NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 354

TOXICOLOGY AND CARCINOGENESIS STUDIES OF DIMETHOXANE

(CAS NO. 828-00-2)

(COMMERCIAL GRADE)

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF DIMETHOXANE

(CAS NO. 828-00-2)

(COMMERCIAL GRADE)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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September 1989

NTP TR 354

NIH Publication No. 89-2809

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

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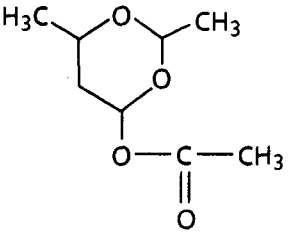

DIMETHOXANE

CAS No. 828-00-2

$C_8H_{14}O_4$ Molecular weight 174.2

Synonyms: acetomethoxan; acetomethoxane; 6-acetoxy-2,4-dimethyl-*m*-dioxane; 2,6-dimethyl-*m*-dioxan-4-yl acetate; 2,6-dimethyl-*m*-dioxan-4-ol acetate; 2,6-dimethyl-1,3-dioxan-4-ol acetate

ABSTRACT

Dimethoxane is used as an antimicrobial agent in water-based paints, dyestuffs, fabric softeners, sizings, and spinning emulsions. In the past, it was used in lipsticks and other cosmetic preparations. Toxicology and carcinogenesis studies were conducted by administering commercial-grade dimethoxane (80% pure; none of the impurities exceeded 3%) in corn oil by gavage to groups of F344/N rats and $B6C3F_1$ mice of each sex one time or 5 days per week for 16 days, 13 weeks, 15 months, or 2 years. Clinical pathology analyses were performed at 15 months in the 2-year studies. Commercial-grade dimethoxane was studied because that is the grade to which humans are generally exposed. The same lot of commercial-grade dimethoxane was used in genetic toxicology tests for mutagenicity in *Salmonella typhimurium*, for sister chromatid exchanges (SCEs) and chromosomal aberrations in Chinese hamster ovary (CHO) cells, and for sex-linked recessive lethal mutations and translocations in Drosophila.

Sixteen-Day Studies: In the 16-day studies, rats and mice received 0, 125, 250, 500, 1,000, or 2,000 mg/kg dimethoxane in corn oil per day. Deaths occurred in rats and in male mice that received 2,000 mg/kg. Body weights of rats and mice were similar to those of vehicle controls. Compound-related clinical signs were not seen in surviving rats. Hemorrhage and necrosis of the stomach were observed in rats in the 2,000 mg/kg group which died before the end of the studies. Lesions of the forestomach, including inflammation, hyperplasia, hyperkeratosis, and ulceration, occurred in rats that received 250-2,000 mg/kg. Mice that received 500-2,000 mg/kg dimethoxane had lesions of the forestomach including erosion, ulceration, hyperplasia, and hyperkeratosis. Forestomach lesions were not seen at 125 or 250 mg/kg.

Thirteen-Week Studies: No compound-related deaths occurred in rats. Doses used were 0, 31, 62, 125, 250, or 500 mg/kg dimethoxane in corn oil by gavage. The final mean body weights of rats that received 500 mg/kg were 17% lower than that of vehicle controls for males and 5% lower for females. Ulceration, inflammation, and acanthosis with hyperkeratosis of the stratified squamous epithelium of the forestomach were seen in rats that received 500 mg/kg. Forestomach lesions were not seen in males that received 31 mg/kg or in females that received 31, 62, or 125 mg/kg.

All mice lived to the end of the studies (doses used were 0, 31, 62, 125, 250, or 500 mg/kg dimethoxane in corn oil by gavage). Final mean body weights of dosed and vehicle control mice were similar.

Minimal-to-mild acanthosis and hyperkeratosis of the squamous epithelium of the forestomach were seen in 4/10 high dose male and 1/10 high dose female mice.

Because of the forestomach lesions observed in rats and mice and reduced body weight observed for male rats, doses selected for the 2-year studies were 0, 62.5, or 125 mg/kg dimethoxane in corn oil, given by gavage 5 days per week to groups of 60 male rats; 0, 125, or 250 mg/kg to groups of 60 female rats; and 0, 250, or 500 mg/kg to groups of 58 or 60 mice of each sex. Ten animals per sex and species from each dose group were killed 15 months after initiation of the studies to determine toxicity, preneoplastic lesions, and early induced neoplasia.

Fifteen-Month Studies: Minimal diffuse acanthosis and hyperplasia of the forestomach were seen in 7/10 female rats at 250 mg/kg, 7/10 males at 125 mg/kg, and 1/9 male and 1/9 female vehicle controls. Acanthosis of the forestomach was seen in 7/10 male and 6/10 female mice at 500 mg/kg. Harderian gland adenomas were seen in one high dose male and one high dose female mouse. A harderian gland adenocarcinoma was seen in a second high dose female mouse. No compound-related effects were observed for clinical chemical or hematologic values or for organ weights for rats or mice.

Body Weight and Survival in the Two-Year Studies: Mean body weights of dosed and vehicle control rats and mice of each sex were generally similar. No significant differences in survival were observed between any groups of rats (male: vehicle control, 23/50; low dose, 28/50; high dose, 21/50; female: 30/50; 31/50; 24/50) or mice (male: 33/50; 27/48; 29/50; female: 36/50; 35/50; 34/50).

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: At no site was a significantly increased incidence of neoplastic lesions observed in dosed male or female rats or in dosed female mice. Acanthosis and hyperkeratosis were increased in the forestomach of high dose rats; acanthosis, hyperkeratosis, focal hyperplasia, and chronic active inflammation were increased in the forestomach of dosed mice. The incidence of squamous cell papillomas of the forestomach was increased in high dose male mice (vehicle control, 2/47; low dose, 3/47; high dose, 7/50). A squamous cell carcinoma of the forestomach was present in another high dose male mouse. Although the incidence of squamous cell papillomas in the high dose group was not significantly different from that in the vehicle controls, the incidence exceeded the highest observed in historical corn oil gavage vehicle controls (3/49). Other than a single squamous cell papilloma in the esophagus of a low dose male mouse, no hyperplastic or neoplastic lesions were seen outside the stomach of dosed mice which could be related to the administration of dimethoxane. Despite the observation of three harderian gland neoplasms in mice killed at 15 months, no increase in the incidences of harderian gland neoplasms was seen in dosed mice in the 2-year studies (male: 2/48; 2/48; 2/48; female: 2/48; 0/49; 2/50).

Genetic Toxicology: Dimethoxane was mutagenic in strain TA100 of *S. typhimurium* in the presence but not the absence of exogenous metabolic activation; it was not mutagenic in strains TA98, TA1535, or TA1537 with or without activation. Dimethoxane induced SCEs and chromosomal aberrations in CHO cells both with and without exogenous metabolic activation. Dimethoxane induced sex-linked recessive lethal mutations in Drosophila when administered by abdominal injection to adult males; no induction of reciprocal translocations was observed in adult males after injection of dimethoxane.

Conclusions: Under the conditions of these 2-year corn oil gavage studies, there was *no evidence of carcinogenic activity** of dimethoxane for male F344/N rats receiving 62.5 or 125 mg/kg or for female F344/N rats receiving 125 or 250 mg/kg per day. There was *equivocal evidence of carcinogenic activity* of dimethoxane for male $B6C3F_1$ mice, as indicated by an increased incidence of forestomach neoplasms. There was *no evidence of carcinogenic activity* for female $B6C3F_1$ mice receiving 250 or 500 mg/kg per day. Acanthosis and hyperkeratosis occurred at increased incidences in the forestomach of high dose rats. Inflammation, acanthosis with hyperkeratosis, and focal hyperplasia occurred at increased incidences in the forestomach of dosed mice.

SUMMARY OF THE TWO-YEAR GAVAGE AND GENETIC TOXICOLOGY STUDIES OF DIMETHOXANE

Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Dose			
0, 62.5, or 125 mg/kg dimethoxane in corn oil 5 d/wk	0, 125, or 250 mg/kg dimethoxane in corn oil 5 d/wk	0, 250, or 500 mg/kg dimethoxane in corn oil 5 d/wk	0, 250, or 500 mg/kg dimethoxane in corn oil 5 d/wk
Body weights in the 2-year study			
Dosed and vehicle control groups similar	Dosed and vehicle control groups similar	Dosed and vehicle control groups similar	Dosed and vehicle control groups similar
Survival rates in the 2-year study			
23/50; 28/50; 21/50	30/50; 31/50; 24/50	33/50; 27/48; 29/50	36/50; 35/50; 34/50
Nonneoplastic effects			
Acanthosis and hyperkeratosis of the forestomach	Acanthosis and hyperkeratosis of the forestomach	Acanthosis, hyperkeratosis, focal hyperplasia, and chronic inflammation of the forestomach	Acanthosis, hyperkeratosis, focal hyperplasia, and chronic inflammation of the forestomach
Neoplastic effects			
None	None	Forestomach squamous cell neoplasms (2/47; 3/47; 8/50)	None
Level of evidence of carcinogenic activity			
No evidence	No evidence	Equivocal evidence	No evidence
Genetic toxicology			

Salmonella	CHO Cells in Vitro		Drosophila	
(gene mutation)	SCE	Aberration	Sex-linked Rec. Lethals	Reciprocal Translocation
Negative without S9; positive with S9	Positive with and without S9	Positive with and without S9	Positive	Negative

*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 page 9.

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results ("Clear Evidence" and "Some Evidence"); one category for uncertain findings ("Equivocal Evidence"); one category for no observable effects ("No Evidence"); and one category for experiments that 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 to neoplastic lesions;
- Some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- Combining benign and malignant tumor 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.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Dimethoxane is based on 13-week studies that began in August 1981 and ended in November 1981 and on 2-year studies that began in August 1982 and ended in August 1984 at Battelle Columbus Laboratories (Columbus, OH).

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PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on dimethoxane on October 3, 1988, 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 DIMETHOXANE

On October 3, 1988, the draft Technical Report on the toxicology and carcinogenesis studies of dimethoxane received public 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. K.M. Abdo, NIEHS, began the discussion by reviewing the experimental design, results, and proposed conclusions (no evidence of carcinogenic activity for male and female rats or female mice, equivocal evidence of carcinogenic activity for male mice).

Dr. Ashby, a principal reviewer, agreed with the conclusions. He asked for clarification as to why the conclusion for male mice was not some evidence of carcinogenic activity, since in a previous study (benzyl acetate, NTP TR 250), similar incidences of squamous papillomas of the forestomach were the basis for a conclusion of some evidence of carcinogenic activity. Dr. Abdo answered that the conclusion for male mice in the benzyl acetate study was based primarily on increased incidences of liver tumors, with supporting evidence from lesions of the forestomach. Dr. S. Eustis, NIEHS, added that, with the exception of a carcinoma in a high dose mouse, the forestomach neoplasms were papillomas that met only the minimum pathology requirements for diagnosis of a papilloma. Dr. Ashby opined that impurities (20%) might play a role in the toxicity of this chemical; more specifically, the genetic toxicity was probably due to two of the impurities, acetaldehyde and crotonaldehyde.

Dr. Garman, the second principal reviewer, agreed with the conclusions. He asked for a brief discussion concerning human exposure to the hydrolysis products of dimethoxane and suggested that a repeat of an earlier inadequate water gavage study be considered. Dr. Abdo said that the literature would be searched for information on the toxicity and chemical disposition of the major contaminants and hydrolysis products and relevant data would be added to the Report [see page 13]. Dr. Garman asked for clarification of the terminology used in describing the pathology diagnoses, especially in distinguishing between acanthosis and hyperplasia of the forestomach.

Dr. Klaassen, the third principal reviewer, agreed with the conclusions.

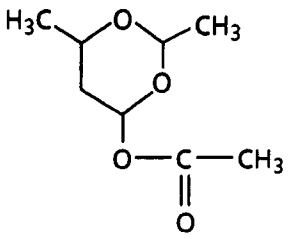
Dr. M. Manowitz, Givaudan Corporation, said that he believed that his company was the only manufacturer of dimethoxane and, under contract, had conducted a skin painting study in CD®-1 Swiss Webster albino mice in the mid 1970's. The 80-week study gave no indication of local or systemic oncogenic or other toxic effects. The study was not published, but a report of the study was submitted to the National Cancer Institute. Dr. Manowitz also pointed out that the chemical is not used in cosmetic preparations or in products that are ingested or directly applied to human skin. Dr. J. Huff, NIEHS, recommended that this study be published.

Dr. Ashby moved that the Technical Report on dimethoxane be accepted with the revisions discussed and with the conclusions as written for male and female rats and female mice, no evidence of carcinogenic activity, and for male mice, equivocal evidence of carcinogenic activity. Dr. Klaassen seconded the motion, which was approved unanimously by the nine panelists.

I. INTRODUCTION

Physical and Chemical Properties
Production and Use
Environmental Occurrence and Human Exposure
Toxicity
Evidence for Carcinogenicity
Metabolism
Genetic Toxicology
Study Rationale

I. INTRODUCTION



DIMETHOXANE

CAS No. 828-00-2

$C_8H_{14}O_4$ Molecular weight 174.2

Synonyms: acetomethoxan; acetomethoxane; 6-acetoxy-2,4-dimethyl-*m*-dioxane; 2,6-dimethyl-*m*-dioxan-4-yl acetate; 2,6-dimethyl-*m*-dioxan-4-ol acetate; 2,6-dimethyl-1,3-dioxan-4-ol acetate

Dimethoxane is an antimicrobial agent used primarily to protect against spoilage in water-based latex paint. Dimethoxane was first prepared in 1943 by reaction of 2,4-dimethyl-6-hydroxy-*m*-dioxane with acetic anhydride in pyridine (IARC, 1977).

Physical and Chemical Properties

Dimethoxane is a clear yellow to light amber liquid with a mustard-like odor. It has a melting point of less than −25° C, a boiling point of 74°-75° C at 6 mm mercury, and a specific gravity of 1.069-1.076 at 25° C. It is miscible with water and many organic solvents (Hawley, 1981; Merck, 1983). Dimethoxane hydrolyzes in aqueous solutions to produce acetic acid and the corresponding free alcohol (IARC, 1977).

Production and Use

The TSCA Initial Inventory (USEPA, 1987) reported the domestic production of between 100,000 and 1,000,000 pounds of dimethoxane in 1977 in one plant. The TSCA Inventory did not report any importation of dimethoxane in 1977. According to the National Occupational Exposure Survey, 25,600 workers in a wide variety of industries and occupations are exposed to dimethoxane; approximately 20% of the exposed workers are female (NIOSH, 1988).

Dimethoxane is used at concentrations of 500-1,500 ppm as an antimicrobial agent to protect against spoilage due to bacteria, fungi, and yeast in water-based paints, cutting oils, dyestuffs, fabric softeners, latex emulsions, sizings, adhesives, antistatic lubricants, and spinning emulsions. It is also used at a concentration of 0.03%-0.1% as a preservative for resin emulsions and inks. In the past, dimethoxane was used in cosmetics as a preservative (IARC, 1977). A U.S. patent was issued in 1962 for its use as a gasoline additive (Merck, 1983).

Environmental Occurrence and Human Exposure

No information was found on the environmental occurrence or fate of dimethoxane. Exposure to dimethoxane was noted in hospitals and in manufacturing plants (NIOSH, 1988).

Toxicity

Very little information on the toxicity of dimethoxane was found in the literature. The reported oral LD_{50} value for dimethoxane in rats is 1,930 mg/kg (NIOSH, 1980).

Allergic contact dermatitis was reported in a textile worker who was occupationally exposed to dimethoxane. Results of patch tests suggested that sensitization was caused by acetaldehyde and crotonaldehyde (two impurities reported to be present in technical-grade dimethoxane) (Shmunes and Kempton, 1980). Persons exposed to dioxane at 50 ppm in the air for 6 hours showed slight irritation of the conjunctiva, and those exposed at more than 200 ppm developed

irritation of the mucous membranes of the eyes, nose, and throat. One case of allergic contact eczema caused by dioxane was reported (Arbete och Halsa, 1983).

Evidence for Carcinogenicity

Redistilled dimethoxane in drinking water (1% prepared once per day) was carcinogenic for male Wistar rats; it produced malignant hepatomas in 8/25 rats but none in the controls (Hoch-Ligeti et al., 1974; IARC, 1977). In this study, 25 male rats were given the chemical for 613 days; 14 controls received tap water. The experiment was terminated 90 days after the last day of dosing. This study was considered to be somewhat limited because of the small number of animals used in the study.

Dimethoxane (1% solution in either water or acetone) applied dermally was not carcinogenic to groups of 50 male and 50 female CD®-1 Swiss Webster mice (Givaudan Corp., 1977). The dose used was 0.1 ml/mouse applied twice per week for 80 weeks to a shaven dorsal area of the skin close to the base of the neck. In this study, the chemical did not produce any change in survival and body weight.

Metabolism

No information was found on the metabolism of dimethoxane. In rats, 1,4-dioxane is metabolized to 2-hydroxyethoxyacetic acid and dioxanone (Braun and Young, 1977). Dioxanone can be formed from 2-hydroxyethoxyacetic acid in an acidic environment (Young et al., 1976). Dioxane can also enhance its own transformation as shown by an increase in liver microsomal protein levels, including those of cytochrome b5, cytochrome P450, and cytochrome c reductase, after intramuscular injection or oral administration to mice (Mungikar and Pawar, 1979).

Genetic Toxicology

The only mutagenicity data available for dimethoxane are those from NTP studies presented in this Report. Dimethoxane was mutagenic in *Salmonella typhimurium* strain TA100 when exposure occurred in the presence of exogenous metabolic activation; it was not mutagenic in strain TA100 without metabolic activation or in strains TA98, TA1535, or TA1537 with or without activation (Mortelmans et al., 1986; see Table 24). Dimethoxane induced sex-linked recessive lethal mutations in Drosophila when administered by abdominal injection to adult Canton-S males (Woodruff et al., 1985; see Table 27); no induction of reciprocal translocations was observed (Woodruff et al., 1985; see Table 28).

Study Rationale

Dimethoxane was nominated and selected for study by the National Cancer Institute because of a suggestion from the results of one experiment (involving 14 control and 25 exposed male rats) that this chemical may be considered to be carcinogenic in drinking water (Hoch-Ligeti et al., 1974). An additional reason for the nomination was the potential for widespread human exposure resulting from its use as an antimicrobial agent in many products such as textiles and water-based paints and inks. Because of the positive results of the one oral carcinogenicity study, administration of dimethoxane by gavage was recommended. Because dimethoxane undergoes hydrolysis in an aqueous environment, corn oil was selected as the vehicle. Supplemental single-administration and 7-week dermal studies were conducted to determine the absorption and toxicity of undiluted dimethoxane (Appendix G).

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF DIMETHOXANE

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

SINGLE-ADMINISTRATION STUDIES

- Supplemental Studies
- Analytical Methods for Supplemental Studies

SIXTEEN-DAY STUDIES

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II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF DIMETHOXANE

Commercial-grade (greater than 80% pure) dimethoxane was obtained in one lot (lot no. 6270-79) from Givaudan Corporation (Clifton, New Jersey). Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, Missouri). MRI reports on the analyses performed in support of the dimethoxane studies are on file at the National Institute of Environmental Health Sciences.

The study chemical was identified as dimethoxane by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The infrared (Figure 1), nuclear magnetic resonance (Figure 2), and ultraviolet/visible spectra were consistent with those expected for the structure of dimethoxane. The infrared spectrum was consistent with the literature spectrum (Sadtler, 1977).

The purity of dimethoxane was determined by elemental analysis, Karl Fischer water analysis, acid titration with sodium hydroxide (which is indicative of both the hydrolysis of the acetate group to acetic acid and the oxidation of aldehydes to acids), hydroxylamine titration, and thin-layer and gas chromatography. Thin-layer chromatographic analysis was performed on silica gel plates with methylene chloride:methanol (95:5) (solvent system 1) and with *iso*-octane:ethyl acetate (30:70) (solvent system 2). Gas chromatographic analysis was performed with flame ionization detection and either a 1% SP1000 column (system 1) or a 20% SP2100/0.1% Carbowax 1500 column (system 2). Results of elemental analysis for carbon were slightly low (98.7% of theoretical value), and that for hydrogen was in agreement with the theoretical value. Water content was 0.62%. Titration with sodium hydroxide of acids produced after refluxing with hydroxylamine hydrochloride indicated a purity of 88.4%. Titration of the unreacted study chemical with 0.1 N sodium hydroxide indicated an acid content of 22.0 meq/mol. Thin-layer chromatography indicated a major spot with one minor impurity, three trace impurities, and one slight trace impurity by solvent system 1 and a major spot and two minor and two slight trace impurities by solvent system 2. Gas chromatography by system 1 indicated that the percent purity of dimethoxane (a total of two major isomers) was approximately 84%, with more than 30 minor impurities present. Gas chromatography by system 2 gave similar results. The discrepancy between the titration value and the gas chromatography results probably arises because some impurities have titratable carbonyl groups. A sample of the study material was subjected to further analysis at MRI. Gas chromatographic/mass spectrometric analysis with a DB-5 fused silica capillary column identified four isomers of dimethoxane, which accounted for approximately 80% of the total peak area of the sample. The remaining approximately 20% was impurities, which were identified by their mass spectra. These impurities included acetaldehyde, acetic acid, 3-hydroxybutanol (aldol), vinyl acetate, 2-butenal (crotonaldehyde), dimethylfuran, 7-hydroxy-2,4-octadienol, and three isomers each of hydroxyhexenal, 2,4-dimethyl-1,3-dioxane, and 2,4-dimethyl-6-hydroxy-1,3-dioxane. The concentration of these impurities in the study material was not determined. In addition, a sample of the study material was returned to the manufacturer for analysis and found to contain approximately 80% dimethoxane. Impurities identified by the manufacturer included acetaldehyde (0.2%), vinyl acetate (1.4%), and crotonaldehyde and its corresponding aldol (1.8%). Other impurities eluting before (referred to as "lights") and after (referred to as "heavies") dimethoxane accounted for 1.7% and 18.3%, respectively, of the total amount of the commercial product.

Stability studies performed by gas chromatography with the same column as that described above for system 2 indicated that dimethoxane was stable as a bulk chemical when kept for 2 weeks at temperatures up to 60° C. A darkening of the sample at 60° C was observed, but decomposition was not detected by the chromatographic system. Stability of the bulk chemical during the studies was monitored quarterly at the study laboratory by comparing the analysis of the bulk study material with that of a frozen reference sample. Initially, gas chromatography (system 1) and acid titration were used for the

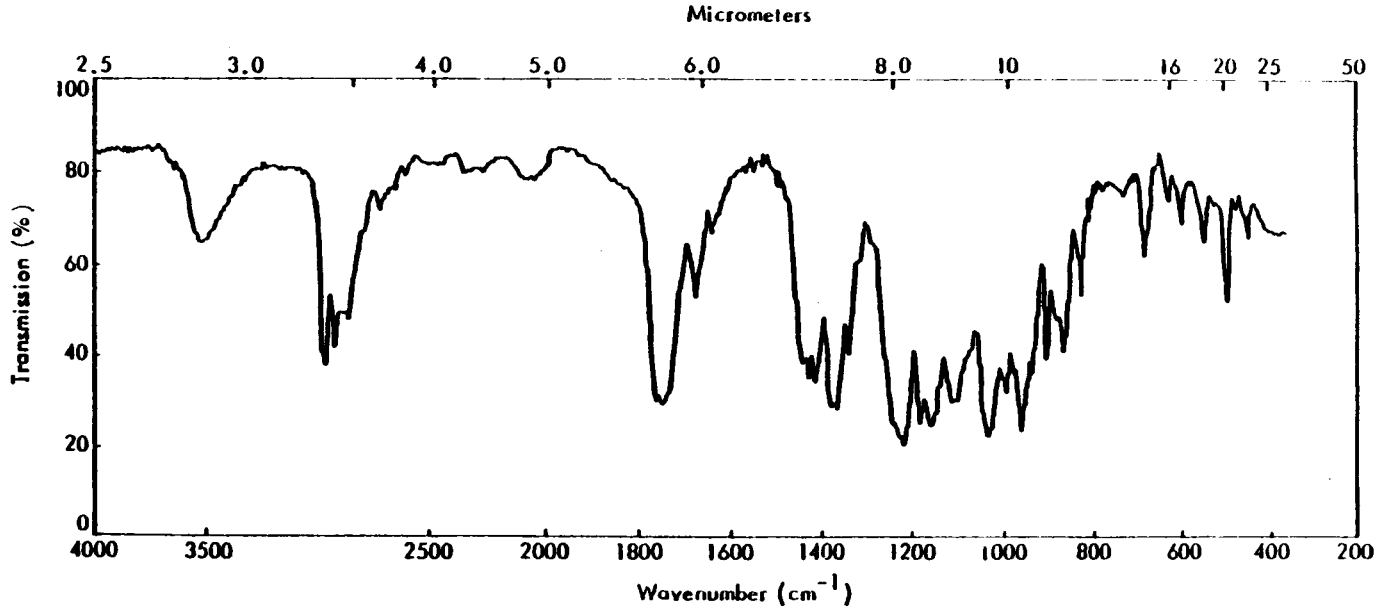

FIGURE 1. INFRARED ABSORPTION SPECTRUM OF DIMETHOXANE (LOT NO. 6270-79)

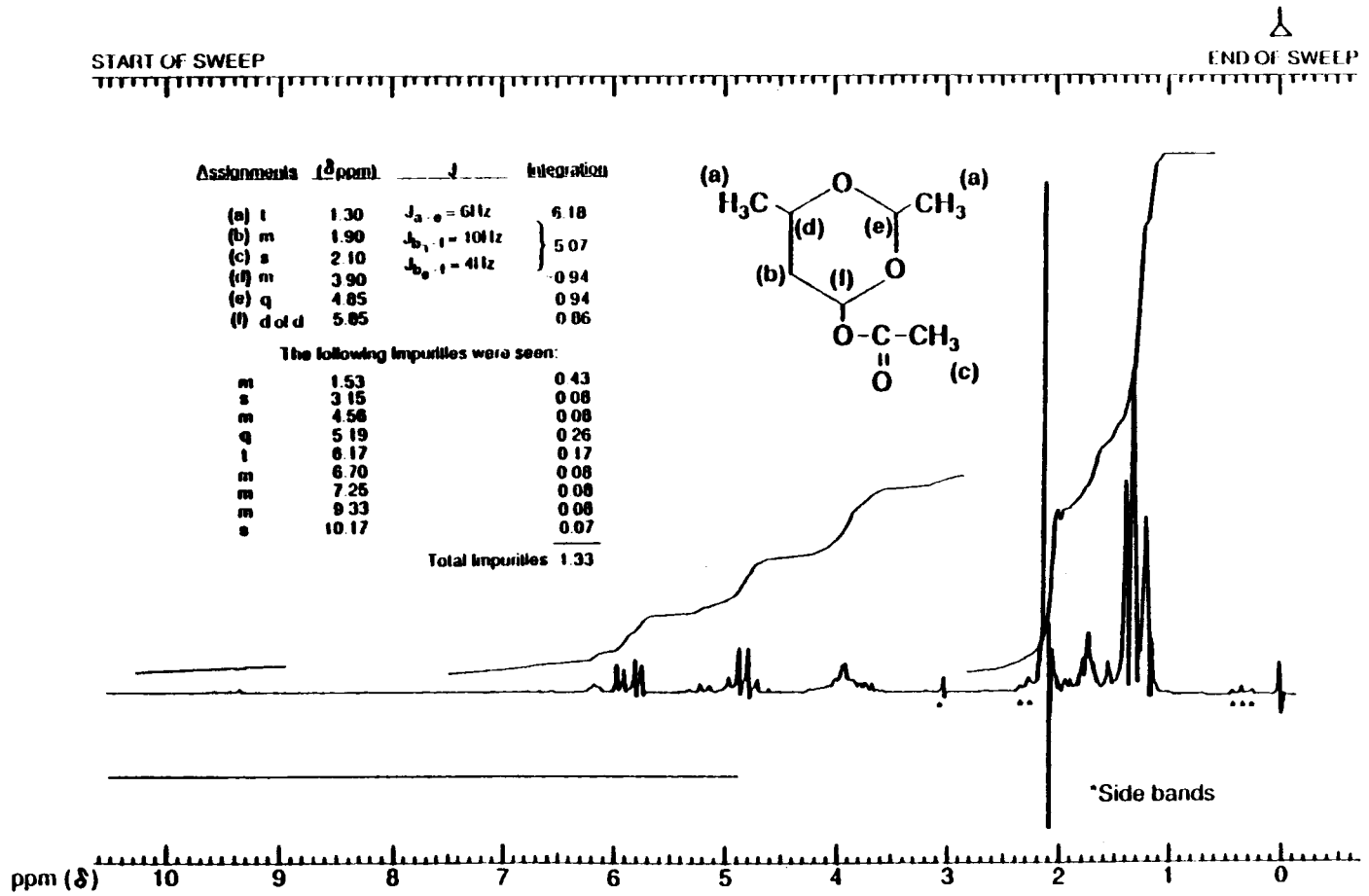

FIGURE 2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF DIMETHOXANE (LOT NO. 6270-79)

bulk chemical reanalysis. The initial gas chromatographic method was later replaced by a gas chromatographic method that used a DB-5 fused silica capillary column. There were some increases in the acid content of the study and reference samples during the course of the studies. However, the gas chromatographic reanalysis indicated no notable breakdown of the study material during the studies. Therefore, it is concluded that the dimethoxane study material remained stable during the studies.

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

Dimethoxane and corn oil were mixed (w/v) to give the desired concentrations (Table 1). Each lot of corn oil used in these studies was analyzed for peroxide content before its first use and one time per month while in use. The method used was the official method of the American Oil Chemists' Society (Mehlenbacher et al., 1972). The maximum allowable level of peroxide in NTP studies is 3 meq/kg. The lots of corn oil used for the dimethoxane study were determined to contain less than 3 meq/kg peroxide. The stability of dimethoxane in corn oil (180 mg/ml) was determined by gas chromatography with system 2 after extraction with methanol. The study chemical in corn oil was found to be stable for up to 14 days at room temperature in the dark and for up to 3 hours when exposed to light and air. Analysis of dose mixtures during the toxicity studies was conducted by extraction with methanol or by dilution with acetone and gas chromatographic analysis, system 2. Dose mixtures were analyzed two times during the 13-week studies (Table 2).

During the 2-year studies, the dose preparations were analyzed at approximately 8-week intervals. For the dimethoxane studies, the mixtures were formulated within ±10% of the target concentrations 98% (56/57) of the time throughout the studies (Table 3). Referee analyses were periodically performed by the analytical chemistry laboratory. Generally good agreement was found between laboratories (Table 4).

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

Single-Administration Studies	Sixteen-Day Studies	Thirteen-Week Studies	Fifteen-Month Studies	Two-Year Studies
Preparation				
Weighed amount of chemical dissolved in appropriate quantity of corn oil for stock solution. Diluted with corn oil for dose mixture	Weighed amount of chemical dissolved in appropriate quantity of corn oil. Serial dilution to volume with corn oil	Appropriate weight of chemical and corn oil mixed in graduated mixing cylinder. Serial dilution to volume with corn oil	Appropriate quantities of chemical and corn oil mixed by inversion in a stoppered mixing column for the highest dose. Serial dilution to volume with corn oil	Same as 15-mo studies
Maximum Storage Time				
2 wk	2 wk	2 wk	2 wk	2 wk
Storage Conditions				
Room temperature in foil-wrapped glass bottles	Room temperature in foil-wrapped glass bottles	Room temperature in amber glass bottles	Same as 13-wk studies	Same as 13-wk studies

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

Date Mixed	Concentration of Dimethoxane in Corn Oil (mg/ml) Target	Determined (a)	Determined as a Percent of Target
08/12/81	6.25	6.82	109.1
	12.5	12.93	103.4
	25.0	25.69	102.9
	50.0	49.53	99.1
	100.0	99.48	99.5
10/03/81	6.25	6.70	107.2
	12.5	13.00	104.0
	25.0	26.45	105.8
	50.0	49.92	99.8
	100.0	93.44	93.4

(a) Results of duplicate analysis

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

Date Mixed	Concentration of Dimethoxane in Corn Oil for Target Concentration (mg/ml) (a) 12.5	25	50	100
08/16/82	--	--	48.8	97.4
08/23/82	12.2	24.1	48.3	--
10/05/82	12.8	24.2	48.2	97.0
12/07/82	13.0	26.1	51.9	99.5
01/17/83	12.8	25.4	50.5	102.3
03/23/83	13.6	25.7	47.2	(b) 87.1
03/25/83	--	--	--	(c) 101.2
05/10/83	12.8	24.8	49.0	94.4
07/12/83	13.4	26.7	53.4	105.5
08/29/83	12.8	24.7	49.3	97.7
10/25/83	13.4	26.2	50.6	96.8
12/19/83	13.1	25.4	49.8	97.9
02/13/84	13.0	25.1	50.4	99.7
04/02/84	13.6	25.5	51.0	99.7
06/05/84	12.1	24.8	49.5	98.0
07/31/84	13.3	25.7	50.9	98.7
Mean (mg/ml)	13.0	25.3	49.9	98.0
Standard deviation	0.46	0.75	1.58	4.09
Coefficient of variation (percent)	3.5	3.0	3.2	4.2
Range (mg/ml)	12.1-13.6	24.1-26.7	47.2-53.4	87.1-105.5
Number of samples	14	14	15	14

(a) Results of duplicate analysis
(b) Out of specifications; not used in studies.
(c) Remix; not included in the mean.

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

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (mg/ml) Study Laboratory (a)	Referee Laboratory (b)
08/16/82	50	48.8	48.7
01/17/83	12.5	12.8	12.8
08/29/83	25	24.7	25.2
02/13/84	100	99.7	98.2
04/02/84	12.5	13.6	13.5

(a) Results of duplicate analysis
(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 observed for 16 days before the studies began. Groups of five rats and five mice of each sex were administered a single dose of 0, 175, 350, 700, 1,400, or 2,800 mg/kg dimethoxane in corn oil by gavage. Rats and mice were fasted overnight before they were dosed.

Immediately after dosing, all animals that received 2,800 mg/kg dimethoxane and all vehicle controls were placed in individual metabolism cages for urine collection at 24 and 48 hours. Urine was collected by cage for mice. Animals were returned to their cages at the end of 48 hours. Animals were observed two times per day for 14 days. Details of animal maintenance are presented in Table 5. Supplemental dermal studies are described in Appendix G.

Supplemental Studies

Twenty-eight male rats and 28 male mice were administered 2,800 mg/kg dimethoxane in corn oil by gavage. Rats and mice were fasted overnight before they were dosed. Four animals were killed 15 or 30 minutes or 1, 2, or 4 hours after dosing. Blood was collected from the vena cava of rats and the brachial plexus of mice.

Analytical Methods for Supplemental Studies

Blood and urine from the studies were analyzed for dimethoxane by gas chromatographic analysis. Lysed blood or urine was forced through a C_{18} Sep-Pak column. The dimethoxane was extracted with an isopropanol:chloroform (1:3) solvent. Gas chromatographic analysis was performed with flame ionization detection and a 20% SP2100/0.1% Carbowax 1500 column.

SIXTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Harlan Industries and were held for 12 days (rats) or 13 days (mice) before the studies began. The rats were 6 weeks old when placed on study, and the mice were 8 weeks old. Groups of five rats and five mice of each sex were administered 0, 125, 250, 500, 1,000, or 2,000 mg/kg dimethoxane in corn oil by gavage 5 days a week for 12 doses over 16 days.

Animals were housed five per cage. Water and feed were available ad libitum. The rats and mice were observed two times per day and were weighed on days 1, 7, and 16. Details of animal maintenance are presented in Table 5. A necropsy was performed on all animals. The weights for whole body, liver, thymus, heart, kidney, brain, and lungs were recorded at necropsy. Tissues and groups examined microscopically are given in Table 5.

THIRTEEN-WEEK STUDIES

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

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

Single-Administration Studies	Sixteen-Day Studies	Thirteen-Week Studies	Fifteen-Month Studies	Two-Year Studies
EXPERIMENTAL DESIGN				
Size of Study Groups				
5 males and 5 females of each species; groups of 28 males of each species for the supplemental studies	5 males and 5 females of each species	10 males and 10 females of each species	10 males and 10 females of each species	48 or 50 males and 50 females of each species
Doses				
0, 175, 350, 700, 1,400, or 2,800 mg/kg dimethoxane in corn oil by gavage; supplemental studies--2,800 mg/kg; dose vol--5 ml/kg	0, 125, 250, 500, 1,000, or 2,000 mg/kg dimethoxane in corn oil by gavage; dose vol--5 ml/kg	0, 31, 62, 125, 250, or 500 mg/kg dimethoxane in corn oil by gavage; dose vol--5 ml/kg	Rats--male: 0, 62.5, or 125 mg/kg dimethoxane in corn oil by gavage; female: 0, 125, or 250 mg/kg; mice--0, 250, or 500 mg/kg; dose vol--5 ml/kg	Same as 15-mo studies
Date of First Dose				
3/9/81	Rats--5/18/81; mice--5/19/81	Rats--male: 8/18/81; female: 8/19/81; mice--male: 8/20/81; female: 8/21/81	Rats--8/30/82; mice--8/23/82	Same as 15-mo studies
Date of Last Dose				
N/A	Rats--6/2/81; mice--6/3/81	Rats--male: 11/16/81; female: 11/17/81; mice--male: 11/18/81; female: 11/19/81	Rats--12/6/83; mice--11/22/83	Rats--8/17/84; mice--8/10/84
Duration of Dosing				
Single dose	5 d/wk; 12 doses over 16 d	5 d/wk for 13 wk	5 d/wk for 66 wk (rats) or 65 wk (mice)	5 d/wk for 103 wk
Type and Frequency of Observation				
Observed 2 × d	Observed 2 × d; weighed initially and 1 × wk thereafter	Observed 2 × d; weighed initially and 1 × wk thereafter	Observed 2 × d; weighed initially, 1 × wk for 12 wk, and then 1 × mo	Same as 15-mo studies
Necropsy, Histologic Examinations, and Supplemental Analyses				
Necropsy performed on all animals alive at the end of the studies; histologic exams not performed. Vehicle control and high dose animals placed in metabolism cages immediately after dosing; urine collected individually from rats and by group from mice over 24-h intervals for 2 d. Four animals of each species from the supplemental groups killed with carbon dioxide 15 or 30 min or 1, 2, or 4 h	Necropsy performed on all animals; tissues examined histologically for vehicle control and 1,000 and 2,000 mg/kg rats and 1,000 mg/kg mice. Stomach of all rats and all mice except the 125 mg/kg group examined histologically. Brain, heart, kidneys, liver, lungs, and thymus weighed at necropsy	Necropsy performed on all animals; tissues examined histologically for vehicle control and high dose groups, 1 female rat from the 62 mg/kg group, and 1 male and 2 female rats from the 31 mg/kg groups. Stomach and mammary gland of all dosed rats and stomach of all dosed mice except from the 31 mg/kg group examined histologically. Weights of brain, heart, liver, lungs, right kidney, right testis, and thymus recorded at necropsy	Necropsy performed on all animals; the following tissues examined histologically for vehicle control and high dose groups: adrenal glands, brain, colon, esophagus, eyes (if grossly abnormal), femur or sternebrae or vertebrae including marrow, gallbladder (mice), gross lesions and tissue masses with regional lymph nodes, harderian gland (mice), heart, kidneys, liver, lungs and mainstem bronchi, mammary gland, mandibular or mesenteric lymph	Necropsy performed on all animals; histologic exams performed on all rats, all animals dying before mo 22, and all vehicle control and high dose animals killed at the end of the studies; tissues examined are the same as in the 15-mo studies. Forestomach examined for low dose mice; harderian gland examined for low dose mice if grossly abnormal

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

Single-Administration Studies	Sixteen-Day Studies	Thirteen-Week Studies	Fifteen-Month Studies	Two-Year Studies
Necropsy, Histologic Examinations, and Supplemental Analyses (Continued)				
after dosing; blood collected from the brachial plexus. Urine and blood analyzed for dimethoxane			nodes, nose, pancreas, parathyroid glands, pituitary gland, prostate/testes or ovaries/uterus, salivary glands, skin, small intestine, spleen, trachea, stomach, thymus, thyroid gland, and urinary bladder. Tissues examined include forestomach for low dose rats and harderian gland for low dose mice. Weights of brain, heart, liver, and right kidney recorded at necropsy. Hematologic and serum chemical analyses performed on all animals	
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)	Harlan Industries (Indianapolis, IN)	Charles River Breeding Laboratories (Kingston, NY)	Charles River Breeding Laboratories (Kingston, NY)	Charles River Breeding Laboratories (Kingston, NY)
Study Laboratory				
Battelle Columbus Laboratories	Battelle Columbus Laboratories	Battelle Columbus Laboratories	Battelle Columbus Laboratories	Battelle Columbus Laboratories
Method of Animal Identification				
Toe clip	Toe clip	Toe clip	Toe mark	Toe mark
Time Held Before Study				
16 d	Rats--12 d; mice--13 d	Rats--20-21 d; mice--22-23 d	20 d	20 d
Age When Placed on Study				
Rats--7 wk; mice--8 wk	Rats--6 wk; mice--8 wk	Rats--7 wk; mice--8-9 wk	Rats--7-8 wk; mice--8-9 wk	Same as 15-mo studies
Age When Killed				
Rats--9 wk; mice--10 wk	Rats--8-9 wk; mice--10-11 wk	Rats--21 wk; mice--22 wk	Rats--72-73 wk; mice--73-74 wk	Rats--112-113 wk; mice--113-114 wk
Necropsy Dates				
3/24/81-3/25/81	Rats--6/3/81; mice--6/4/81	Rats--male: 11/17/81; rats--female: 11/18/81; mice--male: 11/19/81; mice--female: 11/20/81	Rats--12/7/83; mice--11/23/83	Rats--8/28/84-8/30/84; mice--8/22/84-8/24/84

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

Single-Administration Studies	Sixteen-Day Studies	Thirteen-Week Studies	Fifteen-Month Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)				
Method of Animal Distribution				
Animals distributed to weight classes and then assigned to cages by one random number table and to groups by another 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				
NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Bedding				
Absorb-Dri (Absorb Dri, Inc., Garfield, NJ)	Absorb-Dri hardwood chips (Absorb-Dri, Inc., Garfield, NJ)	Same as 16-d studies	Same as 16-d studies	Same as 16-d studies
Water				
Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Cages				
Polycarbonate (Lab Products, Inc., Garfield or Rochelle Park, NJ)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Cage Filters				
Spun bonded polyester, Du Pont 2024® (Snow Filtration, Cincinnati, OH)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Animals per Cage				
5; supplemental studies--4	5	5	5	5
Other Chemicals on Study in the Same Room				
None	None	None	None	None
Animal Room Environment				
Temp--21°-25° C; hum--40%-60%; fluorescent light 12 h/d; 15 room air changes/h	Target temp--22°-24° C; target hum--40%-60%; fluorescent light 12 h/d; 15 room air changes/h	Temp--21°-23° C; hum--40%-60%; fluorescent light 12 h/d; 15 room air changes/h	Temp--16°-26° C; hum--24%-80%; fluorescent light 12 h/d; 15 room air changes/h	Temp--16°-28° C; hum--24%-80%; fluorescent light 12 h/d; 15 room air changes/h

Four-week-old male and female F344/N rats and 5- to 6-week-old male and female $B6C3F_1$ mice were obtained from Charles River Breeding Laboratories, observed for 20 or 21 days for rats and 22 or 23 days for mice, distributed to weight classes, and assigned to groups according to a table of random numbers. Rats were 7 weeks old when placed on study, and mice were 8-9 weeks old. Groups of 10 rats and 10 mice of each sex were administered 0, 31, 62, 125, 250, or 500 mg/kg dimethoxane in corn oil by gavage, 5 days per week for 13 weeks.

Rats and mice were housed five per cage. Feed and water were available ad libitum. Further experimental details are summarized in Table 5. Animals were observed two times per day; moribund animals were killed. Individual animal weights were recorded one time per week.

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.

FIFTEEN-MONTH AND TWO-YEAR STUDIES

Study Design

Groups of 60 male rats were administered 0, 62.5, or 125 mg/kg dimethoxane in corn oil by gavage, and groups of 60 female rats were administered 0, 125, or 250 mg/kg. Groups of 58 or 60 mice of each sex were administered 0, 250, and 500 mg/kg dimethoxane in corn oil by gavage. Animals received dimethoxane 5 days per week for 15 months or 103 weeks.

At month 15, blood was collected from the vena cava in groups of 10 rats, and blood was collected in groups of 10 mice by cardiac puncture for analyses. Hematologic analyses, including erythrocyte count, leukocyte count, and platelet count, were conducted with an Ortho ELT-8 Laser Hematology Counter. Hematocrit was reported as a percentage of whole blood volume. Hemoglobin was determined spectrophotometrically. Mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration were calculated. Leukocyte differentials were determined manually from blood smears. Analyses of serum for glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, urea nitrogen, alkaline phosphatase, sorbitol dehydrogenase, total protein, albumin, albumin to globulin ratio, creatinine, bilirubin, and cholinesterase were performed with a Gemsaec IV Centrifugal Analyzer. A necropsy was performed, and the liver, brain, heart, and right kidney were weighed. Histopathologic examinations were performed on tissues of mice that received 0 or 500 mg/kg dimethoxane and on tissues of female rats that received 0 or 250 mg/kg dimethoxane and male rats that received 0 or 125 mg/kg. Tissues examined are listed in Table 5. The harderian gland was examined in mice that received 250 mg/kg dimethoxane, and the forestomach was examined in female rats that received 125 mg/kg dimethoxane and male rats that received 62.5 mg/kg.

Source and Specifications of Animals

The male and female F344/N rats and $B6C3F_1$ (C57BL/6N, female × C3H/HeN MTV^-, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Rats were shipped to the study laboratory at 4-5 weeks of age and mice at 5-6 weeks of age. The animals were quarantined at the study laboratory for 3 weeks. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rats were placed on study at 7-8 weeks of age and mice at 8-9 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 E).

Animal Maintenance

Rats and mice were housed five per cage. Cages and racks were rotated. Feed and water were available ad libitum. Further experimental details are summarized in Table 5.

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded once per week for the first 13 weeks and at least once per month thereafter. Body weights were recorded once per week for the first 13 weeks of the study and once per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals including those found dead unless they were missexed. Some tissues were autolyzed, cannibalized, or missing, and 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 the "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 lower 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 groups 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 about 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 the lesions in question are subtle or unless there is an inconsistent diagnosis of lesions by the laboratory pathologist. Nonneoplastic lesions are not examined routinely by the quality assessment pathologist or PWG unless they are considered part of the toxic effect of the chemical.

Statistical Methods

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

Survival Analyses: The probability of survival was estimated by the product-limit procedure of

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

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

Analysis of Tumor Incidence: Three statistical methods are used to analyze tumor incidence data: life table tests, logistic regression, and Fisher exact/Cochran-Armitage trend analyses. Tests of significance include pairwise comparisons of high dose and low dose groups with vehicle controls and tests for overall dose-response trends. For studies in which administration of the study compound 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. The procedures described below also were used to evaluate selected nonneoplastic lesions.

Life Table Analyses--This method of analysis assumes that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and vehicle control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel method (1959) 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.

Logistic Regression Analyses--This method of analysis assumes that all tumors of a given type were "incidental"; i.e., they did not alter the risk of death and were discovered merely as the result of death from an unrelated cause. According to this approach, tumor prevalence was modeled as a logistic function of dose and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if it did not significantly enhance the fit of the model. The dosed and vehicle control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). If the tumor type is nonlethal, this comparison of the time-specific tumor prevalence also provides a comparison of the time-specific tumor incidences (McKnight and Crowley, 1984).

Fisher Exact/Cochran-Armitage Trend Analyses--In addition to survival-adjusted methods, 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 tumor incidence. These two tests are based on the overall proportion of tumor-bearing animals and do not adjust for survival differences.

Analysis of Continuous Variables: The statistical analysis of organ weight to body weight ratios for the 13-week studies was carried out by using Dunnett's test (Dunnett, 1955) or Student's *t*-test if only two groups were compared. The analysis of organ weight to body weight ratios and hematologic data for the 15-month studies was conducted by using the individual animal data and the nonparametric multiple comparison methods of Dunn (1964) and Shirley (1977). Jonckheere's test (Jonckheere, 1954) was used to evaluate the significance of dose-response trends.

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.

GENETIC TOXICOLOGY

Salmonella Protocol: Testing was performed as described by Ames et al. (1975) with modifications listed below and described in greater detail by Haworth et al. (1983) and Mortelmans et al. (1986). Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, Texas). The study chemical was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, and TA1537) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver) for 20 minutes at 37° C before the addition of soft agar supplemented with L-histidine and D-biotin and subsequent plating on minimal glucose agar plates. Incubation was continued for an additional 48 hours.

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

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

Chinese Hamster Ovary Cytogenetics Assay: Testing was performed as reported by Galloway et al. (1985, 1987) and is described briefly below. Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, Texas). Chemicals were tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations both in the presence and absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine (BrdU)-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of the study chemical; the high dose was limited by toxicity or solubility but did not exceed 0.5 mg/ml.

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

present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9.

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

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

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind, and those from a single test were read by the same person. For the SCE test, 50 second-division metaphase cells were usually scored for frequency of SCEs per cell from each dose; 100 (more recently, 200) first-division metaphase cells were scored at each dose for the chromosomal aberration test. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Statistical analyses were conducted on both the slopes of the dose-response curves and the individual dose points. An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. Chromosomal aberration data are presented as percentage of cells with aberrations. As with SCE, both the dose-response curve and individual dose points were statistically analyzed. A statistically significant ($P<0.003$) trend test or a significantly increased dose point ($P<0.05$) was sufficient to indicate a chemical effect.

Drosophila Melanogaster Protocol: The assays for gene mutation and chromosomal translocation induction were performed as described in Woodruff et al. (1985). Study chemicals were supplied as coded aliquots from Radian Corporation (Austin, Texas). Initially, study chemicals were assayed in the sex-linked recessive lethal (SLRL) test by feeding for 3 days to adult Canton-S wild-type males that were no more than 24 hours old at the beginning of treatment. If no response was obtained, the chemical was retested by injection into adult males. If either route of administration produced a positive result, the chemical was assayed for induction of reciprocal translocations (RTs) under the same method of exposure. If, because of the physical nature of the chemical, feeding experiments were not possible, injection was selected as the method of study chemical administration, and a positive result was followed by an RT test.

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

Toxicity tests attempted to set concentrations of study chemical at a level that would produce 30% mortality after 72 hours of feeding or 24 hours after injection, while keeping induced sterility at an acceptable level. For the SLRL test, exposure by feeding was done by allowing Canton-S males (10-20 flies per vial) to feed for 72 hours on a solution of the study chemical in

5% sucrose. In the injection experiments, 24- to 72-hour-old Canton-S males were given a solution of the chemical dissolved in 0.7% saline or peanut oil and 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 matings of 3, 2, and 2 days; sample sperm from successive matings were treated as successively earlier postmeiotic stages. F_1 heterozygous females were allowed to mate with their siblings and then were placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters. (A cluster occurs when a number of mutants from a given male result from a single spontaneous premeiotic mutation event and is identified when the number of mutants from that male exceeds the number predicted by a Poisson distribution.) If a cluster was identified, all data from the male in question were discarded. After 17 days, presumptive lethal mutations were identified as vials containing no wild-type males; these were retested. At least two experiments were performed for each study chemical, resulting in the testing of some 5,000 treated and 5,000 control chromosomes. The only exceptions occurred when the results of the first experiment were clearly positive (induced frequency of recessive lethal mutations equal to or greater than 1%); then, the second trial was not run.

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

For the RT test, the exposure regimen was the same as that for the SLRL test except that small mass matings were used (10 males and 20 females). Exposed males were mated to bw;st or bw;e females for 3 days and discarded. The females were transferred to fresh medium every 3-4 days for a period of about 3 weeks to produce a total of six broods. The results of the SLRL test were used to narrow the germ-cell stage most likely to be affected by the chemical; for example, if earlier germ-cell stages seemed to exhibit increased sensitivity, mating of the males was continued and translocation tests were carried out from the offspring derived from these earlier germ cell stages. F_1 males were mated individually to bw;st females and the progeny were examined for missing classes, which indicate the occurrence of a translocation in the parental male. Suspected RTs were retested. The translocation data were analyzed according to the conditional binomial test (Kastenbaum and Bowman, 1970).

III. RESULTS

RATS

SINGLE-ADMINISTRATION STUDIES

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

FIFTEEN-MONTH STUDIES

TWO-YEAR STUDIES

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

MICE

SINGLE-ADMINISTRATION STUDIES

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

FIFTEEN-MONTH STUDIES

TWO-YEAR STUDIES

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

GENETIC TOXICOLOGY

SINGLE-ADMINISTRATION STUDIES

All male and 4/5 female rats that received 2,800 mg/kg dimethoxane died before the end of the studies. No detectable amount of dimethoxane was found in the urine of rats 24 or 48 hours after they received 2,800 mg/kg dimethoxane. In the supplemental study, no detectable amount of dimethoxane was found in the blood of male rats 15 or 30 minutes or 1, 2, or 4 hours after they received 2,800 mg/kg dimethoxane. Dimethoxane was not detected in blood or urine. This finding does not mean that the compound was not absorbed, since both blood and urine were analyzed for the parent compound only. Dimethoxane is known to undergo hydrolysis in an aqueous medium, so it is not surprising that none was found in either blood or urine.

SIXTEEN-DAY STUDIES

All rats that received 2,000 mg/kg dimethoxane died within 1 week (Table 6). Compound-related clinical signs were not seen in the survivors. The final mean body weight of male rats that received 1,000 mg/kg was 5% lower than that of vehicle controls; the final mean body weights of dosed and vehicle control female rats were similar. The relative liver weights for rats that received 1,000 mg/kg were significantly greater than those for vehicle controls (Table 7). The relative thymus, lung, kidney, and heart weights for dosed and vehicle control rats were not significantly different. Hemorrhage and necrosis of the stomach were seen in rats that died before the end of the studies. Moderate-to-severe inflammation, hyperplasia, and/or hyperkeratosis of the forestomach were observed in 1/5 females receiving 125 mg/kg, 2/5 males and 3/5 females receiving 250 mg/kg, and all males and females receiving 500 or 1,000 mg/kg; ulceration was observed in 1/5 males receiving 250 mg/kg, 1/5 males and 1/5 females receiving 500 mg/kg, and 1/5 males and 3/5 females receiving 1,000 mg/kg.

TABLE 6. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SIXTEEN-DAY GAVAGE STUDIES OF DIMETHOXANE

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	120	185	+65	
125	5/5	120	194	+74	104.9
250	5/5	118	179	+61	96.8
500	5/5	124	188	+64	101.6
1,000	5/5	120	175	+55	94.6
2,000	(d) 0/5	122	(e)	(e)	(e)
FEMALE					
0	5/5	105	136	+31	
125	5/5	100	137	+37	100.7
250	5/5	99	135	+36	99.3
500	5/5	101	135	+34	99.3
1,000	5/5	101	133	+32	97.8
2,000	(f) 0/5	99	(e)	(e)	(e)

(a) Number surviving/number initially in group
(b) Initial mean group body weight
(c) Mean body weight change of the group
(d) Day of death: 2,2,2,2,3
(e) No data are reported due to 100% mortality in this group.
(f) Day of death: 2,2,2,2,7

TABLE 7. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR RATS IN THE SIXTEEN-DAY GAVAGE STUDIES OF DIMETHOXANE (a)

Organ	Vehicle Control	125 mg/kg	250 mg/kg	500 mg/kg	1,000 mg/kg
MALE					
Body weight (grams)	185	194	175	188	175
Liver	57.4 ± 2.37	62.7 ± 2.22	56.3 ± 2.02	56.2 ± 1.55	**69.3 ± 1.16
Thymus	2.1 ± 0.08	2.2 ± 0.10	2.1 ± 0.25	2.1 ± 0.06	2.1 ± 0.15
Brain	9.5 ± 0.23	9.4 ± 0.11	10.1 ± 0.66	9.7 ± 0.13	9.9 ± 0.33
Lungs	7.9 ± 0.51	8.6 ± 1.09	7.3 ± 0.30	7.3 ± 0.12	7.6 ± 0.29
Kidney	5.6 ± 0.12	5.6 ± 0.11	5.7 ± 0.11	6.0 ± 0.42	5.6 ± 0.12
Heart	4.0 ± 0.12	4.0 ± 0.12	4.2 ± 0.16	4.0 ± 0.09	4.1 ± 0.12
FEMALE					
Body weight (grams)	136	137	135	135	133
Liver	50.3 ± 1.67	52.0 ± 1.14	51.3 ± 1.39	52.4 ± 2.34	**59.8 ± 1.00
Thymus	2.5 ± 0.17	2.5 ± 0.26	2.5 ± 0.09	2.3 ± 0.08	2.1 ± 0.15
Brain	12.5 ± 0.24	12.5 ± 0.25	12.6 ± 0.34	14.7 ± 2.38	12.3 ± 0.09
Lungs	9.7 ± 0.40	8.7 ± 0.23	8.1 ± 0.29	13.2 ± 6.95	9.0 ± 1.06
Kidney	6.0 ± 0.20	5.8 ± 0.16	5.8 ± 0.03	6.2 ± 0.46	6.0 ± 0.14
Heart	4.4 ± 0.10	4.3 ± 0.10	4.3 ± 0.12	5.8 ± 1.67	4.2 ± 0.10

(a) Mean ± standard error in milligrams of organ per gram of body weight, for groups of five animals; P values vs. the vehicle controls by Dunnett's test (Dunnett, 1955).
**P<0.01

THIRTEEN-WEEK STUDIES

No compound-related deaths occurred (doses up to 500 mg/kg dimethoxane in corn oil by gavage) (Table 8). The final mean body weight of rats that received 500 mg/kg was 17% lower than that of vehicle controls for males and 5% lower for females. The relative kidney, brain, and lung weights for male rats at 500 mg/kg were slightly greater than those for vehicle controls (Table 9). Compound-related lesions were restricted to the forestomach and consisted of minimal-to-severe acanthosis and hyperkeratosis of the stratified squamous epithelium, ulceration, and inflammation (Table 10). The incidence and severity of the acanthosis and hyperkeratosis decreased with decreasing dose. Ulceration and inflammation occurred only at doses of 250 and 500 mg/kg. No forestomach lesions were seen in the 31 mg/kg group of males or in the 31, 62, or 125 mg/kg groups of females. Minimal lesions were seen in a few 62 mg/kg males.

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

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	8/10	140 ± 2	369 ± 9	+229 ± 7	
31	9/10	140 ± 2	350 ± 11	+210 ± 10	95
62	10/10	143 ± 1	357 ± 6	+214 ± 7	97
125	10/10	140 ± 2	352 ± 7	+212 ± 7	95
250	10/10	140 ± 2	346 ± 6	+206 ± 5	94
500	9/10	139 ± 2	306 ± 10	+167 ± 9	83
FEMALE					
0	10/10	114 ± 2	200 ± 4	+86 ± 3	
31	8/10	114 ± 2	195 ± 3	+82 ± 3	98
62	9/10	113 ± 2	203 ± 4	+91 ± 3	102
125	10/10	114 ± 1	206 ± 5	+92 ± 4	103
250	10/10	114 ± 2	200 ± 2	+86 ± 2	100
500	9/10	111 ± 2	189 ± 4	+77 ± 3	95

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

TABLE 9. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF DIMETHOXANE (a)

Organ	Vehicle Control	31 mg/kg	62 mg/kg	125 mg/kg	250 mg/kg	500 mg/kg
MALE						
Number weighed (b)	8	9	10	9	10	9
Body weight (grams)	364	346	354	349	346	307
Liver	44.0 ± 2.07	43.3 ± 1.14	43.0 ± 1.08	42.8 ± 0.89	(c) 44.9 ± 1.44	44.8 ± 1.33
Thymus	0.9 ± 0.06	0.9 ± 0.04	0.9 ± 0.07	0.9 ± 0.03	(c) 1.0 ± 0.05	0.9 ± 0.07
Kidney	3.4 ± 0.13	3.7 ± 0.10	3.6 ± 0.09	3.7 ± 0.08	3.7 ± 0.06	**3.9 ± 0.10
Heart	2.9 ± 0.15	2.9 ± 0.08	3.0 ± 0.07	3.0 ± 0.07	3.1 ± 0.09	3.1 ± 0.10
Brain	5.3 ± 0.11	5.5 ± 0.07	5.5 ± 0.07	5.5 ± 0.10	5.6 ± 0.06	**6.3 ± 0.19
Lungs	4.3 ± 0.31	*5.8 ± 0.38	5.0 ± 0.25	5.0 ± 0.28	5.2 ± 0.29	*5.6 ± 0.31
Right testis	4.2 ± 0.11	4.4 ± 0.06	4.1 ± 0.09	4.2 ± 0.07	4.4 ± 0.09	4.5 ± 0.12
FEMALE						
Number weighed (b)	10	8	9	10	10	9
Body weight (grams)	198	193	202	206	200	191
Liver	34.6 ± 0.84	35.4 ± 0.37	37.0 ± 0.93	35.1 ± 1.19	36.0 ± 0.66	37.5 ± 1.02
Thymus	1.3 ± 0.05	1.2 ± 0.06	1.4 ± 0.09	1.3 ± 0.04	1.4 ± 0.04	1.2 ± 0.05
Kidney	3.5 ± 0.10	3.6 ± 0.07	3.6 ± 0.08	3.5 ± 0.06	3.6 ± 0.05	3.8 ± 0.07
Heart	3.3 ± 0.08	3.3 ± 0.05	3.3 ± 0.13	3.3 ± 0.06	3.6 ± 0.09	3.6 ± 0.10
Brain	9.3 ± 0.16	9.3 ± 0.17	9.0 ± 0.21	8.9 ± 0.12	9.3 ± 0.12	9.5 ± 0.09
Lungs	6.1 ± 0.31	(d) 7.0 ± 0.45	(e) 6.9 ± 0.44	(c) 6.5 ± 0.44	6.9 ± 0.29	6.3 ± 0.28

(a) Mean ± standard error in milligram of organ per gram of body weight; P values vs. the vehicle controls by Dunnett's test (Dunnett, 1955).
(b) Unless otherwise specified
(c) Nine animals were weighed.
(d) Seven animals were weighed.
(e) Eight animals were weighed.
*$P<0.05$
**$P<0.01$

TABLE 10. NUMBER OF RATS WITH FORESTOMACH LESIONS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF DIMETHOXANE (a)

Lesion	Vehicle Control	31 mg/kg	62 mg/kg	125 mg/kg	250 mg/kg	500 mg/kg
MALE						
Acanthosis	0	0	4 (1)	6 (1)	10 (1-3)	10 (2-4)
Hyperkeratosis	0	0	4 (1)	0	10 (1-3)	10 (2-4)
Inflammation	0	0	0	0	0	1 (1)
Ulceration	0	0	0	0	0	1 (1)
FEMALE						
Acanthosis	0	0	0	0	9 (1-2)	9 (2-3)
Hyperkeratosis	0	0	0	0	8 (1-2)	9 (2-3)
Inflammation	0	0	0	0	0	1 (1)
Ulceration	0	0	0	0	1 (1)	1 (3)

(a) Ten animals were examined in each group. Results are based on the report of the Pathology Quality Assessment/Pathology Working Group review of the study pathologist's findings dated July 9, 1982. Numbers in parentheses are the ranges of lesion severity grades: 1 = minimal; 2 = mild; 3 = moderate; 4 = severe.

Dose Selection Rationale: Because of lower body weights in males receiving 500 mg/kg and the severity of forestomach lesions in males receiving 250 or 500 mg/kg and in females receiving 500 mg/kg, doses of dimethoxane selected for rats for the 15-month and 2-year studies were 62.5 and 125 mg/kg for males and 125 and 250 mg/kg for females, administered in corn oil by gavage 5 days per week.

FIFTEEN-MONTH STUDIES

Minimal diffuse acanthosis and hyperplasia of the forestomach were seen in 7/10 females receiving 250 mg/kg, 7/10 males receiving 125 mg/kg, and 1/9 male and 1/9 female vehicle controls. No compound-related effects on organ weights or on results of clinical chemical or hematologic analyses were observed (Tables 11 and 12).

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed and vehicle control rats were generally similar throughout the studies (Table 13 and Figure 3). No compound-related clinical signs were seen.

TABLE 11. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR RATS IN THE FIFTEEN-MONTH GAVAGE STUDIES OF DIMETHOXANE (a)

Organ	Vehicle Control	62 mg/kg	125 mg/kg	250 mg/kg
MALE				
Body weight (grams)	458 ± 4.8	462 ± 7.9	477 ± 10.0	
Liver	34.2 ± 0.63	32.4 ± 0.63	32.7 ± 0.65	
Brain	4.5 ± 0.08	4.3 ± 0.05	4.4 ± 0.10	
Heart	2.5 ± 0.07	2.5 ± 0.08	2.5 ± 0.04	
Kidney	3.0 ± 0.05	3.0 ± 0.05	2.9 ± 0.08	
FEMALE				
Body weight (grams)	274 ± 7.9		278 ± 7.2	284 ± 5.5
Liver	33.2 ± 0.57		32.5 ± 0.71	31.9 ± 0.58
Brain	6.9 ± 0.24		6.5 ± 0.17	6.5 ± 0.14
Heart	2.8 ± 0.08		2.8 ± 0.04	2.9 ± 0.09
Kidney	3.1 ± 0.08		3.0 ± 0.05	3.0 ± 0.06

(a) Mean ± standard error in milligrams of organ per gram of body weight, for groups of 10 animals; comparisons were made by Dunn's test or by Shirley's test (Dunn, 1964; Shirley, 1977). No significant differences were found.

TABLE 12. ANALYSIS OF HEMATOLOGIC AND CLINICAL CHEMICAL DATA FOR RATS IN THE FIFTEEN-MONTH GAVAGE STUDIES OF DIMETHOXANE (a)

Analysis	Vehicle Control	62.5 mg/kg	125 mg/kg	250 mg/kg
MALE				
Leukocytes (1,000/mm^3)	6.87 ± 0.953	6.74 ± 0.276	6.23 ± 0.276	
Lymphocytes (1,000/mm^3)	3.84 ± 0.345	4.18 ± 0.226	4.03 ± 0.191	
Segmented neutrophils (1,000/mm^3)	2.84 ± 0.615	2.37 ± 0.335	1.99 ± 0.155	
Eosinophils (1,000/mm^3)	0.17 ± 0.045	0.15 ± 0.025	0.17 ± 0.050	
Bands (1,000/mm^3)	0.02 ± 0.015	0.03 ± 0.014	0.01 ± 0.007	
Hematocrit (percent)	47.8 ± 0.83	47.4 ± 1.17	46.9 ± 0.69	
Hemoglobin (g/dl)	16.0 ± 0.25	15.8 ± 0.31	15.9 ± 0.17	
Mean corpuscular hemoglobin (pg)	16.3 ± 0.12	16.0 ± 0.11	16.2 ± 0.19	
Mean corpuscular hemoglobin concentration (g/dl)	33.5 ± 0.20	33.4 ± 0.24	33.9 ± 0.22	
Mean corpuscular volume (μ^3)	48.8 ± 0.39	48.0 ± 0.49	47.6 ± 0.58	
Nucleated erythrocytes (per 100 leukocytes)	1.5 ± 0.67	0.4 ± 0.16	0.3 ± 0.15	
Platelets (1,000/mm^3)	480 ± 31.0	418 ± 26.5	471 ± 29.8	
Erythrocytes (10^6/mm^3)	9.824 ± 0.125	9.837 ± 0.195	9.842 ± 0.164	
Albumin/globulin ratio	1.79 ± 0.061	1.82 ± 0.058	1.94 ± 0.075	
Albumin (g/dl)	(b) 4.23 ± 0.050	4.17 ± 0.058	4.22 ± 0.049	
Alkaline phosphatase (IU)	(b) 113 ± 6.3	118 ± 3.6	116 ± 7.3	
Blood urea nitrogen (mg/dl)	16.0 ± 0.67	16.8 ± 0.61	17.3 ± 0.58	
Cholinesterase (IU/liter)	(b) 1,254 ± 45	1,323 ± 74	1,205 ± 51	
Creatinine (mg/dl)	0.63 ± 0.033	0.70 ± 0.103	0.60 ± 0.039	
Sorbitol dehydrogenase (IU/liter)	(b) 33.4 ± 4.54	33.5 ± 3.47	37.5 ± 5.39	
Serum glutamic-oxaloacetic transaminase (IU/liter)	95.6 ± 11.93	91.0 ± 9.47	88.2 ± 5.39	
Serum glutamic-pyruvic transaminase (IU/liter)	(b) 48.2 ± 5.43	49.3 ± 3.32	59.8 ± 6.18	
Total bilirubin (mg/dl)	0.23 ± 0.013	0.24 ± 0.031	0.19 ± 0.008	
Total protein (g/dl)	6.37 ± 0.184	6.46 ± 0.088	6.42 ± 0.061	
FEMALE				
Leukocytes (1,000/mm^3)	4.26 ± 0.372		4.03 ± 0.239	4.24 ± 0.315
Lymphocytes (1,000/mm^3)	2.49 ± 0.128		2.58 ± 0.138	2.95 ± 0.241
Segmented neutrophils (1,000/mm^3)	1.67 ± 0.265		1.34 ± 0.114	1.18 ± 0.131
Eosinophils (1,000/mm^3)	0.07 ± 0.025		0.06 ± 0.016	0.07 ± 0.019
Bands (1,000/mm^3)	0.016 ± 0.007		0.040 ± 0.019	0.013 ± 0.010
Hematocrit (percent)	45.4 ± 0.54		45.9 ± 0.38	45.9 ± 0.46
Hemoglobin (g/dl)	15.6 ± 0.11		15.6 ± 0.10	15.7 ± 0.19
Mean corpuscular hemoglobin (pg)	18.4 ± 0.14		18.3 ± 0.06	18.5 ± 0.16
Mean corpuscular hemoglobin concentration (g/dl)	34.4 ± 0.21		34.0 ± 0.27	34.3 ± 0.28
Mean corpuscular volume (μ^3)	53.5 ± 0.58		53.9 ± 0.43	54.1 ± 0.23
Nucleated erythrocytes (per 100 leukocytes)	2.9 ± 0.84		2.3 ± 0.30	2.7 ± 0.68
Platelets (1,000/mm^3)	354 ± 24.5		384 ± 16.0	368 ± 21.6
Erythrocytes (10^6/mm^3)	8.459 ± 0.092		8.517 ± 0.066	8.480 ± 0.073
Albumin/globulin ratio	2.48 ± 0.128		2.36 ± 0.094	2.60 ± 0.085
Albumin (g/dl)	5.02 ± 0.134		5.00 ± 0.098	4.96 ± 0.079
Alkaline phosphatase (IU)	(b) 128 ± 5.1		130 ± 6.4	139 ± 6.7
Blood urea nitrogen (mg/dl)	19.2 ± 0.74		20.1 ± 1.08	18.6 ± 0.86
Cholinesterase (IU/liter)	3,863 ± 197		3,877 ± 130	3,889 ± 89
Creatinine (mg/dl)	0.66 ± 0.060		0.63 ± 0.052	0.63 ± 0.052
Sorbitol dehydrogenase (IU/liter)	(b) 42.0 ± 8.07		45.2 ± 7.91	(b) 48.9 ± 8.32
Serum glutamic-oxaloacetic transaminase (IU/liter)	86.9 ± 8.07		94.5 ± 9.22	99.0 ± 9.22
Serum glutamic-pyruvic transaminase (IU/liter)	54.4 ± 6.37		58.5 ± 6.54	(b) 59.7 ± 7.51
Total bilirubin (mg/dl)	0.23 ± 0.031		0.23 ± 0.027	0.20 ± 0.014
Total protein (g/dl)	7.07 ± 0.122		7.13 ± 0.096	6.88 ± 0.068

(a) Mean ± standard error, for 10 animals unless otherwise specified; no significant differences were found vs. the vehicle controls by Dunn's test or Shirley's test (Dunn, 1964; Shirley, 1977).
(b) Nine animals were examined.

TABLE 13. MEAN BODY WEIGHTS OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHOXANE

Week on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. Weighed	Low Dose Av. Wt. (grams)	Low Dose Wt. (percent of veh. controls)	Low Dose No. Weighed	High Dose Av. Wt. (grams)	High Dose Wt. (percent of veh. controls)	High Dose No. Weighed
MALE				**62.5 mg/kg**			**125 mg/kg**	
0	138	60	139	101	60	137	99	60
2	178	60	177	99	60	171	96	60
3	197	60	198	101	60	194	98	60
4	217	60	219	101	60	217	100	60
5	240	60	239	100	60	240	100	60
6	251	60	253	101	60	253	101	60
7	264	60	260	98	60	261	99	60
8	281	60	280	100	60	282	100	60
9	295	60	293	99	60	296	100	60
10	297	60	299	101	60	304	102	60
11	311	60	309	99	60	314	101	60
12	327	60	325	99	60	329	101	60
13	331	60	329	99	60	329	99	60
18	367	60	364	99	60	371	101	60
22	382	60	374	98	60	389	102	60
26	403	60	390	97	60	404	100	60
30	414	60	402	97	60	411	99	60
34	425	60	411	97	60	424	100	60
38	425	60	417	98	60	429	101	60
42	434	60	425	98	59	437	101	59
46	440	60	437	99	59	448	102	59
50	449	60	443	99	59	454	101	59
54	457	59	452	99	59	466	102	58
58	464	59	460	99	57	472	102	58
62	465	59	463	100	55	473	102	57
66	465	58	461	99	55	474	102	57
70	471	(a) 48	462	98	(a) 45	479	102	(a) 47
74	471	46	462	98	44	476	101	46
78	470	45	459	98	42	473	101	44
82	468	43	464	99	41	483	103	36
86	468	40	464	99	40	478	102	34
90	466	39	463	99	38	478	103	31
94	466	36	464	100	37	475	102	26
98	448	31	457	102	35	469	105	24
102	437	28	455	104	31	460	105	21
104	428	26	452	106	28	451	105	21
FEMALE				**125 mg/kg**			**250 mg/kg**	
0	108	60	108	100	60	107	99	60
2	128	60	129	101	60	128	100	60
3	135	60	136	101	60	136	101	59
4	145	60	146	101	60	146	101	59
5	153	60	153	100	60	156	102	59
6	162	60	160	99	60	160	99	59
7	165	60	165	100	60	164	99	59
8	171	60	170	99	60	169	99	59
9	174	60	174	100	60	172	99	59
10	180	60	179	99	60	179	99	59
11	182	60	180	99	60	181	99	59
12	184	60	184	100	60	185	101	59
13	184	59	184	100	60	187	102	59
18	197	59	196	99	60	196	99	59
22	204	59	205	100	59	205	100	59
26	212	59	208	98	59	205	97	59
30	217	59	211	97	59	210	97	58
34	223	59	220	99	59	219	98	58
38	223	59	225	101	59	224	100	56
42	230	58	229	100	59	227	99	56
46	234	58	235	100	59	233	100	55
50	243	58	240	99	59	240	99	55
54	253	58	249	98	59	252	100	55
58	262	58	259	99	59	263	100	54
62	266	58	266	100	59	270	102	54
66	271	57	272	100	59	276	102	54
70	281	(a) 46	281	100	(a) 48	281	100	(a) 44
74	286	45	292	102	48	287	100	44
78	287	44	286	100	43	287	100	39
82	294	42	297	101	42	295	100	34
86	296	39	301	102	41	302	102	33
90	296	37	303	102	39	302	102	30
94	305	34	307	101	39	303	99	30
98	307	33	306	100	37	302	98	26
102	305	31	308	101	35	302	99	25
104	304	30	302	99	34	305	100	24

(a) Interim kill occurred.

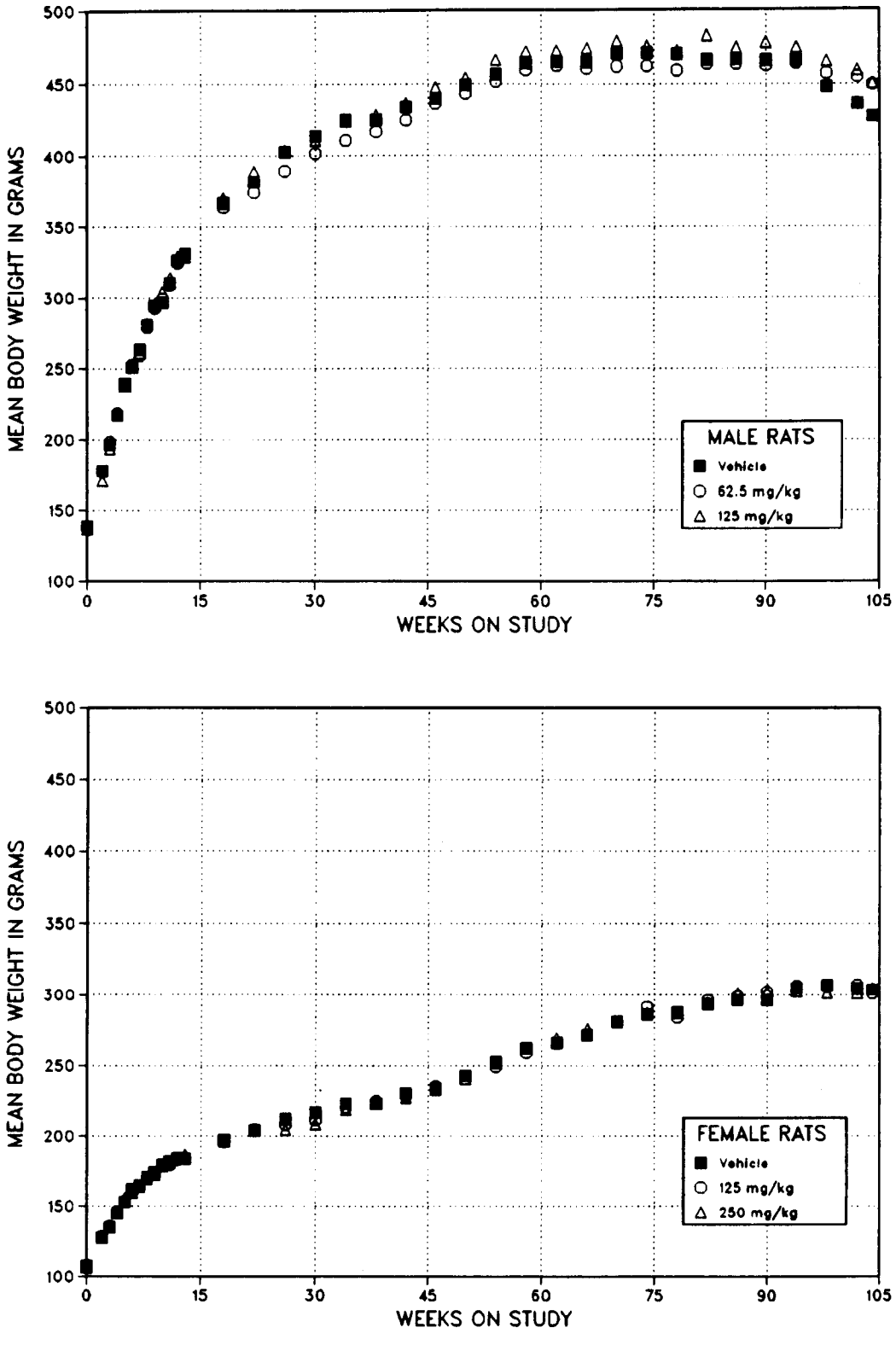

FIGURE 3. GROWTH CURVES FOR RATS ADMINISTERED DIMETHOXANE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats administered dimethoxane at the doses used in these studies and for vehicle controls are shown in Table 14 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 statistically significant or biologically noteworthy changes in the incidences of rats with nonneoplastic lesions of the forestomach. At no site were the incidences of neoplastic lesions significantly increased in dosed rats.

Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one animal group, and historical control incidences for the neoplasms mentioned in this section are presented in Appendixes A and B for male and female rats, respectively.

Forestomach: Acanthosis was observed at increased incidences in dosed rats (male: vehicle control, 5/50; low dose, 9/50; high dose, 23/50; female: 0/50; 8/50; 44/50). Hyperkeratosis was observed at increased incidences in high dose male and dosed female rats (male: 1/50; 0/50; 10/50; female: 0/50; 5/50; 22/50). Acanthosis and hyperkeratosis often occurred together and consisted of focal thickening of the stratified squamous epithelium with the accumulation of keratin on the surface, often near the junction of the forestomach with the glandular stomach (Figure 5). A forestomach with normal epithelium is shown in Figure 6. Squamous cell papillomas were seen in one high dose male and one high dose female but in no other groups of male or female rats.

TABLE 14. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHOXANE

	Vehicle Control	62.5 mg/kg	125 mg/kg	250 mg/kg
MALE (a)				
Animals initially in study (b)	50	50	50	
Natural deaths	4	4	6	
Moribund kills	21	15	12	
Accidentally killed (c)	2	3	11	
Animals surviving until study termination	23	28	21	
Survival P values (d)	0.655	0.375	0.784	
FEMALE (a)				
Animals initially in study (b)	50		50	50
Natural deaths	6		3	2
Moribund kills	12		13	13
Accidentally killed (c)	2		3	11
Animals surviving until study termination	30		31	24
Survival P values (d)	1.000		0.721	1.000

(a) First day of termination period: 730
(b) An additional 10 animals were initially present in each group and killed on day 465.
(c) Deaths probably due to errors in gavage procedures
(d) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

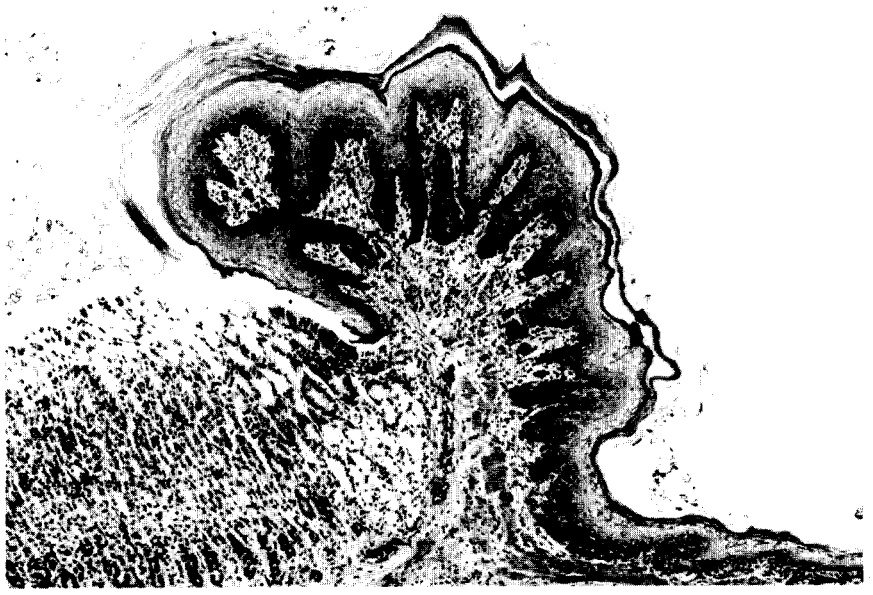

Figure 5. Forestomach of high dose female rat CID no. 665. The stratified squamous epithelium at the junction of the forestomach with the glandular stomach is thickened (acanthosis).

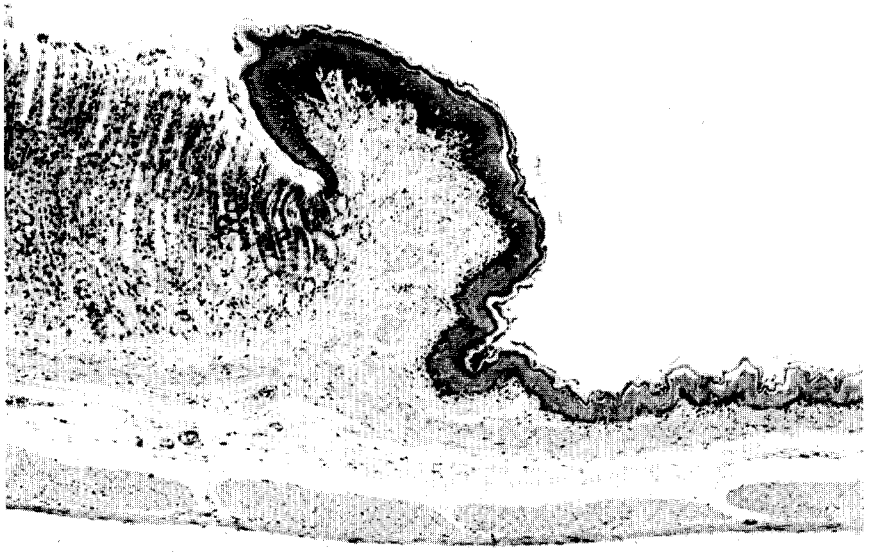

Figure 6. Forestomach of vehicle control male rat CID no. 43. The epithelium is normal.

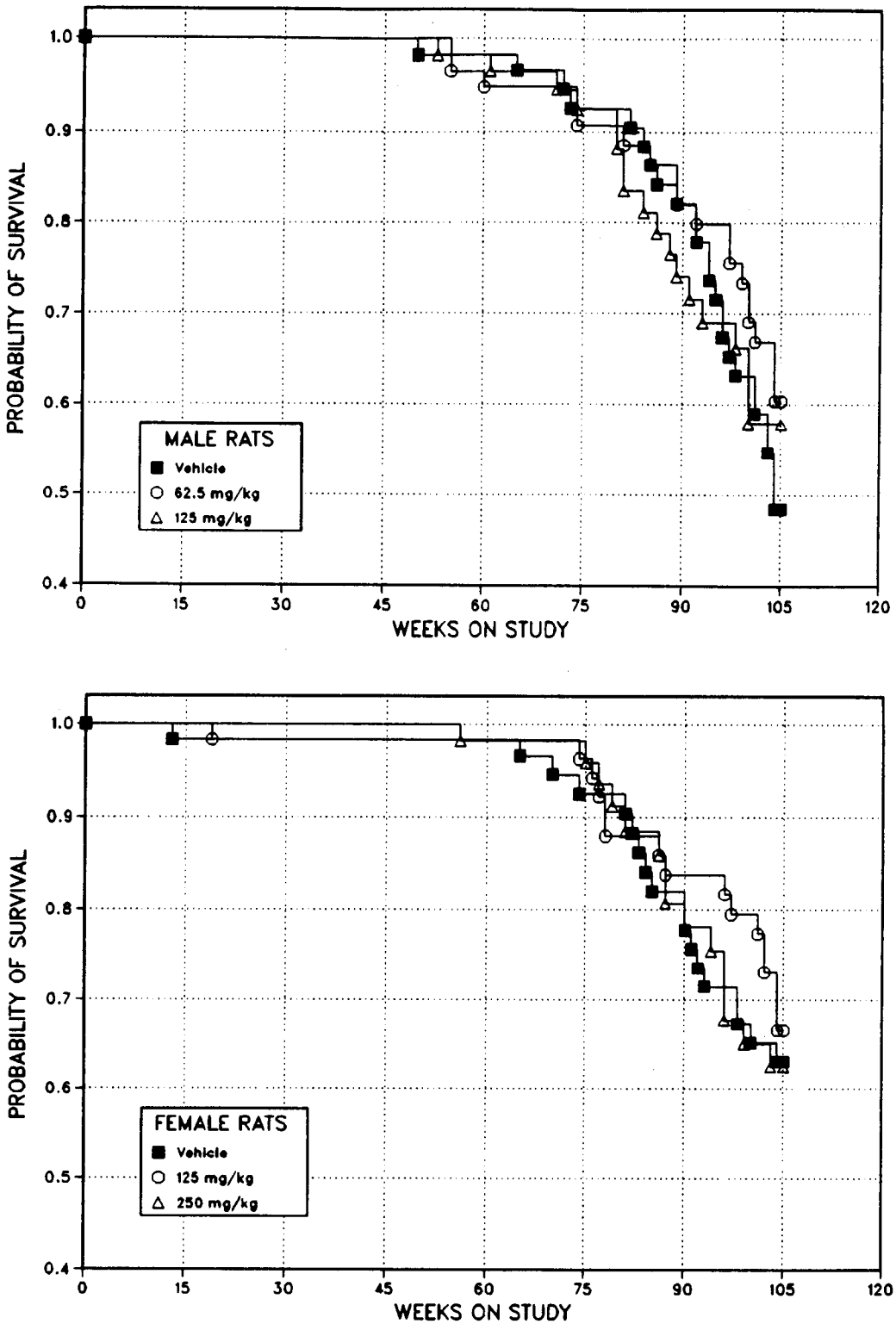

FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED DIMETHOXANE IN CORN OIL BY GAVAGE FOR TWO YEARS

SINGLE-ADMINISTRATION STUDIES

Four of five males and 4/5 females that received 2,800 mg/kg dimethoxane died within 24 hours. No compound-related clinical signs were seen. No detectable amount of dimethoxane was found in the urine of mice 24 or 48 hours after they received 2,800 mg/kg dimethoxane. In the supplemental study, no detectable amount of dimethoxane was found in the blood of male mice 15 or 30 minutes or 1, 2, or 4 hours after they received 2,800 mg/kg dimethoxane. Dimethoxane was not detected in blood or urine. This finding does not mean that the compound was not absorbed, since both blood and urine were analyzed for the parent compound only.

SIXTEEN-DAY STUDIES

One male mouse that received 2,000 mg/kg dimethoxane died before the end of the studies (Table 15). Mice that received 2,000 mg/kg had rough hair coats. Weight gain did not appear to be related to dimethoxane administration. The relative kidney weight of male mice that received 2,000 mg/kg and the relative liver weights of male and female mice that received 2,000 mg/kg and of male mice that received 1,000 mg/kg were significantly greater than those for vehicle controls (Table 16). Erosion and ulceration of the forestomach occurred in some animals in the 500, 1,000, and 2,000 mg/kg groups. All mice that received 1,000 or 2,000 mg/kg dimethoxane had diffuse, squamous epithelial hyperplasia of the forestomach accompanied by severe hyperkeratosis. A similar but less severe lesion was seen at lower doses (3/5 males and 2/5 females receiving 500 mg/kg). No compound-related stomach lesions were seen at 250 mg/kg.

TABLE 15. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SIXTEEN-DAY GAVAGE STUDIES OF DIMETHOXANE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	23.8	25.2	+1.4	
125	5/5	22.8	24.0	+1.2	95.2
250	5/5	23.2	23.8	+0.6	94.4
500	5/5	21.8	24.8	+3.0	98.4
1,000	5/5	22.6	25.4	+2.8	100.8
2,000	(d) 4/5	22.0	23.8	+1.8	94.4
FEMALE					
0	5/5	18.4	20.2	+1.8	
125	5/5	18.2	19.0	+0.8	94.1
250	5/5	18.8	19.4	+0.6	96.0
500	5/5	18.2	20.0	+1.8	99.0
1,000	5/5	18.0	20.6	+2.6	102.0
2,000	5/5	18.2	18.8	+0.6	93.1

(a) Number surviving/number initially in group
(b) Initial mean group body weight
(c) Mean body weight change of the group
(d) Day of death: 2

TABLE 16. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR MICE IN THE SIXTEEN-DAY GAVAGE STUDIES OF DIMETHOXANE (a)

Organ	Vehicle Control	125 mg/kg	250 mg/kg	500 mg/kg	1,000 mg/kg	2,000 mg/kg
MALE						
Number weighed	5	5	5	5	5	4
Body weight (grams)	25.2	24.4	23.8	24.8	25.4	23.8
Liver	55.2 ± 2.29	56.6 ± 1.77	54.3 ± 2.65	56.4 ± 1.35	*64.3 ± 1.90	**70.3 ± 2.40
Thymus	1.7 ± 0.11	2.0 ± 0.16	2.0 ± 0.23	1.9 ± 0.22	2.0 ± 0.14	1.7 ± 0.24
Kidney	9.9 ± 0.40	10.1 ± 0.22	10.0 ± 0.55	10.0 ± 0.60	10.7 ± 0.26	11.2 ± 0.33
Heart	5.9 ± 0.12	6.3 ± 0.36	5.8 ± 0.34	5.4 ± 0.15	5.6 ± 0.27	6.8 ± 0.77
Brain	17.1 ± 0.69	18.5 ± 0.38	*19.3 ± 0.54	18.6 ± 0.25	18.1 ± 0.73	19.1 ± 0.67
Lungs	8.5 ± 0.48	7.3 ± 0.79	9.1 ± 0.66	8.3 ± 0.23	9.3 ± 0.92	9.2 ± 0.82
FEMALE						
Number weighed	5	5	5	5	5	5
Body weight (grams)	20.2	19.0	19.4	20.0	20.6	18.8
Liver	53.1 ± 1.46	54.2 ± 2.27	60.6 ± 3.40	56.9 ± 2.10	60.1 ± 3.51	**67.5 ± 3.08
Thymus	2.7 ± 0.31	2.9 ± 0.09	3.4 ± 0.21	3.0 ± 0.29	3.0 ± 0.19	2.6 ± 0.33
Kidney	9.2 ± 0.18	8.3 ± 0.09	9.1 ± 0.52	9.0 ± 0.23	9.9 ± 0.44	10.1 ± 0.32
Heart	5.9 ± 0.18	5.9 ± 0.14	6.7 ± 0.51	5.1 ± 1.10	6.1 ± 0.37	6.8 ± 0.30
Brain	22.5 ± 0.61	22.7 ± 0.81	23.9 ± 1.07	22.4 ± 0.24	23.5 ± 0.53	23.8 ± 0.85
Lungs	9.1 ± 0.44	7.6 ± 1.21	8.2 ± 1.24	7.9 ± 1.64	10.3 ± 0.33	10.5 ± 0.52

(a) Mean ± standard error in milligrams of organ per gram of body weight; P values vs. the vehicle controls by Dunnett's test (Dunnett, 1955).
*P<0.05
**P<0.01

THIRTEEN-WEEK STUDIES

All mice lived to the end of the studies (doses up to 500 mg/kg dimethoxane in corn oil by gavage) (Table 17). Final mean body weights were not related to dose. The relative liver weights for dosed male mice were lower than those for vehicle controls, and the relative kidney weights for dosed female mice were greater than those for vehicle controls (Table 18). Minimal-to-mild acanthosis and hyperkeratosis of the stratified squamous epithelium of the forestomach occurred in 4/10 male and 1/10 female mice that received 500 mg/kg. These lesions consisted of a diffuse increase in thickness of the stratified squamous epithelium, with accumulation of keratin on the surface.

Dose Selection Rationale: Because of the lack of life-threatening, compound-related lesions in the 13-week studies, the two highest doses (250 and 500 mg/kg) of dimethoxane were selected for mice for the 15-month and 2-year studies. These doses were administered in corn oil by gavage 5 days per week for 103 weeks. Higher doses were not selected because of the severity of the stomach lesions seen at 1,000 and 2,000 mg/kg in the 16-day studies.

TABLE 17. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF DIMETHOXANE

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	26.6 ± 0.3	33.4 ± 0.7	+6.8 ± 0.7	
31	10/10	26.2 ± 0.4	35.3 ± 1.0	+9.1 ± 1.1	105.7
62	10/10	25.9 ± 0.3	33.9 ± 1.2	+8.0 ± 1.0	101.5
125	10/10	26.1 ± 0.4	32.8 ± 0.6	+6.7 ± 0.7	98.2
250	10/10	25.9 ± 0.4	36.2 ± 1.5	+10.3 ± 1.2	108.4
500	10/10	26.3 ± 0.4	33.3 ± 0.6	+7.0 ± 0.6	99.7
FEMALE					
0	10/10	20.2 ± 0.3	26.3 ± 0.5	+6.1 ± 0.6	
31	10/10	20.4 ± 0.3	26.1 ± 0.5	+5.7 ± 0.5	99.2
62	10/10	20.5 ± 0.3	27.4 ± 0.5	+6.9 ± 0.5	104.2
125	10/10	20.1 ± 0.3	25.6 ± 0.5	+5.5 ± 0.4	97.3
250	10/10	20.3 ± 0.2	26.1 ± 0.5	+5.8 ± 0.4	99.2
500	10/10	20.3 ± 0.3	26.5 ± 0.4	+6.2 ± 0.5	100.8

(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 group ± standard error of the mean

TABLE 18. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF DIMETHOXANE (a)

Organ	Vehicle Control	31 mg/kg	62 mg/kg	125 mg/kg	250 mg/kg	500 mg/kg
MALE						
Body weight (grams)	33.3	35.5	34.0	32.7	36.0	33.4
Liver	59.3 ± 2.15	*53.2 ± 1.03	*53.1 ± 1.22	54.2 ± 1.32	**52.4 ± 1.32	56.9 ± 1.43
Thymus	1.0 ± 0.09	1.1 ± 0.10	1.1 ± 0.14	1.1 ± 0.11	1.1 ± 0.09	0.9 ± 0.05
Right kidney	10.1 ± 0.40	9.1 ± 0.31	9.6 ± 0.49	9.6 ± 0.33	9.0 ± 0.43	10.4 ± 0.29
Heart	6.0 ± 0.31	5.5 ± 0.30	5.1 ± 0.30	5.2 ± 0.20	*4.9 ± 0.21	5.3 ± 0.22
Brain	13.9 ± 0.29	12.9 ± 0.43	13.6 ± 0.62	14.2 ± 0.34	12.9 ± 0.59	14.1 ± 0.30
Lungs	8.2 ± 0.45	8.0 ± 0.62	8.6 ± 1.21	7.3 ± 0.26	7.1 ± 0.42	8.7 ± 0.54
Right testis	3.6 ± 0.11	3.3 ± 0.15	3.5 ± 0.22	3.6 ± 0.13	3.3 ± 0.22	3.3 ± 0.12
FEMALE						
Body weight (grams)	26.3	26.2	27.4	25.6	25.9	26.3
Liver	51.7 ± 1.26	53.1 ± 0.75	51.8 ± 1.00	52.5 ± 1.01	52.7 ± 1.56	*56.3 ± 1.21
Thymus	1.6 ± 0.08	1.5 ± 0.07	1.7 ± 0.06	1.7 ± 0.11	1.7 ± 0.11	1.6 ± 0.09
Right kidney	6.7 ± 0.15	7.4 ± 0.32	*7.8 ± 0.22	**8.0 ± 0.26	**7.9 ± 0.22	**8.2 ± 0.26
Heart	5.2 ± 0.19	5.0 ± 0.18	4.9 ± 0.10	5.1 ± 0.17	5.3 ± 0.19	5.6 ± 0.24
Brain	18.0 ± 0.41	17.9 ± 0.44	17.6 ± 0.27	18.2 ± 0.22	18.4 ± 0.35	18.3 ± 0.38
Lungs	10.3 ± 0.83	9.3 ± 0.38	8.7 ± 0.31	9.2 ± 0.37	8.8 ± 0.28	9.9 ± 0.66

(a) Mean ± standard error in milligrams of organ per gram of body weight, for groups of 10 animals; P values vs. the vehicle controls by Dunnett's test (Dunnett, 1955).
*P<0.05
**P<0.01

FIFTEEN-MONTH STUDIES

A harderian gland adenoma was seen in 1/10 high dose male and 1/10 high dose female mice. A harderian gland adenocarcinoma was seen in a second high dose female mouse. Hepatocellular adenomas were seen in 2/10 vehicle control males, 1/10 vehicle control females, and 2/10 high dose males; hepatocellular carcinomas were seen in 1/10 vehicle control males and 1/10 high dose males. An alveolar/bronchiolar carcinoma was present in 1/10 high dose males. Acanthosis of the forestomach was observed in 7/10 high dose males and in 6/10 high dose females. No compound-related effects on organ weights or on results of clinical chemical or hematologic analyses were observed (Tables 19 and 20).

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed and vehicle control mice were generally similar throughout the studies (Table 21 and Figure 7). No compound-related clinical signs were observed.

TABLE 19. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR MICE IN THE FIFTEEN-MONTH GAVAGE STUDIES OF DIMETHOXANE (a)

Organ	Vehicle Control	250 mg/kg	500 mg/kg
MALE			
Body weight (grams)	44.1 ± 1.72	44.3 ± 2.05	41.7 ± 1.16
Brain	10.6 ± 0.47	10.7 ± 0.58	11.2 ± 0.26
Liver	53.4 ± 3.75	55.0 ± 2.36	65.2 ±10.72
Kidney	9.2 ± 0.25	9.2 ± 0.46	9.2 ± 0.17
FEMALE			
Body weight (grams)	37.6 ± 1.82	40.9 ± 1.53	36.5 ± 1.37
Brain	12.9 ± 0.70	11.7 ± 0.50	13.5 ± 0.53
Liver	41.8 ± 1.09	39.6 ± 0.74	*46.4 ± 1.52
Kidney	5.8 ± 0.20	5.6 ± 0.16	**6.9 ± 0.34

(a) Mean ± standard error in milligrams of organ per gram of body weight, for groups of 10 animals; P values vs. the vehicle controls by Dunn's test or Shirley's test (Dunn, 1964; Shirley, 1977).
*P<0.05
**P<0.01

TABLE 20. ANALYSIS OF HEMATOLOGIC AND CLINICAL CHEMICAL DATA FOR MICE IN THE FIFTEEN-MONTH GAVAGE STUDIES OF DIMETHOXANE (a)

Analysis	Vehicle Control	250 mg/kg	500 mg/kg
MALE			
Number examined (b)	10	10	9
Leukocytes (1,000/mm^3)	(c) 5.97 ± 0.635	6.64 ± 0.636	6.42 ± 0.593
Lymphocytes (1,000/mm^3)	(c) 3.10 ± 0.291	4.13 ± 0.533	3.81 ± 0.664
Segmented neutrophils (1,000/mm^3)	(c) 2.72 ± 0.470	2.31 ± 0.468	2.50 ± 0.392
Eosinophils (1,000/mm^3)	(c) 0.13 ± 0.047	0.18 ± 0.089	0.09 ± 0.030
Bands (1,000/mm^3)	(c) 0.02 ± 0.014	0.01 ± 0.007	0.02 ± 0.010
Hematocrit (percent)	44.5 ± 1.08	44.7 ± 3.34	(d) 47.5 ± 2.16
Hemoglobin (g/dl)	15.1 ± 0.34	15.1 ± 1.19	(d) 16.1 ± 1.02
Mean corpuscular hemoglobin (pg)	15.1 ± 0.17	15.2 ± 0.26	(d) 15.1 ± 0.33
Mean corpuscular hemoglobin concentration (g/dl)	33.9 ± 0.38	33.6 ± 0.38	(d) 33.6 ± 0.54
Mean corpuscular volume (μ^3)	44.8 ± 0.57	45.3 ± 0.96	(d) 45.1 ± 1.31
Platelets (1,000/mm^3)	671 ± 56.3	662 ± 96.6	(d) 673 ± 93.4
Erythrocytes (10^6/mm^3)	9.978 ± 0.288	(e) 9.369 ± 0.696	10.002 ± 0.388
Albumin/globulin ratio	2.01 ± 0.111	1.95 ± 0.134	2.05 ± 0.115
Albumin (g/dl)	3.58 ± 0.142	3.43 ± 0.145	3.70 ± 0.278
Alkaline phosphatase (IU)	25.1 ± 1.72	26.8 ± 2.25	27.4 ± 0.78
Blood urea nitrogen (mg/dl)	23.1 ± 0.75	**28.8 ± 1.12	(d) 26.4 ± 1.27
Cholinesterase (IU/liter)	6,080 ± 408	5,846 ± 419	6,203 ± 375
Creatinine (mg/dl)	0.51 ± 0.067	0.48 ± 0.025	0.50 ± 0.041
Sorbitol dehydrogenase (IU/liter)	(e) 56.4 ± 3.68	(e) 75.0 ± 7.45	*84.2 ± 15.09
Serum glutamic-oxaloacetic transaminase (IU/liter)	101 ± 12.9	(f) 96 ± 9.0	114 ± 19.9
Serum glutamic-pyruvic transaminase (IU/liter)	45.2 ± 15.12	(e) 49.2 ± 14.85	65.2 ± 31.83
Total bilirubin (mg/dl)	0.29 ± 0.021	0.30 ± 0.022	0.30 ± 0.023
Total protein (g/dl)	5.40 ± 0.174	5.24 ± 0.114	5.52 ± 0.377
FEMALE			
Number examined	10	10	10
Leukocytes (1,000/mm^3)	3.88 ± 0.360	2.90 ± 0.228	3.74 ± 0.410
Lymphocytes (1,000/mm^3)	2.86 ± 0.252	2.35 ± 0.209	2.73 ± 0.316
Segmented neutrophils (1,000/mm^3)	0.97 ± 0.276	0.50 ± 0.048	0.93 ± 0.157
Eosinophils (1,000/mm^3)	0.05 ± 0.016	0.05 ± 0.016	0.07 ± 0.024
Bands (1,000/mm^3)	0.00 ± 0.00	0.00 ± 0.00	0.0086 ± 0.0059
Hematocrit (percent)	46.1 ± 1.30	48.5 ± 0.72	46.8 ± 0.84
Hemoglobin (g/dl)	15.6 ± 0.41	*16.6 ± 0.26	15.6 ± 0.28
Mean corpuscular hemoglobin (pg)	15.3 ± 0.15	15.5 ± 0.11	15.4 ± 0.13
Mean corpuscular hemoglobin concentration (g/dl)	33.9 ± 0.34	34.1 ± 0.25	33.4 ± 0.27
Mean corpuscular volume (μ^3)	45.3 ± 0.40	45.4 ± 0.27	46.2 ± 0.25
Platelets (1,000/mm^3)	334 ± 53.3	382 ± 51.3	385 ± 30.6
Erythrocytes (10^6/mm^3)	10.18 ± 0.25	10.73 ± 0.13	10.15 ± 0.17
Albumin/globulin ratio	3.66 ± 0.116	3.62 ± 0.178	3.71 ± 0.114
Albumin (g/dl)	4.02 ± 0.049	4.00 ± 0.126	3.98 ± 0.042
Alkaline phosphatase (IU)	72.2 ± 5.89	54.8 ± 5.63	63.1 ± 4.57
Blood urea nitrogen (mg/dl)	26.9 ± 0.91	25.9 ± 1.54	24.0 ± 1.37
Cholinesterase (IU/liter)	7,829 ± 140	*8,488 ± 166	7,805 ± 239
Creatinine (mg/dl)	0.45 ± 0.027	0.47 ± 0.021	0.42 ± 0.020
Sorbitol dehydrogenase (IU/liter)	63.6 ± 6.98	56.5 ± 3.48	48.1 ± 3.31
Serum glutamic-oxaloacetic transaminase (IU/liter)	259 ± 26.8	249 ± 37.1	*184 ± 17.7
Serum glutamic-pyruvic transaminase (IU/liter)	59.5 ± 8.24	42.7 ± 3.96	**37.6 ± 1.85
Total bilirubin (mg/dl)	0.27 ± 0.020	0.27 ± 0.031	0.26 ± 0.029
Total protein (g/dl)	5.13 ± 0.076	5.25 ± 0.083	5.06 ± 0.050

(a) Mean ± standard error; P values vs. the vehicle controls by Dunn's test or Shirley's test (Dunn, 1964; Shirley, 1977).
(b) Unless otherwise specified
(c) Seven animals were examined.
(d) Ten animals were examined.
(e) Nine animals were examined.
(f) Eight animals were examined.
*P<0.05
**P<0.01

TABLE 21. MEAN BODY WEIGHTS OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHOXANE

Week on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. Weighed	250 mg/kg Av. Wt. (grams)	250 mg/kg Wt. (percent of veh. controls)	250 mg/kg No. Weighed	500 mg/kg Av. Wt. (grams)	500 mg/kg Wt. (percent of veh. controls)	500 mg/kg No. Weighed
MALE								
0	24.2	60	23.6	97.5	60	23.3	96.3	60
1	24.0	60	25.1	104.6	59	25.0	104.2	60
2	26.2	60	26.3	100.4	58	26.7	101.9	60
3	27.3	60	27.4	100.4	58	28.1	102.9	60
4	26.9	60	29.0	107.8	58	29.5	109.7	60
5	28.5	60	29.8	104.6	57	30.1	105.6	60
6	29.8	60	30.3	101.7	57	30.6	102.7	60
7	29.0	60	31.2	107.6	57	31.4	108.3	60
8	31.0	60	31.0	100.0	57	31.1	100.3	60
9	30.3	60	31.6	104.3	57	32.1	105.9	60
10	32.0	60	31.3	97.8	57	31.5	98.4	60
11	32.7	60	32.4	99.1	57	32.2	98.5	60
12	32.6	60	32.7	100.3	57	32.7	100.3	60
13	34.0	60	34.2	100.6	57	34.3	100.9	60
18	34.9	59	34.5	98.9	56	36.0	103.2	60
22	35.2	59	36.1	102.6	56	36.1	102.6	60
26	36.4	59	35.7	98.1	56	37.9	104.1	60
30	38.0	59	37.9	99.7	56	38.7	101.8	59
34	37.6	59	38.6	102.7	55	39.5	105.1	59
38	39.6	59	39.7	100.3	55	40.6	102.5	59
42	39.9	59	39.7	99.5	54	41.2	103.3	59
46	40.5	59	40.8	100.7	54	41.2	101.7	58
50	40.1	59	40.3	100.5	54	41.6	103.7	58
54	42.3	59	42.5	100.5	54	43.5	102.8	58
58	43.2	59	42.8	99.1	54	44.2	102.3	58
62	42.9	59	43.0	100.2	54	44.2	103.0	57
66	43.1	59	43.7	101.4	52	44.2	102.6	57
70	43.8	(a) 49	43.6	99.5	(a) 41	43.3	98.9	(a) 46
74	43.2	48	44.2	102.3	40	44.1	102.1	45
78	42.9	45	43.5	101.4	39	43.5	101.4	45
82	42.2	43	42.4	100.5	36	42.5	100.7	42
86	41.5	43	42.2	101.7	36	42.1	101.4	41
90	40.6	41	40.6	100.0	33	41.1	101.2	39
94	39.6	41	40.2	101.5	33	40.5	102.3	38
98	40.6	38	38.5	94.8	30	40.7	100.2	34
102	40.2	36	39.4	98.0	27	39.7	98.8	30
104	39.6	34	39.5	99.7	27	39.5	99.7	29
FEMALE								
0	18.2	60	18.0	98.9	60	18.2	100.0	60
1	19.5	60	18.8	96.4	60	19.4	99.5	60
2	20.7	60	20.4	98.6	60	20.8	100.5	60
3	21.9	60	20.7	94.5	60	21.7	99.1	60
4	22.1	60	22.3	100.9	59	22.1	100.0	60
5	22.9	60	23.3	101.7	59	23.0	100.4	60
6	23.6	60	23.6	100.0	59	23.4	99.2	60
7	24.0	60	24.1	100.4	59	24.3	101.3	60
8	24.2	60	24.5	101.2	59	24.8	102.5	60
9	24.2	60	24.7	102.1	59	24.7	102.1	60
10	24.8	60	24.6	99.2	59	25.2	101.6	60
11	25.5	60	25.8	101.2	59	26.0	102.0	60
12	24.5	60	25.5	104.1	59	25.4	103.7	60
13	26.3	60	26.4	100.4	59	26.9	102.3	60
18	27.7	60	27.0	97.5	59	28.2	101.8	60
22	29.0	60	28.8	99.3	59	29.8	102.8	60
26	30.8	60	30.2	98.1	59	31.0	100.6	60
30	30.8	60	31.2	101.3	59	31.0	100.6	59
34	32.7	60	32.6	99.7	59	33.0	100.9	59
38	33.4	60	33.8	101.2	59	33.4	100.0	59
42	34.8	60	35.3	101.4	59	35.3	101.4	58
46	35.9	60	35.7	99.4	59	36.0	100.3	58
50	34.3	60	35.8	104.4	58	35.4	103.2	58
54	36.1	60	37.6	104.2	58	36.9	102.2	58
58	38.1	60	38.4	100.8	58	40.5	106.3	58
62	38.8	59	39.1	100.8	58	40.6	104.6	58
66	39.5	59	40.7	103.0	57	40.9	103.5	58
70	41.9	(a) 48	42.4	101.2	(a) 47	42.9	102.4	(a) 47
74	42.5	48	43.4	102.1	47	44.0	103.5	45
78	41.8	47	41.9	100.2	47	41.8	100.0	45
82	42.9	47	43.4	101.2	47	43.4	101.2	45
86	42.9	43	43.9	102.3	47	45.2	105.4	44
90	42.6	42	42.7	100.2	42	44.4	104.2	44
94	41.6	39	43.6	104.8	40	44.7	107.5	39
98	41.0	39	43.6	106.3	38	45.1	110.0	37
102	40.3	38	43.5	107.9	35	44.4	110.2	34
104	40.9	36	43.5	106.4	35	44.1	107.8	34

(a) Interim kill occurred.

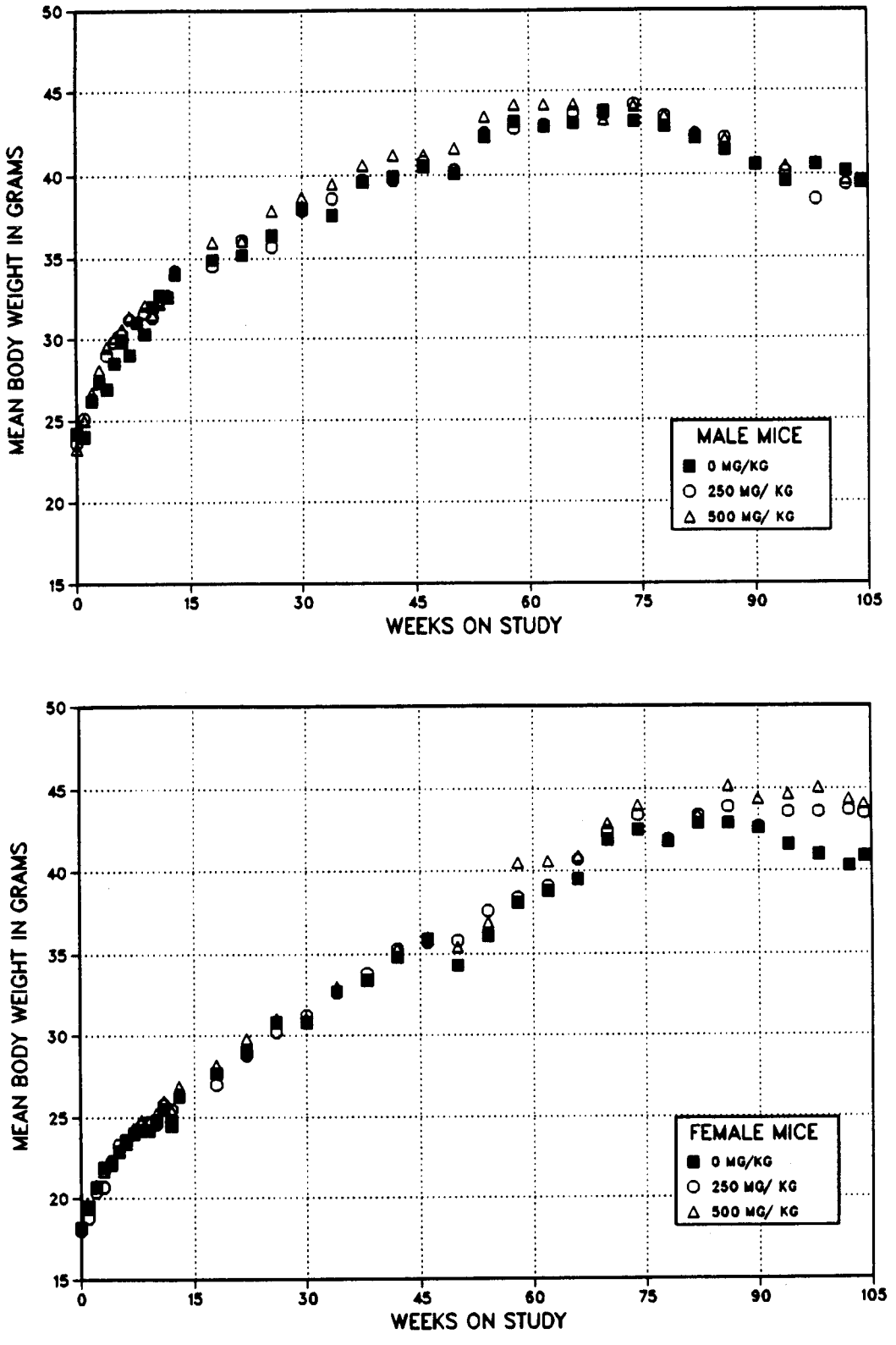

FIGURE 7. GROWTH CURVES FOR MICE ADMINISTERED DIMETHOXANE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice administered dimethoxane at the doses used in these studies and for vehicle controls are shown in Table 22 and in the Kaplan and Meier curves in Figure 8. No significant differences in survival were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the forestomach.

Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one animal group, and historical control incidences for the neoplasms mentioned in this section are presented in Appendixes C and D for male and female mice, respectively.

TABLE 22. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHOXANE

	Vehicle Control	250 mg/kg	500 mg/kg
MALE (a)			
Animals initially in study (b)	50	50	50
Natural deaths	11	10	12
Moribund kills	6	11	9
Animals missexed	0	2	0
Animals surviving until study termination	33	27	29
Survival P values (c)	0.493	0.614	0.509
FEMALE (a)			
Animals initially in study (b)	50	50	50
Natural deaths	7	9	7
Moribund kills	7	5	9
Animals missing	0	1	0
Animals surviving until study termination	36	35	34
Survival P values (c)	0.768	1.000	0.837

(a) First day of termination period: 731
(b) An additional 10 animals were placed on study in each group and killed on day 458.
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

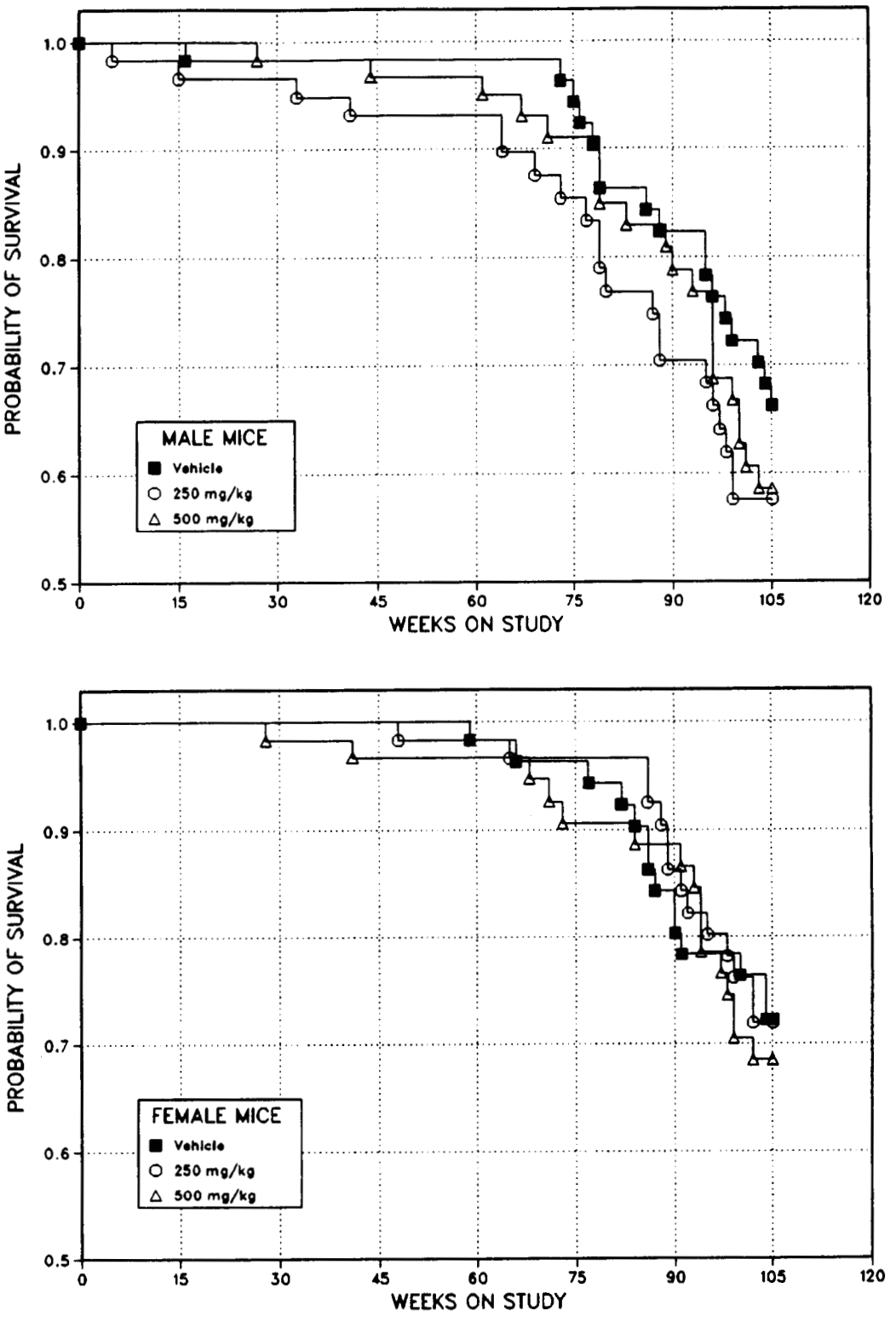

FIGURE 8. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED DIMETHOXANE IN CORN OIL BY GAVAGE FOR TWO YEARS

Figure 9. Focal hyperplasia of the forestomach epithelium in high dose male mouse CID no. 492. Note the thickened, folded epithelium, the accumulation of keratin on the surface, and the inflammatory cells in the submucosa.

Figure 10. Focal hyperplasia of the forestomach epithelium in high dose male mouse CID no. 531. There is a small ulcer in the center of the lesion.

Figure 11. Squamous cell papilloma of the forestomach of low dose male mouse CID no. 323. The stratified squamous epithelium forms thick, irregular folds and a few papillae.

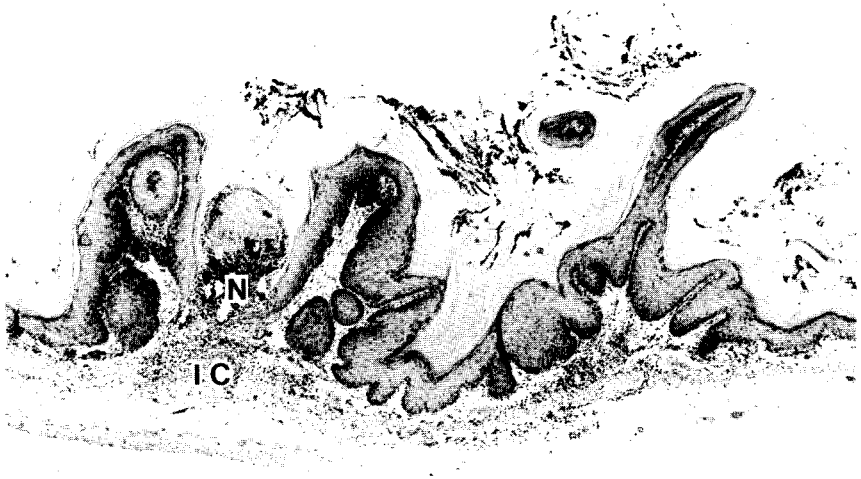

Figure 12. Squamous cell papilloma of the forestomach of high dose male mouse CID no. 571. The stratified squamous epithelium is increased in thickness and forms prominent folds and a few papillae. Note the area of necrosis (N) and inflammatory cell in the submucosa (IC). H&E

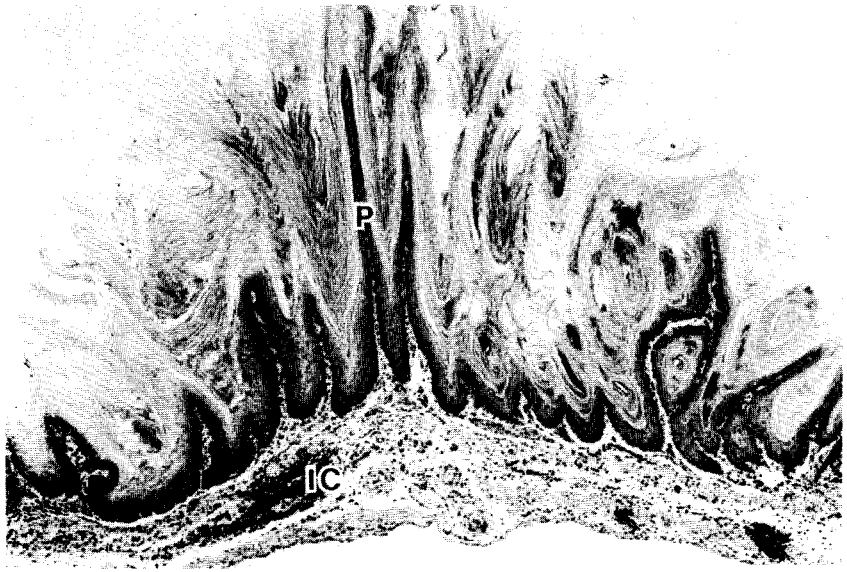

Figure 13. Squamous cell papilloma of the forestomach of high dose male mouse CID no. 533. This papilloma does not have the narrow stalk and complex branching structure of a typical papilloma but consists of multiple individual papillae (P) protruding into the lumen of the stomach. The submucosa contains inflammatory cells (IC). H&E

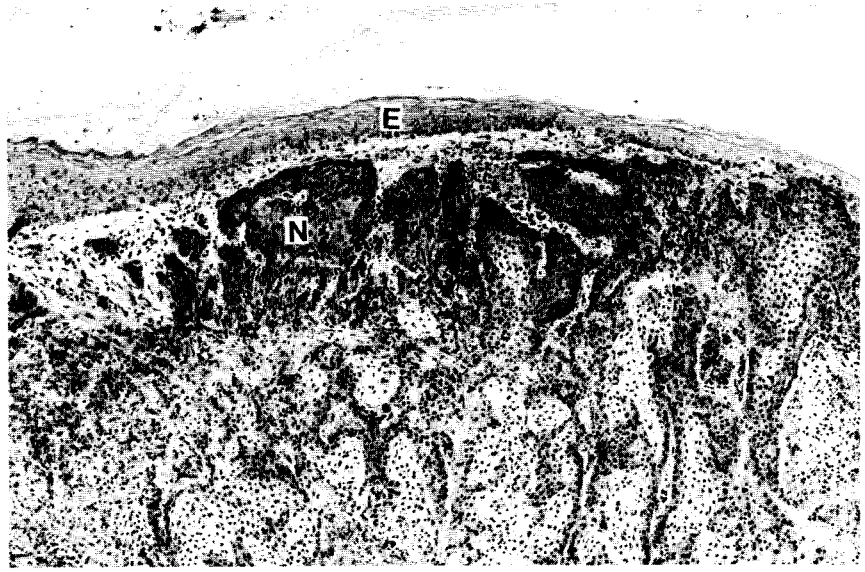

Figure 14. Squamous cell carcinoma of the forestomach of high dose male mouse CID no. 534. Irregular branching cords of neoplastic stratified squamous epithelium (N) extend deep into the submucosa. The surface epithelium (E) is intact and normal in this region of the neoplasm. H&E

Forestomach: Acanthosis, hyperkeratosis of the stratified squamous epithelium, chronic active inflammation, and focal hyperplasia were observed at increased incidences in dosed mice (Table 23). The epithelial lesions generally were located at or near the junction of the forestomach and glandular stomach and consisted of slight hyperplasia of the stratified squamous epithelium with thickening of the overlying keratin layer. Focal hyperplasia consisting of a localized nodular thickening of the stratified squamous epithelium was also increased in dosed mice (Figures 9 and 10). The incidence of squamous papillomas was increased in high dose male mice compared with that in vehicle controls. A squamous cell carcinoma of the forestomach was observed in one other high dose male mouse. The forestomach papillomas consisted of multiple papillary, rarely branching projections composed of a central core of fibrous connective tissue covered by a thickened layer of stratified squamous epithelium (Figures 11 to 13). No cellular atypia or dysplasia of the proliferating epithelium was observed. These lesions typically had a broad base, rather than being attached by a narrow stalk as is usual for a papilloma, and met the minimum requirements for a diagnosis of papilloma. A squamous cell carcinoma of the forestomach, which had invaded the glandular stomach, was present in a single high dose male (Figure 14). This neoplasm metastasized to the liver, mesentery, pancreas, and genital system (coagulating gland, epididymis, and prostate).

TABLE 23. ANALYSIS OF FORESTOMACH LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHOXANE (a)

Lesion	Vehicle Control	250 mg/kg	500 mg/kg
MALE			
Acanthosis	2/47 (4%)	4/47 (9%)	20/50 (40%)
Hyperkeratosis	1/47 (2%)	1/47 (2%)	23/50 (46%)
Chronic Active Inflammation	0/47 (0%)	0/47 (0%)	5/50 (10%)
Focal Hyperplasia	2/47 (4%)	7/47 (15%)	11/50 (22%)
Squamous Papilloma			
Overall Rates	2/47 (4%)	3/47 (6%)	7/50 (14%)
Adjusted Rates	5.1%	11.1%	18.7%
Terminal Rates	1/33 (3%)	3/27 (11%)	2/29 (7%)
Day of First Observation	542	731	550
Life Table Tests	P=0.044	P=0.412	P=0.073
Logistic Regression Tests	P=0.057	P=0.454	P=0.117
Squamous Cell Carcinoma	0/47 (0%)	0/47 (0%)	1/50 (2%)
Squamous Papilloma or Squamous Cell Carcinoma (b)			
Overall Rates	2/47 (4%)	3/47 (6%)	8/50 (16%)
Adjusted Rates	5.1%	11.1%	20.5%
Terminal Rates	1/33 (3%)	3/27 (11%)	2/29 (7%)
Day of First Observation	542	731	469
Life Table Tests	P=0.024	P=0.412	P=0.044
Logistic Regression Tests	P=0.033	P=0.454	P=0.087
FEMALE			
Acanthosis	0/49 (0%)	5/48 (10%)	23/48 (48%)
Hyperkeratosis	0/49 (0%)	4/48 (8%)	27/48 (56%)
Chronic Active Inflammation	0/49 (0%)	4/48 (8%)	6/48 (13%)
Focal Hyperplasia	3/49 (6%)	14/48 (29%)	22/48 (46%)
Squamous Papilloma	3/49 (6%)	3/48 (6%)	1/48 (2%)

(a) The statistical analyses used are discussed in Section II (Statistical Methods) and Table C3 (footnotes).
(b) Historical incidence at study laboratory (mean ± SD): 4/230 (2% ± 2%); historical incidence in NTP studies: 32/1,937 (2% ± 2%)

Dimethoxane was mutagenic when tested with a preincubation protocol in *Salmonella typhimurium* strain TA100 in the presence but not in the absence of Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9; it was not mutagenic in strains TA98, TA1535, or TA1537 with or without S9 (Table 24). In cytogenetic tests with Chinese hamster ovary (CHO) cells, dimethoxane induced a highly significant increase in sister chromatid exchanges (SCEs) within a dose range of 1.1-12.6 µg/ml in the absence of S9; with Aroclor 1254-induced male Sprague Dawley rat liver S9, a significant increase in SCEs was observed over a range of 11-110 µg/ml dimethoxane (Table 25). In addition, dimethoxane induced chromosomal aberrations and cell cycle delay in CHO cells with and without S9. Without S9, doses of 20.2 and 22.7 µg/ml produced abnormal metaphases in 100% of cells scored; with S9, 75% of cells exposed to 176 µg/ml and more dimethoxane contained aberrations (Table 26). Dimethoxane induced sex-linked recessive lethal mutations in Drosophila when administered by abdominal injection to adult Canton-S males (Table 27); no induction of reciprocal translocations was observed (Table 28).

TABLE 24. MUTAGENICITY OF DIMETHOXANE IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/Plate (b)			
TA100		−S9			
		Trial 1	Trial 2	Trial 3	
	0	118 ± 0.7	129 ± 3.8	163 ± 3.1	
	33	126 ± 3.5	--	--	
	100	113 ± 12.3	133 ± 6.2	156 ± 3.6	
	333	98 ± 2.6	125 ± 9.4	146 ± 3.8	
	1,000	119 ± 9.2	122 ± 11.3	164 ± 4.1	
	2,000	--	143 ± 1.2	173 ± 6.7	
	2,150	134 ± 12.3	--	--	
	2,500	--	15 ± 9.2	--	
	3,333	--	--	(c) 289 ± 26.3	
Trial summary		Negative	Negative	Equivocal	
Positive control (d)		1,379 ± 61.1	1,429 ± 67.5	284 ± 43.1	
TA100		+S9 (hamster)		+S9 (rat)	
		Trial 1	Trial 2	Trial 1	Trial 2
	0	107 ± 4.9	112 ± 9.7	115 ± 3.4	145 ± 5.6
	100	106 ± 5.7	--	105 ± 15.6	--
	333	111 ± 11.5	--	96 ± 1.7	--
	1,000	105 ± 6.1	123 ± 12.9	109 ± 8.7	138 ± 4.7
	3,333	156 ± 3.3	140 ± 2.6	135 ± 2.1	136 ± 1.5
	4,444	--	154 ± 11.5	--	145 ± 13.4
	5,500	--	271 ± 20.4	--	--
	5,555	--	--	--	245 ± 14.2
	6,666	(c) 278 ± 18.4	(c) 299 ± 33.7	(c) 219 ± 33.3	(c) 753 ± 59.3
Trial summary		Positive	Positive	Equivocal	Positive
Positive control (d)		1,313 ± 49.5	2,894 ± 8.4	916 ± 17.5	719 ± 28.9
TA1535		−S9	+S9 (hamster)	+S9 (rat)	
	0	22 ± 3.7	1 ± 3.0	7 ± 2.3	
	33	23 ± 0.9	--	--	
	100	16 ± 1.9	1 ± 1.5	1 ± 1.5	
	333	19 ± 2.3	1 ± 3.7	7 ± 0.6	
	1,000	17 ± 2.3	11 ± 1.2	11 ± 0.6	
	2,150	18 ± 2.5	--	--	
	3,333	--	6 ± 0.9	7 ± 1.3	
	6,666	--	5 ± 0.3	7 ± 1.5	
Trial summary		Negative	Negative	Negative	
Positive control (d)		968 ± 21.7	99 ± 12.7	77 ± 8.5	
TA1537		−S9	+S9 (hamster)	+S9 (rat)	
	0	9 ± 1.2	1 ± 3.2	8 ± 1.9	
	33	7 ± 0.3	--	--	
	100	9 ± 2.3	8 ± 1.3	9 ± 1.2	
	333	8 ± 3.3	1 ± 0.9	9 ± 1.8	
	1,000	5 ± 0.9	6 ± 0.6	8 ± 1.8	
	2,150	6 ± 0.9	--	--	
	3,333	--	8 ± 1.2	8 ± 1.8	
	6,666	--	(c) 6 ± 1.2	(c) 6 ± 1.5	
Trial summary		Negative	Negative	Negative	
Positive control (d)		111 ± 11.4	15 ± 9.6	9 ± 6.2	

TABLE 24. MUTAGENICITY OF DIMETHOXANE IN *SALMONELLA TYPHIMURIUM* (Continued)

Strain	Dose (µg/plate)	Revertants/Plate (b)		
TA98		−S9	+S9 (hamster)	+S9 (rat)
	0	21 ± 2.4	24 ± 0.3	26 ± 0.6
	33	20 ± 1.9	--	--
	100	23 ± 2.3	29 ± 1.3	27 ± 2.9
	333	20 ± 1.2	28 ± 2.4	26 ± 2.9
	1,000	18 ± 2.6	28 ± 2.2	32 ± 5.2
	2,150	20 ± 3.0	--	--
	3,333	--	16 ± 1.5	27 ± 2.0
	6,666	(c) 8 ± 1.7	(c) 2 ± 1.7	--
Trial summary		Negative	Negative	Negative
Positive control (d)		1,886 ± 9.4	1,509 ± 76.3	855 ± 39.2

(a) Study performed at EG&G Mason Research Institute. Data are presented in Mortelmans et al. (1986). Cells and study compound or solvent (dimethyl sulfoxide) were incubated in the absence of exogenous metabolic activation (−S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 µg/plate dose is the solvent control.
(b) Revertants are presented as mean ± standard error from three plates.
(c) Slight toxicity
(d) Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was used with TA98, sodium azide was used with TA100 and TA1535, and 9-aminoacridine was used with TA1537.

TABLE 25. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY DIMETHOXANE (a)

	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 1--Summary: Positive								
Dimethyl sulfoxide		50	1,055	506	0.48	10.1	25.7	
Dimethoxane	0.36	50	1,054	574	0.54	11.5	25.7	113.9
	1.1	50	1,046	611	0.58	12.2	25.7	120.8
	3.66	50	1,049	1,621	1.55	32.4	25.7	320.8
Mitomycin C	0.001	50	1,038	637	0.61	12.7	25.7	125.7
	0.02	5	105	194	1.85	38.8	25.7	384.2
Trial 2--Summary: Positive								
Dimethyl sulfoxide		50	1,040	511	0.49	10.2	26.2	
Dimethoxane	7.6	50	1,048	1,303	1.24	26.1	26.2	255.9
	10.1	50	1,048	1,620	1.55	32.4	26.2	317.6
	12.6	50	1,059	2,285	2.16	45.7	(d) 33.2	448.0
Mitomycin C	0.001	50	1,048	592	0.56	11.8	26.2	115.7
	0.01	5	101	198	1.96	39.6	26.2	388.2
+S9 (e)--Summary: Positive								
Dimethyl sulfoxide		50	1,045	502	0.48	10.0	25.7	
Dimethoxane	11	50	1,046	621	0.59	12.4	25.7	124.0
	36.6	50	1,053	1,000	0.95	20.0	25.7	200.0
	110	50	1,046	1,476	1.41	29.5	(d) 33.5	295.0
Cyclophosphamide	0.4	50	1,054	816	0.77	16.3	25.7	163.0
	2	5	105	208	1.98	41.6	25.7	416.0

(a) Study performed at Litton Bionetics, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway et al. (1985, 1987). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent as described in (c) and (e) below and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air dried, and stained.
(b) SCEs/cell of culture exposed to study chemical relative to those of culture exposed to solvent
(c) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then BrdU was added, and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and colcemid was added, and incubation was continued for 2-3 hours.
(d) Because some chemicals induce a delay in the cell division cycle, harvest times are occasionally extended to maximize the proportion of second division cells available for analysis.
(e) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. 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 26. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY DIMETHOXANE (a)

−S9 (b)					+S9 (c)				
Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Harvest time: 22.0 hours (d)					Harvest time: 21.8 hours (d)				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	4	0.04	4.0		100	7	0.07	4.0
Dimethoxane					Dimethoxane				
12.6	100	5	0.05	5.0	126	100	9	0.09	9.0
15.1	100	23	0.23	20.0	176	50	90	1.80	76.0
20.2	25	214	8.56	100.0	198	50	88	1.76	74.0
22.7	10	82	8.20	100.0					
Summary: Positive					Summary: Positive				
Mitomycin C					Cyclophosphamide				
0.04	50	19	0.38	22.0	12.5	50	21	0.42	26.0

(a) Study performed at Litton Bionetics, Inc.; Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway et al. (1985, 1987). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent as indicated in (b) and (c). Cells were arrested in first metaphase by addition of colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.

(b) In the absence of S9, cells were incubated with study compound or solvent for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid was added for an additional 2-3 hours followed by harvest.

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

(d) Because of significant chemical induced cell cycle delay, incubation time prior to addition of colcemid was lengthened to provide sufficient metaphases at harvest.

TABLE 27. INDUCTION OF SEX-LINKED RECESSIVE LETHAL MUTATIONS IN DROSOPHILA BY DIMETHOXANE (a)

Route of Exposure	Dose (ppm)	Induced Incidence of Deaths (percent)	Induced Incidence of Sterility (percent)	No. of Lethals/No. of X Chromosomes Tested			Overall Total (b)
				Mating 1	Mating 2	Mating 3	
Injection	6,000	2	0	3/1,516	1/1,439	1/1,417	5/4,372 (0.11%)
	0			0/1,993	3/1,926	1/1,766	4/5,685 (0.07%)
Injection	10,000	0	3	2/1,043	4/677	2/739	8/2,459 (0.33%)
	0			0/1,033	0/978	1/784	1/2,795 (0.04%)
Injection	12,500	17	14	2/1,543	2/1,080	2/1,086	6/3,709 (0.16%)
	0			2/2,062	3/1,884	1/1,651	6/5,597 (0.11%)

(a) Study performed at University of Wisconsin–Madison. Data are presented in Woodruff et al. (1985). Exposure was done by injecting 24-hour-old Canton-S males with a solution of dimethoxane dissolved in 0.7% saline and allowing 24 hours for recovery. Exposed males were mated to three *Basc* females for 3 days and given fresh females at 2-day intervals to produce three broods of 3, 2, and 2 days; sample sperm from successive matings were treated as spermatozoa (mating 1), spermatids (mating 2), and spermatocytes (mating 3). F_1 heterozygous females were crossed to their siblings and placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters; clusters were removed. After 17 days, presumptive lethal mutations were identified as vials containing no wild-type males; these were retested. Results were significant at the 5% level (Margolin et al., 1983).
(b) Combined total number of lethal mutations/number of X chromosomes tested for three mating trials

TABLE 28. INDUCTION OF RECIPROCAL TRANSLOCATIONS IN DROSOPHILA BY DIMETHOXANE (a)

Route of Exposure	Dose (ppm)	Transfers (translocations/total F_1 tested)						Total No. of Tests	Total No. of Translocations	Total Translocations (percent)
		1	2	3	4	5	6			
Injection	12,000	0/1,305	0/1,247	0/1,037	0/803	0/533	0/345	5,270	0	0.00
Historical control	0							116,163	2	0.0017

(a) Study performed at University of Wisconsin–Madison. Data are presented in Woodruff et al. (1985). Exposed males were mated to three bw;st females for 3 days and discarded. The females were transferred to fresh medium every 3-4 days to produce a total of six cultures, and then they were discarded. In this manner, sample sperm from successive cultures were stored for increasing lengths of time. Individual F_1 males were backcrossed to bw;st females, and the F_2 generation was screened for pseudolinkage. This procedure allows the recovery of translocations involving the Y, second, or third chromosomes in any combination. Presumptive translocations were retested. Results were not significant at the 5% level (Kastenbaum and Bowman, 1970).

IV. DISCUSSION AND CONCLUSIONS

Genetic Toxicology
Results of Short-Term Studies
Results of the Fifteen-Month and Two-Year Studies
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Conclusions

IV. DISCUSSION AND CONCLUSIONS

Dimethoxane is an antimicrobial agent used primarily as a preservative in water-based paints, cutting oils, fabric softeners, inks, polymers, and spinning emulsions. It was nominated and selected for toxicology and carcinogenesis studies because of widespread human exposure and because in a limited drinking water study, it was reported to cause malignant liver tumors in male Wistar rats (Hoch-Ligeti et al., 1974). The chemical used was a typical commercial grade of approximately 80% purity and, according to the manufacturer, also contained acetaldehyde (0.2%), vinyl acetate (1.4%), crotonaldehyde and its corresponding aldol (1.8%), and 25 other unidentified impurities; none of the unidentified impurities was present at more than 3.0%.

Single-administration, 16-day, 13-week, 15-month, and 2-year studies of dimethoxane were conducted in F344/N rats and B6C3F$_1$ mice. The compound was administered in corn oil because of its instability in water.

The toxic effects of dimethoxane appeared to be associated with the primary site of chemical application, i.e., the stomach in the gavage studies and the skin in the dermal studies (Appendix G).

Genetic Toxicology

Genetic toxicology studies were conducted in *Salmonella typhimurium*, in Chinese hamster ovary (CHO) cells for sister chromatid exchanges (SCEs) and chromosomal aberrations, and in Drosophila for sex-linked recessive lethal mutations and translocations.

Dimethoxane is clearly mutagenic in Salmonella (see Table 24) and produced SCEs (see Table 25) and chromosomal aberrations (see Table 26) in cultured CHO cells. Sex-linked recessive lethal mutations, but not reciprocal translocations, were induced in Drosophila (see Tables 27 and 28). This genetic activity might be attributable to the 6-hydroxy analog of dimethoxane. Dimethoxane has been shown to hydrolyze in aqueous solutions to produce acetic acid and the 6-hydroxy analog (IARC, 1977). In the genetic toxicology studies described in this report, dimethoxane was tested in aqueous media.

Acetaldehyde and crotonaldehyde (present at 0.2% and 1.8% in the commercial-grade dimethoxane used in these 2-year studies) may have contributed to the genetic toxicity observed with dimethoxane. These two compounds are genetically active and were mutagenic to Salmonella (Haworth et al., 1983) and/or to Drosophila (Woodruff et al., 1985; Mortelmans et al., 1986).

Results of Short-Term Studies

In the single-administration and 16-day gavage studies, deaths occurred in rats and male mice dosed with 2,000 mg/kg or more. Compound-related lesions observed after administration for 16 days were squamous epithelial hyperplasia and hyperkeratosis of the forestomach in rats receiving 250 mg/kg or more and in mice receiving 500 mg/kg or more. Notable toxic effects observed in the 13-week gavage studies were limited to the forestomach. Ulceration and inflammation of the forestomach were observed in rats dosed with 500 mg/kg. Acanthosis (hyperplasia of the squamous epithelium) and hyperkeratosis of the squamous epithelium were observed in male rats at doses higher than 31 mg/kg, in female rats at doses higher than 125 mg/kg, and in male and female mice at 500 mg/kg. The forestomach lesions in rats and mice were judged to be less severe at lower doses.

In the 13-week studies, rats appeared to be more responsive than mice to the forestomach toxicity of dimethoxane administered in corn oil by gavage, since the lowest doses that caused compound-related forestomach lesions in rats were lower (two to eight times) than those needed to produce similar lesions in mice. Male rats appeared to be more responsive than female rats; male and female mice were equally responsive to the toxic effects of this compound. Based on these results, the doses of dimethoxane selected for the 2-year studies were 62.5 or 125 mg/kg for male rats, 125 or 250 mg/kg for female rats, and 250 or 500 mg/kg for male and female mice.

Results of the Fifteen-Month and Two-Year Studies

Body weight and survival of dosed male and female rats were similar to those of vehicle

controls. Administration of other antibiotics (tetracycline hydrochloride and oxytetracycline hydrochloride) for 2 years increased the survival of rats but had no influence on body weights of rats (Deichmann et al., 1964; NTP, 1987, 1989a). This effect on survival was not seen with dimethoxane.

Based on the results of the 13-week studies and presence of compound-related histopathologic lesions in the forestomach of rats in the 2-year studies, the doses for the 2-year studies were determined to be adequate. In the 2-year studies, acanthosis and hyperkeratosis were increased in high dose rats. Squamous papillomas of the forestomach were seen in one high dose male and one high dose female rat.

The findings of no evidence of carcinogenicity in the current studies in rats appear to contrast with the carcinogenic response observed with dimethoxane in a drinking water study in male Wistar rats (Hoch-Ligeti et al., 1974). The disparity could be related to the difference in the size of the dose. Based on average body weight and water consumption, the average dose of dimethoxane the rats received in the drinking water study was 850 mg/kg body weight per day. This dose is three to seven times the highest doses (125 and 250 mg/kg) received by male or female rats in the present studies. Additionally, in the drinking water studies, animals were exposed continuously to dimethoxane, whereas in the gavage studies, a single bolus was used.

At 15 months, harderian gland neoplasms were seen in one high dose male and two high dose female mice. However, no increase in the incidence of harderian gland neoplasms was seen at 2 years (Tables C1 and D1). Acanthosis of the forestomach was seen in almost half the male and female mice in the high dose groups.

In the 2-year studies, body weight and survival of dosed and vehicle control mice were similar. There were dimethoxane-related increases in the incidences of acanthosis, hyperkeratosis, and chronic inflammation of the forestomach in dosed mice relative to those in vehicle controls. These forestomach lesions were seen in mice in the 13-week studies, and acanthosis was seen in mice that were killed at 15 months. Squamous cell papillomas of the forestomach occurred in two vehicle control, three low dose, and seven high dose male mice; one carcinoma occurred in another high dose male. Papillomas and papillomas or carcinomas (combined) occurred with positive trends. Pairwise comparisons between vehicle control and low or high dose male mice were not statistically significant. The historical incidences of these neoplasms are low at the study laboratory (papilloma: 4/230, 1.7%; carcinoma: 0/230) and throughout the Program (papilloma: 23/1,937, 1.2%; carcinoma: 9/1,937, 0.5%; Table C4). No increased incidences of forestomach neoplasms were seen in female mice, and a forestomach papilloma was observed in one high dose rat of each sex.

The spectrum of lesions observed in the forestomach of rats and mice given dimethoxane by gavage for 16 days or 13 weeks indicates that the chemical is cytotoxic. The ulceration, inflammation, and hyperplasia of the stratified squamous epithelium most likely are a response to cell necrosis and/or an accelerated rate of cell differentiation, keratinization, and loss. Epithelial hyperplasia is a common response to irritants and "promoters" (Argyris, 1985). Diffuse hyperplasia (diagnosed as acanthosis) and focal hyperplasia of the stratified squamous epithelium occurred also in mice given dimethoxane for 2 years. In male mice, there was a slight dose-related increase in squamous cell papillomas. The etiology of this forestomach lesion is unknown, and whether the marginal increase is related to the process of carcinogenesis or to chronic irritation of the forestomach mucosa is uncertain. The papillomas generally consisted of broad-based exophytic papillary structures and, therefore, met the minimum morphologic criteria for a diagnosis of papilloma; however, there was no cellular atypia or dysplasia to suggest progression to malignancy. Although little is known concerning the potential for forestomach papillomas to regress or progress to overt neoplasia, the forestomach epithelium is a stratified squamous epithelium like that of the skin, and squamous papillomas of the forestomach are similar morphologically to those of the skin (Odashima, 1979). In the two-stage model of skin carcinogenesis, one application of an initiator is followed by repeated applications of a promoter; a preponderance of papillomas is induced,

and 90%-95% of these have been shown to regress (Burns et al., 1976a,b; Colburn, 1980). Studies of the induction and regression kinetics of papillomas suggest that there are two populations of papillomas: a large population that regresses after cessation of chemical application (conditional or promoter-dependent papillomas) and a very small population of autonomous papillomas that persist (Burns et al., 1976a,b). At present, it is unknown whether autonomous papillomas arise directly from conditional papillomas in a sequential series of events beginning with a single cell or whether they arise from different populations of cells (Chu et al., 1987). This issue is important because squamous cell carcinomas have been proposed to arise primarily from autonomous but not conditional papillomas, and the latter may not reflect a true carcinogenic response. In initiation-promotion studies, more than 90% of the squamous cell carcinomas develop from papillomas, but the conversion rate is low (Hennings et al., 1983).

Other studies on the population kinetics of papillomas of the skin indicate that promoters generally do not increase the conversion rate of papillomas to carcinomas, whereas initiators do (Hennings et al., 1983). These studies suggest that further genetic changes to papilloma cells are required for the development of malignant neoplasms.

Several chemicals given in corn oil by gavage in NTP studies induced forestomach tumors in B6C3F$_1$ mice (Table 29). All these chemicals are known irritants, are mutagenic (except benzyl acetate) in the majority of genotoxicity tests (Table 30), and cause an increase in the incidence of nonneoplastic (epithelial hyperplasia, acanthosis, or hyperkeratosis) and neoplastic (papilloma or carcinoma) lesions of the forestomach of mice of each sex. Of the chemicals listed, only two (benzyl acetate and dimethylvinyl chloride) induced tumors at other sites. Dimethoxane shares all the features common to these forestomach carcinogens, except that it increased the incidence of papillomas only in male B6C3F$_1$ mice and only to a marginal extent. In view of the above discussion, the increase in squamous cell papillomas of the forestomach of male mice could be attributed to dimethoxane administration.

Audit

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

Conclusions

Under the conditions of these 2-year corn oil gavage studies, there was *no evidence of carcinogenic activity** of dimethoxane for male F344/N rats receiving 62.5 or 125 mg/kg or for female F344/N rats receiving 125 or 250 mg/kg per day. There was *equivocal evidence of carcinogenic activity* of dimethoxane for male B6C3F$_1$ mice, as indicated by an increased incidence of forestomach neoplasms. There was *no evidence of carcinogenic activity* for female B6C3F$_1$ mice receiving 250 or 500 mg/kg per day. Acanthosis and hyperkeratosis occurred at increased incidences in the forestomach of high dose rats. Inflammation, acanthosis with hyperkeratosis, and focal hyperplasia occurred at increased incidences in the forestomach of dosed 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 page 9.

TABLE 29. INCIDENCES OF FORESTOMACH SQUAMOUS CELL NEOPLASMS IN B6C3F$_1$ MICE GIVEN VARIOUS CHEMICALS IN CORN OIL BY GAVAGE FOR UP TO TWO YEARS

Study	Male			Female			References
	Dose (mg/kg)	Papilloma	Carcinoma	Dose (mg/kg)	Papilloma	Carcinoma	
Ethyl acrylate							
	0	0/48	0/48	0	1/50	0/50	NTP, 1986a
	100	4/47	2/47	100	4/49	1/49	
	200	9/50	5/50	200	5/48	2/48	
Diglycidyl resorcinol ether							
	0	0/47	0/47	0	0/47	0/47	NTP, 1986b
	50	4/49	14/49	50	5/49	12/49	
	100	10/50	25/50	100	10/49	23/49	
1,2-Dibromo-3-chloropropane							
	0	0/20	0/20	0	0/20	0/20	NCI, 1978
	80-130	0/46	43/46	60-130	0/50	50/50	
	160-260	0/49	47/49	120-260	0/48	47/48	
Dimethylvinyl chloride							
	0	0/48	1/48	0	0/50	0/50	NTP, 1986c
	100	42/47	3/47	100	1/47	40/47	
	200	35/44	8/44	200	3/43	36/43	
3-Chloro-2-methylpropene							
	0	3/49	0/49	0	0/50	0/50	NTP, 1986d
	100	19/49	5/49	100	15/48	1/48	
	200	30/49	7/49	200	29/44	2/44	
Dichlorvos							
	0	1/50	0/50	0	5/49	0/49	NTP, 1989b
	10	1/50	0/50	20	6/49	0/49	
	20	9/50	0/50	40	18/50	2/50	
Benzyl acetate							
	0	3/49	1/49	0	0/50	0/50	NTP, 1986e
	500	3/48	1/48	500	0/50	0/50	
	1,000	9/49	2/49	1,000	4/48	0/48	
Dimethoxane							
	0	2/47	0/47	0	3/49	0/49	Current studies
	250	3/47	0/47	250	3/48	0/48	
	500	7/50	1/50	500	1/48	0/48	

TABLE 30. MUTAGENICITY OF VARIOUS CHEMICALS THAT INDUCE FORESTOMACH NEOPLASMS IN B6C3F$_1$ MICE AFTER ADMINISTRATION IN CORN OIL BY GAVAGE FOR UP TO TWO YEARS

Study	Salmonella	Mouse Lymphoma	In Vitro Cytogenetics		Drosophila	
			SCE	Aberration	Sex-linked Rec. Lethals	Reciprocal Translocation
Ethyl acrylate	–	+	+	+	–	–
Diglycidyl resorcinol ether	+	+	+	+	+	+
1,2-Dibromo-3-chloropropane	+	+	+	+	+	+
Dimethylvinyl chloride	+	+	+	–	+	+
3-Chloro-2-methylpropene	–	+	+	+	On test	On test
Dichlorvos	+	+	+	+		
Benzyl acetate	–	+	–	–	On test	On test
Dimethoxane	+	Not tested	+	+	+	–
Benzaldehyde	–	+	+	–	–	

V. REFERENCES

V. REFERENCES

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APPENDIX A

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

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	60	60	60
Animals removed	60	60	60
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large, rectum	(49)	(47)	(47)
Mesothelioma malignant			1 (2%)
Intestine small, ileum	(50)	(45)	(45)
Mesothelioma malignant		1 (2%)	
Intestine small, jejunum	(49)	(50)	(49)
Mesothelioma malignant		1 (2%)	
Liver	(50)	(50)	(50)
Leukemia mononuclear	19 (38%)	14 (28%)	9 (18%)
Mesothelioma malignant			1 (2%)
Neoplastic nodule		1 (2%)	
Mesentery	*(50)	*(50)	*(50)
Leukemia mononuclear			1 (2%)
Mesothelioma malignant	2 (4%)	1 (2%)	1 (2%)
Pancreas	(50)	(50)	(50)
Leukemia mononuclear	3 (6%)		
Mesothelioma malignant		1 (2%)	
Acinus, adenoma, multiple	1 (2%)		
Salivary glands	(50)	(50)	(50)
Leukemia mononuclear	1 (2%)	1 (2%)	
Stomach, forestomach	(50)	(50)	(50)
Papilloma squamous			1 (2%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(50)
Leukemia mononuclear	2 (4%)	1 (2%)	1 (2%)
Mesothelioma malignant, metastatic, uncertain primary site		1 (2%)	
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(50)	(49)
Adenoma		1 (2%)	
Carcinoma	1 (2%)	1 (2%)	1 (2%)
Leukemia mononuclear	6 (12%)	4 (8%)	3 (6%)
Adrenal gland, medulla	(50)	(50)	(50)
Leukemia mononuclear	6 (12%)	4 (8%)	3 (6%)
Pheochromocytoma benign	5 (10%)	9 (18%)	4 (8%)
Bilateral, pheochromocytoma benign		1 (2%)	
Islets, pancreatic	(49)	(50)	(50)
Adenoma	2 (4%)	1 (2%)	
Adenoma, multiple	1 (2%)		
Carcinoma			1 (2%)
Parathyroid gland	(49)	(46)	(47)
Adenoma	2 (4%)		
Leukemia mononuclear	1 (2%)		
Pituitary gland	(49)	(50)	(49)
Leukemia mononuclear	2 (4%)	1 (2%)	
Pars distalis, adenoma	13 (27%)	7 (14%)	11 (22%)
Thyroid gland	(50)	(50)	(50)
Bilateral, C-cell, adenoma	1 (2%)	2 (4%)	2 (4%)
C-cell, adenoma	12 (24%)	10 (20%)	8 (16%)
C-cell, carcinoma	2 (4%)	2 (4%)	
Follicular cell, adenoma		3 (6%)	
Follicular cell, carcinoma		1 (2%)	1 (2%)

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

	Vehicle Control	Low Dose	High Dose
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Epididymis	(48)	(50)	(50)
Mesothelioma malignant	1 (2%)	1 (2%)	1 (2%)
Preputial gland	(48)	(47)	(49)
Adenoma		2 (4%)	2 (4%)
Prostate	(50)	(50)	(50)
Leukemia mononuclear	1 (2%)		
Seminal vesicle	*(50)	*(50)	*(50)
Mesothelioma malignant		1 (2%)	
Testes	(50)	(50)	(50)
Mesothelioma malignant	1 (2%)	1 (2%)	1 (2%)
Bilateral, mesothelioma malignant	1 (2%)		
Bilateral, interstitial cell, adenoma	32 (64%)	34 (68%)	33 (66%)
Interstitial cell, adenoma	13 (26%)	9 (18%)	11 (22%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(50)	(50)
Femoral, leukemia mononuclear	2 (4%)		
Lymph node	(50)	(50)	(50)
Carcinoma, metastatic, thyroid gland		1 (2%)	
Mediastinal, leukemia mononuclear	9 (18%)	8 (16%)	5 (10%)
Pancreatic, leukemia mononuclear	3 (6%)		1 (2%)
Renal, leukemia mononuclear			1 (2%)
Lymph node, mandibular	(50)	(50)	(49)
Leukemia mononuclear	11 (22%)	5 (10%)	4 (8%)
Squamous cell carcinoma, metastatic, skin		1 (2%)	
Spleen	(50)	(50)	(50)
Leiomyosarcoma	1 (2%)		
Leukemia mononuclear	19 (38%)	14 (28%)	9 (18%)
Mesothelioma malignant		1 (2%)	1 (2%)
Thymus	(38)	(40)	(38)
Leukemia mononuclear	2 (5%)		1 (3%)
INTEGUMENTARY SYSTEM			
Mammary gland	(42)	(43)	(42)
Fibroadenoma	1 (2%)	1 (2%)	2 (5%)
Skin	(50)	(50)	(50)
Keratoacanthoma	1 (2%)	3 (6%)	2 (4%)
Lipoma		1 (2%)	
Papilloma squamous	1 (2%)	1 (2%)	
Squamous cell carcinoma		1 (2%)	
Sebaceous gland, adenoma			1 (2%)
Subcutaneous tissue, fibroma	2 (4%)	1 (2%)	1 (2%)
Subcutaneous tissue, fibrosarcoma		2 (4%)	2 (4%)
MUSCULOSKELETAL SYSTEM			
None			
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Astrocytoma malignant		1 (2%)	
Granular cell tumor malignant	1 (2%)		
Leukemia mononuclear	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	2 (4%)		
Alveolar/bronchiolar carcinoma			1 (2%)
Carcinoma, metastatic, uncertain primary site		1 (2%)	
Leukemia mononuclear	14 (28%)	10 (20%)	8 (16%)
Nose	(50)	(48)	(50)
Leukemia mononuclear	1 (2%)		
SPECIAL SENSES SYSTEM			
Zymbal gland	*(50)	*(50)	*(50)
Carcinoma		1 (2%)	
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Carcinoma			1 (2%)
Leukemia mononuclear	13 (26%)	11 (22%)	7 (14%)
Mesothelioma malignant			1 (2%)
Urinary bladder	(49)	(49)	(49)
Leukemia mononuclear	1 (2%)		
Mesothelioma malignant		1 (2%)	
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Leukemia mononuclear	19 (38%)	14 (28%)	9 (18%)
Mesothelioma malignant	2 (4%)	1 (2%)	1 (2%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	60	60	60
Moribund	21	15	12
Dead	4	4	6
Terminal sacrifice	23	28	21
Dosing accident	2	3	11
Scheduled sacrifice	10	10	10
TUMOR SUMMARY			
Total animals with primary neoplasms **	50	47	48
Total primary neoplasms	115	111	95
Total animals with benign neoplasms	50	45	48
Total benign neoplasms	89	87	78
Total animals with malignant neoplasms	24	23	16
Total malignant neoplasms	26	24	17
Total animals with secondary neoplasms ***		4	
Total secondary neoplasms		4	
Total animals with malignant neoplasms--uncertain primary site		2	

* Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
*** 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 DIMETHOXANE: VEHICLE CONTROL

WEEKS ON STUDY	050	065	072	073	077	080	082	084	085	086	089	092	092	094	094	095	096	096	097	098	101	101	103	104
CARCASS ID	063	035	013	065	071	103	091	024	072	032	085	083	095	094	015	061	104	045	025	055	111	112	034	064	023
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X	X	X	X			X	X			X		X	X	X	X	X		
Mesentery		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant														X				X							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																						X			
Acinus, adenoma, multiple																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																						X			
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																						X	X		
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Leukemia mononuclear							X						X	X								X			
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X						X	X								X			
Pheochromocytoma benign							X						X												
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									X
Adenoma, multiple																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X	
Leukemia mononuclear																						X			
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																						X			
Pars distalis, adenoma	X		X					X			X					X			X	X			X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																X									
C-cell, adenoma									X				X		X					X					X
C-cell, carcinoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Coagulating gland	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+
Ductus deferens	+			+								+				+		+					+		+
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Mesothelioma malignant														X											
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																						X			
Seminal vesicle	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant																		X							
Bilateral, mesothelioma malignant														X											
Bilateral, interstitial cell, adenoma						X			X	X			X	X			X		X		X	X	X		
Interstitial cell, adenoma		X	X	X	X			X				X			X	X		X		X				X	

+: Tissue examined microscopically
: Not examined
−: Present but not examined microscopically
I: Insufficient tissue

M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

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

WEEKS ON STUDY	1 0 4	1 0 4	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	TOTAL:
CARCASS ID	0 3 1	0 5 4	0 1 4	0 2 1	0 2 2	0 3 3	0 4 1	0 4 2	0 4 3	0 4 4	0 5 1	0 5 2	0 5 3	0 6 2	0 7 3	0 7 4	0 7 5	0 8 1	0 8 2	0 8 4	0 9 2	0 9 3	1 0 1	1 0 2	1 0 5	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X				X									X			X		X						19
Mesentery	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant																										2
Pancreas	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X																			X						3
Acinus, adenoma, multiple															X											1
Salivary glands	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Stomach	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+	+	+	+	+	–	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																	X									1
Leukemia mononuclear	X																			X						6
Adrenal gland, medulla	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X																			X						6
Pheochromocytoma benign																		X				X	X			5
Islets, pancreatic	+	+	+	+	+	+	–	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma															X											2
Adenoma, multiple	X																									1
Parathyroid gland	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Adenoma					X																					2
Leukemia mononuclear																										1
Pituitary gland	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear	X																									2
Pars distalis, adenoma	X										X						X	X								13
Thyroid gland	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma																										1
C-cell, adenoma				X					X									X		X	X		X	X		12
C-cell, carcinoma									X				X													2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Coagulating gland	+	+	+	+	+	+		+		+	+	+	+	+	+	+	+	+		+	+		+	+		43
Ductus deferens	+					+	+		+	+	+		+						+		+	+		+	+	19
Epididymis	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mesothelioma malignant																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	48
Prostate	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant																										1
Bilateral, mesothelioma malignant																										1
Bilateral, interstitial cell, adenoma	X		X	X	X	X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X	X	32
Interstitial cell, adenoma		X															X									13

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

WEEKS ON STUDY	050	065	072	073	077	080	082	084	085	086	089	092	092	094	094	095	096	096	097	098	101	101	103	103	104
CARCASS ID	063	035	013	065	071	103	091	024	072	032	085	083	095	094	015	061	104	045	025	055	011	012	034	064	023
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, leukemia mononuclear																	X								
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, leukemia mononuclear				X			X			X			X	X			X					X			
Pancreatic, leukemia mononuclear													X									X			
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X	X		X			X	X			X					X			
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																	X								
Leukemia mononuclear				X			X	X	X	X			X	X			X		X	X	X	X	X		
Thymus	+	M	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		M	+
Leukemia mononuclear																	X					X			
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma															X										
Papilloma squamous																									
Subcutaneous tissue, fibroma												X						X							
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor malignant															X										
Leukemia mononuclear																						X			
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Leukemia mononuclear				X			X		X	X			X	X			X				X	X	X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																						X			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye																									
Harderian gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X		X	X			X	X			X					X	X		
Ureter	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra				+																					
Urinary bladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																						X			

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

WEEKS ON STUDY	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	0311	0514	0114	0221	0222	0333	0411	0423	0444	0451	0452	0453	0462	0473	0474	0475	0481	0482	0484	0492	0493	0101	0102	0105	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femoral, leukemia mononuclear		X																							2
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, leukemia mononuclear		X																	X						9
Pancreatic, leukemia mononuclear																			X						3
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X																	X						11
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																									1
Leukemia mononuclear	X	X				X								X			X		X						19
Thymus	M	M	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	I	+	M	M	+	+	+	38
Leukemia mononuclear								·																	2
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	M-	+	M	+	+	M	M	+	+	+	+	+	M	+	+	+	+	42
Fibroadenoma																								X	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																									1
Papilloma squamous																					X				1
Subcutaneous tissue, fibroma																									2
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor malignant																									1
Leukemia mononuclear																									1
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma											X												X		2
Leukemia mononuclear	X	X												X					X						14
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																									1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																									
Eye		+	+																		+				3
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X												X					X						13
Ureter	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urethra					+				+									+	+		+				6
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																									1

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

WEEKS ON STUDY	039	055	055	058	060	074	074	077	081	085	089	089	092	097	097	099	100	100	101	104	104	104	105	105	105
CARCASS ID	265	261	321	333	271	295	291	253	282	344	301	334	342	264	284	293	255	272	275	311	312	314	251	252	254
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	A	A	+	A	+	+	+	+	+	+	+	+	+	A	+	–	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	A	A	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Mesothelioma malignant																				X					
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant																				X					
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X		X	X			X			X				X	X	X	X
Neoplastic nodule																									
Mesentery	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant																				X					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant																				X					
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																		X							
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X																
Mesothelioma malignant, metastatic, uncertain primary site																				X					
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X	
Carcinoma		X																							
Leukemia mononuclear									X									X						X	
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X									X						X	
Pheochromocytoma benign									X			X					X							X	
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X			
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																		X							
Pars distalis, adenoma														X		X			X						
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma												X		X			X	X	X			X			
C-cell, carcinoma																					X				
Follicular cell, adenoma																	X	X							
Follicular cell, carcinoma																									
GENERAL BODY SYSTEM																									
Tissue, NOS								+																	
GENITAL SYSTEM																									
Coagulating gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ductus deferens				+	+				+				+	+			+	+	+	+		+		+	+
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant																				X					
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	M	+	+	+
Adenoma													X												
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant																				X					
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant																				X					
Bilateral, interstitial cell, adenoma							X	X			X		X	X	X	X	X	X		X	X	X	X	X	X
Interstitial cell, adenoma						X			X	X		X													

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	26 2	26 3	27 3	27 4	28 1	28 3	28 5	29 2	29 4	30 2	30 3	30 4	30 5	31 3	31 5	32 2	32 3	32 4	32 5	33 1	33 2	33 5	34 1	34 3	34 5	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Mesothelioma malignant																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X													X		X			X				X		14
Neoplastic nodule																	X									1
Mesentery	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	48
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Mesothelioma malignant, metastatic, uncertain primary site																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma																										1
Leukemia mononuclear																				X						4
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																				X						4
Pheochromocytoma benign		X				X		X		X	X															9
Bilateral, pheochromocytoma benign																									X	1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Pars distalis, adenoma	X		X			X			X																	7
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma																				X	X					2
C-cell, adenoma		X						X	X							X										10
C-cell, carcinoma			X																							2
Follicular cell, adenoma																								X		3
Follicular cell, carcinoma					X																					1
GENERAL BODY SYSTEM																										
Tissue, NOS																										1
GENITAL SYSTEM																										
Coagulating gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ductus deferens	+	+	+		+	+							+	+	+	+	+			+	+		+			25
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	47
Adenoma																				X						2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma malignant																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant																										1
Bilateral, interstitial cell, adenoma		X	X	X	X	X	X			X	X	X		X	X		X	X	X	X	X		X	X	X	34
Interstitial cell, adenoma	X								X				X			X						X				9

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

WEEKS ON STUDY	039	055	055	058	060	074	074	077	081	085	089	089	092	097	097	099	100	100	101	104	104	104	104	105	105	105
CARCASS ID	265	261	321	333	271	295	291	253	282	344	301	334	342	264	284	293	255	272	275	311	312	314	251	252	254
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																					X					
Mediastinal, leukemia mononuclear									X		X	X			X							X		X	X	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	
Leukemia mononuclear															X			X								
Squamous cell carcinoma, metastatic, skin														X												
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X		X	X			X			X			X		X	X	X	X
Mesothelioma malignant																				X						
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
INTEGUMENTARY SYSTEM																										
Mammary gland	+	M	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Fibroadenoma																				X						
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																						X				
Lipoma																										
Papilloma squamous																		X								
Squamous cell carcinoma														X												
Subcutaneous tissue, fibroma																										
Subcutaneous tissue, fibrosarcoma																										
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant					X																					
Spinal cord										+																
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uncertain primary site								X																		
Leukemia mononuclear									X		X	X			X			X						X	X	
Nose	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
SPECIAL SENSES SYSTEM																										
Eye				M								+			+											
Harderian gland	M	M	M	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	
Zymbal gland																					+					
Carcinoma																					X					
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X		X	X			X			X				X		X	X	
Ureter	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra																				+						
Urinary bladder	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant																				X						

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	262	263	273	274	281	283	285	292	294	302	303	304	305	313	315	322	323	324	325	331	332	335	341	343	345	TISSUES	TUMORS
HEMATOPOIETIC SYSTEM																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Carcinoma, metastatic, thyroid gland																										1	
Mediastinal, leukemia mononuclear														X												8	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Leukemia mononuclear														X		X				X						5	
Squamous cell carcinoma, metastatic, skin																										1	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Leukemia mononuclear		X												X		X				X				X		14	
Mesothelioma malignant																										1	
Thymus	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	M	+	M	+	M	M	40	
INTEGUMENTARY SYSTEM																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	43	
Fibroadenoma																										1	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Keratoacanthoma								X				X														3	
Lipoma							X																			1	
Papilloma squamous																										1	
Squamous cell carcinoma																										1	
Subcutaneous tissue, fibroma															X											1	
Subcutaneous tissue, fibrosarcoma											X										X					2	
MUSCULOSKELETAL SYSTEM																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
NERVOUS SYSTEM																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Astrocytoma malignant																										1	
Spinal cord																										1	
RESPIRATORY SYSTEM																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Carcinoma, metastatic, uncertain primary site																										1	
Leukemia mononuclear														X		X				X						10	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
SPECIAL SENSES SYSTEM																											
Eye																										2	
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45	
Zymbal gland																										1	
Carcinoma																										1	
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Leukemia mononuclear														X		X				X						11	
Ureter	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	48	
Urethra		+																								2	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Mesothelioma malignant																										1	

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

WEEKS ON STUDY	040	053	061	071	074	077	079	080	080	080	080	080	081	081	084	086	088	088	089	090	091	091	092	093	095
CARCASS ID	39 5	47 5	37 1	41 5	37 2	43 4	43 3	40 2	42 5	44 1	38 4	45 4	38 1	44 4	41 1	44 3	46 1	42 2	45 5	40 1	38 3	41 2	41 4	42 1	46 5
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	A	M	+	+	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	M	M
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant																					X				
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Intestine small, jejunum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X														X							X	
Mesothelioma malignant																					X				
Mesentery	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+		+	+	+	+	+	+		+
Leukemia mononuclear																									
Mesothelioma malignant																					X				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous													X												
Stomach glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																	X								
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Leukemia mononuclear			X														X								
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X														X								
Pheochromocytoma benign																					X				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																						X			
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X					X								X	X		X							
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C cell, adenoma																									
C cell, adenoma			X									X					X				X				
Follicular cell, carcinoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Coagulating gland	+	+			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+
Ductus deferens			+	+		+					+	+			+	+		+		+					+
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant																					X				
Penis																									
Preputial gland	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma					X							X													
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant																					X				
Bilateral, interstitial cell, adenoma						X		X	X	X	X						X		X	X	X		X	X	X
Interstitial cell, adenoma				X	X		X					X	X		X							X			

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

WEEKS ON STUDY	0 9 8	1 0 0	1 0 0	1 0 0	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	TOTAL:
CARCASS ID	4 5 1	4 0 3	4 5 3	4 4 2	3 7 3	3 7 4	3 7 5	3 8 2	3 8 5	3 9 1	3 9 2	3 9 3	3 9 4	4 0 4	4 0 5	4 1 3	4 2 3	4 2 4	4 3 1	4 3 2	4 3 5	4 4 5	4 5 2	4 6 2	4 6 3	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	39
Intestine large, colon	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	M	+	+	+	+	+	47
Mesothelioma malignant																										1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X		X	X	X		X						X										9
Mesothelioma malignant																										1
Mesentery	+	●		+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	●	+	+	+	46
Leukemia mononuclear						X																				1
Mesothelioma malignant																										1
Pancreas	+	+	●	+	+	+	+	+	+	+	+	+	+	+	+	+	●	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	●	+	+	+	+	+	+	●	+	+	+	+	+	+	+	●	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	●	●	+	+	+	+	+	+	+	+	50
Stomach, forestomach	●	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																							X			1
Leukemia mononuclear						X																				3
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear						X																				3
Pheochromocytoma benign														X						X			X			4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	I	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X			X									X				X	X				X			11
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma					X													X								2
C-cell, adenoma										X	X				X				X							8
Follicular cell, carcinoma																				X						1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Coagulating gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Ductus deferens	+	+	+	+			+					+	+	+	+				+	+			+			22
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant																										1
Penis																+										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant																										1
Bilateral, interstitial cell, adenoma	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X		X	X	X		X	X	33
Interstitial cell, adenoma		X														X			X				X			11

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

WEEKS ON STUDY	040	053	061	071	074	077	079	080	080	080	080	080	081	081	084	086	088	088	089	090	091	091	092	093	095
CARCASS ID	395	475	371	415	372	434	433	402	425	441	384	454	381	444	411	443	461	422	455	401	383	412	414	421	465
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, leukemia mononuclear			X														X								
Pancreatic, leukemia mononuclear			X																						
Renal, leukemia mononuclear			X																						
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X														X								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X														X						X		
Mesothelioma malignant																					X				
Thymus	+	M	+	+	+	+	+	+	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	M
Leukemia mononuclear			X																						
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	M	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Fibroadenoma				X									X												
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																X									
Sebaceous gland, adenoma																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma																			X						
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Leukemia mononuclear			X														X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear																									
Eye									+		+														
Harderian gland	+	I	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Leukemia mononuclear			X														X								
Mesothelioma malignant																					X				
Ureter	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+
Urethra																									
Urinary bladder	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	098	100	100	100	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	451	403	453	442	373	374	375	382	385	391	392	393	394	404	405	413	423	424	431	432	435	445	452	462	463	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, leukemia mononuclear				X		X				X																5
Pancreatic, leukemia mononuclear																										1
Renal, leukemia mononuclear																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear						X				X																4
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X		X	X	X		X						X										9
Mesothelioma malignant																										1
Thymus	+	M	+	+	+	+	+	M	M	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	M	38
Leukemia mononuclear																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	42
Fibroadenoma																										2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma				X																						2
Sebaceous gland, adenoma																	X									1
Subcutaneous tissue, fibroma					X																					1
Subcutaneous tissue, fibrosarcoma																					X					2
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																	X									1
Leukemia mononuclear				X		X	X	X		X						X										8
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear								+																		1
Eye						+													+			+				5
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma								X																		1
Leukemia mononuclear				X		X	X	X		X																7
Mesothelioma malignant																										1
Ureter	+	+		+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Urethra																		+	+							2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	49

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

	Vehicle Control	62.5 mg/kg	125 mg/kg
Adrenal Medulla: Pheochromocytoma			
Overall Rates (a)	5/50 (10%)	10/50 (20%)	4/50 (8%)
Adjusted Rates (b)	17.3%	30.8%	17.1%
Terminal Rates (c)	3/23 (13%)	7/28 (25%)	3/21 (14%)
Day of First Observation	571	563	634
Life Table Tests (d)	P=0.539N	P=0.201	P=0.593N
Logistic Regression Tests (d)	P=0.533N	P=0.127	P=0.582N
Cochran-Armitage Trend Test (d)	P=0.440N		
Fisher Exact Test (d)		P=0.131	P=0.500N
Pancreatic Islets: Adenoma			
Overall Rates (a)	3/49 (6%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	11.9%	3.4%	0.0%
Terminal Rates (c)	1/22 (5%)	0/28 (0%)	0/21 (0%)
Day of First Observation	726	724	
Life Table Tests (d)	P=0.072N	P=0.265N	P=0.152N
Logistic Regression Tests (d)	P=0.070N	P=0.253N	P=0.156N
Cochran-Armitage Trend Test (d)	P=0.058N		
Fisher Exact Test (d)		P=0.301N	P=0.117N
Pancreatic Islets: Adenoma or Carcinoma			
Overall Rates (a)	3/49 (6%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	11.9%	3.4%	3.4%
Terminal Rates (c)	1/22 (5%)	0/28 (0%)	0/21 (0%)
Day of First Observation	726	724	635
Life Table Tests (d)	P=0.248N	P=0.265N	P=0.378N
Logistic Regression Tests (d)	P=0.235N	P=0.253N	P=0.360N
Cochran-Armitage Trend Test (d)	P=0.196N		
Fisher Exact Test (d)		P=0.301N	P=0.301N
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	13/49 (27%)	7/50 (14%)	11/49 (22%)
Adjusted Rates (b)	35.7%	21.5%	36.0%
Terminal Rates (c)	3/23 (13%)	4/28 (14%)	5/21 (24%)
Day of First Observation	349	674	371
Life Table Tests (d)	P=0.494N	P=0.080N	P=0.561N
Logistic Regression Tests (d)	P=0.356N	P=0.097N	P=0.363N
Cochran-Armitage Trend Test (d)	P=0.355N		
Fisher Exact Test (d)		P=0.096N	P=0.407N
Skin: Keratoacanthoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	2.8%	10.3%	7.3%
Terminal Rates (c)	0/23 (0%)	2/28 (7%)	0/21 (0%)
Day of First Observation	656	724	598
Life Table Tests (d)	P=0.326	P=0.355	P=0.409
Logistic Regression Tests (d)	P=0.359	P=0.311	P=0.508
Cochran-Armitage Trend Test (d)	P=0.399		
Fisher Exact Test (d)		P=0.309	P=0.500
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	5.5%	10.7%	12.4%
Terminal Rates (c)	0/23 (0%)	3/28 (11%)	2/21 (10%)
Day of First Observation	641	730	619
Life Table Tests (d)	P=0.341	P=0.561	P=0.412
Logistic Regression Tests (d)	P=0.350	P=0.500	P=0.465
Cochran-Armitage Trend Test (d)	P=0.412		
Fisher Exact Test (d)		P=0.500	P=0.500

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

	Vehicle Control	62.5 mg/kg	125 mg/kg
Testis: Interstitial Cell Adenoma			
Overall Rates (a)	45/50 (90%)	43/50 (86%)	44/50 (88%)
Adjusted Rates (b)	97.8%	97.7%	100.0%
Terminal Rates (c)	22/23 (96%)	27/28 (96%)	21/21 (100%)
Day of First Observation	450	514	493
Life Table Tests (d)	P=0.254	P=0.152N	P=0.256
Logistic Regression Tests (d)	P=0.402	P=0.578N	P=0.501
Cochran-Armitage Trend Test (d)	P=0.439N		
Fisher Exact Test (d)		P=0.380N	P=0.500N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	13/50 (26%)	12/50 (24%)	10/50 (20%)
Adjusted Rates (b)	41.9%	34.4%	36.1%
Terminal Rates (c)	7/23 (30%)	6/28 (21%)	6/21 (29%)
Day of First Observation	593	619	423
Life Table Tests (d)	P=0.426N	P=0.360N	P=0.472N
Logistic Regression Tests (d)	P=0.376N	P=0.500N	P=0.406N
Cochran-Armitage Trend Test (d)	P=0.277N		
Fisher Exact Test (d)		P=0.500N	P=0.318N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	14/50 (28%)	14/50 (28%)	10/50 (20%)
Adjusted Rates (b)	45.5%	39.4%	36.1%
Terminal Rates (c)	8/23 (35%)	7/28 (25%)	6/21 (29%)
Day of First Observation	593	619	423
Life Table Tests (d)	P=0.352N	P=0.422N	P=0.387N
Logistic Regression Tests (d)	P=0.312N	P=0.587N	P=0.329N
Cochran-Armitage Trend Test (d)	P=0.210N		
Fisher Exact Test (d)		P=0.588N	P=0.241N
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	0.0%	9.2%	0.0%
Terminal Rates (c)	0/23 (0%)	1/28 (4%)	0/21 (0%)
Day of First Observation		694	
Life Table Tests (d)	P=0.591	P=0.150	(e)
Logistic Regression Tests (d)	P=0.597	P=0.121	(e)
Cochran-Armitage Trend Test (d)	P=0.640		
Fisher Exact Test (d)		P=0.121	(e)
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	0/50 (0%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	0.0%	12.6%	4.8%
Terminal Rates (c)	0/23 (0%)	2/28 (7%)	1/21 (5%)
Day of First Observation		694	730
Life Table Tests (d)	P=0.333	P=0.087	P=0.482
Logistic Regression Tests (d)	P=0.314	P=0.065	P=0.482
Cochran-Armitage Trend Test (d)	P=0.390		
Fisher Exact Test (d)		P=0.059	P=0.500
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (a)	19/50 (38%)	14/50 (28%)	9/50 (18%)
Adjusted Rates (b)	47.4%	39.7%	33.4%
Terminal Rates (c)	4/23 (17%)	8/28 (29%)	5/21 (24%)
Day of First Observation	507	563	423
Life Table Tests (d)	P=0.070N	P=0.155N	P=0.107N
Logistic Regression Tests (d)	P=0.024N	P=0.204N	P=0.028N
Cochran-Armitage Trend Test (d)	P=0.017N		
Fisher Exact Test (d)		P=0.198N	P=0.022N

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

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression 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 125 mg/kg and vehicle control groups.

TABLE A4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHOXANE

	Vehicle Control	Low Dose	High Dose
Animals initially in study	60	60	60
Animals removed	60	60	60
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Esophagus	(49)	(50)	(50)
Hemorrhage, acute		1 (2%)	
Inflammation, chronic active		2 (4%)	2 (4%)
Intestine large, colon	(50)	(49)	(49)
Parasite metazoan		3 (6%)	3 (6%)
Intestine large, rectum	(49)	(47)	(47)
Parasite metazoan	6 (12%)	7 (15%)	3 (6%)
Intestine small, ileum	(50)	(45)	(45)
Inflammation, chronic active			1 (2%)
Liver	(50)	(50)	(50)
Basophilic focus	24 (48%)	17 (34%)	18 (36%)
Clear cell focus	1 (2%)	2 (4%)	
Degeneration, cystic	2 (4%)	1 (2%)	3 (6%)
Hematopoietic cell proliferation			1 (2%)
Hepatodiaphragmatic nodule	2 (4%)	1 (2%)	2 (4%)
Hyperplasia, nodular		1 (2%)	
Inflammation, chronic	11 (22%)	6 (12%)	13 (26%)
Inflammation, necrotizing	1 (2%)		2 (4%)
Necrosis, coagulative	1 (2%)	1 (2%)	1 (2%)
Vacuolization cytoplasmic		1 (2%)	2 (4%)
Mesentery	(49)	(49)	(46)
Hemorrhage, chronic		1 (2%)	1 (2%)
Inflammation, chronic active	4 (8%)	13 (27%)	9 (20%)
Mineralization		3 (6%)	5 (11%)
Necrosis			1 (2%)
Pancreas	(50)	(50)	(50)
Ectopic tissue			1 (2%)
Inflammation, chronic active	2 (4%)		1 (2%)
Acinus, atrophy	18 (36%)	22 (44%)	21 (42%)
Acinus, hyperplasia		2 (4%)	1 (2%)
Duct, ectasia	1 (2%)	2 (4%)	1 (2%)
Stomach, forestomach	(50)	(50)	(50)
Acanthosis, focal	5 (10%)	9 (18%)	23 (46%)
Edema	1 (2%)		
Hyperkeratosis, diffuse			2 (4%)
Hyperkeratosis, focal	1 (2%)		8 (16%)
Hyperplasia, focal	2 (4%)	1 (2%)	3 (6%)
Inflammation, chronic		1 (2%)	
Inflammation, chronic active	1 (2%)	1 (2%)	
Ulcer	1 (2%)		
Stomach, glandular	(50)	(49)	(50)
Inflammation, chronic active	1 (2%)		
Tooth	(50)	(49)	(50)
Dysplasia		1 (2%)	
Inflammation, chronic active	2 (4%)	1 (2%)	2 (4%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(50)
Cardiomyopathy, chronic	45 (90%)	48 (96%)	46 (92%)
Foreign body			2 (4%)
Inflammation, chronic active		2 (4%)	3 (6%)
Atrium, thrombus	1 (2%)	5 (10%)	1 (2%)
Coronary artery, inflammation, chronic active		1 (2%)	1 (2%)

TABLE A4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHOXANE (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
Adrenal gland	(50)	(50)	(50)
Accessory adrenal cortical nodule	1 (2%)		
Adrenal gland, cortex	(50)	(50)	(49)
Atrophy			1 (2%)
Degeneration, fatty	5 (10%)	7 (14%)	7 (14%)
Hyperplasia	12 (24%)	19 (38%)	18 (37%)
Hypertrophy	1 (2%)	2 (4%)	
Necrosis, coagulative			1 (2%)
Adrenal gland, medulla	(50)	(50)	(50)
Hyperplasia	13 (26%)	18 (36%)	13 (26%)
Islets, pancreatic	(49)	(50)	(50)
Hyperplasia	1 (2%)		
Pituitary gland	(49)	(50)	(49)
Pars distalis, cyst	6 (12%)	6 (12%)	9 (18%)
Pars distalis, hemorrhage, acute	1 (2%)		
Pars distalis, hyperplasia	9 (18%)	8 (16%)	11 (22%)
Pars intermedia, cyst			1 (2%)
Thyroid gland	(50)	(50)	(50)
Inflammation, chronic active			1 (2%)
C-cell, hyperplasia	14 (28%)	16 (32%)	14 (28%)
Follicle, cyst		1 (2%)	
Follicular cell, hyperplasia	5 (10%)		
GENERAL BODY SYSTEM			
Tissue, NOS		(1)	
Hemorrhage, acute		1 (100%)	
GENITAL SYSTEM			
Epididymis	(48)	(50)	(50)
Inflammation, chronic active	2 (4%)		
Preputial gland	(48)	(47)	(49)
Hyperplasia	2 (4%)	4 (9%)	1 (2%)
Inflammation, chronic active	45 (94%)	43 (91%)	42 (86%)
Duct, ectasia			2 (4%)
Prostate	(50)	(50)	(50)
Cyst	1 (2%)	2 (4%)	
Inflammation, chronic active	24 (48%)	23 (46%)	22 (44%)
Seminal vesicle	(48)	(49)	(48)
Inflammation, chronic active			1 (2%)
Testes	(50)	(50)	(50)
Cyst	1 (2%)		
Hemorrhage, chronic			1 (2%)
Inflammation, chronic active			1 (2%)
Mineralization	8 (16%)	16 (32%)	7 (14%)
Interstitial cell, hyperplasia	27 (54%)	33 (66%)	33 (66%)
Seminiferous tubule, atrophy	40 (80%)	38 (76%)	34 (68%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(50)	(50)
Femoral, hyperplasia, reticulum cell	1 (2%)		2 (4%)
Femoral, myelofibrosis	2 (4%)		
Lymph node	(50)	(50)	(50)
Mediastinal, cyst			1 (2%)
Mediastinal, edema, acute			1 (2%)
Mediastinal, hemorrhage, acute			1 (2%)
Lymph node, mandibular	(50)	(50)	(49)
Cyst		6 (12%)	2 (4%)
Hyperplasia, plasma cell		1 (2%)	

TABLE A4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHOXANE (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
Spleen	(50)	(50)	(50)
Fibrosis	3 (6%)	2 (4%)	2 (4%)
Hematopoietic cell proliferation	1 (2%)	1 (2%)	3 (6%)
Infarct, chronic		1 (2%)	
INTEGUMENTARY SYSTEM			
Mammary gland	(42)	(43)	(42)
Hyperplasia, cystic	38 (90%)	43 (100%)	39 (93%)
Inflammation, chronic active			1 (2%)
Skin	(50)	(50)	(50)
Acanthosis	1 (2%)	1 (2%)	1 (2%)
Fibrosis	1 (2%)		
Hyperkeratosis	2 (4%)	3 (6%)	2 (4%)
Inflammation, chronic active	3 (6%)	2 (4%)	
MUSCULOSKELETAL SYSTEM			
None			
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Compression	7 (14%)	3 (6%)	4 (8%)
Hemorrhage, acute	3 (6%)	1 (2%)	1 (2%)
Hydrocephalus	7 (14%)	3 (6%)	3 (6%)
Necrosis	1 (2%)		
Spinal cord		(1)	
White matter, degeneration		1 (100%)	
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Bacterium, multiple			1 (2%)
Foreign body	2 (4%)	6 (12%)	9 (18%)
Inflammation, chronic	21 (42%)	11 (22%)	15 (30%)
Alveolar epithelium, hyperplasia	4 (8%)	5 (10%)	3 (6%)
Mediastinum, hemorrhage, acute		1 (2%)	
Mediastinum, inflammation, chronic active		2 (4%)	4 (8%)
Nose	(50)	(48)	(50)
Fibrosis		1 (2%)	
Foreign body		9 (19%)	
Inflammation, chronic active	2 (4%)	6 (13%)	1 (2%)
Nasolacrimal duct, inflammation, chronic active		1 (2%)	
Nasolacrimal duct, inflammation, suppurative	3 (6%)	3 (6%)	2 (4%)
Trachea	(49)	(50)	(50)
Hemorrhage, acute		1 (2%)	
Inflammation, chronic active		2 (4%)	
SPECIAL SENSES SYSTEM			
Ear			(1)
Acanthosis			1 (100%)
Hyperkeratosis			1 (100%)
Eye	(3)	(2)	(5)
Lens, cataract	3 (100%)	1 (50%)	1 (20%)
Retina, atrophy	3 (100%)	1 (50%)	1 (20%)

TABLE A4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHOXANE (Continued)

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Cyst		1 (2%)	2 (4%)
Hemorrhage, chronic		1 (2%)	
Infarct, chronic			1 (2%)
Inflammation, necrotizing	1 (2%)		
Mineralization			1 (2%)
Nephropathy, chronic	47 (94%)	49 (98%)	47 (94%)
Urinary bladder	(49)	(49)	(49)
Dilatation	1 (2%)		

APPENDIX B

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

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	60	60	60
Animals removed	60	60	60
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Liver	(50)	(49)	(50)
Histiocytic sarcoma			1 (2%)
Leukemia mononuclear	12 (24%)	14 (29%)	12 (24%)
Neoplastic nodule		1 (2%)	1 (2%)
Mesentery	*(50)	*(50)	*(50)
Leukemia mononuclear		1 (2%)	
Pancreas	(50)	(50)	(50)
Leukemia mononuclear		2 (4%)	
Salivary glands	(48)	(50)	(49)
Leukemia mononuclear		2 (4%)	
Stomach, forestomach	(50)	(50)	(50)
Papilloma squamous, multiple			1 (2%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(50)
Leukemia mononuclear	3 (6%)		1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(50)	(50)
Adenoma		1 (2%)	2 (4%)
Leukemia mononuclear	6 (12%)	7 (14%)	8 (16%)
Bilateral, adenoma	1 (2%)		
Medulla, granulosa theca tumor malignant, metastatic, ovary			1 (2%)
Adrenal gland, medulla	(50)	(50)	(49)
Leukemia mononuclear	6 (12%)	7 (14%)	8 (16%)
Pheochromocytoma benign	2 (4%)		
Islets, pancreatic	(50)	(50)	(50)
Adenoma			1 (2%)
Pituitary gland	(48)	(49)	(50)
Leukemia mononuclear		6 (12%)	2 (4%)
Pars distalis, adenoma	13 (27%)	13 (27%)	7 (14%)
Thyroid gland	(50)	(50)	(50)
Bilateral, C-cell, adenoma	1 (2%)	1 (2%)	1 (2%)
C-cell, adenoma	12 (24%)	11 (22%)	6 (12%)
C-cell, carcinoma	2 (4%)	1 (2%)	1 (2%)
Follicular cell, carcinoma	1 (2%)		1 (2%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Clitoral gland	(47)	(46)	(48)
Adenoma	1 (2%)		
Ovary	(50)	(49)	(50)
Granulosa theca tumor malignant			1 (2%)
Granulosa theca tumor benign			1 (2%)
Histiocytic sarcoma			1 (2%)
Leukemia mononuclear	1 (2%)	2 (4%)	1 (2%)

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

	Vehicle Control	Low Dose	High Dose
GENITAL SYSTEM (Continued)			
Uterus	(50)	(49)	(50)
Adenocarcinoma	1 (2%)		1 (2%)
Leukemia mononuclear		1 (2%)	
Polyp stromal	5 (10%)	3 (6%)	2 (4%)
Polyp stromal, multiple	1 (2%)		
Sarcoma stromal		2 (4%)	
Vagina	*(50)	*(50)	*(50)
Polyp			1 (2%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(50)	(50)
Femoral, leukemia mononuclear		1 (2%)	3 (6%)
Femoral, lymphoma malignant histiocytic		1 (2%)	1 (2%)
Lymph node	(50)	(50)	(50)
Inguinal, leukemia mononuclear		1 (2%)	
Mediastinal, leukemia mononuclear	4 (8%)	5 (10%)	4 (8%)
Mesenteric, leukemia mononuclear			2 (4%)
Pancreatic, leukemia mononuclear		1 (2%)	
Lymph node, mandibular	(47)	(50)	(49)
Leukemia mononuclear	6 (13%)	6 (12%)	4 (8%)
Spleen	(50)	(50)	(50)
Leukemia mononuclear	12 (24%)	14 (28%)	12 (24%)
INTEGUMENTARY SYSTEM			
Mammary gland	(47)	(50)	(47)
Adenoma	2 (4%)		1 (2%)
Fibroadenoma	12 (26%)	10 (20%)	10 (21%)
Fibroadenoma, multiple	2 (4%)	1 (2%)	3 (6%)
Skin	(50)	(50)	(50)
Basal cell carcinoma			1 (2%)
Granulosa theca tumor malignant, metastatic, ovary			1 (2%)
Squamous cell carcinoma		1 (2%)	
Subcutaneous tissue, fibroma	1 (2%)		
Subcutaneous tissue, sarcoma		1 (2%)	
MUSCULOSKELETAL SYSTEM			
None			
NERVOUS SYSTEM			
Brain	(50)	*(50)	(50)
Astrocytoma malignant		1 (2%)	
Histiocytic sarcoma			1 (2%)
Leukemia mononuclear	1 (2%)	1 (2%)	
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Basal cell carcinoma, metastatic, skin			1 (2%)
Granulosa theca tumor malignant, metastatic, ovary			1 (2%)
Histiocytic sarcoma			1 (2%)
Leukemia mononuclear	7 (14%)	10 (20%)	8 (16%)

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

	Vehicle Control	Low Dose	High Dose
SPECIAL SENSES SYSTEM			
Zymbal gland	*(50)	*(50)	*(50)
Carcinoma	1 (2%)		
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Leukemia mononuclear	8 (16%)	9 (18%)	8 (16%)
Urinary bladder	(49)	(48)	(48)
Papilloma	1 (2%)	1 (2%)	
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Leukemia mononuclear	12 (24%)	14 (28%)	12 (24%)
Lymphoma malignant histiocytic		1 (2%)	1 (2%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	60	60	60
Moribund	12	13	13
Terminal sacrifice	30	31	24
Dead	6	3	2
Dosing accident	2	3	11
Scheduled sacrifice	10	10	10
TUMOR SUMMARY			
Total animals with primary neoplasms **	41	37	32
Total primary neoplasms	71	63	59
Total animals with benign neoplasms	35	28	26
Total benign neoplasms	54	42	37
Total animals with malignant neoplasms	14	20	16
Total malignant neoplasms	17	21	22
Total animals with secondary neoplasms ***			2
Total secondary neoplasms			4

* Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
*** 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 DIMETHOXANE: VEHICLE CONTROL

WEEKS ON STUDY	013	039	065	070	072	074	081	082	083	084	085	090	090	091	092	093	098	098	100	104	105	105	105	105	105
CARCASS ID	195	245	355	172	173	223	131	182	183	225	211	151	201	143	194	181	163	134	212	133	132	141	142	144	145
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	+	A	+	+	+	A	+	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	M	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	A	+	+	+	A	+	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X		X		X						X		X	X								
Mesentery	+		+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X												X	X								
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X		X		X								X	X								
Bilateral, adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X		X		X								X	X								
Pheochromocytoma benign																				X			X		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Pituitary gland	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma									X		X			X			X				X	X	X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma														X		X			X			X			
C-cell, carcinoma																							X		
Follicular cell, carcinoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Adenoma												X													
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																	X								
Oviduct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Polyp stromal							X			X															X
Polyp stromal, multiple																									
Vagina							+																		

+: Tissue examined microscopically
: Not examined
--: Present but not examined microscopically
I: Insufficient tissue

M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	152	153	154	155	161	162	164	165	171	174	175	184	185	191	192	193	202	203	204	205	213	214	215	221	222	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X		X				X	X							X	X						12
Mesentery	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	47
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear												X														6
Bilateral, adenoma																								X		1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear												X														6
Pheochromocytoma benign																										2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	I	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma		X		X	X				X								X								X	13
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma													X													1
C-cell, adenoma					X			X			X			X			X					X		X	X	12
C-cell, carcinoma																X										2
Follicular cell, carcinoma																X										1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	47
Adenoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Oviduct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																				X						1
Polyp stromal									X	X																5
Polyp stromal, multiple			X																							1
Vagina			+																							2

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

WEEKS ON STUDY	013	039	065	070	072	074	081	082	083	084	085	090	090	091	092	093	098	098	100	104	105	105	105	105	105
CARCASS ID	195	245	135	172	173	223	131	182	183	225	211	151	201	143	194	181	163	134	212	133	132	141	142	144	145
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, leukemia mononuclear				X				X								X	X								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Leukemia mononuclear				X		X		X								X	X								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X		X		X						X		X	X								
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							X		
Fibroadenoma			X									X	X					X	X						
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																	X								
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X		X		X						X		X	X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye	+																								
Harderian gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal gland																									
Carcinoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X		X		X						X		X	X								
Ureter		+	+					+							+			+		+			+		+
Urinary bladder	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma																									

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	152	153	154	155	161	162	164	165	171	174	175	184	185	191	192	193	202	203	204	205	213	214	215	221	222	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, leukemia mononuclear																										4
Lymph node, mandibular	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	47
Leukemia mononuclear																			X							6
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X		X				X	X							X	X						12
Thymus	M	+	+	+	M	M	+	M	+	M	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	41
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma						X																				2
Fibroadenoma											X			X			X	X	X			X		X		12
Fibroadenoma, multiple							X																		X	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma											X															1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																			X							7
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye					+																					2
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Zymbal gland					+																					1
Carcinoma					X																					1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear												X							X							8
Ureter			+			+	+													+						12
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma																			X							1

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

WEEKS ON STUDY	019	066	074	076	077	077	078	078	086	087	088	096	097	101	102	102	104	104	104	105	105	105	105	105	105
CARCASS ID	535	544	501	524	523	565	534	564	521	491	542	563	562	573	505	582	323	574	581	492	493	494	495	502	503
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Leukemia mononuclear								X				X		X		X	X	X	X						
Neoplastic nodule																									
Mesentery	+		+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+
Leukemia mononuclear																	X								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X									X								
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X									X								
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Leukemia mononuclear								X				X		X		X	X		X						
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X				X		X		X	X		X						
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	I
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X				X				X	X		X						
Pars distalis, adenoma									X						X			X				X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C cell, adenoma																									
C cell, adenoma																			X		X			X	
C cell, carcinoma							X																		
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																X	X								
Oviduct	+		+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X																	
Polyp stromal								X																	
Sarcoma stromal				X									X												

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	50401	51101	51202	51303	51404	51505	52202	52505	53101	53303	54101	54303	54505	55101	55202	55303	55404	55505	56101	57101	57202	57505	58303	58404	58505	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear	X		X					X	X						X		X		X							14
Neoplastic nodule																									X	1
Mesentery	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	46
Leukemia mononuclear																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X																	1
Leukemia mononuclear								X																		7
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear								X																		7
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	49
Leukemia mononuclear								X																		6
Pars distalis, adenoma	X		X	X	X		X										X		X		X				X	13
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma																									X	1
C-cell, adenoma					X	X			X			X		X				X	X		X					11
C-cell, carcinoma																										1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	46
Ovary	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										2
Oviduct	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Uterus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
Polyp stromal								X															X			3
Sarcoma stromal																										2

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

WEEKS ON STUDY	0 1 9	0 6 6	0 7 4	0 7 6	0 7 7	0 7 7	0 7 8	0 7 8	0 8 6	0 8 7	0 8 8	0 9 6	0 9 7	1 0 1	1 0 2	1 0 2	1 0 4	1 0 4	1 0 4	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5
CARCASS ID	5 3 5	5 4 4	5 0 1	5 2 4	5 2 3	5 6 5	5 3 4	5 6 4	5 2 1	4 9 1	5 4 2	5 6 3	5 6 2	5 7 3	5 0 5	5 8 2	5 3 2	5 7 4	5 8 1	4 9 2	4 9 3	4 9 4	4 9 5	5 0 2	5 0 3
HEMATOPOIETIC SYSTEM																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, leukemia mononuclear																	X							
Femoral, lymphoma malignant histiocytic																								
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inguinal, leukemia mononuclear																	X							
Mediastinal, leukemia mononuclear								X						X		X	X							
Pancreatic, leukemia mononuclear																	X							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X				X		X		X	X							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X				X		X		X	X	X	X					
Thymus	+	+	M	+	+	+	+	M	+	+	M	M	+	+	+	M	M	+	+	M	M	+	+	+
INTEGUMENTARY SYSTEM																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma					X					X			X					X	X					X
Fibroadenoma, multiple																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma							X																	
Subcutaneous tissue, sarcoma			X																					
MUSCULOSKELETAL SYSTEM																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+
Astrocytoma malignant																								
Leukemia mononuclear								X																
RESPIRATORY SYSTEM																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X				X		X		X	X		X					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																								
Eye																								
Harderian gland	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X				X		X		X	X		X					
Ureter	+	+	+		+					+					+	+						+	+	+
Urethra									+															
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Papilloma																								

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	504	511	512	513	514	515	522	525	531	533	541	543	545	551	552	553	554	555	561	571	572	575	583	584	585	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femoral, leukemia mononuclear																										1
Femoral, lymphoma malignant histiocytic																									X	1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Inguinal, leukemia mononuclear																										1
Mediastinal, leukemia mononuclear																	X									5
Pancreatic, leukemia mononuclear																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear								X																		6
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X					X	X						X		X		X							14
Thymus	+	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	38
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma												X	X	X			X									10
Fibroadenoma, multiple								X																		1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Subcutaneous tissue, sarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Astrocytoma malignant		X																								1
Leukemia mononuclear																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X							X							X		X									10
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye	+																				+					2
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear								X							X		X									9
Ureter					+							+			+		+	+		+				+		17
Urethra						+																				2
Urinary bladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Papilloma					X																					1

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

WEEKS ON STUDY	0 0 3	0 3 0	0 3 7	0 3 7	0 4 3	0 5 6	0 7 4	0 7 5	0 7 7	0 7 7	0 7 7	0 7 8	0 7 9	0 8 0	0 8 0	0 8 1	0 8 6	0 8 7	0 8 7	0 9 0	0 9 4	0 9 6	0 9 6	0 9 6	0 9 9
CARCASS ID	6 1 5	7 1 5	6 6 5	7 2 5	7 0 5	7 2 4	6 3 3	6 3 5	6 5 1	6 8 3	6 8 4	6 6 4	6 5 3	6 2 4	6 4 1	6 1 4	6 4 5	6 5 4	6 9 3	6 2 1	6 9 2	6 1 1	6 3 4	6 5 2	6 1 3
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	A	+	+	+	+	A	+	+	+	+	A	A	+	A	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	A	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	A	+	+	+	+	A	+	+	+	+	A	A	+	A	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	A	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																						X			
Leukemia mononuclear								X					X								X			X	X
Neoplastic nodule																									
Mesentery	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous, multiple																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Leukemia mononuclear								X					X								X			X	X
Medulla, granulosa theca tumor malignant, metastatic, ovary																							X		
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+
Leukemia mononuclear								X					X								X			X	X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	M	+	+	+	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									X
Pars distalis, adenoma																X		X					X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma																			X			X			
C-cell, carcinoma																		X							
Follicular cell, carcinoma																			X						
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa theca tumor malignant																							X		
Granulosa theca tumor benign																							X		
Histiocytic sarcoma																						X			
Leukemia mononuclear								X																	
Oviduct	+	+		+	A		+		+		+	+	+	+	+	+	+	+	+	+	+	+		+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Polyp stromal							X		X																
Vagina						+																			
Polyp						X																			

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

WEEKS ON STUDY	103	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	625	612	622	623	631	632	642	643	644	655	661	662	663	671	672	673	674	675	681	682	685	691	694	695	701	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	46
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear	X	X	X			X								X						X		X				12
Neoplastic nodule										X																1
Mesentery	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous, multiple																							X			1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X																							1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X						X										2
Leukemia mononuclear	X		X			X																				8
Medulla, granulosa theca tumor malignant, metastatic, ovary																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear	X		X			X																				8
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma											X															1
Parathyroid gland	+	+	M	+	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X																									2
Pars distalis, adenoma	X		X								X	X														7
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma			X																							1
C-cell, adenoma	X					X			X															X		6
C-cell, carcinoma																										1
Follicular cell, carcinoma																										1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	48
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa theca tumor malignant																										1
Granulosa theca tumor benign																										1
Histiocytic sarcoma																										1
Leukemia mononuclear																										1
Oviduct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma	X																									1
Polyp stromal																										2
Vagina																										1
Polyp																										1

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

WEEKS ON STUDY	003	030	037	037	043	056	074	075	077	077	077	078	079	080	080	081	086	087	087	090	094	096	096	096	099
CARCASS ID	615	715	665	725	705	724	633	635	651	683	684	664	653	624	641	611	645	654	693	621	692	611	634	652	613
HEMATOPOIETIC SYSTEM																									
Blood																+			+						
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, leukemia mononuclear								X																X	X
Femoral, lymphoma malignant histiocytic																		X							
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, leukemia mononuclear								X					X												X
Mesenteric, leukemia mononuclear								X																	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X																	X
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X					X								X			X	X
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	M	+	M
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X							
Fibroadenoma																			X	X	X				
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																				•				X	
Granulosa theca tumor malignant, metastatic, ovary																							X		
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																						X			
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma, metastatic, skin																								X	
Granulosa theca tumor malignant, metastatic, ovary																							X		
Histiocytic sarcoma																						X			
Leukemia mononuclear								X					X								X			X	X
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye						+																		+	
Harderian gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X					X								X			X	X
Ureter	+			+	+						+					+	+		+			+			
Urinary bladder	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	103	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	625	612	622	623	631	632	642	643	644	655	661	662	663	671	672	673	674	675	681	682	685	691	694	695	701	TISSUES / TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										2
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femoral, leukemia mononuclear																										3
Femoral, lymphoma malignant histiocytic																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, leukemia mononuclear						X																				4
Mesenteric, leukemia mononuclear			X																							2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Leukemia mononuclear			X			X																				4
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X	X			X								X						X		X				12
Thymus	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	41
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma																										1
Fibroadenoma	X	X			X					X		X							X		X					10
Fibroadenoma, multiple			X				X																X			3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																										1
Granulosa theca tumor malignant, metastatic, ovary																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma, metastatic, skin																										1
Granulosa theca tumor malignant, metastatic, ovary																										1
Histiocytic sarcoma																										1
Leukemia mononuclear	X		X			X																				8
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye																	+		+							4
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X			X																				8
Ureter							+							+						+		+	+	+	+	15
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48

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

	Vehicle Control	125 mg/kg	250 mg/kg
Mammary Gland: Fibroadenoma			
Overall Rates (a)	14/50 (28%)	11/50 (22%)	13/50 (26%)
Adjusted Rates (b)	38.9%	29.5%	45.6%
Terminal Rates (c)	9/30 (30%)	6/31 (19%)	9/24 (38%)
Day of First Observation	449	533	607
Life Table Tests (d)	P=0.406	P=0.286N	P=0.422
Logistic Regression Tests (d)	P=0.507	P=0.291N	P=0.520
Cochran-Armitage Trend Test (d)	P=0.454N		
Fisher Exact Test (d)		P=0.322N	P=0.500N
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (a)	16/50 (32%)	11/50 (22%)	14/50 (28%)
Adjusted Rates (b)	44.7%	29.5%	47.3%
Terminal Rates (c)	11/30 (37%)	6/31 (19%)	9/24 (38%)
Day of First Observation	449	533	604
Life Table Tests (d)	P=0.478	P=0.163N	P=0.483
Logistic Regression Tests (d)	P=0.502N	P=0.155N	P=0.586N
Cochran-Armitage Trend Test (d)	P=0.368N		
Fisher Exact Test (d)		P=0.184N	P=0.414N
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	13/48 (27%)	13/49 (27%)	7/50 (14%)
Adjusted Rates (b)	36.2%	38.6%	23.6%
Terminal Rates (c)	8/30 (27%)	10/30 (33%)	3/24 (13%)
Day of First Observation	580	599	567
Life Table Tests (d)	P=0.221N	P=0.560N	P=0.249N
Logistic Regression Tests (d)	P=0.144N	P=0.549N	P=0.151N
Cochran-Armitage Trend Test (d)	P=0.075N		
Fisher Exact Test (d)		P=0.566N	P=0.087N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	13/50 (26%)	12/50 (24%)	7/50 (14%)
Adjusted Rates (b)	39.0%	38.7%	25.2%
Terminal Rates (c)	10/30 (33%)	12/31 (39%)	4/24 (17%)
Day of First Observation	634	730	607
Life Table Tests (d)	P=0.199N	P=0.451N	P=0.240N
Logistic Regression Tests (d)	P=0.168N	P=0.393N	P=0.192N
Cochran-Armitage Trend Test (d)	P=0.090N		
Fisher Exact Test (d)		P=0.500N	P=0.105N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	15/50 (30%)	13/50 (26%)	8/50 (16%)
Adjusted Rates (b)	45.1%	40.1%	27.4%
Terminal Rates (c)	12/30 (40%)	12/31 (39%)	4/24 (17%)
Day of First Observation	634	541	604
Life Table Tests (d)	P=0.162N	P=0.361N	P=0.203N
Logistic Regression Tests (d)	P=0.121N	P=0.320N	P=0.149N
Cochran-Armitage Trend Test (d)	P=0.064N		
Fisher Exact Test (d)		P=0.412N	P=0.077N
Uterus: Stromal Polyp			
Overall Rates (a)	6/50 (12%)	3/49 (6%)	2/50 (4%)
Adjusted Rates (b)	17.4%	8.8%	4.6%
Terminal Rates (c)	4/30 (13%)	2/30 (7%)	0/24 (0%)
Day of First Observation	562	544	515
Life Table Tests (d)	P=0.136N	P=0.249N	P=0.202N
Logistic Regression Tests (d)	P=0.087N	P=0.249N	P=0.132N
Cochran-Armitage Trend Test (d)	P=0.090N		
Fisher Exact Test (d)		P=0.254N	P=0.134N

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

	Vehicle Control	125 mg/kg	250 mg/kg
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (a)	12/50 (24%)	14/50 (28%)	12/50 (24%)
Adjusted Rates (b)	31.4%	36.5%	38.5%
Terminal Rates (c)	6/30 (20%)	7/31 (23%)	6/24 (25%)
Day of First Observation	485	544	523
Life Table Tests (d)	P=0.342	P=0.480	P=0.394
Logistic Regression Tests (d)	P=0.452	P=0.434	P=0.519
Cochran-Armitage Trend Test (d)	P=0.546		
Fisher Exact Test (d)		P=0.410	P=0.592N

(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 logistic regression 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 B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHOXANE

	Vehicle Control	Low Dose	High Dose
Animals initially in study	60	60	60
Animals removed	60	60	60
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Esophagus	(50)	(50)	(50)
Foreign body	1 (2%)		
Hemorrhage, acute	1 (2%)		1 (2%)
Inflammation, chronic active	1 (2%)		3 (6%)
Perforation			1 (2%)
Intestine large, cecum	(44)	(47)	(45)
Concretion			1 (2%)
Inflammation, chronic active			1 (2%)
Parasite metazoan		1 (2%)	1 (2%)
Intestine large, colon	(48)	(50)	(50)
Diverticulum	1 (2%)		
Parasite metazoan		1 (2%)	4 (8%)
Intestine large, rectum	(47)	(47)	(46)
Parasite metazoan	4 (9%)	4 (9%)	2 (4%)
Liver	(50)	(49)	(50)
Basophilic focus	40 (80%)	35 (71%)	34 (68%)
Clear cell focus	3 (6%)	3 (6%)	3 (6%)
Degeneration, cystic		1 (2%)	
Eosinophilic focus			1 (2%)
Hematopoietic cell proliferation			1 (2%)
Hepatodiaphragmatic nodule	6 (12%)		4 (8%)
Inflammation, chronic	23 (46%)	18 (37%)	21 (42%)
Inflammation, necrotizing			1 (2%)
Necrosis, coagulative	1 (2%)		
Vacuolization cytoplasmic		2 (4%)	
Mesentery	(47)	(46)	(49)
Inflammation, chronic active	2 (4%)	1 (2%)	1 (2%)
Mineralization	1 (2%)		
Pancreas	(50)	(50)	(50)
Acinus, atrophy	14 (28%)	19 (38%)	12 (24%)
Salivary glands	(48)	(50)	(49)
Inflammation, chronic active	1 (2%)		
Acinus, atrophy	1 (2%)		
Duct, hyperplasia	1 (2%)		
Stomach, forestomach	(50)	(50)	(50)
Acanthosis, diffuse			3 (6%)
Acanthosis, focal		8 (16%)	41 (82%)
Hyperkeratosis, diffuse			10 (20%)
Hyperkeratosis, focal		5 (10%)	12 (24%)
Hyperplasia, focal		1 (2%)	3 (6%)
Inflammation, chronic active	1 (2%)	3 (6%)	
Ulcer		3 (6%)	
Stomach, glandular	(50)	(49)	(50)
Inflammation, chronic active	1 (2%)		
CARDIOVASCULAR SYSTEM			
Blood vessel	(49)	(50)	(50)
Inflammation, chronic active			1 (2%)
Heart	(50)	(50)	(50)
Bacterium, multiple		1 (2%)	1 (2%)
Cardiomyopathy, chronic	37 (74%)	33 (66%)	32 (64%)
Foreign body		1 (2%)	2 (4%)
Infarct		1 (2%)	
Inflammation, chronic active		3 (6%)	6 (12%)

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHOXANE (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(50)	(50)
Degeneration, fatty	3 (6%)	13 (26%)	7 (14%)
Hyperplasia	17 (34%)	20 (40%)	18 (36%)
Hypertrophy	1 (2%)		1 (2%)
Necrosis, coagulative		1 (2%)	4 (8%)
Adrenal gland, medulla	(50)	(50)	(49)
Hyperplasia	5 (10%)	5 (10%)	8 (16%)
Parathyroid gland	(46)	(43)	(42)
Cyst		1 (2%)	
Hyperplasia		2 (5%)	
Pituitary gland	(48)	(49)	(50)
Pars distalis, cyst	19 (40%)	21 (43%)	28 (56%)
Pars distalis, hemorrhage, acute	1 (2%)		
Pars distalis, hyperplasia	20 (42%)	18 (37%)	15 (30%)
Pars distalis, pigmentation, hemosiderin			4 (8%)
Pars intermedia, cyst		1 (2%)	
Thyroid gland	(50)	(50)	(50)
Hemorrhage, chronic			1 (2%)
Inflammation, chronic active			2 (4%)
C-cell, hyperplasia	26 (52%)	24 (48%)	27 (54%)
Follicle, cyst		1 (2%)	
Follicular cell, hyperplasia		1 (2%)	1 (2%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Clitoral gland	(47)	(46)	(48)
Fibrosis			1 (2%)
Hyperplasia	5 (11%)	7 (15%)	2 (4%)
Inflammation, chronic active	1 (2%)	3 (7%)	7 (15%)
Necrosis, caseous		2 (4%)	
Duct, dilatation		2 (4%)	
Ovary	(50)	(49)	(50)
Atrophy		3 (6%)	1 (2%)
Cyst	3 (6%)	4 (8%)	2 (4%)
Uterus	(50)	(49)	(50)
Dilatation	5 (10%)	5 (10%)	2 (4%)
Diverticulum			1 (2%)
Hemorrhage	2 (4%)	1 (2%)	
Inflammation, chronic active			3 (6%)
Prolapse	1 (2%)		
Endometrium, hyperplasia, cystic, glandular	2 (4%)	6 (12%)	8 (16%)
Vagina	(2)		(1)
Inflammation, chronic active			1 (100%)
Prolapse	1 (50%)		
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(50)	(50)
Femoral, hyperplasia, reticulum cell	5 (10%)	1 (2%)	2 (4%)
Lymph node	(50)	(50)	(50)
Inguinal, cyst	1 (2%)		
Mediastinal, hyperplasia, lymphoid			1 (2%)
Mediastinal, hyperplasia, plasma cell			1 (2%)
Mediastinal, inflammation, chronic active		1 (2%)	
Mediastinal, lymphocyte, necrosis, acute			1 (2%)
Mesenteric, hemorrhage, acute			1 (2%)
Pancreatic, thrombus		1 (2%)	

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHOXANE (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
Spleen	(50)	(50)	(50)
Fibrosis	1 (2%)		
Hematopoietic cell proliferation	3 (6%)	3 (6%)	4 (8%)
Hyperplasia, lymphoid			1 (2%)
Hyperplasia, reticulum cell			1 (2%)
Infarct, chronic		1 (2%)	
Thymus	(41)	(38)	(41)
Cyst	3 (7%)		2 (5%)
Hyperplasia, lymphoid			1 (2%)
Necrosis		1 (3%)	
INTEGUMENTARY SYSTEM			
Mammary gland	(47)	(50)	(47)
Cyst		2 (4%)	
Hyperplasia, cystic	47 (100%)	49 (98%)	43 (91%)
Skin	(50)	(50)	(50)
Acanthosis		1 (2%)	
Cyst epithelial inclusion			1 (2%)
Edema			1 (2%)
Hyperkeratosis		1 (2%)	
MUSCULOSKELETAL SYSTEM			
None			
NERVOUS SYSTEM			
Brain	(50)	(49)	(50)
Compression	5 (10%)	8 (16%)	4 (8%)
Hemorrhage, acute	3 (6%)	2 (4%)	2 (4%)
Hydrocephalus	1 (2%)	9 (18%)	4 (8%)
Pigmentation, hemosiderin			1 (2%)
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Bacterium			1 (2%)
Foreign body	2 (4%)	4 (8%)	6 (12%)
Inflammation, chronic	12 (24%)	11 (22%)	11 (22%)
Alveolar epithelium, hyperplasia	3 (6%)		2 (4%)
Mediastinum, bacterium, multiple		1 (2%)	1 (2%)
Mediastinum, foreign body			1 (2%)
Mediastinum, hemorrhage, acute			3 (6%)
Mediastinum, inflammation, chronic active		1 (2%)	7 (14%)
Pleura, hyperplasia			1 (2%)
Nose	(50)	(50)	(50)
Foreign body	1 (2%)	7 (14%)	1 (2%)
Inflammation, chronic active	1 (2%)	5 (10%)	3 (6%)
Nasolacrimal duct, inflammation, suppurative	2 (4%)	3 (6%)	2 (4%)
Trachea	(50)	(50)	(50)
Foreign body			1 (2%)
Hemorrhage, acute			1 (2%)
Inflammation, chronic active			1 (2%)

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHOXANE (Continued)

	Vehicle Control	Low Dose	High Dose
SPECIAL SENSES SYSTEM			
Eye	(2)	(2)	(4)
Hemorrhage, acute	1 (50%)		
Lens, cataract	1 (50%)	2 (100%)	2 (50%)
Retina, atrophy	1 (50%)	2 (100%)	2 (50%)
Harderian gland	(49)	(49)	(49)
Atrophy		1 (2%)	
Inflammation, chronic active			1 (2%)
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Cyst	1 (2%)		1 (2%)
Infarct, chronic	1 (2%)		1 (2%)
Mineralization	3 (6%)	2 (4%)	1 (2%)
Nephropathy, chronic	38 (76%)	35 (70%)	26 (52%)
Urinary bladder	(49)	(48)	(48)
Dilatation			1 (2%)

APPENDIX C

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

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	60	60	60
Animals removed	60	60	60
Animals examined histopathologically	50	48	50
ALIMENTARY SYSTEM			
Esophagus	(49)	*(48)	(50)
Adenocarcinoma, metastatic, uncertain primary site	1 (2%)		
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Fibrosarcoma, metastatic, skin		1 (2%)	
Papilloma squamous		1 (2%)	
Intestine small, ileum	(44)	*(48)	(44)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Lymphoma malignant mixed	1 (2%)		
Intestine small, jejunum	(47)	*(48)	(44)
Lymphoma malignant histiocytic		1 (2%)	2 (5%)
Lymphoma malignant lymphocytic		1 (2%)	
Lymphoma malignant mixed	1 (2%)		
Lymphoid tissue, lymphoma malignant histiocytic	2 (4%)		
Liver	(49)	*(48)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Cholangiocarcinoma	1 (2%)		
Fibrosarcoma, metastatic, skin		1 (2%)	
Hemangiosarcoma		1 (2%)	1 (2%)
Hemangiosarcoma, multiple	3 (6%)		1 (2%)
Hepatocellular carcinoma	9 (18%)	8 (17%)	6 (12%)
Hepatocellular carcinoma, multiple		2 (4%)	
Hepatocellular adenoma	6 (12%)	5 (10%)	11 (22%)
Hepatocellular adenoma, multiple	1 (2%)		2 (4%)
Lymphoma malignant histiocytic	1 (2%)		
Lymphoma malignant lymphocytic		1 (2%)	
Lymphoma malignant	1 (2%)		
Sarcoma	1 (2%)		
Squamous cell carcinoma, metastatic, stomach			1 (2%)
Mesentery	*(50)	*(48)	*(50)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Carcinosarcoma, metastatic, uncertain primary site	1 (2%)		
Fibrosarcoma, metastatic, skin		1 (2%)	
Hemangiosarcoma			1 (2%)
Lymphoma malignant histiocytic	1 (2%)		
Squamous cell carcinoma, metastatic, stomach			1 (2%)
Pancreas	(48)	*(48)	(49)
Adenocarcinoma, metastatic, uncertain primary site	1 (2%)		
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Lymphoma malignant histiocytic	2 (4%)		
Squamous cell carcinoma, metastatic, stomach			1 (2%)

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

	Vehicle Control	Low Dose	High Dose
ALIMENTARY SYSTEM (Continued)			
Stomach, forestomach	(47)	(47)	(50)
Papilloma squamous	1 (2%)	3 (6%)	7 (14%)
Papilloma squamous, multiple	1 (2%)		
Squamous cell carcinoma			1 (2%)
Stomach, glandular	(47)	(20)	(50)
Adenocarcinoma	1 (2%)		
Squamous cell carcinoma			1 (2%)
CARDIOVASCULAR SYSTEM			
Heart	(49)	*(48)	(50)
Adenocarcinoma, metastatic, uncertain primary site	1 (2%)		
Carcinosarcoma, metastatic, uncertain primary site	1 (2%)		
Sarcoma, metastatic, uncertain primary site	1 (2%)		
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	*(48)	(50)
Adenocarcinoma, metastatic, uncertain primary site	1 (2%)		
Adenoma	1 (2%)		
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Capsule, adenoma	5 (10%)		3 (6%)
Adrenal gland, medulla	(50)	*(48)	(50)
Pheochromocytoma benign	2 (4%)		
Islets, pancreatic	(48)	*(48)	(49)
Adenoma	1 (2%)		
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Pituitary gland	(46)	*(48)	(41)
Pars distalis, carcinoma		1 (2%)	
Thyroid gland	(49)	*(48)	(50)
Follicular cell, adenoma	1 (2%)	1 (2%)	1 (2%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Coagulating gland	*(50)	*(48)	*(50)
Squamous cell carcinoma, metastatic, stomach			1 (2%)
Epididymis	(50)	*(48)	(47)
Fibrosarcoma, metastatic, skin		1 (2%)	
Squamous cell carcinoma, metastatic, stomach			1 (2%)
Prostate	(48)	*(48)	(49)
Squamous cell carcinoma, metastatic, stomach			1 (2%)
Seminal vesicle	*(50)	*(48)	*(50)
Fibrosarcoma, metastatic, skin		1 (2%)	

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

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	*(48)	(50)
Femoral, hemangiosarcoma	1 (2%)		1 (2%)
Lymph node	(50)	*(48)	(49)
Axillary, fibrosarcoma, metastatic, skin		1 (2%)	
Bronchial, alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Inguinal, fibrosarcoma, metastatic, skin		1 (2%)	
Mediastinal, lymphoma malignant histiocytic	1 (2%)		
Mediastinal, sarcoma, metastatic, uncertain primary site	1 (2%)		
Mesenteric, lymphoma malignant histiocytic	2 (4%)		1 (2%)
Mesenteric, lymphoma malignant lymphocytic	1 (2%)	1 (2%)	
Mesenteric, lymphoma malignant mixed	1 (2%)		
Pancreatic, lymphoma malignant histiocytic		1 (2%)	
Pancreatic, lymphoma malignant mixed	1 (2%)		
Renal, lymphoma malignant lymphocytic	1 (2%)		
Lymph node, mandibular	(48)	*(48)	(49)
Adenocarcinoma, metastatic, uncertain primary site	1 (2%)		
Lymphoma malignant histiocytic	1 (2%)		
Lymphoma malignant lymphocytic	1 (2%)		
Lymphoma malignant mixed	1 (2%)		
Spleen	(49)	*(48)	(50)
Adenocarcinoma, metastatic, uncertain primary site	1 (2%)		
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Fibrosarcoma, metastatic, skin		1 (2%)	
Hemangioma			2 (4%)
Hemangiosarcoma	1 (2%)	1 (2%)	1 (2%)
Lymphoma malignant histiocytic	4 (8%)	1 (2%)	2 (4%)
Lymphoma malignant lymphocytic	2 (4%)	1 (2%)	
Lymphoma malignant	1 (2%)		
Lymphoma malignant mixed	2 (4%)		
Squamous cell carcinoma, metastatic, stomach			1 (2%)
Thymus	(27)	*(48)	(24)
Lymphoma malignant lymphocytic	1 (4%)		
Sarcoma, metastatic, uncertain primary site	1 (4%)		
INTEGUMENTARY SYSTEM			
Skin	(50)	*(48)	(49)
Subcutaneous tissue, fibroma	2 (4%)		4 (8%)
Subcutaneous tissue, fibrosarcoma	8 (16%)	9 (19%)	5 (10%)
Subcutaneous tissue, fibrosarcoma, multiple	2 (4%)	1 (2%)	
Subcutaneous tissue, hemangiosarcoma		1 (2%)	1 (2%)
Subcutaneous tissue, sarcoma			1 (2%)
MUSCULOSKELETAL SYSTEM			
Skeletal muscle	*(50)	*(48)	*(50)
Fibrosarcoma, metastatic, skin		3 (6%)	
Lymphoma malignant lymphocytic		1 (2%)	
Diaphragm, squamous cell carcinoma, metastatic, stomach			1 (2%)

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

	Vehicle Control	Low Dose	High Dose
NERVOUS SYSTEM			
None			
RESPIRATORY SYSTEM			
Lung	(49)	*(48)	(50)
Adenocarcinoma, metastatic, uncertain primary site	1 (2%)		
Alveolar/bronchiolar adenoma	8 (16%)	2 (4%)	8 (16%)
Alveolar/bronchiolar adenoma, multiple			1 (2%)
Alveolar/bronchiolar carcinoma		2 (4%)	4 (8%)
Carcinosarcoma, metastatic, uncertain primary site	1 (2%)		
Fibrosarcoma, metastatic, skin		1 (2%)	
Hepatocellular carcinoma, metastatic, liver	3 (6%)	3 (6%)	1 (2%)
Lymphoma malignant lymphocytic	1 (2%)	1 (2%)	
Lymphoma malignant	1 (2%)		
Sarcoma, metastatic, uncertain primary site	1 (2%)		
Squamous cell carcinoma, metastatic, stomach			1 (2%)
SPECIAL SENSES SYSTEM			
Harderian gland	(48)	*(48)	(48)
Adenoma	2 (4%)	2 (4%)	2 (4%)
URINARY SYSTEM			
Kidney	(50)	*(48)	(50)
Adenocarcinoma, metastatic, uncertain primary site	1 (2%)		
Adenoma	1 (2%)		
Alveolar/bronchiolar carcinoma, metastatic, lung			2 (4%)
Fibrosarcoma, metastatic, skin		1 (2%)	
Lymphoma malignant histiocytic	1 (2%)		
Lymphoma malignant lymphocytic	1 (2%)		
Lymphoma malignant mixed	1 (2%)		
Squamous cell carcinoma, metastatic, stomach			1 (2%)
Urethra	*(50)	*(48)	*(50)
Transitional epithelium, carcinoma		1 (2%)	
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(48)	*(50)
Hemangiosarcoma	4 (8%)	3 (6%)	3 (6%)
Lymphoma malignant histiocytic	4 (8%)	1 (2%)	3 (6%)
Lymphoma malignant mixed	2 (4%)		
Lymphoma malignant lymphocytic	2 (4%)	1 (2%)	
Lymphoma malignant	1 (2%)		
Hemangioma			2 (4%)

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

	Vehicle Control	Low Dose	High Dose
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	60	60	60
Terminal sacrifice	33	27	29
Moribund	6	11	9
Dead	11	10	12
Scheduled sacrifice	10	10	10
Wrong sex		2	
TUMOR SUMMARY			
Total animals with primary neoplasms **	38	31	37
Total primary neoplasms	67	43	65
Total animals with benign neoplasms	18	13	26
Total benign neoplasms	32	14	41
Total animals with malignant neoplasms	29	26	18
Total malignant neoplasms	35	29	24
Total animals with secondary neoplasms ***	6	7	3
Total secondary neoplasms	18	16	22
Total animals with malignant neoplasms--uncertain primary site	3		

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
*** 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 DIMETHOXANE: VEHICLE CONTROL

WEEKS ON STUDY	016	073	075	076	078	079	079	086	088	095	095	096	098	099	103	104	105	105	105	105	105	105	105	105
CARCASS ID	055	025	045	104	095	024	083	071	042	043	064	082	103	022	091	073	041	111	112	113	114	115	121	231
ALIMENTARY SYSTEM																								
Esophagus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uncertain primary site				X																				
Gallbladder	M	A	+	A	A	+	M	+	A	+	A	A	A	M	M	+	+	M	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	A	+	M	+	A	+	A	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	A	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	A	+	+	+	M	+	A	+	+	+	M	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	M	+	+	+	+	+	+	M	M	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	+	+	+	M	M	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																								
Intestine small, jejunum	+	+	+	+	+	+	+	+	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																								
Lymphoid tissue, lymphoma malignant histiocytic								X																
Liver	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma					X																			
Hemangiosarcoma, multiple										X		X							X					
Hepatocellular carcinoma		X		X		X	X							X							X			
Hepatocellular adenoma				X																	X		X	
Hepatocellular adenoma, multiple																								
Lymphoma malignant histiocytic								X																
Lymphoma malignant															X									
Sarcoma														X										
Mesentery		+	+	+	+	+	+	+				+		+		+		+	+	+	+	+	+	
Carcinosarcoma, metastatic, uncertain primary site					X																			
Lymphoma malignant histiocytic								X																
Pancreas	M	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uncertain primary site				X																				
Lymphoma malignant histiocytic								X												X				
Salivary glands	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	M	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	M	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																								
Papilloma squamous, multiple					X																			
Stomach, glandular	M	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma				X																				
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																								
Blood vessel		+	+	+	+	+	+	+	+	+	+	+		+	+	+	+		+	+	+		+	+
Heart	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uncertain primary site				X																				
Carcinosarcoma, metastatic, uncertain primary site					X																			
Sarcoma, metastatic, uncertain primary site														X										
ENDOCRINE SYSTEM																								
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uncertain primary site				X																				
Adenoma																								
Capsule, adenoma																						X		
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																								
Islets, pancreatic	M	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X		
Parathyroid gland	M	+	+	+	+	+	+	+	M	+	M	+	M	+	+	M	+	+	+	+	+	M	+	+
Pituitary gland	M	+	+	+	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																								
GENERAL BODY SYSTEM																								
None																								
GENITAL SYSTEM																								
Coagulating gland	+	+	+	+	+	+	+	+			+	+	+		+	+	+	+	+	+	+	+	+	+
Ductus deferens	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																								
Preputial gland																						+		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	M	+	M	+	M	M	+	+	+	M	M	M	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+: Tissue examined microscopically
: Not examined
−: Present but not examined microscopically
I: Insufficient tissue

M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	0332	0333	0334	0335	0444	0551	0552	0553	0554	0561	0562	0563	0565	0572	0574	0575	0581	0584	0585	0592	0593	0594	0601	0602	0605	TISSUES / TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, metastatic, uncertain primary site																										1
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	36
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	45
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Lymphoma malignant mixed													X													1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant mixed													X													1
Lymphoid tissue, lymphoma malignant histiocytic		X																								2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cholangiocarcinoma																										1
Hemangiosarcoma, multiple																										3
Hepatocellular carcinoma		X				X										X										9
Hepatocellular adenoma			X								X									X					6
Hepatocellular adenoma, multiple				X																						1
Lymphoma malignant histiocytic																										1
Lymphoma malignant																										1
Sarcoma																										1
Mesentery	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	41
Carcinosarcoma, metastatic, uncertain primary site																										1
Lymphoma malignant histiocytic																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma, metastatic, uncertain primary site																										1
Lymphoma malignant histiocytic																										2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Papilloma squamous								X																		1
Papilloma squamous, multiple																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenocarcinoma																										1
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+	+	+	+	+	+			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, metastatic, uncertain primary site																										1
Carcinosarcoma, metastatic, uncertain primary site																										1
Sarcoma, metastatic, uncertain primary site																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, uncertain primary site																										1
Adenoma				X																						1
Capsule, adenoma											X						X		X	X						5
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign				X												X										2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	M	+	+	+	+	41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma														X												1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Coagulating gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+			45
Ductus deferens	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+		47
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Penis				+				+																		2
Preputial gland	+			+				+		+				+												6
Prostate	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

WEEKS ON STUDY	016	073	075	076	078	079	079	086	088	095	095	096	098	099	103	104	105	105	105	105	105	105	105	105	105
CARCASS ID	055	025	045	104	095	024	083	071	042	043	064	082	103	022	091	073	041	111	112	113	114	115	121	123	131
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, hemangiosarcoma												X													
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, lymphoma malignant histiocytic																				X					
Mediastinal, sarcoma, metastatic, uncertain primary site														X											
Mesenteric, lymphoma malignant histiocytic								X																	
Mesenteric, lymphoma malignant lymphocytic									X																
Mesenteric, lymphoma malignant mixed																							X		
Pancreatic, lymphoma malignant mixed									X																
Renal, lymphoma malignant lymphocytic																									
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uncertain primary site				X																					
Lymphoma malignant histiocytic																				X					
Lymphoma malignant lymphocytic									X																
Lymphoma malignant mixed																							X		
Spleen	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uncertain primary site				X																					
Hemangiosarcoma																									
Lymphoma malignant histiocytic								X												X					
Lymphoma malignant lymphocytic									X																
Lymphoma malignant															X										
Lymphoma malignant mixed																							X		
Thymus	M	M	M	M	M	M	M	M	+	+	M	M	M	+	M	+	+	+	+	+	M	M	+	M	M
Lymphoma malignant lymphocytic									X																
Sarcoma, metastatic, uncertain primary site														X											
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	M	M	+	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma			X						X	X	X		X												
Subcutaneous tissue, fibrosarcoma, multiple																X	X								
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord																									
RESPIRATORY SYSTEM																									
Lung	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uncertain primary site				X																					
Alveolar/bronchiolar adenoma							X														X				
Carcinosarcoma, metastatic, uncertain primary site					X																				
Hepatocellular carcinoma, metastatic, liver		X																			X				
Lymphoma malignant lymphocytic																									
Lymphoma malignant															X										
Sarcoma, metastatic, uncertain primary site														X											
Nose	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye									+																
Harderian gland	M	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uncertain primary site				X																					
Adenoma																									
Lymphoma malignant histiocytic																				X					
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																									
Ureter			+	+	+	+	+	+		+	+	+	+	+		+	+	+	+	+	+	+			+
Urethra					+		+	+				+		+					+	+					+
Urinary bladder	+	+	+	+	+	+	+	+	A	+	+	+	+	M	A	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	0322	0333	0345	0355	0444	0551	0552	0553	0554	0561	0562	0563	0565	0572	0574	0575	0581	0584	0585	0592	0593	0594	0611	0612	0615	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femoral, hemangiosarcoma																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, lymphoma malignant histiocytic																										1
Mediastinal, sarcoma, metastatic, uncertain primary site																										1
Mesenteric, lymphoma malignant histiocytic		X																								2
Mesenteric, lymphoma malignant lymphocytic																										1
Mesenteric, lymphoma malignant mixed													X													1
Pancreatic, lymphoma malignant mixed																										1
Renal, lymphoma malig. lymphocytic																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma, metastatic, uncertain primary site																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, metastatic, uncertain primary site																										1
Hemangiosarcoma										X																1
Lymphoma malignant histiocytic		X							X																	4
Lymphoma malignant lymphocytic																					X					2
Lymphoma malignant																										1
Lymphoma malignant mixed													X													2
Thymus	+	+	+	M	+	+	M	+	M	+	+	+	+	+	+	M	+	M	M	+	M	+	+	+	+	27
Lymphoma malignant lymphocytic																										1
Sarcoma, metastatic, uncertain primary site																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma																			X			X				2
Subcutaneous tissue, fibrosarcoma			X	X												X										8
Subcutaneous tissue, fibrosarcoma, multiple																										2
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spinal cord							+																			1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, metastatic, uncertain primary site																										1
Alveolar/bronchiolar adenoma				X										X			X		X	X			X			8
Carcinosarcoma, metastatic, uncertain primary site																										1
Hepatocellular carcinoma, metastatic, liver		X																								3
Lymphoma malignant lymphocytic																					X					1
Lymphoma malignant																										1
Sarcoma, metastatic, uncertain primary site																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Eye																										1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma			X																		X					2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, uncertain primary site																										1
Adenoma																				X						1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																					X					1
Lymphoma malignant mixed													X													1
Ureter	+	+	+		+	+	+	+	+	+	+	+	+		+	+	+	+	+	+		+	+	+	+	41
Urethra	+	+			+	+	+		+	+					+		+	+			+	+	+	+	+	23
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47

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

WEEKS ON STUDY	001	002	005	015	033	041	064	064	069	073	077	079	079	080	087	088	088	095	096	097	098	099	099	105	105
CARCASS ID	335	362	305	004	285	295	303	284	253	261	325	131	433	141	302	265	291	331	311	422	262	123	332	251	252
ALIMENTARY SYSTEM																									
Esophagus			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Fibrosarcoma, metastatic, skin															X										
Papilloma squamous																		X							
Gallbladder			+	+	A	A	+	+	M	+	A	+	+	+	+	+	A	A	+	+	+	+	+		
Intestine large			+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine large, cecum			M	+	M	+	A	+		+	A	+	+	+	+	+	+	A	+	+	+	+	+		
Intestine large, colon			+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine large, rectum			M	+	+	A	A	+		+	A	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine small			+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine small, duodenum			+	+	+	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine small, ileum			M	+	+	+	A	+	A	+	A	+	+	+	+	+	+	A	+	+	+	+	+		
Intestine small, jejunum			M	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic											X														
Liver			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Fibrosarcoma, metastatic, skin															X										
Hemangiosarcoma																									
Hepatocellular carcinoma								X	X		X	X									X		X		
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma							X					X									X				
Lymphoma malignant lymphocytic											X														
Mesentery			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+		+	+	+		
Fibrosarcoma, metastatic, skin															X										
Pancreas			+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+		
Salivary glands			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Stomach			+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+		
Stomach, forestomach			+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																								X	
Stomach, glandular			+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+		
Tooth			+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+		
CARDIOVASCULAR SYSTEM																									
Blood vessel			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Heart			+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
ENDOCRINE SYSTEM																									
Adrenal gland			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Adrenal gland, cortex			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Adrenal gland, medulla			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Islets, pancreatic			+	+	+	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+		
Parathyroid gland			M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+		
Pituitary gland			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+		
Pars distalis, carcinoma										X															
Thyroid gland			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Coagulating gland			+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Ductus deferens			+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+		
Epididymis			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Fibrosarcoma, metastatic, skin															X										
Penis						+		+								+	+								
Preputial gland						+										+	+				+	+			
Prostate			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Seminal vesicle			+		+	+	+	+	+	+	+	+	+	+	+		+	+	+	+		+	+		
Fibrosarcoma, metastatic, skin															X										
Testes			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	254	255	263	264	271	272	273	274	275	281	282	283	292	293	294	301	315	321	322	323	324	331	334	341	344	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus																										21
Fibrosarcoma, metastatic, skin																										1
Papilloma squamous																										1
Gallbladder	+																									16
Intestine large																										19
Intestine large, cecum																										15
Intestine large, colon																										19
Intestine large, rectum																										16
Intestine small																									+	20
Intestine small, duodenum																										18
Intestine small, ileum																										16
Intestine small, jejunum																									+	19
Lymphoma malignant histiocytic																									X	1
Lymphoma malignant lymphocytic																										1
Liver	+				+			+							+	+				+	+					28
Fibrosarcoma, metastatic, skin																										1
Hemangiosarcoma								X																		1
Hepatocellular carcinoma	X														X											8
Hepatocellular carcinoma, multiple																				X	X					2
Hepatocellular adenoma					X																X					5
Lymphoma malignant lymphocytic																										1
Mesentery																										19
Fibrosarcoma, metastatic, skin																										1
Pancreas																										20
Salivary glands																										21
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Papilloma squamous																				X					X	3
Stomach, glandular																										20
Tooth																										20
CARDIOVASCULAR SYSTEM																										
Blood vessel																										21
Heart																										21
ENDOCRINE SYSTEM																										
Adrenal gland																										21
Adrenal gland, cortex																										21
Adrenal gland, medulla																										21
Islets, pancreatic																										19
Parathyroid gland																										19
Pituitary gland																										20
Pars distalis, carcinoma																										1
Thyroid gland																								+		22
Follicular cell, adenoma																								X		1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Coagulating gland																										20
Ductus deferens																										20
Epididymis																										21
Fibrosarcoma, metastatic, skin																										1
Penis																										4
Preputial gland															+											6
Prostate																										21
Seminal vesicle					+									+												20
Fibrosarcoma, metastatic, skin																										1
Testes																										21

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

WEEKS ON STUDY	001	002	005	015	033	041	064	064	069	073	077	079	079	080	087	088	088	095	096	097	098	099	099	105	105
CARCASS ID	335	362	305	304	285	295	303	284	253	261	325	313	343	314	302	265	291	333	311	342	262	312	332	251	252
HEMATOPOIETIC SYSTEM																									
Bone marrow			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Lymph node			+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+		
Axillary, fibrosarcoma, metastatic, skin																									
Inguinal, fibrosarcoma, metastatic, skin																						X			
Mesenteric, lymphoma malignant lymphocytic											X														
Pancreatic, lymphoma malignant histiocytic																									
Lymph node, mandibular			+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+		
Spleen			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Fibrosarcoma, metastatic, skin															X										
Hemangiosarcoma																									
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic											X														
Thymus			+	+	M	M	+	M	+	+	+	M	+	+	M	+	+	+	M	M	M	+	M		
INTEGUMENTARY SYSTEM																									
Mammary gland			M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M		
Skin			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+
Subcutaneous tissue, fibrosarcoma												X			X				X	X		X			X
Subcutaneous tissue, fibrosarcoma, multiple																		X							
Subcutaneous tissue, hemangiosarcoma												X													
MUSCULOSKELETAL SYSTEM																									
Bone			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+
Skeletal muscle			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Fibrosarcoma, metastatic, skin															X				X			X			
Lymphoma malignant lymphocytic											X														
NERVOUS SYSTEM																									
Brain			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
RESPIRATORY SYSTEM																									
Lung			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Alveolar/bronchiolar adenoma																		X							
Alveolar/bronchiolar carcinoma																									
Fibrosarcoma, metastatic, skin															X										
Hepatocellular carcinoma, metastatic, liver												X									X				
Lymphoma malignant lymphocytic											X														
Nose			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Trachea			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
SPECIAL SENSES SYSTEM																									
Eye																									
Harderian gland			+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	I	+	+	+	+	+		+
Adenoma																									
URINARY SYSTEM																									
Kidney			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Fibrosarcoma, metastatic, skin															X										
Ureter				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Urethra				+	+	+		+	+		+	+	+	+	+			+	+	+	+		+		
Transitional epithelium, carcinoma																		X							
Urinary bladder			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	254	255	263	264	271	272	273	274	275	281	282	283	292	293	294	301	315	321	322	323	324	331	334	341	344	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow																										21
Lymph node			+																		+		+		+	24
Axillary, fibrosarcoma, metastatic, skin			X																							1
Inguinal, fibrosarcoma, metastatic, skin																										1
Mesenteric, lymphoma malignant lymphocytic																										1
Pancreatic, lymphoma malignant histiocytic																									X	1
Lymph node, mandibular																										20
Spleen		+									+										+		+		+	26
Fibrosarcoma, metastatic, skin																										1
Hemangiosarcoma											X															1
Lymphoma malignant histiocytic																									X	1
Lymphoma malignant lymphocytic																										1
Thymus																										12
INTEGUMENTARY SYSTEM																										
Mammary gland																										33
Skin		+	+	+				+	+						+	+		+		+		+	+		9
Subcutaneous tissue, fibrosarcoma		X	X	X																						1
Subcutaneous tissue, fibrosarcoma, multiple																										1
Subcutaneous tissue, hemangiosarcoma																										
MUSCULOSKELETAL SYSTEM																										
Bone				+	+			+	+						+	+		+		+					30
Skeletal muscle																										21
Fibrosarcoma, metastatic, skin																										3
Lymphoma malignant lymphocytic																										1
NERVOUS SYSTEM																										
Brain																										21
RESPIRATORY SYSTEM																										
Lung	+													+	+								+			25
Alveolar/bronchiolar adenoma															X											2
Alveolar/bronchiolar carcinoma														X									X			2
Fibrosarcoma, metastatic, skin																										1
Hepatocellular carcinoma, metastatic, liver	X																									3
Lymphoma malignant lymphocytic																										1
Nose																										21
Trachea																										21
SPECIAL SENSES SYSTEM																										
Eye							+																			1
Harderian gland				+	+		+							+									+			25
Adenoma							X																X			2
URINARY SYSTEM																										
Kidney		+																							+	23
Fibrosarcoma, metastatic, skin																										1
Ureter		+																								21
Urethra																										15
Transitional epithelium, carcinoma																										1
Urinary bladder																										21

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

WEEKS ON STUDY	0 2 7	0 4 4	0 6 1	0 6 7	0 7 1	0 7 9	0 7 9	0 7 9	0 8 3	0 8 9	0 9 0	0 9 3	0 9 6	0 9 6	0 9 6	0 9 6	0 9 9	1 0 0	1 0 0	1 0 1	1 0 3	1 0 5	1 0 5	1 0 5	1 0 5
CARCASS ID	5 6 5	5 6 4	5 3 5	5 3 4	5 8 5	5 4 1	5 0 1	5 1 3	5 1 1	5 8 4	5 8 2	5 1 2	5 0 3	5 0 4	5 0 5	5 3 3	5 2 5	5 2 1	5 1 5	5 7 5	5 7 4	4 9 1	4 9 2	4 9 3	4 9 4
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																X									
Gallbladder	A	A	M	M	+	+	A	+	+	A	+	+	+	+	+	A	+	+	+	M	A	+	+	+	+
Intestine large	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	M	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+
Intestine large, colon	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+
Intestine large, rectum	+	+	A	A	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	
Intestine small	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	A	+	+	+	+	+	A	+	+	+	+	+	M	+	+	+	A	A	+	+	+	+
Intestine small, ileum	M	M	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																X									
Intestine small, jejunum	A	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+
Lymphoma malignant histiocytic																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																X									
Hemangiosarcoma																									
Hemangiosarcoma, multiple																			X						
Hepatocellular carcinoma			X								X					X									
Hepatocellular adenoma							X	X		X									X					X	X
Hepatocellular adenoma, multiple																									
Squamous cell carcinoma, metastatic, stomach				X																					
Mesentery	+		+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																X									
Hemangiosarcoma										X															
Squamous cell carcinoma, metastatic, stomach				X																					
Pancreas	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																X									
Squamous cell carcinoma, metastatic, stomach				X																					
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous							X	X							X	X					X				
Squamous cell carcinoma				X																					
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma				X																					
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Blood vessel		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																X									
Capsule, adenoma																							X	X	
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																X									
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	M	M	+	+	+	I	M	M	M	+	+	M	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Coagulating gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, stomach				X																					
Ductus deferens	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+		+		
Epididymis	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+
Squamous cell carcinoma, metastatic, stomach				X																					
Penis																	+								
Preputial gland												+					+								
Prostate	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, stomach				X																					
Seminal vesicle	+	M	+	+	M	+	+	+		+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	495	502	514	522	523	524	531	532	542	543	544	545	551	552	553	554	555	561	562	563	571	572	573	581	583	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Gallbladder	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	39
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	44
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Lymphoma malignant histiocytic			X												X											2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Hemangiosarcoma																X										1
Hemangiosarcoma, multiple																										1
Hepatocellular carcinoma										X						X									X	6
Hepatocellular adenoma			X				X				X							X		X						11
Hepatocellular adenoma, multiple																							X	X		2
Squamous cell carcinoma, metastatic, stomach																										1
Mesentery	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Hemangiosarcoma																										1
Squamous cell carcinoma, metastatic, stomach																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Squamous cell carcinoma, metastatic, stomach																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous		X																			X					7
Squamous cell carcinoma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Blood vessel		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	47
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Capsule, adenoma																							X			3
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Parathyroid gland	+	+	+	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	41
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																				X						1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Coagulating gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma, metastatic, stomach																										1
Ductus deferens		+	+		+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell carcinoma, metastatic, stomach																										1
Penis																										1
Preputial gland		+																								3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma, metastatic, stomach																										1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

WEEKS ON STUDY	027	044	061	067	071	079	079	079	083	089	090	093	096	096	096	096	099	099	100	100	101	103	105	105	105
CARCASS ID	56 5	56 4	53 5	53 4	58 5	54 1	50 1	51 3	51 1	58 4	58 2	51 2	50 3	50 4	50 5	53 3	52 5	52 1	51 5	57 5	57 4	49 1	49 2	49 3	49 4
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, hemangiosarcoma										X															
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bronchial, alveolar/bronchiolar carcinoma, metastatic, lung																X									
Mesenteric, lymphoma malignant histiocytic																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																X									
Hemangioma																							X		
Hemangiosarcoma										X															
Lymphoma malignant histiocytic																									
Squamous cell carcinoma, metastatic, stomach				X																					
Thymus	+	+	M	M	M	M	+	+	+	+	M	M	M	+	M	M	M	+	+	M	+	+	M	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																			X				X		
Subcutaneous tissue, fibrosarcoma						X						X						X	X						
Subcutaneous tissue, hemangiosarcoma										X															
Subcutaneous tissue, sarcoma																	X								
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Diaphragm, squamous cell carcinoma, metastatic, stomach				X																					
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X													X				
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma							X				X					X									
Hepatocellular carcinoma, metastatic, liver											X														
Squamous cell carcinoma, metastatic, stomach				X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Adenoma														X											
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung											X					X									
Squamous cell carcinoma, metastatic, stomach				X																					
Ureter	+		+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+				+	+	
Urethra								+				+			+		+	+	+				+	+	+
Urinary bladder	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	495	502	514	522	523	524	531	532	542	543	544	545	551	552	553	554	555	561	562	563	571	572	573	581	583	TOTAL: TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femoral, hemangiosarcoma																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Bronchial, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Mesenteric, lymphoma malignant histiocytic			X																							1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Hemangioma												X														2
Hemangiosarcoma																										1
Lymphoma malignant histiocytic															X		X									2
Squamous cell carcinoma, metastatic, stomach																										1
Thymus	M	+	+	+	+	M	M	+	M	M	M	M	+	M	M	+	M	M	+	+	M	M	+	M	+	24
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcutaneous tissue, fibroma										X									X							4
Subcutaneous tissue, fibrosarcoma					X																					5
Subcutaneous tissue, hemangiosarcoma																										1
Subcutaneous tissue, sarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Diaphragm, squamous cell carcinoma, metastatic, stomach																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X				X	X		X								X				X	8
Alveolar/bronchiolar adenoma, multiple							X																			1
Alveolar/bronchiolar carcinoma																	X									4
Hepatocellular carcinoma, metastatic, liver																										1
Squamous cell carcinoma, metastatic, stomach																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																									X	2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										2
Squamous cell carcinoma, metastatic, stomach																										1
Ureter	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Urethra	+	+	+	+		+		+	+		+	+	+		+	+	+	+	+	+			+	+	+	29
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48

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

	Vehicle Control	250 mg/kg	500 mg/kg
Adrenal Cortex: Adenoma			
Overall Rates (a)	6/50 (12%)	(b) 0/21 (0%)	3/50 (6%)
Adjusted Rates (c)	18.2%		10.3%
Terminal Rates (d)	6/33 (18%)		3/29 (10%)
Day of First Observation	731		731
Life Table Test (e)			P=0.306N
Logistic Regression Test (e)			P=0.306N
Fisher Exact Test (e)			P=0.243N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	7/49 (14%)	(b) 5/28 (18%)	13/50 (26%)
Adjusted Rates (c)	19.9%		37.8%
Terminal Rates (d)	6/33 (18%)		9/29 (31%)
Day of First Observation	530		550
Life Table Test (e)			P=0.069
Logistic Regression Test (e)			P=0.094
Fisher Exact Test (e)			P=0.115
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	9/49 (18%)	(b) 10/28 (36%)	6/50 (12%)
Adjusted Rates (c)	21.7%		16.9%
Terminal Rates (d)	4/33 (12%)		3/29 (10%)
Day of First Observation	509		423
Life Table Test (e)			P=0.359N
Logistic Regression Test (e)			P=0.188N
Fisher Exact Test (e)			P=0.274N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	14/49 (29%)	(b) 12/28 (43%)	19/50 (38%)
Adjusted Rates (c)	35.2%		51.0%
Terminal Rates (d)	9/33 (27%)		12/29 (41%)
Day of First Observation	509		423
Life Table Test (e)			P=0.137
Logistic Regression Test (e)			P=0.230
Fisher Exact Test (e)			P=0.217
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	8/49 (16%)	(b) 2/25 (8%)	9/50 (18%)
Adjusted Rates (c)	23.0%		28.4%
Terminal Rates (d)	7/33 (21%)		7/29 (24%)
Day of First Observation	549		551
Life Table Test (e)			P=0.395
Logistic Regression Test (e)			P=0.450
Fisher Exact Test (e)			P=0.518
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	0/49 (0%)	(b) 2/25 (8%)	4/50 (8%)
Adjusted Rates (c)	0.0%		10.6%
Terminal Rates (d)	0/33 (0%)		1/29 (3%)
Day of First Observation			550
Life Table Test (e)			P=0.060
Logistic Regression Test (e)			P=0.076
Fisher Exact Test (e)			P=0.061
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	8/49 (16%)	(b) 4/25 (16%)	13/50 (26%)
Adjusted Rates (c)	23.0%		36.7%
Terminal Rates (d)	7/33 (21%)		8/29 (28%)
Day of First Observation	549		550
Life Table Test (e)			P=0.111
Logistic Regression Test (e)			P=0.146
Fisher Exact Test (e)			P=0.176

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

	Vehicle Control	250 mg/kg	500 mg/kg
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	2/50 (4%)	0/48 (0%)	4/50 (8%)
Adjusted Rates (c)	6.1%	0.0%	13.1%
Terminal Rates (d)	2/33 (6%)	0/27 (0%)	3/29 (10%)
Day of First Observation	731		697
Life Table Tests (e)	P=0.189	P=0.283N	P=0.281
Logistic Regression Tests (e)	P=0.192	P=0.283N	P=0.284
Cochran-Armitage Trend Test (e)	P=0.223		
Fisher Exact Test (e)		P=0.258N	P=0.339
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	10/50 (20%)	10/48 (21%)	5/50 (10%)
Adjusted Rates (c)	24.1%	29.2%	13.6%
Terminal Rates (d)	3/33 (9%)	4/27 (15%)	1/29 (3%)
Day of First Observation	519	551	549
Life Table Tests (e)	P=0.185N	P=0.402	P=0.197N
Logistic Regression Tests (e)	P=0.122N	P=0.507	P=0.130N
Cochran-Armitage Trend Test (e)	P=0.115N		
Fisher Exact Test (e)		P=0.558	P=0.131N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	12/50 (24%)	10/48 (21%)	8/50 (16%)
Adjusted Rates (c)	29.2%	29.2%	22.8%
Terminal Rates (d)	5/33 (15%)	4/27 (15%)	4/29 (14%)
Day of First Observation	519	551	549
Life Table Tests (e)	P=0.288N	P=0.563	P=0.326N
Logistic Regression Tests (e)	P=0.210N	P=0.516N	P=0.240N
Cochran-Armitage Trend Test (e)	P=0.192N		
Fisher Exact Test (e)		P=0.447N	P=0.227N
Subcutaneous Tissue: Sarcoma or Fibrosarcoma			
Overall Rates (a)	10/50 (20%)	10/48 (21%)	6/50 (12%)
Adjusted Rates (c)	24.1%	29.2%	16.1%
Terminal Rates (d)	3/33 (9%)	4/27 (15%)	1/29 (3%)
Day of First Observation	519	551	549
Life Table Tests (e)	P=0.263N	P=0.402	P=0.287N
Logistic Regression Tests (e)	P=0.188N	P=0.507	P=0.206N
Cochran-Armitage Trend Test (e)	P=0.179N		
Fisher Exact Test (e)		P=0.558	P=0.207N
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	12/50 (24%)	10/48 (21%)	9/50 (18%)
Adjusted Rates (c)	29.2%	29.2%	25.1%
Terminal Rates (d)	5/33 (15%)	4/27 (15%)	4/29 (14%)
Day of First Observation	519	551	549
Life Table Tests (e)	P=0.374N	P=0.563	P=0.419N
Logistic Regression Tests (e)	P=0.291N	P=0.516N	P=0.328N
Cochran-Armitage Trend Test (e)	P=0.269N		
Fisher Exact Test (e)		P=0.447N	P=0.312N
Forestomach: Squamous Papilloma			
Overall Rates (a)	2/47 (4%)	3/47 (6%)	7/50 (14%)
Adjusted Rates (c)	5.1%	11.1%	18.7%
Terminal Rates (d)	1/33 (3%)	3/27 (11%)	2/29 (7%)
Day of First Observation	542	731	550
Life Table Tests (e)	P=0.044	P=0.412	P=0.073
Logistic Regression Tests (e)	P=0.057	P=0.454	P=0.117
Cochran-Armitage Trend Test (e)	P=0.059		
Fisher Exact Test (e)		P=0.500	P=0.095

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

	Vehicle Control	250 mg/kg	500 mg/kg
Forestomach: Squamous Papilloma or Squamous Cell Carcinoma			
Overall Rates (a)	2/47 (4%)	3/47 (6%)	8/50 (16%)
Adjusted Rates (c)	5.1%	11.1%	20.5%
Terminal Rates (d)	1/33 (3%)	3/27 (11%)	2/29 (7%)
Day of First Observation	542	731	469
Life Table Tests (e)	P=0.024	P=0.412	P=0.044
Logistic Regression Tests (e)	P=0.033	P=0.454	P=0.087
Cochran-Armitage Trend Test (e)	P=0.032		
Fisher Exact Test (e)		P=0.500	P=0.056
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	4/50 (8%)	(b,f) 3/48 (6%)	3/50 (6%)
Adjusted Rates (c)	10.7%		8.7%
Terminal Rates (d)	2/33 (6%)		1/29 (3%)
Day of First Observation	664		623
Life Table Test (e)			P=0.546N
Logistic Regression Test (e)			P=0.513N
Fisher Exact Test (e)			P=0.500N
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	4/50 (8%)	(b,f) 3/48 (6%)	5/50 (10%)
Adjusted Rates (c)	10.7%		15.3%
Terminal Rates (d)	2/33 (6%)		3/29 (10%)
Day of First Observation	664		623
Life Table Test (e)			P=0.442
Logistic Regression Test (e)			P=0.475
Fisher Exact Test (e)			P=0.500
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	9/50 (18%)	(b,f) 2/48 (4%)	3/50 (6%)
Adjusted Rates (c)	24.2%		10.3%
Terminal Rates (d)	6/33 (18%)		3/29 (10%)
Day of First Observation	600		731
Life Table Test (e)			P=0.096N
Logistic Regression Test (e)			P=0.074N
Fisher Exact Test (e)			P=0.061N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Incomplete sampling of tissues
(c) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(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 logistic regression 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).
(f) Twenty-eight livers and 26 spleens were examined microscopically.

TABLE C4. HISTORICAL INCIDENCE OF STOMACH SQUAMOUS CELL TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED COIN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Papilloma	Carcinoma	Papilloma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	0/48	0/48	0/48
1,2-Dichlorobenzene	0/46	0/46	0/46
1,4-Dichlorobenzene	0/45	0/45	0/45
Benzene	2/46	0/46	2/46
Xylenes	2/45	0/45	2/45
TOTAL	4/230 (1.7%)	0/230 (0.0%)	4/230 (1.7%)
SD (b)	2.41%	0.00%	2.41%
Range (c)			
High	2/45	0/48	2/45
Low	0/48	0/48	0/48
Overall Historical Incidence			
TOTAL	(d) 23/1,937 (1.2%)	9/1,937 (0.5%)	(d) 32/1,937 (1.7%)
SD (b)	2.00%	0.89%	2.43%
Range (c)			
High	3/49	1/45	4/49
Low	0/50	0/50	0/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes two papillomas, NOS

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	60	60	60
Animals removed	60	60	60
Animals examined histopathologically	50	48	50
ALIMENTARY SYSTEM			
Intestine large, cecum	(46)	(15)	(45)
Hyperplasia, lymphoid	1 (2%)		
Intestine large, colon	(47)	(19)	(47)
Parasite metazoan	1 (2%)	1 (5%)	2 (4%)
Intestine large, rectum	(45)	(16)	(44)
Inflammation, necrotizing			1 (2%)
Intestine small, duodenum	(44)	(18)	(43)
Inflammation, necrotizing		1 (6%)	1 (2%)
Intestine small, ileum	(44)	(16)	(44)
Hyperplasia, lymphoid	1 (2%)		
Intestine small, jejunum	(47)	(19)	(44)
Hyperplasia, lymphoid	1 (2%)		
Liver	(49)	(28)	(50)
Cyst		1 (4%)	
Degeneration, fatty			1 (2%)
Hematopoietic cell proliferation	2 (4%)		8 (16%)
Hepatodiaphragmatic nodule	1 (2%)		
Infarct		1 (4%)	
Inflammation, chronic		1 (4%)	
Inflammation, necrotizing		2 (7%)	1 (2%)
Leukocytosis			2 (4%)
Necrosis, coagulative	5 (10%)	4 (14%)	2 (4%)
Thrombus		1 (4%)	
Mesentery	(41)	(19)	(48)
Inflammation, chronic active	1 (2%)		2 (4%)
Thrombus			1 (2%)
Pancreas	(48)	(20)	(49)
Cyst			1 (2%)
Inflammation, chronic active		1 (5%)	
Acinus, atrophy	1 (2%)	2 (10%)	2 (4%)
Acinus, hyperplasia	2 (4%)		
Duct, ectasia			1 (2%)
Salivary glands	(49)	(21)	(50)
Inflammation, chronic active	1 (2%)		
Stomach, forestomach	(47)	(47)	(50)
Acanthosis		4 (9%)	20 (40%)
Acanthosis, focal	2 (4%)		
Cyst			1 (2%)
Hyperkeratosis		1 (2%)	23 (46%)
Hyperkeratosis, focal	1 (2%)		
Hyperplasia, focal	2 (4%)	7 (15%)	11 (22%)
Inflammation, chronic active			5 (10%)
Stomach, glandular	(47)	(20)	(50)
Cyst	1 (2%)		5 (10%)
Diverticulum	1 (2%)		
Dysplasia	1 (2%)		
Tooth	(50)	(20)	(50)
Dysplasia	8 (16%)	1 (5%)	3 (6%)
Inflammation, chronic active	2 (4%)		6 (12%)
CARDIOVASCULAR SYSTEM			
Heart	(49)	(21)	(50)
Cardiomyopathy, chronic	1 (2%)		
Inflammation, chronic active		1 (5%)	
Valve, bacterium		1 (5%)	

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

	Vehicle Control	Low Dose	High Dose
CARDIOVASCULAR SYSTEM			
Heart (Continued)	(49)	(21)	(50)
Valve, inflammation, chronic active		1 (5%)	
Valve, thrombus		1 (5%)	
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(21)	(50)
Accessory adrenal cortical nodule			1 (2%)
Cyst			2 (4%)
Degeneration, fatty			1 (2%)
Hematopoietic cell proliferation			1 (2%)
Hyperplasia	1 (2%)		1 (2%)
Hypertrophy			3 (6%)
Adrenal gland, medulla	(50)	(21)	(50)
Hyperplasia	5 (10%)	1 (5%)	4 (8%)
Islets, pancreatic	(48)	(19)	(49)
Hyperplasia			1 (2%)
Parathyroid gland	(41)	(19)	(45)
Cyst	3 (7%)		1 (2%)
Pituitary gland	(46)	(20)	(41)
Pars distalis, cyst	2 (4%)		1 (2%)
Thyroid gland	(49)	(22)	(50)
Follicle, cyst	1 (2%)	1 (5%)	2 (4%)
Follicular cell, hyperplasia	7 (14%)	1 (5%)	3 (6%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Coagulating gland	(45)	(20)	(49)
Hyperplasia			1 (2%)
Penis	(2)	(4)	(1)
Hemorrhage		1 (25%)	
Preputial gland	(6)	(6)	(3)
Inflammation, chronic active		2 (33%)	1 (33%)
Duct, dilatation	4 (67%)	2 (33%)	2 (67%)
Prostate	(48)	(21)	(49)
Inflammation, chronic active		1 (5%)	3 (6%)
Seminal vesicle	(43)	(20)	(46)
Inflammation, chronic active		1 (5%)	1 (2%)
Testes	(50)	(21)	(50)
Inflammation, necrotizing	1 (2%)		
Mineralization	1 (2%)		
Germinal epithelium, degeneration		1 (5%)	
Seminiferous tubule, atrophy			1 (2%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(21)	(50)
Femoral, hyperplasia		5 (24%)	6 (12%)
Lymph node	(50)	(24)	(49)
Axillary, hyperplasia, plasma cell		1 (4%)	1 (2%)
Inguinal, hyperplasia, plasma cell		1 (4%)	
Lumbar, hyperplasia, plasma cell		1 (4%)	
Mediastinal, inflammation, suppurative			1 (2%)
Mesenteric, angiectasis	10 (20%)	6 (25%)	17 (35%)
Mesenteric, cyst		1 (4%)	
Mesenteric, hematopoietic cell proliferation	12 (24%)	5 (21%)	17 (35%)
Mesenteric, hyperplasia, lymphoid	1 (2%)		
Mesenteric, thrombus		1 (4%)	

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

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
Lymph node, mandibular	(48)	(20)	(49)
Hyperplasia, lymphoid			1 (2%)
Hyperplasia, plasma cell			3 (6%)
Inflammation, chronic active		1 (5%)	
Pigmentation, hemosiderin			2 (4%)
Spleen	(49)	(26)	(50)
Hematopoietic cell proliferation	23 (47%)	10 (38%)	23 (46%)
Thymus	(27)	(12)	(24)
Cyst	1 (4%)	2 (17%)	1 (4%)
Necrosis		1 (8%)	
INTEGUMENTARY SYSTEM			
Skin	(50)	(33)	(49)
Alopecia	1 (2%)		3 (6%)
Fibrosis	3 (6%)		2 (4%)
Hyperkeratosis		1 (3%)	
Inflammation, chronic active	9 (18%)	6 (18%)	8 (16%)
Metaplasia, osseous		1 (3%)	
Necrosis, coagulative		1 (3%)	
Parasite external	1 (2%)		3 (6%)
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(30)	(50)
Joint, femur, tibia, metaplasia, osseous		1 (3%)	
Joint, tarsal, metaplasia, osseous	23 (46%)	15 (50%)	22 (44%)
NERVOUS SYSTEM			
Brain	(49)	(21)	(50)
Compression		1 (5%)	
RESPIRATORY SYSTEM			
Lung	(49)	(25)	(50)
Edema, acute	1 (2%)		
Hemorrhage, acute	1 (2%)		
Inflammation, chronic active	2 (4%)		
Leukocytosis		2 (8%)	1 (2%)
Thrombus			1 (2%)
Alveolar epithelium, hyperplasia	6 (12%)		
Nose	(49)	(21)	(50)
Inflammation, suppurative	1 (2%)	1 (5%)	
Nasolacrimal duct, inflammation, suppurative	2 (4%)	2 (10%)	2 (4%)
SPECIAL SENSES SYSTEM			
Eye	(1)	(1)	
Atrophy	1 (100%)		
Lens, cataract		1 (100%)	
Harderian gland	(48)	(25)	(48)
Hyperplasia	1 (2%)	1 (4%)	
Inflammation, chronic active		1 (4%)	

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

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
Kidney	(50)	(23)	(50)
Cyst	1 (2%)		1 (2%)
Glomerulosclerosis	1 (2%)		
Hydronephrosis	1 (2%)	5 (22%)	1 (2%)
Infarct	1 (2%)	1 (4%)	1 (2%)
Inflammation, chronic active		1 (4%)	
Inflammation, suppurative		1 (4%)	1 (2%)
Mineralization		2 (9%)	3 (6%)
Necrosis, coagulative	1 (2%)		1 (2%)
Nephropathy, chronic	27 (54%)	4 (17%)	24 (48%)
Artery, necrosis, fibrinoid		1 (4%)	
Ureter	(41)	(21)	(43)
Dilatation		1 (5%)	
Urethra	(23)	(15)	(29)
Inflammation, suppurative		1 (7%)	
Urinary bladder	(47)	(21)	(48)
Dilatation		5 (24%)	1 (2%)
Inflammation, chronic active		1 (5%)	1 (2%)

APPENDIX D

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

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	60	60	60
Animals removed	60	60	60
Animals examined histopathologically	50	49	50
ALIMENTARY SYSTEM			
Esophagus	(50)	*(49)	(50)
Lymphoma malignant lymphocytic	1 (2%)		
Gallbladder	(44)	*(49)	(45)
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant lymphocytic		1 (2%)	1 (2%)
Lymphoma malignant mixed			1 (2%)
Intestine large, cecum	(46)	*(49)	(48)
Leiomyoma			1 (2%)
Lymphoma malignant lymphocytic			1 (2%)
Intestine small, duodenum	(46)	*(49)	(45)
Polyp adenomatous			1 (2%)
Intestine small, jejunum	(48)	*(49)	(45)
Lymphoma malignant histiocytic	1 (2%)		
Lymphoma malignant lymphocytic	1 (2%)	1 (2%)	
Lymphoma malignant mixed		1 (2%)	
Liver	(50)	*(49)	(50)
Choriocarcinoma, metastatic, ovary			1 (2%)
Hemangioma		1 (2%)	
Hemangiosarcoma	1 (2%)		
Hepatocellular carcinoma	2 (4%)		1 (2%)
Hepatocellular carcinoma, multiple		2 (4%)	
Hepatocellular adenoma	7 (14%)	3 (6%)	4 (8%)
Histiocytic sarcoma	1 (2%)		
Ito cell tumor, NOS			1 (2%)
Lymphoma malignant histiocytic	5 (10%)	2 (4%)	3 (6%)
Lymphoma malignant lymphocytic	2 (4%)	4 (8%)	4 (8%)
Lymphoma malignant			1 (2%)
Lymphoma malignant mixed			4 (8%)
Mesentery	*(50)	*(49)	*(50)
Lymphoma malignant histiocytic	1 (2%)		1 (2%)
Lymphoma malignant lymphocytic	2 (4%)	4 (8%)	4 (8%)
Lymphoma malignant			1 (2%)
Lymphoma malignant mixed			1 (2%)
Pancreas	(49)	*(49)	(49)
Lymphoma malignant histiocytic	4 (8%)	1 (2%)	1 (2%)
Lymphoma malignant lymphocytic	1 (2%)	3 (6%)	2 (4%)
Lymphoma malignant mixed			4 (8%)
Salivary glands	(48)	*(49)	(49)
Lymphoma malignant histiocytic	3 (6%)	1 (2%)	1 (2%)
Lymphoma malignant lymphocytic		3 (6%)	3 (6%)
Lymphoma malignant mixed			2 (4%)
Stomach, forestomach	(49)	(48)	(48)
Lymphoma malignant histiocytic		1 (2%)	
Lymphoma malignant lymphocytic		1 (2%)	2 (4%)
Lymphoma malignant mixed			1 (2%)
Papilloma squamous	3 (6%)	3 (6%)	1 (2%)
Stomach, glandular	(49)	(12)	(48)
Adenoma		1 (8%)	
Lymphoma malignant lymphocytic		1 (8%)	3 (6%)
Lymphoma malignant mixed			1 (2%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	*(49)	(50)
Histiocytic sarcoma	1 (2%)		
Lymphoma malignant lymphocytic		3 (6%)	4 (8%)

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	*(49)	(50)
Lymphoma malignant histiocytic	1 (2%)	1 (2%)	1 (2%)
Lymphoma malignant lymphocytic		2 (4%)	1 (2%)
Capsule, adenoma			1 (2%)
Adrenal gland, medulla	(49)	*(49)	(50)
Lymphoma malignant lymphocytic			1 (2%)
Pheochromocytoma benign	1 (2%)		1 (2%)
Pituitary gland	(47)	*(49)	(45)
Lymphoma malignant lymphocytic		1 (2%)	
Pars distalis, adenoma	6 (13%)	4 (8%)	6 (13%)
Thyroid gland	(50)	*(49)	(47)
Lymphoma malignant lymphocytic		1 (2%)	1 (2%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Ovary	(49)	*(49)	(50)
Cystadenoma		1 (2%)	1 (2%)
Granulosa theca tumor benign	1 (2%)		
Lymphoma malignant histiocytic	1 (2%)	1 (2%)	1 (2%)
Lymphoma malignant lymphocytic	2 (4%)	3 (6%)	3 (6%)
Lymphoma malignant			2 (4%)
Mixed tumor benign			1 (2%)
Yolk sac carcinoma			1 (2%)
Uterus	(50)	*(49)	(50)
Histiocytic sarcoma			1 (2%)
Lymphoma malignant histiocytic	1 (2%)	1 (2%)	1 (2%)
Lymphoma malignant lymphocytic		1 (2%)	1 (2%)
Polyp stromal	3 (6%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	*(49)	(50)
Hemangiosarcoma	1 (2%)		
Lymphoma malignant lymphocytic		1 (2%)	
Femoral, hemangiosarcoma	1 (2%)		
Femoral, histiocytic sarcoma	1 (2%)		
Femoral, lymphoma malignant histiocytic	1 (2%)		
Femoral, lymphoma malignant lymphocytic			2 (4%)
Femoral, lymphoma malignant mixed			1 (2%)
Lymph node	(50)	*(49)	(50)
Lymphoma malignant lymphocytic		1 (2%)	
Axillary, lymphoma malignant lymphocytic		1 (2%)	
Deep cervical, lymphoma malignant histiocytic	1 (2%)	1 (2%)	
Deep cervical, lymphoma malignant lymphocytic		1 (2%)	
Inguinal, lymphoma malignant histiocytic	2 (4%)		
Lumbar, lymphoma malignant histiocytic	1 (2%)	2 (4%)	1 (2%)
Lumbar, lymphoma malignant lymphocytic	1 (2%)	2 (4%)	1 (2%)
Lumbar, lymphoma malignant			1 (2%)
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Mediastinal, histiocytic sarcoma	1 (2%)		
Mediastinal, lymphoma malignant histiocytic	3 (6%)	1 (2%)	1 (2%)
Mediastinal, lymphoma malignant lymphocytic	2 (4%)	4 (8%)	3 (6%)
Mediastinal, lymphoma malignant mixed			2 (4%)
Mediastinal, osteosarcoma, metastatic, skin		1 (2%)	

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

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
Lymph node (Continued)	(50)	*(49)	(50)
Mediastinal, mesenteric, fibrosarcoma, metastatic, skin			1 (2%)
Mesenteric, lymphoma malignant histiocytic	4 (8%)	2 (4%)	1 (2%)
Mesenteric, lymphoma malignant lymphocytic	2 (4%)	4 (8%)	3 (6%)
Mesenteric, lymphoma malignant			1 (2%)
Mesenteric, lymphoma malignant mixed		1 (2%)	1 (2%)
Pancreatic, lymphoma malignant histiocytic	4 (8%)	1 (2%)	
Pancreatic, lymphoma malignant lymphocytic		2 (4%)	1 (2%)
Pancreatic, lymphoma malignant mixed			1 (2%)
Renal, lymphoma malignant histiocytic	1 (2%)	2 (4%)	1 (2%)
Renal, lymphoma malignant lymphocytic	2 (4%)	1 (2%)	2 (4%)
Renal, lymphoma malignant			2 (4%)
Renal, lymphoma malignant mixed			1 (2%)
Lymph node, mandibular	(48)	*(49)	(49)
Lymphoma malignant histiocytic	5 (10%)	2 (4%)	2 (4%)
Lymphoma malignant lymphocytic	2 (4%)	4 (8%)	3 (6%)
Lymphoma malignant			1 (2%)
Lymphoma malignant mixed			5 (10%)
Spleen	(50)	*(49)	(50)
Hemangiosarcoma	1 (2%)	1 (2%)	
Histiocytic sarcoma	1 (2%)		
Lymphoma malignant histiocytic	10 (20%)	3 (6%)	3 (6%)
Lymphoma malignant lymphocytic	4 (8%)	6 (12%)	5 (10%)
Lymphoma malignant			2 (4%)
Lymphoma malignant mixed		2 (4%)	6 (12%)
Thymus	(31)	*(49)	(31)
Histiocytic sarcoma	1 (3%)		
Lymphoma malignant histiocytic	1 (3%)		
Lymphoma malignant lymphocytic		4 (8%)	3 (10%)
Lymphoma malignant mixed			3 (10%)
INTEGUMENTARY SYSTEM			
Mammary gland	(44)	*(49)	(40)
Adenocarcinoma	1 (2%)		2 (5%)
Adenoma			1 (3%)
Skin	(50)	*(49)	(49)
Basosquamous tumor malignant			1 (2%)
Lymphoma malignant histiocytic		1 (2%)	
Lymphoma malignant lymphocytic		2 (4%)	1 (2%)
Subcutaneous tissue, fibrosarcoma	1 (2%)	3 (6%)	2 (4%)
Subcutaneous tissue, osteosarcoma, metastatic, bone		1 (2%)	
MUSCULOSKELETAL SYSTEM			
Bone	(50)	*(49)	(50)
Osteosarcoma		1 (2%)	
Skeletal muscle	*(50)	*(49)	*(50)
Fibrosarcoma, metastatic, skin		1 (2%)	
Lymphoma malignant histiocytic		1 (2%)	
Lymphoma malignant lymphocytic	2 (4%)	2 (4%)	3 (6%)
Lymphoma malignant mixed			1 (2%)
NERVOUS SYSTEM			
Brain	(50)	*(49)	(50)
Lymphoma malignant histiocytic	2 (4%)		1 (2%)
Lymphoma malignant lymphocytic	1 (2%)	1 (2%)	2 (4%)

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

	Vehicle Control	Low Dose	High Dose
RESPIRATORY SYSTEM			
Lung	(50)	*(49)	(50)
Alveolar/bronchiolar adenoma	3 (6%)	1 (2%)	3 (6%)
Alveolar/bronchiolar adenoma, multiple			1 (2%)
Alveolar/bronchiolar carcinoma	1 (2%)		1 (2%)
Basosquamous tumor malignant, metastatic, skin			1 (2%)
Choriocarcinoma, metastatic, ovary			1 (2%)
Histiocytic sarcoma	1 (2%)		
Lymphoma malignant histiocytic	4 (8%)	1 (2%)	2 (4%)
Lymphoma malignant lymphocytic	2 (4%)	4 (8%)	5 (10%)
Lymphoma malignant			1 (2%)
Lymphoma malignant mixed			3 (6%)
Osteosarcoma, metastatic, bone		1 (2%)	
Mediastinum, alveolar/bronchiolar carcinoma			1 (2%)
Nose	(50)	*(49)	(50)
Lymphoma malignant lymphocytic			1 (2%)
Trachea	(49)	*(49)	(50)
Lymphoma malignant lymphocytic		1 (2%)	
SPECIAL SENSES SYSTEM			
Harderian gland	(48)	*(49)	(50)
Adenoma	2 (4%)		1 (2%)
Carcinoma			1 (2%)
Lymphoma malignant lymphocytic		1 (2%)	2 (4%)
URINARY SYSTEM			
Kidney	(50)	*(49)	(50)
Lymphoma malignant histiocytic	5 (10%)	1 (2%)	2 (4%)
Lymphoma malignant lymphocytic	1 (2%)	4 (8%)	4 (8%)
Lymphoma malignant			1 (2%)
Lymphoma malignant mixed			4 (8%)
Urinary bladder	(49)	*(49)	(49)
Lymphoma malignant histiocytic	1 (2%)	1 (2%)	
Lymphoma malignant lymphocytic		2 (4%)	4 (8%)
Lymphoma malignant mixed			2 (4%)
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(49)	*(50)
Hemangiosarcoma	3 (6%)	1 (2%)	
Lymphoma malignant lymphocytic	4 (8%)	6 (12%)	5 (10%)
Lymphoma malignant histiocytic	10 (20%)	3 (6%)	5 (10%)
Lymphoma malignant mixed		3 (6%)	6 (12%)
Hemangioma		1 (2%)	
Lymphoma malignant			2 (4%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	60	60	60
Terminal sacrifice	36	35	34
Moribund	7	5	9
Dead	7	9	7
Scheduled sacrifice	10	10	10
Missing		1	

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

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary neoplasms **	32	26	33
Total primary neoplasms	55	34	53
Total animals with benign neoplasms	20	13	17
Total benign neoplasms	26	15	23
Total animals with malignant neoplasms	18	18	22
Total malignant neoplasms	29	19	29
Total animals with secondary neoplasms ***		2	4
Total secondary neoplasms		4	5
Total animals with neoplasms--uncertain benign or malignant			1
Total uncertain neoplasms			1

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
*** 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 DIMETHOXANE: VEHICLE CONTROL

WEEKS ON STUDY	059	066	077	082	084	086	086	087	090	090	091	100	104	104	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	194	225	142	211	143	132	214	144	155	152	204	175	222	135	131	133	134	141	145	151	153	154	161	162	163
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic					X																				
Gallbladder	+	A	A	+	A	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	A	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Intestine small, ileum	+	A	+	A	M	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic									X																
Lymphoma malignant lymphocytic														X											
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma		X																							
Hepatocellular adenoma																X					X				
Histiocytic sarcoma	X																								
Lymphoma malignant histiocytic				X			X		X																
Lymphoma malignant lymphocytic					X																				
Mesentery	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+	+	+	+
Lymphoma malignant histiocytic									X																
Lymphoma malignant lymphocytic					X									X											
Pancreas	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic									X																
Lymphoma malignant lymphocytic					X																				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic							X		X																
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous												X													
Stomach, glandular	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Blood vessel		+	+	+	+		+	+	+	+		+	+	+	+	+	+	+	+		+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																								
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic									X																
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Pheochromocytoma benign																									
Islets, pancreatic	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma										X									X					X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
Tissue, NOS									+				+												
GENITAL SYSTEM																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa theca tumor benign																		X							
Lymphoma malignant histiocytic									X																
Lymphoma malignant lymphocytic					X									X											
Oviduct	+	+	+	+	+	+	+	+	+	+	+			+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic									X																
Polyp stromal											X														

+: Tissue examined microscopically
: Not examined
−: Present but not examined microscopically
I: Insufficient tissue

M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	164	165	171	172	173	174	181	182	183	184	185	191	192	193	195	201	202	203	205	212	213	215	221	223	224	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	44
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma											X															1
Hepatocellular carcinoma												X														2
Hepatocellular adenoma	X											X					X	X							X	7
Histiocytic sarcoma																										1
Lymphoma malignant histiocytic					X							X														5
Lymphoma malignant lymphocytic			X																							2
Mesentery	+	+	+	+	+	+	+				+	+	+		+	+	+	+	+	+	+	+	+	+	+	41
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant histiocytic												X	X		X											4
Lymphoma malignant lymphocytic																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	48
Lymphoma malignant histiocytic												X														3
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma squamous													X								X					3
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign					X																					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	47
Pars distalis, adenoma													X	X		X										6
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GENERAL BODY SYSTEM																										
Tissue, NOS																									+	3
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granulosa theca tumor benign																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										2
Oviduct	+	+	+	+	+		+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	46
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Polyp stromal																		X							X	3

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

WEEKS ON STUDY	059	066	077	082	084	088	086	087	090	090	091	100	104	104	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	194	225	142	211	143	132	214	144	155	152	204	175	222	135	131	133	134	141	145	151	153	154	161	162	163
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma						X																			
Femoral, hemangiosarcoma						X																			
Femoral, histiocytic sarcoma	X																								
Femoral, lymphoma malignant histiocytic				X																					
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Deep cervical, lymphoma malignant histiocytic									X																
Inguinal, lymphoma malignant histiocytic									X																
Lumbar, lymphoma malignant histiocytic									X																
Lumbar, lymphoma malignant lymphocytic					X																				
Mediastinal, histiocytic sarcoma	X																								
Mediastinal, lymphoma malignant histiocytic									X																
Mediastinal, lymphoma malignant lymphocytic					X									X											
Mesenteric, lymphoma malignant histiocytic									X																
Mesenteric, lymphoma malignant lymphocytic					X					X															
Pancreatic, lymphoma malignant histiocytic							X		X																
Renal, lymphoma malignant histiocytic																									
Renal, lymphoma malignant lymphocytic					X									X											
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic				X			X		X																
Lymphoma malignant lymphocytic					X					X															
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma	X																								
Lymphoma malignant histiocytic				X			X		X																
Lymphoma malignant lymphocytic					X					X				X											
Thymus	+	M	+	M	M	+	+	+	M	M	+	+	M	+	M	+	M	+	M	+	+	+	+	+	M
Histiocytic sarcoma	X																								
Lymphoma malignant histiocytic							X																		
INTEGUMENTARY SYSTEM																									
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M
Adenocarcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma							X																		
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic					X																				
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic									X																
Lymphoma malignant lymphocytic					X																				
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Histiocytic sarcoma	X																								
Lymphoma malignant histiocytic				X					X																
Lymphoma malignant lymphocytic					X																				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear													+												
Eye																									
Harderian gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Adenoma																					X				
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic							X		X																
Lymphoma malignant lymphocytic					X																				
Ureter	+		+			+	+			+	+	+		+		+		+		+		+			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic									X																

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	164	165	171	172	173	174	181	182	183	184	185	191	192	193	195	201	202	203	205	212	213	215	221	223	224	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Femoral, hemangiosarcoma																										1
Femoral, histiocytic sarcoma																										1
Femoral, lymphoma malignant histiocytic																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Deep cervical, lymphoma malignant histiocytic																										1
Inguinal, lymphoma malignant histiocytic					X																					2
Lumbar, lymphoma malig. histiocytic																										1
Lumbar, lymphoma malig. lymphocytic																										1
Mediastinal, histiocytic sarcoma																										1
Mediastinal, lymphoma malignant histiocytic					X							X														3
Mediastinal, lymphoma malignant lymphocytic																										2
Mesenteric, lymphoma malignant histiocytic					X							X	X													4
Mesenteric, lymphoma malignant lymphocytic																										2
Pancreatic, lymphoma malignant histiocytic										X		X														4
Renal, lymphoma malignant histiocytic												X														1
Renal, lymphoma malig lymphocytic																										2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	48
Lymphoma malignant histiocytic					X							X														5
Lymphoma malignant lymphocytic																										2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma				X																						1
Histiocytic sarcoma																										1
Lymphoma malignant histiocytic					X					X	X	X	X		X									X		10
Lymphoma malignant lymphocytic			X																							4
Thymus	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	M	M	M	M	M	M	+	+	M	+	31
Histiocytic sarcoma																										1
Lymphoma malignant histiocytic																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenocarcinoma											X															1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic			X																							2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic											X															2
Lymphoma malignant lymphocytic																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X						X											X					3
Alveolar/bronchiolar carcinoma					X																					1
Histiocytic sarcoma																										1
Lymphoma malignant histiocytic					X								X													4
Lymphoma malignant lymphocytic			X																							2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Ear																										1
Eye															+											1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																					X					2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic											X	X	X													5
Lymphoma malignant lymphocytic																										1
Ureter					+		+				+		+													16
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Lymphoma malignant histiocytic																										1

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

WEEKS ON STUDY	003	048	065	086	086	088	089	089	091	092	095	098	099	102	102	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	405	461	385	463	384	464	443	392	445	372	381	393	452	412	444	371	373	374	375	382	383	391	394	395	395	401
ALIMENTARY SYSTEM																											
Esophagus		+	+	+	+	+	+	+	+	+	+	+	+	+	+												
Gallbladder		A	A	A	+	+	A	A	+	A	+	M	+	A	+												
Lymphoma malignant lymphocytic															X												
Intestine large		+	+	+	+	+	+	+	+	+	+	+	+	A	+												
Intestine large, cecum		M	+	+	+	+	+	M	+	A	+	+	+	A	+												
Intestine large, colon		A	+	+	+	+	+	+	+	+	+	+	+	A	+												
Intestine large, rectum		M	+	+	+	+	+	+	+	+	+	A	+	A	+												
Intestine small		+	+	+	+	+	+	+	+	+	+	+	+	A	+								+				
Intestine small, duodenum		A	A	+	+	+	A	A	+	+	+	A	+	A	+												
Intestine small, ileum		M	+	+	+	+	A	+	+	A	+	+	+	A	+												
Intestine small, jejunum		M	+	+	+	+	+	+	+	+	+	+	+	A	+								+				
Lymphoma malignant lymphocytic													X														
Lymphoma malignant mixed																							X				
Liver		+	+	+	+	+	+	+	+	+	+	+	+	+	+		+										+
Hemangioma																											
Hepatocellular carcinoma, multiple							X										X										
Hepatocellular adenoma												X															
Lymphoma malignant histiocytic											X																X
Lymphoma malignant lymphocytic								X					X	X	X												
Mesentery				+	+	+	+	+	+	+	+		+	+	+												
Lymphoma malignant lymphocytic							X	X						X	X												
Pancreas		A	+	+	+	+	+	+	+	+	+	+	+	+	+					+			+				
Lymphoma malignant histiocytic											X																
Lymphoma malignant lymphocytic								X						X	X												
Salivary glands		M	+	+	+	+	+	+	+	+	+	+	+	+	+												
Lymphoma malignant histiocytic											X																
Lymphoma malignant lymphocytic								X						X	X												
Stomach		A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach		A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic											X																
Lymphoma malignant lymphocytic															X												
Papilloma squamous																				X			X				
Stomach, glandular		A	+	+	+	+	+	+	+	+	+	+	+	A	+												
Adenoma											X																
Lymphoma malignant lymphocytic															X												
Tooth		+	+	+	+	+	+	+	+	+	+	+	+	+	+												
CARDIOVASCULAR SYSTEM																											
Blood vessel		+		+	+	+	+		+	+	+	+	+	+													
Heart		+	+	+	+	+	+	+	+	+	+	+	+	+	+												
Lymphoma malignant lymphocytic							X	X							X												
ENDOCRINE SYSTEM																											
Adrenal gland		+	+	+	+	+	+	+	+	+	+	+	+	+	+												
Adrenal gland, cortex		+	+	+	+	+	+	+	+	+	+	+	+	+	+												
Lymphoma malignant histiocytic											X																
Lymphoma malignant lymphocytic								X							X												
Adrenal gland, medulla		+	+	+	+	+	+	+	+	+	+	+	+	+	+												
Islets, pancreatic		A	+	+	+	+	+	+	+	+	+	+	+	+	+												
Parathyroid gland		M	+	M	+	+	+	+	+	+	+	+	+	+	M												
Pituitary gland		+	+	+	+	+	+	+	+	+	+	+	+	M	+			+		+			+	M			
Lymphoma malignant lymphocytic															X												
Pars distalis, adenoma																		X		X							
Thyroid gland		+	+	+	+	+	+	+	+	+	+	+	+	+	+												
Lymphoma malignant lymphocytic															X												
GENERAL BODY SYSTEM																											
None																											
GENITAL SYSTEM																											
Ovary		+	+	+	+	+	+	+	+	M	+	+	+	+	+	+				+		+					
Cystadenoma																											
Lymphoma malignant histiocytic											X																
Lymphoma malignant lymphocytic								X						X	X												
Oviduct		+	+	+	+		+	+	+	+	+	+	+	+	+												
Uterus		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				+	+	+	+	+	+		
Lymphoma malignant histiocytic											X																
Lymphoma malignant lymphocytic															X												
Polyp stromal																											

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL.
CARCASS ID	403	402	404	411	413	414	415	421	422	423	424	425	431	432	433	434	435	441	442	451	453	454	455	462	465		TISSUES TUMORS
ALIMENTARY SYSTEM																											
Esophagus																											14
Gallbladder																											6
Lymphoma malignant lymphocytic																											1
Intestine large																											13
Intestine large, cecum																											10
Intestine large, colon																											12
Intestine large, rectum																											11
Intestine small																											14
Intestine small, duodenum																											8
Intestine small, ileum																											10
Intestine small, jejunum																											13
Lymphoma malignant lymphocytic																											1
Lymphoma malignant mixed																											1
Liver							+														+		+				19
Hemangioma																					X						1
Hepatocellular carcinoma, multiple																											2
Hepatocellular adenoma							X																X				3
Lymphoma malignant histiocytic																											2
Lymphoma malignant lymphocytic																											4
Mesentery																											11
Lymphoma malignant lymphocytic																											4
Pancreas																											15
Lymphoma malignant histiocytic																											1
Lymphoma malignant lymphocytic																											3
Salivary glands																											13
Lymphoma malignant histiocytic																											1
Lymphoma malignant lymphocytic																											3
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Lymphoma malignant histiocytic																											1
Lymphoma malignant lymphocytic																											1
Papilloma squamous																					X						3
Stomach, glandular																											12
Adenoma																											1
Lymphoma malignant lymphocytic																											1
Tooth																											14
CARDIOVASCULAR SYSTEM																											
Blood vessel																											11
Heart																											14
Lymphoma malignant lymphocytic																											3
ENDOCRINE SYSTEM																											
Adrenal gland																											14
Adrenal gland, cortex																											14
Lymphoma malignant histiocytic																											1
Lymphoma malignant lymphocytic																											2
Adrenal gland, medulla																											14
Islets, pancreatic																											13
Parathyroid gland																											11
Pituitary gland										+	+	+															19
Lymphoma malignant lymphocytic																											1
Pars distalis, adenoma										X	X																4
Thyroid gland																											14
Lymphoma malignant lymphocytic																											1
GENERAL BODY SYSTEM																											
None																											
GENITAL SYSTEM																											
Ovary						+				+	+			+								+					21
Cystadenoma											X																1
Lymphoma malignant histiocytic																											1
Lymphoma malignant lymphocytic																											3
Oviduct																											13
Uterus		+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+		+	+	+	+	+		43
Lymphoma malignant histiocytic																											1
Lymphoma malignant lymphocytic																											1
Polyp stromal		X																									1

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

WEEKS ON STUDY	003	048	065	086	086	088	089	089	091	092	095	098	099	102	102	105	105	105	105	105	105	105	105	105	105
CARCASS ID	405	461	385	463	384	464	443	392	445	372	381	393	452	412	444	371	733	744	755	822	833	391	944	955	401
HEMATOPOIETIC SYSTEM																									
Bone marrow		+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Lymphoma malignant lymphocytic															X										
Lymph node		M	+	+	+	M	+	+	+	+	+	+	+	+	+							+			+
Lymphoma malignant lymphocytic							X																		
Axillary, lymphoma malignant lymphocytic															X										
Deep cervical, lymphoma malignant histiocytic											X														
Deep cervical, lymphoma malignant lymphocytic															X										
Lumbar, lymphoma malignant histiocytic											X														X
Lumbar, lymphoma malignant lymphocytic								X							X										
Mediastinal, lymphoma malignant histiocytic											X														
Mediastinal, lymphoma malignant lymphocytic								X					X	X	X										
Mediastinal, osteosarcoma, metastatic, skin			X																						
Mesenteric, lymphoma malignant histiocytic											X														X
Mesenteric, lymphoma malignant lymphocytic								X					X	X	X										
Mesenteric, lymphoma malignant mixed																						X			
Pancreatic, lymphoma malignant histiocytic											X														
Pancreatic, lymphoma malignant lymphocytic								X					X												
Renal, lymphoma malignant histiocytic											X														X
Renal, lymphoma malignant lymphocytic															X										
Lymph node, mandibular		M	+	+	+	M	+	+	+	+	+	+	+	+	+										+
Lymphoma malignant histiocytic											X														X
Lymphoma malignant lymphocytic								X					X	X	X										
Spleen		+	+	+	+	+	+	+	+	+	+	+	+	+	+								+		+
Hemangiosarcoma																									
Lymphoma malignant histiocytic											X														X
Lymphoma malignant lymphocytic							X	X					X	X	X										
Lymphoma malignant mixed																									
Thymus		M	+	M	M	M	+	+	M	+	+	+	+	+	+										
Lymphoma malignant lymphocytic							X	X						X	X										
INTEGUMENTARY SYSTEM																									
Mammary gland		M	M	+	+	M	+	M	+	+	+	+	+	+	+										
Skin		M	+	+	+	+	+	+	+	+	+	+	+	+	+								+		
Lymphoma malignant histiocytic											X														
Lymphoma malignant lymphocytic								X							X										
Subcutaneous tissue, fibrosarcoma				X						X													X		
Subcutaneous tissue, osteosarcoma, metastatic, bone			X																						
MUSCULOSKELETAL SYSTEM																									
Bone		+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Osteosarcoma			X																						
Skeletal muscle			+	+	+	+	+	+	+	+	+	+	+	+	+										
Fibrosarcoma, metastatic, skin										X															
Lymphoma malignant histiocytic											X														
Lymphoma malignant lymphocytic							X								X										
NERVOUS SYSTEM																									
Brain		+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Lymphoma malignant lymphocytic															X										
RESPIRATORY SYSTEM																									
Lung		+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Alveolar/bronchiolar adenoma								X																	
Lymphoma malignant histiocytic											X														
Lymphoma malignant lymphocytic							X	X						X	X										
Osteosarcoma, metastatic, bone			X																						
Nose		+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Trachea		+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Lymphoma malignant lymphocytic															X										
SPECIAL SENSES SYSTEM																									
Harderian gland		+	+	+	M	M	+	M	+	+	+	+	+	+	+										
Lymphoma malignant lymphocytic															X										
URINARY SYSTEM																									
Kidney		+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Lymphoma malignant histiocytic											X														
Lymphoma malignant lymphocytic							X	X						X	X										
Ureter						+					+		+	+											
Urinary bladder		A	+	+	+	+	+	+	+	+	+	+	+	A	+										
Lymphoma malignant histiocytic											X														
Lymphoma malignant lymphocytic								X							X										

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	403	402	404	411	413	414	415	421	422	423	424	425	431	432	433	434	435	441	442	451	453	454	455	462	465	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow																										14
Lymphoma malignant lymphocytic																										1
Lymph node										+										+						16
Lymphoma malignant lymphocytic																										1
Axillary, lymphoma malignant lymphocytic																										1
Deep cervical, lymphoma malignant histiocytic																										1
Deep cervical, lymphoma malignant lymphocytic																										1
Lumbar, lymphoma malig histiocytic																										2
Lumbar, lymphoma malig. lymphocytic																										2
Mediastinal, lymphoma malignant histiocytic																										1
Mediastinal, lymphoma malignant lymphocytic																										4
Mediastinal, osteosarcoma, metastatic, skin																										1
Mesenteric, lymphoma malignant histiocytic																										2
Mesenteric, lymphoma malignant lymphocytic																										4
Mesenteric, lymphoma malignant mixed																										1
Pancreatic, lymphoma malignant histiocytic																										1
Pancreatic, lymphoma malignant lymphocytic																										2
Renal, lymphoma malignant histiocytic																										2
Renal, lymphoma malig lymphocytic																										1
Lymph node, mandibular																										13
Lymphoma malignant histiocytic																										2
Lymphoma malignant lymphocytic																										4
Spleen				+	+	+	+									+				+			+			23
Hemangiosarcoma																							X			1
Lymphoma malignant histiocytic				X																						3
Lymphoma malignant lymphocytic						X																				6
Lymphoma malignant mixed							X									X										2
Thymus																										9
Lymphoma malignant lymphocytic																										4
INTEGUMENTARY SYSTEM																										
Mammary gland																										10
Skin																										14
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										2
Subcutaneous tissue, fibrosarcoma																										3
Subcutaneous tissue, osteosarcoma, metastatic, bone																										1
MUSCULOSKELETAL SYSTEM																										
Bone																										14
Osteosarcoma																										1
Skeletal muscle																										13
Fibrosarcoma, metastatic, skin																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										2
NERVOUS SYSTEM																										
Brain																										14
Lymphoma malignant lymphocytic																										1
RESPIRATORY SYSTEM																										
Lung																										14
Alveolar/bronchiolar adenoma																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										4
Osteosarcoma, metastatic, bone																										1
Nose																										14
Trachea																										14
Lymphoma malignant lymphocytic																										1
SPECIAL SENSES SYSTEM																										
Harderian gland																										11
Lymphoma malignant lymphocytic																										1
URINARY SYSTEM																										
Kidney																										14
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										4
Ureter																										4
Urinary bladder																										12
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										2

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

WEEKS ON STUDY	028	041	068	071	073	084	091	093	094	094	094	097	098	099	099	102	105	105	105	105	105	105	105	105	105
CARCASS ID	625	624	664	635	683	675	695	684	682	685	663	703	702	612	691	705	611	613	614	615	621	622	623	631	632
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	M	+	+	+	+	+	+	+	+	A	+	+	A	+	A	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic						X																			
Lymphoma malignant lymphocytic			X																						
Lymphoma malignant mixed																									
Intestine large	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Leiomyoma																			X						
Lymphoma malignant lymphocytic			X																						
Intestine large, colon	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, rectum	M	+	+	+	+	+	+	+	M	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+
Polyp adenomatous																							X		
Intestine small, ileum	A	+	+	+	+	+	+	+	+	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	M	+	+	A	+	A	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Choriocarcinoma, metastatic, ovary		X																							
Hepatocellular carcinoma																									
Hepatocellular adenoma													X				X								
Ito cell tumor, NOS																									
Lymphoma malignant histiocytic						X																			
Lymphoma malignant lymphocytic			X				X		X				X												
Lymphoma malignant														X											
Lymphoma malignant mixed																									
Mesentery		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic						X																			
Lymphoma malignant lymphocytic			X				X		X				X												
Lymphoma malignant														X											
Lymphoma malignant mixed																									
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic						X																			
Lymphoma malignant lymphocytic			X						X																
Lymphoma malignant mixed																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic						X																			
Lymphoma malignant lymphocytic									X				X												
Lymphoma malignant mixed																									
Stomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic									X				X												
Lymphoma malignant mixed																									
Papilloma squamous																									
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic			X						X				X												
Lymphoma malignant mixed																									
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+		+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic			X				X		X				X												
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic						X																			
Lymphoma malignant lymphocytic			X																						
Capsule adenoma																		X							
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic			X																						
Pheochromocytoma benign																									
Islets, pancreatic	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	M	M	M	+	+	+	I	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma															X		X	X				X			
Thyroid gland	A	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic													X												
GENERAL BODY SYSTEM																									
Tissue NOS																+									
GENITAL SYSTEM																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Lymphoma malignant histiocytic						X																			
Lymphoma malignant lymphocytic			X						X				X												
Lymphoma malignant														X		X									
Mixed tumor benign																		X							
Yolk sac carcinoma		X																							
Oviduct	+			+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic			X																						

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	633	634	641	642	643	644	645	651	652	653	654	655	661	662	665	671	672	673	674	681	692	693	694	701	704	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																						X				1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leiomyoma																										1
Lymphoma malignant lymphocytic																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	45
Polyp adenomatous																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Choriocarcinoma, metastatic, ovary																										1
Hepatocellular carcinoma												X														1
Hepatocellular adenoma									X			X														4
Ito cell tumor, NOS																				X						1
Lymphoma malignant histiocytic				X	X																					3
Lymphoma malignant lymphocytic																										4
Lymphoma malignant																										1
Lymphoma malignant mixed						X	X	X										X								4
Mesentery	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										4
Lymphoma malignant																										1
Lymphoma malignant mixed																						X				1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										2
Lymphoma malignant mixed						X	X	X														X				4
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic														X												3
Lymphoma malignant mixed							X															X				2
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant lymphocytic																										2
Lymphoma malignant mixed							X																			1
Papilloma squamous	X																									1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant lymphocytic																										3
Lymphoma malignant mixed																						X				1
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+		+	+	+	45
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										4
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										1
Capsule, adenoma																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Pheochromocytoma benign																									X	1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Pars distalis, adenoma						X	X																			6
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	47
Lymphoma malignant lymphocytic																										1
GENERAL BODY SYSTEM																										
Tissue, NOS																					+					2
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma														X												1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										3
Lymphoma malignant																										2
Mixed tumor benign																										1
Yolk sac carcinoma																										1
Oviduct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma														X												1
Lymphoma malignant histiocytic														X												1
Lymphoma malignant lymphocytic																										1

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

WEEKS ON STUDY	028	041	068	071	073	084	091	093	094	094	094	097	098	099	099	102	105	105	105	105	105	105	105	105	105
CARCASS ID	625	624	664	635	683	675	695	684	682	685	663	703	702	612	691	705	611	613	614	615	621	622	623	631	632
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, lymphoma malignant lymphocytic			X										X												
Femoral, lymphoma malignant mixed																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lumbar, lymphoma malignant histiocytic						X																			
Lumbar, lymphoma malignant lymphocytic			X																						
Lumbar, lymphoma malignant																X									
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung							X																		
Mediastinal, lymphoma malignant histiocytic						X																			
Mediastinal, lymphoma malignant lymphocytic			X						X				X												
Mediastinal, lymphoma malignant mixed										X															
Mediastinal, mesenteric, fibrosarcoma, metastatic, skin													X												
Mesenteric, lymphoma malignant histiocytic						X																			
Mesenteric, lymphoma malignant lymphocytic			X						X				X												
Mesenteric, lymphoma malignant																X									
Mesenteric, lymphoma malignant mixed										X															
Pancreatic, lymphoma malignant lymphocytic									X																
Pancreatic, lymphoma malignant mixed										X															
Renal, lymphoma malignant histiocytic						X																			
Renal, lymphoma malignant lymphocytic			X						X																
Renal, lymphoma malignant														X		X									
Renal, lymphoma malignant mixed										X															
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic						X																			
Lymphoma malignant lymphocytic			X						X				X												
Lymphoma malignant																X									
Lymphoma malignant mixed																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic						X																			
Lymphoma malignant lymphocytic			X				X		X				X												
Lymphoma malignant														X		X									
Lymphoma malignant mixed										X															
Thymus	M	+	+	M	M	M	M	+	+	M	+	M	+	+	+	+	+	M	+	+	+	+	M	M	M
Lymphoma malignant lymphocytic			X						X				X												
Lymphoma malignant mixed																									
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	+	+	M	+	+	+	M	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+
Adenocarcinoma									X																
Adenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+
Basosquamous tumor malignant					X																				
Lymphoma malignant lymphocytic													X												
Subcutaneous tissue, fibrosarcoma													X									X			
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic			X						X				X												
Lymphoma malignant mixed																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic						X																			
Lymphoma malignant lymphocytic			X										X												

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	633	634	641	642	643	644	645	651	652	653	654	655	661	662	665	671	672	673	674	681	692	693	694	701	704	TOTAL: TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femoral, lymphoma malignant lymphocytic																										2
Femoral, lymphoma malignant mixed								X																		1
Lymph node	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lumbar, lymphoma malig. histiocytic																										1
Lumbar, lymphoma malig. lymphocytic																										1
Lumbar, lymphoma malignant																										1
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Mediastinal, lymphoma malignant histiocytic																										1
Mediastinal, lymphoma malignant lymphocytic																										3
Mediastinal, lymphoma malig. mixed						X																				2
Mediastinal, mesenteric, fibrosarcoma, metastatic, skin																										1
Mesenteric, lymphoma malignant histiocytic																										1
Mesenteric, lymphoma malignant lymphocytic																										3
Mesenteric, lymphoma malignant																										1
Mesenteric, lymphoma malignant mixed																										1
Pancreatic, lymphoma malignant lymphocytic																										1
Pancreatic, lymphoma malignant mixed																										1
Renal, lymphoma malignant histiocytic																										1
Renal, lymphoma malig. lymphocytic																										2
Renal, lymphoma malignant																										2
Renal, lymphoma malignant mixed																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant histiocytic					X																					2
Lymphoma malignant lymphocytic																										3
Lymphoma malignant																										1
Lymphoma malignant mixed						X	X	X										X				X				5
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic				X	X																					3
Lymphoma malignant lymphocytic														X												5
Lymphoma malignant																										2
Lymphoma malignant mixed						X	X	X										X				X				6
Thymus	+	+	+	M	+	+	+	+	+	M	+	M	+	M	+	M	+	M	+	M	+	M	+	+	+	31
Lymphoma malignant lymphocytic																										3
Lymphoma malignant mixed						X	X	X																		3
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	M	+	+	40
Adenocarcinoma				X																						2
Adenoma																				X						1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Basosquamous tumor malignant																										1
Lymphoma malignant lymphocytic																										1
Subcutaneous tissue, fibrosarcoma																										2
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										3
Lymphoma malignant mixed																						X				1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										2

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

WEEKS ON STUDY	028	041	068	071	073	084	091	093	094	094	094	097	098	099	099	102	105	105	105	105	105	105	105	105	105
CARCASS ID	625	624	664	635	683	675	695	684	682	685	663	703	702	812	691	705	811	813	814	815	821	822	823	831	832
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																			X						
Alveolar/bronchiolar adenoma, multiple																							X		
Alveolar/bronchiolar carcinoma							X																		
Basosquamous tumor malignant, metastatic, skin					X																				
Choriocarcinoma, metastatic, ovary		X																							
Lymphoma malignant histiocytic						X																			
Lymphoma malignant lymphocytic			X				X		X				X												
Lymphoma malignant														X											
Lymphoma malignant mixed										X															
Mediastinum, alveolar/bronchiolar carcinoma							X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic			X																						
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye														+											
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Carcinoma																									
Lymphoma malignant lymphocytic			X										X												
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic						X																X			
Lymphoma malignant lymphocytic			X				X		X				X												
Lymphoma malignant														X											
Lymphoma malignant mixed																									
Ureter				+	+	+			+	+	+	+		+	+					+					
Urinary bladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic							X		X				X												
Lymphoma malignant mixed																									

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	633	634	641	642	643	644	645	651	652	653	654	655	661	662	665	671	672	673	674	681	692	693	694	701	704	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																	X						X			3
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma																										1
Basosquamous tumor malignant, metastatic, skin																										1
Choriocarcinoma, metastatic, ovary																										1
Lymphoma malignant histiocytic					X																					2
Lymphoma malignant lymphocytic															X											5
Lymphoma malignant																										1
Lymphoma malignant mixed						X	X																			3
Mediastinum, alveolar/bronchiolar carcinoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye																				+	+					3
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma		X																								1
Lymphoma malignant lymphocytic																										2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										2
Lymphoma malignant lymphocytic																										4
Lymphoma malignant																										1
Lymphoma malignant mixed						X	X	X										X								4
Ureter		+		+						+	+									+			+			16
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic															X											4
Lymphoma malignant mixed							X															X				2

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

	Vehicle Control	250 mg/kg	500 mg/kg
Liver: Hepatocellular Adenoma			
Overall Rates (a)	7/50 (14%)	(b) 3/19 (16%)	4/50 (8%)
Adjusted Rates (c)	19.4%		11.2%
Terminal Rates (d)	7/36 (19%)		3/34 (9%)
Day of First Observation	731		680
Life Table Test (e)			P=0.292N
Logistic Regression Test (e)			P=0.282N
Fisher Exact Test (e)			P=0.262N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	8/50 (16%)	(b) 5/19 (26%)	4/50 (8%)
Adjusted Rates (c)	21.1%		11.2%
Terminal Rates (d)	7/36 (19%)		3/34 (9%)
Day of First Observation	462		680
Life Table Test (e)			P=0.205N
Logistic Regression Test (e)			P=0.186N
Fisher Exact Test (e)			P=0.178N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	3/50 (6%)	(b) 1/14 (7%)	4/50 (8%)
Adjusted Rates (c)	8.3%		11.8%
Terminal Rates (d)	3/36 (8%)		4/34 (12%)
Day of First Observation	731		731
Life Table Test (e)			P=0.468
Logistic Regression Test (e)			P=0.468
Fisher Exact Test (e)			P=0.500
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	(b) 1/14 (7%)	5/50 (10%)
Adjusted Rates (c)	11.1%		13.8%
Terminal Rates (d)	4/36 (11%)		4/34 (12%)
Day of First Observation	731		634
Life Table Test (e)			P=0.477
Logistic Regression Test (e)			P=0.483
Fisher Exact Test (e)			P=0.500
Mammary Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	1/50 (2%)	0/49 (0%)	3/50 (6%)
Adjusted Rates (c)	2.8%	0.0%	8.1%
Terminal Rates (d)	1/36 (3%)	0/35 (0%)	2/34 (6%)
Day of First Observation	731		653
Life Table Tests (e)	P=0.172	P=0.506N	P=0.298
Logistic Regression Tests (e)	P=0.171	P=0.506N	P=0.297
Cochran-Armitage Trend Test (e)	P=0.177		
Fisher Exact Test (e)		P=0.505N	P=0.309
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	6/47 (13%)	(b) 4/19 (21%)	6/45 (13%)
Adjusted Rates (c)	16.8%		17.0%
Terminal Rates (d)	5/34 (15%)		5/34 (15%)
Day of First Observation	629		688
Life Table Test (e)			P=0.619N
Logistic Regression Test (e)			P=0.612N
Fisher Exact Test (e)			P=0.589

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

	Vehicle Control	250 mg/kg	500 mg/kg
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	1/50 (2%)	3/49 (6%)	2/50 (4%)
Adjusted Rates (c)	2.2%	7.2%	5.5%
Terminal Rates (d)	0/36 (0%)	1/35 (3%)	1/34 (3%)
Day of First Observation	596	601	680
Life Table Tests (e)	P=0.398	P=0.322	P=0.488
Logistic Regression Tests (e)	P=0.423	P=0.338	P=0.512
Cochran-Armitage Trend Test (e)	P=0.400		
Fisher Exact Test (e)		P=0.301	P=0.500
Forestomach: Squamous Papilloma			
Overall Rates (a)	3/49 (6%)	3/48 (6%)	1/48 (2%)
Adjusted Rates (c)	8.0%	8.6%	3.0%
Terminal Rates (d)	2/36 (6%)	3/35 (9%)	1/33 (3%)
Day of First Observation	697	731	731
Life Table Tests (e)	P=0.270N	P=0.647	P=0.340N
Logistic Regression Tests (e)	P=0.252N	P=0.660N	P=0.316N
Cochran-Armitage Trend Test (e)	P=0.246N		
Fisher Exact Test (e)		P=0.651	P=0.316N
Uterus: Stromal Polyp			
Overall Rates (a)	3/50 (6%)	1/43 (2%)	0/50 (0%)
Adjusted Rates (c)	7.9%	3.4%	0.0%
Terminal Rates (d)	2/36 (6%)	1/29 (3%)	0/34 (0%)
Day of First Observation	633	731	
Life Table Tests (e)	P=0.068N	P=0.361N	P=0.124N
Logistic Regression Tests (e)	P=0.067N	P=0.362N	P=0.123N
Cochran-Armitage Trend Test (e)	P=0.065N		
Fisher Exact Test (e)		P=0.368N	P=0.121N
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	3/50 (6%)	(b,f,g) 1/49 (2%)	0/50 (0%)
Adjusted Rates (c)	7.7%		0.0%
Terminal Rates (d)	2/36 (6%)		0/34 (0%)
Day of First Observation	596		
Life Table Test (e)			P=0.131N
Logistic Regression Test (e)			P=0.119N
Fisher Exact Test (e)			P=0.121N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	14/50 (28%)	(b,f) 12/49 (24%)	18/50 (36%)
Adjusted Rates (c)	32.5%		42.1%
Terminal Rates (d)	8/36 (22%)		10/34 (29%)
Day of First Observation	574		474
Life Table Test (e)			P=0.252
Logistic Regression Test (e)			P=0.262
Fisher Exact Test (e)			P=0.260

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Incomplete sampling of tissues
(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 logistic regression 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).
(f) Nineteen livers and 23 spleens were examined microscopically.
(g) A hemangioma was also observed.

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHOXANE

	Vehicle Control	Low Dose	High Dose
Animals initially in study	60	60	60
Animals removed	60	60	60
Animals examined histopathologically	50	49	50
ALIMENTARY SYSTEM			
Gallbladder	(44)	(6)	(45)
Cyst	1 (2%)		
Intestine large, colon	(48)	(12)	(48)
Parasite metazoan			2 (4%)
Intestine small, duodenum	(46)	(8)	(45)
Amyloid deposition		1 (13%)	
Intestine small, jejunum	(48)	(13)	(45)
Hyperplasia, lymphoid			1 (2%)
Liver	(50)	(19)	(50)
Angiectasis			1 (2%)
Basophilic focus			1 (2%)
Hematopoietic cell proliferation	11 (22%)	1 (5%)	11 (22%)
Hyperplasia, lymphoid			1 (2%)
Infarct	1 (2%)		
Inflammation, chronic	3 (6%)		
Inflammation, necrotizing			2 (4%)
Leukocytosis	2 (4%)		2 (4%)
Necrosis, coagulative	2 (4%)	1 (5%)	2 (4%)
Pigmentation, hemosiderin	3 (6%)		
Mesentery	(41)	(11)	(49)
Inflammation, chronic active	4 (10%)	2 (18%)	2 (4%)
Necrosis, coagulative			1 (2%)
Pancreas	(49)	(15)	(49)
Cyst		1 (7%)	
Hyperplasia, lymphoid			1 (2%)
Inflammation, suppurative	1 (2%)		
Necrosis, coagulative	1 (2%)		
Acinus, atrophy	3 (6%)	1 (7%)	1 (2%)
Salivary glands	(48)	(13)	(49)
Infiltration cellular, lymphocytic	1 (2%)		
Stomach, forestomach	(49)	(48)	(48)
Acanthosis		5 (10%)	23 (48%)
Hyperkeratosis		4 (8%)	27 (56%)
Hyperplasia, focal	3 (6%)	14 (29%)	22 (46%)
Hyperplasia, lymphoid		1 (2%)	1 (2%)
Inflammation, chronic active		4 (8%)	6 (13%)
Ulcer	1 (2%)		
Stomach, glandular	(49)	(12)	(48)
Cyst	1 (2%)		4 (9%)
Inflammation, chronic active			1 (2%)
Epithelium, hyperplasia	1 (2%)		
Tooth	(50)	(14)	(50)
Dysplasia			3 (6%)
Inflammation, chronic active	1 (2%)		
CARDIOVASCULAR SYSTEM			
Heart	(50)	(14)	(50)
Cardiomyopathy, chronic	1 (2%)		
Fibrosis	1 (2%)		
Inflammation, chronic active	1 (2%)		
Necrosis, fibrinoid	1 (2%)		

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHOXANE (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
Adrenal gland	(50)	(14)	(50)
Accessory adrenal cortical nodule	1 (2%)		
Adrenal gland, cortex	(50)	(14)	(50)
Cyst			2 (4%)
Degeneration, fatty	1 (2%)		1 (2%)
Hematopoietic cell proliferation			1 (2%)
Hypertrophy			2 (4%)
Necrosis, coagulative		1 (7%)	
Adrenal gland, medulla	(49)	(14)	(50)
Hematopoietic cell proliferation			1 (2%)
Hyperplasia	3 (6%)		1 (2%)
Islets, pancreatic	(49)	(13)	(49)
Hyperplasia			1 (2%)
Pituitary gland	(47)	(19)	(45)
Pars distalis, cyst	2 (4%)		
Pars distalis, hyperplasia	14 (30%)	3 (16%)	18 (40%)
Thyroid gland	(50)	(14)	(47)
Follicle, cyst		1 (7%)	1 (2%)
Follicular cell, hyperplasia	9 (18%)		2 (4%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Ovary	(49)	(21)	(50)
Atrophy	6 (12%)	2 (10%)	3 (6%)
Cyst	18 (37%)	9 (43%)	21 (42%)
Inflammation, chronic active	5 (10%)		1 (2%)
Mineralization	3 (6%)		1 (2%)
Uterus	(50)	(43)	(50)
Angiectasis	1 (2%)		
Bacterium	1 (2%)		
Hemorrhage			1 (2%)
Inflammation, suppurative	6 (12%)	4 (9%)	5 (10%)
Thrombus		1 (2%)	
Endometrium, hyperplasia, cystic, glandular	40 (80%)	40 (93%)	45 (90%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(14)	(50)
Femoral, hyperplasia	4 (8%)		3 (6%)
Femoral, myelofibrosis	2 (4%)		2 (4%)
Lymph node	(50)	(16)	(50)
Mediastinal, hyperplasia, lymphoid			1 (2%)
Mediastinal, inflammation, suppurative	1 (2%)		
Mediastinal, pigmentation, hemosiderin			1 (2%)
Mesenteric, angiectasis	1 (2%)	2 (13%)	
Mesenteric, cyst	1 (2%)		
Mesenteric, hematopoietic cell proliferation	1 (2%)	2 (13%)	
Lymph node, mandibular	(48)	(13)	(49)
Pigmentation, hemosiderin	6 (13%)		4 (8%)
Spleen	(50)	(23)	(50)
Hematopoietic cell proliferation	26 (52%)	6 (26%)	23 (46%)
Hyperplasia, lymphoid	1 (2%)		3 (6%)
Necrosis, coagulative			1 (2%)
Thymus	(31)	(9)	(31)
Necrosis	1 (3%)		

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHOXANE (Continued)

	Vehicle Control	Low Dose	High Dose
INTEGUMENTARY SYSTEM			
Mammary gland	(44)	(10)	(40)
Hyperplasia, cystic	17 (39%)		28 (70%)
Skin	(50)	(14)	(49)
Fibrosis			1 (2%)
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(14)	(50)
Joint, tarsal, metaplasia, osseous	2 (4%)		
Skeletal muscle	(50)	(13)	(50)
Fibrosis			1 (2%)
NERVOUS SYSTEM			
Brain	(50)	(14)	(50)
Compression	1 (2%)		1 (2%)
Hydrocephalus			1 (2%)
Infiltration cellular, lymphocytic	1 (2%)		
Inflammation, suppurative	1 (2%)		
RESPIRATORY SYSTEM			
Lung	(50)	(14)	(50)
Edema		1 (7%)	
Hyperplasia, lymphoid			2 (4%)
Infiltration cellular, lymphocytic			2 (4%)
Inflammation, chronic active	1 (2%)		2 (4%)
Leukocytosis	1 (2%)		3 (6%)
Alveolar epithelium, hyperplasia		1 (7%)	1 (2%)
Nose	(50)	(14)	(50)
Nasolacrimal duct, inflammation, suppurative			2 (4%)
SPECIAL SENSES SYSTEM			
Eye	(1)		(3)
Lens, cataract			1 (33%)
Retina, atrophy			1 (33%)
Harderian gland	(48)	(11)	(50)
Hyperplasia	3 (6%)		1 (2%)
URINARY SYSTEM			
Kidney	(50)	(14)	(50)
Cyst	1 (2%)		
Glomerulosclerosis	1 (2%)	1 (7%)	1 (2%)
Hyperplasia, lymphoid			1 (2%)
Infarct, chronic	2 (4%)		
Inflammation, chronic active	2 (4%)		
Metaplasia, osseous	1 (2%)		
Mineralization	1 (2%)		
Nephropathy, chronic	4 (8%)		6 (12%)
Urinary bladder	(49)	(12)	(49)
Hyperplasia, lymphoid			1 (2%)
Inflammation, chronic active			1 (2%)

APPENDIX E

SENTINEL ANIMAL PROGRAM

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APPENDIX E. SENTINEL ANIMAL PROGRAM

Methods

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via 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. Data from animals surviving 24 months were collected from 5/50 randomly selected vehicle control animals of each sex and species. The blood from each animal was collected and clotted, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral 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) (6,12,18 mo) Poly (polyoma virus) MVM (minute virus of mice) Ectro (infectious ectromelia) Sendai	M. Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus)	MHV (mouse hepatitis virus) GDVII (24 mo)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai	RCV (rat coronavirus) (6 mo)	RCV/SDA (sialodacryoadenitis virus) (12,18, 24 mo)

Results

Results are presented in Table E1.

TABLE E1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR MICE IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHOXANE (a)

Interval (months)	Number of Animals	Positive Serologic Reaction for
RATS		
6	--	None positive
12	--	None positive
18	--	None positive
24	--	None positive
MICE		
6	--	None positive
12	6/10	MHV
18	6/7	MHV
24	9/10	MHV
	1/10	GDVII

(a) Blood samples were taken from sentinel animals at 6, 12, and 18 months after the start of dosing and from the vehicle control animals just before they were killed; samples were sent to Microbiological Associates (Bethesda, MD) for determination of antibody titers.

APPENDIX F

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

Pelleted Diet: July 1982 to July 1984

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

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TABLE F1. 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
Dried brewer's 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) NCI, 1976; NIH, 1978
(b) Ingredients ground to pass through a U.S. Standard Screen No. 16 before being mixed

TABLE F2. 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
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 F3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	23.13 ± 1.08	21.3-26.3	25
Crude fat (percent by weight)	5.13 ± 0.59	3.3-6.3	25
Crude fiber (percent by weight)	3.47 ± 0.53	2.8-5.6	25
Ash (percent by weight)	6.63 ± 0.38	5.7-7.3	25
Amino Acids (percent of total diet)			
Arginine	1.32 ± 0.072	1.310-1.390	5
Cystine	0.319 ± 0.088	0.218-0.400	5
Glycine	1.146 ± 0.063	1.060-1.210	5
Histidine	0.571 ± 0.026	0.531-0.603	5
Isoleucine	0.914 ± 0.030	0.881-0.944	5
Leucine	1.946 ± 0.056	1.850-1.990	5
Lysine	1.280 ± 0.067	1.200-1.370	5
Methionine	0.436 ± 0.165	0.306-0.699	5
Phenylalanine	0.938 ± 0.158	0.665-1.05	5
Threonine	0.855 ± 0.035	0.824-0.898	5
Tryptophan	0.277 ± 0.221	0.156-0.671	5
Tyrosine	0.618 ± 0.086	0.564-0.769	5
Valine	1.108 ± 0.043	1.050-1.170	5
Essential Fatty Acids (percent of total diet)			
Linoleic	2.290 ± 0.313	1.83-2.52	5
Linolenic	0.258 ± 0.040	0.210-0.308	5
Vitamins			
Vitamin A (IU/kg)	12,584 ± 4,612	4,100-24,000	25
Vitamin D (IU/kg)	4,450 ± 1,382	3,000-6,300	4
α-Tocopherol (ppm)	43.58 ± 6.92	31.1-48.0	5
Thiamine (ppm)	17.6 ± 3.8	12.0-27.0	25
Riboflavin (ppm)	7.6 ± 0.85	7.58-8.2	5
Niacin (ppm)	97.8 ± 31.68	65.0-150.0	5
Pantothenic acid (ppm)	30.06 ± 4.31	23.0-34.0	5
Pyridoxine (ppm)	7.68 ± 1.31	5.60-8.8	5
Folic acid (ppm)	2.62 ± 0.89	1.80-3.7	5
Biotin (ppm)	0.254 ± 0.053	0.19-0.32	5
Vitamin B_{12} (ppb)	24.21 ± 12.66	10.6-38.0	5
Choline (ppm)	3,122 ± 416.8	2,400-3,430	5
Minerals			
Calcium (percent)	1.30 ± 0.13	1.11-1.63	25
Phosphorus (percent)	0.97 ± 0.06	0.87-1.10	25
Potassium (percent)	0.900 ± 0.098	0.772-0.971	3
Chloride (percent)	0.513 ± 0.114	0.380-0.635	5
Sodium (percent)	0.323 ± 0.043	0.258-0.371	5
Magnesium (percent)	0.167 ± 0.012	0.151-0.181	5
Sulfur (percent)	0.304 ± 0.064	0.268-0.420	5
Iron (ppm)	410.3 ± 94.04	262.0-523.0	5
Manganese (ppm)	90.29 ± 7.15	81.7-99.4	5
Zinc (ppm)	52.78 ± 4.94	46.1-58.2	5
Copper (ppm)	10.72 ± 2.76	8.09-15.39	5
Iodine (ppm)	2.95 ± 1.05	1.52-3.82	4
Chromium (ppm)	1.85 ± 0.25	1.44-2.09	5
Cobalt (ppm)	0.681 ± 0.14	0.490-0.780	4

TABLE F4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.53 ± 0.15	0.17-0.77	25
Cadmium (ppm) (a)	<0.10		25
Lead (ppm)	0.74 ± 0.62	0.33-3.37	25
Mercury (ppm) (a)	<0.05		25
Selenium (ppm)	0.32 ± 0.07	0.13-0.42	25
Aflatoxins (ppb) (a)	<5.0		25
Nitrate nitrogen (ppm) (b)	9.20 ± 4.64	0.10-22.0	25
Nitrite nitrogen (ppm) (b)	1.37 ± 1.69	0.10-7.20	25
BHA (ppm) (c)	4.08 ± 4.76	2.0-17.0	25
BHT (ppm) (c)	2.80 ± 2.57	1.0-12.0	25
Aerobic plate count (CFU/g) (d)	46,112 ± 34,525	6,600-130,000	25
Coliform (MPN/g) (e)	49.2 ± 125	3.0-460	25
E. coli (MPN/g) (a)	≤3.0		25
Total nitrosamines (ppb) (f)	5.67 ± 5.81	1.8-30.9	25
N-Nitrosodimethylamine (ppb) (f)	4.61 ± 5.81	0.8-30.0	25
N-Nitrosopyrrolidine (ppb) (f)	1.06 ± 0.26	0.81-1.70	25
Pesticides (ppm)			
α-BHC (a,g)	<0.01		25
β-BHC (a)	<0.02		25
γ-BHC-Lindane (a)	<0.01		25
δ-BHC (a)	<0.01		25
Heptachlor (a)	<0.01		25
Aldrin (a)	<0.01		25
Heptachlor epoxide (a)	<0.01		25
DDE (a)	<0.01		25
DDD (a)	<0.01		25
DDT (a)	<0.01		25
HCB (a)	<0.01		25
Mirex (a)	<0.01		25
Methoxychlor (a)	<0.05		25
Dieldrin (a)	<0.01		25
Endrin (a)	<0.01		25
Telodrin (a)	<0.01		25
Chlordane (a)	<0.05		25
Toxaphene (a)	<0.1		25
Estimated PCBs (a)	<0.2		25
Ronnel (a)	<0.01		25
Ethion (a)	<0.02		25
Trithion (a)	<0.05		25
Diazinon (a)	<0.1		25
Methyl parathion (a)	<0.02		25
Ethyl parathion (a)	<0.02		25
Malathion (h)	0.12 ± 0.09	<0.05-0.45	25
Endosulfan I (a)	<0.01		25
Endosulfan II (a)	<0.01		25
Endosulfan sulfate (a)	<0.03		25

(a) All values were less than the detection limit, given in the table as the mean.
(b) Source of contamination: alfalfa, grains, and fish meal
(c) Source of contamination: soy oil and fish meal
(d) CFU = colony-forming unit
(e) MPN = most probable number
(f) All values were corrected for percent recovery.
(g) BHC = hexachlorocyclohexane or benzene hexachloride
(h) Fifteen lots contained more than 0.05 ppm.

APPENDIX G

SINGLE-ADMINISTRATION AND SEVEN-WEEK DERMAL STUDIES OF DIMETHOXANE

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APPENDIX G. DERMAL STUDIES

I. Materials and Methods for the Dermal Studies of Dimethoxane

The dermal studies were conducted with lot no. 6270-79, the same lot used for the gavage studies.

A. Preparation and Characterization of Dose Mixtures

For the single-administration studies, a weighed quantity of dimethoxane was dissolved in an appropriate quantity of acetone to prepare a stock solution (Table G1). Serial dilutions were made with acetone. Undiluted dimethoxane was used for the 7-week studies. No analysis of the dose mixtures was performed.

B. Single-Administration Studies

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and observed for 16 days before the studies began. Groups of five female and five male rats were administered a 0.3 ml (3 × 0.1 ml) dermal application of 0, 175, 350, 700, 1,400, or 2,800 mg/kg dimethoxane in acetone to the clipped dorsal interscapular region. Groups of five female and five male mice were administered a single 0.1 ml application of 0, 58, 115, 230, 460, or 920 mg/kg dimethoxane in acetone to the clipped dorsal interscapular region.

Immediately after dosing, all animals that received 2,800 mg/kg dimethoxane by dermal application, all vehicle controls, and all mice that received dermal applications of dimethoxane in acetone were placed in individual metabolism cages for urine collection at 24 and 48 hours. Animals were returned to their cages at the end of 48 hours. Animals were observed two times per day for 14 days. Details of animal maintenance for the dermal studies are presented in Table G2.

C. Supplemental Studies

Twenty-eight male rats were administered a 0.3 ml (3 × 0.1 ml) dermal application of 2,800 mg/kg dimethoxane in acetone to the (1 cm × 2 cm) clipped dorsal interscapular region. Twenty-eight male mice received a single 0.1 ml application of 954 mg/kg dimethoxane in acetone to the (1 cm × 2 cm) clipped dorsal interscapular region. Rats and mice were fasted overnight before they were dosed. Four animals were killed 15 or 30 minutes or 1, 2, 4, 12, or 24 hours after dosing. Blood was collected from the vena cava of rats and the brachial plexus of mice.

TABLE G1. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE DERMAL STUDIES OF DIMETHOXANE

Single-Administration Studies	Seven-Week Studies
Preparation Weighed quantity of dimethoxane dissolved in appropriate quantity of acetone for stock solution. Serial dilutions made with acetone	Used neat
Maximum Storage Time 2 wk	Not applicable
Storage Conditions Room temperature in foil-wrapped glass bottles	Placed in foil-wrapped bottles 1 × d

TABLE G2. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE DERMAL STUDIES OF DIMETHOXANE

Single-Administration Studies	Seven-Week Studies
EXPERIMENTAL DESIGN	
Size of Study Groups	
5 males and 5 females of each species; groups of 28 male rats and mice used for supplemental studies	5 males and 5 females of each species
Doses	
Rats--0, 175, 350, 700, 1,400, or 2,800 mg/kg dimethoxane in acetone by dermal application; mice--0, 58, 115, 230, 460, or 920 mg/kg; dose vol--rats: 0.3 (3 × 0.1) ml; mice: 0.1 ml; supplemental studies--rats: 2,800 mg/kg; mice: 954 mg/kg	Rats--0.3 ml (3,000 mg/kg) undiluted dimethoxane by dermal application; mice--0.1 ml (5,100 mg/kg); controls were untreated
Date of First Dose	
3/10/81	Rats--5/18/81; mice--5/19/81
Date of Last Dose	
N/A	7/5/81
Duration of Dosing	
Single dose	7 d/wk; rats--49 d, mice--48 d
Type and Frequency of Observation	
Observed 2 × d	Observed 2 × d; weighed on d 1, 9, 17, 24, and 45 and at termination
Necropsy, Histologic Examinations, and Supplemental Analyses	
Necropsy performed on all animals alive at the end of the studies; histologic examinations not performed. Vehicle control and high dose animals placed in individual metabolism cages immediately after dosing and urine collected over 24-h intervals for 2 d after dosing; mouse urine was subsequently pooled before analysis. Four animals from supplemental study groups of each species killed with carbon dioxide 15 or 30 min or 1, 2, 4, 12, or 24 h after dosing; blood collected from the brachial plexus. Urine and blood were analyzed for dimethoxane	Necropsy and histologic examinations performed on all animals; skin from application site of dosed animals and from the lumbar region of the controls examined histologically. Brain, heart, liver, lungs, right kidney, right testis, and thymus weights recorded at necropsy
ANIMALS AND ANIMAL MAINTENANCE	
Strain and Species	
F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice
Animal Source	
Charles River Breeding Laboratories (Portage, MI)	Harlan Industries (Indianapolis, IN)
Study Laboratory	
Battelle Columbus Laboratories	Battelle Columbus Laboratories
Method of Animal Identification	
Toe clip	Toe clip
Time Held Before Study	
16 d	Rats--12 d; mice--13 d
Age When Placed on Study	
Rats--7 wk; mice--8 wk	Rats--6 wk; mice--8 wk
Age When Killed	
Rats--9 wk; mice--10 wk	Rats--13 wk; mice--15 wk

TABLE G2. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE DERMAL STUDIES OF DIMETHOXANE (Continued)

Single-Administration Studies	Seven-Week Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)	
Necropsy Dates 3/24/81-3/25/81	7/6/81
Method of Animal Distribution Animals distributed to weight classes and assigned to cages by one table of random numbers and to groups by another table of random numbers	Same as single-administration studies
Feed NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum	Same as single-administration studies
Bedding Absorb-Dri (Absorb-Dri, Inc., Garfield, NJ)	Absorb-Dri hardwood chips (Absorb-Dri, Inc., Garfield, NJ)
Water Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as single-administration studies
Cages Polycarbonate (Lab Products, Inc., Garfield, NJ)	Same as single-administration studies
Cage Filters Spun-bonded polyester, Du Pont 2024® (Snow Filtration, Cincinnati, OH)	Same as single-administration studies
Animals per Cage 1; supplemental studies--4	Dosed animals--1; controls--5
Other Chemicals on Study in the Same Room None	None
Animal Room Environment Temp--21°-25° C; hum--40%-60%; fluorescent light 12 h/d; 15 room air changes/h	Temp--22°-24° C; hum--40%-60%; fluorescent light 12 h/d; 15 room air changes/h

D. Analytical Methods for Supplemental Studies

Blood and urine from the studies were analyzed for dimethoxane by gas chromatographic analysis. Lysed blood or urine was forced through a C_{18} Sep-Pak column. The dimethoxane was extracted with an isopropanol:chloroform (1:3) solvent. Gas chromatographic analysis was performed with flame ionization detection and a 20% SP2100/0.1% Carbowax 1500 column.

E. Seven-Week Studies

Seven-week dermal studies were conducted to determine the absorption and toxicity of undiluted dimethoxane. Male and female F344/N rats and male and female $B6C3F_1$ mice were obtained from Harlan Industries and were held for 12 days (rats) or 13 days (mice) before the studies began. The rats were 6 weeks old when placed on study, and the mice were 8 weeks old.

Five rats of each sex were given dermal applications of 0.3 ml (3 × 0.1 ml) undiluted dimethoxane to the (1 cm × 2 cm) clipped interscapular region for 49 consecutive days. Five mice of each sex were given dermal applications of 0.1 ml undiluted dimethoxane to the clipped interscapular region for 48 consecutive days. The mean dose per day was 3,000 mg/kg for rats and 5,100 mg/kg for mice.

Dosed animals were housed one per cage, and controls were housed five per cage. Water and feed were available ad libitum. The rats and mice were observed two times per day and were weighed on days 1, 9, 17, 24, and 45 and at the end of the studies. Details of animal maintenance are presented in Table G2. At the end of the studies, animals were killed and a necropsy was performed. Skin sections were collected from the interscapular application site of dosed animals and from the lumbar region of controls. The weights for liver, thymus, brain, heart, right kidney, lungs, and right testis were recorded at necropsy.

II. Results of the Dermal Studies of Dimethoxane

A. Rats

1. Single-Administration Studies: All rats lived to the end of the studies (doses up to 2,800 mg/kg dimethoxane in acetone). No detectable amount of dimethoxane was found in the urine of rats 24 or 48 hours after they received 2,800 mg/kg dimethoxane in acetone by dermal application. In the supplemental study, no detectable amount of dimethoxane was found in the blood of male rats 15 or 30 minutes or 1, 2, 4, 12, or 24 hours after they received 2,800 mg/kg dimethoxane in acetone by dermal application. Dimethoxane was not detected in blood or urine. This finding does not mean that the compound was not absorbed through the skin, since blood and urine were analyzed for the parent compound only.

2. Seven-Week Studies: All rats lived to the end of the studies (dose of 3,000 mg/kg dimethoxane by dermal application) (Table G3). The final mean body weights of rats that received 3,000 mg/kg were 14% lower than those of controls. The relative liver and kidney weights for dosed female rats, the relative heart and brain weights for dosed rats, and the relative thymus and lung weights for dosed male rats were marginally greater than those for controls (Table G4). The skin at the site of application appeared thickened and brown. Epidermal hyperplasia and hyperkeratosis and sebaceous gland hyperplasia were seen at the site of application in dosed animals.

B. Mice

1. Single-Administration Studies: All mice lived to the end of the studies (doses up to 920 mg/kg dimethoxane in acetone by dermal application). No compound-related clinical signs were observed, and no dimethoxane was detected in the urine of mice 24 or 48 hours after dosing. In the supplemental study, no detectable amount of dimethoxane was found in the blood of male mice 15 or 30 minutes or 1, 2, 4, 12, or 24 hours after they received 954 mg/kg dimethoxane in acetone by dermal application. Dimethoxane was not detected in blood or urine. This finding does not mean that the compound was not absorbed through the skin, since blood and urine were analyzed for the parent compound only.

TABLE G3. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SEVEN-WEEK DERMAL STUDIES OF DIMETHOXANE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
0	5/5	123	262	+139	
3,000	5/5	118	224	+106	85.5
FEMALE					
0	5/5	105	179	+74	
3,000	5/5	101	154	+53	86.0

(a) Number surviving/number initially in group
(b) Initial mean group body weight
(c) Mean body weight change of the group

TABLE G4. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR RATS IN THE SEVEN-WEEK DERMAL STUDIES OF DIMETHOXANE (a)

Organ	Male Control	Male 3,000 mg/kg	Female Control	Female 3,000 mg/kg
Body weight (grams)	262	224	179	154
Liver	53.4 ± 1.06	51.8 ± 2.09	46.3 ± 1.57	*50.6 ± 0.79
Thymus	1.1 ± 0.06	*1.3 ± 0.06	1.6 ± 0.06	1.8 ± 0.07
Kidney	4.7 ± 0.10	5.0 ± 0.12	4.7 ± 0.11	**5.3 ± 0.14
Heart	3.3 ± 0.07	*3.6 ± 0.12	3.7 ± 0.14	*4.0 ± 0.08
Brain	6.9 ± 0.25	*7.8 ± 0.22	9.8 ± 0.16	***11.1 ± 0.19
Lungs	5.8 ± 0.24	*6.5 ± 0.23	6.7 ± 0.39	7.1 ± 0.38
Right testis	5.1 ± 0.14	5.4 ± 0.19	--	--

(a) Mean ± standard error in milligrams of organ per gram of body weight, for groups of five animals; P values vs. the controls by Student's *t*-test.
*P<0.05
**P<0.01
***P<0.001

2. Seven-Week Studies: One dosed female mouse (dose of 5,100 mg/kg dimethoxane by dermal application) died before the end of the studies (Table G5). The final mean body weight of dosed male mice was 13% lower than that of controls. Body weight data of dosed female mice could not be interpreted because the final mean body weight of controls was lower than that usually observed. The relative liver, kidney, and heart weights for dosed mice and the relative brain and lung weights for dosed male mice were significantly greater than those for controls (Table G6). The skin at the site of application was thickened. Epidermal hyperplasia and hyperkeratosis, sebaceous gland hyperplasia, necrosis, inflammation, and ulceration were seen at the site of application in dosed mice.

TABLE G5. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SEVEN-WEEK DERMAL STUDIES OF DIMETHOXANE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
0	5/5	23.6	30.0	+6.4	
5,100	5/5	23.0	26.2	+3.2	87.3
FEMALE					
0	5/5	19.8	21.6	+1.8	
5,100	4/5	19.0	23.5	+4.5	108.8

(a) Number surviving/number initially in group
(b) Initial mean group body weight
(c) Mean body weight change of the group

TABLE G6. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR MICE IN THE SEVEN-WEEK DERMAL STUDIES OF DIMETHOXANE (a)

Organ	Male Control	Male 5,100 mg/kg	Female Control	Female 5,100 mg/kg
Body weight (grams)	30.0	26.2	21.6	23.2
Liver	59.4 ± 1.86	**69.8 ± 2.33	51.1 ± 0.34	***68.5 ± 1.69
Thymus	1.4 ± 0.08	1.3 ± 0.14	2.3 ± 0.19	2.0 ± 0.29
Kidney	9.5 ± 0.19	*10.5 ± 0.36	7.9 ± 0.46	*9.7 ± 0.29
Heart	5.4 ± 0.09	*6.2 ± 0.31	5.5 ± 0.34	*7.4 ± 0.55
Brain	14.5 ± 0.56	**16.7 ± 0.38	20.4 ± 0.71	20.0 ± 0.78
Lungs	7.0 ± 0.20	**8.4 ± 0.35	11.2 ± 1.95	10.1 ± 0.34
Right testis	3.9 ± 0.21	4.1 ± 0.12	--	--

(a) Mean ± standard error in milligrams of organ per gram of body weight, for groups of five animals, except for the dosed female group that contained four animals; P values vs. the controls by Student's *t*-test.
*P<0.05
**P<0.01
***P<0.001

APPENDIX H

AUDIT SUMMARY

APPENDIX H. AUDIT SUMMARY

The pathology specimens, experimental data, study documents, and draft (September 1987) NTP Technical Report No. 354 for the 2-year studies of dimethoxane in rats and mice were audited for the National Institute of Environmental Health Sciences (NIEHS) at the National Toxicology Program (NTP) Archives during September, October, and November 1987 by Dynamac Corporation. The audit included review of:

(1) All records concerning animal receipt, quarantine, randomization, and disposition prior to study start.
(2) All inlife records including protocol, correspondence, animal husbandry, environmental conditions, dosing, external masses, mortality, animal identification, and serology.
(3) Body weight and clinical observation data for a random 10% sample of animals in each study group.
(4) All chemistry records.
(5) All postmortem records for individual animals concerning disposition codes, condition codes, tissue accountability, correlation of masses or clinical signs recorded at the last inlife observation with gross observations and microscopic diagnoses, and correlations between gross observations and microscopic diagnoses.
(6) All wet tissue bags for inventory and wet tissues from a random 20% sample of 2-year and interim-kill animals in all study groups, plus other relevant cases, to evaluate the integrity of individual animal identity and to examine for untrimmed potential lesions.
(7) Blocks and slides of tissues from a random 20% sample of animals from 2-year and interim-kill animals in each study group, plus animals with less than complete or correct identification, to examine for proper match and inventory.
(8) All red-lined diagnoses on the intermediate pathology table to verify incorporation of changes into the final tables.
(9) Correlation between the data, results, and procedures for the 2-year studies presented in the draft of the Technical Report and the records available at the NTP Archives.

Procedures and events during the exposure phase of the studies were documented adequately by the archival records, with a few minor exceptions: some temperature and humidity records for the animal room; some of the rack rotations; and documents for analytical chemistry support work. Review of data for the entire exposure phase indicated that husbandry practices had no adverse impact on animals during the course of the studies. Records documented that doses were prepared, stored, analyzed, and administered to animals according to protocols. A 10% random sample of group mean body weights were recalculated and found to be accurate. Of the external masses observed in life, all 102 in rats and 53/55 in mice were correlated with necropsy observations. Clinical pathology data were found to be presented correctly in drafts of the Technical Report. Survival records for all animals were reviewed and found to be correct except for the dates of death for one rat and one mouse. The dates recorded at necropsy for these animals differed by 1 day from those entered into the computer at removal, and these differences had no effect on the overall survival values for the study groups.

Review of the pathology specimens showed that individual animal identifiers (clipped toes) were present and correct in the residual tissue bags for 69/94 rats and 63/92 mice examined. Review of the entire data trail for animals with less than complete and correct identifiers indicated that the integrity of individual animal identity had been maintained. The audit found 15 untrimmed potential lesions in rats and 14 in mice. Because several of these involved the forestomach, additional histopathologic examinations were performed to complete the evaluation. Intestinal segments were not opened for 85/94 rats and 85/92 mice; however, no potential lesions were evident by external examination. All gross observations made at necropsy were correlated with microscopic observations, except for one in a nontarget organ of one rat and one mouse. Tissue blocks and slides matched each other properly. All post-Pathology Working Group changes of diagnoses had been incorporated in the

final pathology tables except one involving nomenclature of an ovarian carcinoma that was metastatic to liver and lung of a high dose female mouse.

Full details about these and other audit findings are presented in the audit reports that are on file at the NIEHS. In conclusion, the data and results presented in the preliminary draft Technical Report are supported by the records at the NTP Archives.