–
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																								
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell			X	X	X				X		X				X	X	X	X	X	X		X	X		X

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

ANIMAL NUMBER	C 002	C 004	C 005	C 011	C 012	C 014	C 016	C 019	C 020	C 023	C 024	C 027	C 030	C 031	C 032	C 034	C 036	C 037	C 040	C 041	C 042	C 043	C 046	C 048	C 049	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	+	N	N	N	N	*50
Basal cell tumor																X					X					1
Keratoacanthoma																										1
Subcutaneous tissue	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	+	N	N	N	N	*50
Fibroma																					X					1
RESPIRATORY SYSTEM																										
Lungs and bronchi	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	18
Osteosarcoma, metastatic																										1
Trachea	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	14
Nasal cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma																										1
HEMATOPOIETIC SYSTEM																										
Bone marrow	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	12
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia, mononuclear cell								X		X																2
Lymph nodes	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	+	–	–	16
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	12
CIRCULATORY SYSTEM																										
Heart	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	12
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS																										1
Salivary gland	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	12
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia, mononuclear cell																X										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	13
Esophagus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	11
Stomach	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	11
Small intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
Large intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	9
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	12
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	49
Carcinoma, NOS																										1
Adenoma, NOS	X		X	X	X	X			X			X					X		X				X			17
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma			X	X						X								X				X				11
Pheochromocytoma, malignant						X							X			X							X	X		6
Thyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	13
Parathyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	7
Pancreatic islets	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	13
Islet cell carcinoma																										2
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	*50
Fibroadenoma														X												1
Testis	–	+	–	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	41
Interstitial cell tumor		X			X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X	X	34
Prostate	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	13
NERVOUS SYSTEM																										
Brain	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	14
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell			X		X							X			X		X	X	X	X	X	X	X	X	X	27

* Animals necropsied

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

ANIMAL NUMBER	C 10	C 14	C 12	C 22	C 36	C 27	C 08	C 20	C 49	C 39	C 38	C 04	C 35	C 16	C 40	C 15	C 21	C 13	C 30	C 43	C 29	C 01	C 02	C 03	C 05
WEEKS ON STUDY	041	065	066	066	076	080	081	085	089	090	092	096	096	097	098	099	101	102	102	102	103	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma	X																								
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic										X															
Alveolar/bronchiolar adenoma																									
Mesothelioma, NOS																					X				
Trachea	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenomatous polyp, NOS																									X
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	−	+	−	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Thymoma, benign																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																					X				
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule						X																			
Hepatocellular carcinoma									X	X			X												
Bile duct	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+
Large intestine	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	−	+	−	−	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																							X		
Adenoma, NOS			X									X				X						X			
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma											X										X		X	X	
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																						X			
C-cell adenoma																									
Parathyroid	+	−	+	−	+	+	+	−	−	+	−	−	+	−	−	+	+	+	+	+	+	+	+	+	−
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																		X							
Islet cell carcinoma																						X			
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	+	N	N	+	+	N	N	N	N	N	N	N	+	N	N	+	N	+	+
Testis	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor					X			X		X	X	X		X	X	X	X	X	X	X	X			X	X
Mesothelioma, NOS																			X						
Prostate	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																		X							
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma																									
Adenoma, NOS															X										
Epididymis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS																			X						
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, NOS														X											
Astrocytoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell					X				X	X	X		X			X			X						X
Lower leg, NOS																									
Osteosarcoma						X																			

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

ANIMAL NUMBER	C 0 0 6	C 0 0 7	C 0 0 9	C 0 1 1	C 0 1 7	C 0 1 8	C 0 1 9	C 0 2 3	C 0 2 4	C 0 2 5	C 0 2 6	C 0 2 8	C 0 3 1	C 0 3 2	C 0 3 3	C 0 3 4	C 0 3 7	C 0 4 1	C 0 4 2	C 0 4 4	C 0 4 5	C 0 4 6	C 0 4 7	C 0 4 8	C 0 5 0	TOTAL:
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	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	*50
Neurilemoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma												X														1
Mesothelioma, NOS																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenomatous polyp, NOS																										1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	–	40
Thymoma, benign																X										1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma, NOS																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule																						X	X			3
Hepatocellular carcinoma													X													4
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Transitional cell papilloma										X																1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																										1
Adenoma, NOS		X	X										X						X					X		9
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma									X				X			X	X			X		X	X		X	12
Pheochromocytoma, malignant					X								X													2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma																				X						2
C-cell adenoma																	X							X		2
Parathyroid	+	+	+	–	+	+	–	+	+	+	–	+	+	+	+	–	+	–	+	+	+	+	+	+	+	36
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																										1
Islet cell carcinoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	N	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Interstitial cell tumor	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	38
Mesothelioma, NOS																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS																										1
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma					X																					1
Adenoma, NOS													X	X											X	4
Epididymis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor, NOS								X																		2
Astrocytoma																			X							1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell	X					X		X	X				X					X			X	X	X	X		18
Lower leg, NOS																										
Osteosarcoma																										1

* Animals necropsied

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

	Vehicle Control	100 mg/kg	200 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	3/50 (6%)	0/18 (0%)	1/50 (2%)
Adjusted Rates (b)	8.9%	(c)	3.4%
Terminal Rates (d)	0/19 (0%)		1/29 (3%)
Week of First Observation	89		104
Life Table Test (e)			P=0.230N
Incidental Tumor Test (e)			P=0.421N
Fisher Exact Test (e)			P=0.309N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	0/18 (0%)	1/50 (2%)
Adjusted Rates (b)	11.1%	(c)	3.4%
Terminal Rates (d)	0/19 (0%)		1/29 (3%)
Week of First Observation	89		104
Life Table Test (e)			P=0.133N
Incidental Tumor Test (e)			P=0.324N
Fisher Exact Test (e)			P=0.181N
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	23/50 (46%)	30/50 (60%)	18/50 (36%)
Adjusted Rates (b)	65.5%	76.0%	48.2%
Terminal Rates (d)	9/19 (47%)	17/26 (65%)	11/29 (38%)
Week of First Observation	85	73	76
Life Table Tests (e)	P=0.028N	P=0.454	P=0.047N
Incidental Tumor Tests (e)	P=0.188N	P=0.111	P=0.301N
Cochran-Armitage Trend Test (e)	P=0.184N		
Fisher Exact Test (e)		P=0.115	P=0.208N
Liver: Neoplastic Nodule			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	3/49 (6%)
Adjusted Rates (b)	15.8%	0.0%	9.0%
Terminal Rates (d)	3/19 (16%)	0/26 (0%)	2/29 (7%)
Week of First Observation	104		80
Life Table Tests (e)	P=0.468N	P=0.070N	P=0.498N
Incidental Tumor Tests (e)	P=0.528N	P=0.070N	P=0.567N
Cochran-Armitage Trend Test (e)	P=0.593		
Fisher Exact Test (e)		P=0.121N	P=0.651
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	1/50 (2%)	0/50 (0%)	4/49 (8%)
Adjusted Rates (b)	4.5%	0.0%	10.4%
Terminal Rates (d)	0/19 (0%)	0/26 (0%)	1/29 (3%)
Week of First Observation	103		89
Life Table Tests (e)	P=0.118	P=0.459N	P=0.256
Incidental Tumor Tests (e)	P=0.033	P=0.545N	P=0.072
Cochran-Armitage Trend Test (e)	P=0.079		
Fisher Exact Test (e)		P=0.500N	P=0.175
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Overall Rates (a)	4/50 (8%)	0/50 (0%)	7/49 (14%)
Adjusted Rates (b)	19.6%	0.0%	18.7%
Terminal Rates (d)	3/19 (16%)	0/26 (0%)	3/29 (10%)
Week of First Observation	103		80
Life Table Tests (e)	P=0.285	P=0.033N	P=0.444
Incidental Tumor Tests (e)	P=0.129	P=0.042N	P=0.211
Cochran-Armitage Trend Test (e)	P=0.161		
Fisher Exact Test (e)		P=0.059N	P=0.251

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

	Vehicle Control	100 mg/kg	200 mg/kg
Pituitary Gland: Adenoma			
Overall Rates (a)	26/50 (52%)	17/49 (35%)	9/50 (18%)
Adjusted Rates (b)	77.0%	52.3%	26.5%
Terminal Rates (d)	12/19 (63%)	11/25 (44%)	6/29 (21%)
Week of First Observation	66	88	66
Life Table Tests (e)	P<0.001N	P=0.014N	P<0.001N
Incidental Tumor Tests (e)	P<0.001N	P=0.058N	P<0.001N
Cochran-Armitage Trend Test (e)	P<0.001N		
Fisher Exact Test (e)		P=0.062N	P<0.001N
Pituitary Gland: Carcinoma			
Overall Rates (a)	3/50 (6%)	1/49 (2%)	1/50 (2%)
Adjusted Rates (b)	9.1%	2.3%	3.4%
Terminal Rates (d)	1/19 (5%)	0/25 (0%)	1/29 (3%)
Week of First Observation	79	89	104
Life Table Tests (e)	P=0.172N	P=0.291N	P=0.251N
Incidental Tumor Tests (e)	P=0.313N	P=0.452N	P=0.381N
Cochran-Armitage Trend Test (e)	P=0.202N		
Fisher Exact Test (e)		P=0.316N	P=0.309N
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	29/50 (58%)	18/49 (37%)	10/50 (20%)
Adjusted Rates (b)	81.1%	53.4%	29.7%
Terminal Rates (d)	13/19 (68%)	11/25 (44%)	7/29 (24%)
Week of First Observation	66	88	66
Life Table Tests (e)	P<0.001N	P=0.007N	P<0.001N
Incidental Tumor Tests (e)	P<0.001N	P=0.035N	P<0.001N
Cochran-Armitage Trend Test (e)	P<0.001N		
Fisher Exact Test (e)		P=0.027N	P<0.001N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	23/50 (46%)	11/49 (22%)	12/50 (24%)
Adjusted Rates (b)	75.6%	31.7%	38.3%
Terminal Rates (d)	12/19 (63%)	5/26 (19%)	10/29 (34%)
Week of First Observation	85	89	92
Life Table Tests (e)	P<0.001N	P=0.002N	P<0.001N
Incidental Tumor Tests (e)	P=0.009N	P=0.011N	P=0.007N
Cochran-Armitage Trend Test (e)	P=0.012N		
Fisher Exact Test (e)		P=0.012N	P=0.018N
Adrenal Gland: Malignant Pheochromocytoma			
Overall Rates (a)	4/50 (8%)	6/49 (12%)	2/50 (4%)
Adjusted Rates (b)	18.5%	22.2%	6.9%
Terminal Rates (d)	3/19 (16%)	5/26 (19%)	2/29 (7%)
Week of First Observation	95	103	104
Life Table Tests (e)	P=0.123N	P=0.555	P=0.176N
Incidental Tumor Tests (e)	P=0.161N	P=0.503	P=0.213N
Cochran-Armitage Trend Test (e)	P=0.291N		
Fisher Exact Test (e)		P=0.357	P=0.339N
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	25/50 (50%)	17/49 (35%)	13/50 (26%)
Adjusted Rates (b)	82.5%	49.9%	41.5%
Terminal Rates (d)	14/19 (74%)	10/26 (38%)	11/29 (38%)
Week of First Observation	85	89	92
Life Table Tests (e)	P<0.001N	P=0.013N	P<0.001N
Incidental Tumor Tests (e)	P=0.003N	P=0.054N	P=0.002N
Cochran-Armitage Trend Test (e)	P=0.009N		
Fisher Exact Test (e)		P=0.090N	P=0.012N

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

	Vehicle Control	100 mg/kg	200 mg/kg
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	3/50 (6%)	0/13 (0%)	2/49 (4%)
Adjusted Rates (b)	15.8%	(c)	6.9%
Terminal Rates (d)	3/19 (16%)		2/29 (7%)
Week of First Observation	104		104
Life Table Test (e)			P=0.309N
Incidental Tumor Test (e)			P=0.309N
Fisher Exact Test (e)			P=0.510N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	0/13 (0%)	2/49 (4%)
Adjusted Rates (b)	24.6%	(c)	6.9%
Terminal Rates (d)	4/19 (21%)		2/29 (7%)
Week of First Observation	103		104
Life Table Test (e)			P=0.084N
Incidental Tumor Test (e)			P=0.108N
Fisher Exact Test (e)			P=0.226N
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	2/13 (15%)	2/50 (4%)
Adjusted Rates (b)	11.9%	(c)	6.4%
Terminal Rates (d)	1/19 (5%)		1/29 (3%)
Week of First Observation	90		102
Life Table Test (e)			P=0.356N
Incidental Tumor Test (e)			P=0.577N
Fisher Exact Test (e)			P=0.500N
Preputial Gland: Adenoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	4/50 (8%)
Adjusted Rates (b)	12.9%	0.0%	12.8%
Terminal Rates (d)	2/19 (11%)	0/26 (0%)	3/29 (10%)
Week of First Observation	91		98
Life Table Tests (e)	P=0.557	P=0.084N	P=0.621N
Incidental Tumor Tests (e)	P=0.448	P=0.116N	P=0.566
Cochran-Armitage Trend Test (e)	P=0.406		
Fisher Exact Test (e)		P=0.121N	P=0.500
Preputial Gland: Adenoma or Squamous Cell Carcinoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	5/50 (10%)
Adjusted Rates (b)	12.9%	0.0%	16.2%
Terminal Rates (d)	2/19 (11%)	0/26 (0%)	4/29 (14%)
Week of First Observation	91		98
Life Table Tests (e)	P=0.398	P=0.084N	P=0.564
Incidental Tumor Tests (e)	P=0.302	P=0.116N	P=0.443
Cochran-Armitage Trend Test (e)	P=0.252		
Fisher Exact Test (e)		P=0.121N	P=0.357
Testis: Interstitial Cell Tumor			
Overall Rates (a)	43/50 (86%)	34/41 (83%)	38/48 (79%)
Adjusted Rates (b)	97.7%	100.0%	90.4%
Terminal Rates (d)	18/19 (95%)	21/21 (100%)	25/29 (86%)
Week of First Observation	85	75	76
Life Table Tests (e)	P=0.002N	P=0.024N	P=0.005N
Incidental Tumor Tests (e)	P=0.158N	P=0.637N	P=0.295N
Cochran-Armitage Trend Test (e)	P=0.223N		
Fisher Exact Test (e)		P=0.453N	P=0.266N

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

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

TABLE A4a. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN CONTROL MALE F344/N RATS (a)

Study	Incidence in Controls		
	Neoplastic Nodule	Carcinoma	Neoplastic Nodule or Carcinoma
Historical Incidence in All Water Gavage Controls (b)			
Chlorpheniramine maleate	4/50	1/50	5/50
Tetrakis(hydroxymethyl)phosphonium chloride	1/50	0/50	1/50
Tetrakis(hydroxymethyl)phosphonium sulfate	3/50	0/50	3/50
TOTAL	8/150 (5.3%)	1/150 (0.7%)	9/150 (6.0%)
SD (c)	3.06%	1.15%	4.00%
Range (d)			
High	4/50	1/50	5/50
Low	1/50	0/50	1/50
Overall Historical Incidence in Untreated Controls			
TOTAL	83/1,969 (4.2%)	19/1,969 (1.0%)	101/1,969 (5.1%)
SD (c)	4.72%	1.37%	4.73%
Range (d)			
High	12/50	3/50	12/50
Low	0/50	0/90	0/50

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

TABLE A4b. HISTORICAL INCIDENCE OF PITUITARY GLAND TUMORS IN CONTROL MALE F344/N RATS (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence in All Water Gavage Controls (b)			
Chlorpheniramine maleate	12/50	0/50	12/50
Tetrakis(hydroxymethyl)phosphonium chloride	17/50	1/50	18/50
Tetrakis(hydroxymethyl)phosphonium sulfate	21/50	0/50	21/50
TOTAL	50/150 (33.3%)	1/150 (0.7%)	51/150 (34.0%)
SD (c)	9.02%	1.15%	9.17%
Range (d)			
High	21/50	1/50	21/50
Low	12/50	0/50	12/50
Overall Historical Incidence in Untreated Controls			
TOTAL	(e) 387/1,861 (20.8%)	(f) 41/1,861 (2.2%)	(e,f) 428/1,861 (23.0%)
SD (c)	11.25%	2.88%	11.10%
Range (d)			
High	24/46	5/45	25/46
Low	2/39	0/50	2/39

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) All studies were conducted at Battelle Columbus Laboratories.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes adenomas diagnosed as NOS, chromophobe, acidophil, or basophil
(f) Includes adenocarcinomas, NOS, carcinomas, NOS, and chromophobe carcinomas

TABLE A4c. HISTORICAL INCIDENCE OF ADRENAL GLAND TUMORS IN CONTROL MALE F344/N RATS (a)

Study	Incidence in Controls		
	Pheochromocytoma	Malignant Pheochromocytoma	Pheochromocytoma or Malignant Pheochromocytoma
Historical Incidence in All Water Gavage Controls (b)			
Chlorpheniramine maleate	21/49	0/49	21/49
Tetrakis(hydroxymethyl)phosphonium chloride	19/50	0/50	19/50
Tetrakis(hydroxymethyl)phosphonium sulfate	22/50	1/50	23/50
TOTAL	62/149 (41.6%)	1/149 (0.7%)	63/149 (42.3%)
SD (c)	3.19%	1.15%	4.03%
Range (d)			
High	22/50	1/50	23/50
Low	19/50	0/50	19/50
Overall Historical Incidence in Untreated Controls			
TOTAL	427/1,950 (21.9%)	30/1,950 (1.5%)	452/1,950 (23.2%)
SD (c)	12.41%	2.00%	12.39%
Range (d)			
High	31/49	4/49	32/49
Low	2/50	0/50	3/50

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

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

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Inflammation, acute focal			1 (2%)
Inflammation, chronic		1 (2%)	
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Vegetable foreign body			1 (2%)
Hemorrhage			1 (2%)
Inflammation, acute	2 (4%)		4 (8%)
Inflammation, acute diffuse			1 (2%)
Inflammation, chronic			2 (4%)
Infection, fungal	2 (4%)	1 (2%)	5 (10%)
Metaplasia, squamous			3 (6%)
*Nasal turbinate	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		6 (12%)
Metaplasia, osseous			1 (2%)
*Larynx	(50)	(50)	(50)
Inflammation, acute	1 (2%)		1 (2%)
#Lung/bronchus	(50)	(18)	(50)
Inflammation, chronic focal			1 (2%)
Histiocytosis			1 (2%)
#Lung	(50)	(18)	(50)
Ectopia	1 (2%)		
Congestion, NOS	7 (14%)	2 (11%)	1 (2%)
Edema, NOS		1 (6%)	
Hemorrhage	1 (2%)		1 (2%)
Inflammation, chronic			1 (2%)
Pneumonia, interstitial chronic	2 (4%)	1 (6%)	5 (10%)
Fibrosis, focal	1 (2%)		
Pigmentation, NOS	3 (6%)		1 (2%)
Hyperplasia, adenomatous	8 (16%)	1 (6%)	3 (6%)
Metaplasia, osseous	1 (2%)		
Histiocytosis	15 (30%)	3 (17%)	13 (26%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(12)	(50)
Hyperplasia, NOS	1 (2%)		
Myelofibrosis	1 (2%)		3 (6%)
#Spleen	(50)	(50)	(49)
Congestion, NOS		1 (2%)	
Abscess, chronic	1 (2%)		
Fibrosis	3 (6%)	5 (10%)	3 (6%)
Degeneration, hyaline			1 (2%)
Necrosis, NOS	2 (4%)	2 (4%)	
Pigmentation, NOS	7 (14%)	6 (12%)	13 (27%)
Histiocytosis		1 (2%)	1 (2%)
Hyperplasia, lymphoid		1 (2%)	
Hematopoiesis	1 (2%)	3 (6%)	2 (4%)
#Splenic capsule	(50)	(50)	(49)
Inflammation, chronic		1 (2%)	
Fibrosis, multifocal	1 (2%)		
#Mandibular lymph node	(50)	(16)	(50)
Cyst, NOS	1 (2%)		1 (2%)
Hemorrhage	1 (2%)		
Hyperplasia, lymphoid			1 (2%)

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

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Mediastinal lymph node	(50)	(16)	(50)
Cyst, NOS			1 (2%)
Hemorrhage	3 (6%)		1 (2%)
Inflammation, acute		1 (6%)	
Inflammation, chronic			3 (6%)
#Mesenteric lymph node	(50)	(16)	(50)
Cyst, NOS	1 (2%)		2 (4%)
Hemorrhage	3 (6%)		2 (4%)
#Thymus	(44)	(12)	(40)
Atrophy, NOS		2 (17%)	
CIRCULATORY SYSTEM			
#Brain	(50)	(14)	(50)
Thrombosis, NOS		3 (21%)	
#Lung	(50)	(18)	(50)
Thrombosis, NOS	1 (2%)	2 (11%)	
#Heart	(50)	(12)	(50)
Myxomatosis, cardiac valve	1 (2%)		3 (6%)
Inflammation, chronic	5 (10%)	1 (8%)	4 (8%)
Fibrosis, multifocal	36 (72%)	4 (33%)	34 (68%)
#Endocardium	(50)	(12)	(50)
Thrombosis, NOS	9 (18%)		9 (18%)
*Aorta	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
*Pulmonary artery	(50)	(50)	(50)
Mineralization			1 (2%)
Thrombosis, NOS			1 (2%)
Inflammation, chronic focal			2 (4%)
*Gastric artery	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
*Superior pancreaticoduodenal artery	(50)	(50)	(50)
Inflammation, chronic			2 (4%)
*Testicular artery	(50)	(50)	(50)
Inflammation, acute			1 (2%)
Inflammation, chronic	1 (2%)		3 (6%)
*Hepatic vein	(50)	(50)	(50)
Thrombosis, NOS			1 (2%)
#Liver	(50)	(50)	(49)
Thrombosis, NOS	1 (2%)		
Thrombus, organized		1 (2%)	
DIGESTIVE SYSTEM			
*Hard palate	(50)	(50)	(50)
Epidermal inclusion cyst	1 (2%)		
Inflammation, acute focal	1 (2%)		
*Soft palate	(50)	(50)	(50)
Epidermal inclusion cyst	1 (2%)		
#Salivary gland	(49)	(12)	(49)
Inflammation, focal			2 (4%)
Inflammation, chronic	2 (4%)		1 (2%)
Hyperplasia, intraductal	1 (2%)		
#Parotid gland	(49)	(12)	(49)
Inflammation, chronic	1 (2%)		
Atrophy, NOS	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Liver	(50)	(50)	(49)
Congestion, NOS	1 (2%)	1 (2%)	
Inflammation, acute		1 (2%)	
Abscess, NOS		1 (2%)	
Inflammation, chronic focal	2 (4%)	3 (6%)	9 (18%)
Scar			1 (2%)
Peliosis hepatis	12 (24%)	8 (16%)	2 (4%)
Necrosis, focal			2 (4%)
Pigmentation, NOS		2 (4%)	1 (2%)
Cytoplasmic vacuolization	3 (6%)	2 (4%)	1 (2%)
Cytologic alteration, NOS	14 (28%)	11 (22%)	30 (61%)
#Liver/centrilobular	(50)	(50)	(49)
Congestion, NOS	1 (2%)		2 (4%)
Fibrosis		1 (2%)	
Necrosis, NOS	6 (12%)	7 (14%)	2 (4%)
Pigmentation, NOS		1 (2%)	
Cytoplasmic vacuolization	4 (8%)		2 (4%)
#Liver/hepatocytes	(50)	(50)	(49)
Hyperplasia, NOS	5 (10%)	11 (22%)	12 (24%)
#Bile duct	(50)	(50)	(49)
Hyperplasia, NOS	43 (86%)	39 (78%)	40 (82%)
#Pancreas	(50)	(13)	(50)
Accessory structure			1 (2%)
Cystic ducts			2 (4%)
Inflammation, chronic	1 (2%)		2 (4%)
Cytoplasmic vacuolization	1 (2%)		
#Pancreatic duct	(50)	(13)	(50)
Hyperplasia, focal			1 (2%)
#Pancreatic acinus	(50)	(13)	(50)
Atrophy, NOS	20 (40%)	2 (15%)	15 (30%)
#Esophagus	(50)	(11)	(49)
Inflammation, chronic			1 (2%)
#Glandular stomach	(50)	(11)	(49)
Pigmentation, NOS			1 (2%)
#Forestomach	(50)	(11)	(49)
Cyst, NOS			1 (2%)
Hemorrhage	1 (2%)		
Inflammation, acute	1 (2%)	1 (9%)	1 (2%)
Ulcer, acute	1 (2%)		
Inflammation, chronic	1 (2%)	1 (9%)	
Erosion	1 (2%)		2 (4%)
#Jejunum	(42)	(8)	(47)
Fibrosis, diffuse	1 (2%)		
Metaplasia, osseous	1 (2%)		
#Colon	(42)	(9)	(45)
Inflammation, acute	1 (2%)		
Degeneration, hyaline	1 (2%)		
*Rectum	(50)	(50)	(50)
Degeneration, hyaline	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(50)	(49)
Cyst, NOS	1 (2%)		
Edema, NOS		1 (2%)	
Pyelonephritis, NOS	2 (4%)	1 (2%)	
Scar			1 (2%)
Nephropathy	48 (96%)	46 (92%)	45 (92%)
Pigmentation, NOS	1 (2%)		1 (2%)

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

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM (Continued)			
#Kidney/pelvis	(50)	(50)	(49)
Dilatation, NOS		1 (2%)	
Hyperplasia, epithelial	1 (2%)		
#Urinary bladder	(48)	(12)	(48)
Hemorrhage	3 (6%)		1 (2%)
Inflammation, acute	3 (6%)	1 (8%)	
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic	1 (2%)		1 (2%)
#Urinary bladder/serosa	(48)	(12)	(48)
Inflammation, chronic			1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(49)	(50)
Cyst, NOS		6 (12%)	1 (2%)
Pigmentation, NOS	1 (2%)		
Hyperplasia, NOS	4 (8%)	8 (16%)	8 (16%)
Angiectasis	1 (2%)	3 (6%)	
#Adrenal	(50)	(49)	(50)
Accessory structure	1 (2%)		
Hemorrhage	1 (2%)		
#Adrenal cortex	(50)	(49)	(50)
Cyst, NOS			1 (2%)
Congestion, NOS			1 (2%)
Hemorrhage		1 (2%)	
Inflammation, acute		1 (2%)	
Necrosis, NOS	1 (2%)	2 (4%)	1 (2%)
Cytoplasmic vacuolization	3 (6%)	5 (10%)	2 (4%)
Hypertrophy, focal	1 (2%)		
Hyperplasia, focal		1 (2%)	
Angiectasis	1 (2%)		
Metaplasia, osseous	1 (2%)		
#Adrenal medulla	(50)	(49)	(50)
Calcinosis circumscripta		1 (2%)	
Hyperplasia, NOS	18 (36%)	22 (45%)	20 (40%)
#Thyroid	(50)	(13)	(49)
Embryonal duct cyst	2 (4%)		
Colloid cyst	1 (2%)		
Hyperplasia, C-cell	6 (12%)		1 (2%)
Hyperplasia, follicular cell			2 (4%)
#Pancreatic islets	(50)	(13)	(50)
Hyperplasia, NOS	1 (2%)		2 (4%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Galactocele	1 (2%)	1 (2%)	
Inflammation, acute		1 (2%)	
Inflammation, chronic		1 (2%)	
Hyperplasia, NOS		1 (2%)	
*Preputial gland	(50)	(50)	(50)
Dilatation, NOS	1 (2%)		
Inflammation, acute	5 (10%)	2 (4%)	7 (14%)
Inflammation, active chronic		2 (4%)	
Inflammation, chronic		1 (2%)	
Hyperplasia, NOS		2 (4%)	2 (4%)
#Prostate	(50)	(13)	(48)
Inflammation, acute	6 (12%)	2 (15%)	3 (6%)
Inflammation, active chronic	2 (4%)		1 (2%)
Inflammation, chronic			3 (6%)
Hyperplasia, NOS	2 (4%)		5 (10%)

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

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM (Continued)			
*Seminal vesicle	(50)	(50)	(50)
Inflammation, active chronic	1 (2%)		
#Testis	(50)	(41)	(48)
Cyst, NOS	1 (2%)		
Hemorrhage	1 (2%)		1 (2%)
Inflammation, acute	1 (2%)		
Atrophy, NOS	36 (72%)	26 (63%)	34 (71%)
Hyperplasia, interstitial cell	7 (14%)	3 (7%)	12 (25%)
#Testis/tubule	(50)	(41)	(48)
Mineralization	2 (4%)	2 (5%)	1 (2%)
*Epididymis	(50)	(50)	(50)
Inflammation, chronic	1 (2%)	1 (2%)	1 (2%)
Fibrosis, focal		1 (2%)	
NERVOUS SYSTEM			
#Cerebral ventricle	(50)	(14)	(50)
Hemorrhage	1 (2%)		
#Cerebrum	(50)	(14)	(50)
Cytoplasmic vacuolization			1 (2%)
#Brain	(50)	(14)	(50)
Hemorrhage			1 (2%)
Infarct, NOS	3 (6%)	1 (7%)	1 (2%)
#Hippocampus	(50)	(14)	(50)
Necrosis, NOS	1 (2%)		
*Spinal cord	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
Demyelinization	1 (2%)		
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Hemorrhage	2 (4%)	1 (2%)	5 (10%)
Inflammation, acute	1 (2%)		
Inflammation, chronic diffuse	1 (2%)		
*Eye/anterior chamber	(50)	(50)	(50)
Inflammation, acute	1 (2%)	1 (2%)	
*Eye/sclera	(50)	(50)	(50)
Metaplasia, osseous	31 (62%)	40 (80%)	35 (70%)
*Eye/cornea	(50)	(50)	(50)
Inflammation, acute	1 (2%)	1 (2%)	1 (2%)
*Eye/choroid	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
*Eye/iris	(50)	(50)	(50)
Synechia, posterior		1 (2%)	
*Eye/retina	(50)	(50)	(50)
Atrophy, NOS	5 (10%)	11 (22%)	41 (82%)
*Eye/crystalline lens	(50)	(50)	(50)
Cataract	8 (16%)	5 (10%)	27 (54%)
*Nasolacrimal duct	(50)	(50)	(50)
Inflammation, acute	1 (2%)		2 (4%)
*Harderian gland	(50)	(50)	(50)
Hemorrhage		1 (2%)	
Inflammation, acute		4 (8%)	
Inflammation, active chronic		1 (2%)	
Inflammation, chronic		4 (8%)	1 (2%)
Inflammation, chronic focal	4 (8%)	2 (4%)	15 (30%)
*Ear	(50)	(50)	(50)
Inflammation, active chronic	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Hyperplasia, NOS			5 (10%)
*Skull	(50)	(50)	(50)
Hyperplasia, focal			1 (2%)
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Inflammation, chronic diffuse	1 (2%)		
*Abdominal cavity	(50)	(50)	(50)
Necrosis, fat	1 (2%)		
*Pleura	(50)	(50)	(50)
Inflammation, chronic focal	1 (2%)		
*Mesentery	(50)	(50)	(50)
Accessory structure	1 (2%)		
Inflammation, active chronic	1 (2%)		
Inflammation, chronic	3 (6%)	1 (2%)	2 (4%)
Inflammation, granulomatous	1 (2%)	1 (2%)	
Granuloma, NOS	1 (2%)		
Necrosis, fat	7 (14%)	7 (14%)	13 (26%)
ALL OTHER SYSTEMS			
Adipose tissue			
Inflammation, granulomatous	1		
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX B

SUMMARY OF LESIONS IN FEMALE RATS

IN THE TWO-YEAR GAVAGE STUDY

OF METHYL CARBAMATE

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

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Carcinoma, NOS		1 (2%)	
Basal cell carcinoma	1 (2%)		
Keratoacanthoma	1 (2%)	1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)		
Fibroma	2 (4%)	1 (2%)	
Fibrosarcoma		1 (2%)	
Neurilemoma, unclear primary or metastatic			1 (2%)
RESPIRATORY SYSTEM			
*Nasal turbinate	(50)	(50)	(50)
Adenomatous polyp, NOS		1 (2%)	
*Larynx	(50)	(50)	(50)
Fibrosarcoma, invasive			1 (2%)
#Lung	(50)	(11)	(50)
Carcinoma, NOS, metastatic		1 (9%)	
Alveolar/bronchiolar adenoma	1 (2%)		1 (2%)
Alveolar/bronchiolar carcinoma			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	17 (34%)	11 (22%)	7 (14%)
#Spleen	(50)	(50)	(50)
Leukemia, mononuclear cell		1 (2%)	3 (6%)
#Liver	(50)	(50)	(49)
Leukemia, mononuclear cell		1 (2%)	
#Thymus	(49)	(9)	(45)
Thymoma, benign		1 (11%)	
CIRCULATORY SYSTEM			
*Vagina	(50)	(50)	(50)
Hemangiosarcoma			1 (2%)
DIGESTIVE SYSTEM			
*Soft palate	(50)	(50)	(50)
Squamous cell carcinoma			1 (2%)
*Tooth	(50)	(50)	(50)
Odontoma, NOS			1 (2%)
#Salivary gland	(45)	(9)	(50)
Fibrosarcoma			1 (2%)
#Liver	(50)	(50)	(49)
Neoplastic nodule			5 (10%)
Hepatocellular carcinoma			2 (4%)
#Jejunum	(47)	(10)	(47)
Sarcoma, NOS	1 (2%)		
*Rectum	(50)	(50)	(50)
Sarcoma, NOS, invasive	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
#Kidney	(50)	(47)	(49)
Neurilemoma, metastatic			1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(50)	(49)
Carcinoma, NOS	3 (6%)	1 (2%)	1 (2%)
Adenoma, NOS	21 (42%)	24 (48%)	23 (47%)
#Adrenal	(49)	(50)	(49)
Cortical adenoma	3 (6%)	2 (4%)	
#Adrenal cortex	(49)	(50)	(49)
Rhabdomyosarcoma, metastatic	1 (2%)		
#Adrenal medulla	(49)	(50)	(49)
Pheochromocytoma	4 (8%)	1 (2%)	2 (4%)
#Thyroid	(50)	(9)	(50)
Follicular cell adenoma	4 (8%)		
C-cell adenoma	2 (4%)		3 (6%)
C-cell carcinoma			2 (4%)
#Pancreatic islets	(50)	(10)	(49)
Islet cell adenoma			1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Carcinoma, NOS		1 (2%)	
Adenoma, NOS	4 (8%)	5 (10%)	3 (6%)
Fibroma	1 (2%)		
Fibroadenoma	15 (30%)	11 (22%)	6 (12%)
*Clitoral gland	(50)	(50)	(50)
Adenoma, NOS	3 (6%)	4 (8%)	3 (6%)
*Vagina	(50)	(50)	(50)
Squamous cell carcinoma			1 (2%)
Sarcoma, NOS	1 (2%)		
#Uterus	(50)	(49)	(49)
Squamous cell carcinoma	1 (2%)		
Endometrial stromal polyp	10 (20%)	11 (22%)	7 (14%)
#Cervix uteri	(50)	(49)	(49)
Sarcoma, NOS		1 (2%)	
#Uterus/endometrium	(50)	(49)	(49)
Carcinoma, NOS	1 (2%)		
NERVOUS SYSTEM			
#Cerebrum	(50)	(10)	(50)
Glioma, NOS			1 (2%)
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Squamous cell carcinoma	1 (2%)		1 (2%)
MUSCULOSKELETAL SYSTEM			
*Mandible	(50)	(50)	(50)
Odontoma, NOS	1 (2%)		
*Femur	(50)	(50)	(50)
Osteosarcoma	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Rhabdomyosarcoma, metastatic	1 (2%)		
*Peritoneum	(50)	(50)	(50)
Rhabdomyosarcoma, metastatic	1 (2%)		
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Neurilemoma, metastatic			1 (2%)
Diaphragm			
Sarcoma, NOS			1
Rhabdomyosarcoma	1		
Site unknown			
Rhabdomyosarcoma	1		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	16	5	12
Moribund sacrifice	5	9	3
Terminal sacrifice	29	36	34
Dosing accident			1
TUMOR SUMMARY			
Total animals with primary tumors**	47	43	42
Total primary tumors	102	80	79
Total animals with benign tumors	40	38	35
Total benign tumors	71	62	49
Total animals with malignant tumors	25	16	17
Total malignant tumors	30	18	23
Total animals with secondary tumors##	2	1	2
Total secondary tumors	4	1	3
Total animals with tumors uncertain--benign or malignant	1		6
Total uncertain tumors	1		6
Total animals with tumors uncertain--primary or metastatic			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 RATS IN THE TWO-YEAR GAVAGE STUDY OF METHYL CARBAMATE: VEHICLE CONTROL

ANIMAL NUMBER	C 4 9	C 0 3	C 5 0	C 3 8	C 3 6	C 1 5	C 4 5	C 2 6	C 4 3	C 3 9	C 1 2	C 0 4	C 0 5	C 0 2	C 4 2	C 1 1	C 0 7	C 1 9	C 3 1	C 4 4	C 4 8	C 0 1	C 0 6	C 0 8	C 0 9
WEEKS ON STUDY	0 5 1	0 5 9	0 7 3	0 7 5	0 7 6	0 8 1	0 8 3	0 8 5	0 8 5	0 8 7	0 9 1	0 9 2	0 9 3	0 9 7	0 9 7	0 9 8	0 9 9	0 9 9	0 9 9	1 0 0	1 0 3	1 0 4	1 0 4	1 0 4	1 0 4
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS	X																								
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	−
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Large intestine	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Rectum	N	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+
Sarcoma, NOS, invasive						X																			
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	−	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS										X												X			
Adenoma, NOS						X		X	X			X	X		X			X		X	X		X		
Adrenal	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																	X								
Pheochromocytoma																									
Rhabdomyosarcoma, metastatic							X																		
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma											X														
C cell adenoma																									
Parathyroid	+	+	+	+	+	−	+	+	+	+	−	+	+	−	+	+	+	−	+	+	+	+	+	−	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Adenoma, NOS													X			X									
Fibroma																									
Fibroadenoma							X				X						X		X						X
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS											X	X													X
Vagina	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS						X																			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Squamous cell carcinoma													X												
Endometrial stromal polyp								X				X					X								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	+	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma													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
Osteosarcoma																									
Odontoma, 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
Rhabdomyosarcoma, metastatic							X																		
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
Rhabdomyosarcoma, metastatic							X																		
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell			X	X	X			X				X		X			X			Y			X		
Diaphragm, NOS																									
Rhabdomyosarcoma							X																		
Site unknown																									
Rhabdomyosarcoma							X																		

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

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

ANIMAL NUMBER	C 110	C 113	C 114	C 118	C 117	C 118	C 120	C 121	C 122	C 123	C 124	C 125	C 127	C 128	C 129	C 130	C 132	C 133	C 134	C 135	C 137	C 140	C 141	C 146	C 147	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Basal cell carcinoma																									X	1
Keratoacanthoma														X												1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibroma				X									X													2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																			X							1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Sarcoma, NOS																							X			1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS, invasive																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																X										3
Adenoma, NOS		X	X					X				X	X	X	X		X	X			X				X	21
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma				X																	X					3
Pheochromocytoma				X	X					X							X									4
Rhabdomyosarcoma, metastatic																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma						X															X			X		4
C-cell adenoma																		X					X			2
Parathyroid	+	–	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	42
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS																				X					X	4
Fibroma												X														1
Fibroadenoma	X	X	X				X				X					X	X				X		X		X	15
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																										3
Vagina	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS							X																			1
Squamous cell carcinoma																										1
Endometrial stromal polyp				X		X	X	X										X					X		X	10
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma																							X			1
Odontoma, 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
Rhabdomyosarcoma, metastatic																										1
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Rhabdomyosarcoma, metastatic																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell					X	X				X	X					X					X		X		X	17
Diaphragm, NOS																										
Rhabdomyosarcoma																										1
Site unknown																										
Rhabdomyosarcoma																										1

* Animals necropsied

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

ANIMAL NUMBER	C 1 1 6	C 2 2 4	C 3 3 3	C 3 3 9	C 2 2 6	C 3 3 0	C 4 4 7	C 5 5 0	C 2 2 7	C 2 2 8	C 3 3 7	C 2 2 9	C 1 1 3	C 2 2 0	C 0 1 1	C 0 2 2	C 0 3 3	C 0 4 4	C 0 5 5	C 0 6 6	C 0 7 7	C 0 8 8	C 0 9 9	C 1 1 0	C 1 1 1
WEEKS ON STUDY	0 2 1	0 6 3	0 6 5	0 7 7	0 7 9	0 7 9	0 7 9	0 8 5	0 8 8	0 8 9	0 9 5	0 9 9	1 0 0	1 0 3	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
INTEGUMENTARY SYSTEM																									
Skin	+	N	+	+	+	+	+	+	+	+	N	N	N	N	N	+	N	N	N	N	N	N	N	N	+
Carcinoma, NOS	X																								
Keratoacanthoma																X									
Subcutaneous tissue	+	N	+	+	+	+	+	+	+	+	N	N	N	N	N	+	N	N	N	N	N	N	N	N	+
Fibroma																									
Fibrosarcoma								X																	
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Carcinoma, NOS, metastatic	X																								
Trachea	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Nasal cavity	+	+	N	+	+	+	+	+	+	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenomatous polyp, NOS									X																
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–
Thymus	+	+	–	+	+	+	+	+	–	+	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–
Thymoma, benign														X											
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
DIGESTIVE SYSTEM																									
Salivary gland	+	+	–	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																				X					
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	–	+	+	+	+	+	+	+	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–
Esophagus	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Stomach	+	+	–	+	+	+	+	+	+	+	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–
Small intestine	+	+	–	+	+	+	+	+	+	+	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–
Large intestine	+	+	–	+	+	+	+	+	+	+	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	–	–	+	–	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS			X		X		X					X			X		X	X	X			X		X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																X									
Pheochromocytoma																									X
Thyroid	+	+	–	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Parathyroid	+	+	–	+	–	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	N	+	+	+	+	+	+	N	+	N	N	+	+	N	+	N	+	N	+	N	N	+
Carcinoma, NOS																									
Adenoma, NOS							X															X			X
Fibroadenoma									X			X			X			X		X					
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS											X														
Uterus	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS										X															
Endometrial stromal polyp				X				X							X						X				
Ovary	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell		X		X	X	X				X			X												

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

ANIMAL NUMBER	C 112	C 114	C 115	C 117	C 118	C 119	C 121	C 122	C 123	C 125	C 131	C 132	C 134	C 135	C 136	C 138	C 140	C 141	C 142	C 143	C 144	C 145	C 146	C 148	C 149	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	N	N	+	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
Keratoacanthoma																										1
Subcutaneous tissue	N	N	+	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibroma			X																							1
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	11
Carcinoma, NOS, metastatic																										1
Trachea	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
Nasal cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenomatous polyp, NOS																										1
HEMATOPOIETIC SYSTEM																										
Bone marrow	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia, mononuclear cell					X																					1
Lymph nodes	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	11
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	9
Thymoma, benign																										1
CIRCULATORY SYSTEM																										
Heart	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
DIGESTIVE SYSTEM																										
Salivary gland	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	9
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia, mononuclear cell																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
Esophagus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
Stomach	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
Small intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
Large intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Urinary bladder	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS			X																							1
Adenoma, NOS	X					X	X	X		X				X	X		X		X		X	X		X	X	24
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																				X						2
Pheochromocytoma																										1
Thyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	9
Parathyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	7
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	+	N	+	N	N	N	+	N	N	+	+	N	+	N	N	+	+	N	N	+	+	*50
Carcinoma, NOS																				X						1
Adenoma, NOS					X												X									5
Fibroadenoma							X				X				X							X			X	X	11
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS						X							X							X						4
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, NOS																										1
Endometrial stromal polyp										X	X			X	X	X			X			X				11
Ovary	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	+	12
NERVOUS SYSTEM																										
Brain	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell	X							X												X		X		X		11

* Animals necropsied

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

ANIMAL NUMBER	C 2 3	C 0 2	C 1 7	C 2 9	C 2 1	C 3 9	C 2 4	C 0 7	C 4 4	C 1 2	C 1 6	C 1 5	C 1 4	C 3 5	C 4 8	C 0 1	C 0 3	C 0 4	C 0 5	C 0 6	C 0 8	C 0 9	C 1 0	C 1 1	C 1 3
WEEKS ON STUDY	0 6 3	0 6 5	0 6 5	0 7 5	0 8 5	0 8 8	0 8 9	0 9 0	0 9 0	0 9 1	0 9 3	0 9 5	0 9 6	0 9 9	0 9 9	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, unclear primary or metastatic										X															
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, invasive										X															
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																X									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	−	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma			X																						
Odontoma, NOS																								X	
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma										X															
Liver	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									X
Hepatocellular carcinoma										X															
Bile duct	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	−	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	−	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, metastatic																									
Urinary bladder	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS								X																	
Adenoma, NOS	X	X			X												X	X			X	X	X		X
Adrenal	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									X
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																			X						
C-cell carcinoma																	X								
Parathyroid	−	−	−	−	+	+	+	+	+	+	−	−	+	−	+	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS										X												X			
Fibroadenoma																								X	
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																X			X						
Vagina	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma																									
Hemangiosarcoma																					X				
Uterus	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp						X				X		X													
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma, NOS				X																					
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
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
Neurilemoma, metastatic																									
Leukemia, mononuclear cell						X			X		X	X	X				X								
Diaphragm, NOS																									
Sarcoma, NOS																									

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

ANIMAL NUMBER	C 1 1 8	C 1 1 9	C 2 2 0	C 2 2 2	C 2 2 5	C 2 2 6	C 2 2 7	C 2 2 8	C 3 3 0	C 3 3 1	C 3 3 2	C 3 3 3	C 3 3 4	C 3 3 6	C 3 3 7	C 3 3 8	C 4 4 0	C 4 4 1	C 4 4 2	C 4 4 3	C 4 4 5	C 4 4 6	C 4 4 7	C 4 4 9	C 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	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Neurilemoma, unclear prim or meta																									X	1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X																							1
Alveolar/bronchiolar carcinoma																								X		1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma, invasive																										1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia, mononuclear cell	X																								X	3
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	45
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma																										1
Odontoma, NOS																										1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule							X							X									X	X		5
Hepatocellular carcinoma														X												2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neurilemoma, metastatic																									X	1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS																										1
Adenoma, NOS		X	X	X	X	X			X	X	X							X	X		X	X	X	X		23
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma										X																2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C cell adenoma																						X		X		3
C cell carcinoma	X																									2
Parathyroid	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	41
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma												X														1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS																			X							3
Fibroadenoma	X			X	X						X			X												6
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS							X																			3
Vagina	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma																								X		1
Hemangiosarcoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endometrial stromal polyp		X					X						X		X											7
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma, NOS																										1
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	+	*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
Neurilemoma, metastatic																									X	1
Leukemia, mononuclear cell														X												7
Diaphragm, NOS																										
Sarcoma, NOS																							X			1

* Animals necropsied

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

	Vehicle Control	100 mg/kg	200 mg/kg
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	8.8%	5.0%	0.0%
Terminal Rates (c)	2/29 (7%)	1/36 (3%)	0/35 (0%)
Week of First Observation	51	85	
Life Table Tests (d)	P=0.066N	P=0.444N	P=0.101N
Incidental Tumor Tests (d)	P=0.102N	P=0.456N	P=0.198N
Cochran-Armitage Trend Test (d)	P=0.082N		
Fisher Exact Test (d)		P=0.500N	P=0.121N
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	17/50 (34%)	13/50 (26%)	10/50 (20%)
Adjusted Rates (b)	43.8%	29.8%	24.3%
Terminal Rates (c)	9/29 (31%)	7/36 (19%)	5/35 (14%)
Week of First Observation	73	63	88
Life Table Tests (d)	P=0.047N	P=0.159N	P=0.060N
Incidental Tumor Tests (d)	P=0.092N	P=0.319N	P=0.116N
Cochran-Armitage Trend Test (d)	P=0.071N		
Fisher Exact Test (d)		P=0.257N	P=0.088N
Liver: Neoplastic Nodule			
Overall Rates (a)	0/50 (0%)	0/50 (0%)	5/49 (10%)
Adjusted Rates (b)	0.0%	0.0%	14.3%
Terminal Rates (c)	0/29 (0%)	0/36 (0%)	5/35 (14%)
Week of First Observation			104
Life Table Tests (d)	P=0.008	(e)	P=0.051
Incidental Tumor Tests (d)	P=0.008	(e)	P=0.051
Cochran-Armitage Trend Test (d)	P=0.006		
Fisher Exact Test (d)		(e)	P=0.027
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Overall Rates (a)	0/50 (0%)	0/50 (0%)	6/49 (12%)
Adjusted Rates (b)	0.0%	0.0%	16.4%
Terminal Rates (c)	0/29 (0%)	0/36 (0%)	5/35 (14%)
Week of First Observation			91
Life Table Tests (d)	P=0.004	(e)	P=0.029
Incidental Tumor Tests (d)	P=0.003	(e)	P=0.026
Cochran-Armitage Trend Test (d)	P=0.002		
Fisher Exact Test (d)		(e)	P=0.012
Pituitary Gland: Adenoma			
Overall Rates (a)	21/50 (42%)	24/50 (48%)	23/49 (47%)
Adjusted Rates (b)	54.2%	59.4%	59.8%
Terminal Rates (c)	12/29 (41%)	20/36 (56%)	20/35 (57%)
Week of First Observation	81	65	63
Life Table Tests (d)	P=0.431N	P=0.511N	P=0.474N
Incidental Tumor Tests (d)	P=0.469	P=0.382	P=0.492
Cochran-Armitage Trend Test (d)	P=0.347		
Fisher Exact Test (d)		P=0.344	P=0.385
Pituitary Gland: Carcinoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	1/49 (2%)
Adjusted Rates (b)	9.2%	2.8%	2.3%
Terminal Rates (c)	2/29 (7%)	1/36 (3%)	0/35 (0%)
Week of First Observation	87	104	90
Life Table Tests (d)	P=0.167N	P=0.249N	P=0.261N
Incidental Tumor Tests (d)	P=0.188N	P=0.263N	P=0.297N
Cochran-Armitage Trend Test (d)	P=0.207N		
Fisher Exact Test (d)		P=0.309N	P=0.316N

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

	Vehicle Control	100 mg/kg	200 mg/kg
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	24/50 (48%)	25/50 (50%)	24/49 (49%)
Adjusted Rates (b)	60.6%	62.0%	60.7%
Terminal Rates (c)	14/29 (48%)	21/36 (58%)	20/35 (57%)
Week of First Observation	81	65	63
Life Table Tests (d)	P=0.276N	P=0.345N	P=0.316N
Incidental Tumor Tests (d)	P=0.444N	P=0.564	P=0.505N
Cochran-Armitage Trend Test (d)	P=0.501		
Fisher Exact Test (d)		P=0.500	P=0.541
Adrenal Gland: Cortical Adenoma			
Overall Rates (a)	3/49 (6%)	2/50 (4%)	0/49 (0%)
Adjusted Rates (b)	9.6%	5.6%	0.0%
Terminal Rates (c)	2/29 (7%)	2/36 (6%)	0/35 (0%)
Week of First Observation	99	104	
Life Table Tests (d)	P=0.058N	P=0.410N	P=0.097N
Incidental Tumor Tests (d)	P=0.080N	P=0.491N	P=0.131N
Cochran-Armitage Trend Test (d)	P=0.081N		
Fisher Exact Test (d)		P=0.490N	P=0.121N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	4/49 (8%)	1/50 (2%)	2/49 (4%)
Adjusted Rates (b)	13.8%	2.8%	5.7%
Terminal Rates (c)	4/29 (14%)	1/36 (3%)	2/35 (6%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.174N	P=0.119N	P=0.252N
Incidental Tumor Tests (d)	P=0.174N	P=0.119N	P=0.252N
Cochran-Armitage Trend Test (d)	P=0.238N		
Fisher Exact Test (d)		P=0.175N	P=0.339N
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	4/50 (8%)	0/9 (0%)	0/50 (0%)
Adjusted Rates (b)	12.6%	(f)	0.0%
Terminal Rates (c)	3/29 (10%)		0/35 (0%)
Week of First Observation	91		
Life Table Test (d)			P=0.047N
Incidental Tumor Test (d)			P=0.052N
Fisher Exact Test (d)			P=0.059N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	2/50 (4%)	0/9 (0%)	3/50 (6%)
Adjusted Rates (b)	6.9%	(f)	8.6%
Terminal Rates (c)	2/29 (7%)		3/35 (9%)
Week of First Observation	104		104
Life Table Test (d)			P=0.586
Incidental Tumor Test (d)			P=0.586
Fisher Exact Test (d)			P=0.500
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	2/50 (4%)	0/9 (0%)	5/50 (10%)
Adjusted Rates (b)	6.9%	(f)	14.3%
Terminal Rates (c)	2/29 (7%)		5/35 (14%)
Week of First Observation	104		104
Life Table Test (d)			P=0.296
Incidental Tumor Test (d)			P=0.296
Fisher Exact Test (d)			P=0.218

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

	Vehicle Control	100 mg/kg	200 mg/kg
Mammary Gland: Adenoma			
Overall Rates (a)	4/50 (8%)	5/50 (10%)	3/50 (6%)
Adjusted Rates (b)	11.9%	13.0%	8.0%
Terminal Rates (c)	2/29 (7%)	4/36 (11%)	2/35 (6%)
Week of First Observation	93	79	91
Life Table Tests (d)	P=0.352N	P=0.600	P=0.433N
Incidental Tumor Tests (d)	P=0.437N	P=0.472	P=0.543N
Cochran-Armitage Trend Test (d)	P=0.427N		
Fisher Exact Test (d)		P=0.500	P=0.500N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	15/50 (30%)	11/50 (22%)	6/50 (12%)
Adjusted Rates (b)	44.3%	28.7%	17.1%
Terminal Rates (c)	11/29 (38%)	9/36 (25%)	6/35 (17%)
Week of First Observation	83	88	104
Life Table Tests (d)	P=0.006N	P=0.114N	P=0.008N
Incidental Tumor Tests (d)	P=0.011N	P=0.191N	P=0.014N
Cochran-Armitage Trend Test (d)	P=0.019N		
Fisher Exact Test (d)		P=0.247N	P=0.024N
Mammary Gland: Fibroma or Fibroadenoma			
Overall Rates (a)	16/50 (32%)	11/50 (22%)	6/50 (12%)
Adjusted Rates (b)	47.4%	28.7%	17.1%
Terminal Rates (c)	12/29 (41%)	9/36 (25%)	6/35 (17%)
Week of First Observation	83	88	104
Life Table Tests (d)	P=0.003N	P=0.075N	P=0.004N
Incidental Tumor Tests (d)	P=0.006N	P=0.131N	P=0.007N
Cochran-Armitage Trend Test (d)	P=0.011N		
Fisher Exact Test (d)		P=0.184N	P=0.014N
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (a)	17/50 (34%)	16/50 (32%)	9/50 (18%)
Adjusted Rates (b)	47.4%	40.6%	24.7%
Terminal Rates (c)	11/29 (38%)	13/36 (36%)	8/35 (23%)
Week of First Observation	83	79	91
Life Table Tests (d)	P=0.017N	P=0.278N	P=0.024N
Incidental Tumor Tests (d)	P=0.034N	P=0.469N	P=0.044N
Cochran-Armitage Trend Test (d)	P=0.047N		
Fisher Exact Test (d)		P=0.500N	P=0.055N
Mammary Gland: Adenoma, Fibroma, or Fibroadenoma			
Overall Rates (a)	18/50 (36%)	16/50 (32%)	9/50 (18%)
Adjusted Rates (b)	50.3%	40.6%	24.7%
Terminal Rates (c)	12/29 (41%)	13/36 (36%)	8/35 (23%)
Week of First Observation	83	79	91
Life Table Tests (d)	P=0.010N	P=0.209N	P=0.014N
Incidental Tumor Tests (d)	P=0.020N	P=0.376N	P=0.026N
Cochran-Armitage Trend Test (d)	P=0.030N		
Fisher Exact Test (d)		P=0.417N	P=0.035N
Mammary Gland: Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	6/50 (12%)	3/50 (6%)
Adjusted Rates (b)	11.9%	15.8%	8.0%
Terminal Rates (c)	2/29 (7%)	5/36 (14%)	2/35 (6%)
Week of First Observation	93	79	91
Life Table Tests (d)	P=0.349N	P=0.480	P=0.433N
Incidental Tumor Tests (d)	P=0.431N	P=0.357	P=0.543N
Cochran-Armitage Trend Test (d)	P=0.429N		
Fisher Exact Test (d)		P=0.370	P=0.500N

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

	Vehicle Control	100 mg/kg	200 mg/kg
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	10/50 (20%)	(g) 11/49 (22%)	7/49 (14%)
Adjusted Rates (b)	29.9%	28.3%	17.7%
Terminal Rates (c)	7/29 (24%)	9/36 (25%)	4/35 (11%)
Week of First Observation	85	77	88
Life Table Tests (d)	P=0.165N	P=0.518N	P=0.204N
Incidental Tumor Tests (d)	P=0.230N	P=0.583	P=0.282N
Cochran-Armitage Trend Test (d)	P=0.277N		
Fisher Exact Test (d)		P=0.479	P=0.314N
Clitoral Gland: Adenoma			
Overall Rates (a)	3/50 (6%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (b)	8.3%	10.6%	8.6%
Terminal Rates (c)	1/29 (3%)	3/36 (8%)	3/35 (9%)
Week of First Observation	91	95	104
Life Table Tests (d)	P=0.507N	P=0.574	P=0.599N
Incidental Tumor Tests (d)	P=0.565N	P=0.483	P=0.629N
Cochran-Armitage Trend Test (d)	P=0.579		
Fisher Exact Test (d)		P=0.500	P=0.661

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the 100 mg/kg and vehicle control groups.
(f) Incomplete sampling of tissues
(g) A sarcoma, NOS, was observed in an animal without a polyp.

TABLE B4a. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN CONTROL FEMALE F344/N RATS (a)

Study	Incidence in Controls	
	Neoplastic Nodule	Neoplastic Nodule or Carcinoma
Historical Incidence in All Water Gavage Controls (b)		
Chlorpheniramine maleate	2/50	2/50
Tetrakis(hydroxymethyl)phosphonium chloride	0/50	0/50
Tetrakis(hydroxymethyl)phosphonium sulfate	3/49	3/49
TOTAL	5/149 (3.4%)	5/149 (3.4%)
SD (c)	3.11%	3.11%
Range (d)		
High	3/49	3/49
Low	0/50	0/50
Overall Historical Incidence in Untreated Controls		
TOTAL	57/2,015 (2.8%)	(e) 59/2,015 (2.9%)
SD (c)	2.86%	3.04%
Range (d)		
High	5/50	5/50
Low	0/50	0/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) All studies were conducted at Battelle Columbus Laboratories.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Three hepatocellular carcinomas have been observed in untreated control groups. The greatest incidence of hepatocellular carcinomas observed was 2/50; one of these two tumors was in an animal also bearing a neoplastic nodule.

TABLE B4b. HISTORICAL INCIDENCE OF MAMMARY GLAND TUMORS IN CONTROL FEMALE F344/N RATS (a)

Study	Incidence of Fibroadenomas in Controls
Historical Incidence in All Water Gavage Controls (b)	
Chlorpheniramine maleate	14/50
Tetrakis(hydroxymethyl)phosphonium chloride	11/50
Tetrakis(hydroxymethyl)phosphonium sulfate	21/49
TOTAL	46/149 (30.9%)
SD (c)	10.74%
Range (d)	
High	21/49
Low	11/50
Overall Historical Incidence in Untreated Controls	
TOTAL	(e) 582/2,021 (28.8%)
SD (c)	10.35%
Range (d)	
High	24/49
Low	5/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) All studies were conducted at Battelle Columbus Laboratories.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes 558 fibroadenomas; 4 cystfibroadenomas; 14 adenomas, NOS; 6 cystadenomas; and 2 papillary cystadenomas. One fibroma was also observed.

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

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Ulcer, acute			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Inflammation, active chronic		1 (2%)	
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Vegetable foreign body	1 (2%)		
Hemorrhage			1 (2%)
Inflammation, acute	3 (6%)	1 (2%)	2 (4%)
Infection, fungal	2 (4%)		
*Nasal turbinate	(50)	(50)	(50)
Inflammation, chronic focal	1 (2%)		2 (4%)
#Tracheal muscle	(50)	(10)	(50)
Inflammation, chronic focal			1 (2%)
#Lung	(50)	(11)	(50)
Mineralization	1 (2%)		
Vegetable foreign body			1 (2%)
Congestion, NOS	3 (6%)	1 (9%)	3 (6%)
Hemorrhage	3 (6%)	1 (9%)	2 (4%)
Inflammation, chronic focal			1 (2%)
Granuloma, NOS	1 (2%)		
Inflammation granulomatous focal			1 (2%)
Scar			1 (2%)
Pigmentation, NOS	1 (2%)		
Hyperplasia, adenomatous	2 (4%)		1 (2%)
Metaplasia, osseous	1 (2%)		
Histiocytosis	26 (52%)	4 (36%)	31 (62%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(10)	(50)
Hypoplasia, NOS	1 (2%)		1 (2%)
Hyperplasia, NOS		1 (10%)	1 (2%)
Myelofibrosis	1 (2%)		
Hyperplasia, reticulum cell	4 (8%)		2 (4%)
#Spleen	(50)	(50)	(50)
Hemorrhage			1 (2%)
Inflammation, chronic focal	1 (2%)		
Necrosis, NOS	1 (2%)	2 (4%)	
Pigmentation, NOS	20 (40%)	25 (50%)	40 (80%)
Hyperplasia, lymphoid		2 (4%)	
Hematopoiesis	7 (14%)	5 (10%)	1 (2%)
#Splenic capsule	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
#Mandibular lymph node	(49)	(11)	(50)
Cyst, NOS		1 (9%)	4 (8%)
Hemorrhage			1 (2%)
#Mediastinal lymph node	(49)	(11)	(50)
Hemorrhage			1 (2%)
Inflammation, chronic			1 (2%)
#Mesenteric lymph node	(49)	(11)	(50)
Hemorrhage	1 (2%)	1 (9%)	2 (4%)
Inflammation, chronic	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Lung	(50)	(11)	(50)
Hyperplasia, lymphoid			1 (2%)
#Liver	(50)	(50)	(49)
Hematopoiesis	2 (4%)	1 (2%)	
#Adrenal cortex	(49)	(50)	(49)
Hematopoiesis	1 (2%)		
#Thymus	(49)	(9)	(45)
Cyst, NOS			1 (2%)
CIRCULATORY SYSTEM			
#Brain	(50)	(10)	(50)
Thrombosis, NOS		1 (10%)	
*Nasal cavity	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)		
#Heart	(50)	(10)	(50)
Myxomatosis, cardiac valve	2 (4%)	1 (10%)	2 (4%)
Mineralization	1 (2%)		
Inflammation, chronic	6 (12%)		15 (30%)
Inflammation, chronic focal	1 (2%)		
Fibrosis, multifocal	17 (34%)	1 (10%)	29 (58%)
#Endocardium	(50)	(10)	(50)
Thrombosis, NOS	1 (2%)		1 (2%)
#Cardiac valve	(50)	(10)	(50)
Inflammation, chronic			1 (2%)
*Artery	(50)	(50)	(50)
Inflammation, chronic focal			1 (2%)
*Aorta	(50)	(50)	(50)
Inflammation, necrotizing			1 (2%)
Inflammation, active chronic	1 (2%)		
*Coronary artery	(50)	(50)	(50)
Mineralization	1 (2%)		
Inflammation, active chronic			2 (4%)
Inflammation, chronic focal			3 (6%)
*Mesenteric artery	(50)	(50)	(50)
Mineralization	1 (2%)		
*Renal artery	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
#Hepatic sinusoid	(50)	(50)	(49)
Foam cell		1 (2%)	
DIGESTIVE SYSTEM			
#Salivary gland	(45)	(9)	(50)
Inflammation, acute	1 (2%)		
Cytoplasmic vacuolization	1 (2%)		
Atrophy, NOS			2 (4%)
#Parotid gland	(45)	(9)	(50)
Inflammation, acute	1 (2%)		
Cytoplasmic vacuolization		2 (22%)	
#Liver	(50)	(50)	(49)
Cyst, NOS		1 (2%)	
Congestion, NOS	1 (2%)		1 (2%)
Inflammation, chronic			1 (2%)
Inflammation, chronic focal	13 (26%)	17 (34%)	31 (63%)
Fibrosis, focal		1 (2%)	
Scar	2 (4%)		1 (2%)
Peliosis hepatis	2 (4%)	2 (4%)	1 (2%)
Necrosis, NOS	1 (2%)	4 (8%)	1 (2%)
Mitotic alteration		1 (2%)	

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

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM			
#Liver (Continued)	(50)	(50)	(49)
Cytoplasmic vacuolization	5 (10%)	3 (6%)	3 (6%)
Cytologic alteration, NOS	25 (50%)	40 (80%)	46 (94%)
#Liver/centrilobular	(50)	(50)	(49)
Congestion, NOS	2 (4%)	2 (4%)	1 (2%)
Necrosis, NOS	3 (6%)		2 (4%)
Cytoplasmic vacuolization	3 (6%)	1 (2%)	1 (2%)
#Liver/hepatocytes	(50)	(50)	(49)
Hyperplasia, NOS	6 (12%)	2 (4%)	16 (33%)
#Bile duct	(50)	(50)	(49)
Hyperplasia, NOS	14 (28%)	13 (26%)	14 (29%)
#Pancreas	(50)	(10)	(49)
Inflammation, chronic	2 (4%)	1 (10%)	
#Pancreatic acinus	(50)	(10)	(49)
Atrophy, NOS	11 (22%)	1 (10%)	7 (14%)
#Stomach	(50)	(10)	(49)
Mineralization	1 (2%)		
#Glandular stomach	(50)	(10)	(49)
Pigmentation, NOS	1 (2%)		1 (2%)
#Forestomach	(50)	(10)	(49)
Ulcer, NOS		1 (10%)	
Inflammation, chronic focal	1 (2%)		
#Duodenal muscularis	(47)	(10)	(47)
Mineralization	1 (2%)		
#Colonic muscularis	(48)	(10)	(47)
Mineralization	1 (2%)		
#Cecum	(48)	(10)	(47)
Erosion	1 (2%)		
*Rectum	(50)	(50)	(50)
Mineralization	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(47)	(49)
Mineralization	1 (2%)		
Hydronephrosis	1 (2%)		
Cyst, NOS	2 (4%)		
Inflammation, chronic		1 (2%)	
Pyelonephritis, chronic	1 (2%)		
Nephropathy	40 (80%)	36 (77%)	42 (86%)
Infarct, acute	1 (2%)		
Pigmentation, NOS	3 (6%)		
#Kidney/pelvis	(50)	(47)	(49)
Mineralization	1 (2%)		1 (2%)
#Urinary bladder	(46)	(10)	(49)
Hyperplasia, epithelial		1 (10%)	
Metaplasia, osseous			1 (2%)
ENDOCRINE SYSTEM			
#Pituitary	(50)	(50)	(49)
Ectopia			1 (2%)
#Anterior pituitary	(50)	(50)	(49)
Cyst, NOS	2 (4%)	13 (26%)	5 (10%)
Hemorrhage	1 (2%)	1 (2%)	1 (2%)
Pigmentation, NOS	1 (2%)		1 (2%)
Hyperplasia, NOS	10 (20%)	8 (16%)	4 (8%)
Angiectasis	11 (22%)	8 (16%)	6 (12%)

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Adrenal	(49)	(50)	(49)
Congestion, NOS			1 (2%)
Hypertrophy, focal		1 (2%)	
#Adrenal cortex	(49)	(50)	(49)
Congestion, NOS		2 (4%)	1 (2%)
Inflammation, chronic	1 (2%)		
Necrosis, NOS	1 (2%)		3 (6%)
Cytoplasmic change, NOS	1 (2%)		
Cytoplasmic vacuolization		7 (14%)	2 (4%)
Hyperplasia, NOS		2 (4%)	
Hyperplasia, focal	1 (2%)	1 (2%)	
Angiectasis	1 (2%)		2 (4%)
#Adrenal medulla	(49)	(50)	(49)
Hyperplasia, NOS	9 (18%)	8 (16%)	2 (4%)
Hyperplasia, focal	2 (4%)		
#Thyroid	(50)	(9)	(50)
Embryonal duct cyst	2 (4%)	1 (11%)	
Hyperplasia, C-cell	7 (14%)		7 (14%)
#Parathyroid	(42)	(7)	(41)
Hyperplasia, NOS	1 (2%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Galactocele	11 (22%)	3 (6%)	3 (6%)
Hyperplasia, NOS		1 (2%)	
*Clitoral gland	(50)	(50)	(50)
Dilatation/ducts		1 (2%)	
Cyst, NOS	1 (2%)		1 (2%)
Inflammation, acute	8 (16%)	1 (2%)	9 (18%)
Abscess, NOS			1 (2%)
Inflammation, active chronic		2 (4%)	1 (2%)
Inflammation, chronic			1 (2%)
Hyperplasia, NOS		3 (6%)	
*Vagina	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
#Uterus	(50)	(49)	(49)
Hemorrhage		1 (2%)	1 (2%)
Inflammation, acute	1 (2%)	1 (2%)	1 (2%)
#Uterine serosa	(50)	(49)	(49)
Fibrosis, focal		1 (2%)	
#Cervix uteri	(50)	(49)	(49)
Hyperplasia, stromal	1 (2%)		
#Uterus/endometrium	(50)	(49)	(49)
Hyperplasia, cystic	8 (16%)	7 (14%)	7 (14%)
#Ovary	(50)	(12)	(50)
Cyst, NOS	6 (12%)	1 (8%)	2 (4%)
NERVOUS SYSTEM			
#Cerebrum	(50)	(10)	(50)
Hemorrhage			1 (2%)
Infarct, NOS	1 (2%)		
#Brain	(50)	(10)	(50)
Hemorrhage		1 (10%)	1 (2%)
Infarct, NOS	1 (2%)		2 (4%)
#Cerebral cortex	(50)	(10)	(50)
Status spongiosus			1 (2%)
*Spinal cord	(50)	(50)	(50)
Hemorrhage		1 (2%)	

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

	Vehicle Control	Low Dose	High Dose
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Hemorrhage	1 (2%)	2 (4%)	1 (2%)
Inflammation, acute	1 (2%)	1 (2%)	
*Eye/sclera	(50)	(50)	(50)
Metaplasia, osseous	6 (12%)	24 (48%)	24 (48%)
*Eye/cornea	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
Inflammation, chronic	1 (2%)		1 (2%)
*Eye/retina	(50)	(50)	(50)
Atrophy, NOS	10 (20%)	23 (46%)	43 (86%)
*Eye/crystalline lens	(50)	(50)	(50)
Cataract	7 (14%)	9 (18%)	41 (82%)
*Eyelid	(50)	(50)	(50)
Abscess, NOS			1 (2%)
Inflammation, chronic			1 (2%)
*Nasolacrimal duct	(50)	(50)	(50)
Inflammation, acute	2 (4%)	2 (4%)	3 (6%)
*Harderian gland	(50)	(50)	(50)
Ectopia		1 (2%)	
Inflammation, acute		1 (2%)	
Inflammation, chronic focal	7 (14%)	15 (30%)	30 (60%)
*Middle ear	(50)	(50)	(50)
Inflammation, acute			1 (2%)
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Osteomalacia	1 (2%)		
Hyperplasia, diffuse	3 (6%)		1 (2%)
*Skull	(50)	(50)	(50)
Hyperplasia, diffuse	1 (2%)		
*Maxilla	(50)	(50)	(50)
Abscess, NOS			1 (2%)
BODY CAVITIES			
*Mesentery	(50)	(50)	(50)
Inflammation, chronic	4 (8%)		3 (6%)
Necrosis, fat	4 (8%)	5 (10%)	3 (6%)
ALL OTHER SYSTEMS			
Adipose tissue			
Inflammation, active chronic		1	
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX C

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF METHYL CARBAMATE

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

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma	1 (2%)		
Fibrosarcoma	2 (4%)	2 (4%)	3 (6%)
Fibrous histiocytoma, malignant		1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(49)
Hepatocellular carcinoma, metastatic	2 (4%)	2 (4%)	4 (8%)
Alveolar/bronchiolar adenoma	11 (22%)	6 (12%)	8 (16%)
Alveolar/bronchiolar carcinoma		2 (4%)	2 (4%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS	2 (4%)		1 (2%)
Malignant lymphoma, undifferentiated type		1 (2%)	
Malignant lymphoma, lymphocytic type	1 (2%)	3 (6%)	
Malignant lymphoma, histiocytic type		1 (2%)	1 (2%)
Malignant lymphoma, mixed type		6 (12%)	4 (8%)
#Bone marrow	(50)	(8)	(48)
Mast cell sarcoma	1 (2%)		
#Spleen	(49)	(18)	(47)
Malignant lymphoma, mixed type		1 (6%)	
#Mandibular lymph node	(48)	(18)	(45)
Mast cell sarcoma, metastatic	1 (2%)		
#Mesenteric lymph node	(48)	(18)	(45)
Malignant lymphoma, lymphocytic type			1 (2%)
Malignant lymphoma, mixed type	1 (2%)		
#Liver	(50)	(50)	(49)
Malignant lymphoma, undifferentiated type		1 (2%)	
Malignant lymphoma, mixed type		1 (2%)	
#Forestomach	(50)	(8)	(45)
Mast cell sarcoma	1 (2%)		
#Jejunum	(41)	(13)	(42)
Malignant lymphoma, lymphocytic type			1 (2%)
*Prepuce	(50)	(50)	(50)
Mast cell tumor			1 (2%)
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		
#Liver	(50)	(50)	(49)
Hemangiosarcoma		1 (2%)	
#Pancreas	(50)	(9)	(47)
Hemangioma	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(49)
Hepatocellular adenoma	9 (18%)	12 (24%)	7 (14%)
Hepatocellular carcinoma	5 (10%)	6 (12%)	10 (20%)
#Forestomach	(50)	(8)	(45)
Squamous cell papilloma	2 (4%)		2 (4%)
#Jejunum	(41)	(13)	(42)
Adenomatous polyp, NOS		1 (8%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(49)
Tubular cell adenoma		1 (2%)	
ENDOCRINE SYSTEM			
#Adrenal	(49)	(7)	(47)
Cortical adenoma	2 (4%)		1 (2%)
#Adrenal medulla	(49)	(7)	(47)
Pheochromocytoma	1 (2%)		
#Thyroid	(50)	(8)	(47)
Follicular cell adenoma	2 (4%)		
REPRODUCTIVE SYSTEM			
#Testis	(49)	(8)	(47)
Interstitial cell tumor	2 (4%)		
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS	2 (4%)	1 (2%)	
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	19	9	20
Moribund sacrifice	2	5	1
Terminal sacrifice	28	35	28
Dosing accident	1	1	
Accidentally killed, nda			1

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

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	27	35	28
Total primary tumors	47	47	42
Total animals with benign tumors	21	20	17
Total benign tumors	33	21	18
Total animals with malignant tumors	12	23	18
Total malignant tumors	14	26	23
Total animals with secondary tumors##	3	2	4
Total secondary tumors	3	2	4
Total animals with tumors uncertain-- benign or malignant			1
Total uncertain tumors			1

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

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

ANIMAL NUMBER	C017	C007	C019	C031	C023	C008	C029	C020	C046	C004	C005	C050	C038	C030	C037	C014	C002	C026	C013	C049	C032	C025	C001	C003	C006
WEEKS ON STUDY	015	055	057	060	061	062	064	065	067	071	072	078	085	089	089	092	094	094	098	098	100	102	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Fibrosarcoma																								X	
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																		X							
Alveolar/bronchiolar adenoma											X		X							X		X			X
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell sarcoma																									
Spleen	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Mast cell sarcoma, metastatic																									
Thymus	+	−	+	+	+	+	+	+	+	−	+	+	+	−	+	−	−	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																								X	
Hepatocellular carcinoma													X	X				X							X
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	N	N	N	N	+	N	N	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Mast cell sarcoma																									
Small intestine	+	+	+	+	+	+	−	+	+	+	+	+	+	−	−	−	−	−	−	+	−	−	+	+	+
Large intestine	+	+	+	+	+	+	−	+	−	+	−	+	+	−	+	−	−	+	+	+	−	−	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma											X														
Pheochromocytoma																									
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	N	+	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor																								X	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																							X		
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangiosarcoma																									
Malignant lymphoma, NOS																	X					X			
Malignant lymphoma, lymphocytic type						X																			

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

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

ANIMAL NUMBER	C 0 9	C 1 0	C 1 1	C 1 2	C 1 5	C 1 6	C 1 8	C 2 1	C 2 2	C 2 4	C 2 7	C 2 8	C 3 3	C 3 4	C 3 5	C 3 6	C 3 9	C 4 0	C 4 1	C 4 2	C 4 3	C 4 4	C 4 5	C 4 7	C 4 8	TOTAL:
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	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma	X																									1
Fibrosarcoma				X																						2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																			X							2
Alveolar/bronchiolar adenoma	X												X		X					X	X		X			11
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell sarcoma															X											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Malignant lymphoma, mixed type													X													1
Mast cell sarcoma, metastatic															X											1
Thymus	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	43
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma								X					X	X			X	X			X		X		X	9
Hepatocellular carcinoma																			X							5
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	N	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma														X												1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma														X											X	2
Mast cell sarcoma															X											1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma																							X			2
Pheochromocytoma		X																								1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma					X			X																		2
Parathyroid	–	–	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	34
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	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor																		X								2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS										X																2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangiosarcoma				X																						1
Malignant lymphoma, NOS																										2
Malignant lymphoma, lymphocytic type																										1

* Animals necropsied

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

ANIMAL NUMBER	C 0 7	C 4 5	C 3 0	C 1 1	C 3 3	C 1 3	C 2 5	C 4 7	C 4 8	C 4 1	C 2 2	C 0 3	C 1 5	C 0 1	C 3 8	C 0 2	C 0 4	C 0 5	C 0 6	C 0 8	C 0 9	C 1 0	C 1 2	C 1 4	C 1 6
WEEKS ON STUDY	0 1 5	0 4 8	0 5 7	0 6 4	0 6 5	0 6 7	0 7 0	0 7 8	0 9 6	0 9 7	1 0 0	1 0 1	1 0 1	1 0 3	1 0 3	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N
Fibrosarcoma		X																		X					
Fibrous histiocytoma, malignant										X															
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																		X							
Alveolar/bronchiolar adenoma				X																				X	X
Alveolar/bronchiolar carcinoma																					X				
Trachea	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Spleen	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	–	–	–	–	–	–	+	–
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	+	+	+	+	–	+	+	+	–	+	+	–	+	+	–	–	–	–	–	–	–	–	–
Thymus	+	+	–	+	–	+	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma						X	X									X	X					X		X	
Hepatocellular carcinoma																		X							
Hemangiosarcoma																									
Malignant lymphoma, undifferentiated type																									
Malignant lymphoma, mixed type																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	N	+	N	N	+	N	N	N	+	N	+	N	N	N	N	N	N	N	N	N	+	N
Pancreas	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Esophagus	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Stomach	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Small intestine	+	+	+	–	+	–	+	–	–	–	–	–	–	–	–	+	–	+	–	–	–	–	–	–	+
Adenomatous polyp, NOS																									
Large intestine	+	+	+	–	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma													X												
Urinary bladder	+	+	+	+	+	+	+	+	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Adrenal	+	+	+	+	+	+	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Thyroid	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Parathyroid	–	+	+	+	–	+	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	N	+	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Prostate	–	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, undifferentiated type												X													
Malignant lymphoma, lymphocytic type								X		X					X										
Malignant lymphoma, histiocytic type																X									
Malignant lymphoma, mixed type									X				X											X	

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

ANIMAL NUMBER	C 17	C 18	C 19	C 20	C 21	C 23	C 24	C 26	C 27	C 28	C 29	C 31	C 32	C 34	C 35	C 36	C 37	C 39	C 40	C 42	C 43	C 44	C 46	C 49	C 50	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	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma																										2
Fibrous histiocytoma, malignant																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																									X	2
Alveolar/bronchiolar adenoma		X				X																	X			6
Alveolar/bronchiolar carcinoma																			X							2
Trachea	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
HEMATOPOIETIC SYSTEM																										
Bone marrow	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
Spleen	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+	–	–	–	–	18
Malignant lymphoma, mixed type																				X						1
Lymph nodes	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	+	–	–	+	+	18
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	7
CIRCULATORY SYSTEM																										
Heart	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
DIGESTIVE SYSTEM																										
Salivary gland	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	9
Liver	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma														X	X	X				X	X	X				12
Hepatocellular carcinoma		X			X					X												X			X	6
Hemangiosarcoma													X													1
Malignant lymphoma, undiffer type																								X		1
Malignant lymphoma, mixed type					X																					1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	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
Pancreas	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	9
Esophagus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
Stomach	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
Small intestine	+	–	–	–	–	–	–	–	+	–	–	–	–	–	–	+	–	–	–	–	+	–	–	–	+	13
Adenomatous polyp, NOS																									X	1
Large intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	7
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma																										1
Urinary bladder	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	9
ENDOCRINE SYSTEM																										
Pituitary	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	9
Adrenal	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	7
Thyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
Parathyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	5
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
Prostate	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	7
NERVOUS SYSTEM																										
Brain	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS							X																			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, undiffer type																										1
Malignant lymphoma, lymphocytic type																										3
Malignant lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type	X																		X		X					6

* Animals necropsied

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

ANIMAL NUMBER	C 3 7	C 4 5	C 2 7	C 4 3	C 0 3	C 2 1	C 2 2	C 3 0	C 1 7	C 0 5	C 3 5	C 2 0	C 3 1	C 4 7	C 2 4	C 0 2	C 1 1	C 2 8	C 2 6	C 4 4	C 1 9	C 0 6	C 0 1	C 0 4	C 0 7
WEEKS ON STUDY	0 1 0	0 3 5	0 3 8	0 3 8	0 4 0	0 5 0	0 5 2	0 5 2	0 5 4	0 6 1	0 6 1	0 6 3	0 6 3	0 6 4	0 7 1	0 7 2	0 8 1	0 8 6	0 9 2	0 9 3	0 9 4	0 9 5	1 0 4	1 0 4	1 0 4
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																			X						
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																		X			X		X		
Alveolar/bronchiolar adenoma																X					X		X		
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	A	A	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	A	A	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, lymphocytic type																									
Thymus	+	+	+	+	+	+	A	A	–	–	+	+	+	–	–	+	+	–	+	+	–	–	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma										X			X		X	X									
Hepatocellular carcinoma										X	X	X						X		X	X	X	X		
Bile duct	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	N	N	N	N	+	+	+	N	+	+	+	N	+	N	+	+	+	+	+
Pancreas	+	+	+	+	+	+	A	A	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	A	A	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	A	A	–	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	+	+	+	+	+	+	A	A	–	–	+	+	+	–	+	+	+	–	–	–	+	+	+	+	+
Malignant lymphoma, lymphocytic type																							X		
Large intestine	+	+	+	+	+	–	A	A	–	–	+	+	+	–	–	+	+	–	+	–	–	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	A	A	–	+	+	+	+	–	+	+	+	–	+	–	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	A	A	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Thyroid	+	+	+	+	+	+	A	A	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	–	–	+	+	–	–	A	A	+	–	+	–	–	–	–	–	+	+	+	+	–	+	–	–	+
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	+	+	+	+	+	+	+	A	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	A	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+
Penis	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
Mast cell tumor																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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																									
Malignant lymphoma, mixed type																									

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

ANIMAL NUMBER	C 0 0 8	C 0 0 9	C 0 1 0	C 0 1 2	C 0 1 3	C 0 1 4	C 0 1 5	C 0 1 6	C 0 1 8	C 0 2 3	C 0 2 5	C 0 2 9	C 0 3 2	C 0 3 3	C 0 3 4	C 0 3 6	C 0 3 8	C 0 3 9	C 0 4 0	C 0 4 1	C 0 4 2	C 0 4 6	C 0 4 8	C 0 4 9	C 0 5 0	TOTAL:
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	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma													X								X					3
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic																					X					4
Alveolar/bronchiolar adenoma				X	X		X						X	X												8
Alveolar/bronchiolar carcinoma													X	X												2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	45
Malignant lymphoma, lymphocytic type	X																									1
Thymus	+	−	+	+	−	−	+	+	−	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	35
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma																	X		X					X		7
Hepatocellular carcinoma																					X				X	10
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Squamous cell papilloma	X															X										2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Malignant lymphoma, lymphocytic type																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	39
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Cortical adenoma																							X			1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid	+	−	−	−	+	+	−	+	−	+	−	−	+	−	+	+	+	+	+	+	+	+	+	+	+	27
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Penis	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
Mast cell tumor																								X		1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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
Malignant lymphoma, histiocytic type									X	X					X				X							1
Malignant lymphoma, mixed type																										4

* Animals necropsied

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

	Vehicle Control	500 mg/kg	1,000 mg/kg
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	2/50 (4%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	7.1%	4.8%	10.0%
Terminal Rates (c)	2/28 (7%)	1/35 (3%)	2/28 (7%)
Week of First Observation	104	48	92
Life Table Tests (d)	P=0.393	P=0.633N	P=0.492
Incidental Tumor Tests (d)	P=0.499	P=0.568N	P=0.474
Cochran-Armitage Trend Test (d)	P=0.406		
Fisher Exact Test (d)		P=0.691	P=0.500
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	10.7%	4.8%	10.0%
Terminal Rates (c)	3/28 (11%)	1/35 (3%)	2/28 (7%)
Week of First Observation	104	48	92
Life Table Tests (d)	P=0.581	P=0.419N	P=0.656
Incidental Tumor Tests (d)	P=0.501N	P=0.359N	P=0.641
Cochran-Armitage Trend Test (d)	P=0.588		
Fisher Exact Test (d)		P=0.500N	P=0.661
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	11/50 (22%)	6/50 (12%)	8/49 (16%)
Adjusted Rates (b)	33.4%	16.1%	26.2%
Terminal Rates (c)	7/28 (25%)	5/35 (14%)	6/28 (21%)
Week of First Observation	72	64	72
Life Table Tests (d)	P=0.271N	P=0.069N	P=0.341N
Incidental Tumor Tests (d)	P=0.347N	P=0.142N	P=0.444N
Cochran-Armitage Trend Test (d)	P=0.265N		
Fisher Exact Test (d)		P=0.144N	P=0.323N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	11/50 (22%)	8/50 (16%)	8/49 (16%)
Adjusted Rates (b)	33.4%	21.7%	26.2%
Terminal Rates (c)	7/28 (25%)	7/35 (20%)	6/28 (21%)
Week of First Observation	72	64	72
Life Table Tests (d)	P=0.276N	P=0.164N	P=0.341N
Incidental Tumor Tests (d)	P=0.351N	P=0.289N	P=0.444N
Cochran-Armitage Trend Test (d)	P=0.273N		
Fisher Exact Test (d)		P=0.306N	P=0.323N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	2.2%	(e)	7.1%
Terminal Rates (c)	0/28 (0%)		2/28 (7%)
Week of First Observation	62		104
Life Table Test (d)			P=0.483
Incidental Tumor Test (d)			P=0.463
Fisher Exact Test (d)			P=0.500
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	1/50 (2%)	8/50 (16%)	4/50 (8%)
Adjusted Rates (b)	3.6%	(e)	14.3%
Terminal Rates (c)	1/28 (4%)		4/28 (14%)
Week of First Observation	104		104
Life Table Test (d)			P=0.176
Incidental Tumor Test (d)			P=0.176
Fisher Exact Test (d)			P=0.181

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

	Vehicle Control	500 mg/kg	1,000 mg/kg
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	4/50 (8%)	14/50 (28%)	8/50 (16%)
Adjusted Rates (b)	11.6%	(e)	27.4%
Terminal Rates (c)	1/28 (4%)		7/28 (25%)
Week of First Observation	62		93
Life Table Test (d)			P=0.167
Incidental Tumor Test (d)			P=0.094
Fisher Exact Test (d)			P=0.178
Liver: Hepatocellular Adenoma			
Overall Rates (a)	9/50 (18%)	12/50 (24%)	7/49 (14%)
Adjusted Rates (b)	32.1%	31.7%	19.8%
Terminal Rates (c)	9/28 (32%)	10/35 (29%)	3/28 (11%)
Week of First Observation	104	67	61
Life Table Test (d)	P=0.370N	P=0.518	P=0.419N
Incidental Tumor Test (d)	P=0.417N	P=0.451	P=0.459N
Cochran-Armitage Trend Test (d)	P=0.368N		
Fisher Exact Test (d)		P=0.312	P=0.410N
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	5/50 (10%)	6/50 (12%)	10/49 (20%)
Adjusted Rates (b)	14.6%	17.1%	27.5%
Terminal Rates (c)	2/28 (7%)	6/35 (17%)	3/28 (11%)
Week of First Observation	85	104	61
Life Table Test (d)	P=0.082	P=0.611N	P=0.114
Incidental Tumor Test (d)	P=0.039	P=0.357	P=0.032
Cochran-Armitage Trend Test (d)	P=0.090		
Fisher Exact Test (d)		P=0.500	P=0.122
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	14/50 (28%)	17/50 (34%)	16/49 (33%)
Adjusted Rates (b)	44.2%	45.4%	41.3%
Terminal Rates (c)	11/28 (39%)	15/35 (43%)	6/28 (21%)
Week of First Observation	85	67	61
Life Table Tests (d)	P=0.329	P=0.572N	P=0.360
Incidental Tumor Tests (d)	P=0.212	P=0.351	P=0.206
Cochran-Armitage Trend Test (d)	P=0.347		
Fisher Exact Test (d)		P=0.333	P=0.388

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) Only 18 spleens and 18 lymph nodes were examined.

TABLE C4. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN CONTROL MALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence in All Water Gavage Controls			
Chlorpheniramine maleate (b)	10/50	6/50	16/50
Tetrakis(hydroxymethyl)phosphonium chloride (b)	8/49	10/49	17/49
Tetrakis(hydroxymethyl)phosphonium sulfate (b)	9/48	10/48	18/48
Chlorinated trisodium phosphate (c)	6/50	9/50	14/50
TOTAL	33/197 (16.8%)	35/197 (17.8%)	65/197 (33.0%)
SD (d)	3.53%	4.07%	4.05%
Range (e)			
High	10/50	10/48	18/48
Low	6/50	6/50	14/50
Overall Historical Incidence in Untreated Controls			
TOTAL	228/2,084 (10.9%)	424/2,084 (20.3%)	627/2,084 (30.1%)
SD (d)	7.29%	6.85%	7.78%
Range (e)			
High	(f) 22/50	16/50	(g) 29/50
Low	0/50	4/50	8/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Studies conducted at Battelle Columbus Laboratories
(c) Studies conducted at EG&G Mason Research Institute
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.
(f) Second highest: 11/50
(g) Second highest: 20/50

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF METHYL CARBAMATE

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Inflammation, acute suppurative	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Hemorrhage			1 (2%)
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Hemorrhage	1 (2%)		
*Larynx	(50)	(50)	(50)
Hemorrhage			1 (2%)
#Trachea	(50)	(8)	(49)
Inflammation, acute	1 (2%)		3 (6%)
#Lung/bronchiole	(50)	(50)	(49)
Inflammation, acute	3 (6%)		
#Lung	(50)	(50)	(49)
Congestion, NOS	3 (6%)		5 (10%)
Edema, NOS			1 (2%)
Hemorrhage	2 (4%)	1 (2%)	1 (2%)
Lymphocytic inflammatory infiltrate	32 (64%)	37 (74%)	22 (45%)
Inflammation, interstitial			1 (2%)
Inflammation, active chronic	1 (2%)		6 (12%)
Inflammation, chronic	2 (4%)		
Pigmentation, NOS	1 (2%)		1 (2%)
Hyperplasia, adenomatous	13 (26%)	19 (38%)	24 (49%)
Histiocytosis	11 (22%)	7 (14%)	21 (43%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(8)	(48)
Hyperplasia, NOS	1 (2%)	2 (25%)	
#Spleen	(49)	(18)	(47)
Angiectasis	1 (2%)		
Hyperplasia, lymphoid	1 (2%)		1 (2%)
Hematopoiesis	2 (4%)	2 (11%)	2 (4%)
#Splenic follicles	(49)	(18)	(47)
Necrosis, NOS	5 (10%)	2 (11%)	3 (6%)
#Lymph node	(48)	(18)	(45)
Necrosis, diffuse			1 (2%)
Hyperplasia, lymphoid	1 (2%)		
#Mandibular lymph node	(48)	(18)	(45)
Pigmentation, NOS			1 (2%)
#Mediastinal lymph node	(48)	(18)	(45)
Hemorrhage			1 (2%)
Inflammation, acute	1 (2%)		
#Mesenteric lymph node	(48)	(18)	(45)
Hemorrhage	13 (27%)	2 (11%)	4 (9%)
Hyperplasia, lymphoid	1 (2%)	1 (6%)	
Hematopoiesis	3 (6%)		1 (2%)
#Inguinal lymph node	(48)	(18)	(45)
Hyperplasia, lymphoid	2 (4%)		1 (2%)
#Liver	(50)	(50)	(49)
Hematopoiesis	2 (4%)		1 (2%)
#Peyer's patch	(41)	(13)	(42)
Hyperplasia, lymphoid	1 (2%)		

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF METHYL CARBAMATE (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Duodenum	(41)	(13)	(42)
Hyperplasia, lymphoid		1 (8%)	
#Jejunum	(41)	(13)	(42)
Hyperplasia, lymphoid	1 (2%)	2 (15%)	1 (2%)
#Ileum	(41)	(13)	(42)
Hyperplasia, lymphoid			3 (7%)
#Cecum	(42)	(7)	(39)
Hyperplasia, lymphoid			1 (3%)
#Thymus	(43)	(7)	(35)
Embryonal duct cyst		2 (29%)	1 (3%)
Atrophy, NOS	2 (5%)	1 (14%)	2 (6%)
CIRCULATORY SYSTEM			
#Mesenteric lymph node	(48)	(18)	(45)
Thrombosis, NOS			1 (2%)
#Lung	(50)	(50)	(49)
Thrombosis, NOS	1 (2%)		
#Heart	(50)	(8)	(48)
Mineralization			1 (2%)
Inflammation, chronic	4 (8%)		2 (4%)
Fibrosis			2 (4%)
Pigmentation, NOS			1 (2%)
#Right ventricle	(50)	(8)	(48)
Thrombosis, NOS		1 (13%)	
*Blood vessel	(50)	(50)	(50)
Thrombosis, NOS		1 (2%)	
*Artery	(50)	(50)	(50)
Periarteritis			1 (2%)
*Aorta	(50)	(50)	(50)
Inflammation, active chronic	1 (2%)		
*Coronary artery	(50)	(50)	(50)
Inflammation, necrotizing	1 (2%)	1 (2%)	
Inflammation, active chronic			1 (2%)
*Superior pancreaticoduodenal artery	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
*Mesenteric artery	(50)	(50)	(50)
Inflammation, necrotizing	1 (2%)	1 (2%)	
#Urinary bladder	(48)	(9)	(44)
Thrombosis, NOS			1 (2%)
DIGESTIVE SYSTEM			
*Tooth	(50)	(50)	(50)
Congenital malformation, NOS	4 (8%)		
Inflammation, acute			1 (2%)
#Salivary gland	(49)	(9)	(49)
Inflammation, chronic	34 (69%)	1 (11%)	14 (29%)
#Liver	(50)	(50)	(49)
Cyst, NOS	1 (2%)		1 (2%)
Hemorrhage			1 (2%)
Inflammation, acute		2 (4%)	
Inflammation, chronic	4 (8%)	3 (6%)	2 (4%)
Fibrosis, multifocal		1 (2%)	
Mitotic alteration		1 (2%)	
Cytoplasmic vacuolization	4 (8%)	2 (4%)	1 (2%)
Cytologic alteration, NOS	1 (2%)	3 (6%)	
Multinucleate giant cell	14 (28%)	31 (62%)	31 (63%)
#Liver/centrilobular	(50)	(50)	(49)
Congestion, NOS			1 (2%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF METHYL CARBAMATE (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Liver/hepatocytes	(50)	(50)	(49)
Necrosis, NOS	2 (4%)	2 (4%)	2 (4%)
Hyperplasia, NOS	2 (4%)	1 (2%)	1 (2%)
*Gallbladder	(50)	(50)	(50)
Inflammation, active chronic	1 (2%)		
Inflammation, chronic			1 (2%)
Hyperplasia, adenomatous			1 (2%)
#Pancreas	(50)	(9)	(47)
Inflammation, acute	1 (2%)		
Inflammation, chronic	5 (10%)		
Cytoplasmic vacuolization	2 (4%)		
#Pancreatic acinus	(50)	(9)	(47)
Atrophy, NOS	3 (6%)	1 (11%)	1 (2%)
#Esophagus	(50)	(8)	(47)
Inflammation, acute	1 (2%)		1 (2%)
#Esophageal adventitia	(50)	(8)	(47)
Hemorrhage		1 (13%)	
#Glandular stomach	(50)	(8)	(45)
Mineralization	1 (2%)		
Inflammation, acute	1 (2%)		
#Jejunum	(41)	(13)	(42)
Ulcer, NOS			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(49)
Mineralization	9 (18%)	2 (4%)	4 (8%)
Hydronephrosis		1 (2%)	
Cyst, NOS	1 (2%)		
Pyelonephritis, acute	3 (6%)		3 (6%)
Inflammation, chronic	27 (54%)	16 (32%)	8 (16%)
Scar	1 (2%)	1 (2%)	
Nephrosis, NOS			1 (2%)
#Renal papilla	(50)	(50)	(49)
Congestion, NOS	1 (2%)		
Hemorrhage	1 (2%)		
Necrosis, NOS	2 (4%)	1 (2%)	1 (2%)
#Kidney/tubule	(50)	(50)	(49)
Regeneration, NOS	3 (6%)	6 (12%)	6 (12%)
#Urinary bladder	(48)	(9)	(44)
Calculus, gross observation only			1 (2%)
Congestion, NOS	2 (4%)		
Hemorrhage	2 (4%)	1 (11%)	2 (5%)
Inflammation, acute	1 (2%)		2 (5%)
Inflammation, chronic	2 (4%)		
Mitotic alteration			1 (2%)
Hyperplasia, epithelial	1 (2%)		
*Urethra	(50)	(50)	(50)
Hemorrhage	2 (4%)		
Inflammation, acute	5 (10%)		
Ulcer, acute			1 (2%)
Inflammation, acute focal			1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(9)	(47)
Cyst, NOS	1 (2%)		
#Adrenal/capsule	(49)	(7)	(47)
Hyperplasia, NOS	34 (69%)	3 (43%)	24 (51%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF METHYL CARBAMATE (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Adrenal cortex	(49)	(7)	(47)
Necrosis, NOS			1 (2%)
Hypertrophy, NOS	1 (2%)	1 (14%)	6 (13%)
#Adrenal medulla	(49)	(7)	(47)
Hyperplasia, NOS	1 (2%)	1 (14%)	2 (4%)
#Thyroid	(50)	(8)	(47)
Embryonal duct cyst	9 (18%)		8 (17%)
Colloid cyst			2 (4%)
Inflammation, chronic			1 (2%)
#Parathyroid	(34)	(5)	(27)
Inflammation, chronic	1 (3%)		
#Pancreatic islets	(50)	(9)	(47)
Hyperplasia, NOS	1 (2%)		
REPRODUCTIVE SYSTEM			
*Penis	(50)	(50)	(50)
Inflammation, acute	1 (2%)		1 (2%)
*Prepuce	(50)	(50)	(50)
Vegetable foreign body			1 (2%)
Inflammation, chronic			2 (4%)
*Preputial gland	(50)	(50)	(50)
Dilatation, NOS		1 (2%)	
Inflammation, NOS	3 (6%)	1 (2%)	1 (2%)
Inflammation, acute			1 (2%)
#Prostate	(50)	(7)	(47)
Hemorrhage	1 (2%)		1 (2%)
Inflammation, acute	3 (6%)	1 (14%)	1 (2%)
Inflammation, active chronic	1 (2%)		1 (2%)
Inflammation, chronic	3 (6%)		
*Seminal vesicle	(50)	(50)	(50)
Inflammation, NOS	1 (2%)	2 (4%)	2 (4%)
#Testis	(49)	(8)	(47)
Spermatocele			1 (2%)
Atrophy, NOS		1 (13%)	2 (4%)
#Testis/tubule	(49)	(8)	(47)
Mineralization	2 (4%)		8 (17%)
*Epididymis	(50)	(50)	(50)
Inflammation, chronic	4 (8%)		
Granuloma, spermatic			2 (4%)
NERVOUS SYSTEM			
#Brain/meninges	(50)	(8)	(49)
Hemorrhage			1 (2%)
#Brain	(50)	(8)	(49)
Mineralization	31 (62%)	4 (50%)	12 (24%)
Cyst, NOS		1 (13%)	
SPECIAL SENSE ORGANS			
*Eye/cornea	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
Inflammation, chronic	1 (2%)		
*Eye/crystalline lens	(50)	(50)	(50)
Cataract	1 (2%)		3 (6%)
*Middle ear	(50)	(50)	(50)
Inflammation, acute suppurative		1 (2%)	

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF METHYL CARBAMATE (Continued)

	Vehicle Control	Low Dose	High Dose
MUSCULOSKELETAL SYSTEM			
*Skeletal muscle	(50)	(50)	(50)
Inflammation, NOS	2 (4%)		
*Intervertebral disc	(50)	(50)	(50)
Herniated nucleus pulposus			1 (2%)
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Inflammation, acute	1 (2%)		1 (2%)
*Peritoneum	(50)	(50)	(50)
Inflammation, acute suppurative	1 (2%)	1 (2%)	
*Pleura	(50)	(50)	(50)
Inflammation, acute	1 (2%)		1 (2%)
Inflammation, acute suppurative	1 (2%)		
*Epicardium	(50)	(50)	(50)
Inflammation, acute	2 (4%)		
Inflammation, chronic	1 (2%)		
*Mesentery	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
Necrosis, fat		1 (2%)	1 (2%)
ALL OTHER SYSTEMS			
Craniobuccal pouch			
Cyst, NOS	2		1
SPECIAL MORPHOLOGY SUMMARY			
Auto/necropsy/histo perf			1
Auto/necropsy/no histo			1

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

APPENDIX D

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF METHYL CARBAMATE

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

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Neurilemoma, malignant		1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(49)	(50)	(50)
Adenocarcinoma, NOS, metastatic		1 (2%)	
Alveolar/bronchiolar adenoma	6 (12%)	4 (8%)	3 (6%)
Alveolar/bronchiolar carcinoma	1 (2%)	1 (2%)	1 (2%)
Sarcoma, NOS, metastatic		1 (2%)	
Osteosarcoma, metastatic	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS	1 (2%)		1 (2%)
Malignant lymphoma, lymphocytic type	1 (2%)		3 (6%)
Malignant lymphoma, histiocytic type	4 (8%)	6 (12%)	4 (8%)
Malignant lymphoma, mixed type	8 (16%)	5 (10%)	4 (8%)
#Spleen	(48)	(14)	(49)
Malignant lymphoma, histiocytic type			1 (2%)
#Mesenteric lymph node	(48)	(16)	(50)
Malignant lymphoma, NOS			1 (2%)
Malignant lymphoma, mixed type		1 (6%)	
#Lung	(49)	(50)	(50)
Malignant lymphoma, NOS		1 (2%)	
#Liver	(49)	(50)	(50)
Malignant lymphoma, mixed type			1 (2%)
CIRCULATORY SYSTEM			
*Site unknown	(50)	(50)	(50)
Hemangioma	1 (2%)		
#Uterus	(49)	(29)	(50)
Hemangioma		1 (3%)	
DIGESTIVE SYSTEM			
#Liver	(49)	(50)	(50)
Hepatocellular adenoma	4 (8%)	5 (10%)	4 (8%)
Hepatocellular carcinoma	1 (2%)	2 (4%)	2 (4%)
#Forestomach	(47)	(6)	(47)
Squamous cell papilloma		1 (17%)	1 (2%)
#Colon	(45)	(4)	(41)
Adenomatous polyp, NOS	1 (2%)		
URINARY SYSTEM			
#Kidney	(49)	(49)	(50)
Osteosarcoma, metastatic	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Pituitary intermedia	(49)	(40)	(48)
Adenoma, NOS	1 (2%)		
#Anterior pituitary	(49)	(40)	(48)
Adenoma, NOS	9 (18%)	3 (8%)	
#Adrenal	(48)	(6)	(49)
Cortical adenoma	2 (4%)	1 (17%)	
#Adrenal medulla	(48)	(6)	(49)
Pheochromocytoma, malignant	1 (2%)		
#Thyroid	(48)	(5)	(49)
Follicular cell adenoma	2 (4%)		2 (4%)
#Pancreatic islets	(46)	(6)	(49)
Islet cell carcinoma			1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenocarcinoma, NOS		1 (2%)	
#Uterus	(49)	(29)	(50)
Sarcoma, NOS, invasive		1 (3%)	
Leiomyosarcoma			1 (2%)
Endometrial stromal polyp		1 (3%)	
Endometrial stromal sarcoma	1 (2%)		
Neurofibrosarcoma	1 (2%)		
#Ovary	(49)	(15)	(48)
Cystadenoma, NOS	1 (2%)	1 (7%)	
Teratoma, NOS		1 (7%)	
NERVOUS SYSTEM			
#Brain	(49)	(6)	(50)
Glioma, NOS			1 (2%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Malignant melanoma			1 (2%)
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS	1 (2%)	1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Vertebra	(50)	(50)	(50)
Osteosarcoma	1 (2%)		
BODY CAVITIES			
*Thoracic cavity	(50)	(50)	(50)
Osteosarcoma	1 (2%)		
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Osteosarcoma, metastatic	1 (2%)		
Neurilemoma, metastatic		1 (2%)	
Lower leg			
Sarcoma, NOS		1	

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

	Vehicle Control	Low Dose	High Dose
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	9	11	9
Moribund sacrifice	2	3	6
Terminal sacrifice	38	36	31
Dosing accident	1		4
TUMOR SUMMARY			
Total animals with primary tumors**	32	28	27
Total primary tumors	49	38	32
Total animals with benign tumors	22	13	10
Total benign tumors	28	18	10
Total animals with malignant tumors	20	19	21
Total malignant tumors	21	19	22
Total animals with secondary tumors##	2	3	
Total secondary tumors	3	4	
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 D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF METHYL CARBAMATE: VEHICLE CONTROL

ANIMAL NUMBER	C 4 3	C 0 2	C 1 5	C 3 0	C 3 5	C 2 6	C 3 8	C 1 9	C 1 3	C 1 0	C 0 7	C 2 1	C 0 1	C 0 3	C 0 4	C 0 5	C 0 6	C 0 8	C 0 9	C 1 1	C 1 2	C 1 4	C 1 6	C 1 7	C 1 8
WEEKS ON STUDY	0 1 1	0 6 4	0 6 4	0 6 6	0 7 5	0 8 1	0 8 3	0 8 4	0 8 6	0 8 9	0 9 0	0 9 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	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma															X		X								X
Alveolar/bronchiolar carcinoma																									
Osteosarcoma, metastatic																							X		
Trachea	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Spleen	+	−	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	−	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	A	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	−	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																	X	X			X			X	
Hepatocellular carcinoma																								X	
Bile duct	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	+	N	N	+	+	N	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	−	+	−	+	+	+	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	−	+	+	+	+	+	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	−	A	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	−	+	+	+	+	+	−	A	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenomatous polyp, NOS																					X				
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic																							X		
Urinary bladder	+	−	+	−	+	+	+	+	A	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS			X											X	X					X				X	
Adrenal	+	+	+	+	−	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									X
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																						X	X		
Parathyroid	+	−	−	+	−	+	−	+	A	−	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	N	+	+	+	+	N	N	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+
Uterus	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal sarcoma																	X								
Neurofibrosarcoma																									
Ovary	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma				X																					
BODY CAVITIES																									
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma																							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
Osteosarcoma, metastatic				X																					
Malignant lymphoma, NOS					X																				
Malignant lymphoma, lymphocytic type										X															
Malignant lymphoma, histiocytic type												X													
Malignant lymphoma, mixed type														X	X	X					X				
Site unknown																									
Hemangioma																									

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

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

ANIMAL NUMBER	C 2 0	C 2 2	C 2 3	C 2 4	C 2 5	C 2 7	C 2 8	C 2 9	C 3 1	C 3 2	C 3 3	C 3 4	C 3 6	C 3 7	C 3 9	C 4 0	C 4 1	C 4 2	C 4 4	C 4 5	C 4 6	C 4 7	C 4 8	C 4 9	C 5 0	TOTAL:
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	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma		X			X		X																			6
Alveolar/bronchiolar carcinoma															X											1
Osteosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma																										4
Hepatocellular carcinoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	47
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	46
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenomatous polyp, NOS																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	49
Osteosarcoma, metastatic																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	45
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS					X			X											X		X				X	10
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	48
Cortical adenoma																		X								2
Pheochromocytoma, malignant																									X	1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma																										2
Parathyroid	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	-	+	+	+	38
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	*50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endometrial stromal sarcoma																										1
Neurofibrosarcoma								X																		1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma, NOS												X														1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																								X		1
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma																										1
BODY CAVITIES																										
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma																										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
Osteosarcoma, metastatic																										1
Malignant lymphoma, NOS																										1
Malignant lymphoma, lymphocytic type																										1
Malignant lymphoma, histiocytic type									X			X			X											4
Malignant lymphoma, mixed type						X					X										X		X			6
Site unknown																										
Hemangioma	X																									1

* Animals necropsied

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

ANIMAL NUMBER	C 0 5	C 2 8	C 4 6	C 3 8	C 0 7	C 4 3	C 3 7	C 2 6	C 1 1	C 2 5	C 1 3	C 2 0	C 1 7	C 2 9	C 0 1	C 0 2	C 0 3	C 0 4	C 0 6	C 0 8	C 0 9	C 1 0	C 1 2	C 1 4	C 1 5
WEEKS ON STUDY	0 3 3	0 5 0	0 6 1	0 8 1	0 8 8	0 9 1	0 9 5	0 9 7	0 9 8	0 9 8	0 9 9	0 9 9	1 0 2	1 0 3	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Neurilemoma, malignant			X																						
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic													X												
Alveolar/bronchiolar adenoma																								X	X
Alveolar/bronchiolar carcinoma																									
Sarcoma, NOS, metastatic																								X	
Malignant lymphoma, NOS											X														
Trachea	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Spleen	+	+	+	+	+	−	−	+	−	+	−	−	−	+	−	−	−	−	−	−	−	−	+	−	−
Lymph nodes	+	+	+	−	+	+	−	+	−	+	−	+	−	+	−	−	−	−	+	−	−	+	−	+	−
Malignant lymphoma, mixed type																									
Thymus	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma															X					X	X		X		
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−
Esophagus	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Stomach	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Squamous cell papilloma																			X						
Small intestine	+	−	+	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	+	+	−	−	−
Large intestine	+	+	+	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
ENDOCRINE SYSTEM																									
Pituitary	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	+
Adenoma, NOS								X																	
Adrenal	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Cortical adenoma																									
Thyroid	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Parathyroid	+	+	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	N	+	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS													X												
Uterus	+	+	+	+	+	−	+	−	+	−	−	−	−	−	+	+	+	+	−	+	+	+	+	+	+
Sarcoma, NOS, invasive																								X	
Endometrial stromal polyp																					X				
Hemangioma																									
Ovary	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	+	+	−	+
Cystadenoma, NOS																						X			
Teratoma, NOS		X																							
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Neurilemoma, metastatic			X																						
Malignant lymphoma, histiocytic type					X					X		X		X											
Malignant lymphoma, mixed type						X													X				X		
Lower leg, NOS																									
Sarcoma, NOS																								X	

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

ANIMAL NUMBER	C 1 1 6	C 1 1 8	C 1 1 9	C 2 1 1	C 2 2 2	C 2 2 3	C 2 2 4	C 2 2 7	C 3 0	C 3 1 1	C 3 2	C 3 3 3	C 3 4 4	C 3 5	C 3 6	C 3 9	C 4 0	C 4 1	C 4 2	C 4 4 4	C 4 5	C 4 7	C 4 8	C 4 9	C 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	
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Neurilemoma, malignant																									1
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic																									1
Alveolar/bronchiolar adenoma						X																	X		4
Alveolar/bronchiolar carcinoma																								X	1
Sarcoma, NOS, metastatic																									1
Malignant lymphoma, NOS																									1
Trachea	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	5
HEMATOPOIETIC SYSTEM																									
Bone marrow	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	5
Spleen	–	–	–	–	–	–	+	–	+	–	–	–	–	–	–	–	–	+	–	+	+	–	–	–	14
Lymph nodes	–	–	–	–	–	–	+	–	–	–	–	–	+	–	–	–	–	–	–	–	+	–	+	–	16
Malignant lymphoma, mixed type																							X		1
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	6
CIRCULATORY SYSTEM																									
Heart	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	5
DIGESTIVE SYSTEM																									
Salivary gland	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	6
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma						X																	X		5
Hepatocellular carcinoma																	X								2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	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
Pancreas	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	6
Esophagus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	5
Stomach	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	6
Squamous cell papilloma																									1
Small intestine	–	+	–	–	–	–	+	–	+	–	–	–	–	–	–	–	–	+	–	–	+	–	–	–	11
Large intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	5
ENDOCRINE SYSTEM																									
Pituitary	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	40
Adenoma, NOS																				X			X		3
Adrenal	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	6
Cortical adenoma																							X		1
Thyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	5
Parathyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenocarcinoma, NOS																									1
Uterus	–	+	+	+	–	–	–	+	–	+	+	–	+	–	–	–	–	–	–	+	+	+	–	+	29
Sarcoma, NOS, invasive																									1
Endometrial stromal polyp																									1
Hemangioma																				X					1
Ovary	–	–	+	+	–	–	–	+	–	–	–	–	–	–	–	+	–	–	–	–	–	–	+	+	15
Cystadenoma, NOS																									1
Teratoma, NOS																									1
NERVOUS SYSTEM																									
Brain	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	6
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, 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	*50
Neurilemoma, metastatic																									1
Malignant lymphoma, histiocytic type							X		X																6
Malignant lymphoma, mixed type																		X		X					5
Lower leg, NOS																									
Sarcoma, NOS																									1

* Animals necropsied

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

ANIMAL NUMBER	C 4 3	C 0 5	C 3 4	C 2 3	C 0 1	C 1 0	C 4 2	C 4 4	C 3 7	C 1 4	C 0 4	C 1 3	C 2 0	C 3 5	C 5 0	C 2 4	C 0 3	C 4 5	C 0 2	C 0 6	C 0 7	C 0 8	C 0 9	C 1 1	C 1 2
WEEKS ON STUDY	0 1 7	0 5 1	0 5 6	0 6 2	0 6 4	0 6 4	0 6 4	0 6 4	0 6 5	0 8 5	0 8 9	0 9 1	0 9 3	0 9 7	0 9 9	1 0 0	1 0 3	1 0 3	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																				X			X		
Alveolar/bronchiolar carcinoma																X									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, histiocytic type				X																					
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS													X												
Thymus	−	−	+	+	+	+	+	+	−	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																						X			
Hepatocellular carcinoma																									
Malignant lymphoma, mixed type																								X	
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	N	+	+	N	+	N	+	+	N	N	N	+	N	N	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	−	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	+	+	+	+	−	+	+	−	−	−	+	+	−	−	−	+	−	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	−	+	+	−	−	−	+	+	−	−	−	+	−	−	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	−	+	+	−	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																								X	
Parathyroid	−	+	−	+	+	+	−	+	−	−	+	+	+	+	−	−	+	+	+	+	−	+	−	−	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	+	N	N	+	N	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	N
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Ovary	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma, NOS																									
SPECIAL SENSE ORGANS																									
Eye	N	N	+	N	N	+	N	N	N	+	+	+	N	+	N	N	+	N	+	N	N	+	N	N	+
Malignant melanoma						X																			
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS																		X							
Malignant lymphoma, lymphocytic type										X				X											
Malignant lymphoma, histiocytic type																X							X		
Malignant lymphoma, mixed type																			X		X				

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

ANIMAL NUMBER	C 15	C 16	C 17	C 18	C 19	C 21	C 22	C 25	C 26	C 27	C 28	C 29	C 30	C 31	C 32	C 33	C 36	C 38	C 39	C 40	C 41	C 46	C 47	C 48	C 49	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
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X																3
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, histiocytic type																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, NOS																										1
Thymus	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma		X														X									X	4
Hepatocellular carcinoma							X						X													2
Malignant lymphoma, mixed type																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell papilloma			X																							1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	49
Follicular cell adenoma																				X						2
Parathyroid	+	+	−	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	35
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell carcinoma					X																					1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																				X						1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma, NOS										X																1
SPECIAL SENSE ORGANS																										
Eye	+	N	+	N	+	N	+	N	+	+	+	+	+	N	N	+	+	+	+	N	+	+	+	+	+	*50
Malignant melanoma																										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, lymphocytic type																					X					3
Malignant lymphoma, histiocytic type									X														X			4
Malignant lymphoma, mixed type	X																	X								4

* Animals necropsied

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

	Vehicle Control	500 mg/kg	1,000 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	6/49 (12%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (b)	15.8%	11.1%	9.4%
Terminal Rates (c)	6/38 (16%)	4/36 (11%)	3/32 (9%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.261N	P=0.403N	P=0.331N
Incidental Tumor Tests (d)	P=0.261N	P=0.403N	P=0.331N
Cochran-Armitage Trend Test (d)	P=0.178N		
Fisher Exact Test (d)		P=0.357N	P=0.233N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	7/49 (14%)	5/50 (10%)	4/50 (8%)
Adjusted Rates (b)	18.4%	13.9%	12.0%
Terminal Rates (c)	7/38 (18%)	5/36 (14%)	3/32 (9%)
Week of First Observation	104	104	100
Life Table Tests (d)	P=0.296N	P=0.416N	P=0.361N
Incidental Tumor Tests (d)	P=0.253N	P=0.416N	P=0.269N
Cochran-Armitage Trend Test (d)	P=0.199N		
Fisher Exact Test (d)		P=0.365N	P=0.251N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	2.4%	(e)	8.0%
Terminal Rates (c)	0/38 (0%)		1/32 (3%)
Week of First Observation	89		85
Life Table Test (d)			P=0.287
Incidental Tumor Test (d)			P=0.276
Fisher Exact Test (d)			P=0.309
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	4/50 (8%)	6/50 (12%)	5/50 (10%)
Adjusted Rates (b)	10.3%	(e)	13.8%
Terminal Rates (c)	3/38 (8%)		3/32 (9%)
Week of First Observation	94		62
Life Table Test (d)			P=0.418
Incidental Tumor Test (d)			P=0.619N
Fisher Exact Test (d)			P=0.500
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	8/50 (16%)	6/50 (12%)	5/50 (10%)
Adjusted Rates (b)	21.1%	(e)	15.6%
Terminal Rates (c)	8/38 (21%)		5/32 (16%)
Week of First Observation	104		104
Life Table Test (d)			P=0.393N
Incidental Tumor Test (d)			P=0.393N
Fisher Exact Test (d)			P=0.277N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	14/50 (28%)	13/50 (26%)	15/50 (30%)
Adjusted Rates (b)	33.9%	(e)	38.7%
Terminal Rates (c)	11/38 (29%)		9/32 (28%)
Week of First Observation	75		62
Life Table Test (d)			P=0.342
Incidental Tumor Test (d)			P=0.525N
Fisher Exact Test (d)			P=0.500

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

	Vehicle Control	500 mg/kg	1,000 mg/kg
Liver: Hepatocellular Adenoma			
Overall Rates (a)	4/49 (8%)	5/50 (10%)	4/50 (8%)
Adjusted Rates (b)	10.5%	13.9%	12.5%
Terminal Rates (c)	4/38 (11%)	5/36 (14%)	4/32 (13%)
Week of First Observation	104	104	104
Life Table Test (d)	P=0.466	P=0.466	P=0.547
Incidental Tumor Test (d)	P=0.466	P=0.466	P=0.547
Cochran-Armitage Trend Test (d)	P=0.588N		
Fisher Exact Test (d)		P=0.513	P=0.631N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	4/49 (8%)	7/50 (14%)	6/50 (12%)
Adjusted Rates (b)	10.5%	19.4%	18.7%
Terminal Rates (c)	4/38 (11%)	7/36 (19%)	6/32 (19%)
Week of First Observation	104	104	104
Life Table Test (d)	P=0.212	P=0.228	P=0.264
Incidental Tumor Test (d)	P=0.212	P=0.228	P=0.264
Cochran-Armitage Trend Test (d)	P=0.331		
Fisher Exact Test (d)		P=0.274	P=0.383
Pituitary Gland: Adenoma			
Overall Rates (a)	9/49 (18%)	3/40 (8%)	0/48 (0%)
Adjusted Rates (b)	22.7%	9.3%	0.0%
Terminal Rates (c)	8/38 (21%)	2/28 (7%)	0/32 (0%)
Week of First Observation	64	97	
Life Table Tests (d)	P=0.002N	P=0.137N	P=0.005N
Incidental Tumor Tests (d)	P=0.001N	P=0.136N	P=0.004N
Cochran-Armitage Trend Test (d)	P=0.001N		
Fisher Exact Test (d)		P=0.118N	P=0.002N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) Only 14 spleens and 16 lymph nodes were examined.

TABLE D4. HISTORICAL INCIDENCE OF PITUITARY GLAND TUMORS IN CONTROL FEMALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence in All Water Gavage Controls			
Chlorpheniramine maleate (b)	5/46	0/46	5/46
Tetrakis(hydroxymethyl)phosphonium chloride (b)	11/50	0/50	11/50
Tetrakis(hydroxymethyl)phosphonium sulfate (b)	8/43	0/43	8/43
Chlorinated trisodium phosphate (c)	8/45	0/45	8/45
TOTAL	32/184 (17.4%)	0/184 (0.0%)	32/184 (17.4%)
SD (d)	4.67%	0.00%	4.67%
Range (e)			
High	11/50	0/50	11/50
Low	5/46	0/50	5/46
Overall Historical Incidence in Untreated Controls			
TOTAL	177/1,815 (9.8%)	(f) 13/1,815 (0.7%)	(f) 190/1,815 (10.5%)
SD (d)	9.39%	1.44%	9.61%
Range (e)			
High	12/40	3/50	16/50
Low	0/48	0/49	0/48

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Studies conducted at Battelle Columbus Laboratories
(c) Studies conducted at EG&G Mason Research Institute
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.
(f) Includes three adenocarcinomas, NOS

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

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Inflammation, acute			1 (2%)
Abscess, NOS	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Fibrosis, diffuse	1 (2%)		
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Inflammation, acute			3 (6%)
#Lung/bronchiole	(49)	(50)	(50)
Inflammation, acute			1 (2%)
#Lung	(49)	(50)	(50)
Congestion, NOS	1 (2%)		1 (2%)
Hemorrhage			2 (4%)
Bronchopneumonia, NOS			1 (2%)
Lymphocytic inflammatory infiltrate	36 (73%)	40 (80%)	39 (78%)
Inflammation, acute			1 (2%)
Pneumonia, interstitial chronic		1 (2%)	1 (2%)
Pigmentation, NOS		1 (2%)	
Hyperplasia, adenomatous	7 (14%)	10 (20%)	18 (36%)
Histiocytosis	9 (18%)	10 (20%)	21 (42%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(48)	(5)	(50)
Atrophy, NOS	1 (2%)	1 (20%)	1 (2%)
Hyperplasia, NOS	2 (4%)	1 (20%)	
#Spleen	(48)	(14)	(49)
Pigmentation, NOS			2 (4%)
Hyperplasia, lymphoid	4 (8%)		
Hematopoiesis	5 (10%)	3 (21%)	
#Splenic follicles	(48)	(14)	(49)
Atrophy, NOS			1 (2%)
#Mandibular lymph node	(48)	(16)	(50)
Cyst, NOS			2 (4%)
Inflammation, acute necrotizing		1 (6%)	
Pigmentation, NOS			1 (2%)
Plasmacytosis			1 (2%)
Hyperplasia, lymphoid	2 (4%)		
#Mediastinal lymph node	(48)	(16)	(50)
Hemorrhage			1 (2%)
#Mesenteric lymph node	(48)	(16)	(50)
Cyst, NOS	1 (2%)		
Edema, NOS	1 (2%)		
Hemorrhage	2 (4%)	2 (13%)	3 (6%)
Inflammation, active chronic	1 (2%)		
Fibrosis			1 (2%)
Hyperplasia, lymphoid	2 (4%)	1 (6%)	2 (4%)
Hematopoiesis	1 (2%)		1 (2%)
#Liver	(49)	(50)	(50)
Hematopoiesis	3 (6%)	3 (6%)	
#Duodenum	(46)	(11)	(42)
Hyperplasia, lymphoid		1 (9%)	

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

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Jejunum	(46)	(11)	(42)
Hyperplasia, lymphoid			1 (2%)
#Adrenal cortex	(48)	(6)	(49)
Hematopoiesis	1 (2%)		
#Thymus	(47)	(6)	(41)
Embryonal duct cyst		1 (17%)	2 (5%)
Atrophy, NOS	2 (4%)		
Hyperplasia, lymphoid	1 (2%)		
CIRCULATORY SYSTEM			
#Bone marrow	(48)	(5)	(50)
Thrombosis, NOS	1 (2%)		
#Mesenteric lymph node	(48)	(16)	(50)
Thrombosis, NOS	1 (2%)		
#Lung	(49)	(50)	(50)
Embolus, septic		1 (2%)	
#Heart	(50)	(5)	(50)
Mineralization		1 (20%)	
Hemorrhage			1 (2%)
Inflammation, chronic	8 (16%)		1 (2%)
*Artery	(50)	(50)	(50)
Vegetable foreign body			1 (2%)
Inflammation, chronic		1 (2%)	
Inflammation chronic necrotizing			1 (2%)
*Aorta	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
*Coronary artery	(50)	(50)	(50)
Inflammation chronic necrotizing			1 (2%)
Necrosis, NOS			1 (2%)
Metaplasia, osseous			1 (2%)
*Choroidal artery	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
*Cerebral artery	(50)	(50)	(50)
Inflammation, necrotizing			2 (4%)
*Inferior thyroid artery	(50)	(50)	(50)
Inflammation, active chronic			1 (2%)
*Superior pancreaticoduodenal artery	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
*Renal artery	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
*Vesical artery	(50)	(50)	(50)
Inflammation, necrotizing			1 (2%)
*Uterine artery	(50)	(50)	(50)
Inflammation, necrotizing			1 (2%)
DIGESTIVE SYSTEM			
*Tooth	(50)	(50)	(50)
Congenital malformation, NOS			1 (2%)
#Salivary gland	(48)	(6)	(49)
Inflammation, chronic	24 (50%)		6 (12%)
Necrosis, NOS	1 (2%)		
#Liver	(49)	(50)	(50)
Mineralization		1 (2%)	
Inflammation, acute necrotizing			1 (2%)
Inflammation, chronic	12 (24%)	6 (12%)	2 (4%)
Necrosis, NOS	1 (2%)	1 (2%)	1 (2%)
Mitotic alteration		2 (4%)	
Cytoplasmic vacuolization	2 (4%)	2 (4%)	
Basophilic cyto change			1 (2%)
Focal cellular change			1 (2%)

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

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM			
#Liver (Continued)	(49)	(50)	(50)
Cytologic alteration, NOS		2 (4%)	
Hyperplastic nodule		1 (2%)	
Hyperplasia, focal		1 (2%)	
Angiectasis		1 (2%)	1 (2%)
*Gallbladder	(50)	(50)	(50)
Cyst, NOS	1 (2%)		3 (6%)
Inflammation, chronic	4 (8%)		1 (2%)
Hyperplasia, adenomatous			1 (2%)
#Pancreas	(46)	(6)	(49)
Dilatation/ducts	3 (7%)		
Inflammation, acute	1 (2%)	1 (17%)	
Inflammation, chronic	9 (20%)		1 (2%)
#Pancreatic acinus	(46)	(6)	(49)
Atrophy, NOS	5 (11%)	1 (17%)	5 (10%)
Hyperplasia, NOS	1 (2%)		
*Esophageal lumen	(50)	(50)	(50)
Hemorrhage			3 (6%)
*Gastric lumen	(50)	(50)	(50)
Hemorrhage			1 (2%)
*Duodenal lumen	(50)	(50)	(50)
Hemorrhage			1 (2%)
#Esophagus/muscularis	(49)	(5)	(50)
Regeneration, NOS			1 (2%)
#Esophageal adventitia	(49)	(5)	(50)
Vegetable foreign body	1 (2%)		
Necrosis, NOS	1 (2%)		
#Stomach	(47)	(6)	(47)
Inflammation, chronic			1 (2%)
#Glandular stomach	(47)	(6)	(47)
Mineralization			3 (6%)
Erosion			1 (2%)
#Forestomach	(47)	(6)	(47)
Inflammation, chronic			1 (2%)
Erosion	1 (2%)		
#Duodenum	(46)	(11)	(42)
Inflammation, acute	2 (4%)		
#Ileum	(46)	(11)	(42)
Inflammation, acute			1 (2%)
URINARY SYSTEM			
#Kidney	(49)	(49)	(50)
Cyst, NOS	1 (2%)		
Glomerulonephritis, NOS	1 (2%)		
Inflammation, chronic	22 (45%)	11 (22%)	5 (10%)
Nephrosis, NOS	1 (2%)	3 (6%)	
Metaplasia, osseous			1 (2%)
#Kidney/capsule	(49)	(49)	(50)
Inflammation, acute suppurative		1 (2%)	
#Kidney/tubule	(49)	(49)	(50)
Regeneration, NOS	2 (4%)	1 (2%)	
#Kidney/pelvis	(49)	(49)	(50)
Dilatation, NOS		1 (2%)	
#Urinary bladder	(45)	(5)	(46)
Inflammation, chronic	1 (2%)		1 (2%)

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(40)	(48)
Cyst, NOS	1 (2%)		
Congestion, NOS	1 (2%)		
Hyperplasia, NOS	10 (20%)	1 (3%)	1 (2%)
Hyperplasia, focal	1 (2%)		
#Adrenal/capsule	(48)	(6)	(49)
Hyperplasia, NOS	41 (85%)	4 (67%)	46 (94%)
#Adrenal cortex	(48)	(6)	(49)
Necrosis, coagulative			1 (2%)
Atrophy, NOS	1 (2%)		
Hypertrophy, focal			1 (2%)
#Adrenal medulla	(48)	(6)	(49)
Hyperplasia, NOS			1 (2%)
#Thyroid	(48)	(5)	(49)
Embryonal duct cyst	2 (4%)		9 (18%)
Colloid cyst	1 (2%)		
Inflammation, NOS	8 (17%)		
Hyperplasia, follicular cell	2 (4%)		1 (2%)
#Pancreatic islets	(46)	(6)	(49)
Hyperplasia, NOS	1 (2%)		1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
Metaplasia, squamous	1 (2%)		
*Vagina	(50)	(50)	(50)
Inflammation, acute suppurative	1 (2%)		
#Uterus	(49)	(29)	(50)
Inflammation, acute	4 (8%)	2 (7%)	2 (4%)
Abscess, NOS	1 (2%)		
Inflammation, chronic	1 (2%)		
Angiectasis	1 (2%)		1 (2%)
#Cervix uteri	(49)	(29)	(50)
Inflammation, acute	2 (4%)		
Inflammation, active chronic	1 (2%)		
#Uterus/endometrium	(49)	(29)	(50)
Hyperplasia, cystic	37 (76%)	19 (66%)	34 (68%)
#Fallopian tube	(49)	(29)	(50)
Hyperplasia, cystic	1 (2%)		
#Ovary	(49)	(15)	(48)
Ectopia		1 (7%)	
Cyst, NOS	8 (16%)	10 (67%)	9 (19%)
Hemorrhage		1 (7%)	
Inflammation, NOS	2 (4%)		
Inflammation, acute		1 (7%)	
Metaplasia, osseous			1 (2%)
NERVOUS SYSTEM			
#Brain	(49)	(6)	(50)
Mineralization	24 (49%)	2 (33%)	16 (32%)
Perivascular cuffing	1 (2%)		
Malacia			1 (2%)
#Hippocampus	(49)	(6)	(50)
Necrosis, focal	1 (2%)		
*Spinal cord	(50)	(50)	(50)
Demyelinization			1 (2%)

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

	Vehicle Control	Low Dose	High Dose
SPECIAL SENSE ORGANS			
*Eye/cornea	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
*Eye/crystalline lens	(50)	(50)	(50)
Cataract		1 (2%)	
*Nasolacrimal duct	(50)	(50)	(50)
Inflammation, acute			1 (2%)
*Middle ear	(50)	(50)	(50)
Inflammation, acute suppurative		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Fibrous dysplasia	1 (2%)		1 (2%)
*Vertebra	(50)	(50)	(50)
Fracture, NOS			1 (2%)
BODY CAVITIES			
*Thoracic cavity	(50)	(50)	(50)
Vegetable foreign body			1 (2%)
Inflammation, NOS	1 (2%)		1 (2%)
*Abdominal cavity	(50)	(50)	(50)
Inflammation, NOS	3 (6%)		1 (2%)
*Mesentery	(50)	(50)	(50)
Necrosis, fat	1 (2%)	1 (2%)	
ALL OTHER SYSTEMS			
None			
SPECIAL MORPHOLOGY SUMMARY			
Auto/necropsy/histo perf	1		

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

APPENDIX E

GENETIC TOXICOLOGY OF METHYL CARBAMATE

TABLE E1. MUTAGENICITY OF METHYL CARBAMATE IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/plate (b) −S9 Trial 1	−S9 Trial 2	+S9 (hamster) Trial 1	+S9 (hamster) Trial 2	+S9 (rat) Trial 1	+S9 (rat) Trial 2
TA100	0	107 ± 5.0	110 ± 10.3	109 ± 4.2	147 ± 24.6	124 ± 12.4	120 ± 5.7
	100	95 ± 10.8	75 ± 29.6	110 ± 16.1	114 ± 24.8	113 ± 15.9	120 ± 8.7
	333	101 ± 4.2	93 ± 25.1	107 ± 9.3	106 ± 3.2	104 ± 3.2	99 ± 17.0
	1,000	105 ± 5.9	103 ± 15.5	124 ± 0.7	102 ± 20.9	130 ± 3.0	107 ± 3.1
	3,333	95 ± 1.5	98 ± 14.0	110 ± 4.7	126 ± 1.0	125 ± 10.2	103 ± 7.1
	10,000	101 ± 3.5	102 ± 8.0	102 ± 1.3	124 ± 6.7	123 ± 3.8	79 ± 10.0
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (c)	291 ± 8.8	238 ± 18.6	1,863 ± 16.2	481 ± 5.9	819 ± 28.0	714 ± 68.4
TA1535	0	16 ± 3.3	19 ± 5.5	6 ± 1.5	14 ± 1.0	6 ± 0.3	7 ± 0.6
	100	14 ± 1.5	25 ± 3.3	6 ± 1.2	9 ± 0.7	8 ± 0.3	10 ± 2.3
	333	12 ± 2.4	16 ± 2.3	6 ± 1.2	9 ± 1.9	9 ± 1.8	13 ± 0.6
	1,000	11 ± 1.5	22 ± 0.6	8 ± 2.7	12 ± 2.3	9 ± 0.3	9 ± 1.2
	3,333	14 ± 1.2	23 ± 3.1	5 ± 0.9	10 ± 1.7	6 ± 1.5	8 ± 0.9
	10,000	15 ± 0.7	20 ± 1.2	6 ± 1.2	9 ± 1.5	5 ± 1.2	7 ± 2.6
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (c)	246 ± 8.8	265 ± 19.3	415 ± 9.5	256 ± 29.3	221 ± 17.0	285 ± 27.5
TA97	0	120 ± 8.5	189 ± 5.5	174 ± 8.1	233 ± 12.5	161 ± 16.2	188 ± 13.8
	100	125 ± 1.5	179 ± 22.2	159 ± 3.5	187 ± 22.2	198 ± 16.2	213 ± 9.3
	333	133 ± 9.7	182 ± 14.7	164 ± 20.0	216 ± 14.5	213 ± 9.3	214 ± 15.9
	1,000	126 ± 8.7	196 ± 19.0	147 ± 9.3	216 ± 12.2	197 ± 12.7	214 ± 6.7
	3,333	129 ± 10.1	188 ± 8.4	157 ± 7.4	200 ± 14.6	202 ± 6.1	214 ± 18.2
	10,000	130 ± 10.1	179 ± 20.5	143 ± 10.7	202 ± 9.3	197 ± 4.7	200 ± 19.6
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (c)	1,156 ± 22.0	879 ± 21.2	1,885 ± 76.9	1,135 ± 20.6	1,452 ± 80.7	1,528 ± 105.9
TA98	0	15 ± 1.5	16 ± 1.5	29 ± 1.9	33 ± 5.5	24 ± 0.9	31 ± 2.4
	100	9 ± 2.9	16 ± 4.7	21 ± 1.5	20 ± 1.2	21 ± 2.7	23 ± 1.7
	333	14 ± 3.5	15 ± 1.5	24 ± 4.3	19 ± 1.3	21 ± 1.7	22 ± 4.2
	1,000	14 ± 0.9	18 ± 1.9	29 ± 4.4	22 ± 1.2	29 ± 0.9	17 ± 4.6
	3,333	14 ± 1.5	17 ± 2.5	27 ± 1.2	18 ± 0.9	20 ± 2.7	17 ± 1.5
	10,000	18 ± 2.5	16 ± 3.5	22 ± 5.6	18 ± 3.3	21 ± 3.1	20 ± 0.3
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (c)	396 ± 24.4	458 ± 41.2	1,105 ± 7.8	384 ± 54.4	328 ± 26.0	124 ± 35.7

(a) Study performed at SRI International. The detailed protocol is presented in Haworth et al. (1983). Cells and study compound or solvent (distilled water) were incubated in the absence of exogenous metabolic activation (−S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 µg/plate dose is the solvent control.
(b) Revertants are presented as mean ± standard error from three plates.
(c) Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-o-phenylenediamine was used with TA98, sodium azide was used with TA100 and TA1535, and 9-aminoacridine was used with TA97.

TABLE E2. MUTAGENICITY OF METHYL CARBAMATE IN MOUSE L5178Y LYMPHOMA CELLS (a,b)

Compound	Concentration (μg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutant Count	Mutant Fraction (c)
-S9					
Studies performed at SRI International					
Trial 1					
Distilled water		92.3 ± 2.2	100.0 ± 11.2	111.0 ± 9.6	40.3 ± 2.8
Methyl carbamate					
	1,049	81.0 ± 8.0	84.0 ± 25.0	110.0 ± 0.0	45.5 ± 4.5
	1,311	84	99	126	50
	1,638	80.0 ± 4.0	73.5 ± 4.5	120.0 ± 24.0	49.5 ± 7.5
	2,048	88.5 ± 8.5	116.0 ± 8.0	172.5 ± 13.5	(d) 66.0 ± 11.0
	2,560	87.5 ± 13.5	95.5 ± 20.5	134.5 ± 21.5	51.5 ± 0.5
	3,200	72.5 ± 3.5	64.5 ± 14.5	99.5 ± 1.5	46.0 ± 3.0
	4,000	80.0 ± 2.0	76.5 ± 0.5	96.5 ± 7.5	40.5 ± 4.5
	5,000	87.5 ± 8.5	92.0 ± 42.0	101.0 ± 13.0	38.5 ± 1.5
Ethyl methanesulfonate					
	500	48.3 ± 1.8	34.3 ± 4.3	1,058.7 ± 38.6	(d) 736.3 ± 50.5
Trial 2					
Distilled water		73.5 ± 1.6	99.8 ± 4.3	100.0 ± 12.1	45.5 ± 6.5
Methyl carbamate					
	512	80.5 ± 5.5	118.5 ± 4.5	117.0 ± 1.0	49.0 ± 4.0
	1,024	76.5 ± 1.5	122.5 ± 4.5	123.0 ± 4.0	54.0 ± 3.0
	2,048	76.5 ± 10.5	98.5 ± 2.5	78.0 ± 4.0	34.5 ± 2.5
	2,560	64.0 ± 3.0	95.0 ± 2.0	81.0 ± 7.0	42.5 ± 5.5
	3,200	65.0 ± 5.0	98.0 ± 10.0	84.0 ± 5.0	43.0 ± 1.0
	4,000	77.0 ± 4.0	102.0 ± 10.0	130.0 ± 5.0	56.5 ± 0.5
	5,000	74.0 ± 4.0	96.0 ± 3.0	99.5 ± 0.5	45.0 ± 3.0
Ethyl methanesulfonate					
	500	25.7 ± 1.8	20.3 ± 1.9	874.0 ± 23.9	(d) 1,150.3 ± 58.4
Trial 3					
Distilled water		91.5 ± 1.6	100.3 ± 2.0	73.8 ± 16.3	26.8 ± 5.6
Methyl carbamate					
	1,638	79.3 ± 3.7	81.0 ± 2.1	78.3 ± 4.2	33.0 ± 0.6
	2,048	80.0 ± 4.9	91.7 ± 2.4	70.7 ± 12.6	30.3 ± 6.9
	2,560	80.3 ± 0.9	87.0 ± 2.5	63.0 ± 11.5	26.0 ± 5.0
	3,200	82.7 ± 7.4	91.3 ± 9.6	60.7 ± 19.3	26.0 ± 10.0
	4,000	95.3 ± 3.5	91.3 ± 6.7	90.7 ± 4.9	32.0 ± 1.5
	5,000	94.0 ± 0.0	94.5 ± 5.5	74.0 ± 13.0	26.5 ± 4.5
Ethyl methanesulfonate					
	500	55.0 ± 1.2	38.0 ± 1.0	935.0 ± 3.0	(d) 568.3 ± 13.3

TABLE E2. MUTAGENICITY OF METHYL CARBAMATE IN MOUSE L5178Y LYMPHOMA CELLS
(Continued)

Compound	Concentration (µg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutant Count	Mutant Fraction (c)
– S9 (Continued)					
Studies performed at Litton Bionetics, Inc.					
Trial 1					
Distilled water		94.3 ± 4.4	100.0 ± 8.1	53.5 ± 4.2	19.0 ± 1.2
Methyl carbamate					
	156	102.0 ± 1.0	96.5 ± 5.5	42.5 ± 11.5	14.0 ± 4.0
	313	101.5 ± 1.5	94.5 ± 10.5	50.5 ± 5.5	17.0 ± 2.0
	625	95.0 ± 6.0	96.5 ± 2.5	38.5 ± 17.5	13.0 ± 5.0
	1,250	96.5 ± 7.5	100.0 ± 2.0	42.5 ± 7.5	14.5 ± 1.5
	2,500	94.5 ± 1.5	95.5 ± 4.5	58.0 ± 9.0	20.5 ± 2.5
	5,000	91.5 ± 3.5	96.5 ± 7.5	36.5 ± 1.5	13.0 ± 0.0
Ethyl methanesulfonate					
	500	46.0 ± 9.7	24.0 ± 4.0	961.0 ± 76.1	(d) 730.0 ± 88.2
Trial 2					
Distilled water		77.5 ± 2.2	100.3 ± 3.9	37.3 ± 5.2	16.0 ± 2.5
Methyl carbamate					
	313	89.0 ± 5.8	107.7 ± 14.7	46.7 ± 9.6	17.3 ± 2.7
	625	98.0 ± 4.7	145.0 ± 0.6	39.3 ± 3.8	13.7 ± 0.7
	1,250	106.0 ± 2.3	163.7 ± 11.0	30.3 ± 3.8	9.3 ± 1.2
	2,500	110.5 ± 3.5	158.5 ± 5.5	27.5 ± 0.5	8.0 ± 0.0
	5,000	113	160	49	14
Ethyl methanesulfonate					
	500	48.3 ± 8.6	38.0 ± 12.0	671.7 ± 31.0	(d) 492.0 ± 71.9
+ Noninduced S9 (e)					
Studies performed at Litton Bionetics, Inc.					
Trial 1					
Distilled water		77.0 ± 4.1	100.0 ± 6.9	43.0 ± 5.4	19.0 ± 3.3
Methyl carbamate					
	313	70.3 ± 5.2	81.0 ± 2.5	54.7 ± 6.1	26.0 ± 2.5
	625	74.7 ± 9.1	68.3 ± 1.8	54.7 ± 9.4	24.0 ± 1.5
	1,250	75.0 ± 3.6	83.0 ± 7.4	44.7 ± 3.7	20.0 ± 2.1
	2,500	82.0 ± 7.0	77.0 ± 1.0	44.0 ± 10.0	17.5 ± 2.5
	5,000	72.7 ± 1.2	82.3 ± 6.0	43.7 ± 5.9	20.3 ± 2.7
Methylcholanthrene					
	7	68.3 ± 5.6	55.3 ± 3.3	228.0 ± 26.3	(d) 110.7 ± 4.8

TABLE E2. MUTAGENICITY OF METHYL CARBAMATE IN MOUSE L5178Y LYMPHOMA CELLS (Continued)

Compound	Concentration (μg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutant Count	Mutant Fraction (c)
+ Noninduced S9 (e) (Continued)					
Trial 2					
Distilled water		104.5 ± 1.8	100.0 ± 7.1	52.0 ± 3.1	16.8 ± 1.1
Methyl carbamate	313	97.0 ± 5.6	86.3 ± 7.4	56.7 ± 10.7	19.3 ± 3.0
	625	88.3 ± 3.0	80.0 ± 3.2	42.7 ± 1.8	16.0 ± 0.6
	1,250	87.3 ± 3.2	89.0 ± 2.6	41.3 ± 3.4	15.7 ± 0.7
	2,500	89.7 ± 7.4	105.7 ± 6.6	43.7 ± 3.3	16.3 ± 0.9
	5,000	87.0 ± 4.5	88.0 ± 2.5	46.0 ± 4.6	17.7 ± 1.8
Methylcholanthrene	7	94.7 ± 5.8	60.0 ± 1.7	254.0 ± 12.5	(d) 89.7 ± 0.9
+ Induced S9 (f)					
Studies performed at SRI International					
Trial 1					
Distilled water		85.0 ± 2.9	100.3 ± 4.4	93.0 ± 6.7	36.7 ± 3.7
Methyl carbamate	588	73.0 ± 1.0	107.0 ± 6.0	110.5 ± 27.5	50.0 ± 12.0
	840	84.0 ± 5.7	95.0 ± 11.5	124.0 ± 3.1	50.0 ± 4.4
	1,201	93.3 ± 8.8	97.7 ± 8.8	104.3 ± 4.9	37.7 ± 1.9
	1,715	95.0 ± 4.0	92.7 ± 3.8	93.7 ± 8.3	32.7 ± 1.7
	2,450	103.3 ± 2.3	98.7 ± 2.2	97.7 ± 4.6	31.7 ± 1.3
	3,500	99.0 ± 3.8	96.7 ± 5.7	101.7 ± 0.7	34.3 ± 1.2
	5,000	90.7 ± 3.0	94.0 ± 3.5	93.0 ± 11.4	33.7 ± 3.7
Methylcholanthrene	5	79.3 ± 2.2	72.3 ± 1.5	368.0 ± 2.3	(d) 155.0 ± 3.6
Trial 2					
Distilled water		76.0 ± 2.5	100.0 ± 7.1	58.3 ± 0.3	25.7 ± 1.2
Methyl carbamate	2,048	70	82	39	19
	2,560	59.5 ± 5.5	70.5 ± 5.5	57.5 ± 11.5	33.0 ± 9.0
	3,200	65.5 ± 1.5	104.0 ± 6.0	49.0 ± 13.0	25.0 ± 6.0
	4,000	63	81	84	45
	5,000	71.5 ± 0.5	84.0 ± 1.0	54.0 ± 18.0	25.5 ± 8.5
Methylcholanthrene	5	56.3 ± 1.5	56.7 ± 3.2	224.7 ± 8.4	(d) 132.3 ± 2.6

TABLE E2. MUTAGENICITY OF METHYL CARBAMATE IN MOUSE L5178Y LYMPHOMA CELLS
(Continued)

Compound	Concentration (μg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutant Count	Mutant Fraction (c)
+ Induced S9 (f) (Continued)					
Studies performed at Litton Bionetics, Inc.					
Trial 1					
Distilled water		94.8 ± 6.9	99.8 ± 6.3	63.5 ± 11.6	22.0 ± 2.6
Methyl carbamate					
	156	84.5 ± 13.5	89.5 ± 11.5	57.5 ± 0.5	23.0 ± 4.0
	313	110	82	85	26
	625	74.0 ± 3.0	104.0 ± 2.0	50.5 ± 2.5	23.0 ± 2.0
	1,250	96.0 ± 4.0	98.5 ± 0.5	78.0 ± 17.0	27.0 ± 5.0
	2,500	89.0 ± 10.0	99.5 ± 3.5	54.0 ± 4.0	20.5 ± 0.5
	5,000	100.5 ± 3.5	103.0 ± 9.0	66.5 ± 3.5	22.0 ± 2.0
Methylcholanthrene					
	5	42.0 ± 2.5	18.7 ± 2.2	393.0 ± 4.9	(d) 314.3 ± 21.1
Trial 2					
Distilled water		78.3 ± 1.9	100.0 ± 3.3	34.5 ± 3.0	14.8 ± 1.7
Methyl carbamate					
	313	62.0 ± 9.2	64.3 ± 6.6	43.0 ± 2.1	(d) 24.0 ± 2.3
	625	56.7 ± 11.1	63.0 ± 13.5	45.7 ± 9.3	(d) 28.3 ± 6.7
	1,250	74.7 ± 3.4	81.0 ± 6.4	49.3 ± 11.3	21.7 ± 4.1
	2,500	76.0 ± 11.0	91.3 ± 18.0	47.0 ± 4.5	21.3 ± 2.4
	5,000	73.7 ± 6.9	87.7 ± 3.8	43.3 ± 7.0	20.0 ± 4.0
Methylcholanthrene					
	5	46.0 ± 2.5	18.0 ± 1.0	259.7 ± 20.2	(d) 190.7 ± 18.8

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

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

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

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

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

(f) Same experimental method as (e) except that S9 was from the liver of Aroclor 1254-induced F344 rats.

TABLE E3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY METHYL CARBAMATE (a)

Compound	Dose (µg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
−S9 (c)								
Trial No. 1--Summary: Negative								
Medium		50	1,040	370	0.36	7.4	26.5	--
Methyl carbamate	160	50	1,037	395	0.38	7.9	26.5	106.8
	500	50	1,031	403	0.39	8.1	26.5	109.5
	1,600	50	1,024	360	0.35	7.2	26.5	97.3
	5,000	50	1,039	423	0.41	8.5	26.5	114.9
Mitomycin C	0.010	50	1,038	2,539	2.45	50.8	26.5	686.5
Trial No. 2--Summary: Equivocal								
Medium		50	1,033	378	0.37	7.6	26.0	--
Methyl carbamate	2,000	50	1,036	355	0.34	7.1	26.0	93.4
	3,000	50	1,030	389	0.38	7.8	26.0	102.6
	4,000	50	1,014	422	0.42	8.4	26.0	110.5
	5,000	50	1,043	430	0.41	8.6	26.0	113.2
Mitomycin C	0.005	50	1,039	1,301	1.25	26.0	26.0	342.1
+S9 (d)								
Trial No. 1--Summary: Negative								
Medium		50	1,042	383	0.37	7.7	26.5	--
Methyl carbamate	160	50	1,042	392	0.38	7.8	26.5	101.3
	500	50	1,042	374	0.36	7.5	26.5	97.4
	1,600	50	1,044	377	0.36	7.5	26.5	97.4
	5,000	50	1,040	371	0.36	7.4	26.5	96.1
Cyclophosphamide	1.500	50	1,052	1,123	1.07	22.5	26.5	292.2
Trial No. 2--Summary: Negative								
Medium		50	1,044	437	0.42	8.7	26.0	--
Methyl carbamate	2,000	50	1,039	407	0.39	8.1	26.0	93.1
	3,000	50	1,039	354	0.34	7.1	26.0	81.6
	4,000	50	1,046	397	0.38	7.9	26.0	90.8
	5,000	50	1,049	369	0.35	7.4	26.0	85.1
Cyclophosphamide	1.500	50	1,042	1,430	1.37	28.6	26.0	328.7

TABLE E3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY METHYL CARBAMATE (Continued)

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

TABLE E4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY METHYL CARBAMATE (a)

Dose (μg/ml)	Total Cells	−S9 (b) No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (μg/ml)	Total Cells	+S9 (c) No. of Abs	Abs/ Cell	Percent Cells with Abs
Trial 1--Harvest time: 12.0 hours					Trial 1--Harvest time: 12.0 hours				
Medium					Medium				
	100	0	0.00	0		100	0	0.00	0
Methyl carbamate					Methyl carbamate				
2,000	100	2	0.02	2	2,000	100	2	0.02	2
3,000	100	5	0.05	4	3,000	100	0	0.00	0
4,000	100	2	0.02	2	4,000	100	1	0.01	1
5,000	100	1	0.01	1	5,000	100	1	0.01	1
Summary: Negative					Summary: Negative				
Mitomycin C					Cyclophosphamide				
0.500	100	96	0.96	57	50	100	57	0.57	39

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

TABLE E5. INDUCTION OF SEX-LINKED RECESSIVE LETHAL MUTATIONS IN DROSOPHILA BY METHYL CARBAMATE (a)

Route of Exposure	Dose (ppm)	Incidence of Deaths (percent)	Incidence of Sterility (percent)	No. of Lethals/No. of X Chromosomes Tested Mating 1	Mating 2	Mating 3	Overall Total
Injection	25,000	36	3	2/2,009	2/1,787	4/1,553	8/5,349 (0.15%)
	0			2/1,879	2/1,800	0/1,178	4/4,857 (0.08%)
Feeding	35,000	15	0	1/1,867	3/1,617	1/1,336	5/4,820 (0.10%)
	0			1/1,213	3/1,105	1/972	5/3,290 (0.15%)
Feeding	50,000	48	13	0/392	1/265	0/252	1/909 (0.11%)
	0			0/885	0/811	0/766	0/2,462 (0.00%)

(a) Study performed at the University of Wisconsin, Madison. A detailed protocol of the sex-linked recessive lethal assay was presented by Zimmering et al. (1985). In the feeding experiments, 24-hour-old Canton-S males were fed a solution of the study chemical dissolved in 5% sucrose for 3 days. In the injection experiments, 24-hour-old Canton-S males were treated with a solution of the chemical dissolved in 0.7% saline and allowed 24 hours to recover. Exposed males were mated to three Basc females for 3 days and given fresh females at 2-day intervals to produce three broods of 3, 2, and 2 days; successive matings sample sperm treated as spermatozoa (mating 1), spermatids (mating 2), and spermatocytes (mating 3). F_1 heterozygous females were crossed to their siblings and placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters; none was found. After 17 days, presumptive lethal mutations were identified as vials containing no wild-type males; these were retested. Results were not significant at the 5% level (Margolin et al., 1983).

TABLE E6. INDUCTION OF UNSCHEDULED DNA SYNTHESIS IN PRIMARY RAT HEPATOCYTE CULTURES BY METHYL CARBAMATE (a)

Compound	Dose (µg/ml)	Net Nuclear Grain Count (b)	Percent Cells in Repair (c)	Overall Net Nuclear Grain Count (d)	Overall Percent Cells in Repair (d)
Methyl carbamate	1	−1.16 ± 0.29	0	−2.57 ± 0.27	1
		−4.07 ± 0.58	2		
		−2.47 ± 0.42	2		
	5	−0.094 ± 0.29	2	−2.00 ± 0.29	1
		−3.07 ± 0.45	0		
	10	−3.10 ± 0.42	0	−1.21 ± 0.30	6
		−0.075 ± 0.18	0		
		0.20 ± 0.70	20		
	25	−0.03 ± 0.42	6	−2.41 ± 0.38	4
		−5.62 ± 0.85	6		
		−1.57 ± 0.34	0		
	50	−1.55 ± 0.54	8	−1.40 ± 0.28	5
		−0.55 ± 0.43	6		
		−2.10 ± 0.47	2		
	100	0.01 ± 0.54	4	−0.30 ± 0.26	3
		0.80 ± 0.39	8		
		−1.55 ± 0.37	0		
	250	−0.03 ± 0.33	4	−0.43 ± 0.33	4
		−0.84 ± 0.56	4		
	500	−1.82 ± 0.37	0	−1.79 ± 0.22	0
		−1.88 ± 0.32	0		
		−1.67 ± 0.44	2		
	1,000	−1.74 ± 0.37	0	−1.73 ± 0.20	0
		−1.16 ± 0.21	0		
		−2.29 ± 0.40	0		
Negative control (medium)	0	−0.95 ± 0.36	0	−1.23 ± 0.20	1
		−1.05 ± 0.23	0		
		−3.28 ± 0.85	4		
Control (doubly distilled water)	0	−0.43 ± 0.18	0	−1.18 ± 0.16	0
		−1.12 ± 0.28	0		
		−2.00 ± 0.34	0		
Dimethyl sulfoxide	1%	−0.83 ± 0.29	0	−1.29 ± 0.19	1
		−1.99 ± 0.39	2		
		−1.03 ± 0.31	0		
Positive control (2-acetylaminofluorene)	5	Too numerous to count			
	10	Too numerous to count			

(a) Study performed at the National Center for Toxicological Research. A detailed description of the protocol was presented by Oldham et al. (1980). Primary rat hepatocytes were isolated by perfusion from male F344 rat liver, allowed to attach to coverslips for 2 hours, and then incubated with the study compound in the presence of [methyl-^{3}H]thymidine for 18-24 hours. The solvent used was dimethyl sulfoxide; the positive control was 2-acetylaminofluorene. Highest dose of study compound was determined by solubility or toxicity but did not exceed 1,000 µg/ml. After chemical exposure, cells were washed, fixed, and prepared for autoradiography. The coverslips were attached to a glass slide, coated with Kodak NTB-2 emulsion, and stored at 4° C for 6-7 days in the dark. After development, the cells were examined microscopically and the silver grains representing incorporation of [methyl-^{3}H]thymidine during unscheduled DNA synthesis (UDS) were observed and counted.
(b) The net nuclear grain count was determined by subtracting the grain count from a nuclear-sized area over the cytoplasm from the nuclear count for each of 50 cells randomly selected on the coverslip. The mean net nuclear grain count for the 50 cells per coverslip was determined. A total of 150 cells per concentration were counted. The test was considered positive when the mean net nuclear grain count from 150 cells per concentration was five or more and/or when a chemical caused a concentration-related increase in UDS and/or a reproducible response at the highest noncytotoxic concentration tested. The test was considered negative if the above criteria were not met.
(c) Percent cells in repair (those cells exhibiting at least five net nuclear grains per cell) for each coverslip
(d) Represents mean net nuclear grain count and percent cells in repair for 150 cells per test concentration

APPENDIX F

SENTINEL ANIMAL PROGRAM

APPENDIX F. SENTINEL ANIMAL PROGRAM

I. Methods

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

Fifteen B6C3F$_1$ mice and 15 F344/N rats of each sex were selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group were killed at 6, 12, and 18 months on study. 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) Sendai (6, 18 mo)	M. Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus) Sendai (12 mo)	MHV (mouse hepatitis virus) *M. pul.* (*Mycoplasma pulmonis*)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai (6, 18 mo)	RCV (rat coronavirus) Sendai (12 mo)	*M. pul.*

II. Results

Results are presented in Table F1.

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

Interval (months)	No. of Animals	Positive Serologic Reaction for
RATS		
6	8/10	Sendai
12	1/10	PVM
	10/10	Sendai
18	9/10	Sendai
MICE		
6	9/10	Sendai
12	10/10	Sendai
18	7/10	Sendai

(a) Blood samples were taken from sentinel animals at 6, 12, and 18 months after the start of dosing. Samples were sent to Microbiological Associates (Bethesda, MD) for the Animal Disease Screening Program.

APPENDIX G

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

Pellet Diet: April 1981 to April 1983

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

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

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

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

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

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

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

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

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	23.8 ± 0.87	22.2-25.3	24
Crude fat (percent by weight)	5.0 ± 0.45	4.2-5.7	24
Crude fiber (percent by weight)	3.3 ± 0.23	2.9-3.8	24
Ash (percent by weight)	6.4 ± 0.37	5.7-7.1	24
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	1.279 ± 0.075	1.20-1.37	4
Methionine	0.422 ± 0.187	0.306-0.699	4
Phenylalanine	0.909 ± 0.167	0.665-1.04	4
Threonine	0.844 ± 0.029	0.824-0.886	4
Tryptophan	0.187	0.171-0.211	3
Tyrosine	0.631 ± 0.094	0.566-0.769	4
Valine	1.11 ± 0.050	1.05-1.17	4
Essential Fatty 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)	11,183 ± 2,211	840-1,800	24
Vitamin D (IU/kg)	3,650	3,000-6,300	2
α-Tocopherol (ppm)	41.53 ± 7.52	31.1-48.9	4
Thiamine (ppm) (b)	16.4 ± 2.17	13.0-21.0	23
Riboflavin (ppm)	7.5 ± 0.96	6.1-8.2	4
Niacin (ppm)	85.0 ± 14.2	65.0-97.0	4
Pantothenic acid (ppm)	29.3 ± 4.6	23.0-34.0	4
Pyridoxine (ppm)	7.6 ± 1.5	5.6-8.8	4
Folic acid (ppm)	2.8 ± 0.88	1.8-3.7	4
Biotin (ppm)	0.27 ± 0.05	0.21-0.32	4
Vitamin B_{12} (ppb)	21.0 ± 11.9	11.0-38.0	4
Choline (ppm)	3,302.0 ± 120.0	3,200-3,430	4
Minerals			
Calcium (percent)	1.22 ± 0.11	1.08-1.53	24
Phosphorus (percent)	0.97 ± 0.04	0.88-1.1	24
Potassium (percent)	0.862 ± 0.10	0.772-0.970	3
Chloride (percent)	0.546 ± 0.10	0.442-0.635	4
Sodium (percent)	0.311 ± 0.038	0.258-0.350	4
Magnesium (percent)	0.169 ± 0.133	0.151-0.181	4
Sulfur (percent)	0.316 ± 0.070	0.270-0.420	4
Iron (ppm)	447.0 ± 57.3	409-523	4
Manganese (ppm)	90.6 ± 8.20	81.7-95.5	4
Zinc (ppm)	53.6 ± 5.27	46.1-58.6	4
Copper (ppm)	10.77 ± 3.19	8.09-15.39	4
Iodine (ppm)	2.95 ± 1.05	1.52-3.82	4
Chromium (ppm)	1.81 ± 0.28	1.44-2.09	4
Cobalt (ppm)	0.68 ± 0.14	0.49-0.80	4

(a) One to four batches of feed analyzed for nutrients reported in this table were manufactured during 1983-1985.
(b) One batch (7/22/81) not analyzed for thiamine.

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

Contaminant	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.46 ± 0.10	<0.29-0.70	24
Cadmium (ppm) (a)	<0.1	<0.1-0.1	25
Lead (ppm)	0.95 ± 0.76	0.33-3.37	25
Mercury (ppm) (a)	<0.05		24
Selenium (ppm)	0.29 ± 0.07	0.13-0.40	24
Aflatoxins (ppb) (b)	<10	<5.0-<10.0	24
Nitrate nitrogen (ppm) (c)	10.24 ± 4.1	3.8-22.0	24
Nitrite nitrogen (ppm) (c)	2.0 ± 1.6	<0.4-6.9	24
BHA (ppm) (d)	6.1 ± 4.9	<0.4-17.0	24
BHT (ppm) (d)	3.3 ± 2.6	<0.9-12.0	24
Aerobic plate count (CFU/g) (e)	39,879 ± 27,920	4,900-88,000	24
Coliform (MPN/g) (f)	15.5 ± 22.7	<3-93	23
Coliform (MPN/g) (g)	34.0 ± 93.4	<3-460	24
E. coli (MPN/g) (h)	<3		24
Total nitrosamines (ppb) (i, j)	3.7 ± 2.7	0.8-9.3	23
Total nitrosamines (ppb) (k, j)	15.2 ± 56.4	0.8-279.5	24
N-Nitrosodimethylamine (ppb) (l, j)	2.7 ± 2.5	0.8-8.3	23
N-Nitrosodimethylamine (ppb) (m, j)	14.1 ± 56.3	0.8-278.0	24
N-Nitrosopyrrolidine (ppb)	1.2 ± 0.5	<0.9-2.9	24
Pesticides (ppm) (d)			
α-BHC (a,n)	<0.01		24
β-BHC (a)	<0.02		24
γ-BHC-Lindane (a)	<0.01		24
δ-BHC (a)	<0.01		24
Heptachlor (a)	<0.01		24
Aldrin (a)	<0.01		24
Heptachlor epoxide (a)	<0.01		24
DDE (a)	<0.01		24
DDD (a)	<0.01		24
DDT (a)	<0.01		24
HCB (a)	<0.01		24
Mirex (a)	<0.01		24
Methoxychlor (o)	<0.05	0.09 (8/26/81)	24
Dieldrin (a)	<0.01		24
Endrin (a)	<0.01		24
Telodrin (a)	<0.01		24
Chlordane (a)	<0.05		24
Toxaphene (a)	<0.1		24
Estimated PCBs (a)	<0.2		24
Ronnel (a)	<0.01		24
Ethion (a)	<0.02		24
Trithion (a)	<0.05		24
Diazinon (a)	<0.1		24
Methyl parathion (a)	<0.02		24
Ethyl parathion (a)	<0.02		24
Malathion (p)	0.09 ± 0.06	<0.05-0.27	24
Endosulfan I	<0.01		18
Endosulfan II	<0.01		18
Endosulfan sulfate	<0.03		18

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

(a) All values were less than the detection limit. The detection limit is given as the mean.
(b) Detection limit reduced from 10 ppb to 5 ppb after 7/81
(c) Sources of contamination: alfalfa, grains, and fish meal
(d) Sources of contamination: soy oil and fish meal
(e) CFU = colony forming unit
(f) Mean, standard deviation, and range exclude one very high value of 460 MPN/g obtained for the batch produced on 9/23/82; MPN = most probable number.
(g) Mean, standard deviation, and range include the high value given in footnote f.
(h) All values were less than 3 MPN/g.
(i) Mean, standard deviation, and range exclude one very high value of 279.5 obtained for the batch produced on 4/27/81.
(j) All values were corrected for percent recovery.
(k) Mean, standard deviation, and range include the high value given in footnote i.
(l) Mean, standard deviation, and range exclude one very high value of 278 obtained for the batch produced on 4/27/81.
(m) Mean, standard deviation, and range include the value given in footnote l.
(n) BHC = hexachlorocyclohexane or benzene hexachloride
(o) There was one observation above the detection limit. The value and the date it was obtained are given under the range.
(p) Ten batches contained more than 0.05 ppm.

APPENDIX H

DATA AUDIT SUMMARY

APPENDIX H. DATA AUDIT SUMMARY

The experimental data, records, and pathology materials for the long-term gavage studies of methyl carbamate in F344/N rats and B6C3F$_1$ mice were examined for completeness, consistency, and accuracy and for procedures consistent with Good Laboratory Practice requirements. The studies were conducted at Microbiological Associates, Bethesda, Maryland, under a subcontract with Tracor Jitco, Inc., from the National Cancer Institute. Rats were exposed to methyl carbamate from June 29, 1981, to June 17, 1983, and mice from June 22, 1981, to June 10, 1983. The studies consisted of 6-, 12-, and 18-month studies and 2-year studies. The studies began during June 1981, before NTP's requirement of compliance to Good Laboratory Practice requirements (October 1981) but were completed when the requirement for compliance was in effect.

The audit was conducted at the NTP Archives, Research Triangle Park, North Carolina, from February 3 to February 18, 1986, by the following personnel of the Product Safety Assessment Division of Dynamac Corporation: T. Arledge, D.V.M.; J. Bhandari, D.V.M., Ph.D.; M. Blumenthal, B.S.; R. Bowman, B.S.; A. Bridge, B.S.; J. Giorgino, B.S.; D. Hothi, D.V.M., Ph.D.; D. Mull, B.S.; S. Shrivastava, Ph.D. The complete audit has been reviewed and approved by the NTP and is on file at NIEHS, Research Triangle Park, North Carolina.

The inlife toxicology data review included examination of all records pertaining to animal shipping, husbandry, dosing, clinical observations, palpable mass observations, mortality, diagnostic serology, and environmental conditions. Body weight data and clinical observations were reviewed for a random 10% sample of the animals. The audit noted that records for preliminary health check and release to study, documentation for the change in identifying special study animals, and feed analysis were missing. No other problems were found in the inlife toxicology data.

The analytical chemistry review included examination of the following: records for chemical shipment and receipt; Midwest Research Institute data for identity, purity, and stability; recommendations for analytical methods, dose preparation, and storage conditions; and records for bulk chemical reanalysis, referee analysis, chemical use, dose preparation, and water analysis. No discrepancies were found in the analytical chemistry data, except that records for the disposal of the surplus chemical were missing.

The pathology review included examination of all Individual Animal Data Records (IADRs) for correlation between gross observations and microscopic diagnoses, microscopic descriptions vs. diagnoses, disposition codes, and condition codes vs. hours until necropsy. All of the wet tissue bags were counted; 10% of the data entries were checked; the quality assurance report and 100% of the Individual Animal Tumor Pathology (IATP) tables of the 2-year studies were examined for tissue accountability; 10% of the diagnoses on IATP tables and IADRs of the 2-year studies were compared; a 10% random sample of wet tissues plus gross observation and microscopic diagnosis were compared for unidentified lesions and animal identification; and a slide/block match was performed for 100% of the vehicle control and high dose groups for the 2-year and 6-, 12-, and 18-month studies. In the 34 rats and mice examined from the 2-year studies, two untrimmed potential lesions were found in rats and three in mice. There were 25 mislabeled rat slides out of 2,552 and 34 mislabeled mouse slides out of 1,720. Thirty-six rat and nine mouse slides from the 6-, 12-, and 18-month studies were without matching tissue blocks.

The minor discrepancies noted in the audit of the inlife toxicology, analytical chemistry, and pathology data were not considered to have influenced the interpretation of the studies, and the data are considered adequate to support the 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
251	Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
267	Propylene Oxide
269	Telone II®
271	HC Blue No. 1
272	Propylene
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
281	H.C. Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No. 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethy)phosphonium Sulfate and Tetrakis(hydroxymethy)phosphonium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	*o*-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane
307	Ephedrine Sulfate
308	Chlorinated Paraffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	*n*-Butyl Chloride
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
324	Boric Acid
325	Pentachloronitrobenzene
327	Xylenes (Mixed)

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