NATIONAL TOXICOLOGY PROGRAM Technical Report Series No. 461



TOXICOLOGY AND CARCINOGENESIS

STUDIES OF NITROMETHANE

(CAS NO. 75-52-5)

IN F344/N RATS AND B6C3F1 MICE

(INHALATION STUDIES)

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

FOREWORD

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

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

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

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

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NTP TECHNICAL REPORT

ON THE

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CONTENTS

ABSTRACT	· · · · · · · · · · · · · · · · · · ·	5
EXPLANATION	1 OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY	11
TECHNICAL R	EPORTS REVIEW SUBCOMMITTEE	12
SUMMARY OF	TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS	13
INTRODUCTIO	DN	15
MATERIALS A	ND METHODS	21
RESULTS		33
DISCUSSION A	ND CONCLUSIONS	65
REFERENCES	•••••••••••••••••••••••••••••••••••••••	69
Appendix A	Summary of Lesions in Male Rats in the 2-Year Inhalation Study of Nitromethane	75
Appendix B	Summary of Lesions in Female Rats in the 2-Year Inhalation Study of Nitromethane	117
Appendix C	Summary of Lesions in Male Mice in the 2-Year Inhalation Study of Nitromethane	151
Appendix D	Summary of Lesions in Female Mice in the 2-Year Inhalation Study of Nitromethane	187
Appendix E	Genetic Toxicology	227
Appendix F	Organ Weights and Organ-Weight-to-Body-Weight Ratios	235
Appendix G	Hematology and Clinical Chemistry Results	241
Appendix H	Reproductive Tissue Evaluations and Estrous Cycle Characterization	249
Appendix I	Neurobehavioral Evaluation Results	253
Appendix J	Chemical Characterization and Generation of Chamber Concentrations	255
Appendix K	Ingredients, Nutrient Composition, and Contaminant Levels in NIH-07 Rat and Mouse Ration	277
Appendix L	Sentinel Animal Program	28 1

4

ABSTRACT

CH_3NO_2

NITROMETHANE

CAS No. 75-52-5

Molecular Weight: 61.04

Synonym: Nitrocarbol

Nitromethane is used as a rocket and engine fuel; as a synthesis intermediate for agricultural fumigants, biocides, and other products; as a solvent; and as an explosive in mining, oil-well drilling, and seismic exploration. It has been detected in air, in surface and drinking water, and in cigarette smoke. Nitromethane was studied because of the potential for widespread human exposure and because it is structurally related to the carcinogens 2-nitropropane and tetranitromethane. Male and female F344/N rats and B6C3F₁ mice received nitromethane (purity 98% or greater) by inhalation for 16 days, 13 weeks, or 2 years. Genetic toxicology studies were conducted in Salmonella typhimurium, cultured Chinese hamster ovary cells, and peripheral blood erythrocytes of mice.

16-DAY STUDY IN RATS

Groups of five male and five female rats were exposed to 0, 94, 188, 375, 750, or 1,500 ppm nitromethane by inhalation, 6 hours per day, 5 days per week, for 16 days. All rats survived until the end of the study. The mean body weight gain of male rats in the 1,500 ppm group was slightly but significantly less than that of the controls; the final mean body weights and mean body weight gains of exposed females were similar to those of the controls. Clinical findings in all male and female rats in the 1,500 ppm groups included increased preening, rapid breathing, hyperactivity early in the study, and hypoactivity and loss of coordination in the hindlimbs near the end of the study. The relative liver weights of all exposed groups of male rats and the absolute and relative liver weights of females exposed to 375 ppm or greater were significantly greater than those of the controls.

Minimal to mild degeneration of the olfactory epithelium was observed in the nose of males and females exposed to 375 ppm or greater. Sciatic nerve degeneration was present in all male and female rats exposed to 375 ppm or greater; rats exposed to 750 or 1,500 ppm also had reduced myelin around sciatic axons.

16-DAY STUDY IN MICE

Groups of five male and five female mice were exposed to 0, 94, 188, 375, 750, or 1,500 ppm nitromethane by inhalation, 6 hours per day, 5 days per week, for 16 days. All mice survived to the end of the study. The final mean body weights and weight gains of exposed males and females were similar to those of the controls. Clinical findings included hypoactivity and tachypnea in male and female mice in the 1,500 ppm groups. Absolute and relative liver weights of male mice in the 750 and 1,500 ppm groups and female mice in all exposed groups and the relative liver weight of males in the

375 ppm group were significantly greater than those of the controls. Degeneration of the olfactory epithelium of the nose was observed microscopically in all males and females exposed to 375 ppm or greater; this lesion was of minimal severity in males and minimal to mild severity in females.

13-WEEK STUDY IN RATS

Groups of 10 male and 10 female rats were exposed to 0, 94, 188, 375, 750, or 1,500 ppm nitromethane by inhalation, 6 hours per day, 5 days per week, for 13 weeks. All rats survived to the end of the study. The final mean body weight and weight gain of male rats in the 1,500 ppm group were significantly less than those of the controls. Clinical findings included hindlimb paralysis in rats in the 750 and 1,500 ppm groups.

Inhalation exposure of rats to nitromethane resulted in an exposure concentration-dependent, microcvtic, responsive anemia; anemia was most pronounced in males and females exposed to 375 ppm or greater. The presence of schistocytes, Heinz bodies, and spherocytes and increased mean cell hemoglobin concentration and methemoglobin concentration were evidence that a hemolytic process was occurring; this hemolytic process could have accounted, in part, for Thrombocytosis accompanied the the anemia. anemia and would be consistent with a reactive bone marrow or could have been due to the erroneous inclusion of small erythrocyte fragments as part of the platelet count. On day 23, transient decreases in serum triiodothyronine, thyroxine, and free thyroxine were observed in male rats exposed to 375 ppm or greater and female rats exposed to 750 or 1,500 ppm. There was little or no pituitary response to the thyroid hormone decreases, as evidenced by the lack of significantly increased concentrations of thyroidstimulating hormone in exposed rats.

No biologically significant differences in organ weights were observed. The forelimb and hindlimb grip strengths of males in the 1,500 ppm group were significantly less than those of the controls. The hindlimb grip strengths of females in the 750 and 1,500 ppm groups were also significantly less than the control value. Minimal to mild hyperplasia of the bone marrow was observed microscopically in male rats in the 750 and 1,500 ppm groups and in females exposed to 188 ppm or greater. Nasal lesions in exposed males and females included olfactory epithelial degeneration in males and females exposed to 375 ppm or greater and in one female exposed to 188 ppm and respiratory epithelial hyaline droplets and goblet cell hyperplasia in males and females in the 750 and 1,500 ppm groups; the severity of nasal lesions in males and females was minimal to mild. Males and females exposed to 375 ppm or greater had minimal to mild degeneration of the sciatic nerve and the lumbar spinal cord.

13-WEEK STUDY IN MICE

Groups of 10 male and 10 female mice were exposed to 0, 94, 188, 375, 750, or 1,500 ppm nitromethane by inhalation, 6 hours per day, 5 days per week, for 13 weeks. All mice survived to the end of the study. The final mean body weights and weight gains of exposed mice were generally similar to those of the controls. There were no treatment-related clinical findings.

The absolute right kidney weights of all groups of exposed male mice except the 1,500 ppm group and of females exposed to 188 ppm or greater and the relative right kidney weights of all groups of exposed males and of females in the 750 and 1,500 ppm groups were significantly greater than those of the controls. The absolute liver weight of male mice in the 750 ppm group and the relative liver weights of males exposed to 375 ppm or greater were significantly greater than those of the controls.

Olfactory epithelial degeneration and respiratory epithelial hyaline droplets were observed microscopically in all male and female mice exposed to 375 ppm or greater. Degeneration also occurred in females in the 188 ppm group, and hyaline droplets occurred in females in the 94 and 188 ppm groups. The average severity of the nasal lesions ranged from minimal to mild in males. In females, the average severity of olfactory epithelial degeneration ranged from minimal to mild and the severity of respiratory epithelial hyaline droplets ranged from minimal to moderate. All males and nine females in the 1,500 ppm groups also had minimal extramedullary hematopoiesis of the spleen.

2-Year Study in Rats

Groups of 50 male and 50 female rats were exposed to 0, 94, 188, or 375 ppm nitromethane by inhalation, 6 hours per day, 5 days per week, for 103 weeks.

Survival, Body Weights, and Clinical Findings

There were no significant differences in survival rates between exposed and control male or female rats. The mean body weight of females in the 375 ppm group was slightly greater than that of the control group; the mean body weights of exposed males were generally similar to the mean body weight of the controls throughout the study. Clinical findings were consistent with incidences of mammary gland neoplasms in females exposed to 188 or 375 ppm; no hindlimb paralysis, as occurred in rats in the 13-week study, was observed in male or female rats in the 2-year study.

Pathology Findings

The incidences of mammary gland fibroadenoma and fibroadenoma, adenoma, or carcinoma (combined) in female rats in the 188 and 375 ppm groups were significantly greater than those in the controls. Additionally, the incidence of mammary gland carcinoma in the 375 ppm group was significantly greater than in the controls.

2-YEAR STUDY IN MICE

Groups of 50 male and 50 female mice were exposed to 0, 188, 375, or 750 ppm nitromethane by inhalation, 6 hours per day, 5 days per week, for 103 weeks.

Survival, Body Weights, and Clinical Findings

The survival rate of females in the 750 ppm group was marginally greater than that of the controls. The mean body weights of exposed females were generally slightly greater than the mean body weights of the controls during the study but were generally similar to the mean body weight of the controls at the end of the study. The mean body weights of exposed males were similar to those of the controls throughout the study. Clinical findings included swelling around the eyes and exophthalmos in exposed males and females; these findings were coincident with harderian gland neoplasms.

Pathology Findings

The incidences of harderian gland adenoma and adenoma or carcinoma (combined) in exposed mice increased with increasing exposure concentration and were significantly greater in males and females in the 375 and 750 ppm groups than those in the controls. The incidences of harderian gland carcinoma in males and females in the 375 and 750 ppm groups were also slightly greater than those in the controls.

Female mice in the 188 and 750 ppm groups had significantly greater incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) than the controls. The incidences of liver eosinophilic focus increased with increasing exposure concentration, and the incidences in the 375 and 750 ppm groups were significantly greater than the control incidence.

The incidences of alveolar/bronchiolar carcinoma in male mice in the 750 ppm group and female mice in the 375 ppm group were significantly greater than those in the controls. Females in the 750 ppm group also had a significantly greater incidence of alveolar/ bronchiolar adenoma or carcinoma (combined) and a slightly greater incidence of alveolar/bronchiolar adenoma than the controls. Females in the 375 ppm group had a significantly greater incidence of cellular infiltration of histiocytes in the lung than the controls.

The incidences of degeneration and metaplasia of the olfactory epithelium and hyaline degeneration of the respiratory epithelium were significantly greater in exposed male and female mice than those in the controls. Additionally, males in the 375 and 750 ppm groups had significantly greater incidences of inflammation of the nasolacrimal duct than did the controls.

GENETIC TOXICOLOGY

Nitromethane was not mutagenic in any tests performed by the NTP. It did not induce mutations in *Salmonella typhimurium*, with or without S9 metabolic activation, and no induction of sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells exposed to nitromethane was noted with or without S9. No increase in the frequency of micronucleated erythrocytes was observed in peripheral blood samples of male and female mice at the end of the 13-week inhalation study of nitromethane.

evidence of carcinogenic activity of nitromethane in female F344/N rats based on increased incidences of mammary gland fibroadenomas and carcinomas. There was clear evidence of carcinogenic activity of nitromethane in male $B6C3F_1$ mice based on increased incidences of harderian gland adenomas and carcinomas. There was clear evidence of carcinogenic activity in female $B6C3F_1$ mice, based on increased incidences of liver neoplasms (primarily adenomas) and harderian gland adenomas and carcinomas. Increased incidences of alveolar/bronchiolar adenomas and carcinomas in male and female mice exposed to nitromethane were also considered to be related to chemical administration.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was no evidence of carcinogenic activity* of nitromethane in male F344/N rats exposed to 94, 188, or 375 ppm. There was clear

Exposure to nitromethane by inhalation for 2 years resulted in increased incidences of nasal lesions including degeneration and metaplasia of the olfactory epithelium and degeneration of the respiratory epithelium in male and female mice.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 13.

•	Male F344/N Rats	Female F344/N Rats	Male B6C3F, Mice	Female B6C3F ₁ Mice
Exposure concentrations	0, 94, 188, or 375 ppm	0, 94, 188, or 375 ppm	0, 188, 375, or 750 ppm	0, 188, 375, or 750 ppm
Body weights	Exposed groups similar to controls	375 ppm group slightly greater than controls	Exposed groups similar to controls	Exposed groups similar to controls
2-Year survival rates	13/50, 16/50, 14/50, 8/50	28/50, 19/50, 30/50, 23/50	31/50, 36/50, 30/50, 29/50	25/50, 28/50, 26/50, 36/50
Nonneoplastic effects	None	None	Nose: olfactory epithelium, degeneration (0/50, 10/49, 50/50, 50/50); olfactory epithelium, metaplasia (0/50, 1/49, 41/50, 49/50); respiratory epithelium, hyaline degeneration (5/50, 5/49, 50/50, 50/50)	Nose: olfactory epithelium, degeneration (0/50, 22/49, 50/50, 50/50); olfactory epithelium, metaplasia (0/50, 2/49, 46/50, 48/50); respiratory epithelium, hyaline degeneration (16/50, 39/49, 50/50, 50/50)
Neoplastic effects	None	<u>Mammary gland</u> : fibroadenoma (19/50, 21/50, 33/50, 36/50); carcinoma (2/50, 7/50, 1/50, 11/50); fibroadenoma, adenoma, or carcinoma (21/50, 25/50, 34/50, 41/50)	Harderian gland: adenoma (9/50, 10/50, 19/50, 32/50); carcinoma (1/50, 1/50, 6/50, 5/50); adenoma or carcinoma (10/50, 11/50, 25/50, 37/50) Lung: alveolar/ bronchiolar carcinoma (2/50, 3/50, 3/50, 11/50); alveolar/ bronchiolar adenoma or carcinoma (13/50, 13/50, 12/50, 20/50)	Harderian gland: adenoma (5/50, 7/50, 16/50, 19/50); adenoma or carcinoma (6/50, 9/50, 20/50, 21/50) Liver: hepatocellular adenoma (14/50, 25/49, 17/49, 35/50); hepatocellular adenoma or carcinoma (19/50, 34/49, 22/49, 40/50) Lung: alveolar/ bronchiolar adenoma (3/50, 3/50, 2/49, 9/50); alveolar/ bronchiolar carcinoma (0/50, 3/50, 5/49, 3/50); alveolar/ bronchiolar adenoma
	Na anidaraa	Class suid-	Clean avidence	or carcinoma (3/50, 6/50, 6/49, 12/50)
Level of evidence of carcinogenic activity	No evidence	Clear evidence	Clear evidence	Clear evidence

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Nitromethane

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Nitromethane (continued)

Genetic	toxicology
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Salmonella typhimurium gene mutations:

Sister chromatid exchanges
Cultured Chinese hamster ovary cells in vitro:
Chromosomal aberrations
Cultured Chinese hamster ovary cells in vitro:
Micronucleated erythrocytes
Mouse peripheral blood in vivo:

Negative in strains TA98, TA100, TA1535, and TA1537 with and without S9 $\,$

Negative with and without S9

Negative with and without S9

Negative

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on nitromethane on December 5, 1995, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

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

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On December 5, 1995, the draft Technical Report on the toxicity and carcinogenesis studies of nitromethane received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. J.H. Roycroft, NIEHS, introduced the toxicity and carcinogenesis studies of nitromethane by discussing the uses, describing the experimental design, reporting on the survival and body weight effects, and commenting on chemical-related neoplastic lesions in female rats and male and female mice and nonneoplastic lesions in male and female mice. The proposed conclusions for the 2-year studies in rats and mice were *no evidence of carcinogenic activity* in male F344/N rats and *clear evidence of carcinogenic activity* in female F344/N rats and male and female B6C3F₁ mice.

Dr. Russo, a principal reviewer, agreed with the proposed conclusions and found the report otherwise acceptable.

Dr. Ryan, the second principal reviewer, agreed with the proposed conclusions. She noted that 375 ppm female rats weighed more than the controls and wondered whether this could be related to chemical effects on the thyroid gland and, further, what impact the weight effect might have had on the increased incidence of mammary gland tumors. Dr. Rovcroft responded that transient thyroid gland effects were seen early in the 13-week studies but not at the end and were not observed in the 2-year study, so he did not think the thyroid gland had an impact. Dr. J.K. Haseman, NIEHS, described a model developed by Dr. S. Seilkop using NTP historical control data to predict how certain tumors are affected by body weight and how body weights at certain ages are predictive of subsequent tumor development. Using the model, one would predict a 51% incidence of mammary gland tumors in 375 ppm female rats, while the actual incidence in the study was 82%. Dr. Haseman said in this case the increase in body weights could not account for the increase in tumors.

Dr. LeBoeuf, the third principal reviewer, agreed with the proposed conclusions in principle. He questioned whether the increases in hepatocellular adenomas alone in female mice were sufficient to support the conclusion of clear evidence. Dr. Rovcroft said the incidences of 51% and 70% in the 188 and 750 ppm groups well exceeded the concurrent control incidence of 28% as well as the highest historical rate of 40% in any of the contemporary inhalation studies and justified their inclusion Dr. LeBoeuf commented that since as support. neurotoxicity was the prime determinant for dose setting for the 2-year rat study, there should have been histopathologic examination of sciatic nerve and spinal cord in animals from this study. Dr. Roycroft observed that the 13-week data indicated sciatic nerve degeneration was less severe than in the 16-day study, although there were obvious clinical observations in the longer study. He noted that the standard protocol calls for cutting sections of sciatic nerve, spinal cord, and other nervous system tissues when neurobehavioral effects are seen clinically, but such effects were not seen in the 2-year nitromethane study. However, Dr. Roycroft reported that subsequently, sections were taken from 375 ppm and control animals, and none of the lesions observed in prechronic studies were seen.

Dr. A. Bollmeier, Angus Chemical Company, said Angus was essentially the only manufacturer of nitroparaffins now in the country. He pointed out the variation among the three batches used for the studies and wondered if this might not play a role in differences in toxicology findings among the 16-day, 13-week, and 2-year studies. Dr. Bollmeier commented that the potential for human exposure estimates by NIOSH were done in 1981 to 1983, while current exposures would be much less, likely less than 10,000. Dr. Russo moved that the Technical Report on nitromethane be accepted with the revisions discussed and with the conclusions as written. Dr. Ryan seconded the motion. Dr. J.R. Bucher, NIEHS, asked that the wording of the statement supporting the level of evidence for female mice be changed to add 'adenomas' after 'liver.' Dr. Brown said this would not be an amendment but should be kept in mind by the members when voting. Dr. Goldsworthy commented that one could argue for the same change with the harderian gland in female mice as the tumor response in this organ is primarily driven by the adenomas. Dr. Bucher proposed also using the less specific word 'neoplasm.' The revised sentence could read: "There was *clear evidence of carcinogenic activity* in female mice based on increased incidences of liver neoplasms (primarily adenomas) and harderian gland adenomas and carcinomas." The motion by Dr. Russo was then accepted unanimously with seven votes.

INTRODUCTION

CHI_3NO_2

NITROMETHANE

CAS No. 75-52-5

Molecular Weight: 61.04

Synonym: Nitrocarbol

CHEMICAL AND PHYSICAL PROPERTIES Nitromethane is a colorless, oily liquid with a moderately strong, disagreeable odor (Merck Index, 1989). Nitromethane has a melting point of -29° C, a boiling point of 101.2° C, a flash point of 112° F, and a lower explosive limit of 7.3%. Its density is 1.1322 at 25° C; the vapor density is 2.11 and the vapor pressure is 27.8 mm Hg at 20° C. Nitromethane is soluble in alcohol, ether, N, N-dimethylformamide, acetone, and alkali and is slightly soluble in water (9.5 g/L at 20° C). Nitromethane will explode when heated under confinement to near its critical temperature (315° C) or when rapidly compressed under adiabatic conditions. The sodium salt is also explosive and bursts into flames upon contact with water.

Production, Use,

and Human Exposure

Nitromethane can be prepared by vapor phase nitration of propane or by the reaction of sodium nitrite with sodium chloroacetate (*Merck Index*, 1989). In the past, nitromethane was used extensively as a chemical stabilizer to prevent the decomposition of various halogenated hydrocarbons such as metal degreasers and aerosol propellants such as 1,1,1-trichloroethane. Nitromethane is used as a fuel or fuel additive to increase the power output of rockets,

racing cars, boats, and model engines. Nitromethane is also used as a synthesis intermediate for a variety of chemicals, such as trichloronitromethane (chloropicrin), an agricultural soil and grain fumigant; the nitroalcohol, 2-hydroxymethyl-2-nitro-1,3-propanediol, which is used as a biocide for cutting fluids and as a source of formaldehyde for cross-linking amino resins; and the alkanolamine, 2-hydroxymethyl-2-amino-1,3-propanediol, which is used as a formaldehyde scavenger in resin curing and polyester resin modification and as a buffer. Nitromethane is used in a variety of solvent applications, such as solvent-extraction separation of aromatics from aliphatic compounds, in the crystallization of nitrofurantoin, as a reaction medium for aluminum chloride in Friedel-Crafts reactions, and as a solvent for resins such as α -cyanoacrylate. Nitromethane is used in mixtures with ammonium nitrate as an explosive in mining, oil-well drilling, and seismic exploration (Biocides, U.S.A., 1974; Remington's Pharmaceutical Sciences, 1975; Kirk-Othmer, 1978, 1981; SRI, International, 1980).

Although nitromethane was reported to the U.S. International Trade Commission for the year 1992, the production volume was not published (USITC, 1994). According to the National Occupational Exposure Survey, approximately 135,000 male and 46,500 female workers in the U.S. were potentially exposed to nitromethane during the years 1981 to 1983 (NIOSH, 1990). The time-weighted average threshold limit value for nitromethane is 20 ppm, or 50 mg/m³ (ACGIH, 1995). The exposure limit of nitromethane permitted by Occupational Safety and Health Administration is 100 ppm or 250 mg/m³ (29 CFR, § 1910). Although an odor threshold of 3.5 ppm has been reported for nitromethane, the odor and sensory symptoms are not dependable warning properties (Davis, 1993). Products containing nitromethane are not widely used by consumers; therefore, consumer exposure to nitromethane from such products is presumed to be low.

Nitromethane has been detected in air and in surface and drinking water; its occurrence in the atmosphere results either from emissions from industrial processes or from its formation as a byproduct of certain chemical reactions. Nitromethane is found in cigarette smoke and is a byproduct of hydrocarbon combustion and munitions manufacture. It is possibly synthesized in the atmosphere by the photolytic reaction of nitrogen dioxide and ethylene.

Nitromethane is fairly reactive and therefore does not persist in the environment; the half-life $(t_{1/2})$ of nitromethane is from 4 to 9 hours in air and about 1 day in water (National Library of Medicine, 1995a). However, because nitromethane is slightly soluble in water and evaporates at about the same rate as water, the $t_{1/2}$ is somewhat dependent on the rate of evaporation. In the atmosphere and in water, nitromethane is degraded through its reaction with hydroxyl radicals; it may also undergo aerobic or anaerobic degradation. It may react with chlorine in water to form trichloronitromethane if the pH of the medium is high (Wade *et al.*, 1977).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION Experimental Animals

Nitromethane is oxidized *in vitro* to formaldehyde, nitrite, and hydrogen peroxide by D-amino acid oxidase prepared from hog kidney (Porter *et al.*, 1972). However, when incubated with rat nasal and liver microsomes to determine if the cytochrome P_{450} -dependent demethylation produces formaldehyde, no formaldehyde was generated from nasal microsomes and only a trace was generated from liver

microsomes (Dahl and Hadley, 1983). Flavoenzymes also oxidize nitromethane. Nitromethane inhibits rabbit liver cytochrome P450 activity, apparently competing for the same ferrohemochrome-binding sites as carbon monoxide (Wade et al., 1977). Dequidt et al. (1973) administered nitromethane to Wistar rats by intraperitoneal injection (2,400 mg/kg) or by inhalation (13,000 ppm for 6 hours) and measured nitrite and methemoglobin concentrations in exposed animals. No methemoglobin was detected in rats treated with nitromethane by either route; nitrite was detected in low concentrations in the heart, lungs, kidneys, and spleen, but not the liver, of rats treated by each route. Following daily 6-hour inhalation exposures to 2,500 ppm nitromethane for 4 days, nitrite concentrations in heart, lung, kidney, and spleen tissues of Wistar rats were similar to those observed following a single exposure. No unchanged nitromethane was present in the organs of animals administered nitromethane intraperitoneally. In rats exposed by inhalation, nitromethane was detected only in the liver (0.27 g/100 g) and was not detected in rats exposed to less than 13,000 ppm.

Humans

No studies of absorption, distribution, metabolism, and excretion of nitromethane in humans were found in the literature (National Library of Medicine, 1995b).

TOXICITY

Experimental Animals

Oral LD_{50} values range from 940 to 1,210 mg/kg for rats (Subbotin, 1967; International Technical Information Institute, 1979) and from 950 to 1,440 mg/kg for mice (Machle *et al.*, 1940). In an early study of nitromethane toxicity performed by Gibbs and Reichert (1891), a minimum lethal dose of 565 to 1,130 mg/kg for dogs was reported. Injections of nitromethane caused lassitude, drowsiness, weakness, salivation, urination, defecation, and vomiting. Nitromethane first accelerated, then retarded, the pulse rate. Treated dogs exhibited progressive weakness, coma, paralysis, and terminal convulsions. Death by respiratory failure usually occurred within 24 hours of injection.

Dogs that were administered a single oral dose of nitromethane at a concentration of 200, 500, 1,000,

or 1.500 mg/kg died within 36 hours (Weatherby, Pathologic examination revealed hepatic 1955). edema, focal areas of necrosis, and cells with enlarged nuclei. Pathologic examinations performed on dogs that were administered a single, nonlethal oral dose of 125 mg/kg nitromethane revealed slight changes in the liver, including mild fatty change of the hepatic parenchyma and a few lymphocytes in the portal areas. Within 48 hours after dosing, regeneration of hepatic cells was observed. Liver damage was more severe as the dose was increased. Kidney damage (swollen glomeruli, swollen proximal and distal convoluted tubules, and hyaline casts in the tubules) was observed only in animals administered 1,500 mg/kg. All other tissues were normal.

Rabbits receiving gavage doses of 750 to 1,000 mg/kg nitromethane displayed progressive weakness and collapse, unsteadiness and incoordination ending in complete ataxia; their breathing was first slowed, then rapid (Machle et al., 1940). There were no changes in blood chemistry variables and no methemoglobin formation. Liver damage (edema, cloudy swelling, and necrosis) was present in all animals that died from administration of the chemical. Inhalation experiments with rabbits, monkeys, and guinea pigs were also performed. The symptoms of nitromethane toxicity following inhalation were similar for each species, although guinea pigs seemed to be somewhat more susceptible than rabbits or monkeys (Machle et al., 1940). Mortality was related to total dose (concentration of exposure multiplied by duration) at concentrations greater than 500 ppm. The LC₁₀ for monkeys was determined to be 1,000 ppm. Rabbits and guinea pigs (two of each species) survived exposure to 30,000 ppm for 15 minutes or 10,000 ppm for 1 hour; however, all died when exposed to 30,000 ppm for 2 hours or 10,000 ppm for 6 hours (Machle et al., 1940). A latency period was observed before the onset of symptoms of nitromethane toxicity and was inversely related to the concentration of nitromethane in the air. Central nervous system effects were observed within 30 minutes to 1 hour after exposure to 30,000 or 50,000 ppm; however, in animals exposed to 10,000 ppm, central nervous system effects were not observed until 5 hours after exposure began. Inhalation of nitromethane first caused restlessness and slight irritation of the respiratory tract. After the latency period, the animals began salivating,

appeared ill, and showed signs of narcosis. As the exposure period progressed, the animals became weak, ataxic, and incoordinated and often exhibited circular movement, convulsions, and twitching. At necropsy, all exposed animals were found to have some liver damage (edema and necrosis). Animals that died from nitromethane inhalation exhibited general visceral and cerebral congestion and acute pulmonary congestion with edema. Application of nitromethane (dose not specified) to the clipped skin of rabbits caused neither skin irritation nor compound-related clinical findings (Machle et al., 1940). In a study comparing hepatotoxicity, groups of three to five BALB/C mice were injected intraperitoneally with 275, 410, or 550 mg nitromethane, 2-nitropropane, or nitroethane per kilogram body weight and were killed 24, 48, 72, or 96 hours after dosing (Daval et al., 1989). Nitromethane and nitroethane were not hepatotoxic; treatment with 550 mg/kg 2-nitropropane caused increases in plasma sorbitol dehydrogenase, alanine aminotransferase, and aspartate aminotransferase activities and caused necrosis, degeneration, and cell proliferation in the liver.

Nitromethane has been used experimentally to cause histidinemia in inbred, weanling male Sprague-Dawley rats (Douay and Kamoun, 1980). The rats were injected subcutaneously with nitromethane at the rate of 0.8 mL of 110 g/L per 100 g body weight once daily for 6 days. Liver histidase in treated rats was 30% that of untreated control animals, while plasma, liver, and brain histidine increased threefold. Paralysis was observed in 61% of treated animals, while 15% displayed seizures. The rate of body weight gain was significantly reduced. No effect was observed on brain serotonin content or in plasma free amino acid concentrations. These findings indicate that animal histidinemia produced by nitromethane treatment is similar to human histidinemia.

In a study comparing the acute toxic effects of nitromethane and nitroethane, 3-month-old male Wistar rats were dosed intraperitoneally with 200 mg/kg of either compound (Zitting *et al.*, 1982). The rats were examined after 4, 24, or 48 hours. Both nitromethane and nitroethane caused an increase in brain acid proteinase and acetylcholine esterase activities. Nitromethane decreased NADPHcytochrome C reductase activity in liver microsomes.

Nitroethane depressed 7-ethoxycoumarin O-deethylase and NADPH-cytochrome C reductase but increased epoxide hydrolase and UDPglucuronosyltransferase activities in liver microsomes. In an earlier study, 2-nitropropane was shown to cause an increase in hepatic epoxide hydrolase and UDP-glucuronosyltransferase and brain acetylcholine esterase activities (Zitting et al., 1982). Rats and rabbits provided drinking water containing 23, 47, or 94 mg nitromethane per kilogram body weight for 2 months had increased alanine transaminase and aspartate transaminase activities and α - and γ -globulin concentrations, liver impairment (decreased plasma prothrombin), and increased whole blood cholinesterase; there were no effects on blood cell morphology (Subbotin, 1967). However, in studies in which rats and rabbits were provided drinking water containing 0.05, 0.5, or 12.5 mg/kg nitromethane for 6 months, serum alanine and aspartate transaminase activities were increased only in animals administered 12.5 mg/kg (Subbotin, 1967).

In a 6-month inhalation study, Sprague-Dawley rats and New Zealand white rabbits were exposed to 98 or 745 ppm nitromethane or 27 or 207 ppm 2-nitropropane for 7 hours per day, 5 days per week, for 6 months (Lewis et al., 1979). Interim evaluations were conducted on days 2 and 10 for rats and at 1 and 3 months for rats and rabbits. No deaths were attributed to nitromethane or 2-nitropropane administration in either species. Rats exposed to 745 ppm nitromethane did not gain weight as rapidly as the controls. There were no effects on hematologic parameters, prothrombin time, or alanine transaminase activity in either species, and no methemoglobin was produced in animals exposed to nitromethane. Rabbits in both groups exposed to nitromethane had depressed serum thyroxin concentrations throughout the study (statistically significant at 1 month for the 745 ppm group and at 6 months for both groups); this effect did not occur in animals exposed to 2-nitropropane. Rats and rabbits exposed to 745 ppm nitromethane also had greater thyroid gland weights than the controls. At all time points, lung weights of rats exposed to nitromethane were reduced. Lung and liver weights of rats exposed to 207 ppm 2-nitropropane were significantly increased at 3 and 6 months; 2-nitropropane did not cause organ weight effects in rabbits. There were no histopathologic changes related to nitromethane treatment in rats or rabbits at either concentration at any evaluation period. However, rats exposed to 207 ppm 2-nitropropane for 3 months had focal hepatocellular hypertrophy with large hepatocytes and basophilic foci containing small hyperplastic foci. Following 6 months of exposure to 207 ppm 2-nitropropane, all rats had multiple hepatocellular carcinomas (Lewis *et al.*, 1979).

In a study to investigate the potential hepatotoxicity of 1-nitropropane, Griffin *et al.* (1982) exposed male and female Long-Evans rats to 100 ppm 1-nitropropane by inhalation for 7 hours per day, 5 days per week, for up to $21\frac{1}{2}$ months. No treatment-related mortality, weight-gain effects, clinical signs, or effects on hematologic indices were observed. 1-Nitropropane exposure did not cause changes in clinical chemistry indices indicative of hepatotoxicity. No neoplasms or nonneoplastic lesions were attributed to exposure; the liver effects observed in the 2-nitropropane study (Lewis *et al.*, 1979) did not occur in rats exposed to 1-nitropropane.

Male and female Long-Evans rats exposed to 100 or 200 ppm nitroethane by inhalation for 7 hours per day, 5 days per week, for 2 years had no treatmentrelated mortality or effects on body weight gains (Griffin *et al.*, 1988). Hematology and clinical chemistry evaluations performed at the end of the study indicated no treatment-related effects. Additionally, there were no neoplasms or nonneoplastic lesions associated with nitroethane exposure.

Humans

No epidemiological studies of nitromethane alone were found in the literature (National Library of Medicine, 1995b). The estimated oral LD_{50} for humans is 500 mg/kg (Gosselin *et al.*, 1984). Nitromethane and its decomposition products are toxic if ingested or inhaled. Eye and skin irritation has occurred from repeated exposure.

REPRODUCTIVE

AND DEVELOPMENTAL TOXICITY

No information on the reproductive or developmental toxicity of nitromethane in experimental animals or

Introduction

in humans was found in the literature (National Library of Medicine, 1995b).

CARCINOGENICITY

No information on the carcinogenicity of nitromethane in experimental animals was found in the literature; additionally, no epidemiological studies or case reports examining the relationship between exposure to nitromethane and human cancer were found in the literature (National Library of Medicine, 1995b). As discussed previously, Sprague-Dawley rats exposed to 207 ppm 2-nitropropane by inhalation for 6 months had multiple hepatocellular carcinomas (Lewis et al., 1979). Male and female Long-Evans rats exposed to 100 or 200 ppm nitroethane by inhalation for 2 years (Griffin et al., 1988) or to 100 ppm 1-nitropropane by inhalation for 21¹/₂ months (Griffin et al., 1982) had no neoplasms or nonneoplastic lesions associated with treatment.

GENETIC TOXICITY

Little information is available on the mutagenicity of nitromethane, but the results of published studies are uniformly negative. Results for induction of mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 by nitromethane were negative with and without S9 metabolic activation in tests incorporating either the standard plate assay or preincubation (Chiu *et al.*, 1978; Mortelmans *et al.*, 1986; Dayal *et al.*, 1989; Dellarco and Prival, 1989). The nitronate form of nitromethane was negative for induction of mutations in *S. typhimurium* strains

19

TA100 and TA102 (Dayal et al., 1989). No significant increases in sex-linked recessive lethal mutations were noted in germ cells of male Drosophila melanogaster after administration of nitromethane by feeding (Gocke et al., 1981). No induction of micronuclei was observed in bone marrow polychromatic erythrocytes of male NMRI mice administered two intraperitoneal injections of 205 to 1,830 mg nitromethane per kilogram body weight (Gocke et al., 1981). In this test, bone marrow was sampled 6 hours after the second injection, so the effect of the second treatment is not likely to be reflected in these results; 24 hours is the preferred interval between treatment and observation of induced micronuclei. However, this negative result is in agreement with the results of the 13-week micronucleus study conducted by the NTP and presented in this report (Appendix E).

STUDY RATIONALE

Nitromethane was the sole chemical selected from the amines, amides, nitros, nitriles, ureas, and carbamates subclass of air pollutants and was subsequently nominated to the NTP for toxicity and carcinogenicity testing by the National Cancer Institute based on its high potential for human exposure and its structural relationship to 2-nitropropane and tetranitromethane, known animal carcinogens (NTP, 1990, 1994). Inhalation was chosen as the route of exposure because of the volatility of the chemical and because human exposure would likely occur by this route.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF NITROMETHANE

Nitromethane was obtained from W.R. Grace and Company (Lexington, MA) in three lots. Lot 1F 13 06 was used during the 16-day studies and the beginning of the 13-week studies; lot 1-H-0501 was used throughout the remainder of the 13-week studies and at the beginning of the 2-year studies. Lot 1-H-1004 was used throughout the remainder of the 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on the analyses performed in support of the nitromethane studies are on file at the National Institute of Environmental Health Sciences. The methods and results of these studies are detailed in Appendix J. The chemical, a clear, colorless liquid, was identified as nitromethane by infrared, ultraviolet/visible, and nuclear magnetic resonance spectrometry. The purity of each lot was determined by elemental analysis, Karl Fischer water analysis, functional group titration, and two gas chromatographic systems.

For lot 1F 13 06, elemental analyses of carbon and hydrogen agreed with the theoretical values for nitromethane, but results for nitrogen were low. water analysis indicated Karl Fischer $0.022\% \pm 0.004\%$ water. Functional group titration indicated a purity of $100\% \pm 1\%$. Both gas chromatographic systems indicated one impurity with an area greater than 0.1% relative to the major peak. The area of the impurity peak was 0.62% relative to the major peak by one gas chromatographic system and 0.52% relative to the major peak by the second system. The overall purity of lot 1F 13 06 was determined to be approximately 99%. Gas chromatography/mass spectrometry used to identify the impurity indicated that the mass spectrum of the impurity was consistent with that of propionitrile; an additional impurity observed in the sample was identified as 2-nitropropane. The quantity of propionitrile was determined with gas chromatography to be $0.400\% \pm 0.001\%$; the quantity of 2-nitropropane was determined to be $0.017\% \pm 0.000\%$.

For lot 1-H-0501 (batch 2), the supplier indicated a purity of 99.3% for the bulk chemical, with 0.27% nitroethane present as a contaminant. Elemental analyses of carbon and hydrogen by the analytical chemistry laboratory agreed with the theoretical values for nitromethane, but results for nitrogen were Karl Fischer water analysis indicated low. $0.018\% \pm 0.003\%$ water. Functional group titration indicated a purity of $98.9\% \pm 0.8\%$. Gas chromatography indicated three impurities with a combined area of 1.69% relative to the major peak by one system and two impurities with a combined area of 1.49% relative to the major peak by the second system. Batch 3 of lot 1-H-0501 was also analyzed with gas chromatographic system A; one major peak and three impurities with a total peak area 1.71% relative to the major peak were identified. Major peak comparisons of batch 2 with lot 1F 13 06 and of batch 3 with batch 2 were performed with gas chromatography; the results indicated a purity of 99.3% \pm 0.3% for batch 2 of lot 1-H-0501 relative to lot 1F 13 06 and a purity of 99.5% \pm 0.5% for batch 3 relative to batch 2. The overall purity of lot 1-H-0501 was determined to be approximately 98%.

For lot 1-H-1004, the supplier indicated a 99% purity of the bulk chemical, with nitroethane (0.25%) and 2-nitropropane (0.03%) present as contaminants. Elemental analyses of carbon and hydrogen by the analytical chemistry laboratory agreed with the theoretical values for nitromethane, but results for nitrogen were low. Karl Fischer water analysis indicated 0.086% \pm 0.006% water. Functional group titration indicated a purity of 97.8% \pm 0.5%. Gas chromatography indicated three impurities with a combined area of 1.5% relative to the major peak by one system and three impurities with a combined area of 1.9% relative to the major peak by the second system. Major peak comparison of lot 1-H-1004 with lot 1F 13 06 by gas chromatography indicated a purity of $100.3\% \pm 0.9\%$ for lot 1-H-1004 relative to lot 1F 13 06. The overall purity of lot 1-H-1004 was determined to be approximately 98%.

Accelerated stability studies of lots 1F 13 06 and 1-H-0501 of the bulk chemical were conducted with gas chromatography. Nitromethane was determined to be stable as a bulk chemical when stored in Teflon[®]-lined amber glass bottles, protected from light, for up to 2 weeks at temperatures up to 60° C. To ensure stability, the bulk chemical was stored in the original shipping containers (metal drums and amber glass bottles) at room temperature; lot 1F 13 06 was stored under a nitrogen headspace. Stability was monitored by the study laboratory throughout the studies with gas chromatography; no degradation of the bulk chemical was detected.

VAPOR GENERATION AND EXPOSURE SYSTEM

Nitromethane was held in a stainless-steel reservoir under a nitrogen blanket; a MasterFlex variable-speed peristaltic pump head (Cole-Parmer, Inc., Chicago, IL) was used to pump nitromethane through a liquid distribution manifold of stainless steel tubing to heated-wick vaporizers. During the 16-day studies, single vaporizers were used for each of the 750 and 1,500 ppm chambers, and a third vaporizer was located in the vapor distribution system that supplied the 94, 188, and 375 ppm chambers. During the 13-week and 2-year studies, one set of dual vaporizers supplied nitromethane vapor to all chambers. Detailed descriptions of the inhalation chambers and the vapor generation system are provided in Appendix J.

The vapor-laden air was transferred through the distribution line, where it was diluted with HEPAand charcoal-filtered air, to the inhalation chambers; three-way valves mounted in the chamber inlet ducts allowed nitromethane vapors to be diverted to the exhaust until a stable concentration of nitromethane was built up in the distribution line. At each chamber, air moving through the chamber inlet duct was further diluted with HEPA- and charcoal-filtered air to the appropriate nitromethane concentration for the chamber with a metered three-way valve. The study laboratory designed the inhalation exposure chamber (Harford Systems Division of Lab Products, Inc., Aberdeen, MD) so that uniform vapor concentrations could be maintained throughout the chamber with the catch pans in place. A small particle detector (Type CN, Gardner Associates, Schenectady, NY) was used with and without animals in the exposure chambers to ensure that nitromethane vapor, and not aerosol, was produced. No particle counts above the minimum resolvable level of approximately 200 particles/cm³ were detected.

VAPOR CONCENTRATION MONITORING

Chamber concentrations were monitored with an on-line gas chromatograph. The monitor was coupled with the inhalation chambers by a computercontrolled 12-port stream select valve. The gas chromatograph was calibrated by a comparison of chamber concentration data to data from grab samples analyzed by an off-line gas chromatograph; the grab samples were collected in bubblers containing dimethylformamide. The off-line gas chromatograph was calibrated with gravimetrically prepared nitromethane standards. Chamber concentration uniformity was maintained throughout the 16-day, 13-week, and 2-year studies. Summaries of the chamber concentrations for the 16-day, 13-week, and 2-year studies are presented in Tables J1 through J3. The monthly mean exposure concentrations for the 2-year study chambers are presented in Figures J7 through J12.

CHAMBER ATMOSPHERE CHARACTERIZATION

Buildup and decay rates for chamber concentrations were determined with and without animals present in the chambers. The time to achieve 90% of the target concentration after the beginning of vapor generation (T_{90}) ranged from 10 to 13 minutes during the 16-day studies and from 6 to 13 minutes during the 13-week studies. The time for the concentration in the chamber to decay to 10% of the target concentration after vapor generation ended (T_{10}) ranged from 11 to 14 minutes during the 16-day studies and from 11 to

Materials and Methods

15 minutes during the 13-week studies. During the 2-year studies, T_{90} ranged from 11 to 14 minutes without animals and from 5 to 17 minutes with animals in the chambers; T_{10} ranged from 13 to 16 minutes without animals and from 13 to 19 minutes with animals. A T_{90} value of 12 minutes was selected for all studies.

Studies of nitromethane degradation and monitoring for impurities were conducted throughout the studies by comparing bubbler samples to a reference sample of nitromethane. No significant degradation of nitromethane was observed during the studies.

16-DAY STUDIES

Male and female F344/N rats and $B6C3F_1$ mice were obtained from Simonsen Laboratories, Inc. (Gilroy, CA). On receipt, the rats and mice were 5 weeks old. Animals were quarantined for 12 days (rats) or 13 days (mice) and were 7 weeks old on the first day of the studies. Before the studies began, two male and two female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease.

Groups of five male and five female rats and mice were exposed to 0, 94, 188, 375, 750, or 1,500 ppm nitromethane by inhalation, 6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 16 days. Rats and mice received a total of 12 exposures, including two (rats) or three (mice) consecutive exposures before necropsy. Water was available *ad libitum*; feed was available *ad libitum* except during exposure periods. Rats and mice were housed individually. Clinical observations were recorded twice each day for rats and mice. The animals were weighed initially, on day 8, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 1.

At the end of the 16-day studies, a necropsy was performed on all rats and mice. The heart, right kidney, liver, lungs, right testis, thymus, and thyroid glands (rats only) were weighed. Histopathologic examinations were performed on all rats and mice. Following the 13-week studies, sections of the sciatic nerve of rats from the 16-day study were stained with Sevier-Munger Luxol Fast Blue to allow for evaluation of myelin around sciatic nerve axons. The tissues and organs routinely examined are listed in Table 1.

13-WEEK STUDIES

The 13-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to nitromethane and to determine the appropriate exposure concentrations to be used in the 2-year studies.

Male and female F344/N rats and $B6C3F_1$ mice were obtained from Simonsen Laboratories (Gilroy, CA). On receipt, the rats and mice were 4 weeks old. Animals were guarantined for 13 or 14 days and were approximately 6 weeks old on the first day of the studies. Before the studies began, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. Additionally, the kidneys of five male and five female mice were screened to ensure genetic integrity; the genetic profile of these mice was consistent with that of the $B6C3F_1$ strain. At the end of the study, serologic analyses were performed on five male and five female sentinel rats and control mice under the protocols of the NTP Sentinel Animal Program (Appendix L).

Groups of 10 male and 10 female rats and mice were exposed to 0, 94, 188, 375, 750, or 1,500 ppm nitromethane by inhalation, 6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 13 weeks. Additional groups of 10 male and 10 female rats designated for clinical pathology evaluations received the same exposure concentrations as the core study rats. Water was available *ad libitum*; feed was available *ad libitum* except during exposure periods. Rats and mice were housed individually. Clinical observations were recorded weekly. The core study animals were weighed initially, weekly, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 1.

Neurobehavior tests including forelimb and hindlimb grip strength measurements, response to stimulus (tail flick latency), and startle response were performed on all male and female rats in the core study over a 2-day period during week 11. Rats were allowed to acclimate to the testing room for at least 2 hours. Forelimb and hindlimb grip strengths were measured

by allowing each rat to grip a triangular ring with its forepaws; the rat was pulled back along a channel until its forelimb grip was broken. While the backward motion continued, the rat was allowed to grasp a T-bar in the same channel with its hindpaws, then forced to release the bar by continued pulling. The strain required to break the forelimb and hindlimb grip was recorded with a calibrated push-pull strain gauge; for each animal, the means of three successive readings were determined for forelimb and hindlimb grip strength. Tail flick latency was measured with a Tail Flick Analgesiometer (Socrel, Varese, Italy), consisting of an infrared heat source (100 W) with radiant energy of adjustable intensity focused by a parabolic mirror on a photocell. Each rat was placed with its tail on the photocell window and a footpedal was depressed to activate the heat source and a timer; when the rat felt pain and flicked its tail, the photocell became energized, turning off the timer and the heat source. The reaction time was recorded as the time from heat onset to tail flick. Startle response to acoustic stimulation was measured with an SR Lab System (SRI, Scientific and Professional Support Group, La Jolla, CA); this system, which was located in an isolation chamber, measured the response of each rat to a series of six 40-millisecond bursts of 120 dB white noise, spaced 15 seconds apart, after the animal was acclimated to the system for 5 minutes. The maximum response amplitude and the time to reach the maximum response were measured.

Clinical pathology analyses were performed on rats designated for clinical pathology evaluation on days 3 and 23 and on core study rats at the end of the 13-week study. Rats were anesthetized and blood was withdrawn from the retroorbital plexus. Blood for hematology determinations was placed in collection tubes containing potassium EDTA as an anticoagulant. Blood for clinical chemistry evaluations was placed in tubes without anticoagulant and allowed to clot; these samples were then centrifuged and serum was removed. Erythrocyte and leukocyte counts, hematocrit, hemoglobin concentration, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, and platelet counts were measured on an Ortho ELT-8/ds Hematology Counter (Ortho Instruments, Westwood, MA). Differential leukocyte counts, morphologic evaluation of blood cells, and nucleated erythrocyte counts were determined by light microscopic examination of blood films stained with Wright-Giemsa. Methemoglobin was measured within 30 minutes of blood collection with an IL co-oximeter (Instrumentation Laboratory, Inc., Lexington, MA). Clinical chemistry determinations were performed on an Abbott VP chemistry analyzer (Abbott Laboratories, Abbott Park, IL) with commercially available reagents. Serum triiodothyronine, thyroxine, free thyroxine, and thyroidstimulating hormone concentrations were determined by ¹²⁵I radioimmunoassay techniques on a Packard Auto-Gamma counter (Packard Instrument Company, Downers Grove, IL). Reagents for triiodothyronine, thyroxine, and free thyroxine assays were obtained commercially; thyroid-stimulating hormone concentration measurements were performed with reference material obtained from the National Hormone and Pituitary Program. The hematology and clinical chemistry parameters measured are listed in Table 1.

At the end of the 13-week studies, samples were collected for sperm motility and vaginal cytology evaluations from all rats and mice in the 0, 375, 750, and 1,500 ppm groups. The parameters evaluated are listed in Table 1. Methods used were those described in the NTP's sperm motility and vaginal cytology evaluations protocol (NTP, 1987). For 7 consecutive days before the scheduled terminal sacrifice, the vaginal vaults of the females were moistened with saline, if necessary, and samples of vaginal fluid and cells were stained. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and used to ascertain estrous cycle stage (i.e., diestrus, proestrus, estrus, and metestrus). Male animals were evaluated for sperm count and motility. The left epididymis and testis were isolated and weighed. The tail of the epididymis (cauda epididymis) was then removed from the epididymal body (corpus epididymis) and weighed. Test yolk (rats) or modified Tyrode's buffer (mice) was applied to slides, and a small incision was made at the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides, and the numbers of motile and nonmotile spermatozoa were counted for five fields per slide by two observers. Following completion of sperm motility estimates, each left cauda epididymis was placed in buffered saline solution. Caudae were finely minced, and the tissue was incubated in the

Materials and Methods

saline solution and then heat fixed at 65° C. Sperm density was then determined microscopically with the aid of a hemacytometer. To quantify spermatogenesis, the testicular spermatid head count was determined by removing the tunica albuginea and homogenizing the left testis in phosphate-buffered saline containing 10% dimethyl sulfoxide. Homogenization-resistant spermatid nuclei were counted with a hemacytometer.

A necropsy was performed on all core study animals. The heart, right kidney, liver, lungs, right testis, thymus, and thyroid gland (rats only) were weighed. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 μ m, and stained with hematoxylin and eosin; additional sections of the spinal cord and sciatic nerve of rats were stained with Sevier-Munger Luxol Fast Blue to allow for a more complete evaluation of myelin around sciatic nerve axons. A complete histopathologic examination was performed on core study rats and mice in the 0 and 1,500 ppm groups. Additionally, all gross lesions and tissue masses and selected tissues of rats and mice in the lower exposure groups were examined. The tissues and organs examined are listed in Table 1.

2-YEAR STUDIES

Study Design

Groups of 50 male and 50 female rats and mice were exposed to nitromethane by inhalation, 6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 103 weeks. Rats were exposed to 0, 94, 188, or 375 ppm. Mice were exposed to 0, 188, 375, or 750 ppm.

Source and Specification of Animals

Male and female F344/N rats and B6C3F₁ mice were obtained from Simonsen Laboratories, Inc. (Gilroy, CA) for use in the 2-year studies. Rats and mice were quarantined for 14 days before the studies began. Five male and five female rats and mice were selected for parasite evaluation and gross observation of disease. Additionally, the kidneys of five male and five female mice were screened to ensure genetic integrity; the genetic profile of these mice was consistent with that of the B6C3F₁ strain. Rats and mice were approximately 6 weeks old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix L).

Animal Maintenance

Rats and mice were housed individually. Water was available *ad libitum*; feed was available *ad libitum* except during exposure periods. Cages were rotated within the inhalation chambers weekly. Further details of animal maintenance are given in Table 1. Information on feed composition and contaminants is provided in Appendix K.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings were recorded monthly through week 91, then every 2 weeks until the end of the studies. Animals were weighed at the beginning of the studies, weekly through week 12, monthly from week 15 through week 91, every 2 weeks thereafter, and at the end of the studies.

Complete necropsies and microscopic examinations were performed on all rats and mice. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 μ m, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (i.e., adrenal gland, kidney, ovary), samples from each organ were examined. Complete histopathologic examinations were performed on all animals. The sciatic nerves and spinal cords from approximately 15 male and 15 female rats in the 0 and 375 ppm groups were examined. For extended evaluation of renal tubule proliferative lesions in male rats, kidneys were step-sectioned at 1-mm intervals, and four additional sections were obtained from each kidney. The tissues and organs routinely examined are listed in Table 1.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The microscopic 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 evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year studies, a quality assessment pathologist reviewed the lung, nasal cavity, and all neoplasms of all male and female rats; the kidney of all male rats; the mammary gland of all female rats; the sciatic nerve and spinal cord of approximately 15 male and 15 female rats in the 0 and 375 ppm groups; and the harderian gland, liver, lung, and nose and all neoplasms of all male and female mice.

The quality assessment report and the reviewed slides were submitted to the NTP Pathology Working Group (PWG) chairperson, who reviewed selected tissues and addressed any inconsistencies in the diagnoses made by the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chairperson to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without knowledge of dose groups or previously rendered diagnoses. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Thus, the final diagnoses represent a consensus of quality assessment pathologists, the PWG chairperson, and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). For subsequent analyses of the pathology data, the diagnosed lesions for each tissue type were evaluated separately or combined according to the guidelines of McConnell et al. (1986).

STATISTICAL METHODS Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals found dead of other than natural causes were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions as presented in Tables A1, A4, B1, B5, C1, C5, D1, and D5 are given as the number of animals bearing such lesions at a specific anatomic site and the number of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., skin, intestine, harderian gland, and mammary gland) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, B3, C3, and D3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm. i.e., the Kaplan-Meier estimate of the neoplasm incidence that would have been observed at the end of the study in the absence of mortality from all other competing risks (Kaplan and Meier, 1958).

Analysis of Neoplasm Incidences

The majority of neoplasms in these studies were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was logistic regression analysis, which assumed that the diagnosed neoplasms were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, neoplasm prevalence was modeled as a logistic function of chemical exposure and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if the fit of the model was not significantly enhanced. The neoplasm incidences of exposed and 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). When neoplasms are incidental, this comparison of the time-specific neoplasm prevalences also provides a comparison of the time-specific neoplasm incidences (McKnight and Crowley, 1984).

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

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall dose-related trend. Continuity-corrected tests were used in the analysis of neoplasm incidence, and reported P values are one sided. For further discussion of these statistical methods, refer to Haseman (1984).

Using individual animal data from more than 3,000 rats and mice in the NTP historical control database, Seilkop (1995) demonstrated that certain site-specific neoplasms are strongly correlated with body weight. Seilkop also developed a logistic regression model that accurately predicted the control incidence of these neoplasms based on survival and 52-week body weights. The Seilkop model was used in these studies to evaluate the possible impact of survival and body weight differences on the incidence of mammary gland neoplasms in female F344/N rats and liver neoplasms in B6C3F₁ mice, the neoplasms having the strongest correlation with body weights.

Analysis of Nonneoplastic Lesion Incidences Because all nonneoplastic lesions in this study were considered to be incidental to the cause of death or not rapidly lethal, the primary statistical analysis used was a logistic regression analysis in which nonneoplastic lesion prevalence was modeled as a logistic function of chemical exposure and time.

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight and neurobehavior data, which have approximately normal distributions, were analyzed with the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Hematology, clinical chemistry, spermatid, and epididymal spermatozoal data, which have typically skewed distributions, were analyzed with the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic doserelated trend (Dunnett's or Dunn's test). Prior to statistical analysis, extreme values identified by the outlier test of Dixon and Massey (1951) were examined by NTP personnel, and implausible values were eliminated from the analysis. Average severity values were analyzed for significance with the Mann-Whitney U test (Hollander and Wolfe, 1973). Because the vaginal cytology data are proportions (the proportion of the observation period that an animal was in a given estrous stage), an arcsine transformation was used to bring the data into closer conformance with a normality assumption. Treatment effects were investigated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for simultaneous equality of measurements across exposure levels.

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, historical control data can be helpful in the overall assessment of neoplasm incidence in certain instances. Consequently, neoplasm incidences from the NTP historical control database, which is updated yearly, are included in the NTP reports for neoplasms appearing to show compound-related effects.

QUALITY ASSURANCE METHODS

The 13-week and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, these studies were

audited retrospectively by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report were conducted. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff, so all comments had been resolved or were otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICOLOGY

The genetic toxicity of nitromethane was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, and increases in the frequency of micronucleated erythrocytes in mouse peripheral blood. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies of nitromethane are part of a larger effort by the NTP to develop a database that would permit the evaluation of carcinogenicity in experimental animals from the structure and responses of the chemical in short-term *in vitro* and *in vivo* genetic toxicity tests. These genetic toxicity tests were originally developed to study mechanisms of chemically induced DNA damage and to predict carcinogenicity in animals, based on the electrophilic theory of chemical carcinogenesis and the somatic mutation theory (Miller and Miller, 1977; Straus, 1981; Crawford, 1985).

There is a strong correlation between a chemical's potential electrophilicity (structural alert to DNA reactivity), mutagenicity in Salmonella, and carcinogenicity in rodents. The combination of electrophilicity and Salmonella mutagenicity is highly correlated with the induction of carcinogenicity in rats and mice and/or at multiple tissue sites (Ashby and Tennant, 1991). Other in vitro genetic toxicity tests do not correlate well with rodent carcinogenicity (Tennant et al., 1987; Zeiger et al., 1990), although these other tests can provide information on the types of DNA and chromosome effects that can be induced by the chemical being investigated. Data from NTP studies show that a positive response in Salmonella is currently the most predictive in vitro test for rodent carcinogenicity (89% of the Salmonella mutagens were rodent carcinogens), and that there is no complementarity among the in vitro genetic toxicity tests. That is, no battery of tests that included the Salmonella test improved the predictivity of the Salmonella test alone. The predictivity for carcinogenicity of a positive response in bone marrow chromosome aberration or micronucleus tests is not yet defined.

TABLE 1

Experimental Design and Materials and Methods in the Inhalation Studies of Nitromethane

16-Day Studies	13-Week Studies	2-Year Studies
Study Laboratory		
Battelle Pacific Northwest Laboratories (Richland, WA)	Battelle Pacific Northwest Laboratories (Richland, WA)	Battelle Pacific Northwest Laboratories (Richland, WA)
Strain and Species		
Rats: F344/N Mice: B6C3F ₁	Rats: F344/N Mice: B6C3F ₁	Rats: F344/N Mice: B6C3F ₁
Animal Source		
Simonsen Laboratories, Inc. (Gilroy, CA)	Simonsen Laboratories, Inc. (Gilroy, CA)	Simonsen Laboratories, Inc. (Gilroy, CA)
Time Held Before Studies		
Rats: 12 days Mice: 13 days	Rats: 13 (male) or 14 days (female) Mice: 14 days	14 days
Average Age When Studies Began		
7 weeks	6 weeks	7 weeks
Date of First Dose		· ·
Rats: 14 March 1988 Mice: 15 March 1988	Rats: 5 (male) or 6 (female) July 1988 Mice: 6 July 1988	Rats: 7 September 1989 Mice: 31 August 1989
Duration of Dosing		
6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 16 days	6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 13 weeks	6 hours plus T_{s0} (12 minutes) per day, 5 days per week, for 103 weeks
Date of Last Dose		1
Rats: 29 March 1988	Rats: 3 (male) or 4 (female) October	Rats: 28 August 1991
Mice: 30 March 1988	Mice: 5 (male) or 6 (female) October 1988	Mice: 21 August 1991
Necropsy Dates		
Rats: 30 March 1988	Rats: 4 (male) or 5 (female) October	Rats: 9-11 September 1991
Mice: 31 March 1988	1988 Mice: 6 (male) or 7 (female) October 1988	Mice: 3-6 September 1991
Average Age at Necronsy		
9 weeks	Rats: 19 weeks Mice: 19 (male) or 20 weeks (female)	Rats: 111 weeks Mice: 111-112 weeks
Size of Study Groups		
5 males and 5 females	10 males and 10 females	50 males and 50 females
Method of Distribution		
Animals were distributed randomly into groups of approximately equal initial mean body weight.	Same as 16-day studies	Same as 16-day studies

TABLE 1

Experimental Design and Materials and Methods in the Inhalation Studies of Nitromethane (continued)

16-Day Studies	13-Week Studies	2-Year Studies			
Animals ner Cage					
1	1	1			
Method of Animal Identification					
Rats: tail tattoo	Tail tattoo	Tail tattoo			
Mice: toe clip					
Diet					
NIH-07 open formula pelleted diet	Same as 16-day studies	Same as 16-day studies			
(Zeigler Brothers, Inc., Gardners, PA),					
available ad libitum except during					
exposure periods, changed weekly					
Water Distribution					
Softened tap water (City of Richland	Softened tap water (City of Richland	Same as 16-day studies			
municipal supply) via automatic	municipal supply) via automatic	,			
watering system (Systems Engineering,	watering system (Edstrom Industries,				
Napa, CA), available ad libitum	Waterford, WI), available ad libitum				
Cages					
Stainless steel wire-bottom cages (Lab	Same as 16-day studies, but rotated in	Stainless steel wire-bottom cages (Lab			
Products, Inc., Harford Systems,	chamber weekly	Products, Inc., Maywood, NJ);			
Aberdeen, MD); changed weekly and		changed and rotated in chamber weekly			
Totaleu ili chamber dany					
Chambers	· · · · · · · · · · · · · · · · · · ·				
Stainless steel chambers (Lab Products	Same as 16-day studies	Same as 16-day studies			
Inc., Harford Systems, Aberdeen.					
MD), changed weekly					
Chamber Filters					
Single HEPA (Flanders Filters, Inc.,	Same as 16-day studies	Same as 16-day studies			
San Rafael, CA) and charcoal (RSE,		•			
Inc., New Baltimore, MI)					
Chamber Environment		·			
Mean temperature: 22.5° to 24.2° C	Mean temperature: 23.2° to 24.1° C	Mean temperature: 23.9° to 24.3° C			
Mean relative humidity: 51% to 55%	Mean relative humidity: 55% to 57%	(rats), 23.5° to 23.9° C (mice)			
Room fluorescent light: 12 hours/day	Room fluorescent light: 12 hours/day	Mean relative humidity: 55% to 57%			
Chamber air: 14.5 to 15.9 ft ³ /minute	Chamber air: 14.4 to 14.6 ft ³ /minute	(rats), 54% to 56% (mice)			
		Room fluorescent light: 12 hours/day			
		Chamber air: 15.1 to 15.6 ft ³ /minute			
	·	(rats), 14.6 to 14.7 ft'/minute			
		(mice)			
E					
Exposure Concentrations	0 04 199 275 750 or 1 500 mm	Pate: 0. 94 188 or 375 nm			
U, 94, 188, 375, 750, or 1,500 ppm	0, 94, 100, 575, 750, 01 1,500 ppm	Mice: 0 188 375 or 750 ppm			
		11100. 0, 100, 575, 01 750 ppm			

TABLE 1

Experimental Design and Materials and Methods in the Inhalation Studies of Nitromethane (continued)

16-Day Studies	13-Week Studies	2-Year Studies
Type and Frequency of Observation		
Observed and clinical observations	Observed twice daily; animals were weighed initially, weekly, and at the	Observed twice daily; clinical observations were recorded monthly
weighed initially, on day 8, and at the end of the studies.	end of the studies; clinical observations were recorded weekly.	through week 91, then every 2 weeks until the end of the studies. Animals were weighed initially, weekly through week 12, monthly from week 15 through week 91, every 2 weeks thereafter, and at the end of the studies.
Method of Sacrifice		
Asphyxiation with 70% CO_2	Asphyxiation with 70% CO ₂	Asphyxiation with 70% CO_2
Necropsy		
Necropsy performed on all animals.	Necropsy performed on all core study	Necropsy performed on all animals.
Urgans weighed were heart, right kidney liver lungs right testis	animals. Organs weighed were heart,	
thymus, and thyroid glands (rats only).	thymus, and thyroid glands (rats only).	
Clinical Pathology		
None	Blood was collected from all clinical	None
	pathology group rats on days 3 and 23 and from all core study rats at the end of the study for hematology and clinical chemistry. Blood was collected from the retroorbital plexus of animals anesthetized with 70% CO ₂ after 2 or 3 consecutive days of exposure. <i>Hematology:</i> hematocrit, hemoglobin concentration, erythrocyte counts, nucleated erythrocyte counts, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, platelet	
	counts, total leukocyte count and differentiels, and methemoslohin	
	concentration	
	Clinical chemistry: urea nitrogen,	
· · · ·	creatinine, total protein, albumin, and	
	aminotransferase, alkaline phosphatase,	
	creatine kinase, and sorbitol	
	dehydrogenase activities; bile acid, thyroid-stimulating hormone	
	triiodothyronine, and total and free	
	thyroxine concentrations	

TABLE 1

Experimental Design and Materials and Methods in the Inhalation Studies of Nitromethane (continued)

16-Day Studies	13-W	2-Year Studies			
			· · · · · · · · · · · · · · · · · · ·		
Histopathology					-

Histopathology was performed on all rats and mice. In addition to gross lesions and tissue masses, the tissues examined included: brain, larynx, lung and attached tracheobronchial lymph nodes, nose, sciatic nerve (rats), and trachea (longitudinal and transverse sections).

Sperm Motility and Vaginal Cytology Evaluations None

Neurobehavioral Evaluations None Complete histopathology was performed on core study rats and mice in the 0 and 1,500 ppm groups. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, bone and marrow, brain, clitoral gland, epididymis, esophagus, eyes (if grossly abnormal), gallbladder (mice), heart, kidney, large intestine (cecum, colon, and rectum), larynx, liver, lung, lymph nodes (bronchial, mandibular, mediastinal, and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pharynx (if grossly abnormal), pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, skin, small intestine (duodenum, jejunum, and ileum), spinal cord and sciatic nerve (rats), spleen, stomach (forestomach and glandular stomach), testis, thigh muscle, thymus, thyroid gland, trachea, urinary bladder, uterus, and vagina (females in vaginal cytology studies only). Additionally, the bone marrow, lung, and nose of male and female rats; cecum, larynx, and testis of male rats; and the nose and spleen of male and female mice in the 94, 188, 375, and 750 ppm groups were examined until a no-effect level was reached.

Rats and mice in the 0, 375, 750, and 1,500 ppm groups were evaluated. Sperm samples were collected at the end of the studies and evaluated for sperm count and motility. The left cauda, epididymis, and testis were weighed. Vaginal samples were collected for 7 consecutive days before the end of the studies and evaluated for the relative frequency of estrous stages and for estrous cycle length.

Neurobehavior testing was performed on core study rats over a 2-day period during week 11 of the study. Parameters measured included forelimb and hindlimb grip strength, tail flick latency, and startle response. adrenal gland, bone and marrow, brain, clitoral gland, epididymis, esophagus, gallbladder (mice). harderian gland (mice), heart, kidney, large intestine (cecum, colon, and rectum), larynx, liver, lung, lymph nodes (bronchial, mandibular, mediastinal, and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, skin, small intestine (duodenum, jejunum, and ileum), spinal cord and sciatic nerve (a limited review of male and female rats in the 0 and 375 ppm groups), spleen, stomach (forestomach and glandular stomach), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus.

Complete histopathology was

performed on all rats and mice. In

addition to gross lesions and tissue

masses, the tissues examined included:

None

None

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RESULTS

Rats

16-Day Study

All rats survived until the end of the study (Table 2). The mean body weight gain of male rats in the 1,500 ppm group was slightly but significantly less than that of the controls; the final mean body weights and mean body weight gains of exposed females were similar to those of the controls. Clinical findings of toxicity were observed in all male and female rats in the 1,500 ppm groups and included increased preening, rapid breathing, hyperactivity early in the study, and hypoactivity and loss of coordination in the hindlimbs near the end of the study.

The relative liver weights of all exposed groups of male rats and the absolute and relative liver weights of females exposed to 375 ppm or greater were significantly greater than those of the controls (Table F1). The relative kidney weights of male rats in the 750 and 1,500 ppm groups and female rats in the 1,500 ppm group were significantly greater than those of the controls; other differences in organ weights between exposed and control rats were secondary to body weight changes. Absolute and relative lung weights of exposed rats were similar to those of the controls.

Table 2

Survival a	and Body	Weights	of Rats	in the	16-Dav	Inhalation	Study	of	Nitromethane
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			Mean Body Weight ^b	(g)	Final Weight		
Concentration (ppm)	Survival ^a	Initial	Final	Change	Relative to Controls (%)		
Male			. <u></u>				
0	5/5	145 ± 4	182 ± 4	38 ± 2			
94	5/5	147 ± 4	189 ± 5	43 ± 2	104		
188	5/5	146 ± 4	187 ± 5	41 ± 2	103		
375	5/5	145 ± 3	182 ± 6	37 ± 3	100		
750	5/5	144 ± 3	177 ± 4	34 ± 1	97		
1,500	5/5	146 ± 3	171 ± 4	25 ± 3**	94		
Female							
0	5/5	116 ± 2	134 ± 3	17 ± 1			
94	5/5	116 ± 2	135 ± 3	18 ± 3	101		
188	5/5	116 ± 2	133 ± 2	17 ± 1	99		
375	5/5	116 ± 2	133 ± 2	18 ± 2	100		
750	5/5	117 ± 2	132 ± 1	15 ± 2	99		
1,500	5/5	117 ± 2	128 ± 2	11 ± 1	96		

** Significantly different (P≤0.01) from the control group by Williams' or Dunnett's test

^a Number of animals surviving at 16 days/number initially in group

^b Weights and weight changes are given as mean \pm standard error.

All males exposed to 375 ppm or greater, all females in the 750 and 1,500 ppm groups, and four females in the 375 ppm group had degeneration of the olfactory epithelium of the nasal turbinates; this lesion was of minimal to mild severity in exposed males and females (Table 3). There were no exposure-related lesions in the lungs of exposed male or female rats.

During the 16-day study, neurobehavioral effects were not sufficient to warrant evaluation of nervous system tissues. However, because of the hindlimb paralysis and histopathologic effects on the sciatic nerve in the 13-week study, the sciatic nerves from rats in the 16-day study were subsequently evaluated histopathologically. Sciatic nerve degeneration was present in all male and female rats exposed to 375 ppm or greater (Table 3). This lesion was characterized by prominent, diffuse vacuolization and dilatation of the axonal sheaths and increased cellularity, which was apparently due to Schwann cell hyperplasia. The severity of these lesions increased with increasing exposure concentration and ranged from minimal to moderate. Rats exposed to 750 or 1,500 ppm had significantly less myelin around the sciatic axons than did the controls.

Exposure Concentration Selection Rationale: Due to the lack of significant toxicologic or histopathologic effects, including the absence of histopathologic effects in the lung, nitromethane exposure concentrations selected for use in the 13-week study were the same as for the 16-day study. The sciatic nerve degeneration in rats in the 16-day study was not discovered until after the conclusion of the 13-week study.

TABLE 3

Incidences of Selected Nonneoplastic Lesions in Rats in the 16-Day Inhalation Study of Nitromethane

	0 ppm	94 ppm	188 ppm	375 ppm	750 ppm	1,500 ppm
Male						
Nose/Turbinates ^a	5	5	5	5	5	5
Epithelium ^b	0	0	0	5** (1.0) ^c	5** (2.0)	5** (2.0)
Sciatic Nerve Degeneration	4 0	5 0	5 0	5 5** (1.0)	5 5** (2.0)	5 5** (3,0)
Female	y	. ·		, ,	•	
Nose/Turbinates						· · · ·
Degeneration, Olfactory Epithelium	5 0	5 0	5 0	5 4* (1.0)	5 5** (1.8)	5 5** (2.0)
Sciatic Nerve	5	5	5	5	5	5
Degeneration	0	0	0	5** (1.0)	5** (2.0)	5** (3.0)

* Significantly different ($P \le 0.05$) from the control group by the Fisher exact test

** P≤0.01

^a Number of animals with tissue examined microscopically

^D Number of animals with lesion

^c Average severity of lesions in affected rats: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked
13-WEEK STUDY

All rats survived to the end of the study (Table 4). The final mean body weight and weight gain of male rats in the 1,500 ppm group were significantly less than those of the controls. Clinical findings included hindlimb paralysis in all male and female rats in the 1,500 ppm groups, beginning on day 21, and one male and four females in the 750 ppm groups, beginning on day 63.

Hematology and clinical chemistry data are provided in Table G1. Exposure to nitromethane caused an exposure concentration-dependent, microcytic, responsive anemia in rats. The anemia was characterized by mild to moderate decreases in hematocrit values and hemoglobin concentrations, and the microcytosis was evidenced by minimal to moderate decreases in mean cell volume. Hematocrit values and hemoglobin concentrations were less than those of the controls for male and female rats in the 375, 750, and 1,500 ppm groups at all time points and in the 94 and 188 ppm groups at various time points. Additionally, erythrocyte counts on day 3 were minimally to mildly decreased in males exposed to 188 ppm or greater and females exposed to 750 or 1,500 ppm compared those of the controls; this finding is consistent with anemia. The decreases in mean cell volume occurred in all groups of exposed females at all time points and in all groups of exposed males at the end of the study; decreased mean cell volumes indicate increased numbers of smaller erythrocytes in the circulation. Review of erythrocyte size distribution information on day 23 revealed that two distinct populations of erythrocytes were present in rats in the higher exposure groups; one of these populations consisted of smaller

Table 4

Survival and Body Weights of Rats in the 13-Week Inhalation Study of Nitromethane

			g)	Final Weight	
Concentration (ppm)	Survival ^a	Initial	Final	Change	Relative to Controls (%)
Male			·		
0	10/10	107 ± 3	334 ± 7	228 ± 6	
94	10/10	105 ± 2	323 ± 7	218 ± 7	97
188	10/10	113 ± 2	345 ± 4	232 ± 3	103
375	10/10	109 ± 3	336 ± 5	227 ± 4	101
750	10/10	106 ± 2	327 ± 4	221 ± 5	98
1,500	10/10	109 ± 2	295 ± 10**	185 ± 9**	88
Female					
0	10/10	95 ± 1	185 ± 5	90 ± 3	
94	10/10	96 ± 2	197 ± 3	101 ± 2	107
188	10/10	97 ± 2	197 ± 3	100 ± 2	106
375	10/10	95 ± 2	198 ± 5	$103 \pm 4**$	107
750	10/10	96 ± 2	194 ± 4	97 ± 2	105
1,500	10/10	94 ± 2	177 ± 4	84 ± 3	96

** Significantly different ($P \le 0.01$) from the control group by Williams' or Dunnett's test

^a Number of animals surviving at 13 weeks/number initially in group

^b Weights and weight changes are given as mean \pm standard error.

erythrocytes. Additionally, microcytosis was observed in the blood smears of exposed rats; microcytosis is consistent with the decreased mean cell volume. At all time points, mean cell hemoglobin values of exposed rats were decreased compared to those of the controls; these decreases were attributed to the smaller erythrocyte sizes. The mean cell hemoglobin concentrations of males exposed to 750 or 1,500 ppm and females exposed to 1,500 ppm were minimally greater than those of the controls at all time points. Increases in mean cell hemoglobin concentration have been related to erythrocyte hemolysis (in vivo or in vitro). On day 23 and at week 13, a hematopoietic response was evidenced by increased numbers of nucleated ervthrocytes in exposed animals compared to the controls.

Exposure concentration-dependent alterations in erythrocyte morphology occurred at all time points. On day 3, minimal numbers of Heinz bodies were observed in male rats in the 750 and 1,500 ppm groups; other red blood cell changes were present in males and females in the higher exposure groups on day 23 and at week 13. Morphologic alterations of red blood cells included anisocytosis (e.g., microcytes and spherocytes), poikilocytosis (e.g., schistocytes and acanthocytes), polychromasia, and target cells. The presence of Heinz bodies would be consistent with oxidative red blood cell damage. Schistocytes are irregular erythrocyte fragments that usually result from trauma to red blood cells; the presence of these would suggest a hemolytic process. Spherocytes have been observed in conjunction with immunemediated and Heinz body anemias. Polychromasia would be consistent with the presence of young erythrocytes (reticulocytes) and would indicate a bone marrow response to the anemia.

Minimal, exposure concentration-dependent increases in methemoglobin concentration occurred in male and female rats, indicating oxidative red cell injury. Male rats exposed to 375 ppm or greater had minimally increased methemoglobin concentrations compared to the controls at all time points. Methemoglobin concentrations were also minimally increased in females in the 750 and 1,500 ppm groups compared to the controls on day 23 and at 13 weeks. Platelet counts in all groups of exposed rats were mildly to markedly increased compared to the controls at all time points. A review of platelet size distribution information on day 23 revealed a wide size-distribution curve and indicated the presence of significant numbers of large platelets or particles counted as platelets. Increased platelet counts may be consistent with a reactive thrombocytosis, which can be caused by a variety of conditions, including bone marrow response to anemia. In light of the evidence suggestive of a hemolytic process (e.g., schistocytes, Heinz bodies, and increased mean cell hemoglobin concentration and methemoglobin concentration), the erroneous inclusion of small erythrocyte fragments in the platelet count could, in part,

account for the platelet count increases.

On day 23, a hypothyroid state, evidenced by decreased serum triiodothyronine, thyroxine, and free thyroxine, occurred in males exposed to 375 ppm or greater and females exposed to 750 or 1,500 ppm; thyroxine concentrations of female rats in the 188 and 375 ppm groups were also decreased. There was little or no pituitary response to the thyroid hormone decreases, as evidenced by the lack of significantly increased thyroid-stimulating hormone concentrations in exposed rats. The change in thyroid hormone concentrations was transient, and at 13 weeks, hormone concentrations of exposed rats were similar to those of the controls. Differences in other hematology and clinical chemistry variables were not related to exposure and were not considered biologically significant.

No biologically significant differences in organ weights between exposed and control rats were observed (Table F2). The forelimb and hindlimb grip strengths of males in the 1,500 ppm group were significantly less than those of the controls (Table I1). The hindlimb grip strengths of females in the 750 and 1,500 ppm groups were also significantly less than the control value.

Male rats in the 750 and 1,500 ppm groups had significantly lower epididymal spermatozoal motility than the controls; the left cauda, epididymis, and testis weights of males in the 1,500 ppm group were also significantly less than those of the controls (Table H1). There were no biologically significant differences in the length of the estrous cycle or in the

relative amounts of time spent in the various estrous stages between exposed and control females.

At necropsy, no gross lesions were observed that were considered related to nitromethane exposure. Minimal to mild hyperplasia of the bone marrow was observed microscopically in male rats in the 750 and 1,500 ppm groups and in females exposed to 188 ppm or greater (Table 5). Olfactory epithelial degeneration was observed in males and females exposed to 375 ppm or greater and in one female in the 188 ppm group. Respiratory epithelial hyaline droplets and goblet cell hyperplasia were observed in males and females in the 750 and 1,500 ppm groups (Table 5); the severity of nasal lesions in exposed males and females ranged from minimal to mild.

Males and females exposed to 375 ppm or greater had minimal to mild degeneration of the spinal cord and sciatic nerve (Table 5). Sciatic nerve degeneration, as observed in the 16-day study, was observed in most rats exposed to 375 ppm and in all rats exposed to 750 or 1,500 ppm; however, the degeneration in exposed rats in the 13-week study was less severe than that observed in the 16-day study. In rats exposed to 1,500 ppm, the lesion was considered mild and was characterized by focal dilatation, with foci containing eosinophilic debris, and vacuolization of the axonal sheaths. Increased cellularity, presumably due to Schwann cell hyperplasia, was apparent, primarily in rats exposed to 1,500 ppm. The presence of inflammatory cells and myelin debris was less prevalent than in the 16-day study. Minimal to mild degeneration of the lumbar spinal cord was present in some rats exposed to 375 ppm and in all rats exposed to 750 or 1,500 ppm. This lesion was characterized by focal vacuolization in the white matter of the lumbar region of the cord and, to a greater extent, in the spinal nerves. The foci contained eosinophilic, granular debris.

Exposure Concentration Selection Rationale: Due to the increased incidences and severity of degeneration of the sciatic nerve and spinal cord in rats exposed to 750 or 1,500 ppm and to the rather minimal changes in the 375 ppm groups, nitromethane exposure concentrations selected for the 2-year study in rats were 94, 188, and 375 ppm.

	0 ppm	94 ppm	188 ppm	375 ppm	750 ppm	1,500 ppm
Male		· · ·	· · ·	· · · · · ·		<u> </u>
Bone Marrow ^a Hyperplasia ^b	10 0	10 0	10 0	10 0	10 9** (1.1) ^c	10 10** (2.0)
Nose/Turbinates Degeneration, Olfactory	10	d	10	10	10	10
Epithelium Hyaline Droplets, Respiratory	0	• • •	0	9** (1.0)	10** (1.0)	10** (1.0)
Epithelium Hyperplasia, Goblet Cell	0 0.		0	0	1 (1.0)	10** (2.0)
Sciatic Nerve Degeneration	10 0	-	10 0	10 5* (1.0)	10 10** (1.2)	10 10** (1.5)
Spinal Cord Degeneration	10 0	. —	10 0	10 9** (1.0)	10 10** (1.4)	10 10** (2.0)
Female			·	. 		
Bone Marrow Hyperplasia	10 0	10 0	10 1 (2.0)	10 6** (1.0)	10 7** (1.1)	10 10** (1.7)
Nose/Turbinates	10	10	10	10	10	10
Epithelium Hvaline Droplets, Respiratory	. 0	0	1 (1.0)	10** (1.0)	10** (1.2)	10** (1.8)
Epithelium Hyperplasia, Goblet Cell	0 0	0	0 0	0 0	4* (1.0) 2 (1.5)	10** (1.0) 10** (1.7)
Sciatic Nerve Degeneration	10 0	· _ ·	- 10 0	10 8** (1.0)	10 10** (1.1)	10 10** (1.8)
Spinal Cord Degeneration	10 0	· <u> </u>	10 0	10 2 (1.0)	10 10** (1.4)	10 10** (1.9)

Incidences of Selected Nonneoplastic Lesions in Rats in the 13-Week Inhalation Study of Nitromethane

* Significantly different (P \leq 0.05) from the control group by the Fisher exact test

** P≤0.01

^a Number of animals with tissue examined microscopically

^b Number of animals with lesion

^c Average severity of lesions in affected rats: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

^d Not examined at this exposure concentration

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 6 and in the Kaplan-Meier survival curves (Figure 1). There were no significant differences in survival rates between exposed and control male or female rats.

Body Weights and Clinical Findings

Mean body weights are given in Figure 2 and Tables 7 and 8. From week 23 to the end of the

study, the mean body weight of females in the 375 ppm group was slightly greater than that of the control group. The mean body weights of exposed males were generally similar to the mean body weight of the controls throughout the study. Clinical findings (masses on shoulder and torso) consistent with mammary gland neoplasms were observed in females in the 188 and 375 ppm groups during the course of the study; there were no indications of hindlimb paralysis, as observed in the 13-week study, or other treatment-related clinical findings during the study.

TABLE 6

Survival of Rats in the 2-Year Inhalation Study of Nitromethane

	0 ppm		188 ppm 375 j			
Male		<u>,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,</u>				
Animals initially in study	50	50	50	50		
Moribund	33	31	34	39		
Natural deaths	4	3	2	3		
Animals surviving to study termination	13	16	14	8		
Percent probability of survival at end of study ^a	26	32	28	16		
Mean survival (days) ^b	642	631	646	, 640		
Survival analysis ^c	P =0.378	P=1.000N	P=1.000N	P=0.361		
Female		~				
Animals initially in study	50	50	50	50		
Moribund	17	26	18	25		
Natural deaths	5	5	2	2		
Animals surviving to study termination	28	19	30	23		
Percent probability of survival at end of study	56	38	60	46		
Mean survival (days)	683	653	679	670		
Survival analysis	P=0.780	P=0.083	P=0.900N	P=0.404		

^a Kaplan-Meier determinations

^b Mean of all deaths (uncensored, censored, and terminal sacrifice)

^c The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed group columns. A lower mortality in an exposed group is indicated by N.





Kaplan-Meier Survival Curves for Male and Female Rats Exposed to Nitromethane by Inhalation for 2 Years





41

Mean Body Weights and Survival of Male Rats in the 2-Year Inhalation Study of Nitromethane

Weeks	0	ppm		<u>94 ppm</u>			188 ppn	1		375 pp	n
on	Av. Wt.	No. of	Av. Wt	. Wt. (% of	No. of	Av. Wt	. Wt. (% of	No. of	Av. Wt.	Wt. (% of	No. of
Study	• (g) •	Survivors	(g)	controls)	Survivors	(g)	controls)	Survivors	(g)	controls)	Survivors
1	135	50	135	100	50	135	100	50	133	98	50
2	180	50	179	100	50	179	100	50	175	98	50
3	211	50	211	100	50	211	100	50	208	99	50
4	234	50	236	101	50	235	100	50	231	99	50
5	255	50	258	101	50	255	100	50	253	99	50
6	274	50	276	101	50	267	98	50	271	99	50
7	289	50	290	100	50	289	100	50	286	99	50
8	307	50	308	100	50	306	99	50	300	98	50
9	322	50	324	101	50	322	100	50	316	98	50
10	333	50	335	101	50	334	100	50	329	99	50
II.	345.	50	344	100	50	343	100	50	338	98	50
12	354	50	359	102	50	355	100	50	351	99	50
15	379	50	380	100	50	380	100	50	376	99	50
19	409	50	410	100	50	410	100	50	410	100	50
23	425	50	428	101	50	426	100	50	429	101	50
27	441	50	444	101	50	441	100	50	445	101	50
31	456	50	460	101.	50	458	100	50 -	462	101	50
35	470	49	473	101	50	471	100	50	474	101	50
39	480	49	481	100	50	480	100	50	482	101	50
43	489	49	488	100	49	490	100	50	495	101	50
47	495	49	494	100	49	492	99	50	497	101	50
51	502	49	498	99	49	496	99	50	505	101	50
55	510	49	505	99	49	506	99	50	511	100	50
59	516	48	512	99	48	511	99	49	518	100	49
63	518	48	513	99	46	511	99	49	521	101	48
67	521	48	515	99	46	512	98	49	522	100	47
71	526	46	517	98	44	517	98	47	532	101	45
75	529	44	523	99	40	521	98	44	537	102	44
79	531	41	523	98	40	514	97	43	- 532	100	42
83	533	38	518	97	39	518	97	39	531	100	40
87	524	35	521	100	30	505	96	37	530	101	.35
91	522	30	514	99	28	491	94	31	522	100	31
93	512	28	513	100	25	489	95	27	513	100	28
95	501	27	499	100	24	478	95	24	514	103	24
97	503	23	523	104	19	471	94	22	506	100	22
99	500 ·	21	516	103	18	469	94	18	499	. 100	18
101	493	20	511	104	17	463	94	17	499	101	11
103	486	17	501	103	16	462	95	16	502	103	9
Mean for	weeks										
1-13	270		271	100		269	100		266	99	
14-52	455		456	100		454	100	• •	458	101	
53-103	514		514	100	•	496	96		518	101	
	T 4		<i>2</i> .,				- •				

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TABLE 8

Mean Body Weights and Survival of Female Rats in the 2-Year Inhalation Study of Nitromethane

Weeks	0 1	DDM		94 ppm			188 maa	n		נסמ 375	m
on	Av. Wt.	No. of	Av. Wt.	Wt. (% of	No. of	Av. Wt.	Wt. (% of	No. of	Av. Wt.	₩t. (% of	No. of
Study	(g)	Survivors	(g)	controls)	Survivors	(g)	controls)	Survivors	(g)	controls)	Survivors
1	108	50	108	100	50	108	100	50	107	. 99	50
2	130	50	130	100	50	130	99	50	126	97	50
3	143	50	143	100	50	142	99	50	140	98	50
4	151	50	152	100	50	150	99	50	149	99	. 50
5	159	50	161	101	50	160	101	50	159	100	50
6	164	50	166	101	50	167	101	50	165	100	50
7	172	50	174	101	50	173	101	50	171	100	50
8	178	50	181	102	50	180	101	50	177	99	50
9	182	50	186	102	50	186	102	50	182	100	50
10	187	50	189	101	50	191	102	50	188	101	50
11	191	50	193	101	50	194	102	50	191	100	50
12	194	50	196	101	50	198	102	50 ·	196	101	50
15	203	50	206	102	50	209	103	50	207	102	50
19	214	50	218	102	50	221	103	50.	222	104	50
23	220	50	227	103	50	230	105	50	234	107	50
27	230	50	234	102	50	237	103	50	243	106	50
31	239	50	246	103	50	250	104	50	255	107	50
35	250	50	255	102	50	260	104	50	266	106	50
39	261	50	265	102	50	270	104	50	276	106	50
43	272	50	277	102	50	281	103	50	289	107	50
47	282	50	287	102	50	291	103	50	303	107	50
51	294	50	298	101	50	299	102	50	311	106	50
55	306	50	310	101	50	312	102	50	: 322	106	50
59	314	50	317	101	50	321	103	50	332	106	49
63	320	50	323	101	48	324	101	49	337	105	48
67	325	49	329	101	48	337	104	47	344	106	48
71	332	49	337	101	45	342	103	46	353	106	46
75	336	47	346	103	43	350	104	43	358	107	46
79	340	45	346	102	42	358	106	42	364	107	44
83	344	43	352	102	38	364	106	42	367	107	44
87	347	40	359	103	34	365	105	42	367	106	38
91	356	37	364	102	32	375	105	41	370	104	37
93	352	37	362	103	31	370	105	39	372	106	35
95	358	35	359	100	30	367	103	37	371	104	33
97	358	35	361	101	26	370	104	35	375	105	28
99	358	32	357	100	24	371	104	33	375	105	27
101	355	32	353	99	22	371	104	31	377	106	27
103	355	30	350	99	22	369	104	30	376	106	25
Mean for	r weeks										
1-13	163		165	101		165	101		163	100	
14-52	247		251	102		255	103		261	106	
53-103	341		345	101		354	104		360	106	

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions of the mammary gland and kidney and in the incidences of mononuclear cell leukemia. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix A for male rats and Appendix B for female rats.

Mammary Gland: The incidences of fibroadenoma, fibroadenoma or adenoma (combined), and fibroadenoma, adenoma, or carcinoma (combined) in female rats increased with increasing exposure concentration, and the incidences in the 188 and 375 ppm groups were significantly greater than those in the controls (Tables 9 and B3). Additionally, the incidences of carcinoma and adenoma or carcinoma (combined) in the 375 ppm group were significantly greater than those in the controls. The incidences of fibroadenoma and carcinoma exceeded the ranges of historical incidences for these neoplasms in untreated (chamber control) female rats in 2-year NTP inhalation studies (Table B4). No treatment-related mammary gland neoplasms were observed in male rats (Table A1).

The morphology of the mammary gland fibroadenomas was typical, with the lesions characterized by dense, fibrous tissue surrounding scattered glands (Plate 1). Adenomas were composed of glands with scant fibrous tissue. The carcinomas were very cellular lesions (Plate 2) that often contained a well-differentiated glandular formation (Plate 3); other mammary gland carcinomas exhibited a papillary pattern or showed more solid areas of growth. Mammary gland carcinomas contained occasional areas of necrosis and hemorrhage, and in some cases mitotic activity was quite high. The two carcinomas that metastasized to the lung (Plate 4) did not vary appreciably in morphology from the carcinomas that did not metastasize.

Hematopoietic System: The incidences of mononuclear cell leukemia in exposed female rats were lower than the control incidence (0 ppm, 22/50; 94 ppm, 13/50; 188 ppm, 14/50; 375 ppm, 9/50), and the difference was significant in the 375 ppm group (Table B3). The incidences in all exposed groups fell below the historical range (30% to 54%) for leukemias (all types) in female chamber control rats in 2-year NTP inhalation studies. In addition, the incidences of mononuclear cell leukemia in exposed males were slightly, although not significantly, less than the control incidence (35/50, 27/50, 33/50, 25/50; Table A3); however, these decreases was not related to exposure concentration. The biological significance of these decreases is uncertain. However, the incidences in exposed females were well within the range of historical incidences for leukemias in untreated female control rats in NTP noninhalation (feed) studies (14%-52%), and the incidences in exposed males were within or slightly above the range of historical incidences in untreated males (32% - 64%).

Incidences of Neoplasms and Nonneoplastic Lesions of the Mammary Gland in Female Rats in the 2-Year Inhalation Study of Nitromethane

· · ·	0 ppm	94 ppm	188 ppm	375 ppm
Mammary Gland ^a	50	50	50	50
Hyperplasia ^b	0	0	$1(3.0)^{c}$	2 (2.5)
Hyperplasia, Atypical	12 (1.7)	17 (1.2)	14 (1.4)	15 (1.7)
Fibroadenoma				
Overall rate ^d	19/50 (38%)	21/50 (42%)	33/50 (66%)	36/50 (72%)
Ádjusted rate ^e	58.2%	68.5%	80.0%	92.1%
Terminal rate ^f	15/28 (54%)	10/19 (53%)	22/30 (73%)	20/23 (87%)
First incidence (days)	454	435	468	552
Logistic regression test ^g	P<0.001	P=0.219	P=0.003	P<0.001
Adenoma				
Overall rate	2/50 (4%)	0/50 (0%)	0/50 (0%)	2/50 (4%)
Carcinoma ^h				
Overall rate	2/50 (4%)	7/50 (14%)	1/50 (2%)	11/50 (22%)
Adjusted rate	6.0%	29.3%	2.0%	33.0%
Terminal rate	1/28 (4%)	4/19 (21%)	0/30 (0%)	5/23 (22%)
First incidence (days)	631	588	440	425
Logistic regression test	P=0.009	P=0.052	P=0.447N	P=0.011
Fibroadenoma, Adenoma, or Carcin	noma ⁱ		6 -	
Overall rate	21/50 (42%)	25/50 (50%)	34/50 (68%)	41/50 (82%)
Adjusted rate	62.4%	74.9%	80.4%	95.2%
Terminal rate	16/28 (57%)	11/19 (58%)	22/30 (73%)	21/23 (91%)
First incidence (days)	454	435	440	425
Logistic regression test	P<0.001	P=0.112	P=0.006	P<0.001

^a Number of animals necropsied

^b Number of animals with lesion

^c Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

^d Number of animals with neoplasm per number of animals necropsied

e Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

f Observed incidence in animals surviving until the end of the study

^g In the control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to the pairwise comparisons between the controls and that exposed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal. A lower incidence in an exposed group is indicated by N.

h Historical incidence for all 2-year NTP inhalation studies with chamber control groups (mean ± standard deviation): 25/653 (3.8% ± 2.7%); range, 0%-8%. Historical incidence (Battelle Pacific Northwest Laboratories): 14/348 (4.0% ± 2.6%); range, 0%-8%.

ⁱ Historical incidence (all laboratories): 202/653 (30.9% ± 9.1%); range, 16%-46%. Historical incidence (Battelle Pacific Northwest Laboratories): 108/348 (31.0% ± 8.1%); range, 22%-46%.

Kidney: At the end of the study, renal tubule hyperplasia and adenoma were observed in a few exposed males (Tables 10, A3, and A5); the incidences were not related to exposure concentration. The incidences of renal tubule adenoma in exposed males were within or only slightly above the historical incidence range of 0% to 4% for these neoplasms in male chamber control rats in NTP inhalation studies: however, because no hyperplasia or adenomas were observed in the control group, additional step sections of the kidneys of control and exposed males were prepared. Adenomas were observed in step sections of the kidneys of two males in each of the control and 94 ppm groups and four males in the 375 ppm group (Tables 10 and A3), including multiple adenomas in one male each in the 94 and 375 ppm groups. However, the combined incidences of renal tubule adenoma (from the single and step sections) were not significantly different from the control incidence. Renal tubule hyperplasia was also identified in step sections of kidneys from exposed and control males; the incidence in the 375 ppm group (from step sections and combined single and step sections) was slightly, but not significantly, greater than the control incidence.

Renal tubule hyperplasia consisted of tubules that were dilated approximately two to four times the normal diameter with lumens filled by clusters of renal tubule epithelial cells; these cells were somewhat pleomorphic, often with large nuclei with prominent nucleoli, and with cytoplasm varying from eosinophilic to slightly basophilic. Renal tubule adenomas consisted of cells that resembled those in the hyperplasia. However, the adenomas were larger (five or more tubule diameters) and generally had a more complex structure, often consisting of multiple, variably sized tubule-like structures or multiple solid clusters of cells separated by fine bands of stroma.

Nervous System: Histopathologic evaluation of hematoxylin- and eosin-stained sections of spinal cords and sciatic nerves from approximately 15 male and 15 female rats per group from the 0 and 375 ppm groups revealed no significant differences between exposed and control rats.

Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Male Rats in the 2-Year Inhalation Study of Nitromethane

	0 ppm	94 ppm	188 ppm	375 ppm
Single Sections (Standard Ryalu		· · · · · · · · · · · · · · · · · · ·	<u></u>	
Kidnev ^a	50	50	50	50
Nenhropathy ^b	50 (2 8) ^c	50 (2.9)	50 (3.1)	50 (3.2)
Renal Tubule, Hyperplasia	0	3 (2.7)	2 (2.5)	1 (2.0)
Renal Tubule Adenoma ^d				
Overall rate ^e	0/50 (0%)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted rate ^f	0.0%	14.9%	14.3%	12.5%
Terminal rate ^g	0/13 (0%)	1/16 (6%)	2/14 (14%)	1/8 (13%)
First incidence (days)	_i	636	733 (T)	733 (T)
Logistic regression test ^h	P=0.487	P=0.107	P=0.252	P = 0.403
Step Sections (Extended Evaluat	tion)			
Kidnev	50	50	50	50
Renal Tubule, Hyperplasia	6 (2.5)	7 (2.3)	5 (1.4)	12 (2.0)
Renal Tubule, Adenoma				
Overall rate	2/50 (4%)	2/50 (4%)	0/50 (0%)	4/50 (6%)
Adjusted rate	15.4%	12.5%	0.0%	22.7%
Terminal rate	2/13 (15%)	2/16 (13%)	0/14 (0%)	1/8 (13%)
First incidence (days)	733 (T)	733 (T)	_	650
Logistic regression test	P=0.184	P = 0.622N	P=0.219N	P=0.283
Single Sections and Step Section	s (Combined)			
Kidney	50	50	50	50
Renal Tubule, Hyperplasia	6 (2.5)	8 (2.5)	6 (1.7)	12 (2.0)
Renal Tubule, Adenoma				·
Overall rate	2/50 (4%)	5/50 (10%)	2/50 (4%)	5/50 (10%)
Adjusted rate	15.4%	26.3%	14.3%	33.7%
Terminal rate	2/13 (15%)	3/16 (19%)	2/14 (14%)	2/8 (25%)
First incidence (days)	733 (T)	636	733 (T)	650
Logistic regression test	P=0.181	P=0.173	P=0.675N	P=0.158

(T)Terminal sacrifice

^a Number of animals with kidney examined microscopically

^b Number of animals with lesion

^c Average severity of lesions in affected rats: 1=minimal, 2=mild, 3=moderate, 4=marked

^d Historical incidence for all 2-year NTP inhalation studies with chamber control groups (mean ± standard deviation): 6/652

 $(0.9\% \pm 1.3\%)$; range, 0% - 4%. Historical incidence (Battelle Pacific Northwest Laboratories): 5/347 (1.4\% \pm 1.5\%); range, 0% - 4%. Number of animals with neoplasm per number of animals with kidney examined microscopically

f Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

^g Observed incidence in animals surviving until the end of the study

^h In the control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to the pairwise comparisons between the controls and that exposed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal. A lower incidence in an exposed group is indicated by N.

¹ Not applicable; no neoplasms in animal group

MICE 16-DAY STUDY

All mice survived to the end of the study (Table 11). The final mean body weights and mean body weight gains of exposed males and females were similar to those of the controls. Clinical findings included hypoactivity and tachypnea in male and female mice in the 1,500 ppm groups near the end of the study.

The absolute and relative liver weights of male mice in the 750 and 1,500 ppm groups and female mice in all exposed groups were significantly greater than those of the controls (Table F3). The relative liver weight of males in the 375 ppm group was also significantly greater than that of the controls. At necropsy, no lesions were observed grossly that were attributed to nitromethane exposure. Degeneration of the olfactory epithelium of the nose was observed microscopically in all males and females exposed to 375 ppm or greater; this lesion was of minimal severity in males and minimal to mild severity in females.

Exposure Concentration Selection Rationale: Due to the lack of significant toxicologic or histopathologic effects (including the absence of histopathologic effects in the lung), nitromethane exposure concentrations selected for use in the 13-week study were the same as for the 16-day study.

TABLE 11

Survival and Body Weights of Mice in the 16-Day Inhalation Study of Nitromethane

Concentration (ppm)SurvivalaInitialFinalChangeMale0 $5/5$ 24.4 ± 0.3 26.7 ± 0.4 2.2 ± 0.3 94 $5/5$ 24.5 ± 0.3 27.5 ± 0.6 3.0 ± 0.6 188 $5/5$ 24.5 ± 0.2 27.2 ± 0.5 2.8 ± 0.6 375 $5/5$ 24.5 ± 0.2 27.2 ± 0.5 2.8 ± 0.6 375 $5/5$ 24.6 ± 0.2 27.2 ± 0.5 2.5 ± 0.3 1,500 $5/5$ 24.6 ± 0.2 27.2 ± 0.5 2.5 ± 0.3 1,500 $5/5$ 24.5 ± 0.2 27.1 ± 0.4 2.6 ± 0.3 Female0 $5/5$ 18.8 ± 0.3 21.9 ± 0.4 3.1 ± 0.5 94 $5/5$ 18.8 ± 0.3 22.2 ± 0.3 3.4 ± 0.2 188 $5/5$ 18.8 ± 0.3 22.2 ± 0.3 3.4 ± 0.2	
Concentration (ppm)SurvivalaInitialFinalChangeMale0 $5/5$ 24.4 ± 0.3 26.7 ± 0.4 2.2 ± 0.3 94 $5/5$ 24.5 ± 0.3 27.5 ± 0.6 3.0 ± 0.6 188 $5/5$ 24.5 ± 0.2 27.2 ± 0.5 2.8 ± 0.6 375 $5/5$ 24.5 ± 0.2 27.2 ± 0.5 2.8 ± 0.6 375 $5/5$ 24.5 ± 0.2 27.2 ± 0.5 2.5 ± 0.3 750 $5/5$ 24.6 ± 0.2 27.2 ± 0.5 2.5 ± 0.3 $1,500$ $5/5$ 24.5 ± 0.2 27.1 ± 0.4 2.6 ± 0.3 Female0 $5/5$ 18.8 ± 0.3 21.9 ± 0.4 3.1 ± 0.5 94 $5/5$ 18.8 ± 0.3 22.0 ± 0.5 188 $5/5$	Final Weight
Male 0 $5/5$ 24.4 ± 0.3 26.7 ± 0.4 2.2 ± 0.3 94 $5/5$ 24.5 ± 0.3 27.5 ± 0.6 3.0 ± 0.6 188 $5/5$ 24.5 ± 0.2 27.2 ± 0.5 2.8 ± 0.6 375 $5/5$ 24.5 ± 0.2 27.2 ± 0.5 2.8 ± 0.6 375 $5/5$ 24.5 ± 0.2 26.5 ± 0.4 2.0 ± 0.4 750 $5/5$ 24.6 ± 0.2 27.2 ± 0.5 2.5 ± 0.3 1,500 $5/5$ 24.5 ± 0.2 27.1 ± 0.4 2.6 ± 0.3 Female 0 $5/5$ 18.8 ± 0.3 21.9 ± 0.4 3.1 ± 0.5 94 $5/5$ 18.8 ± 0.3 21.9 ± 0.4 3.1 ± 0.5 188 $5/5$ 18.8 ± 0.3 22.0 ± 0.5 3.3 ± 0.5	Relative to Control (%)
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	
94 5/5 24.5 \pm 0.3 27.5 \pm 0.6 3.0 \pm 0.6 188 5/5 24.5 \pm 0.2 27.2 \pm 0.5 2.8 \pm 0.6 375 5/5 24.5 \pm 0.2 27.2 \pm 0.5 2.8 \pm 0.6 375 5/5 24.5 \pm 0.2 27.2 \pm 0.5 2.8 \pm 0.6 750 5/5 24.6 \pm 0.2 27.2 \pm 0.5 2.5 \pm 0.3 1,500 5/5 24.5 \pm 0.2 27.1 \pm 0.4 2.6 \pm 0.3 Female 94 5/5 18.8 \pm 0.3 21.9 \pm 0.4 3.1 \pm 0.5 188 5/5 18.8 \pm 0.3 22.2 \pm 0.3 3.4 \pm 0.2	
188 5/5 24.5 ± 0.2 27.2 ± 0.5 2.8 ± 0.6 375 5/5 24.5 ± 0.2 26.5 ± 0.4 2.0 ± 0.4 750 5/5 24.6 ± 0.2 27.2 ± 0.5 2.5 ± 0.3 1,500 5/5 24.5 ± 0.2 27.2 ± 0.4 2.6 ± 0.3 Female 94 $5/5$ 18.8 ± 0.3 21.9 ± 0.4 3.1 ± 0.5 188 $5/5$ 18.8 ± 0.3 22.2 ± 0.3 3.4 ± 0.2	103
375 $5/5$ 24.5 ± 0.2 26.5 ± 0.4 2.0 ± 0.4 750 $5/5$ 24.6 ± 0.2 27.2 ± 0.5 2.5 ± 0.3 1,500 $5/5$ 24.5 ± 0.2 27.1 ± 0.4 2.6 ± 0.3 Female 0 $5/5$ 18.8 ± 0.3 21.9 ± 0.4 3.1 ± 0.5 94 $5/5$ 18.8 ± 0.2 22.2 ± 0.3 3.4 ± 0.2 188 $5/5$ 18.8 ± 0.3 22.0 ± 0.5 3.3 ± 0.5	102
750 5/5 24.6 \pm 0.2 27.2 \pm 0.5 2.5 \pm 0.3 1,500 5/5 24.5 \pm 0.2 27.1 \pm 0.4 2.6 \pm 0.3 Female 0 5/5 18.8 \pm 0.3 21.9 \pm 0.4 3.1 \pm 0.5 94 5/5 18.8 \pm 0.2 22.2 \pm 0.3 3.4 \pm 0.2 188 5/5 18.8 \pm 0.3 22.0 \pm 0.5 3.3 \pm 0.5	99
1,500 5/5 24.5 ± 0.2 27.1 ± 0.4 2.6 ± 0.3 Female 0 5/5 18.8 ± 0.3 21.9 ± 0.4 3.1 ± 0.5 94 5/5 18.8 ± 0.2 22.2 ± 0.3 3.4 ± 0.2 188 5/5 18.8 ± 0.3 22.0 ± 0.5 3.3 ± 0.5	102
Female 0 $5/5$ 18.8 ± 0.3 21.9 ± 0.4 3.1 ± 0.5 94 $5/5$ 18.8 ± 0.2 22.2 ± 0.3 3.4 ± 0.2 188 $5/5$ 18.8 ± 0.3 22.0 ± 0.5 3.3 ± 0.5	102
Female0 $5/5$ 18.8 ± 0.3 21.9 ± 0.4 3.1 ± 0.5 94 $5/5$ 18.8 ± 0.2 22.2 ± 0.3 3.4 ± 0.2 188 $5/5$ 18.8 ± 0.3 22.0 ± 0.5 3.3 ± 0.5	
0 $5/5$ 18.8 ± 0.3 21.9 ± 0.4 3.1 ± 0.5 94 $5/5$ 18.8 ± 0.2 22.2 ± 0.3 3.4 ± 0.2 188 $5/5$ 18.8 ± 0.3 22.0 ± 0.5 3.3 ± 0.5	
94 5/5 18.8 ± 0.2 22.2 ± 0.3 3.4 ± 0.2 188 5/5 18.8 ± 0.3 22.0 ± 0.5 3.3 ± 0.5	
188 5/5 188 ± 0.3 22.0 ± 0.5 3.3 ± 0.5	102
	101
375 5/5 18.8 ± 0.3 21.8 ± 0.5 3.0 ± 0.5	100
750 5/5 18.8 ± 0.3 22.4 ± 0.3 3.6 ± 0.4	102
1,500 5/5 18.9 ± 0.3 22.3 ± 0.3 3.4 ± 0.4	102

^a Number of animals surviving at 16 days/number initially in group

^b Weights and weight changes are given as mean ± standard error. Differences from the control group were not significant by Dunnett's test.

. m.t.

13-WEEK STUDY

All mice survived to the end of the study (Table 12). The final mean body weights and mean body weight gains of exposed males were similar to those of the controls. The final mean body weights and mean body weight gains of exposed females were similar to or slightly greater than those of the controls. There were no treatment-related clinical findings.

The absolute right kidney weights of all groups of exposed male mice except the 1,500 ppm group and the relative right kidney weights of all groups of exposed males were significantly greater than those of the controls (Table F4); the absolute right kidney weights of females exposed to 188 ppm or greater and the relative right kidney weights of females in the 750 and 1,500 ppm groups were also significantly greater than those of the controls. The absolute liver weight of male mice in the 750 ppm group and the relative liver weights of males exposed to 375 ppm or greater were significantly greater than those of the controls.

Exposed male mice had significantly less epididymal spermatozoal motility than the controls (Table H2). The estrous cycle lengths of exposed females were significantly longer than the cycle length of the controls; exposed females spent more time in metestrus and proestrus and less time in estrus than the controls.

TABLE 12

Survival and Body Weights of Mice in the 13-Week Inhalation Study of Nitromethane

			Final Weight		
Concentration (ppm)	Survival ^a	Initial	Final	Change	Relative to Controls (%)
Male	· · · · · · · · · · · · · · · · · · ·	<u> </u>			<u>, , , , , , , , , , , , , , , , , , , </u>
0	10/10	24.5 ± 0.2	34.3 ± 0.4	9.8 ± 0.4	
94	10/10	24.4 ± 0.2	34.1 ± 0.5	9.7 ± 0.6	100
188	10/10	24.0 ± 0.3	34.3 ± 0.8	10.3 ± 0.7	100
375	10/10	24.1 ± 0.4	34.1 ± 0.7	10.0 ± 0.5	100
750	10/10	24.3 ± 0.3	33.6 ± 0.3	9.3 ± 0.3	98
1,500	10/10	24.4 ± 0.3	34.1 ± 0.6	9.7 ± 0.4	99
Female					
0	10/10	19.8 ± 0.3	28.9 ± 0.7	9.1 ± 0.5	
94	-10/10	19.9 ± 0.3	29.7 ± 0.7	9.8 ± 0.8	103
188	10/10	20.0 ± 0.3	30.9 ± 0.7	10.8 ± 0.6	107
375	10/10	20.4 ± 0.2	$31.7 \pm 0.8*$	11.3 ± 0.8	110
750	10/10	20.4 ± 0.1	29.8 ± 0.6	9.4 \pm 0.6	103
1,500	10/10	20.1 ± 0.3	29.1 ± 0.5	9.1 ± 0.3	101

* Significantly different ($P \le 0.05$) from the control group by Dunnett's test

^a Number of animals surviving at 13 weeks/number initially in group

^b Weights and weight changes are given as mean \pm standard error.

At necropsy, no lesions were observed grossly that were attributed to nitromethane exposure. Olfactory epithelial degeneration and respiratory epithelial hyaline droplets (not observed in the 16-day study) were observed microscopically in all male and female mice exposed to 375 ppm or greater (Table 13). Seven females in the 188 ppm group also had epithelial degeneration; one male and nine females in the 188 ppm groups and two females in the 94 ppm group had hyaline droplets. Olfactory epithelial degeneration was characterized by loss of orderly arrangement of the olfactory epithelium and thinning of the epithelium due to a loss of bipolar sensory neurons. Some of the remaining epithelial (sustentacular) cells contained hyaline droplets. Inflammation associated with these changes was minimal. Olfactory epithelial degeneration was more prominent along the dorsal meatus but was occasionally present along the medial aspects of the ethmoid turbinates close to the septum. Hyaline droplet formation of the respiratory epithelium, similar to that observed in the olfactory epithelium, was striking and was most frequently observed in the epithelium of the nasopharyngeal duct, nasal septum, and medial aspects of the nasal turbinates. The respiratory epithelium near the olfactory epithelium seemed particularly vulnerable.

In males, the average severity of the nasal lesions was minimal in the 188, 375, and 750 ppm groups and mild in the 1,500 ppm group. In females, the severity of olfactory epithelial degeneration was minimal in the 188 and 375 ppm groups and mild in the 750 and 1,500 ppm groups; the severity of respiratory epithelial hyaline droplets was minimal in the 94 and 188 ppm groups, mild in the 375 and 750 ppm groups, and moderate in the 1,500 ppm group.

All males and nine females in the 1,500 ppm groups had minimal extramedullary hematopoiesis of the spleen (Table 13); although this lesion was also observed in a few males and females exposed to 375 or 750 ppm, the incidences were low and the change was very subtle in these groups. No kidney, liver, or lung lesions were observed in exposed mice.

Exposure Concentration Selection Rationale: Due to the increased severity and extent of nasal lesions in mice in the 13-week study compared to those in the 16-day study and to the presence of splenic hematopoiesis in mice in the 1,500 ppm groups, the nitromethane exposure concentrations selected for the 2-year study in mice were 188, 375, and 750 ppm.

Incidences of Selected Nonneoplastic Lesions in Mice in the 13-Week Inhalation Study of Nitromethane

	0 ppm	94 ppm	188 ppm	375 ppm	750 ppm	1,500 ppm
Male		· · · · · ·	,			
Nose/Turbinates ^a	10	10	10	10	10	10
Epithelium ^b Hvaline Droplets, Respiratory	0	• 0	0	10** (1.0) ^c	10** (1.3)	10** (2.0)
Epithelium	0	0	1 (1.0)	10** (1.0)	10** (1.0)	10** (2.0)
Spleen Extramedullary Hematopoiesis	10 0	10 1 (1.0)	10 0	10 1 (1.0)	10 2 (1.0)	10 10** (1.0)
Female						
Nose/Turbinates	10	10	10	10	10	10
Epithelium Hyaline Droplets Respiratory	0	0	7** (1.0)	10** (1.0)	10** (2.0)	10** (3.0)
Epithelium	0	2 (1.0)	9** (1.0)	10** (2.0)	10** (2.0)	10** (3.0)
Spleen Extramedullary Hematopoiesis	10 0	10 0	10 0	10 2 (1.0)	10 3 (1.0)	10 9** (1.0)

** Significantly different ($P \le 0.01$) from the control group by the Fisher exact test a Number of animals with tissue examined microscopically b Number of animals with lesion

с Average severity of lesions in affected mice: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 14 and in the Kaplan-Meier survival curves (Figure 3). The survival rate of females in the 750 ppm group was marginally greater than that of the controls.

Body Weights and Clinical Findings

Mean body weights are given in Tables 15 and 16 and Figure 4. The mean body weights of exposed females were generally slightly greater than the mean body weights of the controls during the study but were generally similar to the mean body weight of the control females at the end of the study. The mean body weights of exposed and control males were similar throughout the study.

Clinical findings included swelling around the eyes and exophthalmos in exposed males and females. These findings were coincident with harderian gland neoplasms.

TABLE 14

Survival of Mice in the 2-Year Inhalation Study of Nitromethane

	0 ppm	188 ppm	375 ppm	750 ppm
Male	<u> </u>			<u></u>
Animals initially in study	50	50	50	50
Moribund	14	11	16	16
Natural deaths	5	3	. 4	5 ·
Animals surviving to study termination	31	36	30	29
Percent probability of survival at end of study ^a	62	72	60	58
Mean survival (days) ^b	681	700	674	687
Survival analysis ^c	P=0.519	P=0.321N	P=0.960	P=0.949
			ter a ser a se	
Female			•••	
Animals initially in study	50	50	50	50
Accidental deaths ^d	2	. Ò	· 1	0
Moribund	16	17	20	12
Natural deaths	7	5	3	2
Animals surviving to study termination	25	28 ^e	26.	36
Percent probability of survival at end of study	52	56	53	72
Mean survival (days)	662	663	673	695
Survival analysis	P=0.046N	P = 1.000N	P=0.993N	P=0.056N

a Kaplan-Meier determinations

Mean of all deaths (uncensored, censored, and terminal sacrifice)

The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed group columns. A negative trend or a lower mortality in an exposed group is indicated by N.

Censored from survival analyses

^e Includes one animal that died during the last week of the study



FIGURE 3

Kaplan-Meier Survival Curves for Male and Female Mice Exposed to Nitromethane by Inhalation for 2 Years

53

Mean Body Weights and Survival of Male Mice in the 2-Year Inhalation Study of Nitromethane

Weeks		ppm		188 ppm			375 pp	<u>n</u>		750 pp	m
on	Av. Wt.	No. of	Av. Wt.	Wt. (% of	No. of	Av. Wt.	Wt. (% o	f No. of	Av. Wt.	Wt. (% of	No. of
Study	(g)	Survivors	(g)	controls)	Survivors	(g)	controls)	Survivors	(g)	controls)	Survivors
1	25.4	50	25.0	98	50	25.3	100	50	25.4	100	50
2	27.7	50	27.0	98	50	27.7	100	50	28.0	101	50
3	28.9	50	28.2	98	50	29.0	100	50	29.2	101	50
4	29.7	50	29.1	98	50	30.2	102	50	30.4	102	50
5	30.6	50	30.0	98	50	30.9	101	50	31.3	102	50
6	31.2	50	30.0	96	50	31.5	101	50	31.9	102	50
7	31.7	50	30.7	97	50	32.2	102	50	32.0	101	50
8	32.3	50	31.6	98	50	32.7	101	50	32.7	101	50
9	33.1	50	32.2	97	50	33.5	101	50	33.8	102	50
10	33.9	50	33.4	99	50	34.2	101	50	34.5	102	50
11	34.3	50	33.3	97	50	34.2	100	50	34.9	102	50
12	35.1	50	34.0	97	50	34.8	99	50	35.5	101	50
15	36.9	50	35.7	97	50	36.2	98	50	. 37.7	102	50
19	39.6	50	38.7	98	50	38.6	. 98	50	40.1	101	50
23	41.3	50	39.5	96	50	39.8	96	50	41.2	100	50
27	43.2	50	42.0	97	50	42.2	98	50	43.3	100	50
31	45.6	50	43.9	96	50	44.5	98	50	45.8	100	50
35	46.6	50	44 7	96	50	45.6	98	50	46.7	100	50
30	47.9	50	46.6	97	50	46.9	98	50	48.0	100	50
43	48.5	50	47 4	98	50	48 1	99	50	49.5	102	50
47	48.7	50	47.8	98	49	47.5	98	50	49.6	102	50
51	48.0	50	: 48.4	99	40	48.4	99	49	50.2	103	50
55	40.5	50	48.7	00	40	40.1	100	48	51.0	103	-50
50	40.0	50	40.7	100	40	50 1	100	48	51.3	103	48
63	50 A	50	40.0	00	40	50.2	100	47	51.7	103	48
67	50.9	48	50.3	00	42	50.0	100	47	51.8	102	48
71	50.8	40	50.5	100	46	50.2	90	47	51.5	101	47
75	51.5	45	50.8	90	46	50.8	99	45	51.7	100	47
79	51.0	43	50.6	98	46	51.2	99	43	51.8	100	46
83	52 1	43	50.0	97	45	52.2	100	39	51.3	99	46
87	51 3	40	50.2	98	45	51.6	101	. 38	51.5	100	42
01	51.5	30	50.5	98	45	51.9	101	38	51.7	101	41
03	50.5	39	50.2	99	43	51.5	102	37	51.4	102	40
05	50.9	35	49.9	98	43	51.3	101	36	50.9	100	39
97	50.5	. 34	49.1	97	42	50.1	99	36	50.6	100	37
00	50.0	· 34	49.1	98	41	49.4	99	35	50.6	101	34
101	49 1	33	48.0	98	- 41	48.4	99	33	50.4	103	30
103	49.2	32	47.7	97	40	48.3	98	32	50.2	102	30
n.								•		*	
Mean for	weeks										
1-13	31.2		30.4	97	• .	31.4	101		31.6	101	
14-52	44.7		43.5	97		43.8	98		45.2	101	
52 102	50 6		10.8	08		50.5	100		51.2	101	

Mean Body Weights and Survival of Female Mice in the 2-Year Inhalation Study of Nitromethane

Weeks	0 1	pom		188 ppm			375 ppr	n		750 pp	n
on	Av. Wt.	No. of	Av. Wt.	Wt. (% of	No. of	Av. Wt.	Wt. (% o	No. of	Av. Wt.	Wt. (% of	No. of
Study	(g)	Survivors	(g)	controls)	Survivors	(g)	controls)	Survivors	(g)	controls)	Survivors
1	19.9	50	20.2	102	50	20.0	101	50	20.1	101	50
2	22.2	50	22.3	101	50	22.4	101	50	22.6	102	50
3	23.0	50	23.5	102	50	23.9	104	50	23.8	104	50
4	23.7	50	24.3	103	50	24.7	104	50	24.9	105	50
5	25.0	50	25.5	102	50	25.7	103	50	25.9	104	50
6	25.5	50	25.7	101	50	26.5	104	50	26.5	104	50
7	25.6	50	26.3	103	50	27.1	106	50	26.5	104	50
8	26.5	50	27.2	103	50	28.1	106	50	28.0	106	49
9	26.9	50	27.5	102	50	28.4	106	50	28.3	105	49
10	27.8	50	28.7	103	50	29.3	105	49	29.2	105	49
11	27.4	50	28.6	104	50	29.6	108	49	29.6	108	49
12	27.9	50	29.0	104	50	29.5	106	49	29.8	107	49
15	29.1	50	31.0	107	50	31.2	107	49	31.6	109	49
19	32.0	50	33.9	106	50	33.6	105	49	34.6	108	49
23	33.1	50	35.6	108	50	35.8	108	49	36.1	109	49
27	35.0	50	37.7	108	50	37.6	107	49	38.2	109	49
31	38.0	50	40.0	105	50	40.6	107	49	40.6	107	49
35	39.6	50	42.0	106	50	42.2	107	49	42.7	108	49
39	42.2	50	44.3	105	50	43.6	103	49	44.2	105	49
43	43.1	49	45.8	106	50	45.7	106	48	45.8	106	49
47	44.2	49	47.1	107	50	45.3	103	48	46.3	105	49
51	45.5	49	47.6	105	49	47.5	104	48	48.0	106	49
55	47.3	47	49.9	106	48	49.1	104	48	49.8	105	49
59	49.1	46	51.5	105	48	50.7	103	48	51.1	104	49
63	49.7	44	52.6	106	46	51.3	103	48	51.7	104	48
67	50.9	44	53.8	106	45	52.7	104	48	52.9	104	48
71	51.6	44	53.8	104	45	53.0	103	48	53.8	104	48
75	51.5	44	53.7	104	45	52.9	103	47	54.3	105	47
79	52.1	44	53.7	103	44	53.7	103	46	54.7	105	46
83	53.3	42	54.6	102	38	53.0	99	44	53.8	101	46
87	52.8	40	53.7	102	38	52.4	99	41	53.7	102	45
91	52.8	36	53 7	102	37	52.1	99	40	54.2	103	44
93	52.0	36	52.7	101	35	52.1	100	37	53.1	102	43
95	52.4	34	52.8	101	32	51.2	98	36	52.9	101	42
97	51 3	32	51.6	101	31	51.2	100	34	52.0	101	42
99	51.2	31	50.6	99	31	49.9	98	32	51.2	100	41
101	50.7	27	50.0	99	29	48.1	95	30	50.1	99	39
101	51.4	25	49.9	97	29	47.0	91	29	49.3	96	38
Maon for	wooke										
1.13	25.1		25 7	102		76 3	. 105		26 3	105	
14-52	38.2		40 5	102		40.3	105		20.5 40 R	107	
53-103	51 3		52 A	102		51 3	100		52.4	102	
33-103	51,5		52,4	102	•	51.5	100	· .	52.4	102	

<u>-</u>.

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Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions of the harderian gland, liver, lung, and nose. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix C for male mice and Appendix D for female mice.

Harderian Gland: The incidences of harderian gland adenoma and adenoma or carcinoma (combined) in exposed mice increased with increasing exposure concentration and were significantly greater in males and females in the 375 and 750 ppm groups than in the controls (Tables 17, C3, and D3). The incidences of these neoplasms in all exposed groups of males and females were greater than the historical control incidences for chamber control mice in 2-year NTP inhalation studies; however, the incidences of adenoma and adenoma or carcinoma (combined) in control males also exceeded the range of historical control incidences (Tables C4a and D4a). The incidences of carcinoma in males and females in the 375 and 750 ppm groups were also slightly greater than the incidences in the controls; although the differences were not statistically significant, the incidences of carcinoma in the 375 and 750 ppm groups were outside the historical incidence range of 0% to 4% for these neoplasms in male and female chamber control mice in 2-year NTP inhalation studies. The incidences of harderian gland hyperplasia in males and females in the 375 ppm groups

TABLE 17

Incidences of Neoplasms and Nonneoplastic Lesions of the Harderian Gland in Mice in the 2-Year Inhalation Study of Nitromethane

	0 ppm	188 ppm	375 ppm	750 ppm
Male	7.00 ⁻⁰⁰ -0			
Harderian Gland ^a	50	50	50	50
Hyperplasia ^b	$2(3.0)^{c}$	2 (1.5)	6 (1.7)	2 (3.5)
Adenoma				
Overall rate ^d	9/50 (18%)	10/50 (20%)	19/50 (38%)	32/50 (64%)
Adjusted rate ^e	26.6%	22.8%	51.9%	75.5%
Terminal rate ^f	7/31 (23%)	4/36 (11%)	13/30 (43%)	19/29 (66%)
First incidence (days)	545	448	520	497
Logistic regression test ^g	P<0.001	P=0.505	P=0.019	P<0.001
Carcinoma ^h				
Overall rate	1/50 (2%)	1/50 (2%)	6/50 (12%)	5/50 (10%)
Adjusted rate	2.6%	2.8%	16.5%	14.7%
Terminal rate	0/31 (0%)	1/36 (3%)	3/30 (10%)	3/29 (10%)
First incidence (days)	653	734 (T)	436	595
Logistic regression test	P=0.036	P=0.762N	P=0.062	P=0.104
Adenoma or Carcinoma ⁱ				
Overall rate	10/50 (20%)	11/50 (22%)	25/50 (50%)	37/50 (74%)
Adjusted rate	28.4%	25.3%	63.2%	83.7%
Terminal rate	7/31 (23%)	5/36 (14%)	16/30 (53%)	22/29 (76%)
First incidence (days)	545	448	436	497
Logistic regression test	P<0.001	P = 0.506	P = 0.001	P<0.001

\$	0 ppm	188 ppm	375 ppm	750 ppm
Female	•			······
Harderian Gland	50	50	50	50
Hyperplasia	3 (1.3)	2 (3.5)	5 (3.0)	1 (1.0)
Adenoma	· · · · · · · · · · · · · · · · · · ·			
Overall rate	5/50 (10%)	7/50 (14%)	16/50 (32%)	19/50 (38%)
Adjusted rate	16.0%	21.4%	43.1%	45.9%
Terminal rate	2/25 (8%)	4/28 (14%)	7/26 (27%)	14/36 (39%)
First incidence (days)	609	639	498	503
Logistic regression test	P<0.001	P=0.380	P=0.008	P=0.003
Carcinoma ^j			· · ·	
Overall rate	1/50 (2%)	2/50 (4%)	4/50 (8%)	3/50 (6%)
Adjusted rate	2.9%	6.7%	14.1%	8.3%
Terminal rate	0/25 (0%)	1/28 (4%)	3/26 (12%)	3/36 (8%)
First incidence (days)	663	693	679	734 (T)
Logistic regression test	P=0.305	P=0.501	P=0.194	P=0.365
- 3	· · · · ·			and the second second
Adenoma or Carcinoma ^k		1 A A A A A A A A A A A A A A A A A A A		
Overall rate	6/50 (12%)	9/50 (18%)	20/50 (40%)	21/50 (42%)
Adjusted rate	18.4%	27.1%	53.5%	50.8%
Terminal rate	2/25 (8%)	5/28 (18%)	10/26 (38%)	16/36 (44%)
First incidence (days)	609	639	498	503
Logistic regression test	P<0.001	P=0.175	P=0.002	P=0.002

Incidences of Neoplasms and Nonneoplastic Lesions of the Harderian Gland in Mice in the 2-Year Inhalation Study of Nitromethane (continued)

(T)Terminal sacrifice

^a Number of animals necropsied

^b Number of animals with lesion

^c Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

^d Number of animals with neoplasm per number of animals necropsied

e Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

f Observed incidence in animals surviving until the end of the study

^g In the control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to the pairwise comparisons between the controls and that exposed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal. A lower incidence in an exposed group is indicated by N.

^h Historical incidence for all 2-year NTP inhalation studies with chamber control groups (mean ± standard deviation): 2/950 (0.2% ± 0.9%); range, 0%-4%. Historical incidence (Battelle Pacific Northwest Laboratories): 2/450 (0.4% ± 1.3%); range, 0%-4%.

¹ Historical incidence (all laboratories): 49/950 (5.2% ± 4.5%); range, 0%-14%. Historical incidence (Battelle Pacific Northwest Laboratories): 38/450 (8.4% ± 4.0%); range, 2%-14%.

^j Historical incidence (all laboratories): 6/941 (0.6% ± 1.4%); range, 0%-4%. Historical incidence (Battelle Pacific Northwest Laboratories): 6/447 (1.3% ± 1.7%); range, 0%-4%.

^k Historical incidence (all laboratories): 32/941 (3.4% ± 4.4%); range, 0%-16%. Historical incidence (Battelle Pacific Northwest Laboratories): 27/447 (6.0% ± 5.0%); range, 0%-16%.

were similar to those in the controls (Tables 17 and C5). Hyperplasias were small focal lesions with increased numbers of secretory cells causing little if any compression of the adjacent parenchyma. Adenomas were generally larger and more expansive and caused compression of the adjacent parenchyma (Plate 5); some cellular atypia was noted, and the cells formed papillary, cystic, and glandular patterns. Harderian gland carcinomas were large neoplasms, often seen at necropsy, that involved the entire gland (Plate 6); many of these neoplasms showed encapsulation or local invasion.

Liver: Female mice in the 188 and 750 ppm groups had significantly greater incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) than the controls (Tables 18 and D3); the incidences of these neoplasms exceeded the historical control ranges of 0% to 40% for hepatocellular adenomas and 3% to 54% for hepatocellular adenomas or carcinomas (combined) for 2-year NTP inhalation studies (Table D4b). Females in the 188 and 750 ppm groups also had greater incidences of multiple hepatocellular adenomas than the controls. The incidences of eosinophilic focus increased with

The incidences of eosinophilic focus increased with increasing exposure concentration, and the incidences in the 375 and 750 ppm groups were significantly greater than the control incidence (Tables 18 and D5).

Eosinophilic foci consisted of isolated foci of increased numbers of hepatocytes and/or enlarged hepatocytes, usually of similar tinctorial nature as the rest of the liver; these lesions, which sometimes caused slight tissue compression, blended into the normal parenchyma at short angles so that a demarcation line was not always easily seen. Hepatocellular adenomas were usually larger than eosinophilic foci and compressed the surrounding tissue; these neoplasms contained basophilic cells and were sharply demarcated from the surrounding parenchyma due to the sharp angle of abutment and contrasting tinctorial quality. Hepatocellular carcinomas were large and irregular, with cellular atypia and pleomorphism, and contained trabecular patterns of cell growth.

Incidences of	Neoplasms	and N	onneoplastic	Lesions	of the	Liver	in	Female	Mice
in the 2-Year	Inhalation	Study	of Nitrometh	ane					

0 ppm	188 ppm	375 ppm	750 ppm
50	40	40	50
4	7	11*	15*
	*. •	1	
14/50 (28%)	25/49 (51%)	17/49 (35%)	35/50 (70%)
45.5%	68.6%	49.0%	83.1%
9/25 (36%)	17/28 (61%)	10/26 (38%)	29/36 (81%)
597	534	498	426
P<0.001	P=0.013	P=0.364	P<0.001
le			
3/50 (6%)	13/49 (27%)**	4/49 (8%)	13/50 (26%)**
10/50 (20%)	14/49 (29%)	8/49 (16%)	12/50 (24%)
29.7%	35.7%	26.6%	25.6%
3/25 (12%)	6/28 (21%)	6/26 (23%)	2/36 (6%)
576	534	548	426
P=0.329	P=0.195	P=0.383N	P=0.200
inoma ^h			
19/50 (38%)	34/49 (69%)	22/49 (45%)	40/50 (80%)
54.6%	82.4%	62.6%	86.9%
10/25 (40%)	21/28 (75%)	14/26 (54%)	30/36 (83%)
576	534	498	426
P=0.001	P<0.001	P=0.368	P<0.001
	$\begin{array}{c} 0 \text{ ppm} \\ \\ 50 \\ 4 \\ \\ 14/50 (28\%) \\ 45.5\% \\ 9/25 (36\%) \\ 597 \\ P < 0.001 \\ \\ 10/50 (20\%) \\ 29.7\% \\ 3/25 (12\%) \\ 576 \\ P = 0.329 \\ \\ \\ 10/50 (38\%) \\ 54.6\% \\ 10/25 (40\%) \\ 576 \\ P = 0.001 \\ \end{array}$	0 ppm 188 ppm 50 49 4 7 $14/50$ (28%) $25/49$ (51%) 45.5% 68.6% $9/25$ (36%) $17/28$ (61%) 597 534 $P < 0.001$ $P = 0.013$ le $3/50$ (6%) $13/49$ (27%)** $10/50$ (20%) $14/49$ (29%) 29.7% 35.7% $3/25$ (12%) $6/28$ (21%) 576 534 $P = 0.329$ $P = 0.195$ sinoma ^h $19/50$ (38%) $34/49$ (69%) 54.6% 82.4% $10/25$ (40%) $21/28$ (75%) 576 534 $P = 0.001$ $P < 0.001$	0 ppm188 ppm375 ppm 50 49494711* $14/50$ (28%)25/49 (51%)17/49 (35%) 45.5% 68.6%49.0% $9/25$ (36%)17/28 (61%)10/26 (38%) 597 534498 $P < 0.001$ $P = 0.013$ $P = 0.364$ le $3/50$ (6%)13/49 (27%)** $4/49$ (8%) $10/50$ (20%)14/49 (29%) $8/49$ (16%) 29.7% 35.7%26.6% $3/25$ (12%) $6/28$ (21%) $6/26$ (23%) 576 534548 $P = 0.329$ $P = 0.195$ $P = 0.383N$ sinomah19/50 (38%) $34/49$ (69%) $22/49$ (45%) 54.6% 82.4% 62.6% $10/25$ (40%) $21/28$ (75%) $14/26$ (54%) 576 534498 $P = 0.001$ $P < 0.001$ $P = 0.368$

* Significantly different (P ≤ 0.05) from the control group by the logistic regression test

** P≤0.01

^a Number of animals with liver examined microscopically

^b Number of animals with lesion

^c Number of animals with neoplasm per number of animals with liver examined microscopically

^d Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

e Observed incidence in animals surviving until the end of the study

- ^f In the control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to the pairwise comparisons between the controls and that exposed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal. A lower incidence in an exposed group is indicated by N.
- ^g Historical incidence for all 2-year NTP inhalation studies with chamber control groups (mean ± standard deviation): 103/937 (11.0% ± 6.7%); range, 0%-30%. Historical incidence (Battelle Pacific Northwest Laboratories): 54/446 (12.1% ± 8.1%); range, 2%-30%.
- ^h Historical incidence (all laboratories): 200/937 (21.3% ± 11.9%); range, 3%-54%. Historical incidence (Battelle Pacific Northwest Laboratories): 95-446 (21.3% ± 14.8%); range, 6%-54%.

Lung: The incidence of alveolar/bronchiolar carcinoma in male mice in the 750 ppm group was significantly greater than that in the controls (Tables 19 and C3) and exceeded the historical control range for these neoplasms in 2-year NTP inhalation studies (Table C4b). The incidence of alveolar/bronchiolar adenoma or carcinoma (combined) in females in the 750 ppm group was also significantly greater than in the controls and exceeded the historical control range (Tables 19, D3, and D4c). The incidence of alveolar/bronchiolar carcinoma in the female 375 ppm group was significantly greater than in controls but was within the historical control range. The incidence of alveolar/bronchiolar adenomas in females in the 750 ppm group also exceeded the historical control range. Females in the 375 ppm group had a

significantly greater incidence of cellular infiltration of histiocytes than the controls (Tables 19 and D5); the incidences of alveolar epithelial hyperplasia in exposed males and females were similar to those of the controls.

Alveolar/bronchiolar adenomas consisted of focal proliferations of cuboidal or columnar cells in alveolar areas; adenomas usually caused compression of surrounding tissue and loss of the basic alveolar structure. Alveolar/bronchiolar carcinomas had cellular anaplasia and compression; there was evidence of tissue invasion. Carcinomas had a higher nucleus:cytoplasm ratio than alveolar/bronchiolar adenomas.

TABLE 19

Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Mice in the 2-Year Inhalation Study of Nitromethane

	0 ppm	188 ppm	375 ppm	750 ppm
Male	<u> </u>		<u></u>	<u></u>
Lung ²	50	50	50	50
Infiltration Collular Histioauta ^b	50 7 (2 A) ^C	JU	3 (3 7)	50
Alveolar Epithelium, Hyperplasia	1 (1.0)	1 (1.0)	3 (2.7)	1 (3.0)
Alveolar/bronchiolar Adenoma		· · ·	· · · ·	
Overall rate ^d	11/50 (22%)	10/50 (20%)	9/50 (18%)	12/50 (24%)
Adjusted rate ^e	30.8%	26.0%	30.0%	35.1%
Terminal rate ^f	8/31 (26%)	8/36 (22%)	9/30 (30%)	8/29 (28%)
First incidence (days)	449	646	734 (T)	497
Logistic regression test ^g	P=0.422	P=0.456N	P=0.412N	P=0.511
Alveolar/bronchiolar Carcinomah			· ·	
Overall rate	2/50 (4%)	3/50 (6%)	3/50 (6%)	11/50 (22%)
Adjusted rate	6.5%	8.3%	10.0%	30.4%
Terminal rate	2/31 (6%)	3/36 (8%)	3/30 (10%)	6/29 (21%)
First incidence (days)	734 (T)	734 (T)	734 (T)	586
Logistic regression test	P=0.001	P=0.569	P=0.485	P=0.009
Alveolar/bronchiolar Adenoma or Ca	rcinoma ⁱ			
Overall rate	13/50 (26%)	13/50 (26%)	12/50 (24%)	20/50 (40%)
Adjusted rate	36.8%	33.9%	40.0%	51.2%
Terminal rate	10/31 (32%)	11/36 (31%)	12/30 (40%)	11/29 (38%)
First incidence (days)	449	646	734 (T)	497
Logistic regression test	P = 0.059	P = 0.517N	P = 0.515N	P = 0.105

Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Mice in the 2-Year Inhalation Study of Nitromethane (continued)

	0 ppm	188 ppm	375 ppm	750 ppm
Female	<u></u>	,		· · · · ·
Iung	50	50	40 ¹	50
Infiltration Cellular Histiocyte	0	1(10)	6* (2 5)	4 (2 8)
Alveolar Epithelium, Hyperplasia	3 (2.3)	1 (2.0)	5 (2.0)	1 (3.0)
Alveolar/bronchiolar Adenoma				
Overall rate	3/50 (6%)	3/50 (6%)	2/49 (4%)	9/50 (18%)
Adjusted rate	11.5%	10.7%	4.3%	22.7%
Terminal rate	2/25 (8%)	3/28 (11%)	0/26 (0%)	6/36 (17%)
First incidence (days)	716	734 (T)	498	426
Logistic regression test	P=0.022	P=0.632N	P=0.514N	P=0.083
Alveolar/bronchiolar Carcinoma ^j		•		
Overall rate	0/50 (0%)	3/50 (6%)	5/49 (10%)	3/50 (6%)
Adjusted rate	0.0%	8.3%	15.0%	7.2%
Terminal rate	0/25 (0%)	1/28 (4%)	2/26 (8%)	1/36 (3%)
First incidence (days)	k	534	602	503
Logistic regression test	P=0.149	P=0.119	P=0.033	P=0.110
Alveolar/bronchiolar Adenoma or Carc	inoma ^l			•
Overall rate	3/50 (6%)	6/50 (12%)	6/49 (12%)	12/50 (24%)
Adjusted rate	11.5%	18.5%	16.8%	28.7%
Terminal rate	2/25 (8%)	4/28 (14%)	2/26 (8%)	7/36 (19%)
First incidence (days)	716	534	498	426
Logistic regression test	P=0.007	P=0.243	P=0.238	P=0.015
				•

* Significantly different ($P \le 0.05$) from the control group by the logistic regression test

(T)Terminal sacrifice

^a Number of animals with lung examined microscopically

^b Number of animals with lesion

^c Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

^d Number of animals with neoplasm per number of animals with lung examined microscopically

^e Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

^f Observed incidence in animals surviving until the end of the study

^g In the control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to the pairwise comparisons between the controls and that exposed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal. A lower incidence in an exposed group is indicated by N.

^h Historical incidence for all 2-year NTP inhalation studies with chamber control groups (mean ± standard deviation): 75/947 (7.9% ± 5.7%); range, 0%-16%. Historical incidence (Battelle Pacific Northwest Laboratories): 37/448 (8.3% ± 5.8%); range, 0%-16%.

¹ Historical incidence (all laboratories): 205/947 (21.7% ± 8.0%); range, 10%-42%. Historical incidence (Battelle Pacific Northwest Laboratories): 108/448 (24.1% ± 9.5%); range, 10%-42%.

j Historical incidence (all laboratories): 38/939 (4.1% ± 3.2%); range, 0%-12%. Historical incidence (Battelle Pacific Northwest Laboratories): 15/446 (3.4% ± 2.4%); range, 0%-6%.

^k Not applicable; no neoplasms in animal group

Historical incidence (all laboratories): 97/939 (10.3% ± 3.7%); range, 0%-16%. Historical incidence (Battelle Pacific Northwest Laboratories): 46/446 (10.3% ± 4.6%); range, 0%-16%.

Nose: The incidences of several nonneoplastic nasal lesions, similar to but more severe than those observed in the 13-week study, were generally significantly greater in exposed male and female mice than those in the controls (Tables 20, C5, and D5). These lesions included degeneration and metaplasia of the olfactory epithelium and hyaline degeneration of the respiratory epithelium (not observed in the 13-week study). The minimal to moderate olfactory degeneration was most prominent along the middle and posterior sections of the dorsal meatus and at the tips of the ethmoid turbinates; this lesion consisted of degeneration and loss of sensory neurons, nerve atrophy, and dilation of Bowman's glands (Plates 7

and 8). The metaplastic lesions, which represented a sequelae to degeneration, were characterized by replacement of the damaged olfactory epithelium with ciliated respiratory epithelium. Hyaline degeneration of the respiratory epithelium was characterized by accumulation of eosinophilic hyaline droplets in cells lining the nasopharyngeal duct, nasal septum, medial surface of the middle nasoturbinates, and some of the glandular epithelium beneath the respiratory epithelium of the middle nasal section. In addition, there was minimal suppurative inflammation of the nasolacrimal duct in males in the 375 and 750 ppm groups. The association of this marginally increased incidence with exposure to nitromethane is uncertain.

TABLE 20

Incidences of Nonneoplastic Lesions of the Nose in Mice in the 2-Year Inhalation Study of Nitromethane

	0 ppm	188 ppm	375 ppm	750 ppm
Male				
Nose ^a	50	49	50	50
Nasolacrimal Duct. Inflammation ^b	$2(1.5)^{c}$	3 (1.3)	10* (1.9)	10* (1.9)
Olfactory Epithelium, Atrophy, Focal	3 (1.0)	8* (1.1)	0	0
Olfactory Epithelium, Degeneration	0	10** (1.1)	50** (2.5)	50** (3.1)
Olfactory Epithelium, Metaplasia	0	1 (2.0)	41** (1.8)	49** (2.0)
Respiratory Epithelium, Degeneration,	-			· · ·
Hyaline	5 (1.0)	5 (1.2)	50** (1.9)	50** (2.0)
Female				
Nose	50	49	50	50
Nasolacrimal Duct, Inflammation	1 (2.0)	0	3 (1.7)	3 (2.0)
Olfactory Epithelium, Atrophy, Focal	2 (1.0)	6 (1.0)	0	0
Olfactory Epithelium, Degeneration	0	22** (1.1)	50** (2.7)	50** (3.2)
Olfactory Epithelium, Metaplasia	0	2 (1.0)	46** (1.9)	48** (2.2)
Respiratory Epithelium, Degeneration,				. ,
Hyaline	16 (1.1)	39** (1.5)	50** (2.0)	50** (2.5) ·

* Significantly different ($P \le 0.05$) from the control group by the logistic regression test

** P≤0.01

^a Number of animals with nose examined microscopically

^b Number of animals with lesion

^c Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

GENETIC TOXICOLOGY

Nitromethane was not mutagenic *in vitro* or *in vivo*. Results of tests for induction of mutations by nitromethane (100 to 10,000 μ g/plate) in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 were negative with and without induced S9 enzymes (Table E1; Mortelmans *et al.*, 1986). No induction of sister chromatid exchanges (Table E2) or chromosomal aberrations (Table E3) was observed in cultured Chinese hamster ovary cells treated with up to 5,000 μ g/mL nitromethane. Nitromethane administered by inhalation for 13 weeks at concentrations up to 1,500 ppm did not induce increased frequencies of micronucleated erythrocytes in the peripheral blood of male or female mice (Table E4).





PLATE 1

Mammary gland fibroadenoma from a female F344/N rat exposed to 375 ppm nitromethane by inhalation for 2 years. The neoplasm contains nests of glands separated by prominent bands of collagen. H&E; $150 \times$

PLATE 2

Mammary gland carcinoma from a female F344/N rat exposed to 375 ppm nitromethane by inhalation for 2 years. The neoplasm has a glandular pattern. H&E; $35 \times$



PLATE 3

Detail of a mammary gland carcinoma from a female F344/N rat exposed to 375 ppm nitromethane by inhalation for 2 years. Mitotic figures are common (arrows). H&E; $240 \times$

PLATE 4

Metastatic mammary gland carcinoma in the lung of a female F344/N rat exposed to 375 ppm nitromethane by inhalation for 2 years. The neoplasm obliterates a major pulmonary vessel (arrows). Bronchus (B). H&E; $35 \times$



PLATE 5

Small harderian gland adenoma (between arrows) from a male B6C3F₁ mouse exposed to 750 ppm nitromethane by inhalation for 2 years. H&E; $11\times$



PLATE 6

Large harderian gland carcinoma (between arrows) from a male $B6C3F_1$ mouse exposed to 750 ppm nitromethane by inhalation for 2 years. The neoplasm nearly surrounds the eye of the mouse. Note the lens (L) of the eye. H&E; $55 \times$



PLATE 7

Normal olfactory epithelium at level II of the nasal cavity of a control male $B6C3F_1$ mouse. Note the plump olfactory epithelium between the arrows. H&E; $340 \times$



PLATE 8

Degeneration of the olfactory epithelium at level II of the nasal cavity in a male $B6C3F_1$ mouse exposed to 750 ppm nitromethane by inhalation for 2 years. Note the attenuated olfactory epithelium between the arrows. H&E; $340 \times$

DISCUSSION AND CONCLUSIONS

Nitromethane was evaluated for toxicity and carcinogenicity in 16-day, 13-week, and 2-year studies in F344/N rats and $B6C3F_1$ mice, with whole body inhalation as the route of exposure.

Although there were a number of effects that were considered treatment related in rats in the 13-week study, most were not of great enough severity or incidence to determine exposure concentrations for the 2-year study. The deciding factor for the selection of exposure concentrations for the 2-year study was the neurotoxicologic findings in the 13-week study: loss of grip strength in males exposed to 1,500 ppm, hindlimb paralysis in rats in the 750 and 1,500 ppm groups, and sciatic nerve and spinal cord lesions in rats exposed to 375 ppm or greater. The effects in rats exposed to 750 ppm or greater were considered too severe, while the lesions observed at 375 ppm were very subtle and were less severe than those observed in the 16-day study. In the absence of significant short-term exposure-related effects, 375 ppm was selected as the highest exposure concentration for the 2-year rat study.

The primary factors influencing the selection of exposure concentrations for the 2-year mouse study were the incidence and severity of nasal lesions in male and female mice exposed to 1,500 ppm in the 13-week study. Also considered in the selection was the presence of extramedullary hematopoiesis of the spleen in male and female mice exposed to 1,500 ppm. Because the nasal lesions were considered too severe, 750 ppm was selected as the highest exposure concentration for the 2-year study.

There was a marked microcytic, regenerative anemia in exposed rats in the 13-week study, accompanied by red cell fragmentation, Heinz body formation, and increased methemoglobin production, although not extensive. Bone marrow hyperplasia, consistent with the anemia, was present in exposed rats. However, as one might expect with such hematotoxic effects, there were no treatment-related findings in the spleen of exposed rats. Incidences of extramedullary hematopoiesis of the spleen were significantly increased in male and female mice exposed to 1,500 ppm in the 13-week study. No hematologic evaluation was performed for mice in this study. Reductions in serum thyroxine concentration and increased thyroid gland weights have been observed in New Zealand white rabbits exposed for 6 months to 745 ppm nitromethane (Lewis *et al.*, 1979). On day 23 of the 13-week study, a hypothyroid state, as evidenced by reduced serum triiodothyronine, thyroxine, and free thyroxine concentrations, was observed in exposed rats. However, this effect was transient in that thyroid gland hormone concentrations and thyroid gland weights were similar to those of the controls at the end of the study.

In the 2-year rat study, neither survival rates nor weight gains were significantly affected by nitro-The lack of neurobehavioral methane exposure. clinical signs and neuropathological changes in the 2-year study suggests that the exposure concentrations were sufficiently low to prevent cumulative neurotoxic effects and that the rats had adapted to any effects that might have occurred early in the study; evaluation of spinal cords and sciatic nerves from male and female rats in the 0 and 375 ppm groups revealed no significant differences between exposed and control rats. There were no treatmentrelated clinical findings other than the gross observation of mammary gland swellings in female rats. Nitromethane exposure caused increased incidences of mammary gland neoplasms in female rats, as evidenced by exposure concentration-related increases in fibroadenoma; carcinoma; and fibroadenoma, adenoma, or carcinoma (combined). While the incidence of mammary gland neoplasms in control female rats (42%) was near the upper bound of the historical control range (16%-46%), the observed control neoplasm incidence was similar to the 46% rate predicted by the Seilkop logistic regression model (Seilkop, 1995) for control animals with an equivalent survival rate and 52-week mean body weight. Moreover, the slightly elevated body weights of females in the 188 and 375 ppm groups.

could not account for the markedly increased incidences of mammary gland neoplasms observed in these groups. There were no treatment-related increases in the incidences of neoplasms or nonneoplastic lesions at any site in male rats. The presence of renal tubule adenomas only in exposed animals (0/50, 3/50, 2/50, 1/50) was investigated by preparing kidney step sections for control and exposed male rats. Additional adenomas were observed in step sections from exposed and control groups (2/50, 2/50, 0/50, 4/50); however, the combined incidences of renal tubule adenoma for step sections and original kidney sections (2/50, 5/50, 2/50, 5/50) did not indicate a significant treatmentrelated increase in the incidence of this neoplasm.

During the 2-year mouse study, the survival rate for females in the 750 ppm group was marginally greater than that of controls. Exposed female mice generally weighed slightly more than the controls; however, body weights of control and exposed females were similar at the end of the study. Survival rates and body weights of treated male mice were similar to those of the controls. The only clinical findings observed during the 2-year study were swelling around the eyes and exophthalmos. These findings were consistent with increased incidences of harderian gland adenomas and carcinomas in exposed mice. The incidences of harderian gland neoplasms in control mice were somewhat greater than the historical control mean; however, the increased incidences of harderian adenomas or carcinomas (combined) were highly significant in males and females exposed to 375 or 750 ppm and were considered to be caused by exposure to nitromethane.

Nitromethane exposure caused a significant increase in the incidences of hepatocellular adenomas and adenomas or carcinomas (combined) in female mice in the 188 and 750 ppm groups. The incidences of multiple adenomas were increased in these two groups as well. The incidences of eosinophilic foci, considered to be part of the continuum of hepatic neoplasms, were marginally increased with increasing exposure concentration. As stated previously, exposed female mice had slightly greater mean body weights and lived slightly longer than control females; moreover, liver neoplasm incidences did correlate with body weight. However, application of the Seilkop logistic regression model (Seilkop, 1995) suggests that marginal body weight differences and/or increased survival rates could not account for the increased incidences of neoplasms observed in the 188 and 750 ppm groups. There is a somewhat unusual inversion in the treatment response in that the 375 ppm group incidence is consistent with the control incidence. The control incidence (38%) is slightly greater than the mean historical control incidence of 21.3%, but is still well within the historical control range (3%-54%). The increased incidences of these hepatocellular neoplasms were considered to be caused by nitromethane exposure.

The secondary nitroalkane 2-nitropropane has been shown to cause increased incidences of hepatocellular neoplasms in rats administered the compound by inhalation (Lewis *et al.*, 1979) or gavage (Fiala *et al.*, 1987). The primary alkanes nitroethane (Griffin *et al.*, 1988), 1-nitropropane (Griffin *et al.*, 1982), and tetranitromethane (NTP, 1990) have not been shown to cause increased incidences of such neoplasms in rats. In addition, tetranitromethane (NTP, 1990) and 3-nitro-3-hexene (Deichman *et al.*, 1963) did not cause hepatocellular neoplasms in mice. No reports of carcinogenicity studies in mice were found in the literature for nitroethane, 1-nitropropane, or 2-nitropropane.

A number of studies have been conducted to investigate the possible mechanism of 2-nitropropaneinduced hepatic neoplasms and the lack of such effects by primary nitroalkanes in rats. The primary and secondary mononitroalkanes exist in a state of equilibrium between the protonated neutral nitroalkanes, the nonprotonated nitronic acid and its anion, or nitronate in aqueous solution. Löfroth et al. (1986) have demonstrated that nitrite is not the major cause of mutagenicity of nitroalkanes in various Salmonella strains. At cellular pH, the secondary nitroalkanes have a much higher relative concentration of the nitronate anion and nitronic acid forms than the primary nitroalkanes; therefore, Löfroth et al. (1986) hypothesized that the anion or the acid may be the ultimate mutagen. In general, the primary nitroalkanes nitromethane, nitroethane, 1-nitropropane, and 1-nitrobutane and their nitronates are not mutagenic (Conaway et al., 1991a; Davis, 2-Nitropropane, its nitronate 2-propyl-1993). 2-nitronate, and the nitronates of 2-nitrobutane and 3-nitropentane are mutagenic (Conaway et al.,

Discussion and Conclusions

1991a). The nitronates were more powerful mutagens than their respective parent compounds. Nitroethane, 1-nitropropane, and 2-nitropropane (Davis et al., 1993) do not induce micronuclei in erythrocytes from mice, similar to nitromethane in the 13-week studies. In human lymphocytes exposed in culture, 2-nitropropane, but not 1-nitropropane, induces chromosomal aberrations and sister chromatid exchanges. Tetranitromethane does induce sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells (NTP, 1990); however, as presented in this report, nitromethane did not induce either. 2-Nitropropane, but not 1-nitropropane, has been shown to induce DNA repair synthesis in rat hepatocytes (Andrae et al., 1988) in vitro and in vivo and cause in vivo oxidative damage to rat liver DNA and RNA (Conaway et al., 1991b), as indicated by the increase in 8-hydroxydeoxyguanosine and 8-hydroxyguanosine. The primary nitroalkanes 1-nitropropane, 1-nitrobutane, and 1-nitropentane did not produce DNA or RNA damage; however, the secondary nitroalkanes 2-nitropropane, 2-nitrobutane, and 2-nitropentane did. The 2-nitroalkanes produce electrochemically active species, presumably modified nucleosides. Conaway et al. (1991b) concluded that the metabolites were responsible for the DNA and RNA damage. Tetranitromethane has been shown to nitrate hydroxyl groups of proteins, primarily of tyrosine residues (Riordan and Vallee, 1972).

Several nitroalkanes have been shown to be metabolized by cytochrome P450 in rat and mouse NADPHdependent hepatic microsomes (Ullrich et al., 1978, Sakurai et al., 1980; Marker and Kulkarni, 1986; Dayal et al., 1991). The specific activities of rat liver microsomes were greatest for 2-nitropropane nitronate and 2-nitropropane, followed by 1-nitropropane, nitromethane, and tetranitromethane. The substrate binding spectrum for nitromethane was different from the other nitro compounds in rat liver microsomes (Sakurai et al., 1980) in that a possible cytochrome P₄₅₀-NO complex was formed. Formaldehyde and possibly nitric oxide were formed. Tetranitromethane had the same spectrum difference as nitromethane, but no formaldehyde was produced. 2-Nitropropane was metabolized to nitrite and acetone. In similar studies, Kuo and Fridovich (1986) have shown that the enzymatic denitrification of 2-nitropropane to acetone also results in the forma-

tion of free radicals, superoxide, and hydrogen peroxide. Cunningham and Matthews (1991) have demonstrated that 2-nitropropane given by gavage to F344/N rats causes hepatic cell proliferation, while 1-nitropropane does not. Chemicals with the aliphatic nitro group (-C-NO₂) have been added to a list of DNA-reactive subgroups recognized by the NTP for possible carcinogenic activity (Tennant and Ashby, 1991). It is not known whether the generation of reactive radicals directly or indirectly is involved in the mechanism of toxicity or carcinogenicity for some primary nitroalkanes and for nitromethane in particular.

Nitromethane exposure caused a significant increase in the incidence of alveolar/bronchiolar carcinomas in male mice exposed to 750 ppm, exceeding the historical control range. Although the incidence of alveolar/bronchiolar carcinomas was significant only in female mice exposed to 375 ppm, carcinomas were also found in the 188 and 750 ppm groups, while none were observed in the controls. In all exposed female groups the incidences of carcinoma were within the historical control range for female mice. The incidence of alveolar/bronchiolar adenoma or carcinoma (combined) was significantly increased in the 750 ppm group of females and was also elevated in the male 750 ppm group. The increased incidences of alveolar/bronchiolar neoplasms were considered to be treatment related in males and females. Exposure to tetranitromethane for 2 years caused increased incidences of alveolar/bronchiolar adenomas and carcinomas in male and female B6C3F1 mice (2 ppm) and F344/N rats (5 ppm) and squamous cell carcinomas of the lung in male and female rats (NTP, 1990).

The only other lesions associated with nitromethane exposure were nonneoplastic nasal lesions that occurred in most exposed male and female mice. These lesions were similar to those observed in the 13-week study, except that they were much more severe following 2 years of exposure to nitromethane. Nasal lesions included degeneration and metaplasia of the olfactory epithelium and hyaline degeneration of the respiratory epithelium. No neoplasms of the nasal cavity were observed in exposed male or female mice. Exposure to tetranitromethane for 2 years caused hyperplasia and metaplasia of the nasal respiratory epithelium in male and female mice (2 ppm) and rats (5 ppm) (NTP, 1990). There was no effect of tetranitromethane exposure on the olfactory epithelium in mice or rats, and no nasal cavity neoplasms were induced by exposure to tetranitromethane.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was no evidence of carcinogenic activity* of nitromethane in male F344/N rats exposed to 94, 188, or 375 ppm. There was clear evidence of carcinogenic activity of nitromethane in female F344/N rats based on increased incidences of mammary gland fibroadenomas and carcinomas. There was *clear evidence of carcinogenic activity* of nitromethane in male $B6C3F_1$ mice based on increased incidences of harderian gland adenomas and carcinomas. There was *clear evidence of carcinogenic activity* in female $B6C3F_1$ mice, based on increased incidences of liver neoplasms (primarily adenomas) and harderian gland adenomas and carcinomas. Increased incidences of alveolar/bronchiolar adenomas and carcinomas in male and female mice exposed to nitromethane were also considered to be related to chemical administration.

Exposure to nitromethane by inhalation for 2 years resulted in increased incidences of nasal lesions including degeneration and metaplasia of the olfactory epithelium and degeneration of the respiratory epithelium in male and female mice.

Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 13.
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APPENDIX A SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR INHALATION STUDY OF NITROMETHANE

TABLE A1	Summary of the Incidence of Neoplasms in Male Rats	-
	in the 2-Year Inhalation Study of Nitromethane	76
TABLE A2	Individual Animal Tumor Pathology of Male Rats	
	in the 2-Year Inhalation Study of Nitromethane	80
TABLE A3	Statistical Analysis of Primary Neoplasms in Male Rats	
	in the 2-Year Inhalation Study of Nitromethane	104
TABLE A4	Summary of the Incidence of Nonneoplastic Lesions in Male Rats	
	in the 2-Year Inhalation Study of Nitromethane	111

Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Nitromethane^a

	0 ppm	94 ppm	188 ppm	375 ppm
Disposition Summary	<u></u>			
Animals initially in study	50	50	50	50
Early deaths				
Moribund	33	31	34	39
Natural deaths	4	3	2	3
Survivors				
Terminal sacrifice	13	16	14	. 8
Animals examined microscopically	50	50	50	50
Alimentary System		· · ·		. <u> </u>
Intestine large colon	(50)	(50)	(50)	(50)
Intestine large, rectum	(50)	(49)	(50)	(49)
Intestine large, recum	(50)	(50)	(50)	(50)
Intestine small, duodenum	(50)	(50)	(50)	(49)
Histiocytic sarcoma	(50)	1 (2%)	(50)	the state of the s
Intestine small jejunum	(50)	(50)	(50)	(50)
Intestine small, jejunom	(50)	(50)	(50)	(50)
Histiocytic sarcoma	(50)	1 (2%)	(00)	(55)
Tiver	(50)	(50)	(50)	(50)
Cholangiocarcinoma	1 (2%)	(00)		(00)
Hepatocellular carcinoma	x (270)		2 (4%)	
Hepatocellular adenoma	1 (2%)	1 (2%)	- () , , , , , , , , , , , , , , , , , ,	2 (4%)
Henatocellular adenoma multiple	· (=//)	- (=///	1 (2%)	,
Histiocytic sarcoma	1 (2%)	1 (2%)	(
Mesentery	(15)	(13)	(10)	(8)
Oral mucosa	(1)	(2)	(1)	
Pharyngeal squamous cell papilloma	(-/	1 (50%)	1 (100%)	••
Pancreas	(50)	(50)	(50)	(50)
Adenoma	1 (2%)	1 (2%)	1 (2%)	
Histiocytic sarcoma		1 (2%)		
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Histiocytic sarcoma	(° -)	1 (2%)		
Stomach, glandular	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		•
Tongue		(1)		(1)
Squamous cell carcinoma		1 (100%)		
Squamous cell papilloma				1 (100%)
Cardiovascular System				(50)
Heart	(50)	(50)	(00)	(30)
Schwannoma malignant	1 (2%)	· . ·		
Endocrine System		· ·		· ·
Adrenal cortex	(50)	(50)	(50)	(50)
Carcinoma	<u> </u>	· · · · · · · · · · · · · · · · · · ·	. /	1 (2%)
Carcinoma, metastatic, Zymbal's glan	nd		•	1 (2%)
Pheochromocytoma malignant, metast	tatic.		•	
adrenal medulla	,	1 (2%)	•	
and all a manager		- \/		

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TABLE A1

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Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Nitromethane (continued)

	0 ppm	94 ppm	188 ppm	375 ppm
Fridogrino System (continued)	<u></u>		<u></u>	
Adrenal modulla	(50)	(50)	(50)	(50)
Carainama matastatia Zumbal'a gland	(30)	(50)	(50)	(30)
Dhaoshromosutoma malignant		1 (79%)	2 (192)	1(2%)
Pheochromocytoma henign	11 (77%)	1(270) 12(24%)	2 (4%)	2(4%)
Bilateral pheochromocytoma malignant	11(22/0) 1(2%)	12 (2470)	15 (50%)	14 (28%)
Bilateral, pheochromocytoma henign	5 (10%)	8 (16%)	6 (12%)	5 (10%)
Islets pancreatic	(50)	(50)	(50)	(50)
Adenoma	8 (16%)	9 (18%)	4 (8%)	1 (2%)
Carcinoma	1 (2%)	1 (2%)	3 (6%)	5 (10%)
Parathyroid gland	(47)	(49)	(49)	(48)
Adenoma	()	1 (2%)	1 (2%)	(10)
Pituitary gland	(50)	(47)	(50)	(49)
Histiocytic sarcoma	(/	1 (2%)	~/	
Pars distalis, adenoma	38 (76%)	36 (77%)	32 (64%)	39 (80%)
Pars intermedia, adenoma			1 (2%)	2 (4%)
Thyroid gland	(50)	(50)	(50)	(50)
Bilateral, C-cell, carcinoma		1 (2%)		
C-cell, adenoma	8 (16%)	5 (10%)	8 (16%)	8 (16%)
C-cell, carcinoma		1 (2%)	1 (2%)	3 (6%)
Follicular cell, adenoma		1 (2%)		
Follicular cell, carcinoma	1 (2%)	1 (2%)	2 (4%)	
General Body System Peritoneum		(1)		(1)
				·
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Preputial gland	(50)	(50)	(50)	(50)
Adenoma	4 (8%)	3 (6%)	3 (6%)	3 (6%)
Carcinoma		1 (2%)	1 (2%)	1 (2%)
Prostate	. (50)	(50)	(50)	(50)
Seminal vesicle	(50)	(50)	(50)	(50)
Histocytic sarcoma	(60)	1 (2%)	(50)	(50)
Dilatoral interatitial call adaptame	(30)	(50)	(50)	(50)
Interstitial cell, adenoma	16 (32%)	11 (22%)	13 (26%)	15 (30%)
		·		·
Hematopoietic System	(50)	(50)	(50)	(50)
Histiocytic sarcoma	(30)	1 (2%)	(50)	(50)
Lymph node	(17)	(13)	(17)	(13)
Deep cervical, carcinoma metastatic	(**)	(10)	(**)	(10)
thyroid gland		1 (8%)		
Iliac, histiocytic sarcoma		1 (8%)		
Renal, histiocytic sarcoma		1 (8%)		
• •		~~~ /		

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Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Nitromethane (continued)

• • • • • • • • • • • • • • • • • • •	0 ppm	94	t ppm	188 ppm	375 ppm
Hematopoietic System (continued)	· .			• •	
Lymph node, bronchial	(48)	(48)	· · ·	(48)	(47)
Osteosarcoma, metastatic, bone	(10)	(10)	(2%)	(40)	(47)
Lymph node, mandibular	(48)	(48)	(2/0)	(48)	(49)
Histiocytic sarcoma	()	1	(2%)	(10)	(4))
Lymph node, mesenteric	(50)	(50)	(270)	(48)	(50)
Histiocytic sarcoma	(1	(2%)	(10)	(50)
Lymph node, mediastinal	(50)	(45)	(_,_,	(50)	(47)
Histiocytic sarcoma		1	(2%)	(20)	
Spleen	(50)	(50)	(270)	(50)	(50)
Fibroma	1 (2%)	1	(2%)	(00)	(50)
Histiocytic sarcoma		1	(2%)	•.	
Thymus	(45)	(45)	(277)	(48)	(46)
Histiocytic sarcoma		1	(2%)		(10)
Thymoma benign			(,	1 (2%)	•
				- (-,-,	
					· · · · · · · · · · · · · · · · · · ·
Integumentary System					
Mammary gland	(28)	· (27)		(31)	(28)
Fibroadenoma	1 (4%)	1	(4%)	1 (3%)	2 (7%)
Skin	(50)	(49)		(50)	(50)
Basal cell carcinoma					2 (4%)
Keratoacanthoma	6 (12%)	2	(4%)	2 (4%)	1 (2%)
Keratoacanthoma, multiple				,	1 (2%)
Squamous cell carcinoma	1 (2%)	2	(4%)	1 (2%)	1 (2%)
Squamous cell papilloma		•			3 (6%)
Sebaceous gland, adenoma	1 (2%)	1	(2%)	•	
Subcutaneous tissue, fibroma	3 (6%)			1 (2%)	
Subcutaneous tissue, fibrosarcoma	3 (6%)				
Subcutaneous tissue, lipoma					1 (2%)
Subcutaneous tissue, osteosarcoma				1 (2%)	
Subcutaneous tissue, sarcoma				2 (4%)	
Subcutaneous tissue, schwannoma malignant		. • ,		198 ⁰ - 1	2 (4%)
Musculoskeletal System	•				
Bone	(50)	(50)		(50)	(50)
Histiocytic sarcoma	1 (2%)				
Osteoma	1 (2%)				•
Osteosarcoma	. ,	1	(2%)		
Skeletal muscle	(2)	· · ·		(1)	(1)
Histiocytic sarcoma	1 (50%)				
Nervous System					1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1
Brain	(50)	(50)		(50)	(50)
Granular cell tumor benign					1 (2%)
Oligodendroglioma benign		1	(2%)		
		-			

Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Nitromethane (continued)

	0 ppm	94 ppm	188 ppm	375 ppm
Respiratory System		· · · · · · · · · · · · · · · · · · ·	- <u></u>	
Larynx	(50)	(50)	(50)	(50)
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	2 (4%)		3 (6%)
Alveolar/bronchiolar carcinoma			2 (4%)	-
Carcinoma, metastatic, thyroid gland		1 (2%)		
Carcinoma, metastatic, Zymbal's gland				1 (2%)
Cholangiocarcinoma, metastatic, liver	1 (2%)			
Histiocytic sarcoma	1 (2%)	1 (2%)		
Osteosarcoma, metastatic, bone		1 (2%)		
Pheochromocytoma malignant, metastatic,				
adrenal medulla	1 (2%)			
Squamous cell carcinoma, metastatic, skin			1 (2%)	
Nose	(50)	(50)	(50)	(50)
Special Senses System		······································		<u></u>
Harderian gland	(1)			
Zymbal's gland		(2)		(1)
Carcinoma		2 (100%)		1 (100%)
	<u> </u>			
Vidnou	(50)	(50)	(50)	(50)
Carcinoma metastatic Zumbal's sland	(50)	(30)	(30)	(30)
Histiocytic sarcoma	1 (2%)	1 (2%)		1 (270)
Lipoma	1 (270)	1 (270)	1 (2%)	•
Renal tubule adenoma		3 (6%)	2(4%)	1 (2%)
Urinary bladder	(50)	(50)	(50)	(50)
Histiocytic sarcoma	(00)	1 (2%)	(20)	(00)
Transitional epithelium, papilloma		1 (2%)		
Systemic Lesions	(50)	(60)	(50)	(50)
Multiple organs	(50)	(50)	(50)	(30)
Alsuocytic sarcoma	1(2%)	1(2%)	22 (66 0)	25 (50.07)
Mesothelioma malignant	1 (2%)	3 (6%)	33 (00%)	1 (2%)
Neepleen Summer				· · · · · · · · · · · · · · · · · · ·
Total animals with primary nearlaster	50	40	50	40
Total animals with primary neoplasms	50	49	50	49
Total animals with benign neonlasms	50	10/	50	47
Total benjan neoplasme	128	4J 104	121	110
Total animals with malignant neonlasma	40	25	20	117
Total malignant neoplasme	40	35 A2	57 50	44
Total animals with metastatic neoplasme	2	3	1	1
Total metastatic neoplasms	2	5	1	4
tour measure neoplasms	2	5	•	-

^a Number of animals examined microscopically at the site and the number of animals with neoplasm

^b Number of animals with any tissue examined microscopically

c Primary neoplasms: all neoplasms except metastatic neoplasms

Individual Animal Tumo	or Patho	logy	of l	Mal	le]	Rat	s i	n t	he	2-3	'ea	r I	Inh	ala	ntic	n S	Stu	ldy	of	Ni	tro	me	th	an	e:	0	pp	m		• *
				2	4	4	4	5	5	5	5	5	5	5	5	5	5	6 6	5 6	6	6	6	6	5 (5 (5 (6 (5		
Number of Days on Study				4	1	9	9	0	1	2	3	5	6	6	8	9	9	0 1	1	1	2	2	4	4 4	4 (5 (6 (5 ·		•
				2	1	0.	1	4	2	8	7	2	5	9	0	0	2	0 1	1	2	3	6	4	1 4	4 (0	4 4	4		
				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0 () (0	0	0	() () () (0 (0		
Carcass ID Number				3	4	2	2	0	1	4	3	2 ·	4	1	1	1	1	3 () () 1	0) 4	4	1 :	5 2	2 (0 3	3		
				5	3	0	2	1	7	7	8	3 .	9	3	2	6	5	77	9) 1	5	2	1	1 (0	1	6	2		
Alimentary System		_																_		_	_		-					_	ر	
Esophagus				+	+	+	+	+	·+	+	+	÷	+	+.	+	+	+	+ [:] -	+ -	+ +	+	+ +	Ļ.	+	+ -	+	+	+		
Intestine large, colon				+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+ -	+ •	+ +	+ +	+ +	Ļ.	+	+	+	+	+.		
intestine large, rectum				•+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ •	+ -	+ +		+ +	- -	+	+	+	+ '	+		
Intestine large, cecum				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ •	+ •	+ +	+ -	+ -		+	+	+	+	+		
Intestine small duodenum		,		+	+	+	+	+	+	+	÷	+	+	+	+	+	+	÷ .	+ -					÷.	+ .	+	+	+		
Intestine small jejunum				÷	÷	÷.	÷	÷.	÷	+	÷	÷	÷	÷	+	÷	÷	÷.	• •		, 		, 	+	+ .	+	÷	÷		
Intestine small ileum								т. Т	- -	т Т	, ,	÷	÷	, _	÷	, ,	<u>.</u>	÷.					L .	.		<u>.</u>	÷.	÷		
liver					т 	· +		+ +	+ +	т _	+ +	т -		т Т	- -	т Т	+ +	т. т.					L .		+	- -	т. -	т. -		
Cholongiocarrinoma					т	т	т	Ŧ	т	т	Ŧ			'	'		•	•	•	'v	-			•			۰.	'		
Unorangiocarcinoma								v												~										
Hepatocellular adenoma								Λ																						
Histiocytic sarcoma																														1
Mesentery						+							+		+		+			-		F				+				
Oral mucosa																														
Pancreas				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ •	+ •	+ +		+ -	<u>-</u> -	+	+ •	+	+	+		
Adenoma					•								х																	
Salivary glands	•			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ ·	+ •	+ +		+ +	+ •	+	+ :	+	+	+		
Stomach, forestomach				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ ·	+ •	+ +		+ -	+ •	+	+	+	+	+		•
Stomach, glandular		۰.		+	+	+	+	+	΄+	+	+	+	+	+	+	+	+	+ ·	+ •	+ +	+ -	+ -	+ •	+	+	+	+	+		
Tooth																					,			•						
Cardiovascular System																												•		
Heart				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ ·	+ •	+ +	+ •	+ -	۰	+	+	+	+	+		• '
Schwannoma malignant	• •																												•, ·	
Endocrine System											_	_	_	_	_															
Adrenal cortex				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ .	+ •	+ +	+ -	+ -	• •	+	+	+	+	+		
Adrenal medulla				+	+	+	+	+	·+	+	+	+	+	+	+	+	+	+ •	+ •	+ +	÷ ۲	+ -	ب ا	+	+	+	+	+		
Pheochromocytoma benign																									:	x				
Bilateral, pheochromocytoma	malignan	t														-	•													
Bilateral pheochromocytoms	henign	•																	,	c										
Islets pancreatic	oomgn .			+	+	+	+	+	+	+	+	+	+	+	+ -	+	+	+ -	+ -		F -	+ -	⊢.	+	+	+	+	+		
Adenoma				-	-	-		'	.'	'		ÿ	ż	•	•	•		ý.	•		, ,	2		•	•	•	•	•		
Adenoma												^	^					^			. *	•								
Carcinoma Demotivered aland					• •			-	+	+	-	-	-	Ŧ	+	Ŧ	т.	ь.	- -		L .	L .	L	+	+	+	+	+		2
Paramyroid gland					- T		-	T	Ţ	Ŧ	Ţ	Ť	Ť	т.	т +	+ +	т _	т -	т. -		г. с.	г. –	L .	- -	т. -	т Т	т Т	1		
Pituitary giand				+	+	-	+	+	+	Ť	Ť	Ť	Ť	т	T V	T V	τ. v	v	т. У	T -			,	Τ.	v v	т. v.	ताः ।	v		
Pars distalis, adenoma				X	X		X		x	Å	X	Å	Å.		A	A	Ą.	<u>^</u>	<u>,</u>		. 1				<u>.</u>	A	т. Т	∧ ⊥		
Thyroid gland				+	+	+	+	+	, † ,	+	+	+	+	+	+	+	+	+ ·	+ •	+ -		+ -		+	-	+	Ŧ	Ŧ		
C-cell, adenoma								Х										x				2	K .	X						
Follicular cell, carcinoma										-						X									<i>.</i> .	. '				
General Body System																														
Carrital Sustar												_	-										-							
Genital System																л.	л.	. د	L		L	L.	L	+	÷	÷	+	+		
Constant and a second size				+	+	• +	+	+	+	.+	+	+	•+	+	+	+	+	+	*	• •	r .	r .	r	Ŧ	+	Ŧ	Ŧ	Ŧ		$\alpha = -1$
Epididymis																									+					
Penis				-			-															1. 1						1		
Penis Preputial gland				. +	+	+	+	+	+	+	+	+	+	.+	+	+	+	+	+	+ -	+	+ .	+	+	+ v	+	+	+	• •	

+: Tissue examined microscopically A: Autolysis precludes examination

M: Missing tissue I: Insufficient tissue X: Lesion present Blank: Not examined

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TABLE A2

simybibiqE ٥۶ Genital System General Body System Follicular cell, carcinoma I 8 ХХ C-cell, adenoma х Х + + + + + + + ++ Thyroid gland ٥۶ + + + + + + + + + + + + x x x x x x x x x Pars distalis, adenoma XXXXX Х ххх хх 38 х ٥\$ + + + + + ++ + + + + + + + + + + + + Pinitary gland + + L† + + + М + + ++ W + + + + + М Parathyroid gland Х **carcinoma** L X + + **emon**abA х хх 8 + Islets, pancreatic ٥۶ + Bilateral, pheochromocytoma benign хх Х х ς Bilateral, pheochromocytoma malignant l Х X X + + П Х Pheochromocytoma benign хх хх х ٥\$ + + + + + silubəm isnərbA xstros IsnstbA ٥۶ Endocrine System 3 Х Schwannoma malignant T ٥۶ nsəH Cardiovascular System I ttooT Stomach, glandular ٥\$ Stomach, forestomach ٥۶ sbnelg yievile2 05 ятопэbA I Pancreas ٥۵ Oral mucosa Ι Mesentery + ۶ĩ + х Histiocytic sarcoma I Hepatocellular adenoma T Cholangiocarcinoma I ٥\$ LIVET Intestine small, ileum ٥\$ Intestine small, jejunum 0۶ ٥۶ Intestine small, duodenum Intestine large, cecum ٥۶ Intestine large, rectum ٥۶ Intestine large, colon ٥۶ + + sugandosI ٥۶ Alimentary System Tumors 8 4 4 6 3 0 4 4 6 3 1 6 7 8 6 2 0 8 4 8 2 0 1 6 6 \ssussiT **4 4 3 5 0 4 5 0 4 3 5 1 0 0 5 4 1 5 1 1 5 3 3 3 3** Carcass ID Number IntoT 0314589002103333445222222 1188001555533333333333333333 Number of Days on Study

Individual Animal Turnor Pathology of Male Rats in the 2-Year Inhalation Study of Nitromethane: 0 ppm (coninued)

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Preputial gland

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Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nitromethane: 0 ppm (continued) 2 4 4 4 5 5 5 5 5 5 5 5 5 5 6 6 6 6 6 6 6 6 6 6 6 Number of Days on Study 9 4 1 9 0 1 2 3 5 6 6 8 9 9 0 1 1 1 2 24 4 6 6 6 8 2 1 0 1 5 9 0 4 2 7 2 0 0 2 1 1 2 3 644044 0 0 0 0 0 0 0 0 Ó 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 **Carcass ID Number** 4 2 2 0 1 1 3 0 0 3 1 4 3 2 4 1 1 1 0 4 4 5 2 0 3 5 3 0 2 1 7 7 8 3 9 3 2 5 -7 7 9 6 1 5 2 1 0 1 6 2 Genital System (continued) Prostate + Seminal vesicle + + + + + Testes + + + + + + + + + ++ + + + + + + + + Bilateral, interstitial cell, adenoma х Х х X хх х Interstitial cell, adenoma х x х Х х хх х Hematopoietic System Bone marrow + Histiocytic sarcoma Lymph node Lymph node, bronchial M Lymph node, mandibular + Lymph node, mesenteric Lymph node, mediastinal Spleen Fibroma Thymus . Μ Μ + + + Integumentary System Mammary gland + M M M+ Μ + + MM + + MMM + + M +Μ + Fibroadenoma Skin Keratoacanthoma Squamous cell carcinoma Sebaceous gland, adenoma Х Subcutaneous tissue, fibroma x х Subcutaneous tissue, fibrosarcoma х Musculoskeletal System Bone Histiocytic sarcoma Osteoma х Skeletal muscle Histiocytic sarcoma **Nervous System** Brain + + + + + + + + + + + + + + + + + **Respiratory System** Larynx Lung + Alveolar/bronchiolar adenoma Cholangiocarcinoma, metastatic, liver X Histiocytic sarcoma Pheochromocytoma malignant, metastatic, adrenal medulla Nose Trachea + + + + + + + + + + + + + + + + + + + +

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Number of Days on Study Carcass ID Number	6 7 0		6 7	6	6	6	7	7	-	-						_			_		-			-			
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	0 4 8		0 4 4	0 3 4	0 2 9	0 0 3	0 4 0	0 2 4	0 0 4	0 4 6	0 3 3	0 2 7	0 1 9	0 0 2	0 0 8	0 2 6	0 4 5	0 1 0	0 2 8	0 1 4	0 1 8	0 2 5	0 3 0	0 3 1	0 3 6	0 3 9	Total Tissues/ Tumors
Genital System (continued)						_			_			_				_									-		<u> </u>
Prostate	+	۲,	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	۲	F	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	4	ŀ	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma						Х	х	Х	х	Х	Х			Х	Х	х	х	х	х		х	Х			Х		22
Interstitial cell, adenoma	Х	<u> </u>		х	_			-				Х	X							x			х	х		Х	16
Hematopoietic System																											
Bone marrow	Ч	F	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																							Х				. 1
Lymph node	-	F	+	+			+					+		+	+							+				+	17
Lymph node, bronchial	-	F	+	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mandibular	4	F	+	+	+	+	+	+	+	+	М	+	Μ	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	4	F	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	-	F	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	Ŧ	+	+	+	+	+	+	+	+	+	50
Spleen	-	۴	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma					х																						1
Thymus	-	ŀ	+	М	÷	Μ	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	÷	+	+	45
Integumentary System			_								_										-						
Mammary gland	-	<u>ب</u>	м	+	+	м	+	м	+	м	м	+	+	+	м	+	м	м	+	+	м	+	M	+	м	+	28
Fibroadenoma				•	•		•		•					•		•	•••		•	•	•••	•		x		•	
Skin	-	F	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma			ý.	•	•	•	'		•	•		•		x	x	•		•	•	•	x	•	x	x	•	. '	6
Squamous cell carcinoma											x			~	~								21	11	٠		1
Sebaceous gland adenoma																											1
Subattanaque tissue fibroma																										v	3
Subcutaneous tissue, fibrogramme																	v								v	Λ	2
Subcutaneous tissue, fibrosarcoma																	<u>х</u>										3
Musculoskeletal System		_																									50
Bone	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																							X				1
Osteoma																											1
Skeletal muscle																							+				2
Histiocytic sarcoma																							X				1
Nervous System																											
Brain	-	۲	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Larynx	4	ŀ	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	-	ł	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma															Х												1
Cholangiocarcinoma, metastatic, liver																											1 .
Histiocytic sarcoma																							х				1
Pheochromocytoma malignant,																											
metastatic, adrenal medulla																								х			1
Nose	-	⊦	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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TABLE A2 Individual Ar

Individual Animal Tumor	Pathology o	f Ma	le]	Ra	ts i	n t	he	2-	Yea	ar	In	hal	ati	on	St	udy	y o	fN	litı	on	ıet	ha	ne	: () p	pm	(con	tinue	d)	
Number of Days on Study	•	2 4 2	4	4 9	4 9 1	5 0 4	5 1 2	5 2 8	5 3 7	5 5 2	5 6 5	5 6 9	5 8 0	5 9 0	5 9 2	6 0 0	6 1 1	, 6 1 1	6 1 2	6 2 3	6 2 6	6 4 4	6 4 4	6 6 0	6 6 4	6 6 4				-
Carcass ID Number	<u>.</u>	0 3 5	0 4 3	0 2 0	0 2 2	0 0 1	0 1 7	0 4 7	0 3 8	0 2 3	0 4 9	0 1 3	0 1 2	0 1 6	0 1 5	0 3 7	0 0 7	0 0 9	0 1 1	0 0 5	0 4 2	0 4 1	0 5 0	0 2 1	0 0 6	0 3 2				-
Special Senses System Eye Harderian gland	· · · · ·				_	+	+						+	<u> </u>																-
Urinary System Kidney Histiocytic sarcoma Urinary bladder		+ +	 + +	· +	· +	+	+	++	+++	+	++	+	++	+	+	++	+ +	 +- `+	+	+	+	+ +	+	++	+ + +	+ +				-
Systemic Lesions Multiple organs Histiocytic sarcoma Leukemia mononuclear Mesothelioma malignant		+	+ x	+ x	+ X	+ x	+	+ x	+ x	+ x	+ x	+ x	+ X	+	+	+ x	+	+ x	+ x	+ x	+	+ x	. +	+ X	+ x	+ X		: 		-

Individual Animal Turno	or Pathology	y of Ma	le	Ra	ts i	in '	the	2	•¥e	ar	ln	ihai	iati	ion	St	ud	y (of 1	Nit	ror	net	ha	me	: () p	pm	(continued)	ł
Number of Days on Study		6 7 0	6 7 3	6 8 1	6 8 4	6 9 2	7 0 8	7 1 9	7 2 0	7 2 0	7 2 5	7 2 7	7 3 0	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 5	<u></u>							
Carcass ID Number		0 4 8	0 4 4	0 3 4	0 2 9	0 0 3	0 4 0	0 2 4	0 0 4	0 4 6	0 3 3	0 2 7	0 1 9	0 0 2	0 0 8	0 2 6	0 4 5	0 1 0	0 2 8	0 1 4	0 1 8	0 2 5	0 3 0	0 3 1	0 3 6	0 3 9	Total Tissues/ Tumors	
Special Senses System Eye Harderian gland	,																										2 1	
Urinary System Kidney Histiocytic sarcoma Urinary bladder		+	• 4	 		 		+ +	 ⊦ +	- + - +	- +	 - +	· +	· +	+	 + - +		- + - +	 + +	+ +	++	++	+ X +	+	+	+	50 1 50	
Systemic Lesions Multiple organs Histiocytic sarcoma Leukemia mononuclear Mesothelioma malignant		+ X	- + : X	+ .+ x X	+ : X	+ + {	+ + X	- + : X	+ +	- + x	- +	- + X	+ x	+ X	+ x	- +	· . +	- + X	+	+ X	+ x	+	+ X X	+ X	+ x	+ x	50 1 35 1	

Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nitromethane: 94 ppm 2 3 4 4 4 4 5 5 5 5 5 5 5, 5 56666 666 66 6 Number of Days on Study 9 9 2 3 9 9 1 2 2 2 7 8 8 8 9 0 0 0 0 0 0 1 3 4 4 2 7 7 9 0 2 5 0 3 4 4 1 68 3 1 4 6 7 8 9 6 6 2 6 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2.2 2 2 2 2 2 2 2 2. Carcass ID Number 2 4 3 0 2 0 0 2 2 0 1 3 2 3 3. 4 3 1 2 3 1 0 4 1 0 7 7 0 2 1 3 3 6 6 7 2 5 9 6 2 3 0 8 4 7 9 534 4 **Alimentary System** Esophagus 4 Intestine large, colon -ţ. Intestine large, rectum Intestine large, cecum + Intestine small, duodenum Histiocytic sarcoma Intestine small, jejunum + Intestine small, ileum Histiocytic sarcoma Liver Hepatocellular adenoma Histiocytic sarcoma Mesentery ÷ Oral mucosa + Pharyngeal, squamous cell papilloma х Pancreas Adenoma Histiocytic sarcoma Salivary glands + + + Stomach, forestomach Histiocytic sarcoma Stomach, glandular Histiocytic sarcoma Tongue Squamous cell carcinoma Tooth Cardiovascular System Heart + + + **Endocrine System** Adrenal cortex Pheochromocytoma malignant, metastatic, adrenal medulla Adrenal medulla Pheochromocytoma malignant Х х Pheochromocytoma benign Bilateral, pheochromocytoma benign Х Islets, pancreatic ++ х Х Adenoma Carcinoma Parathyroid gland Adenoma Pituitary gland + M + ·+ + Histiocytic sarcoma Х хх x x x x x x x x x x Х х Pars distalis, adenoma

86

Lesions in Male Rats

TABLE A2

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Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nitromethane: 94 ppm (continued) 666 6 6 6 66 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 Number of Days on Study 6 6 6 7 7 89 1 3 3 3 3 33 3 3 3 3 3 3 3 3 3 3 5 0 4 5 5 0 7 6 2 4 3 3 3 3 3 3 4 4 5 5 5 5 5 4 4 4 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 Total **Carcass ID Number** 5 0 3 1 10 2 3 2 2 4 4 1 3 4 4 4 3 4 4 0 1 1 1 2 Tissues/ 9 0 6 8 8 1 4 9 2 1 5 3 4 7 0 1 8 9 0 65 2 5 8 1 Tumors **Alimentary System** 50 Esophagus + Intestine large, colon 50 + Intestine large, rectum + 49 м Intestine large, cecum 50 Intestine small, duodenum 50 Histiocytic sarcoma 1 x Intestine small, jejunum 50 Intestine small, ileum 50 +Histiocytic sarcoma 1 50 Liver + + Hepatocellular adenoma х 1 Histiocytic sarcoma Х 1 Mesentery 13 + + + + + + Oral mucosa 2 Pharyngeal, squamous cell papilloma 1 Pancreas 50 Adenoma x 1 Histiocytic sarcoma 1 х Salivary glands 50 Stomach, forestomach 50 + + Histiocytic sarcoma x 1 Stomach, glandular 50 Histiocytic sarcoma Х 1 Tongue 1 Squamous cell carcinoma х 1 Tooth + 2 **Cardiovascular System** Heart 50 + + + + + + + + + ++ + + + ++ + **Endocrine System** 50 Adrenal cortex Pheochromocytoma malignant, metastatic, adrenal medulla 1 Adrenal medulla 50 Pheochromocytoma malignant х 1 х 12 Pheochromocytoma benign х Bilateral, pheochromocytoma benign хх х 8 х Х 50 Islets, pancreatic 9 х Adenoma X х х Carcinoma х 1 Parathyroid gland 49 Adenoma 1 47 Pituitary gland Μ + + Histiocytic sarcoma х 1 Pars distalis, adenoma ххххх X x x x x x x x x x x x x 36

Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nitromethane: 94 ppm (continued)

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N I CD Ct I			2	3	4	4	4	4	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	. 6	6	6				
Number of Days on Study			9	9	2	3	9	9	1	2	2	2	7	8	8	8	9	0	0	0	0	0	0	1	3	4	4				
			2	7	7	9	0	2	5	0	3	4	4	1	6	8	3	1	4	6	7	8	9	6	6	2	6				
			2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2				
Carcass ID Number			2	4	3	0	0	2	0	1	3	2	3	3	4	3	1	2	3	1	0	4	1	0	0	2	2				
	•		0	8	4	7	9	5	3	4	7	7	0	2	1	3	3	6	6	7	2	5	9	4	6	2	3				
Endoaring System (continued)		· · · · · ·															-		-	÷				_							<u> </u>
Thuroid gland			بد	т.	ъ	т.	-	ъ	· L	т	-	ъ	ъ	ъ	-	ᆂ	. ш.	-	ъ	-	Ŧ	Т	т.	-	ـ	-	т				
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Bilateral, C-cen, carcinoma											•		v																		
C-cell, adenoma													X																		
C-cell, carcinoma																															
Follicular cell, adenoma																															
Follicular cell, carcinoma											х																				
General Body System																															
Peritoneum				•																					+						
Genital System			<u> </u>		<u></u>									<u> </u>		_	<u>.</u>					<u> </u>					_		·.		•
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Epiardynnis Proputial gland			-	- T	т 	т -	Ť	т -	т 	т _	· T	т 	т 	т 	T T	т Г	- -	т 	т 	т -	т —		т 	т 	т 	т 	т 				
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Adenoma													X.																		
Carcinoma														-		. '								<i>.</i>						•	
Prostate			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			•	
Seminal vesicle			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			•	•••
Histiocytic sarcoma																											•				
Testes			. +	+	÷.	+	+	+	+	+.	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+	+				
Bilateral, interstitial cell, adenoma						Х	Х						Х	Х		Х			Х	•			Х					•			
Interstitial cell, adenoma					X						Х						X					X		X		х	х	•			
Hematopoietic System																															
Bone marrow		·	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Histiocytic sarcoma			•			÷	·			-	·	-		·	-							-									
Lymph node										+			+			+						+				+	+				
Deen cervical carcinoma metastatic										•	•		•									•				•					
thuroid gland	'•																														
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Lymph node, bronchiai			T V	т	т	т	т	т	т	т	т	т	Ŧ	т	т	т	т	т	т	т	т	Ŧ	т	т	т	т	-				
Osteosarcoma, metastatic, done	. • •																									,					
Lymph node, mandibular			+	+	+	+	. †	+	+	+	. +	+	+	+	+	+	Ŧ	+	+	+	Ŧ	+	+	+	+	Ť	Ŧ	•			
Histiocytic sarcoma				•												÷															
Lymph node, mesenteric			+	+	+	+	+	+ ·	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Histiocytic sarcoma																			•												
Lymph node, mediastinal			+	+	+	+	М	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	÷.,			
Histiocytic sarcoma	-																	·													
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Fibroma		· .																													
Histiocytic sarcoma																												·		•	
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Histiocytic sarcoma																						•			• •						•
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110

Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nitromethane: 94 ppm (continued) 6 6 6 6 6 6 6 7 7 7 7 7 7 7 6 7 7 7 7 7 7 7 7 7 7 Number of Days on Study 5 6 6 6 7 7 8 9 1 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 0 4 5 5 0 7 6 2 4 3 3 3 3 3 3 4 5 5 5 5 4 4 4 4 5 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 Total **Carcass ID Number** 1 1 0 2 3 2 2 4 4 1 3 4 4 4 5 0 3 3 4 4 0 1 1 1 2 Tissues/ 1 4 9 9 2 1 5 3 4 7 0 1 8 9 0 6 5 2 5 8 1 0 6 8 8 Tumors Endocrine System (continued) Thyroid gland 50 + + + + Bilateral, C-cell, carcinoma Х 1 C-cell, adenoma х х х 5 Х C-cell, carcinoma х 1 Follicular cell, adenoma х 1 Follicular cell, carcinoma 1 **General Body System** Peritoneum 1 **Genital System** 50 Epididymis 50 Preputial gland + Adenoma х 3 Carcinoma х 1 Prostate 50 50 Seminal vesicle Histiocytic sarcoma 1 х Testes 50 + + + + + + Bilateral, interstitial cell, adenoma Х х Х Х хх Х Х Х Х Х Х Х ххх 23 Interstitial cell, adenoma х Х х х 11 **Hematopoietic System** 50 Bone marrow Histiocytic sarcoma 1 х Lymph node 13 Deep cervical, carcinoma, metastatic, thyroid gland х 1 Iliac, histiocytic sarcoma х 1 Renal, histiocytic sarcoma Х 1 Lymph node, bronchial 48 M + M + Osteosarcoma, metastatic, bone 1 Lymph node, mandibular 48 Histiocytic sarcoma 1 Lymph node, mesenteric 50 Histiocytic sarcoma 1 Lymph node, mediastinal 45 Histiocytic sarcoma 1 50 Spleen 1 Fibroma х Histiocytic sarcoma 1 45 + + + MThymus Μ + М Histiocytic sarcoma x 1

Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nitromethane: 94 ppm (continued)

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	•	2	2 3	3 4	4	4	4	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6		
Number of Days on Study		9	9 9	2	3	9	9	1	2	2	2	7	8	8	8	9	0	0	0	0	0	0	1	3	4	4		
			2 7	7	9	0	2	5.	0	3	4	4	1	6	8	3	1	4	6	7	8	9	6	6	2	6		
<u> </u>		2	2 2	2 2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
Carcass ID Number		2	2 4	4 3	0	0	2	0	1	3	2	3	3	4	3	1	2	3	1	0	4	1	0	0	2	2		
		() 8	3 4	7	9	5	3	4	7	7	0	2	1	3	3	6	6	7	2	5	9	4	6	2	3		
Integumentary System							÷															_						
Mammary gland		,	M N	vi -	⊦ M	м	м	м	м	+	м	м	м	+	+	м	+	м	м	+	+	м	м	+	+	м		
Fibroadenoma		•								•				,			•			•				•	•			
Skin			+ •	+ +	+ +	+	Μ	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	.+	+	+		
Keratoacanthoma																					• .							
Squamous cell carcinoma																												
Sebaceous gland, adenoma																												
Musculoskeletal System						_					-		_	_	_						-							
Bone			+ •	+ +	+ +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Osteosarcoma	•	, 1	x																									
Nervous System				_		,		·	-		-	-		_									·			_	_	
Brain		•	+ •	+ -	+ +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Oligodendroglioma benign																						х						
				_		_		_				-																
Respiratory System			. .		ц			-	4	-	т	上	т	т	+	т		-	+	+	+	+		+	· -	+		
			+ ·	+ -	 + -	- + - +	+	. .	· +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	· +	+		
Alveolar/bronchiolar adenoma					'.'					'	'	•	•	•				• •	•	. '				.'	•			
Carcinoma, metastatic, thyroid gland						•																					•	
Histiocytic sarcoma	•																											
Osteosarcoma, metastatic, bone			Х																									
Nose			+	+ •	+ +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Trachea			+	+ •	+ +	+	+	+	+	+	+	.+	+	ť	+	+	+	+	+	+	+	+	+	+	+	+		
Special Senses System			_	_				_	-	_	_					_		_		_								
Eye																												
Zymbal's gland				+ ·	+																							
Carcinoma			2	X	K																							
Urinary System									_								_								·			
Kidney			+	+ ·	+ +	- +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Histiocytic sarcoma								,										-										
Renal tubule, adenoma																÷				-				х			. '	
Urinary bladder			+	+ ·	+ +	- • +	• +	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+		
Histiocytic sarcoma												·																
Transitional epithelium, papilloma							_												_	X								
Systemic Lesions					••																							
Multiple organs			+	+ ;	+ +	- +	• +	+	+	+	. +	+	+	+	+	.+	+	+	+	+	+	+	+	+	+	+		
Histiocytic sarcoma							_					۰.																
Leukemia mononuclear				2	Χ.	,	Ň	Х						X	Х	X	,							v	X	X		
Mesothelioma malignant					2									X					-									

Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nitromethane: 94 ppm (continued)

······································																				_		_	_		_			
Number of Days on Study	6 5 0		6 6 4	6 6 5	6 6 5	6 7 0	6 7 7	6 8 6	6 9 2	7 1 4	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7. 3 4	7 3 5	7 3 5	7 3 5	7 3 5		7 3 5	
Carcass ID Number	2 1 0))	2 1 6	2 0 8	2 2 8	2 3 1	2 2 4	2 2 9	2 4 9	2 4 2	2 1 1	2 3 5	2 4 3	2 4 4	2 4 7	2 5 0	2 0 1	2 3 8	2 3 9	2 4 0	2 4 6	2 0 5	2 1 2	2 1 5	2 1 8		2 2 1	Total Tissues/ Tumors
Integumentary System Mammary gland Fibroadenoma Skin Keratoacanthoma Squamous cell carcinoma Sebaceous gland, adenoma	+ + X	+	+	++	+ +	+	м +	+	м +	+ +	м +	+ +	м +	: М +	+ + X	+	+ x + x	+	+ + X	м +	+	+ + X	м +	+	- +	-	++	27 1 49 2 2 1
Musculoskeletal System Bone Osteosarcoma	4	ł	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	ł		÷	+	50 1
Nervous System Brain Oligodendroglioma benign	+	ł	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		÷	+	50 1
Respiratory System Larynx Lung Alveolar/bronchiolar adenoma Carcinoma, metastatic, thyroid gland Histiocytic sarcoma Osteosarcoma, metastatic, bone Nose		+++++++++++++++++++++++++++++++++++++++	+++++	+ + +	+ + X +	+++	+++++++++++++++++++++++++++++++++++++++	+++++	· + · +	++++	+ +	+ +	+++	+++	++++	+++	+++	+ + X +	+++	++++	+++	+ + X	+++++	+ + X	+ + :	 + +	+ + +	50 50 2 1 1 1 50
Special Senses System Eye Zymbal's gland Carcinoma		+	+	+	+	+	+	+		+	+	+	+		+	+	+	+	+	+	+	+				-	+	1 2 2
Urinary System Kidney Histiocytic sarcoma Renal tubule, adenoma Urinary bladder Histiocytic sarcoma Transitional epithelium, papilloma	-	 + +	+	+	+ x + x	+	+	+	• +	+ X +	+	+	+	+	+	+	+	+	+	+	+	+ X +	+	+ +		 +	+	50 1 3 50 1 1
Systemic Lesions Multiple organs Histiocytic sarcoma Leukemia mononuclear Mesothelioma malignant	>	+ K	+ x	+ X	+ x	+	+ x	+	+ x	+	+ X	+ X	+ x	+ x		+ X	+ x	+ x	+	+ x	+ x	+ x	+ X	X		 K	+ x	50 1 27 3

Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nitromethane: 188 ppm 66 7 9 9 0 1 5 6 6 6 8 9 0 1 2 2 2 2 3 3 3 3 4 5 5 Number of Days on Study 9 5 1 2 9 9 8 2 0 1 8 0 0 8 1 1 1 4 9 1 8 8 9 3 0 0 4 4 **Carcass ID Number** 4 0 4 4 2 0 0 4 2 0 3 3 0 3 1 0 3 1 4 3 1 0 2 1 1 9056 1 97971 4 9 4 5 5 0 3 2 3 5 4 7 3 8 5 **Alimentary System** Esophagus + Intestine large, colon + + + Intestine large, rectum + + + Intestine large, cecum Intestine small, duodenum Intestine small, jejunum + + + + + + Intestine small, ileum + + + + + + + Liver Hepatocellular carcinoma X х Hepatocellular adenoma, multiple Mesentery Oral mucosa Pharyngeal, squamous cell papilloma Pancreas Adenoma Salivary glands + Stomach, forestomach + + + + + + + + + Stomach, glandular + + ++ + + + Tooth Cardiovascular System Blood vessel Heart + + + + + + **Endocrine System** Adrenal cortex Adrenal medulla + + + + + + + + х Pheochromocytoma malignant Х х XXX Х Pheochromocytoma benign х х Bilateral, pheochromocytoma benign + + + + + + + + Islets, pancreatic Adenoma Carcinoma Parathyroid gland Adenoma + + Pituitary gland + + + ххх Х Pars distalis, adenoma х х Х х Х х х Х х Х Х Х Pars intermedia, adenoma + Thyroid gland + х C-cell, adenoma х C-cell, carcinoma

General Body System

Follicular cell, carcinoma

None

	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	5	6	7	7	7	8	8	9	0	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	0	5	7	8	8	1	4	2	7	0	8	3	3	3	3	3	4	4	4	4	4	5	5	5	5	
	4	4	4	4	4	4	4	4	4	4	4	4	4	.4	4	4	4	4	4	4	4	4	4	4	4	Total
Carcass ID Number	3	5	4	1	4	1	2	1	2	1	4	0	2	2	2	4	0	1	2	2	3	3	3	3	4	Tissues/
	2	0	2	8	8	1	7	6	4	0	6	2	1	6	8	4	9	3	2	3	0	1	6	8	7	Tumors
limentary System									_											_						
sophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	50
ntestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ntestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	· +	50
ntestine large cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
stestine small duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ntestine small, jejunum		+	+	+	+	+	+	÷	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	50
nestine small jleum	+	, +	+	÷	+	+		+	+	+	+	+	+	, +	+	+	+	+	+	+	+	+	+	+	÷	50
iver		1	÷		1	-	т Т		т —	÷	+	<u> </u>	+	÷	+	÷	, +	+	+	+	÷.	- -	÷	+	+	50
Uenotocellulor caroinoma	T V	т	т	т	т	т	т	т	т	т	т	т	т	т	т	-	т	т	т	Т	· F	т	т	т	-	20
Henetocellular adename multiple	л																									1
Asontan																	L									10
					+				+				+				+									10
Tai mucosa																				+						1
Pharyngeal, squamous cell papilloma																				X						1
ancreas	+	·+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																								Х		1
alivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
tomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+.	+	+	+	+	+	+	+	+	50
tomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ooth								+																		3
Cardiovascular System																										
Blood vessel									+																	1
leart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	50
ndocrine System																										
drenal cortex	+	+	+	+	+	+	+	+.	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
drenal medulla	+	+	+	·+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																		х								2
Pheochromocytoma benign			х						х							х		х	х	х			х		х	15
Bilateral, pheochromocytoma benign					x					x			x	x								x				. 6
slets, nancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	•	x		·		•					•					·					x	x				4
Carcinoma						x														x						
Parathyroid gland	Т		Ŧ	Ŧ	Ŧ	1	Ŧ	+	+	м	÷	Ŧ	+	+	+	÷	+	+	+	+	+	+	+	+	+	۔ ۵۵
Adenoma	т	1	-	-	Т.	.1.		.	v	141			•		'	r.		'		1			÷.	- 1 -	'	
ituitan aland	-			L.	L.	ъ	L.	- L -	л _	L.	+	т	ъ	ъ	Ŧ	т	ـ	-	L.	Ŧ	L				ــ	1 57
Dare distalis adenoma	+	v	Ŧ	Ŧ	v	v	v	v	v	т	v	v	Ŧ	т	т	v	т	т У	v	v	v	v	v	v	Ŧ	20
rais uistans, authuilla Dara intermedia, adarante		л			л	л	Λ	л	л		л	л				Λ		л	л	Λ	л	л	л	л	v	. 32
rais intermedia, adenoma																,									A	-
nyroid giand	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma								X					Х	Х							X	X			х	5
C-cell, carcinoma											х															1
Follicular cell, carcinoma										Х														X		. 2

Spleen

Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nitromethane: 188 ppm (continued) 3 4 4 55 . 5 55 5 5 6666 4 5 6 6 6 6 6 6 6 6 6 Number of Days on Study 9 7 9 9 0 5 8 9 2 1 6 6 6 0 1 2 2 2 3 3 3 3 4 5 5 5 9 9 8 2 0 8 0 0 8 9 1 2 1 8 1 1 1 4 9 1 8 3 0 0 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 **Carcass ID Number** 4 2 0 0 4 2 0 3 3 0 1 1 4 0 4 3 1 0 3 1 4 3 1 0 2 4 7 3 8 5 9 0 5 6 1 9 7 9 7 1 4 9 4 5 5 0 3 2 3 5 Genital System Epididymis + + Preputial gland + + Adenoma Carcinoma Prostate Seminal vesicle + + + Testes + + + + + + + + + Bilateral, interstitial cell, adenoma Х Х х Х Х х XXXX Interstitial cell, adenoma х Х Х Х х Х Hematopoietic System Bone marrow Lymph node Lymph node, bronchial Lymph node, mandibular Lymph node, mesenteric Lymph node, mediastinal

Thymus Thymoma benign Integumentary System Mammary gland MM M M ммм M м + M Fibroadenoma Х Skin + + Keratoacanthoma х Х Squamous cell carcinoma Subcutaneous tissue, fibroma Х Subcutaneous tissue, osteosarcoma Subcutaneous tissue, sarcoma Musculoskeletal System Bone Skeletal muscle **Nervous System** Brain + + **Respiratory System** Larynx Lung Alveolar/bronchiolar carcinoma Squamous cell carcinoma, metastatic, skin х Nose Trachea + + +

Special Senses System Eye

+

Individual Animal Tumor Pathology of	of Mal	e l	Raí	ts i	n t	he	2-7	Yea	ar	Inl	hal	ati	on	St	udy	y o	f P	Jitr	ron	net	ha	ne:	: 1	188	s PI	OM (continued)
Number of Days on Study	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	0	5	7	8	8	1	4	2	7	0	8	3	3	3	3	3	4	4	4	4	4	5	5	5	5	
	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	Total
Carcass ID Number	3	5	4	1	4	1	2	1	2	1	4	0	2	2	2	4	0	1	2	2	3	3	3	3	4	Tissues/
	2	0	2	8	8	1	7	6	4	0	6	2	1	6	8	4	9	3	2	3	0	1	6	8	7.	Tumors
Genital System			• .																							
Epididymis Droputial aland	+	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	Ŧ	v	т	· •	· •	Ŧ	Ŧ	т	Ŧ	Ŧ	Ŧ	Ŧ	Ŧ	Ŧ	Ŧ	Ŧ	Ŧ	Ŧ	Ŧ	Ŧ	v	Ŧ	Ŧ	+	Ŧ	30
Carcinoma		Λ																			Λ					1
Prostate	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	.+	+	+	• +	· +	+	+	+	, +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma			х	Х	Х	х	х			х	х			х	х	х		х	х	х		х	х	х	х	27
Interstitial cell, adenoma	Х							х	х			х	X				Х				х					13
Hematopoietic System							_							-			•••									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+		+		+			+																17
Lymph node, bronchial	+	+	+	• +	+	+	+	М	+	+	+	+	+	+	+	+	+	+	+	+	+	М	+	+	+	48
Lymph node, mandibular	+	+	+	+	• +	+	+	+	+	+	+	Μ	(+	Μ	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	M	[+	+	+	+	М	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mediastinal	+	+	+	• +	· +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	• +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus Thymoma benign	+	+	+	+ +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	48 1
Integumentary System																			· ·							
Mammary gland	+	м	(+		. +	+	+	+	м	+	+	+	+	м	м	м	+	+	+	+	+	+	+	м	м	31
Fibroadenoma		141		•	•	'	•	'	141	•	'	'	•	1.11	141	1.41		'		'	.'	'	'	141		1
Skin	+	+	+	• +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																									X	2
Squamous cell carcinoma																										1
Subcutaneous tissue, fibroma				Х																						1
Subcutaneous tissue, osteosarcoma																										1
Subcutaneous tissue, sarcoma				Х							Х															2
Musculoskeletal System																										
Bone	+	+	+	• +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	_					+	_											_								1
Nervous System																									_	
Brain	+	+	+	+	• +	+	+	+	+	+	+	+	ţ	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	• +	- +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	• +	- +	- +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma	х													Х							,					2
Squamous cell carcinoma, metastatic, skin																										1
Nose	+	- -			- +	. +	+	+	+	+	+	+	. +	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	• +	+	• +	- +	· +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System								_						-			<u> </u>				_		<u> </u>			······
Eye																										1
								_		_																

96

 TABLE A2

 Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nitromethane: 188 ppm (continued)

3 4 4 4 5 5 5 5 5 5 566666 55 6 6 6 6 6 6 6 6 Number of Days on Study 9 7 9 9 0 156 6 68 9. 0 1 2 2 2 2 3 3 3 3 4 5 5 1 4 9 29 2 0 8 8 9 3 0 0 5 1 9 8 0 08 1 1 1 1 8 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 **Carcass ID Number** 1 1 4 0 4 4 2 0 0 4 2 0 3 3 0 3 1 0 3 1 4 3 1 0 2 4 7 3 8 5 9 0 5 6 1 9 7 9 7 1 4 9 4 5 5 0 3 2 3 5 **Urinary System** Kidney + + Lipoma х Renal tubule, adenoma Urinary bladder + + + + + + + + + + + + + + + + + + + + + + + +Systemic Lesions + + Multiple organs + + + + + + + + + + + + + + + + + + + + + Leukemia mononuclear x x x x x x x x x x x x Х хх ххх Х

Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nitromethane: 188 ppm (continued)

										_			_			_			_			_					
Number of Days on Study	6 5 0	6 6 5	6 7 7	6 7 8	6 7 8	6 8 1	6 8 4	6 9 2	7 0 7	7 2 0	7 2 8	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5		
Carcass ID Number	4. 3 2	4 5 0	4 4 2	4 1 8	4 4 8	4 1 1	4 2 7	4 1 6	4 2 4	4 1 0	4 4 6	4 0 2	4 2 1	4 2 6	4 2 8	4 4 4	4 0 9	4 1 3	4 2 2	4 2 3	4 3 0	4 3 1	4 3 6	4 3. 8	4 4 7	Total Tissues/ Tumors	
Urinary System Kidney Lipoma Renal tubule, adenoma Urinary bladder	+	+ +	+	+	++	+	+	+	+	+ +	+	+	+	+	+	+	+ +	+	+	+ X +	+	+ X +	++	+	+	50 1 2 50	
Systemic Lesions Multiple organs Leukemia mononuclear	+ x	+ X	+ X	+ X	+ X	+ X	+	+ X	+	+ X	+ X	+	+ X	+	+ X	+	+ X	+	+ X	+ x	+ x	+ X	+	+	+	50	1

Individual Animal Tumor Pathology of	Ma	le l	Rat	s i	n t	he	2-	Yea	ar	In	hal	ati	on	St	ud	y o	f I	Vit	ror	net	tha	ne	: 3	375	5 pi	pm			
	4	4	4	4	4	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6				-
Number of Days on Study	0 5	2 8	4 4	8 0	9 5	1 6	4 4	5 1	7 1	7 3	8 8	9 0	9 5	0 7	0 8	1 2	1 7	3 0	3 4	3 6	3 8	4 3	5 0	5 0	5 6	•	•		
	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6				-
Carcass ID Number	1 6	3 8	2 4	4 1	5 0	2 6	0 2	4 5	4 9	2 3	1 5	0 3	3. 0	0 9	4 3	3 5	3 9	2 9	3 2	4 6	0 7	2	2	4 8	3 1				
Alimentary System		_																											-
Fsonhagus	_	-	+	+	+	+	т	Ľ.	т	-	+	-	+	-	т	т.	ъ	т	· _	-	-1-	<u>ـ</u>	-	-	-				
Intestine large colon		-	+	+	+			+	т Т	+	+ +	+	+	+ +	+ +	т Т	+ -	т -	+ +	+	+ +	- -	- -	- -	т 				
Intestine large rectum	+	, +	+	+	+	+	+	+	+	+	+	+	, +	-	÷		+	-	+	+	- -	+	- -						
Intestine large, recum	+	-	+	- <u>T</u>	-	+	+	-	+	+	- -	+	+	+	т _	т Т	- -		+	- -	- -		- -		- -				
Intestine small duodenum	 _			, ,	+	+	- -	, 					Ļ	- -	1	. т т	- -	т Т	· ±	. T		т 	-	. <u> </u>	т 				
Intestine small, iciunum	- T - T	- -	. <u>.</u>	- -	+	+ +	т _	т -	- -	- <u>+</u>	+ -	- -	т -	- -	т Т	- -	- -	+	- -	+		- -	+	- -	- -				
Intestine small, jejunani	- T	- -	+	+ +	т _	т 	Ŧ	т -	+	. T 	- -	т. 	+ +	- T	· T	т 	- T	т 	. <u>T</u>	-	- -	т _	- T		. т.				
Liver	- T		- -	+	+	+	+	*	+	+	+	+	+	+	+	Ţ	- r	+	+	+	+	. +	+	· +	+				
Henatocellular adapoma	т	Ŧ	· +	Ŧ	Ŧ	Ŧ	т	Ŧ	Ŧ	Ŧ	Ŧ	Ŧ	т	Ŧ	Ŧ	Ŧ	Ŧ	Ŧ	. 7	Ŧ	Ŧ	Ŧ	、+	Ŧ	T T				
Mesonter:																									Ā				
Deserves					+							+		+					+						+				
Pancreas Salissana alamia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Stomach, forestomach	+	.+	+.	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	· +	+	+				
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Squamous cell papilloma																	•												
Cardiovascular System		_		_																					_				-
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Endocrine System													_								_	_	_						-
Adrenal cortex	· ,+	+	+	+	+	+	·+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Carcinoma																													
Carcinoma metastatic Zymbal's gland											•		x																
Adrenal medulla	+	· +	+	+	+	+	+	. +	+	+	+	+	+	+	+	+	+	+	·+	+	+	+	+	+	+				
Carcinoma metastatic Zymbal's gland		•			•	•	•		•		•	•	x	•		•	•	•	•	•	•	•		•	<i>.</i> •				
Pheochromocytoma malignant													~									•							
Pheochromocytoma henign							v			v		v		v					v		v				v				
Bilateral pheochromocutoma benian	· .						л			Λ		Λ		л			v		л						Λ				
Islate, paparentio	+		-		+	-	т.		4	-	, i	-	4	-		-	~	-				-							
Adapama	т	Ŧ	· +	т	т	Ŧ	Ŧ	т	т	Ŧ	Ŧ	Ŧ	Ŧ	т	. –	T.	Ŧ	т	Ŧ	т	. •	т	. –		Ť				
Correinome																			·				v						
Carcinoma Depathyraid aland									· ,						,				<u>^</u>						+				
Paradityrold gland		· •	т.			T	т •	T	т 		- T	-	т -		Ť	Ť	т. -	-	- T			. <u>.</u>		т -	· -				
Plulary gland	+	+	· + v	Ŧ	+	Ŧ	v	v	T	v	Ť	+ v	v	+ v	+ v	+ v	+ v	+ v	v	+	v	v	v	. T	v				
Pars distans, adenoma			л				^	л	Λ	л	л	л	•	л	л	л	л	л	Λ	v	^	•	л	л	Λ				
Pars intermedia, adenoma		۰.								· .										_ X					,				
Inyrold gland	+	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	.+	+	+	+	+	+	+	+	· +	+				
C-cell, adenoma														••			Х				,			X				·	
C-cell, carcinoma						•								X															
General Body System Peritoneum																									÷				
						_																		<u>.</u>					_
Genital System																													
Epididymis	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• `+	+				
Penis			_									_		_				-											
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	· +	+	+	+	+	+	+	+	+	• +	• +				
Adenoma																							Х						
Carcinoma																								-					
Prostate	+	+	• +	+	+	+	ţ	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+	+	• +	• +				
								-		-		_	_													_			

TABLE A2Individual Animal Tu

Individual Animal Lumor Pathology	y or ivita	ıe	R	aus		a vi	ne	2-	ı e	ar	11 1 1	nai	181	101	13	cua	iy i	OF 1	N 1 N	FO	me	(na	ine	: .	3/2		pin (continued)
· · · ·	6	(5 (6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	6	(5 '	7	8	8	8	8	9	9	9	9	0	0	0	0	1	3	3	3	3	3	3	3	3	3	
· · ·	0	4	4 :	5	1	1	3	8	2	2	8	8	0	0	5	9	9	2	3	3	3	4	4	4	5	5	
	6	_	5 (6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	Total
Carcass ID Number	1	(5	1	0	1	2	1	1	4	0	3	0	3	4	2	4	3	1	1	2	1	2	4	0	3	Tissues/
	9	4	4 (0	8	1	8	2	3	7	5	3	1	4	4	7	0	7	4	7	0	8	1	2	6	6	Tumors
Alimontony System														_		-											
Frenhame	,					,														,	,						50
Esophagus Integrine large colon	- 1		+	+ _	+	+	+	+	+	+	+	+	· +	• +	+	- +		- +	· +	· +	· +	· +	• +	+	+ 1.	+	50
Intestine large, colon	T L		т 	т _	T L	T J	т _	т 	Ţ	т 	- -	т -	· -		т : _		- T	- т 	Т	т Гл	- -	т. Т		т 	- T		30 40
Intestine large, recum	г L		т 	т 	Ť		т 	т 	т 	т 		т 	. <u> </u>	· ·	т. -	- T	т L	- T	. IV.	ι –	т -	т 	· -	т 	 -	- T	49
Intestine angle, cecum	T I	. 1	T M	T L	- -	T	т 1	- -	- -	- -	Ť	т 	ι Γ	· •	· - T		ד י ו		· +	. T	. T	· T	· T	T J	т ,	· +	- 30
Intestine small, duouchum	ד	- 1	IVI I	T	Ť	T	-	Ť		- -		· T	· -	· •	·				· •	· T	· •	· T	· •	т ,	- T	· T	49
Intestine small, jejunum	T		+	т 1	T	+	T	+	+	- -	+	·		• +	די. י	- 4	· - 1		· +	· +	· +	· +	· +	+		· +	50
Liver	+	-	+	+	+	+	+	+	+	+	+	· +	• •	• +	+	- +	• - 1	+	· +	· +	· +	· +	• +	+	+	• +	50
Livei Hanataaallular adanama	т		Ŧ	Ŧ	Ŧ	Ŧ	Ŧ	+	+	+	+	-	• +	- +	+	- +	- 1	- + v	- +	+	-+	+	· •†•	+	Ŧ	+	50
Hepatocellular adenoma																		X									2
Mesentery											+											+	· .			+	8
Pancreas	+	• •	+	+	+	+	+	+	+	+	+	+	· +	• +	• 4	- +	-+	- +	+	+	+	+	• +	+	+	+	50
Salivary glands	-1	•	+	+	+	+	+	+	+	+	+	+	• +	• +	+	- +	+	- +	• +	+	+	+	+	+	+	+	50
Stomach, forestomach	+		+	+	+	+	+	+	+	+	+	+	+	• +	• +	- +	+	- +	+	+	+	+	+	+	+	+	50
Stomach, glandular	+		+	+	+	+	+	+	+	+	+	+	+	• +	• +	- +	+	- +	+	+	+	+	+	+	+	+	50
Tongue				+																							1
Squamous cell papilloma				<u>x</u>		_																	_				I
Cardiovascular System																											
Heart	+	-	+	+	+	+	+	+	+	+	+	+	+	• +	• +	- +		- +	+	+	+	+	+	+	+	+	50
Endocrine System		_																_					·				
Adrenal cortex	+		+	+	+	+	+	+	+	+	+	+	+	• +	• +	- +	- +	• +	+	+	+	+	+	+	+	+	50
Carcinoma											х																1
Carcinoma, metastatic, Zymbal's gland																											1
Adrenal medulla	+		+	+	+	+	+	+	+	+	+	+	+	• +	• +	- +	- +	- +	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, Zymbal's gland																											1
Pheochromocytoma malignant											Х				Х												2
Pheochromocytoma benign					х				х	х					x		х	x							х		14
Bilateral, pheochromocytoma benign						х								x		x								х			5
Islets, pancreatic	+		+	+	+	+	+	+	+	+	+	+	+	• +	. 4	- +	-	- +	+	+	+	+	+	+	+	+	50
Adenoma			•		•	x		•	•		•	•		•				•	•	•	•		•	•			1
Carcinoma	х	•				••				х															x		5
Parathyroid gland	-+		+	+	+	+	+	+	+	+	+	+	+	• +	·Ν	1+		• +	+	+	+	+	+	+	· +	+	48
Pituitary gland	-		+ 1	ŕ	+	+	+	+	+	+	+	+	. +	. +		- +		- +	+	+	+	+	. +	+		+	49
Pars distalis, adenoma	x			•	x	x	•	x	x	x	x	x	x	x	x	x		x	x	x		x	x	x	x	x	39
Pars intermedia, adenoma		•					x			••								-				••		-			2
Thyroid gland	4		+	+	+	+	+	+	+	÷	+	+	. .	. +			-	- +	+	+	+	+	+	+	+	+	50
C-cell adenoma	x		•	•		×.				•	•		•		x	• `	•	'		x	x	x					8
C-cell, carcinoma		•					x							x		•				~		~					3
	··																						_				
General Body System Peritoneum																+											1
Genital System		_														<u> </u>			_			_					
Epididymis	+		+	+	+	+	+	+	+	+	+	+	+	- +	• +	- +	- +	- +	+	+	+	+	+	+	+	+	50
Penis				•	•	•	•	•	•	•			•		+	- '		•	•			•		•	•	•	1
Preputial gland	+		+	+	+	+	+	+	+	+	+	· +		+		- +		- +	. +	+	+	+	+	- +	. +	+	50
Adenoma	•		•	•	·	·	•	•	•	•			'	'		'	x	: '			x				•	•	3
Carcinoma			x																								- 1
Prostate	+		+	+	+	+	+	+	+	+	+	+	.	+		- +	. 4	- +	+	+	+	+	+	+	+	+	50
																		•									

99

388

 TABLE A2
 Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Nitromethane: 375 ppm (continued)

		_				_	_	_			_																	_				
Number of Days on Study				4 0	4 2	4	4 8	4 9	5 1	5 4	5 5	5 7	5 7	5 8	5 9	5 9	6 0	6 0	6 1	6 1	6 3	6 3	6 3	6 3	6 4	6 5	6 5	6 5		~		
· .	_	•		5.	8	4	0.	5	6	4	1	1	3	8.	0	5	7	8	2	7	0	4	6	8	3	0	0	6				
	:			6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6				
Carcass ID Number	•			1: 6	3 8	2 4	4 [.] 1	5 0	2 6	0 2	4 5	4 9	2 3	1 5	0 3	3 0	0 9	4 3	3 5	3 9	2 9	3 2	4 6	0 7	2 2	2 5	4 8	3 1	• •			
Genital System (continued)												-																				
Seminal vesicle				+	+	· +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Testes				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	•			
Bilateral, interstitial cell, adenoma		`				•		X						х									Х					Х				
Interstitial cell, adenoma							х			х						Х		х						x			х					
Hematopoietic System							_																							```		
Bone marrow				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-			
Lymph node					+												+					+	+					+	•			
Lymph node, bronchial				+	+	+	+	+	+	+	+	+	+	+	+	Μ	+	+	+	+	+	+	+	+	+	+	+	+	-			
Lymph node, mandibular	,			+	+	+	+	+	+	+	+	•+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	· +	-			
Lymph node, mesenteric				ŧ	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-		-	
Lymph node, mediastinal				+	+	Μ	+	+	+	+	+	+	+	+	+	+	+	+	Μ	+	+	+	Μ	+	+	+	+	+	•			
Spleen				+	+	+	+	+	+	+	+	+	+	+	+	ʻ +	+	+	+	+	+	+	+	+	+	+	+	+	•			
Thymus				+	+	+	+	+	+	M	+	+	+	+	+	Μ	+	+	+	+	+	+	+	+	+	+	+	+	•	_		
Integumentary System		-									_																					
Mammary gland Fibroadenoma	;			М	M	M	М	М	+	Μ	М	+	+	Μ	+	+	M	+	М	+	+	+	М	+	+	+	+	M	1			
Skin				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	. +	-			
Basal cell carcinoma	•	,		•	<u>.</u>		x										-		-				-									
Keratoacanthoma									·																							
Keratoacanthoma, multiple																																
Squamous cell carcinoma									•																		. •	. •				
Squamous cell papilloma																												-				
Subcutaneous tissue, lipoma																													•			
Subcutaneous tissue, schwannoma																								,								
malignant										х																						•
Musculoskeletal System			-																							•						
Bone	i	÷ .		+	.+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	• +	-			
Skeletal muscle																																,
Nervous System										-		_											-									
Brain	·			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	• +	• +	-			
Granular cell tumor benign															Х																	[.]
Peripheral nerve																																
Spinal cord																																
Respiratory System					_					_															-							
Larynx	۰.			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	• +	- +	- 1	F			۰.
Lung				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	• +	- +	+	F			
Alveolar/bronchiolar adenoma										х										х			Х									
Carcinoma, metastatic, Zymbal's g	gland															х					-	÷							•			
Nose				+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	- 1	• +		ŀ			
Trachea				+	+	+	+	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	- +	• -1	- +		F			

Individual Animal Tumor Pathology	of Mal	e]	Rai	ts i	n t	he	2-`	Yea	ar	In	hal	lati	ion	St	ud	уC	of I	Vit	roi	nei	tha	ne	:	37:	5	pp	M (continued)
Number of Days on Study	6 6 0	6 6 4	6 7 5	6 8 1	6 8 1	6 8 3	6 8 8	6 9 2	6 9 2.	6 9 8	6 9 8	7 0 0	7 0 0	7 0 5	7 0 9	7 1 9	7 3 2	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 5		7 3 5	
Carcass ID Number	6 1 9	6 0 4	6 1 0	6 0 8	6 1 1	6 2 8	6 1 2	6 1 3	6 4 7	6 0 5	6 3 3	6 0 1	6 3 4	6 4 4	6 2 7	6 4 0	6 3 7	6 1 4	6 1 7	6 2 0	6 1 8	6 2 1	6 4 2	6 0 6	}	6 3 6	Total Tissues/ Tumors
Genital System (continued) Seminal vesicle Testes Bilateral, interstitial cell, adenoma Interstitial cell, adenoma	+ + x	+ + X	+ + X	+ +	+ + X	+ + X	+ +	+ + x	+ + X	+	+ + X	+ + X	+ + X	+ +	+ + X	+ + X	+ + X	+ + X	+ + X	+ + X	+ + X	+ + X	+ + X	+ + + X	 + <	+ + x	50 50 16 15
Hematopoietic System Bone marrow Lymph node Lymph node, bronchial Lymph node, mandibular Lymph node, mesenteric Lymph node, mediastinal Spleen Thymus	+ + + + + +	+ + + M + + + + +	· + · + [+ · + · +	· + + + + + + + + + + + + + + + + + + +	+ + + + + + + + + +	+ + + + + + +	+ + + + + + + +	+ M + + + + +	+ + + + + + + +	+ + + + + + + + + + + + + + + + + + +	+ + M + + + + + + + + + + + + + + + + +	· + [+ · + · +	- + + - + - + - + - +	· + · + · + · +	+ + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + + +	+++++++++++++++++++++++++++++++++++++++	+ + + + + + + +	+ + + + + M	+++++++++++++++++++++++++++++++++++++++	+ + + + + + + + +	+ + + + + +	+ + + + + + + + + + + + + + + + + + + +	· + · + · + · +		+ ++++ + H	50 13 47 49 50 47 50 46
Integumentary System Mammary gland Fibroadenoma Skin Basal cell carcinoma Keratoacanthoma Keratoacanthoma, multiple Squamous cell carcinoma Squamous cell papilloma Subcutaneous tissue, lipoma Subcutaneous tissue, schwannoma malignant	M + X	- M	1 M - + X X	[+ - +	+	- M + +	(M	т м + х	+	• +	- + X - +	+	- M - + X	1 +	• +	• +	• +	м + х	+ + x	M +	+	+ x + x	++	·		M +	28 2 50 2 1 1 1 3 1 2
Musculoskeletal System Bone Skeletal muscle	+	+	• +	• +	+	· +	+	+	+	• +	- +	· +	- +	• +	• +	• +	• +	+	+	+	+	+	+		+	+	50 1
Nervous System Brain Granular cell tumor benign Peripheral nerve Spinal cord	+++++++++++++++++++++++++++++++++++++++	+	- [`] +	• +	+	· +	+	+	+	+	• +	• 4	- +	- 4	• +	: 4	• +	•. +	+	+	+	• +	+	• 4	+	+	50 1 1 1
Respiratory System Larynx Lung Alveolar/bronchiolar adenoma Carcinoma, metastatic, Zymbal's gland Nose Trachea	+ + +	+++++++++++++++++++++++++++++++++++++++	- + - + - +	- + - +	· +	· + · +	· + · +	+ + +	+++++++++++++++++++++++++++++++++++++++	· + · +	- + - + - +	- + - + - +	- + - + - +	- + - + - +	- + - + - +	· + · +	· + · +	· + · +	· + · +	· + · +	· + · +	· + · +	+++++++++++++++++++++++++++++++++++++++	- + - + 	+ + +	+ + +	50 50 3 1 50 50

Individual Animal Tumor Patholo	gy of	Mal	e F	Cat s	s ii	n tl	he	2-1	Yea	ar	In	hal	ati	on	St	udy	y o	fſ	Niti	ron	net	ha	ne:		375	pp	m (c	ontinu	ied)
Number of Days on Study		4 0 5	4 2 8	4 4 4	4 8 0	4 9 5	5 1 6	5 4 4	5 5 1	5 7 1	5 7 3	5 8 8	5 9 0	5 9 5	6 0 7	6 0 8	6 1 2	6 1 7	6 3 0	6 3 4	6 3 6	6 3 8	6 4 3	6 5 0	6 5 0	6 5 6			
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Special Senses System Eye Zymbal's gland Carcinoma														+ x												+ :			
Urinary System Kidney Carcinoma, metastatic, Zymbal's gland Renal tubule, adenoma Urinary bladder		+	+++	+	+++	+	+	+++	++	++++	+	+	+	+ X +	+	+	+	+++	++	+	+	+	++	+	.+	.+			
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b) A statistical statistic

Individual Animal Tumor Pathology	of Mal	e	Kai	is i	n î	he	2-)	¥ ea	ar	ln	hal	ati	on	St	ud	y c	1 30	Nit	ror	ne	tha	nne	:	37	5	pp	m (continued)
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Systemic Lesions						_																	-				
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Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Nitromethane

	0 ppm	94 ppm	188 ppm	375 ppm
Adrenal Medulla: Benign Pheochromocytoma	<u></u>			7
Overall rate ^a	16/50 (32%)	20/50 (40%)	21/50 (42%)	19/50 (38%)
Adjusted rate ^b	71.6%	72.9%	77.2%	70.4%
Terminal rate ^c	7/13 (54%)	9/16 (56%)	9/14 (64%)	2/8 (25%)
First incidence (days)	611	574	499	544
Life table test ^d	P=0.098	P=0.338	P=0.239	P=0.101
Logistic regression test ^d	P = 0.302	P = 0.141	P=0.167	P=0.260
Cochran-Armitage test ^d	P=0.346			
Fisher exact test ^d	· · · · · · · · · · · · · · · · · · ·	P=0.266	P=0.204	P=0.338
Adrenal Medulla: Benign or Malignant Pheochrom	ocvtoma			
Overall rate	17/50 (34%)	21/50 (42%)	22/50 (44%)	20/50 (40%)
Adjusted rate	76.3%	76.8%	78.0%	72.2%
Terminal rate	8/13 (62%)	10/16 (63%)	9/14 (64%)	2/8 (25%)
First incidence (days)	611	574	499	544
Life table test	P=0.093	P=0.352	P=0.243	P=0.094
Logistic regression test	P=0.301	P=0.129	P=0.168	P=0.254
Cochran-Armitage test	P=0.348			· .
Fisher exact test		P=0.268	P=0.206	P=0.339
Kidney (Renal Tubule): Adenoma (Single Sections)				
Overall rate	0/50 (0%)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted rate	0.0%	14.9%	14.3%	12.5%
Terminal rate	0/13 (0%)	1/16 (6%)	2/14 (14%)	1/8 (13%)
First incidence (days)	e	636	733 (T)	733 (T)
Life table test	P=0.399	P = 0.125	P=0.252	P=0.403
Logistic regression test	P=0.487	P=0.107	P=0.252	P=0.403
Cochran-Armitage test	P=0.555			
Fisher exact test		P=0.121	P=0.247	P=0.500
Kidney (Renal Tubule): Adenoma (Step Sections)				. :
Overall rate	2/50 (4%)	2/50 (4%)	0/50 (0%)	4/50 (6%)
Adjusted rate	15.4%	12.5%	0.0%	22.7%
Terminal rate	2/13 (15%)	2/16 (13%)	0/14 (0%)	1/8 (13%)
First incidence (days)	733 (T)	733 (T)	<u> </u>	650
Life table test	P=0.129	P=0.622N	P=0.219N	P=0.223
Logistic regression test	P=0.184	P = 0.622N	P=0.219N	P=0.283
Cochran-Armitage test	P=0.233			
Fisher exact test		P=0.691N	P=0.247N	P=0.339
Kidney (Renal Tubule): Adenoma (Single and Step	Sections)			
Overali rate	2/50 (4%)	5/50 (10%)	2/50 (4%)	5/50 (10%)
Adjusted rate	15.4%	26.3%	14.3%	33.7%
Terminal rate	2/13 (15%)	3/16 (19%)	2/14 (14%)	2/8 (25%)
First incidence (days)	733 (T)	636	733 (T)	650
Life table test	P=0.104	P=0.264	P=0.675N	P=0.112
Logistic regression test	P=0.181	P=0.173	P=0.675N	P=0.158
Cochran-Armitage test	P=0.256			
Fisher exact test		P=0.218	P=0.691N	P=0.218

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	0 ppm	94 ppm	188 ppm	375 ppm	
Liver: Hepatocellular Adenoma or Carcinoma	<u></u>			· · · · · · · · · · · · · · · · · · ·	
Overall rate	1/50 (2%)	1/50 (2%)	3/50 (6%)	2/50 (4%)	
Adjusted rate	2.2%	4.0%	9.0%	14.5%	
Terminal rate	0/13 (0%)	0/16 (0%)	0/14 (0%)	0/8 (0%)	
First incidence (days)	504	650	509	656	
Life table test	P = 0.307	P=0.743	P = 0.304	P = 0.447	
Logistic regression test	P = 0.319	P=0.753N	P = 0.264	P = 0.500	
Cochran-Armitage test	P = 0.324				
Fisher exact test		P=0.753N	P=0.309	P=0.500	
Lung: Alveolar/bronchiolar Adenoma					
Overall rate	1/50 (2%)	2/50 (4%)	0/50 (0%)	3/50 (6%)	
Adjusted rate	7.7%	12.5%	0.0%	8.2%	
Terminal rate	1/13 (8%)	2/16 (13%)	0/14 (0%)	0/8 (0%)	
First incidence (days)	733 (T)	733 (T)	_ ` `	544	
Life table test	P=0.178	P=0.574	P=0.485N	P=0.278	
Logistic regression test	P=0.239	P=0.574	P=0.485N	P = 0.305	
Cochran-Armitage test	P=0.242				
Fisher exact test		P=0.500	P=0.500N	P=0.309	
Lung: Alveolar/bronchiolar Adenoma or Carcinoma					
Overall rate	1/50 (2%)	2/50 (4%)	2/50 (4%)	3/50 (6%)	
Adjusted rate	7.7%	12.5%	10.6%	8.2%	
Terminal rate	1/13 (8%)	2/16 (13%)	1/14 (7%)	0/8 (0%)	
First incidence (days)	733 (T)	733 (T)	650	544	
Life table test	P=0.160	P=0.574	P=0.513	P = 0.278	
Logistic regression test	P=0.225	P=0.574	P=0.485	P=0.305	
Cochran-Armitage test	P=0.232				
Fisher exact test		P = 0.500	P=0.500	P=0.309	
Pancreatic Islets: Adenoma					
Overall rate	8/50 (16%)	9/50 (18%)	4/50 (8%)	1/50 (2%)	
Adjusted rate	26.9%	40.6%	20.0%	4.5%	
Terminal rate	0/13 (0%)	5/16 (31%)	2/14 (14%)	0/8 (0%)	
First incidence (days)	552	601	590	681	
Life table test	P = 0.014N	P=0.509	P=0.191N	P=0.029N	
Logistic regression test	P=0.006N	P=0.472	P=0.177N	P=0.018N	
Cochran-Armitage' test	P=0.006N				
Fisher exact test		P=0.500	P=0.178N	P=0.015N	
Pancreatic Islets: Carcinoma					
Overall rate	1/50 (2%)	1/50 (2%)	3/50 (6%)	5/50 (10%)	
Adjusted rate	7.7%	5.9%	14.2%	25.9%	
Terminal rate	1/13 (8%)	0/16 (0%)	1/14 (7%)	1/8 (13%)	
First incidence (days)	733 (T)	714	621	634	
Life table test	P=0.016	P = 0.750N	P=0.318	P=0.068	
Logistic regression test	P=0.026	P=0.747	P=0.297	P=0.089	
Cochran-Armitage test	P=0.031				
Fisher exact test		P=0.753N	P=0.309	P=0.102	

	0 ppm	94 ppm	188 ppm	375 ppm
Pancreatic Islets: Adenoma or Carcinoma				······································
Overall rate	9/50 (18%)	10/50 (20%)	7/50 (14%)	6/50 (12%)
Adjusted rate	32.5%	44.1%	32.2%	29.3%
Terminal rate	1/13 (8%)	5/16 (31%)	3/14(21%)	1/8 (13%)
First incidence (days)	552	601	590	634
Life table test	P = 0.308N	P=0.513	P = 0.393N	P = 0.388N
Logistic regression test	P = 0.186N	P = 0.462	P = 0.389N	P = 0.294N
Cochran-Armitage test	P = 0.181N			
Fisher exact test		P=0.500	P=0.393N	P=0.288N
Pituitary Gland (Pars Distalis). Adenoma				,
Overall rate	38/50 (76%)	36/47 (77%)	32/50 (64%)	39/49 (80%)
Adjusted rate	100.0%	97.1%	84.6%	97.1%
Terminal rate	13/13 (100%)	15/16 (94%)	9/14 (64%)	7/8 (88%)
First incidence (days)	242	490	499	444
Life table test	P = 0.160	P = 0.380N	P=0.228N	P=0.162
Logistic regression test	P = 0.464	P=0.511	P=0.132N	P = 0.424
Cochran-Armitage test	P = 0.446			-
Fisher exact test		P=0.568	P=0.138N	P=0.426
Preputial Gland: Adenoma				
Overall rate	4/50 (8%)	3/50 (6%)	3/50 (6%)	3/50 (6%)
Adjusted rate	15.4%	11.6%	13.1%	24.1%
Terminal rate	0/13 (0%)	0/16 (0%)	1/14 (7%)	1/8 (13%)
First incidence (days)	528	574 .	560	650
Life table test	P=0.530N	P = 0.544N	P = 0.508N	P=0.631N
Logistic regression test	P=0.443N	P=0.503N	P = 0.499N	P=0.512N
Cochran-Armitage test	P = 0.442N			
Fisher exact test		P=0.500N	P=0.500N	P = 0.500N
Preputial Gland: Adenoma or Carcinoma				÷
Overall rate	4/50 (8%)	4/50 (8%)	4/50 (8%)	4/50 (8%)
Adjusted rate	15.4%	15.4%	14.9%	27.2%
Terminal rate	0/13 (0%)	0/16 (0%)	1/14 (7%)	1/8 (13%)
First incidence (days)	528	574	492	650
Life table test	P=0.484	P=0.593	P = 0.634	P=0.510
Logistic regression test	P=0.569N	P=0.639	P=0.037	P=0.033
Cochran-Armitage test	P = 0.5 / 0	D O CADN	D-0 642N	B-0 642N
Fisher exact test		P=0.043N	P=0.043N	r=0.0451
Skin: Squamous Cell Papilloma				
Overall rate	0/50 (0%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	0.0%	13.3%
Terminal rate	0/13 (0%)	0/16 (0%)	0/14 (0%)	0/8 (0%)
First incidence (days)	-	_	_	660
Life table test	P=0.012	_		P = 0.109
Logistic regression test	P = 0.011	 .	·	P=0.113
Cochran-Armitage test	P=0.012		•	5 0 101
Fisher exact test		<u></u>	·	P=0.121

	0 ppm	94 ppm	188 ppm	375 ppm
Skin: Keratoacanthoma				
Overall rate	6/50 (12%)	2/50 (4%)	2/50 (4%)	2/50 (4%)
Adjusted rate	41.0%	10.0%	10.5%	16.3%
Terminal rate	5/13 (38%)	1/16 (6%)	1/14 (7%)	1/8 (13%)
First incidence (days)	673	650	643	675
Life table test	P=0.191N	P=0.092N	P=0.113N	P=0.268N
Logistic regression test	P=0.143N	P=0.155N	P=0.146N	P=0.220N
Cochran-Armitage test	P=0.113N			
Fisher exact test		P=0.134N	P=0.134N	P=0.134N
Skin: Squamous Cell Papilloma or Keratoacanthom	a			
Overall rate	6/50 (12%)	2/50 (4%)	2/50 (4%)	4/50 (8%)
Adjusted rate	41.0%	10.0%	10.5%	24.1%
Terminal rate	5/13 (38%)	1/16 (6%)	1/14 (7%)	1/8 (13%)
First incidence (days)	673	650	643	660
Life table test	P=0.550N	P=0.092N	P=0.113N	P=0.581N
Logistic regression test	P=0.450N	P=0.155N	P=0.146N	P=0.484N
Cochran-Armitage test	P=0.388N			
Fisher exact test		P=0.134N	P=0.134N	P=0.370N
Skin: Squamous Cell Papilloma, Keratoacanthoma,	or Squamous Ce	ll Carcinoma		
Overall rate	7/50 (14%)	4/50 (8%)	3/50 (6%)	5/50 (10%)
Adjusted rate	44.7%	22.0%	12.8%	35.0%
Terminal rate	5/13 (38%)	3/16 (19%)	1/14 (7%)	2/8 (25%)
First incidence (days)	673	650	608	660
Life table test	P=0.563N	P=0.185N	P=0.143N	P=0.614
Logistic regression test	P=0.427N	P=0.305N	P=0.167N	P=0.529N
Cochran-Armitage test	P=0.356N			
Fisher exact test		P=0.262N	P=0.159N	P=0.380N
Skin: Basal Cell Carcinoma or Squamous Cell Carc	inoma			
Overall rate	1/50 (2%)	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted rate	6.3%	12.5%	2.6%	20.5%
Terminal rate	0/13 (0%)	2/16 (13%)	0/14 (0%)	1/8 (13%)
First incidence (days)	725	733 (T)	608	480
Life table test	P=0.138	P=0.548	P=0.758N	P=0.192
Logistic regression test	P = 0.231	P=0.486	P=0.762N	P=0.300
Cochran-Armitage test	P = 0.237			
Fisher exact test		P=0.500	P=0.753N	P=0.309
Skin: Squamous Cell Papilloma, Keratoacanthoma,	Basal Cell Carci	noma, or Squamou	is Cell Carcinoma	l
Overall rate	7/50 (14%)	4/50 (8%)	3/50 (6%)	7/50 (14%)
Adjusted rate	44.7%	22.0%	12.8%	40.9%
Terminal rate	5/13 (38%)	3/16 (19%)	1/14 (7%)	2/8 (25%)
First incidence (days)	673	650	608	480
Life table test	P=0.277	P=0.185N	P=0.143N	P=0.352
Logistic regression test	P=0.438	P=0.305N	P=0.167N	P=0.543
Cochran-Armitage test	P = 0.485			D
Fisher exact test		P = 0.262N	P=0.159N	P=0.613N

·			0 ppm	94 ppm	188 ppm	375 ppm
Skin (Subcutaneous '	Tissue):	Fibroma	<u>,</u>		····	
Overall rate			3/50 (6%)	0/50 (0%)	1/50 (2%)	0/50 (0%)
Adjusted rate			13.9%	0.0%	4.5%	0.0%
Terminal rate			1/13 (8%)	0/16 (0%)	0/14 (0%)	0/8 (0%)
First incidence (days)			623		678	
Life table test			P = 0.098N	P = 0.126N	P = 0.311N	P=0.158N
Logistic regression test			P = 0.087N	P = 0.128N	P = 0.305N	P = 0.125N
Cochran-Armitage test			P = 0.086N			<i>/</i>
Fisher exact test				P=0.121N	P=0.309N	P=0.121N
Skin (Subcutaneous	Tissue):	Fibrosarcoma				
Overall rate			3/50 (6%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
Adjusted rate			18.2%	0.0%	0.0%	0.0%
Terminal rate			2/13 (15%)	0/16 (0%)	0/14 (0%)	0/8 (0%)
First incidence (days)			644	· · · · ·	_	<u> </u>
Life table test			P=0.058N	P=0.105N	P=0.118N	P=0.186N
Logistic regression test			P=0.051N	P=0.133N	P=0.125N	P=0.142N
Cochran-Armitage test			P=0.047N			
Fisher exact test		н — А.	· ·	P=0.121N	P=0.121N	P=0.121N
Skin (Subcutaneous	Tissue):	Fibrosarcoma or Sar	coma		· · ·	
Overall rate			3/50 (6%)	0/50 (0%)	2/50 (4%)	0/50 (0%)
Adjusted rate		· ·	18.2%	0.0%	10.9%	0.0%
Terminal rate	1		2/13 (15%)	0/16 (0%)	0/14 (0%)	0/8 (0%)
First incidence (days)			644	-	678	 , ,
Life table test		N	P=0.168N	P = 0.105N	P=0.494N	P=0.186N
Logistic regression test			P=0.141N	P=0.133N	P=0.517N	P = 0.142N
Cochran-Armitage test			P=0.125N		·	
Fisher exact test		2		P=0.121N	P = 0.500N	P=0.121N
Testes: Adenoma				к. 		
Overall rate			38/50 (76%)	34/50 (68%)	40/50 (80%)	31/50 (62%)
Adjusted rate			100.0%	91.1%	100.0%	100.0%
Terminal rate			13/13 (100%)	13/16 (81%)	14/14 (100%)	8/8 (100%)
First incidence (days)			490	427	395	480
Life table test			P=0.418	P=0.293N	P=0.458	P=0.455
Logistic regression test			P = 0.080N	P = 0.325N	P=0.454	P = 0.073N
Cochran-Armitage test			P = 0.117N			
Fisher exact test				P=0.252N	P=0.405	P=0.097N
Thyroid Gland (C-ce	ell): Ad	enoma				
Overall rate		•	- 8/50 (16%)	5/50 (10%)	8/50 (16%)	8/50 (16%)
Adjusted rate			30.6%	24.7%	42.6%	50.9%
Terminal rate		2	1/13 (8%)	3/16 (19%)	5/14 (36%)	3/8 (38%)
First incidence (days)	· .		504	574	560	617 D 0 404
Life table test	•	· · · · · · · · · · · · · · · · · · ·	P=0.237	P=0.280N	P = 0.598N	P=0.404
Logistic regression test			P=0.407	P = 0.300N	P=0.608	P=0.380
Cochran-Armitage test		•	P=0.433		D O CORNI	$\mathbf{n} = 0 \mathbf{c} 0 7 \mathbf{N}$
Fisher exact test				P=0.277N	P=0.607N	P=0.00/IN

Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Nitromethane (continued)

	0 ppm	94 ppm	188 ppm	375 ppm
Thyroid Gland (C-cell): Carcinoma	<u></u>			<u> </u>
Overall rate	0/50 (0%)	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted rate	0.0%	10.0%	6.7%	14.2%
Terminal rate	0/13 (0%)	1/16 (6%)	0/14 (0%)	0/8 (0%)
First incidence (days)		650	728	607
Life table test	P=0.071	P=0.249	P=0.514	P = 0.101
Logistic regression test	P=0.096	P=0.222	P=0.482	P=0.117
Cochran-Armitage test	P=0.104			
Fisher exact test		P=0.247	P = 0.500	P=0.121
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	8/50 (16%)	7/50 (14%)	9/50 (18%)	11/50 (22%)
Adjusted rate	30.6%	33.3%	46.4%	57.8%
Terminal rate	1/13 (8%)	4/16 (25%)	5/14 (36%)	3/8 (38%)
First incidence (days)	504	574	560	607
Life table test	P=0.079	P=0.488N	P=0.508	P=0.164
Logistic regression test	P=0.174	P=0.536N	P=0.498	P=0.282
Cochran-Armitage test	P=0.198			
Fisher exact test		P=0.500N	P=0.500	P=0.306
All Organs: Mononuclear Cell Leukemia				,
Overall rate	35/50 (70%)	27/50 (54%)	33/50 (66%)	25/50 (50%)
Adjusted rate	88.2%	92.1%	80.3%	90.0%
Terminal rate	9/13 (69%)	14/16 (88%)	7/14 (50%)	6/8 (75%)
First incidence (days)	411	427	499	405
Life table test	P=0.388N	P=0.119N	P=0.441N	P=0.357N
Logistic regression test	P=0.053N	P=0.091N	P=0.410N	P=0.033N
Cochran-Armitage test	P=0.059N			
Fisher exact test		P=0.074N	P=0.415N	P=0.033N
All Organs: Malignant Mesothelioma				
Overall rate	1/50 (2%)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted rate	2.1%	8.1%	0.0%	9.1%
Terminal rate	0/13 (0%)	0/16 (0%)	0/14 (0%)	0/8 (0%)
First incidence (days)	490	439		709
Life table test	P=0.435N	P=0.297	P = 0.500N	P≈0.696
Logistic regression test	P = 0.441N	P=0.324	P=0.588N	P=0.759
Cochran-Armitage test	P=0.409N			
Fisher exact test		P=0.309	P=0.500N	P=0.753N
All Organs: Benign Neoplasms				
Overall rate	50/50 (100%)	45/50 (90%)	50/50 (100%)	47/50 (94%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	13/13 (100%)	16/16 (100%)	14/14 (100%)	8/8 (100%)
First incidence (days)	242	427	395	444
Life table test	P=0.229	P=0.293N	P = 0.530N	P=0.278
Logistic regression test	P=0.139N	P=0.023N	'	P=0.045N
Cochran-Armitage test	P=0.313N			
Fisher exact test		P=0.028N	P = 1.000N	P=0.121N

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Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Nitromethane (continued)

	0 ppm	94 ppm	188 ppm	375 ppm
All Organs: Malignant Neoplasms	<u></u>	<u> </u>		· · · ·
Overall rate	40/50 (80%)	35/50 (70%)	39/50 (78%)	33/50 (66%)
Adjusted rate	92.4%	96.9%	89.6%	96.2%
Terminal rate	10/13 (77%)	15/16 (94%)	10/14 (71%)	7/8 (88%)
First incidence (days)	411	292	395	405
Life table test	P=0.475	P=0.258N	P=0.489N	P=0.529
Logistic regression test	P=0.107N	P=0.197N	P = 0.499N	P=0.087N
Cochran-Armitage test	P=0.112N			
Fisher exact test	· · ·	P=0.178N	P=0.500N	P=0.088N
All Organs: Benign or Malignant Neoplasms				
Overall rate	50/50 (100%)	49/50 (98%)	50/50 (100%)	49/50 (98%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	13/13 (100%)	16/16 (100%)	14/14 (100%)	8/8 (100%)
First incidence (days)	242	292	395	405
Life table test	P=0.210	P = 0.481N	P=0.530N	P=0.210
Logistic regression test	P=0.340N	P=0.510N	¹	P=0.455N
Cochran-Armitage test	P=0.405N	-		
Fisher exact test		P=0.500N	P = 1.000N	P=0.500N

(T)Terminal sacrifice

^a Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, kidney, liver, lung, pancreatic islets, pituitary gland, preputial gland, testes, and thyroid gland; for other tissues, denominator is number of animals necropsied.

^b Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

^c Observed incidence at terminal kill

^d Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table test regards neoplasms 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. For all tests, a negative trend or a lower incidence in an exposure group is indicated by N.

^e Not applicable; no neoplasms in animal group

Value of statistic cannot be computed.

Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Nitromethane^a

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Degeneration, fatty6 (12%)6 (12%)2 (4%)2 (4%)Begeneration, fatty6 (12%)4 (8%)2 (4%)8 (16%)Eosinophilic focus2 (4%)4 (8%)2 (4%)2 (4%)Hepatodiaphragmatic nodule4 (8%)4 (8%)2 (4%)2 (4%)Inflammation, suppurative1 (2%)2 (4%)1 (2%)Mixed cell focus7 (14%)6 (12%)9 (18%)7 (14%)Necrosis1 (2%)2 (4%)1 (2%)2 (4%)Regeneration2 (4%)1 (2%)2 (4%)Thrombosis1 (2%)2 (4%)1 (2%)2 (4%)Bile duct, hyperplasia44 (88%)43 (86%)47 (94%)43 (86%)Centribolular, necrosis7 (14%)1 (2%)2 (4%)Infiltration cellular1 (8%)3 (86%)4 (10%)Artery, inflammation2 (15%)1 (10%)1 (13%)Fat, necrosis12 (80%)7 (54%)9 (90%)6 (75%)Oral nucosa(1)(2)(1)1 (13%)Fat, necrosis1 (100%)1 (50%)1 (50%)Pharyngeal, hyperplasia, squamous1 (100%)1 (50%)50)(50)Pharyngeal, hyperplasia, squamous1 (100%)2 (64%)32 (66%)Artory, Margenelis, Squamous1 (100%)2 (55%)34 (68%)32 (64%)Basophilic focus3 (6%)7 (14%)3 (6%)3 (6%)	Cyst Dependention quatie	10	(29.01)	2	(4%)	1	(2%)	22	(4401)	
Dependention, rate0 (12.%)0 (12.%)2 (4.%)2 (4.%)3 (6.%)Eosinophilic focus2 (4.%)4 (8.%)4 (8.%)3 (6.%)Hepatodiaphragmatic nodule4 (8.%)4 (8.%)2 (4.%)2 (4.%)Inflammation, suppurative1 (2.%)2 (4.%)1 (2.%)2 (4.%)Mixed cell focus7 (14.%)6 (12.%)9 (18.%)7 (14.%)Necrosis1 (2.%)2 (4.%)1 (2.%)2 (4.%)Regeneration2 (4.%)1 (2.%)2 (4.%)Thrombosis1 (2.%)1 (2.%)2 (4.%)Bile duct, hyperplasia44 (88.%)43 (86.%)47 (94.%)43 (86.%)Centrilobular, necrosis7 (14.%)1 (2.%)1 (2.%)2 (4.%)Mesentery(15)(13)(10)(8)Infiltration cellular1 (8.%)1 (10.%)7 (14.%)43 (86.%)Artery, inflanmation2 (15.%)1 (10.%)7 (14.%)1 (13.%)Fat, hemorrhage1 (8.%)1 (10.%)7 (14.%)1 (13.%)Fat, necrosis12 (80.%)7 (54.%)9 (90.%)6 (75.%)Oral mucosa(1)(2)(1)1 (13.%)Gingival, hyperplasia1 (100.%)1 (50.%)50)(50)Pharyngeal, hyperplasia, squamous1 (100.%)28 (56.%)34 (68.%)32 (64.%)Basophilic focus3 (6.%)3 (6.%)32 (64.%)3 (6.%)	Degeneration fatty	19	(30%) (12%)	15	(30%)	10	(32%)	22	(44%) (16%)	
Losinopinite rodus $2 (4\%)$ $4 (8\%)$ $4 (8\%)$ $4 (8\%)$ $2 (4\%)$ Hepatodiaphragmatic nodule $4 (8\%)$ $4 (8\%)$ $2 (4\%)$ $2 (4\%)$ Inflammation, suppurative $1 (2\%)$ $9 (18\%)$ $7 (14\%)$ Mixed cell focus $7 (14\%)$ $6 (12\%)$ $9 (18\%)$ $7 (14\%)$ Necrosis $1 (2\%)$ $2 (4\%)$ $1 (2\%)$ $2 (4\%)$ Regeneration $2 (4\%)$ $1 (2\%)$ $2 (4\%)$ Thrombosis $1 (2\%)$ $2 (4\%)$ $1 (2\%)$ $2 (4\%)$ Bile duct, hyperplasia $44 (88\%)$ $43 (86\%)$ $47 (94\%)$ $43 (86\%)$ Centrilobular, necrosis $7 (14\%)$ $1 (2\%)$ $1 (2\%)$ $2 (4\%)$ Infiltration cellular $1 (8\%)$ $41 (8\%)$ $43 (86\%)$ $47 (94\%)$ $43 (86\%)$ Artery, inflammation $2 (15\%)$ $1 (10\%)$ (11) (8) Fat, hemorrhage $1 (8\%)$ $1 (10\%)$ $(7 (54\%)$ $9 (90\%)$ $6 (75\%)$ Oral mucosa (1) (2) (1) (50%) (50) (50) Gingival, hyperplasia $1 (100\%)$ $1 (10\%)$ $7 (54\%)$ $32 (66\%)$ $32 (64\%)$ Pharyngeal, hyperplasia, squamous $1 (100\%)$ $28 (56\%)$ $34 (68\%)$ $32 (64\%)$ Basophilic focus $3 (6\%)$ $7 (14\%)$ $3 (6\%)$ $3 (6\%)$	Equiparchilic focus	0	(12%)	0	(1270)	2	(4%)	0	(10%)	
Inflammation, suppurative1 (2%)1 (2%)1 (2%)1 (2%)Mixed cell focus7 (14%)6 (12%)9 (18%)7 (14%)Necrosis1 (2%)2 (4%)1 (2%)2 (4%)Regeneration2 (4%)1 (2%)2 (4%)Thrombosis1 (2%)2 (4%)1 (2%)2 (4%)Bile duct, hyperplasia44 (88%)43 (86%)47 (94%)43 (86%)Centrilobular, necrosis7 (14%)1 (2%)1 (2%)2 (4%)Mesentery(15)(13)(10)(8)Infiltration cellular1 (8%)1 (10%)4Artery, inflammation2 (15%)1 (10%)1 (13%)Fat, hemorrhage1 (8%)7 (54%)9 (90%)6 (75%)Oral mucosa(1)(2)(1)1 (50%)1 (10%)Gingival, inflammation, chronic active1 (100%)43 (68%)32 (64%)Pharyngeal, hyperplasia, squamous1 (100%)50)(50)(50)Pharyngeal, hyperplasia, squamous1 (100%)28 (56%)34 (68%)32 (64%)Basophilic focus3 (6%)7 (14%)3 (6%)3 (6%)	Henatodiaphragmatic podule	2	(4%)	4	(8%)	4	(3%)	2	(0%)	
Mixed cell focus7 (14%)6 (12%)9 (18%)7 (14%)Necrosis1 (2%)2 (4%)1 (2%)2 (4%)Regeneration2 (4%)1 (2%)2 (4%)Thrombosis1 (2%)2 (4%)Bile duct, hyperplasia44 (88%)43 (86%)47 (94%)43 (86%)Centrilobular, necrosis7 (14%)1 (2%)1 (2%)2 (4%)Mesentery(15)(13)(10)(8)Infiltration cellular1 (8%)41 (10%)43 (86%)47 (94%)Artery, inflammation2 (15%)1 (10%)1 (13%)Fat, nemorrhage1 (8%)1 (10%)1 (13%)Fat, necrosis12 (80%)7 (54%)9 (90%)6 (75%)Oral mucosa(1)(2)(1)1 (13%)Gingival, hyperplasia, squamous1 (100%)1 (50%)1 (50%)Pharyngeal, hyperplasia, squamous1 (100%)27 (54%)28 (56%)34 (68%)32 (64%)Basophilic focus3 (6%)7 (14%)3 (6%)3 (6%)3 (6%)	Inflammation suppurative	4	(070)	7	(070)	1	(2%)	2	(470)	
Necrosis 1 (2%) 2 (4%) 1 (2%) 2 (4%) Regeneration 2 (4%) 1 (2%) 2 (4%) Thrombosis 1 (2%) 2 (4%) 1 (2%) 2 (4%) Bile duct, hyperplasia 44 (88%) 43 (86%) 47 (94%) 43 (86%) Centrilobular, necrosis 7 (14%) 1 (2%) 1 (2%) 2 (4%) Mesentery (15) (13) (10) (8) Infiltration cellular 1 (8%) 44 (88%) 1 (13%) 1 (13%) Artery, inflammation 2 (15%) 1 (10%) 1 (13%) Fat, hemorrhage 1 (8%) 1 (10%) 1 (13%) Fat, necrosis 12 (80%) 7 (54%) 9 (90%) 6 (75%) Oral mucosa (1) (2) (1) 1 (13%) Gingival, hyperplasia 1 (50%) 1 (50%) 50) 50) Pharyngeal, hyperplasia, squamous 1 (100%) 1 (50%) 50) 50) Pancreas (50) (50) (50) (50) 32 (64%) Basophilic focus 3 (6%) 7 (14%) 3 (6%) 32 (64%)	Mixed cell focus	7	(14%)	6	(12%)	9	(18%)	7	(14%)	
Regeneration2 (4%)1 (2%)2 (4%)Thrombosis1 (2%)43 (86%)47 (94%)43 (86%)Bile duct, hyperplasia44 (88%)43 (86%)47 (94%)43 (86%)Centrilobular, necrosis7 (14%)1 (2%)1 (2%)2 (4%)Mesentery(15)(13)(10)(8)Infiltration cellular1 (8%)47 (94%)43 (86%)Artery, inflammation2 (15%)1 (10%)Artery, mineralization2 (15%)1 (10%)Fat, hemorrhage1 (8%)1 (13%)Fat, necrosis12 (80%)7 (54%)9 (90%)Oral mucosa(1)(2)(1)Gingival, hyperplasia1 (50%)Gingival, inflammation, chronic active1 (50%)Pharyngeal, hyperplasia, squamous1 (100%)Pancreas(50)(50)Atrophy27 (54%)28 (56%)34 (68%)Basophilic focus3 (6%)7 (14%)3 (6%)	Necrosis	. 1	(2%)	2	(4%)	1	(2%)	2	(4%)	
Thrombosis 1 (2%) Bile duct, hyperplasia 44 (88%) 43 (86%) 47 (94%) 43 (86%) Centrilobular, necrosis 7 (14%) 1 (2%) 1 (2%) 2 (4%) Mesentery (15) (13) (10) (8) Infiltration cellular 1 (8%) 43 (86%) 47 (94%) 43 (86%) Artery, inflammation 2 (15%) 1 (10%) (8) Artery, mineralization 2 (15%) 1 (10%) 1 (13%) Fat, hemorrhage 1 (8%) 1 (13%) 1 (13%) Fat, necrosis 12 (80%) 7 (54%) 9 (90%) 6 (75%) Oral mucosa (1) (2) (1) (1) (1) Gingival, hyperplasia 1 (50%) 1 (50%) (1) (50%) (50) Pharyngeal, hyperplasia, squamous 1 (100%) 1 (50%) (50) (50) (50) Pancreas (50) (50) (50) (50) (50) (50) Attrophy 27 (54%) 28 (56%) 34 (68%) 32 (64%) 3 (6%)	Regeneration	2	(4%)	-	()	1	(2%)	2	(4%)	
Bile duct, hyperplasia 44 (88%) 43 (86%) 47 (94%) 43 (86%) Centrilobular, necrosis 7 (14%) 1 (2%) 1 (2%) 2 (4%) Mesentery (15) (13) (10) (8) Infiltration cellular 1 (8%) 43 (86%) 47 (94%) 43 (86%) Artery (15) (13) (10) (8) Artery, inflammation 2 (15%) 1 (10%) 1 (13%) Fat, hemorrhage 1 (8%) 1 (10%) 1 (13%) Fat, necrosis 12 (80%) 7 (54%) 9 (90%) 6 (75%) Oral mucosa (1) (2) (1) (1) (1) Gingival, hyperplasia 1 (50%) 1 (10%) 1 (10%) 1 (10%) Pharyngeal, hyperplasia, squamous 1 (100%) 1 (50%) 50) (50) (50) Pancreas (50) (50) (50) (50) (50) 32 (64%) Basophilic focus 3 (6%) 3 (6%) 7 (14%) 3 (6%) 3 (6%)	Thrombosis					1	(2%)			
Centrilobular, necrosis7 (14%)1 (2%)1 (2%)2 (4%)Mesentery(15)(13)(10)(8)Infiltration cellular1 (8%)1 (10%)Artery, inflammation2 (15%)1 (10%)Artery, mineralization2 (15%)1 (10%)Fat, hemorrhage1 (8%)1 (13%)Fat, necrosis12 (80%)7 (54%)9 (90%)Oral mucosa(1)(2)(1)Gingival, hyperplasia1 (50%)(1)Gingival, inflammation, chronic active1 (50%)Pharyngeal, hyperplasia, squamous1 (100%)Pancreas(50)(50)(50)Atrophy27 (54%)28 (56%)34 (68%)32 (64%)Basophilic focus3 (6%)7 (14%)3 (6%)	Bile duct, hyperplasia	44	(88%)	43	(86%)	47	(94%)	43	(86%)	
Mesentery (15) (13) (10) (8) Infiltration cellular1 (8%)Artery, inflammation2 (15%)Artery, mineralization2 (15%)Artery, mineralization2 (15%)Fat, hemorrhage1 (8%)Fat, necrosis12 (80%)7 (54%)9 (90%)6 (75%)Oral mucosa(1)(2)(1)Gingival, hyperplasia1 (50%)Gingival, inflammation, chronic active1 (50%)Pharyngeal, hyperplasia, squamous1 (100%)Pancreas(50)(50)Atrophy27 (54%)28 (56%)Basophilic focus3 (6%)7 (14%)	Centrilobular, necrosis	7	(14%)	1	(2%)	1	(2%)	2	(4%)	
Infiltration cellular1 (8%)Artery, inflammation2 (15%)Artery, mineralization2 (15%)Fat, hemorrhage1 (8%)Fat, necrosis12 (80%)7 (54%)9 (90%)6 (75%)Oral mucosa(1)(2)(1)Gingival, hyperplasia1 (50%)Gingival, inflammation, chronic active1 (50%)Pharyngeal, hyperplasia, squamous1 (100%)Pancreas(50)(50)Atrophy27 (54%)28 (56%)Basophilic focus3 (6%)7 (14%)	Mesentery	(15)		(13)		(10)		(8)		
Artery, inflammation2 (15%)Artery, mineralization2 (15%)1 (10%)Fat, hemorrhage1 (8%)1 (13%)Fat, necrosis12 (80%)7 (54%)9 (90%)6 (75%)Oral mucosa(1)(2)(1)Gingival, hyperplasia1 (50%)(1) (50%) Pharyngeal, hyperplasia, squamous1 (100%) (50) (50)(50)Pancreas(50)(50)(50)(50)Atrophy27 (54%)28 (56%)34 (68%)32 (64%)Basophilic focus3 (6%)7 (14%)3 (6%)	Infiltration cellular			1	(8%)					
Artery, mineralization2 (15%)1 (10%)Fat, hemorrhage1 (8%)1 (13%)Fat, necrosis12 (80%)7 (54%)9 (90%)6 (75%)Oral mucosa(1)(2)(1)Gingival, hyperplasia1 (50%)(1) (50%) Gingival, inflammation, chronic active1 (50%) (50%) (50) Pharyngeal, hyperplasia, squamous1 (100%) (50) (50) Pancreas(50)(50)(50)Atrophy27 (54%)28 (56%)34 (68%)32 (64%)Basophilic focus3 (6%)7 (14%)3 (6%)	Artery, inflammation			2	(15%)					
Fat, hemorrhage1 (8%)1 (13%)Fat, necrosis12 (80%)7 (54%)9 (90%)6 (75%)Oral mucosa(1)(2)(1)Gingival, hyperplasia1 (50%)(1) $Gingival, inflammation, chronic active1 (50%)$	Artery, mineralization			2	(15%)	- 1	(10%)			
Fat, necrosis 12 (80%) 7 (54%) 9 (90%) 6 (75%) Oral mucosa (1) (2) (1) Gingival, hyperplasia 1 (50%) (1) Gingival, inflammation, chronic active 1 (50%) (50%) Pharyngeal, hyperplasia, squamous 1 (100%) (50) (50) Pancreas (50) (50) (50) (50) Atrophy 27 (54%) 28 (56%) 34 (68%) 32 (64%) Basophilic focus 3 (6%) 7 (14%) 3 (6%)	Fat, hemorrhage			1	(8%)			1	(13%)	
Oral mucosa (1) (2) (1) Gingival, hyperplasia 1 (50%) 1 (50%) Gingival, inflammation, chronic active 1 (50%) 1 (50%) Pharyngeal, hyperplasia, squamous 1 (100%) 50) (50) (50) Pancreas (50) (50) (50) (50) Atrophy 27 (54%) 28 (56%) 34 (68%) 32 (64%) Basophilic focus 3 (6%) 7 (14%) 3 (6%)	Fat, necrosis	12	(80%)	7	(54%)	9	(90%)	6	(75%)	
Gingival, hyperplasia 1 (50%) Gingival, inflammation, chronic active 1 (50%) Pharyngeal, hyperplasia, squamous 1 (100%) Pancreas (50) (50) (50) Atrophy 27 (54%) 28 (56%) 34 (68%) 32 (64%) Basophilic focus 3 (6%) 7 (14%) 3 (6%)	Oral mucosa	(1)		(2)		(1)				
Gingival, inflammation, chronic active 1 (50%) Pharyngeal, hyperplasia, squamous 1 (100%) Pancreas (50) (50) (50) Atrophy 27 (54%) 28 (56%) 34 (68%) 32 (64%) Basophilic focus 3 (6%) 7 (14%) 3 (6%)	Gingival, hyperplasia			1	(50%)					
Pharyngeal, hyperplasia, squamous 1 (100%) Pancreas (50) (50) (50) Atrophy 27 (54%) 28 (56%) 34 (68%) 32 (64%) Basophilic focus 3 (6%) 7 (14%) 3 (6%)	Gingival, inflammation, chronic active			1	(50%)					
Pancreas (50) (50) (50) (50) (50) Atrophy 27 (54%) 28 (56%) 34 (68%) 32 (64%) Basophilic focus 3 (6%) 7 (14%) 3 (6%)	Pharyngeal, hyperplasia, squamous	1	(100%)	(50)		(50)		(50)		
Atrophy $27 (54\%)$ $28 (56\%)$ $34 (68\%)$ $32 (64\%)$ Basophilic focus $3 (6\%)$ $7 (14\%)$ $3 (6\%)$	Pancreas	(50)	(***	(50)	((50)	((0.0))	(50)	(6.4.01)	
Basophilic focus $3(6\%)$ / (14%) $3(6\%)$	Atrophy	27	(54%)	28	(56%)	34	(68%)	32	(64%)	
	Basophilic focus		(40)	3	(0%) (6%)	7	(14%) (10%)	3	(0%) (90%)	
$\begin{array}{cccc} ny p = p a a a a a a a a a $	nyperplasia Hyperplasia focal	2	(4%)	3	(0%) (2%)	5	(10%)	4	(ā%)	
$\frac{1}{2\%}$	Hypertrophy			1	(270)	1	(29)			
Artery inflammation 3 (6%)	Artery inflammation			2	(6%)	1	(270)			
				J	(370)					

^a Number of animals examined microscopically at the site and the number of animals with lesion

Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Nitromethane (continued)

	··· 0 I	opm	94	i ppm		188	ppm		37	5 ppm	
Alimentary System (continued)	~										
Salivary glands	(50)		(50)			(50)			(50)		
Degeneration, fatty			· 1	(2%)							
Stomach, forestomach	(50)		(50)			(50)	•		(50)		
Diverticulum						1	(2%)				
Hyperplasia, squamous			-3	(6%)		1	(2%)		1	(2%)	
Inflammation, acute	3	(6%)	2	(4%)					8	(16%)	
Mineralization						1	(2%)				
Necrosis	. 6	(12%)	4	(8%)		. 3	(6%)		9	(18%)	
Stomach, glandular	(50)		.(50)			(50)			(50)		
Inflammation, acute	1	(2%)				1	(2%)		2	(4%)	i di
Inflammation, chronic	,								1	(2%)	۰,
Mineralization			4	(8%)	• •	2	(4%)			· .	
Necrosis	3	(6%)	1	(2%)		1	(2%)		3	(6%)	
Tooth	(1)		(2)			(3)					
Developmental malformation			•			1	(33%)				
Foreign body			1	(50%)							
Inflammation, chronic active	1	(100%)	2	(100%)		2	(67%)				
na seconda de la companya de la comp											
Cardiovascular System											
Blood vessel						(1)			•		
Aorta, mineralization						1	(100%)				· .
Heart	(50)		(50)			(50)			(50)	•	2
Cardiomyopathy	45	(90%)	49	(98%)		47	(94%)		- 47	(94%)	
Artery, mineralization			. 1	(2%)		1	(2%)				
Atrium, thrombosis	5	(10%)	-		· · ·	. 3	(6%)		2	(4%)	•• •
Endocrine System	Ŀ		- <u></u>						-	. ,	1
Adrenal cortex	(50)		(50)			(50)			(50)	,	`
Accessory adrenal cortical nodule					· ·		-		· 1	(2%)	
Atrophy			3	(6%)		1	(2%)		2	(4%)	1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 -
Hyperplasia	24	(48%)	19	(38%)		22	(44%)		22	(44%)	
Hypertrophy	6	(12%)	. 10	(20%)		- 11	(22%)	•	8	(16%)	
Necrosis	1	(2%)			r	2	(4%)		- 1	(2%)	
Thrombosis					•	1	(2%)				
Vacuolization cytoplasmic	· · 1	(2%)	1	(2%)		4	(8%)		3	(6%)	
Adrenal medulla	(50)		(50)			(50)			(50)		
Hyperplasia	20	(40%)	23	(46%)		27	(54%)		22	(44%)	• •
Necrosis	· 1	(2%)						. •	1	(2%)	, ··
Islets, pancreatic	(50)		. (50)			(50)			(50)		
Hyperplasia	1	(2%)	2	(4%)					1	(2%)	- 11 - 11 - 11 - 11 - 11 - 11 - 11 - 1
Parathyroid gland	(47)		(49)			(49)			(48)		
Hyperplasia	8	(17%)	4	(8%)	· • · ·	5	(10%)		7	(15%)	۰.
Pituitary gland	(50)		(47)			(50)			· 🦾 (49)		
Pars distalis, hyperplasia	7	(14%)	7	(15%)		9	(18%)		. 8	(16%)	
Thyroid gland	(50)		(50)		• `	(50)			(50)		1.1.1
a	24	(68%)	37	(74%)		34	(68%)		41	(82%)	
C-cell, hyperplasia	34	(00%)		(1470)		54	(, , ,	

Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Nitromethane (continued)

	0 F	opm	94	ppm	188	ppm	375	5 ppm
General Body System None	,					<u></u>		
Genital System								·
Epididymis	(50)		(50)		(50)		(50)	
Granuloma sperm							2	(4%)
Preputial gland	(50)		(50)		(50)		(50)	
Cyst			1	(2%)			1	(2%)
Inflammation, chronic active	5	(10%)	3	(6%)	3	(6%)	9	(18%)
Prostate	(50)		(50)		(50)		(50)	
Inflammation, chronic active	7	(14%)	9	(18%)	2	(4%)	8	(16%)
Inflammation, suppurative	4	(8%)	2	(4%)	3	(6%)	6	(12%)
Seminal vesicle	(50)		(50)		(50)		(50)	
Inflammation, chronic active							1	(2%)
Testes	(50)		(50)		(50)		(50)	
Atrophy	4	(8%)	7	(14%)	5	(10%)	6	(12%)
Artery, inflammation			4	(8%)			3	(6%)
Interstitial cell, hyperplasia	17	(34%)	17	(34%)	12	(24%)	16	(32%)
Hematopoietic System								
Bone marrow	(50)		(50)		(50)		(50)	
Congestion	()		1	(2%)				
Myelofibrosis	2	(4%)	-	(1	(2%)	1	(2%)
Thrombosis	1	(2%)	1	(2%)				
Lymph node	(17)	()	(13)		(17)		(13)	
Pancreatic, inflammation, granulomatous	1	(6%)					. ,	
Renal, hemorrhage		. ,	1	(8%)	2	(12%)	2	(15%)
Renal, infiltration cellular, plasma cell	1	(6%)					1	(8%)
Renal, inflammation, granulomatous	1	(6%)	1	(8%)				
Renal, pigmentation	2	(12%)	1	(8%)	2	(12%)	1	(8%)
Lymph node, mandibular	(48)		(48)		(48)		(49)	
Hemorrhage					1	(2%)		
Infiltration cellular, plasma cell	· 1	(2%)	3	(6%)	5	(10%)		
Inflammation, granulomatous	1	(2%)						
Lymph node, mesenteric	(50)		(50)		(48)		(50)	
Hemorrhage			1	(2%)	1	(2%)		
Inflammation, acute			1	(2%)				
Inflammation, granulomatous			1	(2%)	1	(2%)		
Lymph node, mediastinal	(50)	•	(45)		(50)		(47)	
Hemorrhage	2	(4%)	- 1	(2%)	1	(2%)	1	(2%)
Inflammation, granulomatous							1	(2%)
Spleen	(50)		(50)		(50)		(50)	
Fibrosis	14	(28%)	20	(40%)	26	(52%)	19	(38%)
Hematopoietic cell proliferation	1	(2%)	1	(2%)			1	(2%)
Hemorrhage		-	1	(2%)				
Necrosis	1	(2%)					1	(2%)
Thymus	(45)		(45)		(48)		(46)	
Artery, inflammation			1	(2%)				,

113

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Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Nitromethane (continued)

	0 ppm	94 ppm	188 ppm	375 ppm
Integumentary System		······································	· <u>···</u> ····	·····
Mammary gland	(28)	(27)	(31)	(28)
Galactocele	2 (7%)	(=)	2 (6%)	3 (11%)
Hyperplasia	1 (4%)		2 (0,0)	
Hyperplasia, atypical	1 (4%)		•	1 (4%)
Duct, inflammation, chronic	1 (4%)			- (,
Skin	(50)	(49)	(50)	(50)
Cyst	2 (4%)	1 (2%)		()
Hyperkeratosis	3 (6%)	3 (6%)		1 (2%)
Inflammation, chronic active	1(2%)	3 (6%)	1 (2%)	1(2%)
Inflammation, granulomatous	2 (4%)	2(4%)	2(4%)	1 (2%)
Prepuce, inflammation, acute	2(4%)	2 (470)	1 (2%)	1 (270)
Subcutaneous tissue cyst epithelial	2 (470)		· (=,0)	
inclusion	1 (2%)			
Musculoskeletal System	(50)	(50)	(50)	(50)
Fibrous asteodystrophy	(20)	3 (6%)	4 (8%)	2 (4%)
Hyperostosis	1 (2%)	2 (4%)		1 (2%)
Nervous System	(50)	(50)	(50)	(50)
Degeneration	(50)	(30)	(30)	(30)
Degeneration	1 (20)		1(2%)	1 (297)
Hemorrhage	1(2%)		1 (2%)	1(2%)
Hydrocephalus	1 (2%)	•	1 (30)	2 (4%)
Inflammation, chronic			1(2%)	· · · ·
Mineralization	4	1 (20)	1 (2%)	
Artery, inflammation		. 1 (2%)		(1)
Radicular neuropathy				1 (100%)
· · · · · · · · · · · · · · · · · · ·			· · · · · · · · · · · · · · · · · · ·	<u> </u>
Respiratory System				
Larynx	(50)	(50)	(50)	(50)
Metaplasia, squamous	1 (2%)			1 (2%)
Lung	(50)	(50)	(50)	(50)
Congestion	1 (2%)	1 (2%)		1 (2%)
Congestion, chronic	1 (2%)	·		• •
Hemorrhage	1 (2%)			
Inflammation, chronic active	2 (4%)	2 (4%)	1 (2%)	2
Metaplasia, osseous			1 (2%)	1 (2%)
Mineralization			1 (2%)	
Alveolar epithelium, hyperplasia	4 (8%)	8 (16%)	10 (20%)	9 (18%)
Artery, mediastinum, inflammation	•	2 (4%)		
			-	

Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Nitromethane (continued)

	0 ppm	94 ppm	188 ppm	375 ppm
Respiratory System (continued)				
Nose	(50)	(50)	(50)	(50)
Foreign body		1 (2%)	3 (6%)	1 (2%)
Inflammation, chronic active	4 (8%)	1 (2%)	3 (6%)	2 (4%)
Inflammation, suppurative	10 (20%)	3 (6%)	3 (6%)	5 (10%)
Thrombosis	6 (12%)	3 (6%)	5 (10%)	2 (4%)
Nasolacrimal duct, inflammation,				
suppurative		1 (2%)	3 (6%)	
Olfactory epithelium, foreign body		1 (2%)		
Olfactory epithelium, inflammation,				
suppurative		1 (2%)		
Trachea	(50)	(50)	(50)	(50)
Mineralization			1 (2%)	
Epithelium, hyperplasia		1 (2%)		
Special Senses System Eye Cataract Degeneration Retina, atrophy	(2) 2 (100%)	(1) 1 (100%)	(1) 1 (100%)	(1) 1 (100%) 1 (100%)
Urinary System	(50)	(50)	(50)	(50)
Infarct	(30) 2. (4%)	(20)	1 (2%)	()
Mineralization	- ((,,,,)	1 (2%)	2 (4%)	
Nephropathy	50 (100%)	50 (100%)	50 (100%)	50 (100%)
Artery, inflammation		1 (2%)	\/	
Pelvis, dilatation		~/	1 (2%)	
Renal tubule. hyperplasia		3 (6%)	2 (4%)	1 (2%)
Urinary bladder	(50)	(50)	(50)	(50)
Hemorrhage	(00)	1 (2%)	<u>/</u>	N/
Inflammation, suppurative		1 (2%)		
Transitional epithelium, hyperplasia		- (-/-/	1 (2%)	
		5 a.	- </td <td></td>	

APPENDIX B

SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF NITROMETHANE

Table B1	Summary of the Incidence of Neoplasms in Female Rats	
	in the 2-Year Inhalation Study of Nitromethane	118
Table B2	Individual Animal Tumor Pathology of Female Rats	
	in the 2-Year Inhalation Study of Nitromethane	122
TABLE B3	Statistical Analysis of Primary Neoplasms in Female Rats	
	in the 2-Year Inhalation Study of Nitromethane	140
Table B4	Historical Incidence of Mammary Gland Neoplasms	
	in Chamber Control Female F344/N Rats	145
TABLE B5	Summary of the Incidence of Nonneoplastic Lesions in Female Rats	
	in the 2-Year Inhalation Study of Nitromethane	146

Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Nitromethane^a

	2	0 ppm		94. ppm	1	88 ppm	375	ppm
		· ·						
Disposition Summary								
Animals initially in study		50		50		50	5	0
Early deaths	4							
Moribund		17		26		18	2.	5 .
Natural deaths	4	5		5		2		2
Survivors	1							
Terminal sacrifice		28		19	· .	30	. 2	3
Animals examined microscopically	•	50		50		50	5	0
			· •.		· · · ·		<u> </u>	
Alimentary System				•				
Intestine large, colon		(50)		(50)	(5	0)	(50)	
Intestine large, cecum	••••	(50)	<i></i>	(50).	(5	0) · ·	(50)	
Intestine small, duodenum		(50)		(50)	(5	0)	(50)	
Intestine small, jejunum		(50)		(50)	(5	0)	(50)	· •
Intestine small, ileum		(50)		(50)	(5	0)	(50)	:
Liver		(50)		(50)	(5	0)	(50)	
Carcinoma, metastatic, islets, pancreatic	:			1 (2%)				
Hepatocellular adenoma		1 (2%)		1 (2%)		•		•
Histiocytic sarcoma							1 ((2%)
Mesentery		(10)		(11)	(1	2)	(14)	
Carcinoma, metastatic, islets, pancreatic	:			1 (9%)			· •	
Carcinoma, metastatic, urinary bladder							1 ((7%)
Histiocytic sarcoma							1 (7%)
Oral mucosa	5.6	(1)			. (1)	(1)	•
Pharyngeal, squamous cell papilloma	· · ·	1 (100%)				1 (100%)	1 ((100%)
Pancreas	÷.,	(50)		(50)	(5	0)	(50)	
Carcinoma, metastatic, urinary bladder					· .		1 ((2%)
Salivary glands		(50)		(50)		0)	(50)	1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1
Stomach, forestomach		(50)		(50)	(5	0)	(50)	
Stomach, glandular		(50)		(50)	(5	0)	(50)	
Tongue					(1)		
Squamous cell carcinoma						1 (100%)		
					•	• .		
Cardiovascular System							n an an the An an the Antonia	
Heart		(50)		(50)	(5	0)	. (50)	-
Histiocytic sarcoma		(50)		(50)	()		. 1	(2%)
						· .		
Endocrine System	-							· · · ·
Adrenal cortex		(50)	:	(50)	(5	0)	(50)	
Adrenal medulla		(49)		(50)	(4	9)	(50)	
Pheochromocytoma malignant		(12)		(00)		1 (2%)	(1997 - E. S.
Pheochromocytoma complex		1 (2%)			•	- (-),		*
Pheochromocytoma benign	`			1 (2%)		2 (4%)	2	(4%)
Bilateral, pheochromocytoma benign		1 (2%)					2	(4%)
Islets, pancreatic	334 5	(50)		(50)	· (5	0)	(50)	
Adenoma		1 (2%)	-	1 (2%)		3 (6%)	1	(2%)
Carcinoma				1 (2%)				
Parathyroid gland		(50)	· ·	(49)	(5	i0)	(48)	
Adenoma						1 (2%)		

Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Nitromethane (continued)

	0 ppm	94 ppm	188 ppm	375 ppm
Endocrine System (continued)	<u> </u>			
Pituitary gland	(50)	(50)	(50)	(50)
Pars distalis, adenoma	33 (66%)	36 (72%)	39 (78%)	40 (80%)
Pars distalis, carcinoma		,	1 (2%)	
Thyroid gland	(50)	(50)	(50)	(49)
Bilateral, C-cell, adenoma			1 (2%)	
C-cell, adenoma	8 (16%)	9 (18%)	7 (14%)	10 (20%)
C-cell, carcinoma	2 (4%)			3 (6%)
Follicular cell, adenoma		1 (2%)		
General Body System		· · · · · · · · · · · · · · · · · · ·		
None				
Genital System				· · · · · · · · · · · · · · · · · · ·
Clitoral gland	(47)	(46)	(47)	(48)
Adenoma	6 (13%)	4 (9%)	5 (11%)	2 (4%)
Carcinoma	0 (1070)	1 (2%)	3 (6%)	2 (1,0)
Histiocytic sarcoma		- (-//)	- ()	1 (2%)
Bilateral, adenoma	1 (2%)		1 (2%)	,
Ovary	(50)	(50)	(50)	(50)
Granulosa cell tumor benign	(+-)	1 (2%)	1 (2%)	x =- y
Histiocytic sarcoma				1 (2%)
Uterus	(50)	(50)	(50)	(50)
Leiomyoma	1 (2%)			
Polyp stromal	5 (10%)	11 (22%)	6 (12%)	5 (10%)
Polyp stromal, multiple	1 (2%)			1 (2%)
Sarcoma stromal		1 (2%)	1 (2%)	
Hematopoietic System	<u>w_, w,</u>	87 <u></u>	<u>.</u>	<u> </u>
Bone marrow	(50)	(50)	(50)	(50)
Lymph node	(7)	(6)	(9)	(3)
Lymph node, bronchial	(48)	(49)	(47)	(48)
Carcinoma, metastatic, thyroid gland	,	• •		1 (2%)
Lymph node, mandibular	(49)	(48)	(48)	(47)
Lymph node, mesenteric	(50)	(50)	(49)	(50)
Lymph node, mediastinal	(48)	(49)	(50)	(46)
Spleen	(50)	(49)	(50)	(50)
Thymus	(48)	(47)	(45)	(48)
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Adenoma	2 (4%)	\ - /	<u> </u>	2 (4%)
Carcinoma	2 (4%)	4 (8%)	1 (2%)	10 (20%)
Carcinoma, multiple	····/	3 (6%)	<u> </u>	1 (2%)
Fibroadenoma	10 (20%)	15 (30%)	19 (38%)	22 (44%)
Fibroadenoma, multiple	9 (18%)	6 (12%)	14 (28%)	14 (28%)
Histiocytic sarcoma				1 (2%)
Sarcoma metastatic skin		1 (2%)		

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Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Nitromethane (continued)

	0 ppm	94 ppm	188 ppm	375 ppm
Integumentary System (continued)				
Skin	(50)	(50)	(48)	(49)
Squamous cell carcinoma			1 (2%)	
Squamous cell papilloma	1 (2%)	1 (2%)		1 (2%)
Subcutaneous tissue, fibroma	1 (2%)	1 (2%)	•	•
Subcutaneous tissue, fibrosarcoma		1 (2%)		1 (2%)
Subcutaneous tissue, histiocytic sarcoma				1 (2%)
Subcutaneous tissue, sarcoma		1 (2%)		2 (4%)
Subcutaneous tissue, schwannoma				
malignant			1 (2%)	
Subcutaneous tissue, pinna, amelanotic				
melanoma, malignant				1 (2%)
Musaulaskalatal System	<u></u>		· · · · · · · · · · · · · · · · · · ·	<u> </u>
Pone	(50)	(50)	(50)	(50)
Osteosarcoma	1 (2%)	(50)	(50)	(50)
Skeletal muscle	$(1)^{(270)}$	(2)		(1)
Carcinoma, metastatic, urinary bladder	(*)	(2)		1 (100%)
				1 (100%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Astrocytoma benign	1 (2%)			
Carcinoma, metastatic, pituitary gland			1 (2%)	
			. *** ·	· · ·
Respiratory System		•		
Larynx	(50)	(50)	(50)	(49)
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma		1 (2%)	1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma	1 (2%)			
Carcinoma, metastatic, islets, pancreatic		1 (2%)		
Carcinoma, metastatic, mammary gland	•	1 (2%)	1 (2%)	
Histiocytic sarcoma		1 C C C C C C C C C C C C C C C C C C C		1 (2%)
Osteosarcoma, metastatic, bone	1 (2%)	(50)		(50)
Nose	(50)	(50)	(50)	(50)
Trachea	(50)	. (50)	(50)	(30)
Carcinoma, metastatic, lung	1 (2%)		• • • • • • • •	
Special Senses System				
Harderian gland	(3)			
Zymbal's gland	(1)	(1)		(1)
Carcinoma	1 (100%)	1 (100%)		1 (100%)
	- (100,00)	- ()		

Stratification of the state

Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Nitromethane (continued)

	0 ppm	94 ppm	188 ppm	375 ppm
Urinary System		·····	<u> </u>	
Kidney	(50)	(50)	(50)	(50)
Carcinoma, metastatic, urinary bladder				1 (2%)
Lipoma		1 (2%)		
Mesenchymal tumor malignant				1 (2%)
Renal tubule, carcinoma	1 (2%)			
Urinary bladder	(50)	(50)	(49)	(50)
Histiocytic sarcoma				1 (2%)
Transitional epithelium, carcinoma				1 (2%)
Transitional epithelium, papilloma			2 (4%)	
Systemic Lesions	**************************************			······································
Multiple organs ^b	(50)	(50)	(50)	(50)
Histiocytic sarcoma	()	(00)	(2.2)	1 (2%)
Leukemia mononuclear	22 (44%)	13 (26%)	14 (28%)	9 (18%)
Neoplasm Summary		· · · · · · · · · · · · · · · · · · ·		· · · · · · · · · · · · · · · · · · ·
Total animals with primary neoplasms ^c	49	50	50	50
Total primary neoplasms	114	116	127	135
Total animals with benign neoplasms	44	47	48	49
Total benign neoplasms	, 83	90	103	104
Total animals with malignant neoplasms	28	21	20	27
Total malignant neoplasms	31	26	24	31
Total animals with metastatic neoplasms	2	3	2	2
Total metastatic neoplasms	. 2	5	2	5

^a Number of animals examined microscopically at the site and the number of animals with neoplasm

^b Number of animals with any tissue examined microscopically

^c Primary neoplasms: all neoplasms except metastatic neoplasms

					· ·					_																					
				4	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7			
Number of Days on Study				5	1	1	3	4	6	7	8	0	0	3	3	3	5	5	8	9	9	1	1	2	2	3	3	3			
				-4	9	9	9	4	3	3	5	0	4	U	1	1	0	8	1	1	I	3	4	0	/	3	3	3	_		
				. 1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1			
Carcass ID Number				2	1	2	2	0	4	2	4	3	1	3	3	3	2	4	4	0	2	1	1	1	0	2	2	2			
				8	2	1	0	5	6	5	8	4	3	9	6	8	6	3	2	6	7	4	7	9	3	2	3	9			
Alimentary System																		_						·							
Esophagus				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Intestine large, colon				+	+	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+		1	
Intestine large, rectum				+	+	+	+	+	+	+	+	+	+	+	+	+ '	+	+	+	+	+	+	+	+	+	+	+	+			
Intestine large, cecum	•			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ '	+	+	+	·+	+	+	+	+			
Intestine small, duodenum	·			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Intestine small, jejunum	۰.			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+,	+ '	,+	+	+	.+	+	+			
Intestine small, ileum				+	+	+	.+	+	+	+	+	+	+	÷	+	+	+	+	+ '	+	+	+	+	+	+	+	+	÷			·
Liver				+	+	• +	+	+	.+	+	+	+,	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Hepatocellular adenoma	· ·																	Х				5									
Mesentery				+								+					+		+	÷			-		+						
Oral mucosa																						+		·							
Pharyngeal, squamous cell	papilloma	• •						-							:							х	· .					•			
Pancreas	,			+	+	+	+	+	·+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Salivary glands		•		+	. +	+	+	+	+	+	+	+	+	+.	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Stomach, forestomach				+	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷+	+			
Stomach, glandular				+	+	· +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	.+	.+			
Cardiovascular System										-	· .		_								<u> </u>		_					· -		. <u>.</u>	
Heart				+	· +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	`+	+	+			
						_									_				_								<u></u>				
Endocrine System																									•		•		÷		
Adrenal cortex				. +	· +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	.+	+	+	,	•	· · .
Adrenal medulla				+	· +	• +	+	. +	+	+	+	Μ	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Pheochromocytoma comple	x		÷			÷.,																									
Bilateral, pheochromocytom	ia benign			÷					•	•															ŕ .	1					•••
Islets, pancreatic				+	• +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	.+	+			
Adenoma																		·								•					
Parathyroid gland				+	• +	• +	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+.	+	· .		
Pituitary gland	• .			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Pars distalis, adenoma				X	X		Х	X	Х	X	Х		х		X	X		X		X	X	X	X		X			X			
Thyroid gland				+	• +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	.+	+	+	+			
C-cell, adenoma												Х				х											X				
C-cell, carcinoma			_																												
General Body System				_																											· · · ·
None																	•														
Genital System						-		. –									_							-	·						
Clitoral gland				14	ر ا		+	⊥	⊥	+	+			+	+	+	+	+	+	+	+	+	+	· +	· +	+	+	+			
	-			141	. 7	т	Ŧ	Ŧ		r'	т [.]	17			17	x	1.			ι.		'			Ŧ	1	.1.	'			
Rilateral adenome																															
			÷.,	.1			т	ـــ	л.	ъ	ъ	т	ᆂ	ᆂ	Ъ	+	+	4	+	÷	+	+	÷	_ +	+	+	+	+			•
Utanis				+	- + 	- + 	+ _	+ -	+ _	+ +	+ 1	т 	+	т 	т	- -			τ +	-⊤ -+	- -	г Т	т Т	+ +		- -		- -			•
Leiomuoma				-+-	- +	- +	Ŧ	Ŧ		T	Ŧ	т	Ŧ	Ŧ	т	-	T.	T	, ,	Τ	г	Γ.	- -		Ŧ	T		т			
Delug strome!																						y					·¥				
Polyp suomal multiple																						Λ			Ý		л				
																									Λ						
Vagina																			+												

+: Tissue examined microscopically A: Autolysis precludes examination M: Missing tissue I: Insufficient tissue X: Lesion present Blank: Not examined -

TABLE B2

(i) A set of the se

All factors and the second sec

individual Animai Tumor Patholog	y or free	ma	ue.	ĸ	avs	\$ 1E	u ÇX	ie z	2- Y	i ea	ur 1	uni		auic	JN	SIL	Iai	0	1 18	IUI	on	iet	mai	le:	U	' PF	MIL (continued)
	7		7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	3		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
- •	3		3	3	3	4	4	4	4	4	4	4	4	4	4	4	4	5	5	5	5	5	5	5	5	5	
	1		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	ĺ	1	1	1	1	1	1	1	Total
Carcass ID Number	3		4	4	4	0	0	0	0	1	1	1	2	3	3	4	5	0	0	1	1	3	3	3	4	4	Tissues/
	5		0	1	9	1	2	4	8	0	5	8	4	0	2	7	0	7	9	1	6	1	3	7	4	5	Tumors
Alimentary System		-			·											_		_									
Esophagus	-	۴	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	-	F	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+	+	+	50
Intestine large, rectum	_	⊢	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large cecum	-	F	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	· +	+	+	+	50
Intestine small duodenum	_	L	÷	+	+	, +	, +	+	+	+	+	+	+	+	, +	+	+	, +	+	+	+	+	· +	+	+	+	50
Intestine small, jejunum	_	Ļ	+	+	- -	+	, +	+		÷	+	+	+	- +	+	+	+	4		+	· +	+	, +	+	, +	+	50
Intestine small, jejunum	_	ו ב	т "L	1	т -	ч Т	T L	-1 -L	г -	1	, ,	, ,	י ב	т. Т	ب	т 	, ,	т 	, 	т —	، ــــــــــــــــــــــــــــــــــــ	س	י ב	، ــــــــــــــــــــــــــــــــــــ	- -	י ב	50
Liver		r L	T T	Ŧ	т -	т 	- -	т -	т -	т 	т 	т 	т 	т 	т 	- T - L	т 	т 	т 	т Т	т 	т 	т 	т 	т 	+ +	50
Liver Hanata asilular a danama	-	r	Ŧ	т	Ŧ	Ŧ	Ŧ	т	Ŧ	т	т	Ŧ	т	Ŧ	т	Ŧ	Ŧ	Ŧ	т	т	T	-	· •	т	т	Ŧ	50
riepatocenular adenoma																											1
Mesentery													+		+	+			+								10
Urai mucosa																											1
Pharyngeal, squamous cell papilloma																											1
Pancreas	-	ł	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+	+	+	50
Salivary glands	-	F	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	-	F	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+	+	+	50
Stomach, glandular	-	F	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System							_													_							
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Adrenal medulla	· -	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nitromethane: 0 ppm (continued)

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Lymph node, bronchial			· +	+	+	+	+	÷	+	+ •	+ +	+ +	+	+	+	+	+	Μ	+	+	+	+	M	[+	• +	+			,
Lymph node, mandibular			+	+	+	+	+	+	+	+ •	+ +	+ +	+	+	+	+	+`	+	+	+	+	+	+	+	• +	M			
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Lymph node, mediastinal		*	+	• +	+	+	+	M	+	+ -	+ +	F +	+	+	+	+	+	+	+	+	+	+	+	+	- +	+			
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Integumentary System																													
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Osteosarcoma, metastatic, bone					x					. •															•				· .
Nose	• • •		+	+	+	+	+	+	+ ·	+ -	+ +	- +	+	+	+	+	+	+	+	+	+	+	+	+	• +	+			*
Carcinoma metastatic lung			+	+	+	+	+	+	+ ·		+ +	- +	+	+	+	+	+	+	+	+	+ x	+	.+	+	• +	+			
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Urinary System																												· .	• .
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Urinary bladder			+	+	+	+	+	+	+	+ -	+ +	+ +	+	+	+	+	+	+	+	+	+	+	+	+	• +	+			
Systemic Lesions									_						_				,						•				
Multiple organs			+	+	+	+	+	+	+	+ -	+ +	⊦ +	+	+	+	+	+	+	+	+	+	+	+	· +	• +	+			
Leukemia mononuclear				х					2	x y	хх	хх		х	х	х	х	х		х	Х	х		X				-	
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Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nitromethane: 0 ppm (continued) 77777 7 7 7 7 7 7 7 777 77 7 7 7 7 7 7 7 7 Number of Days on Study 4 4 4 5 5 5 5 5 5 5 5 5 5 3 3 3 3 4 4 4 4 4 4 4 4 4 Total 1 1 **Carcass ID Number** 3 4 4 4 0 0 0 0 1 1 1 2 3 3 4 5 0 0 1 1 3 3 3 4 4 Tissues/ 5 0 1 9 1 2 4 8 0 5 8 4 0 2 7 0 7 9 1 6 1 3 7 4 5 Tumors **Hematopoietic System** Bone marrow 50 Lymph node 7 48 Lymph node, bronchial Lymph node, mandibular 49 + Lymph node, mesenteric 50 + + + + + + + + + + + + + Lymph node, mediastinal 48 + + М + + + 50 Spleen + + + + + + + + + + + Thymus 48 м ++ Μ + + + **Integumentary System** Mammary gland 50 Adenoma х х 2 Carcinoma 2 х Х Fibroadenoma Х Х Х хх Х 10 9 Fibroadenoma, multiple Х Х х Х хх Skin 50 + Squamous cell papilloma 1 Subcutaneous tissue, fibroma 1 **Musculoskeletal System** Bone 50 Osteosarcoma 1 Skeletal muscle 1 **Nervous System** Brain 50 Astrocytoma benign 1 **Respiratory System** 50 Larynx + + Lung 50 Alveolar/bronchiolar carcinoma 1 Osteosarcoma, metastatic, bone 1 Nose 50 + 50 Trachea Carcinoma, metastatic, lung 1 Special Senses System 2 Eye + Harderian gland 3 Zymbal's gland 1 + Carcinoma х 1 **Urinary System** 50 Kidney Renal tubule, carcinoma 1 Urinary bladder 50 + + + + + + + + + + + + + + + + + + + + + + Systemic Lesions Multiple organs 50 + + + + + + + + + + + + + + + + ХХ Leukemia mononuclear Х хх хх х 22

Individual Animal Tumo	r Patholo	ogy (of Fe	ma	lle	ка	IS II	n u	ie 4	2- Y	ea	r I	'nh	ala	110	n i	ștu	ay	or I	N	itr	om	let	hai	ie:	9	4 p	pm	·. ·	
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Intestine small, jejunum				+	+ ·	+	+ +	+	+	+	+	+	+	+	+	+	+	+	+.	+	÷	+	. +	+	+	÷	+			
Intestine small, ileum				+	+ -	+ -	+ +	+	.+	+	+	+	÷	÷	+	+	+	+	+	+	+	+	+	+	+	+	+			· · .
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Carcinoma, metastatic, islets,	pancreatic					3	Č.,	•					`.						•*											
Hepatocellular adenoma														~					X		•					٠.,		· . ·		
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Carcinoma, metastatic, islets,	pancreatic					2	C .													•		4					•			
Pancreas				+	+ ·	+ -	+ +	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+.			
Salivary glands				+	+	+ :	+ +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	+			
Stomach, forestomach				+	+	+ -	+ +	+	+	+	+	+	+	+	+	.+	+	+	+	+	+	+	• +	+	+	+	+			
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Adrenal cortex .				+	+	+ •	+ +	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	,+	+	+	+	•		
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Pheochromocytoma benign												·						·												4
Islets, pancreatic				+	+	+ -	+ +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	·+	+	+	+	+	• •		
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C-cell, adenoma											Х								Х				Х		Х			• • •		
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Lesions in Female Rats

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Granulosa cell tumor benign							х																		I
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General Body System	 																								
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C-cell, adenoma						Х		X	Х				Х				Х								6
breig biorydl	+	+ •	+	+	+	+	+	+	+	- +	• +	F +	+ •	+	+	+	+	+	+	+	+	+	+	+	05
Pars distalis, adenoma			X	X	X	X	X		X	CΧ	C X	ΧХ	X	X	X	X		X	X		X	X	X	X	98
Pituitary gland	+	+ •	+	+	+	+	+	+	• +	· +	• +	- +	+ -	+	+	+	+	+	+	+	+	+	+	+	05
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mestine small, ileum	+	+	+	+	+	+	+	+	• +	+ +	- +	+ +	+	+	+	+	+	+	+	+	+	+	+	+	05
muniei, jejunum	+	+	+	+	+	+	+	+	- +	r +	- 4	+ +	+	+	÷	+	+	+	+	+	+	+	+	+	٥۶
ntestine small, duodenum	+-	+	+	+	+	+	+	+	• +	- +	- +	+ +	+ ·	+	+	+	+	+	+	+	+	+	+	+	٥۶
ntestine large, cecum	+	+	+	+	+	+	+	+	• +	r +	- +	+ +	+	+	+	+	+	+	+	+	+	+	+	+	٥۶
ntestine large, rectum	+	+	+	+	+	+	+	+	• +	r +	- +	+ +	+	+	+	+	+	+	+	+	+	+	+	+	٥۶
ntestine large, colon	+	+	+	+	+	+	+	+	• +	- +	- +	+ +	+	+	+	+	+	+	+	+	+	+	+	+	95
sndeusers System	ł	+	+	+	+	+	+	+	• +	- +	- +	+ +	+ ·	+	+	+	+	+	+	+	+	+	+	+	95
	 												<u> </u>	<u> </u>											
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amper of Days on Study	I 6	8 6	0 0	0 Ż	L z	0 £	e e	: E : F	E 9 E 9	е е е е	E 1 E 1	Е Е Е Р	e e	4 3	4 3	4 2	s s	s s	S E	s s	s S	s s	s £	s £	

Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nitromethane: 94 ppm (continued)

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Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nitromethane: 94 ppm (continued) 4 4 5 5 5 5 4 4 4 5 5 5 5 56 6 6 6 6 6 6 6 666 Number of Days on Study 2 3 7 8 9 1 2 5 6 7 7 8 8 8 0 0 2 2 3 6 6 6 6 7 .8 8 906806 1 3 5 3 8 5 2 0 1 16 6 2 4 5 7 2 0 3 3 3 3 3 3 3 3 3 3. 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 **Carcass ID Number** -3 3 3 2 3 4 1 3 0 4 4 3 2 0 1 2 3 1 4 0 1 1 2 4 0 6 8 5 5 5 3 9 2 .9 4 2 6 -6 0 5 8 7 2 1 3 3 1 4 5 4 Hematopoietic System Bone marrow Lymph node Lymph node, bronchial Lymph node, mandibular Lymph node, mesenteric Lymph node, mediastinal Spleen Thymus Μ M + M **Integumentary System** Mammary gland Carcinoma Carcinoma, multiple х хх ххх Fibroadenoma Х x Fibroadenoma, multiple Sarcoma, metastatic, skin Skin Squamous cell papilloma Subcutaneous tissue, fibroma Х Subcutaneous tissue, fibrosarcoma Subcutaneous tissue, sarcoma Musculoskeletal System Bone Skeletal muscle Nervous System Brain + + + + + **Respiratory System** Larynx Lung Alveolar/bronchiolar adenoma Carcinoma, metastatic, islets, pancreatic X Carcinoma, metastatic, mammary gland Nose Trachea + + + + Special Senses System Eye + Zymbal's gland Carcinoma **Urinary System** Kidney Lipoma x Urinary bladder Systemic Lesions Multiple organs + + + + + + + + + + + + + + ххх $\mathbf{X}_{1,\frac{1}{2}},$ х ХХ X х Leukemia mononuclear

Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nitromethane: 94 ppm (continued) 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 77 7 7 7 7 7 7 7 7 Number of Days on Study 3 3 3 3 3 3 3 1 8 0 0 7 0 3 3 3 3 3 3 3 3 4 4 4 5 5 5 5 5 5 5 5 5 3 3 3 3 3 3 3 3 3 Total **Carcass ID Number** 4 1 4 1 4 5 0 1 1 2 2 2 3 4 2 3 3 0 0 0 0 1 2 2 4 Tissues/ 4 0 1 8 2 0 9 1 9 0 7 8 7 7 9 1 3 2 3 6 8 7 4 6 0 Tumors **Hematopoietic System** Bone marrow 50 Lymph node 6 Lymph node, bronchial 49 M + Lymph node, mandibular 48 Μ Μ Lymph node, mesenteric 50 + + + + Lymph node, mediastinal 49 Μ + 49 Spleen + + + + + + + + + + + + + + Thymus + + 47 + **Integumentary System** Mammary gland + + 50 + Carcinoma Х х хх 4 3 Carcinoma, multiple Fibroadenoma Х X X 15 х х хххх Fibroadenoma, multiple х хх х 6 Sarcoma, metastatic, skin 1 Skin + + 50 + x Squamous cell papilloma 1 Subcutaneous tissue, fibroma Х 1 Subcutaneous tissue, fibrosarcoma 1 Subcutaneous tissue, sarcoma х · 1 **Musculoskeletal System** 50 Bone Skeletal muscle · 2 **Nervous System** 50 Brain + ++ + + + + + + + + + + + + + **Respiratory System** Larynx 50 + + + Lung 50 Alveolar/bronchiolar adenoma 1 Carcinoma, metastatic, islets, pancreatic 1 Carcinoma, metastatic, mammary gland х 1 Nose 50 + + Trachea 50 + + Special Senses System Eye 1 Zymbal's gland 1 + х Carcinoma 1 **Urinary System** 50 Kidney + + + + + + + + + + + Lipoma 1 50 Urinary bladder + + + + + + + + + + + + + + Systemic Lesions 50 Multiple organs + + + + ++ + + + + + Leukemia mononuclear х х х х 13

Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nitromethane: 188 ppm

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Number of Days on Study		4	4 1	4	4 0	5	5	5	5 ⊿	6 1	6 3	6 1	6 5	6 5	6	6	6 8	6 0	6 0	7	7	7	7	7	7	7				
Aumoer of Days on Study		2	0	8	1	8	2	3	5	9	8	6	0	7	5	Ó	6	1	8	5	2	3	3	3	3	3				
Carcass ID Number		5 4 9	5 4 3	5 2 0	5 3 6	5 2 9	5 0 6	5 4 2	5 0 4	5 0 9	5 4 8	5 3 5	5 4 7	5 0 8	5 0 7	5 4 1	5 2 5	5 0 1	5 1 2	5 3 2	5 1 1	5 0 2	5 1 4	5 1 7	5 2 3	5 3 1				
Alimentary System		 																											-	
Esophagus		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+				
Intestine large, colon		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Intestine large, rectum		+	+	+	÷	+.	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Intestine large, cecum		+	+	+	+	+	+	+	+	+	+	· +	+	+	+	+	+	+	+	+	. +	+	+	+	+	+				
Intestine small, duodenum		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+				
Intestine small, jejunum		+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Intestine small, ileum		+	+	+	+	+	+	+	+	+	4	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Liver		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Mesentery										÷				+		+				+	+		+							
Oral mucosa			,															+									•			
Pharyngeal, squamous cell papillom	a																	х												
Pancreas		+	+	+	+	+	Ŧ	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	· +	+				
Salivary glands		+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Stomach, forestomach		+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Stomach, glandular		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	+	· +	+				
Tongue									+																					
Squamous cell carcinoma									Х																					
Condiousgaular System	<u> </u>	 																												
Carolovascular System															•						,				• •	· .				· .
Неап	4	+	.+	+	+	+	.+	+	+	+	.+	+	+	+	+	+	+	+	+	+	+	+	+	+	· +·	+				
Endocrine System				-	÷																									:
Adrenal cortex		• +	+	+	+	+	+	+	+	+	+	+	+	+	·+	+	+	+	+	+	+	+	+	+	+	+				
Adrenal medulla	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+				
Pheochromocytoma malignant																														
Pheochromocytoma benign														•												X				
Islets, pancreatic Adenoma		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+.	. +	+	+	+	+	+	+	• +	+				
Parathyroid gland		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ x	+	+	+	+	+	+	+	+	• +	+		•		
Pituitary gland		+	+	+	+	+-	·+	+	4	4	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	· +				
Pars distalis adenoma			'	x		x		x	x	x	x	x	x	x	x	•	ÿ		x	x	x	x	x	x	' x					
Pars distalis, carcinoma									· ·	•••			••				••		••		••	••								
Thyroid gland		+	+	+	+	+	+	+	+	+	+	+	.+	+	+	+	+	÷	4	+	+	+	+	+	• +	• +				
Bilateral C-cell adenoma		•	•	•	•		• •	•		·						•														
C-cell, adenoma														X		5				X			X			-				
Ceneral Body System				_							<u> </u>	_																		
None												<i>.</i>							·											
Carrital Southand					<u> </u>										_															-
Genital System		•		,	v															Т		ì	. 1.	X	г		_			
Cintoral gland		+	+	Ŧ	IVI	Ŧ	Ŧ	Ŧ	Ŧ	+ v	Ŧ	Ŧ	+ v	T	Ŧ	Ť	Ŧ	T	Ŧ	Ŧ	Ŧ	Ŧ	· T	IV	1.7		-			
Adenoma										Ă			л																	
Carcinoma Bilatomi adaptati									•					v													•			
Bilateral, adenoma							÷							<u>л</u>			. 1								. ,		_			
Cremulan call times benier		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Ŧ	+	+	Ŧ	+	+	+	- +	- +	-			
Granulosa cell almor benign		,									•			-			ـــ	i	ъ		L.	J		.1	ر _	ر .	_			
Delve stromal		+	-	Ŧ	+	Ŧ	-	Ŧ	Ŧ	T	Ŧ	T	+	т	Ŧ	Ŧ	Ť	т	Ŧ	T	Ť	+	Ť	7	-	+				
Sarcoma stromal		v v																										•		
Salcona suoma		 A																												
																								_						

7 7. 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 Number of Days on Study 3. 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 5 55 5 5 5 5 5 5 5 3 3 3 3 4 5 5 5 • 4 4 4 4 4 4 4 4 5 5 5 5 5 5 5 5 5 5 5 5 5 55 55 5 5 5 5 5 5 5 5 5 Total **Carcass ID Number** 3 3 4 5 1 1 1 2 2 3 3 4 0 0 1 2 2 2 2 3 3 4 Tissues/ 1 1 4 89 6 0 0 5 6 8 1 8 0 4 4 3 5 3 9 2 4 6 7 3 7 0 5 Tumors **Alimentary System** Esophagus 50 Intestine large, colon 50 Intestine large, rectum 50 50 Intestine large, cecum Intestine small, duodenum 50 Intestine small, jejunum 50 ++ + 4 + + + Intestine small, ileum 50 + ++ + ++ + + + + + + + + + + + + + + + Liver 50 + + Mesentery 12 Oral mucosa 1 Pharyngeal, squamous cell papilloma 1 Pancreas 50 ++ + +50 Salivary glands + + + ++ ++ + + + ++ + +Stomach, forestomach 50 + + + + + + + + + + 50 Stomach, glandular Tongue 1 Squamous cell carcinoma 1 **Cardiovascular System** Heart 50 + + + **Endocrine System** Adrenal cortex 50 ++ + + Adrenal medulla 49 м + Pheochromocytoma malignant x 1 Pheochromocytoma benign 2 Islets, pancreatic + + 50 + Adenoma Х Х 3 Parathyroid gland 50 + Adenoma 1 Pituitary gland 50 +++ + + + + + + + + ++ + ххх ххххх x x x x x x x x x x Pars distalis, adenoma XXXX 39 Pars distalis, carcinoma Х 1 Thyroid gland + 50 + + + + + + + + + + + + + + Bilateral, C-cell, adenoma х 1 C-cell, adenoma Х ХХ Х 7 **General Body System** None **Genital System** Clitoral gland 47 + + M + Adenoma х Х Х 5 Carcinoma Х 3 Х Х Bilateral, adenoma 1 Ovary + + 50 Granulosa cell tumor benign Х 1 Uterus 50 ++ + + + + + + Polyp stromal х х ххх 6 Sarcoma stromal 1

Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nitromethane: 188 ppm (continued)

Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nitromethane: 188 ppm (continued)

Number of Days on Study	÷			4	4	4	4 9	5 0	5 1	5 1	5 4	6 1	6 3	6 4	6 5	6 5	6 6	6 7	6 8	6 9	6 9	7 0	7 1	7 3	7 3	7 3	7 3	7 3				
				2	0	8	1	8	2	3	5	9	8	6	0	7	5	0	6	1	8	5	2	3	3	3	3	3				
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Carcass ID Number				4 9	4 3	2 0	3 6	2 9	0 6	4 2	0 4	0 9	4 8	3 5	4 7	0 8	0 7	4 1	2 5	0 1	1 2	3 2	1 1	0 2	1 4	1 7	2 3	3 1		• •		
Hematonoietic System					_					_		_					·									_	1					
Bone marrow				+	•	+	+	+	+	+	+	+	+	+	+	Ŧ	+	+	+	+	+	+	+	+	+	+	+	÷				'
Lymph node				•		•	•	+	÷	•	•	•	•	•		÷		+	•		•	+	+	•	•	•		•				
Lymph node, bronchial				+	·+·	+	+	+	÷	+	+	+	+	+	м	+	÷	+	м	+	+	+	+	+	+	+	· +	м				
Lymph node, mandibular				м	+	+	+	+	+	÷	+	+	+	+	+	÷	+	+	+	'n	+	+	+	+	+	+	.	· +				
Lymph node, mesenteric				M	+	+		+	÷	÷	÷	+	+	÷.	÷	+	+	÷	+	+	+	4	+	+	+	+	-	+				
I ymph node, mediastinal						, 	, 	Ļ	÷	ż	÷	÷	<u>_</u>	÷	÷	· _	÷	÷	ц Т	, -	÷	. •	÷	, 	ц. Т	<u>т</u>	а —	т —				
Spleen	,			Т.		т 	т Т	т Т	Ŧ	т -	т -	-	т _	Ť	- -		т -	т Т	т Т	.т "т	т 	+ +	- -		+ +	- -	- -	т 				
Thymus				т —	т Т	- -	т 	T. · II	T L	т _	т	т 	.т. .д.	Ŧ	т 	Ť	Ť	т	м	т _	т 	т 	т 	M	т 	т - т	т Т	т 				
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Integumentary System																																
Mammary gland				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷.			
Carcinoma		-			х																								1.1		•	
Fibroadenoma						Х	X					X	•		X						х				X	Х						
Fibroadenoma, multiple											х		х	х			Х					Х	х				X					
Skin				+	М	+	М	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Squamous cell carcinoma																											х					
Subcutaneous tissue, schwannoma																							. '									
malignant																					х											
Musculoskeletal System											_					_	_								<u> </u>							
Bone				+	÷	·+	+	+	+	+	+	+	+	·+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+				
Nervous System						_		-		-							_						-									
Brain				+	Ŧ	4	+	+	+	+	+	+	4	÷	+	+	+	+	+	+	+	+	+	+	+	+	•+	+				
Carcinoma, metastatic, pituitary glar	nd			'		•	·	•	•	•		•	•	•	·	•	•	•	•					·		•	•	•				
Despiratory System										_			· · · ·										-									
Longer					т	т.	Т	Ъ		т	, L	ш	-	-	-	т	т		т		Т	Т	-	́ т	-	ъ	Ŧ	-				
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Alveolar/bronchiolar adenome				т	т	т	т	Τ.	т	т	т	Ŧ	v	т	т	ſ	Т	т	т	T		'	'	. '		'	,	'	•			
Carcinoma matastatic mammany gl	and				v								л											19 A.	• •							
Nosa	anu			ь.	<u>^</u>		<u>н</u> .	-	1	L	а.					Ŧ	-		· _		ъ	т	ì	L		т.	т,	-			· .	
INOSC	÷			+	+	+	+	+	+	1 1	*	+	+	+	+ +	т _	Ť	+	+	+	Ŧ	- -	Ŧ	+	+	- -		т -				
						т 	т 		т —	T	* .	. T.	т —	т —	т —	т	т —	т	<u> </u>	Τ	т	Ţ.	т	т	Ŧ	т	т	т				
Special Senses System			,																													
Eye								+											+													
Uninger Sustem															_	_	-							<u>`</u>						·····		
Videou	**													1 .					,			,	L	Ł				+				
Kioney				+	+		+	+	+	+	+	+	·+-	+	+	+	T		+	T		Ť	Ŧ	1	- T		- -	т 				
Transitional anithalium panilloma				IVI	+	+	+	Ŧ	Ŧ	т	Ţ	Ŧ	т	+.	Ŧ	Ŧ	Ŧ	Ŧ	T	T	Ŧ	т	т	т	т	т	т	Τ.				
							_							_	_					_						-			_			
Systemic Lesions																			-	-	_	-										
Multiple organs	1		÷.,	+	+	+	+	+	·+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	`. +	+	+	+	+				
Leukemia mononuclear									х		х		х					х		х			х		х	х						
		-								_										_	_						_					

Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nitromethane: 188 ppm (continued)

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Number of Days on Study	7 3		7	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3		7 3	
	3	-	3 3	3	3	4	4	4	4	4	4	4	4	4	5	5	5	5	5	5	5	5	5	5	5		5	<u> </u>
Carooss ID Number	5	:	5 :	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5		5	Totai Tianua (
	8	9	9 (+ 6	0	0	5	6	8	1	2 8	0	3 4	4	3	5	3	9	2	2 4	2 6	2 7	3	3 7	4	· .)	.4 5	Tumors
Hematopoietic System				_		_																					,	
Bone marrow	ંન	+ -	+	+	+	+	+	+	+	+	+	+	+	+	• +	+	+	+	+	+	+	+	+	+		F	+	50
Lymph node											+								+				+					9
Lymph node, bronchial	4	+ -	+	+	+	+	+	+	+	+	+	+	+	+	• +	+	+	+	+	+	+	+	+	+	• +	۲	+	47
Lymph node, mandibular	-1		+	+	+	+	+	+	+	+	+	+	+	+	• +	+	` +	+	+	+	+	+	+	+	• +	ŀ	+	48
Lymph node, mesenteric	-	-	+	+	+	+	+	+	+	+	+	+	+	· +	• +	+	+	+	+	+	+	+	+	+	• -+	۲	+	. 49
Lymph node, mediastinal	-	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+	+	+	+	· +	+	+	+	+	- 4	F	+	50
Spleen	-	-	+ `	+	+	+	+	+	+	+	+	+	+	+	• +	+	+	+	+	+	+	+	+	+	· +	F	+	50
Thymus	4	-	+	+	+	М	+	+	+	+	+	+	+	+	·M	[+	+	+	+	I	+	+	+	+	• +	۲	+	45
Integumentary System																				·····								
Mammary gland	4	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+	+	+	+	+	+	+	+	+	· +	F	+	50
Carcinoma																												. 1
Fibroadenoma		2	X C	Х		х		х		Х	Х			Х		Х			Х				Х	Х			х	19
Fibroadenoma, multiple												Х					Х	Х		X	Х	Х			Х	C .		14
Skin	-	-	+	+	+	+	+	+	+	+	+	+	+	• +	• +	+	+	+	+	+	+	+	+	+	· +	F	+	48
Squamous cell carcinoma																												1 -
Subcutaneous tissue, schwannoma																												
malignant				_																								1
Musculoskeletal System													_													-		
Bone	-	+ •	+	+	+	+	+	+	+	+	+	+	+	• +	• +	+	+	+	+	+	+	+	+	+	• +	+	+	50
Nervous System																												
Brain	4	+ ·	+	+	+	+	+	+	+	+	+	+	+	• +	• +	+	+	+	+	+	+	+	+	+	1	۲	+	50
Carcinoma, metastatic, pituitary gland																						Х						1
Respiratory System							•																					
Larynx	-	-	+	+	+	+	+	+	+	+	+	+	+	· +	• +	+	+	+	+	+	+	+	+	+	· +	F	+	50
Lung	-	-	+	+	+	+	+	+	+	+	+	· +	+	• +	- +	+	+	+	+	+	+	+	+	+	• +	F	+	50
Alveolar/bronchiolar adenoma																												1
Carcinoma, metastatic, mammary gland																												1
Nose	4	+	+	+	+	+	+	+	+	+	+	+	+	· +	• +	+	+	+	+	+	+	+	+	+	• +	F	+	50
Trachea		<u>ب</u>	+	÷	+	+	+	+	+	+	+	+	+	• +	• +	+	+	+	+	+	+	+	+	+	• +	⊦	+	50
Special Senses System Eye	_	_																									•	2
Urinary System				<u> </u>																······				-				
Kidney	-	+	+	+	+	+	+	+	+	+	+	+	• +	• +	- +	· +	+	+	+	+	+	+	· +	+	1	⊦	+	50
Urinary bladder	-	┝	+	+	+	+	+	+	+	+	+	+	• +	• +	- +	+	+	+	+	+	+	+	+	+	1	۲	+	49
Transitional epithelium, papilloma													Х			х												2
Systemic Lesions			;																					-				
Multiple organs	4	F	+	+	+	+	+	+	+	+	+	+	• +	• +	- +	+	+	+	+	+	+	+	• +	+	1	ŀ	+	50
Leukemia mononuclear						•					Х	Х			Х				Х				Х				Х	14

3 4 4 4 5 5 5 5 6 6 6 6. 6 6 6 6 6 6 6 6 6 6 6 7 7 Number of Days on Study 8 2 9 9 5 5 9 9 0 0 0 0 33 4 5 6 6 6 7 7 7 8 0 1 7 5 26 47 74 6 2 1 0 5 50 2 0 2 0 4 4 6 4 92 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7.7 **Carcass ID Number** 3 0 0 0 1 0 0 0 2 3 0 4 2 3 1 4 3 1 4 4 3 1. 3 2 1 7 7 9 2 2 5 6 5 3 4 7 8 4 7 ľ 9 6 1 6 4 8 3 9 2 1 **Alimentary System** Esophagus Intestine large, colon Intestine large, rectum Intestine large, cecum Intestine small, duodenum Intestine small, jejunum Intestine small, ileum Liver Histiocytic sarcoma X Mesentery + + X Carcinoma, metastatic, urinary bladder Histiocytic sarcoma Х Oral mucosa Pharyngeal, squamous cell papilloma Pancreas Carcinoma, metastatic, urinary bladder Salivary glands Stomach, forestomach Stomach, glandular **Cardiovascular System** Heart Histiocytic sarcoma Х **Endocrine System** Adrenal cortex Adrenal medulla Pheochromocytoma benign Х Х Bilateral, pheochromocytoma benign Islets, pancreatic Adenoma Parathyroid gland Pituitary gland + + + + + + + + + * * * * * * * * * * Pars distalis, adenoma х x x x x X х X X X х Thyroid gland + + + + + + + + + + ++ х х х х C-cell, adenoma Х X C-cell, carcinoma **General Body System** None **Genital System** Clitoral gland M Adenoma Histiocytic sarcoma Ovary Histiocytic sarcoma Uterus x x Polyp stromal Polyp stromal, multiple

Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nitromethane: 375 ppm

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Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nitromethane: 375 ppm (continued)

								_																			_
Number of Days on Study	7 2 0	7 2 0	7 3 3	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	·																		
Carcass ID Number	7 2 5	7 3 6	7 1 3	7 1 4	7 2 3	7 2 9	7 3 0	7 3 8	7 4 3	7 4 4	7 5 0	7 0 5	7 0 9	7 1 5	7 1 8	7 2 0	7 2 1	7 2 2	7 3 1	7 4 6	7 4 8	7 1 0	7 2 7	7 4 0	7 4 2	Total Tissues/ Tumors	
Alimentary System				_																				_			
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Intestine large, rectum	. +	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Intestine small jejunum	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Intestine small ileum	+		. .	÷	+	+	· _	, +	_	4	+		+	+	+	+	+	÷	+	+	+	, 	+		+	50	
Liver	, 			ـــ	+		+	, _	, ,	, 	, 	, 	_	÷		_	, _	, 		ب		، ـــ	, 	ـــ	, _	50	
Histiocytic sarcoma	· ·	'	'			'	•	'	'		1	Т.	'	7	1	т	'	т	ľ	.1		T.		Ŧ	•	1	
Magenten					т				т																	14	
Carcinoma, metastatic, urinary bladder Histiocytic sarcoma				т	т				Ŧ		Ŧ											т		Ŧ	т	14	
Ural mucosa												+														1	
Pharyngeal, squamous cell papilloma												X														1	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Carcinoma, metastatic, urinary bladder																										1	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Cardiovascular System																						_					
Heart Histiocytic sarcoma	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 1	
Endocrine System	<u> </u>																							_			
Adrenal cortex	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	· +	+	+	+	50	
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Pheochromocytoma benign																										2	
Bilateral, pheochromocytoma benign		x																	х							2	
Islets, pancreatic	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Adenoma																				x						1	
Parathyroid gland	+	+	• +	+	+	М	(+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Pituitary gland	+			· +	. +	+		÷	+	+	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Pars distalis, adenoma	x	x	x	x	x	x	x		•	x	x	x	,	x	x	x	x	x	x	x	x	x		•	x	40	÷
Thyroid gland	+	+		. +	. +	Ń	í +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	·+	49	
C-cell adenoma			x	'	•		• •	ÿ	x	x	'	•	'	•			•	x	•	•	•	'		'	•	10	
C-cell, carcinoma				x				~		~								~				х				3	
None												·						_									
Genital System																											
Clitoral gland	+	- 4	- +	• +	• +	+	+	+	+	ł	+	Μ	+	+	+	+	+	+	+	+	+	• +	+	+	+	48	
Adenoma																					Х		Х			2	
Histiocytic sarcoma																										1	
Ovary	+	• +	• +	• +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Histiocytic sarcoma																										1	
Uterus	+	· -	• +	• +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+	+	+	50	
Polyp stromal											Х		,	Х						Х						5	
Polyp stromal, multiple	• .												Х													1	
_																											

Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nitromethane: 375 ppm (continued)

																_															
Number of Days on Study			3	4	4 9	4 9	5 5	5	5	5	6 0	6 0	6 0	6	6	6	6 4	6 5	6	6	6	6 7	6	6	6	7	7	:			
rumoer of Days on Stady			7	5	2	6	Ő	2	4	7	Õ	4	4	7	4	6	2	1	0	5	5	ó	2	6	8 4	9	2				
			7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7				
Carcass ID Number	•		3 7	0 7	4 7	2 8 -	3 4	1 7	4 9	0 1	3 9	1 6	4 1	0 2	1 2	0 6	0 4	0 8	4 5	2 6	3 5	3 3	0 3	1 9	3 2	2 4	1 1				
Hematopoietic System						<u> </u>	·					_															_			-	
Bone marrow			+	·+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				. ·
Lymph node															+		+								+						
Lymph node, bronchial -		\$	+	+	+	+	+	М	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Carcinoma, metastatic, thyroid gland										•																-					
Lymph node, mandibular	•		+	+	÷	+	+	+	+.	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Lymph node, mesenteric			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Lymph node, mediastinal			М	+	+	+	+	+	М	+	+	+	+	+	+	+	+	+	+	+	`+	. +	+	+	+	+	+				,
Spleen			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	÷	+	+	+				
Thymus			М	+	+	+	+	+	М	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			•	,
Integumentary System	·		Ţ.																												
Mammary gland			+	+	+	+	+	Ŧ	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	· +	.+	+				•
Adenoma																													1	-	
Carcinoma				Х		Х	Х				Х						Х				•										
Carcinoma, multiple																									•	•	Х				
Fibroadenoma								Х	Х		Х	X	Х					х		Х		х	Х	Х	•	Х					
Fibroadenoma, multiple														Х							Х						Х				
Histiocytic sarcoma	•					·							х																		
Skin		,	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	.+	+	+				
Squamous cell papilloma																									•						
Subcutaneous tissue, fibrosarcoma																															
Subcutaneous tissue, histiocytic				•									17					-													. •
sarcoma			v										х																		
Subcutaneous tissue, sarcoma			X			-																					÷.				
melanoma malignant	•																						1.3								
							_					_						_			_					`					
Musculoskeletal System																															,
Bone	•		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Skeletal muscle																								+				•			
Carcinoma, metastatic, urinary bladder	•					•				•												`		X							
Nervous System					•																										÷.
Brain			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				. ,
Spinal cord			•																												
Respiratory System																												•			
Larynx			+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	. +	+	+	+				
Lung			+	.+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Alveolar/bronchiolar adenoma																							х						:	:	
Histiocytic sarcoma						•							X									•									
Nose	• . 		+	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	.+	+	+	+	+	+	+	+	+	+				
1 rachea			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Special Senses System							_			_																				,	•
Eye																					+				+						
Zymbal's gland						,															•			'				·			
Carcinoma		• •																													

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estions in Female Rats

TABLE B2

Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nitromethane: 375 ppm (continued)

Special Senses System Eye Zymbal's gland Carcinoma		+																				+			X +	1 1 7	
Alveolar/bronchiolar adenoma Histiocytic sarcoma Nose Trachea		+ +	+ +	+ +	+ +	+ +	+ +	+++	+ +	+ +	++	• +	- +	+ 4 + 4	+ +	+ +	+ +	+ +	+ +	++	+ +	+ +	+ +	++	+ +	05 05 I I	
Respiratory System Larynx Lung		+ +	+ +	+ +	++	+ +	+ W	+ +	+ +	+ +	• +	• +	⊦ + ⊦ +	+ +	+ -	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	05 67	
Ne rvous System Brain Spinal cord		+	+	+	+	+	+	+	+	÷	· +	+	+ +	+ -	+ + -	+	+	+	+	+	+	+	+	+	+	1 05	
Musculoskeletal System Bone Skeletal muscle Carcinoma, metastatic, urinary bladder		+	+	+	+	+	-+-	+	+	+	· +	- +	⊦ +	+ -	+ -	+	+	+	+	+	+	+	+	+	+	I I OS	
sarcoma Subcutaneous tissue, sarcoma Subcutaneous tissue, pinna, amelanotic melanoma, malignant	0		_									<u> </u>							x	x						T. · ·	<u></u>
Skin Squamous cell papilloma Subcutaneous tissue, fibrosarcoma Subcutaneous tissue, histiocytic		+	x +	м	+	+	+	+	+	+	- +	• 4	X ⊦ +	:	+ -	+	+	+	+	+	+	+	+	+	+	I 6†	
Carcinoma, multiple Carcinoma, multiple Fibroadenoma, multiple Histiocytic sarcoma		x	x	x	х	x	x	x	x	X	X	C	x	X :	X :	х			x	х	x	x	x	x	x	1 14 55 1	
Integumentary System Adamaty Eland Adaroma Carcinoma		+	+	x +	+	x +	+	+	+	+	• +	< 	X + +	+ -	+ •	+	x +	+	+	+	+	÷	x +	+	+	01 7 05	
Carcinoma, metastatic, thyroid gland Lymph node, mandibular Lymph node, mesenteric Spleen Thymus		+ + + +	+ + + + + +	+ + + + +	+ + + + X	+ + + W + +	+ + + + +	+ + + +	+ + + W	+++++++++++++++++++++++++++++++++++++++	· + · + · +	- 4 - 4 - 4 - 4	F + F + F + F +	+ - + - + - + -	+ · + · + ·	+ + + W	+ + + +	+ + + W	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +	+ + + + +	+ + + +	87 05 97 05 1	
Mematopoietic System Bone marrow Lymph node Lymph node, bronchial		+	+ +	+ +	+	+	+	+ +	+	+	- + - +		+ + + +	+ ·	+ •	+	+	+	+	+	+	+	+	W +	+	84 5 05	
Carcass ID Number		s z L	9 E L	Е І L	¢ I L	e Z L	6 て 上	0 E L	8 8 2	, E , t		5 (0) 2	6 9 0 0 <i>L 1</i>	ς Ι L	8 I L	0 Z L	I Z L	Z Z L	ז 3 2	9 † 2	8 † L	0 1 2	L Z L	0 † 2	2 † 2	Total Tissues/ Tumors	<u> </u>
Number of Days on Study		0 7 L	0 Z L	Е Е 2	ב ב ג	3 .E .L	3 2 2	Е Е 2	ε ε . L	5 E	E E E E L L	5 2	+ + E E L L	† £ 2	† E L	† 2 2	† 2 2	₽ 3 2	† 2 1	4 3 1	† € ∠	ς ε ∠	ς ε ∠	ς ε ∠	ς ε ∠		
(nanuuua)							·															-			_		

Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nitromethane: 375 ppm (continued)

				-			No. or other	_					_			_			_									
	3	4	4	4	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7			
Number of Days on Study	8	2	9	9	5	5	9	9	0	0	0	0	3	3	4	5	6	-6	6	7	7	7	8	0	1			
	7	5	2	6	0	2	4	7	0	4	4	7	4	6	2	1	0	5	5	0	2	6	4	9	2			
· · · · · · · · · · · · · · · · · · ·	 7.	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	. 7	7	7	7		•	
Carcass ID Number	3	0	4	2	3	1	4	0	3	1	4	0	1	0	0	0	. 4	2	3	3	0	1	3	2	1			
	7	7	7	8	4	7	9	1	9	6	1	2	2	6	4	8	5	6	5	3	3	9	2	4	1		• •	
Urinary System																												
Kidney	+	+	+	+	+	+	.+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+			•
Carcinoma, metastatic, urinary bladder																				•		Х						
Mesenchymal tumor malignant							Х																			•		
Urinary bladder	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. •		
Histiocytic sarcoma											X																	
Transitional epithelium, carcinoma															-							X						
Systemic Lesions																												
Multiple organs	+	÷	+	+	+	+	+	÷	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	· +	+			
Histiocytic sarcoma		÷.,									Х																	
Leukemia mononuclear								x		Х				•	х			х	÷	Х				х				L.

Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Nitromethane: 375 ppm (continued)

Number of Days on Study	7 2 0	7 2 0	7 3 3	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5																		
Carcass ID Number	7 2 5	7 3 6	7 1 3	7 1 4	7 2 3	7 2 9	7 3 0	7 3 8	7 4 3	7 4 4	7 5 0	7 0 5	7 0 9	7 1 5	7 1 8	7 2 0	7 2 1	7 2 2	7 3 1	7 4 6	7 4 8	7 1 0	7 2 7	7 4 0	7 4 2	Total Tissues/ Tumors
Urinary System Kidney Carcinoma, metastatic, urinary bladder Mesenchymal tumor malignant Urinary bladder Histiocytic sarcoma Transitional epithelium, carcinoma	+	- + · +		- + - +	- + - +		• +	+	+	+	• +	• +		+	+	+	+	+	+	+	+	+	+	+	+	50 1 1 50 1 1
Systemic Lesions Multiple organs Histiocytic sarcoma Leukemia mononuclear	+	• +		- + K	- + x	- +	· +	+	+	+	• +	+	+	+	÷	+	+	+	+	+ x	+	+	+	+	+	50 1 9

	0 ppm	94 ppm	188 ppm	375 ppm	
Advanal Madullas Banian Phasabramaaut		<u>`</u>	<u> </u>		
Overall mea ^a	1/40 (7%)	1/50 (2%)	2/10 (1%)	4/50 (8%)	
Adjusted rate ^b	3.6%	53%	60%	13 5%	
Terminal sate	1/39 (4 %)	1/10 (5%)	0.9% 0/00 (7%)	1/22 (192)	
First incidence (days)	1/26 (4 <i>%</i>) 722 (T)	722(T)	$\frac{2}{29}(7)$	651	
Life table test	755 (1) P=0.065	P=0.673	P=0.512	D-0 147	
Life table test	P=0.063	P=0.673	P=0.512	P = 0.147	
Contrary Armitege tood	P = 0.007	F-0.075	F=0.512	r=0.107	
Eicher exect test	F=0.074	P-0 747N	P-0 500	P-0 187	
risher exact test		r=0.747N	r0,500	1 -0.187	
Adrenal Medulla: Benign, Complex, or M	Ialignant Pheochromocyton	18		÷	
Overall rate	2/49 (4%)	1/50 (2%)	3/49 (6%)	4/50 (8%)	
Adjusted rate	7.1%	5.3%	10.3%	13.5%	
Terminal rate	2/28 (7%)	1/19 (5%)	3/29 (10%)	1/23 (4%)	
First incidence (days)	733 (T)	733 (T)	733 (T)	651	
Life table test	P=0.145	P=0.635N	P=0.516	P=0.277	
Logistic regression test	P=0.150	P=0.635N	P=0.516	P=0.310	
Cochran-Armitage test	P=0.166	•			
Fisher exact test	· .	P=0.492N	P=0.500	P=0.349	
Clitoral Gland: Adenoma	•				
Overall rate	7/47 (15%)	4/46 (9%)	6/47 (13%)	2/48 (4%)	
Adjusted rate	25.0%	19.3%	17.3%	9.1%	·
Terminal rate	6/26 (23%)	3/18 (17%)	3/28 (11%)	2/22 (9%)	
First incidence (days)	631	636	619	733 (T)	• • • •
Life table test	P=0.096N	P = 0.474N	P=0.449N	P=0.117N	
Logistic regression test	P=0.087N	P=0.386N	P=0.505N	P=0.102N	
Cochran-Armitage test	P=0.082N				
Fisher exact test		P=0.274N	P=0.500N	P=0.074N	
Clitoral Gland: Carcinoma					•
Overall rate	0/47 (0%)	1/46 (2%)	3/47 (6%)	0/48 (0%)	
Adjusted rate	0.0%	5.6%	10.7%	0.0%	
Terminal rate	0/26 (0%)	1/18 (6%)	3/28 (11%)	0/22 (0%)	
First incidence (days)	_e	733 (T)	733 (T)	. <u>-</u> :	
Life table test	P=0.620	P=0.427	P=0.133	·	
Logistic regression test	P=0.620	P=0.427	P=0.133		
Cochran-Armitage test	P = 0.626N				
Fisher exact test		P=0.495	P=0.121	<u> </u>	
Clitoral Gland: Adenoma or Carcinoma			· · · · · · · ·		
Overall rate	7/47 (15%)	5/46 (11%)	9/47 (19%)	2/48 (4%)	
Adjusted rate	25.0%	24.7%	27.2%	9.1%	
Terminal rate	6/26 (23%)	4/18 (22%)	6/28 (21%)	2/22 (9%)	
First incidence (days)	631	636	619	733 (T)	
Life table test	P=0.116N	P = 0.625N	P=0.451	P=0.117N	
Logistic regression test	P=0.106N	P=0.534N	P=0.387	P = 0.102N	
Cochran-Armitage test	P=0.099N	···· ,			
Fisher exact test		P=0.395N	P=0.392	P=0.074N	
I MICE CAUVE LODE					
Lesions in Female Rats

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TABLE B3

Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Nitromethane (continued)

			·······	
FISAET EXACT LEST		$\frac{1}{7}$	800.0=4	100.0>4
1251 Serimirage test	100.0>4	7200 d	800 Q* U	100 0 2 4
Fogistic regression test	100.0>4	711.0=4	h = 0.006	100.0>4
ריונה נצטוה נפצו	100.0>4	750.0=4	870'0=d	100.0>4
First incidence (days)	+00 0+ 4 +Ct	432	000 0 4	C7+
I CITINIAL TAIC	(%/C) 87/91	(%85) 61/11	(%5/) 05/77	(%16) 57/17
	(<i>bls</i>) 80/)1	%6't/	% 7 .08	%7.56
	(%7t) 0C/17	(%05) 05/57	(%89) 0C/#F	(%78) 0C/1 7
Maininary Giand: Fibroadenona, Adenona, or C	Carcinoma			
Pro current current condition in the second se				
Fisher exact test		b= 0.262	P=0.181N	P=0.016
Cochran-Armitage test	600.0=q			
Logistic regression test	010.0 = q	9/1.0=q	N691.0=q	810.0 = 9
Life table test	600.0=q	P=0.116	N691.0=4	00.0=q
First incidence (days)	169	885	440	425
Terminal rate	(%11) 87/8	(%12) 61/4	(%0) 0E/O	(%0E) EZ/L
Ajusted Tate	80.61	%E.QL	%0°7	%5.0 4
Overall rate	(%8) 05/7	(%7I) 0S/L	(%2) 05/1	(%97) 05/81
Mammary Gland: Adenoma or Carcinoma				1.
PISDEL EXACT LEST		080.0=4	N005.0=4	P=0.007
1851 Serima S	600°0=4			
rogiance destroy rest	600'0=J	750'0=J	N/##'0=J	110.0=4
דטוני ומטוב ובפו דסמומדוס מסמיסמי לאסל	600.0=4	750.0=4	N684.0=4	000,0=4
	100	000 - u		500 U-a
	(%+) 97/I	(% 17) 61/b	(%0) 05/0	(9677) 5715
Anjma kate	(2017) 80/1	(2010) 01/V	(20) 00/0	(2000) EC/S
Autoria and Autoria	2009 (0(+) 0017	20 2 0 C		20 EE
Mammary Gland: Carcinoma	(2017) 05/2	(20VI) US/L		(2000) 05/11
			00010 -	10010
Fisher exact test		005.0=4	800.0= q	100.0=9
Cochran-Armitage test	T00.0>4			
Logistic regression test	P<0.001	P=0.278	P=0.006	P<0.001
Life table test	100.0>q	101.0 = q	P=0.024	T00.0>4
First incidence (days)	454	432	897	255
Terminal rate	(<i>%LS</i>) 87/91	(%25) 61/01	(%EL) 0E/ZZ	(%28) 52/02
Adjusted rate	%7.19	% S`89	%0.08	%1.26
Overall rate	(%07) 05/02	(%24) 05/12	(%99) OS/EE	(%7L) 0\$/9E
Mammary Gland: Fibroadenoma or Adenoma				· •
Fisher exact test		€1⊅.0=¶	P=0.004	100.0>q
Cochran-Armitage test	100.0> T			
Logistic regression test	P<0.001	P=0.219	b=0.003	100.0>q
דיונה נאסור נפגנ	100.0>4	940°0=d	\$10.0=q	100.0>4
First incidence (days)	424	\$54	897	ZSS
1 emman rate	(%+\$) 87/\$1	(%55) 61/01	(% EL) 0E/77	(%/8) 52/02
	%7°8C	% C'80	%0.08	%1.76
טענומון ומוכ אנווינזפן באיט	(% 85) 0C/KI	(%7+) AC/17	(%00) nc/cc	(%7/) AC/QC
Mammary Gland: Fibroadenoma		(2007) 03/10		
·	· · · · · · · · · · · · · · · · · · ·			·····
	udd o	udd 🏎	udd 881	udd s.s
			- 00 -	

Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Nitromethane (continued) .

	0 ррт	94 ppm	188 ppm	375 ppm
Pancreatic Islats: Adanoma	<u> </u>	· · · · · ·	4	
Overall rate	1/50 (2%)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted rate	3.6%	1/30 (270)	. 3/30 (0%)	A 200
Terminal rate	1/29 (49%)	0/10 (0%)	2/20 (100)	4.3% 1/32 (40)
First incidence (days)	722 (T)	0/19 (0 <i>%</i>)	5/50 (10%) 722 (T)	1/23 (4%) 723 (T)
Life table test	P=0.526	P-0 706	P=0 220	P = 0.718
Longistic regression test	P=0.546	P=0.756N	P = 0.329	P=0.718
Cochran_Armitage test	P=0.555	r0.7501	r =0.349	F=0.718
Fisher exact test	1 -0.555	P=0.753N	P-0 300	P=0.753N
		1-0.7551	1 -0.509	1 -0.75514
Pancreatic Islets: Adenoma or Carcino	na			
Overall rate	1/50 (2%)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted rate	3.6%	4.6%	10.0%	4.3%
Terminal rate	1/28 (4%)	0/19 (0%)	3/30 (10%)	1/23 (4%)
First incidence (days)	733 (T)	488	733 (T)	733 (T)
Life table test	P = 0.596N	P = 0.440	P=0.329	P=0.718
Logistic regression test	P=0.579N	P=0.604	P=0.329	P=0.718
Cochran-Armitage test	P=0.578N			
Fisher exact test		P = 0.500	P=0.309	P=0.753N
Pituitary Gland (Pars Distalis): Adenon	12		·. ·	
Overall rate	33/50 (66%)	36/50 (72%)	39/50 (78%)	40/50 (80%)
Adjusted rate	74.2%	91.8%	88.5%	88.5%
Terminal rate	17/28 (61%)	16/19 (84%)	25/30 (83%)	18/23 (78%)
First incidence (days)	454	488	468	425
Life table test	P = 0.104	P=0.044	P=0.286	P=0.062
Logistic regression test	P=0.056	P=0.262	P = 0.126	P=0.094
Cochran-Armitage test	P=0.063			
Fisher exact test		P=0.333	P=0.133	P=0.088
Pituitary Gland (Pars Distalis): Adenon	na or Carcinoma			
Overall rate	33/50 (66%)	36/50 (72%)	40/50 (80%)	40/50 (80%)
Adjusted rate	74.2%	91.8%	90.8%	88.5%
Terminal rate	17/28 (61%)	16/19 (84%)	26/30 (87%)	18/23 (78%)
First incidence (days)	454	488	468	425
Life table test	P = 0.100	P=0.044	P=0.236	P=0.062
Logistic regression test	P=0.051	P=0.262	P = 0.082	P=0.094
Cochran-Armitage test	P=0.059		· •	
Fisher exact test	· · · · · ·	P=0.333	P=0.088	P=0.088
Skin (Subautaneous Tissue), Fibroma	Fibrasarcoma or Sarcoma			• •
Overall rate	- 1/50 (2%)	3/50 (6%)	0/50 (0%)	3/50 (6%)
Adjusted rate	1/30 (270) 2 0 02	11 5%	0.0%	10.0%
Trajusica late		1/10/5%	0/30 (0%)	1/23 (4%)
First incidence (days)	691	579		387
Life table test	P=0.306	P = 0.221	P=0.500N	P=0.256
Logistic regression test	P=0.300	P=0.221	P=0.501N	P = 0.339
Cochran-Armitage test	P=0.325			
Fisher exact test		P=0.309	P=0.500N	P=0.309

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Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Nitromethane (continued)

	×	0 ppm	94 ppm	188 ppm	375 ppm	
Thyroid Clond (C coll):		<u></u>	<u> </u>		<u> </u>	
Overall rate	Adenoma	9/50 (1607)	0/50 (1907)	9/50 (1601)	10/40 (20.07)	
Adjusted rote		0/JU (10%)	9/30 (16%)	0/30 (10%) 24.50	10/49 (20%)	
Terminal rate		23.3% 6/38 (31%)	55.670 A/10 (21 0%)	24.3% 6/20 (20%)	54.270	
First incidence (days)		600	4/19 (21%)	0/30 (20 <i>%</i>) 657	5742 (25%)	
I ife table test		P-0 304	D-0 252	0.57 P=0.557N	D-0 260	
Life table test		P-0.304	P = 0.232 P = 0.300	P = 0.557 N	P = 0.200 P = 0.320	
Cochran-Armitage test		P = 0.322	1 -0.555	1 -0.006	r = 0.320	
Fisher exact test		1 - 0.540	P=0.500	P=0.607N	P=0.379	
Thyroid Gland (C-cell):	Carcinoma					
Overall rate		2/50 (4%)	0/50 (0%)	0/50 (0%)	3/49 (6%)	
Adjusted rate		7.1%	0.0%	0.0%	11.8%	
Terminal rate		2/28 (7%)	0/19 (0%)	0/30 (0%)	2/22 (9%)	
First incidence (days)		733 (T)			660	
Life table test		P = 0.220	P=0.327N	P=0.223N	P=0.410	
Logistic regression test		P = 0.225	P = 0.327N	P = 0.223N	P = 0.434	
Cochran-Armitage test		P = 0.240			1 00.001	
Fisher exact test			P=0.247N	P=0.247N	P=0.490	
Thyroid Gland (C-cell):	Adenoma or Carcinoma					
Overall rate		10/50 (20%)	9/50 (18%)	8/50 (16%)	12/49 (24%)	
Adjusted rate		32.1%	33.8%	24.5%	42.0%	
Terminal rate		8/28 (29%)	4/19 (21%)	6/30 (20%)	7/22 (32%)	
First incidence (days)		600	561	657	634	
Life table test		P=0.260	P=0.406	P=0.345N	P=0.235	
Logistic regression test		P=0.278	P=0.581	P=0.394N	P=0.301	
Cochran-Armitage test		P=0.306	*	•		
Fisher exact test			P=0.500N	P=0.398N	P=0.384	
Uterus: Stromal Polyp						
Overall rate		6/50 (12%)	11/50 (22%)	6/50 (12%)	6/50 (12%)	
Adjusted rate		19.8%	37.6%	18.3%	22.7%	
Terminal rate		4/28 (14%)	4/19 (21%)	5/30 (17%)	4/23 (17%)	
First incidence (days)		713	428	432	651	
Life table test		P=0.409N	P=0.049	P=0.585N	P=0.485	
Logistic regression test		P=0.362N	P=0.112	P=0.619	P=0.530	
Cochran-Armitage test		P=0.354N				
Fisher exact test			P=0.143	P=0.620N	P=0.620N	
Uterus: Stromal Polyp	or Stromal Sarcoma			,		
Overall rate	•	6/50 (12%)	12/50 (24%)	6/50 (12%)	6/50 (12%)	
Adjusted rate		19.8%	38.9%	18.3%	22.7%	
Terminal rate	·	4/28 (14%)	4/19 (21%)	5/30 (17%)	4/23 (17%)	
First incidence (days)		713	428	432	651	
Life table test		P = 0.374N	P=0.032	P=0.585N	P=0.485	
Logistic regression test		P=0.298N	P = 0.090	P=0.619	P=0.530	
Cochran-Armitage test		P=0.320N				
Fisher exact test			P=0.096	P=0.620N	P=0.620N	

Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Nitromethane (continued)

	0 ppm	94 ppm	188 ppm	375 ppm
All Organs: Mononuclear Cell Leukemia		<u> </u>		
Overall rate	22/50 (44%)	13/50 (26%)	14/50 (28%)	9/50 (18%)
Adjusted rate	52.5%	38.1%	37.6%	27.2%
Terminal rate	9/28 (32%)	3/19 (16%)	8/30 (27%)	3/23 (13%)
First incidence (days)	519	428	512	597
Life table test	P = 0.020N	P=0.268N	P=0.089N	P=0.030N
Logistic regression test	P = 0.005N	P=0.033N	P = 0.124N	P = 0.001N
Cochran-Armitage test	P = 0.007N			
Fisher exact test		P=0.046N	P=0.072N	P=0.004N
All Organs: Benign Neoplasms				
Overall rate	44/50 (88%)	47/50 (94%)	48/50 (96%)	49/50 (98%)
Adjusted rate	97.7%	100.0%	100.0%	100.0%
Terminal rate	27/28 (96%)	19/19 (100%)	30/30 (100%)	23/23 (100%)
First incidence (days)	454	428	432	425
Life table test	P=0.162	P=0.015	P=0.425	P=0.058
Logistic regression test	P=0.021	P = 0.161	P=0.094	P=0.036
Cochran-Armitage test	P=0.035			
Fisher exact test		P=0.243	P=0.134	P=0.056
All Organs: Malignant Neoplasms				
Overall rate	28/50 (56%)	21/50 (42%)	20/50 (40%)	27/50 (54%)
Adjusted rate	63.0%	56.5%	49.8%	65.0%
Terminal rate	12/28 (43%)	6/19 (32%)	11/30 (37%)	10/23 (43%)
First incidence (days)	519	428	432	387
Life table test	P=0.435	P=0.518N	P=0.108N	P=0.412
Logistic regression test	P=0.513	P=0.086N	P=0.078N	P=0.455N
Cochran-Armitage test	P=0.501			
Fisher exact test	· .	P=0.115N	P=0.080N	P=0.500N
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/50 (98%)	50/50 (100%)	50/50 (100%)	50/50 (100%)
Adjusted rate	98.0%	100.0%	100.0%	100.0%
Terminal rate	27/28 (96%)	19/19 (100%)	30/30 (100%)	23/23 (100%)
First incidence (days)	454	428	432	387
Life table test	P=0.347	P=0.034	P=0.513N	P=0.170
Logistic regression test	P=0.313	P=0.577	P=0.486	P=0.539
Cochran-Armitage test	P=0.304			
Fisher exact test		P = 0.500	P = 0.500	P = 0.500

(T)Terminal sacrifice

^a Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, clitoral gland, pancreatic islets, pituitary gland, thyroid gland, and uterus; for other tissues, denominator is number of animals necropsied.

^b Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

^c Observed incidence at terminal kill

^d Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table test regards neoplasms 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. For all tests, a negative trend or a lower incidence in an exposure group is indicated by N.

^e Not applicable; no neoplasms in animal group

Historical Incidence of Mammary Gland Neoplasms in Chamber Control Female F344/N Rats^a

	Incidence in Controls						
Study	Fibroadenoma	Adenoma	Carcinoma	Fibroadenoma, Adenoma, or Carcinoma			
Historical Incidence at Battelle	Pacific Northwest Lab	ooratories		· · · · · · · · · · · · · · · · · · ·			
o-Chlorobenzalmalononitrile (CS2)	16/50	0/50	1/50	17/50			
Acetonitrile	16/48	0/48	2/48	17/48			
2-Chloroacetophenone	12/50	0/50	2/50	13/50			
<i>l</i> -Epinephrine Hydrochloride	10/50	0/50	2/50	11/50			
Chloroethane	11/50	2/50	0/50	13/50			
Hexachlorocyclopentadiene	12/50	0/50	3/50	14/50			
Ozone	20/50	1/50	4/50	23/50			
Total	97/348 (27,9%)	3/348 (0.9%)	14/348 (4.0%)	108/348 (31.0%)			
Standard deviation	7.3%	1.6%	2.6%	8.1%			
Range	20%-40%	0%-4%	0%-8%	22%-46%			
Overall Historical Incidence							
Total	180/653 (27.6%)	8/653 (1.2%)	25/653 (3.8%)	202/653 (30.9%)			
Standard deviation	7.7%	1.5%	2.7%	9.1%			
Range	16%-42%	0%-4%	0%-8%	16%-46%			

^a Data as of 12 May 1995

Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Nitromethane^a

	0 ppm	94 ppm	188 ppm	375 ppm
				<u> </u>
Disposition Summary			50	<u> </u>
Animals initially in study	50	50	50	50,
Early deaths	17	27	10	25
Monbund Natural de attac	1/	20	18	25
Natural deadis	3	5	, 2	· 2
Terminal sacrifice	28	19	30	23
		••		
Animals examined microscopically	50	50	50	50
Alimentary System				· · · · · · · · · · · · · · · · · · ·
Liver	(50)	(50)	(50)	(50)
Angiectasis	2 (4%)	1 (2%)	4 (8%)	5 (10%)
Basophilic focus	41 (82%)	42 (84%)	41 (82%)	41 (82%)
Clear cell focus	6 (12%)	9 (18%)	9 (18%)	7 (14%)
Degeneration, cystic	1 (2%)		1 (2%)	
Degeneration, fatty	9 (18%)	7 (14%)	8 (16%)	5 (10%)
Eosinophilic focus	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Hepatodiaphragmatic nodule	7 (14%)	4 (8%)	3 (6%)	5 (10%)
Inflammation, granulomatous	1 (2%)			1 (2%)
Mixed cell focus	12 (24%)	15 (30%)	11 (22%)	17 (34%)
Necrosis	1 (2%)			1 (2%)
Regeneration	2 (4%)		· · ·	
Bile duct, hyperplasia	10 (20%)	7 (14%)	12 (24%)	9 (18%)
Centrilobular, necrosis	1 (2%)			· · · · ·
Mesentery	(10)	(11)	(12)	(14)
Fat, necrosis	7 (70%)	10 (91%)	10 (83%)	11 (79%)
Pancreas	(50)	(50)	(50)	(50)
Atrophy	20 (40%)	15 (30%)	20 (40%)	24 (48%)
Basophilic focus	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Hyperplasia .	1 (2%)		`	1 (2%)
Metaplasia, hepatocyte		1 (2%)		• • • • • •
Artery, inflammation	• 1 (2%)			1 (2%)
Salivary glands	(50)	(50)	(50)	(50)
Atrophy	1 (2%)	1 (2%)	1 (2%)	
Basophilic focus		. 2 (4%)		·
Stomach, forestomach	(50)	. (50)	(50)	(50)
Diverticulum			1 (2%)	
Hyperplasia, squamous			1 (2%)	1 /0 M X
Inflammation, acute	2 (4%)	1 (2%)	4 (8%)	1 (2%)
Mineralization	بالمحاجد و	- 17 M	E (100)	1 (2%)
Necrosis	4 (8%)	3 (6%)	5 (10%)	0 (12%)
Stomach, glandular	(50)	(50)	(50)	(50)
Inflammation, acute	4 mm m	1. (0.01)	1 (2%)	1 (20)
Mineralization	1 (2%)	1°(2%)	1 (2%)	1 (270) 7 (AQL)
Necrosis	2 (4%)	1 (2%)	1 (270)	2 (+70)
(D) +1				

^a Number of animals examined microscopically at the site and the number of animals with lesion

Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Nitromethane (continued)

	0 ppm	94 ppm	188 ppm	375 ppm
Cardiovascular System	······	- <u></u>	······	
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	42 (84%)	31 (62%)	34 (68%)	39 (78%)
Artery, mineralization		1 (2%)		
Atrium, thrombosis				1 (2%)
Endocrine System			<u></u> .	
Adrenal cortex	(50)	(50)	(50)	(50)
Angiectasis				1 (2%)
Hematopoietic cell proliferation		1 (2%)		. ,
Hyperplasia	6 (12%)	15 (30%)	12 (24%)	13 (26%)
Hypertrophy	16 (32%)	12 (24%)	14 (28%)	12 (24%)
Necrosis				1 (2%)
Vacuolization cytoplasmic		1 (2%)		2 (4%)
Adrenal medulla	(49)	(50)	(49)	(50)
Hyperplasia	3 (6%)	4 (8%)	9 (18%)	8 (16%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia	2 (4%)			
Parathyroid gland	(50)	(49)	(50)	(48)
Hyperplasia	1 (2%)	1 (2%)		(50)
Pituitary gland	(50)	(50)	(50)	(50)
Hyperplasia	1 (0.01)	1 (2%)		
Pars distalls, anglectasis	1 (2%)	9 (1607)	0 (1907)	0 (19%)
Thuroid gland	13 (20%)	8 (10%)	9 (10%)	9 (18%)
C-cell, hyperplasia	41 (82%)	(30) 47 (94%)	(50) 49 (98%)	42 (86%)
General Body System None		<u> </u>		
Genital System	<u></u>			. <u>16</u> 99 <u>-</u> 1 <i>49</i> 7, , 1797,
Clitoral gland	(47)	(46)	(47)	(48)
Hyperplasia	х.			1 (2%)
Inflammation, chronic active	4 (9%)	6 (13%)	4 (9%)	2 (4%)
Ovary	(50)	(50)	(50)	(50)
Cyst	1 (2%)	2 (4%)	5 (10%)	3 (6%)
Inflammation, granulomatous			1 (2%)	
Uterus	(50)	(50)	(50)	(50)
Cyst	1 (2%)			
Hydrometra			1 (2%)	
Hyperplasia	1 (2%)			

Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Nitromethane (continued)

	0 ppm	94	ppm	188	ppm	375	5 ppm	
Hematopoietic System								
Bone marrow	(50)	(50)		(50)		(50)		
Hyperplasia, reticulum cell	1 (2%)	2	(4%)	. 1	(2%)	2	(4%)	
Lymph node	(7)	(6)		(9)		(3)		
Iliac, pigmentation	1 (14%)					1	(33%)	
Pancreatic, hemorrhage		1	(17%)	1	(11%)			
Pancreatic, infiltration cellular, eosinophil						1	(33%)	
Pancreatic, inflammation, granulomatous						1	(33%)	
Renal, hemorrhage	1 (14%)			· 1	(11%)	1	(33%)	
Renal, pigmentation				1	(11%)			
Lymph node, bronchial	(48)	(49)		(47)		(48)		·
Infiltration cellular, eosinophil						1	(2%)	
Inflammation, granulomatous						1	(2%)	
Lymph node, mandibular	(49)	(48)		(48)		(47)		
Hemorrhage					, ·	. 1	(2%)	
Infiltration cellular, plasma cell			•	2	(4%)	1	(2%)	
Lymph node, mesenteric	(50)	. (50)		(49)		(50)		
Hemorrhage	1 (2%)	1	(2%)			. 1	(2%)	
Infiltration cellular, eosinophil						1	(2%)	
Inflammation, granulomatous						1	(2%)	
Lymph node, mediastinal	(48)	(49)		(50)		·(46)		
Hemorrhage	1 (2%)	3	(6%)	. 1	(2%)	2	(4%)	
Inflammation, granulomatous		1	(2%)					
Spleen	(50)	(49)		(50)	(0.01)	(50)	(0.01)	
Fibrosis	2 (4%)	1	(2%)	4	(8%)	1	(2%)	
Hematopoietic cell proliferation		. 3	(6%)			2	(4%)	
Thrombosis	1 (2%)	1	(2%)					
Integumentary System								
Mammary gland	(50)	(50)		(50)		(50)	•	
Galactocele	3 (6%)	1	(2%)	3	(6%)	. 7	(14%)	
Hyperplasia	• •			1	(2%)			
Hyperplasia, atypical	12 (24%)	17	(34%)	14	(28%)	15	(30%)	
Hyperplasia, lobular						2	(4%)	· · · .
Inflammation, granulomatous		1	(2%)					
Inflammation, suppurative		1	(2%)	1	(2%)			
Skin	(50)	(50)		(48)		. (49)) . ·	
Hyperkeratosis		1	(2%)					
Inflammation, acute	1 (2%)							
Inflammation, chronic active	1 (2%)	2	(4%)			1	(2%)	
Inflammation, granulomatous		1	(2%)	•	•			
Sebaceous gland, hypertrophy		. 1	(2%)	· .				
Vulva, inflammation, acute				1	(2%)			
Musculoskolatal System			<u> </u>				ĩ	
Rone	(50)	(50)		(50)	• • •	(50)) •	
Fibrous osteodystrophy	(50)	(50)	(2%)	(50)			•	
Hyperostosis	3 (6%)	1	(2%)			1	(2%)	
Cranium hyperostorie	, 5 (670)		()	1	(2%)	-		-
Femur hyperostosis				1	(2%)			
zomar, ny porosiosis								

Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Nitromethane (continued)

· · · ·	0 ppm	94 ppm	188 ppm	375 ppm
Nervous System		· · · ·		······································
Brain	(50)	(50)	(50)	(50)
Hemorrhage	1 (2%)	2 (4%)		1 (2%)
Hydrocephalus	1 (2%)	1 (2%)	1 (2%)	
Respiratory System				
Larynx	(50)	(50)	(50)	(49)
Metaplasia, squamous	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Lung	(50)	(50)	(50)	(50)
Congestion			1 (2%)	
Fibrosis, focal		1 (2%)		•
Fibrosis, multifocal				1 (2%)
Hemorrhage		1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic active	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Mineralization		1 (2%)		
Alveolar epithelium, hyperplasia	6 (12%)	11 (22%)	7 (14%)	7 (14%)
Artery, mediastinum, inflammation		1		1 (2%)
Artery, mediastinum, mineralization		1 (2%)		
Bronchiole, hyperplasia		1 (2%)		
Bronchiole, metaplasia				1 (2%)
Nose	(50)	(50)	(50)	(50)
Inflammation, chronic active		3 (6%)	2 (4%)	
Inflammation, suppurative	4 (8%)	2 (4%)		1 (2 (1))
Thrombosis		1 (2%)		1 (2%)
Nasolacrimal duct, inflammation,	E (100)	A (D.M.)	6 (12 0)	2 (19)
	5 (10%)	4 (8%)	6 (12%)	2 (470)
Special Senses System				•
Еуе	(2)	(1)	(2)	(4)
Cataract	1 (50%)		1 (50%)	3 (75%)
Degeneration	1 (50%)	1 (100%)		1 (25%)
Retina, atrophy				1 (25%)
Harderian gland	(3)			
Hemorrhage	1 (33%)			
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Infarct	1 (2%)			1 (2%)
Mineralization	• •	1 (2%)		
Nephropathy	49 (98%)	49 (98%)	48 (96%)	49 (98%)
Renal tubule, hyperplasia		1 (2%)		1 (2%)
Urinary bladder	(50)	(50)	(49)	(50)
Transitional epithelium, hyperplasia	1 (2%)			

APPENDIX C SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR INHALATION STUDY OF NITROMETHANE

TABLE C1	Summary of the Incidence of Neoplasms in Male Mice	
	in the 2-Year Inhalation Study of Nitromethane	153
TABLE C2	Individual Animal Tumor Pathology of Male Mice	
	in the 2-Year Inhalation Study of Nitromethane	156
TABLE C3	Statistical Analysis of Primary Neoplasms in Male Mice	
	in the 2-Year Inhalation Study of Nitromethane	176
TABLE C4a	Historical Incidence of Harderian Gland Neoplasms	
	in Chamber Control Male B6C3F ₁ Mice	180
TABLE C4b	Historical Incidence of Alveolar/bronchiolar Neoplasms	
	in Chamber Control Male B6C3F ₁ Mice	181
TABLE C5	Summary of the Incidence of Nonneoplastic Lesions in Male Mice	
	in the 2-Year Inhalation Study of Nitromethane	182

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Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Nitromethane^a

	0 ppm	188 ppm	375 ppm	750 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths	14	11	16	. 16
Moribund Natural deaths	14	11	10	5
Survivors	5	. 3	4	5
Terminal sacrifice	31	36	30	29
		••		
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine small, jejunum	(45)	(49)	(47)	(46)
Intestine small, ileum	(46)	(48)	(46)	(45)
Liver	(50)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)	2 (4%)	2 (4%)	•
Hepatocellular carcinoma	11 (22%)	12 (24%)	8 (16%)	6 (12%)
Hepatocellular carcinoma, multiple	5 (10%)	2 (4%)	2 (4%)	3 (6%)
Hepatocellular adenoma	10 (20%)	10 (20%)	12 (24%)	11 (22%)
Hepatocellular adenoma, multiple	7 (14%)	4 (8%)	1 (2%)	6 (12%)
Hepatocholangiocarcinoma, multiple	1 (2%)			
Histiocytic sarcoma			3 (6%)	
Squamous cell carcinoma, metastatic,				
stomach, forestomach		1 (2%)		
Mesentery	(3)		(6)	(2)
Fat, histiocytic sarcoma	(40)	(60)	2 (33%)	(10)
Pancreas	(49)	(50)	(49)	(49)
Adenoma Visticautia saraama		1 (270)	2 (19%)	
Saliyany glands	(50)	(40)	(50)	(49)
Stomach forestomach	(30)	(50)	(50)	(48)
Histiocytic sarcoma	(+))	(50)	1 (2%)	(40)
Squamous cell carcinoma		1 (2%)	- (-//)	
Squamous cell papilloma		1(2%)		1 (2%)
Stomach, glandular	(48)	(48)	(48)	(48)
Histiocytic sarcoma			1 (2%)	
Cardiovascular System				······································
Heart	(50)	(50)	(50)	(50)
Hepatocellular carcinoma, metastatic, live	er 1 (2%)			
Endocrine System				
Adrenal cortex	(49)	(50)	(49)	(48)
Adenoma				2 (4%)
Bilateral, capsule, adenoma			1 (2%)	
Capsule, adenoma	5 (10%)	1 (2%)	1 (2%)	3 (6%)
Adrenal medulla	(49)	(50)	(49)	(47)
Pheochromocytoma complex			1 (2%)	
Pheochromocytoma benign	(10)	(50)	(40)	1 (2%)
Islets, pancreatic	(49)	(SU)	(49)	(4 9) 1 (2 ⁹⁶)
Adenoma	1 (2%)	3 (0%)		1 (270)

Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Nitromethane (continued)

	0 ppm	188 ppm	375 ppm	750 ppm
Endocrine System (continued) Pituitary gland Pars distalis, adenoma	(47) 1 (2%)	(50)	(46)	(47)
Pars intermedia, adenoma Thyroid gland Follicular cell, adenoma Follicular cell, carcinoma	(50) 1 (2%)	(50) 1 (2%)	1 (2%) (49)	(48) 1 (2%)
General Body System None				
Genital System Epididymis	(50)	(50)	(50)	(49)
Histiocytic sarcoma Prostate Histiocytic sarcoma Seminal vesicle	2 (4%) (49) (49)	(50) (49)	(47) 1 (2%) (49)	(46) (47)
Histiocytic sarcoma Testes Interstitial cell, adenoma	(50) 2 (4%)	(50) 1 (2%)	1 (2%) (50) 1 (2%)	(50) 1 (2%)
Hematopoietic System Bone marrow Hemangiosarcoma	(49) 1 (2%)	(50) 2 (4%)	(50)	(50)
Lymph node Lymph node, bronchial Histiocytic sarcoma	(3) (26)	(1) (26)	(1) (24) 1 (4%)	(2) (28)
Lymph node, mandibular Lymph node, mesenteric Histiocytic sarcoma Lymph node, mediastinal	(40) (47)	(39) (46) (37)	(37) (47) 2 (4%) (36)	(43) (49) 1 (2%) (40)
Histiocytic sarcoma Spleen Hemangiosarcoma	(49) 1 (2%)	(50) 1 (2%)	(50) 1 (3%) (50) 1 (2%)	(49)
Histiocytic sarcoma Thymus	(33)	(34)	1 (2%) (33)	1 (2%) (40)
Integumentary System Skin Prepuce, histiocytic sarcoma Subautanaaus tisaus, harangiosaraama	(49) 1 (2%)	(49)	(49) 1 (2 <i>∞</i>)	(48)
Subcutaneous tissue, histiocytic sarcoma	2 (4%)		I (270)	
Musculoskeletal System				

Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Nitromethane (continued)

	0 ppm	188 ppm	375 ppm	750 ppm	
Nervous System			· · · · · · · · · · · · · · · · · · ·		
Brain Carcinoma, metastatic, harderian gland	(50)	(50)	(50) 1 (2%)	(49)	
	······································		Name and a second s		
Respiratory System	(50)	(50)		(70)	
	(50)	(50)	(50)	(50)	
Alveolar/bronchiolar adenoma	9 (18%)	10 (20%)	8 (10%) 1 (20%)	11 (22%)	
Alveolar/bronchiolar adenoma, multiple	2 (470)	2 (6%)	1 (2%)	1 (2%)	
Alveolar/bronchiolar carcinoma	2 (470)	3 (0%)	3 (0%)	10(20%)	
Carcinoma metastatic harderian gland			1 (2%)	1(2%)	
Henstocellular carcinoma metastatia liver	6 (12%)	1 (79%)	1 (270) A (89%)	2(4%)	
Histocytic sarcoma	0 (12%)	1 (2%)	4 (0 <i>%)</i> 1 (7%)	2 (4%)	
Mediastinum histiocytic sarcoma			1(2%)		
Nose	(50)	(49)	(50)	(50)	
Carcinoma, metastatic, harderian gland	(00)	(47)	1 (2%)	1 (2%)	
		<u>,</u>	<u></u>		
Special Senses System					
Harderian gland	(49)	(50)	(50)	(49)	
Adenoma	9 (18%)	6 (12%)	18 (36%)	25 (51%)	
Adenoma, multiple		4 (8%)	1 (2%)	7 (14%)	
Carcinoma, multiple	I (2%)	1 (2%)	6 (12%)	4 (8%) 1 (2%)	
Ilrinary System			· · · · · · · · · · · · · · · · · · ·		
Kidney	(50)	(50)	(40)	(49)	
Renal tubule adenoma	(50)	(50)	1 (2%)	(4))	
Urinary bladder	(48)	(50)	(49)	(48)	
	<u> </u>		·····		
Systemic Lesions	(50)	(50)	(50)	(50)	
Histiocytic sarcoma	(30)	(50)	(50)	(50)	
Lymphoma malignant	3 (6%)	4 (8%)	2 (4%)	1 (2%)	
Neepleen Summers	<u> </u>	<u> </u>	· · · · · · · · · · · · · · · · · · ·		
Total animals with primary neoplasms ^C	40	20	10	AC	
Total primary neoplasms	40	70	43 75	40 02	
Total animals with benign neonlasms	31	21	22	<u>4</u> 3	
Total benign neoplasms	47	41	46	71	
Total animals with malignant neoplasms	22	25	24	22	
Total malignant neoplasms	29	29	29	27	
Total animals with metastatic neoplasms	6	2	5	4	
Total materials as an large	-	_	-	-	

^a Number of animals examined microscopically at the site and the number of animals with neoplasm

^b Number of animals with any tissue examined microscopically

^c Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE C2

Individual Animal Tumor Patholog	y of l	Mal	e I	Mic	e i	in t	he	2-	Ye	ar	In	ha	lat	ion	St	ud	y c	of l	Nit	roi	net	ha	ne	: () p	pm	L		
Number of Days on Study		4 4 1	4 4 9	4 9 0	5 0 3	5 0 3	5 3 4	5 4 5	5 7 6	5 8 1	6 0 9	6 2 3	6 5 3	6 5 3	6 5 3	6 5 3	6 6 5	7 0 1	7 1 4	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4			
Carcass ID Number		0 1 3	0 4 2	0 3 1	0 1 8	0 2 4	0 1 0	0 1 5	0 3 3	0 4 7	0 3 6	0 4 6	0 0 2	0. 1 2	0 3 9	0 4 8	0 4 5	0 4 1	0 1 9	0 2 3	0 0 1	0 0 8	0 0 9	0 2 0	0 2 7	0 2 9			
Alimentary System														-															
Esophagus		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Gallbladder		+	+	Å	+	+	+	A	М	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+			
Intestine large, colon		+	+	Α	+	+	+	+	+	+	Α	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	+			
Intestine large, rectum		+	+	Α	+	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	`+	+	М	÷	+	+	+			
Intestine large, cecum		+	+	Α	+	+	+	+	+.	+	Α	+	+	Á	+	+	+	+	Α	+	+	+	+	+	+	+			
Intestine small, duodenum		+	+	A	+	+	+	Α	+	+	Μ	(+	+	Α	+	+	+	+	Μ	+	+	.+	+	+	+	+			
Intestine small, jejunum		+	+	Α	+	+	+	Α	+	+	Α	+	+	Α	+	+	+	+	Α	+	.+	+	+	+	+	+			
Intestine small, ileum		+	+	Α	+	+	+	Α	+	+	Α	+	+	+	<u>,</u> +	+	+	+	Α	+	+	+	+	+	+	+			
Liver		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Hemangiosarcoma																					х								
Hepatocellular carcinoma		X			х		х			х	х	Х			Х							-							
Hepatocellular carcinoma, multiple						Х			х				Х			X													
Hepatocellular adenoma			х	Х			х							Х												. X			
Hepatocellular adenoma, multiple								х										•		х									
Hepatocholangiocarcinoma, multiple																								-					· · .
Mesentery								+																					
Pancreas		+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Salivary glands		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Stomach, forestomach		+	+	Α	+	+	+	+	+	+	+	+	+	+	+	· +	+	+	+	+	+	+	.+	+	+	+			
Stomach, glandular		.+	+	Α	+	+	+	+	+	+	Α	+	+	+	+	+	. +	+	+	+	+	+	+	+	+	+			
Tooth				•							+	,					_												
Cardiovascular System									•													•							
Heart	· · .	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Hepatocellular carcinoma, metastatic,																													
liver					х											÷.,												·.	
Endocrine System		_	1																										
Adrenal cortex		+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Capsule, adenoma																										х			
Adrenal medulla		+	+	A	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Islets, pancreatic		+	+	A	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	.+	+	+	+	+	.+	+	+			
Adenoma							Х																			÷.			
Parathyroid gland	۰. ۱	+	+	+	+	+	Μ	+	+	+	+	• +	+	+	+	+	+	Μ	+	Μ	+	+	+	M	+	+			
Pituitary gland	· ·	+	+	+	+	+	+	+	+	+	+	+	· +	• +	+	+	+	+	+	Μ	+	+	+	+	+	+			
Pars distalis, adenoma			,								х																		
Thyroid gland		+	+	+	+	+	+	+	+	. +	+	• ;+	• +	• +	+	-+	+	+	+	+	+	+	+	+	+	+			
Follicular cell, adenoma																								X		• •			
General Body System				-																									
None																													

+: Tissue examined microscopically

A: Autolysis precludes examination

M: Missing tissue I: Insufficient tissue X: Lesion present Blank: Not examined

	7	7	7	7	7	1 7	' 7	1 7	17	' 7		7 7	7 3	7	7	7	7	7	7	7	7	7	7	7	7	7	-
Number of Days on Study	3	3	3	3	3	3	3	3 3	3 3	3		3 3	3 3	3	3	3	3	3	3	3	3	3	3	3	3	3	•
	4	4	4	4	. 4	1 5	5 5	5 5	5.5	5 5	5 4	5 5	5 :	5	5	5	6	6	6	6	6	6	6	7	7	7	
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		3		4). / 					. 0	2 	/	9	4		1	4	1	4	3		<u> </u>	0	
Alimentary System	м			ı																		•	,				49
Callbladdar	IVI	T 1		г - л		+ ·	т : 	+ ·	+ - 	г : 1	т ·	+ ·	τ Γ	T	1	T	Ŧ	+		т 	- T	- -	- T	+		· •	40
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Intestine large, colon		T L			г [.]	т : -	т : _	т ·	т : 15	т : 	г . 1	T '	+ -	т _	T	+	Ť	Ť	- -	т 	Tr L	+		T L	т 	. <u> </u>	40
Intestine large, rectum	+		• -		- ·	+ ·	τ·	τ·	+ ·	+ ·	+ ·	+ ·	+	т	+	+	Ţ	+	+	т ,	+	+		+	· •	· -	H/
Intestine large, cecum	+	-1	• •		+ ·	+ ·	+ ·	+ ·	+	+ ·	+ '	+	+	+	+	+	+	+	+	+	+	+	+	+	· +	• +	40
Intestine small, duodenum	+	+			، ۲	+ ·	τ·	+ I	vi -		т. 1	+	Ť	+	+	+	+ ,	+	+	+	+	+	+	+	· +	· +	· 44 15
Intestine small, jejunum	+	4		г - L	г ·	+ ·	т [.] 1	+ •	+ - 1	т ·	т : 1	+	+	T	+	+	+	+	+	+	+	+	+	+	+	+	4J 16
Intestine small, lieum	+	-1			+ ·	+ ·	+ ·	+ ·	+ •	+ •	+ ·	+	+	+	+	+	+	+	+	+	+	+	+	+	· +	• +	40
Liver	+	1		•••	+ ·	+	+	+	+ •	+ .	+	÷	÷	Ŧ	+	Ŧ	Ŧ	+	+	+	+	+	+	+	· +	• +	50
Hemangiosarcoma				,														v		v					v		÷ 1 11
Hepatocenular carcinoma			2	•									v					л		л					л		11 5 ·
Hepatocellular carcinoma, multiple													л. v			v		v	v					v	,		10
Hepatocenular adenoma	v	v								~		•	л			л		л	Λ	v	v			~			10
Hepatocenular adenoma, multiple	А	- 2	•						v ⁴	^										Λ	л						1
Hepatocholanglocarcinoma, multiple									A																		1
Develop		1	-							.						,											40
Pancreas	+	1		+ -	+ ·	+	+	+ ·	+ ·	+ '	+	+	+	+	+	+	+	+	+	+	+	+	+	-	· +	· T	49
Salivary glands	+	1		+ ·	+	+	+	+ '	+ •	+ '	+	Ť	+	+	-	+	- -	+	+	т ,	+	- T			· T		. 40
Stomacn, torestomacn	+	-		+ •	+	+	+	+ ·	+ •	+ .	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	• •	• +	49
Stomach, glandular	+	1	• •	+ ·	+	+	Ŧ	+	+ ·	+	+	+	+	+	+	+	Ŧ	Ŧ	+	+	+	+	Ŧ	+	• +	- +	48
100th	· · · · · · · · · · · · · · · · · · ·			+										<u>.</u>						+	,						ر
Cardiovascular System																											50
	+			+	Ŧ	+	+	+	+	+	+	+	+	+	Ŧ	+	Ŧ.	+	+	Ŧ	+	+	+	. 1	• •	- T	50
liver																											1
Endocrine System																											
Adrenal cortex	+		+ -	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	- +	49
Capsule, adenoma			2	x :	X				х			х															5
Adrenal medulla	+		۰ ۲	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	· +	+	+	• +	• -1		+ +	49
Islets, pancreatic	+		⊦ •	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +			- +	49
Adenoma																											1
Parathyroid gland	+		F ·	+	+	+	+	+	М	+	+	М	М	+	+	+	+	+	+	+	+	+	• +	N	1 -	H M	i 41
Pituitary gland	+	·I		+	+	+	+	+	+	+	М	+	+	+	+	+	+	+	+	+	+	+	• +	• -1	⊢ -	+ +	47
Pars distalis, adenoma	-	-																							÷.,		1
Thyroid gland	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +		+ -	+ +	50
Follicular cell, adenoma	•								-	-	-						ĺ.										1

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Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nitromethane: 0 ppm (continued) 4 4 4 5 5 5 5 5 566666667 7 7 .7 7 7 7 7 7 Number of Days on Study 4 900 3 4 7 8 0 2 5 5 5 5 6 0 4 1 3 3 3 3 3 .3 3 9 0 3 3 4 5 6 19 3 3 3 3 3 5 1 1 4 1 4 4 4 4 4 4 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 **Carcass ID Number** 1 4 3 1 2 1 1 3 4 3 4 0 1 3 4 4 4 1 2 0 0 0 2 2 2 3 7 6 6 2 2 9 8 93189079 3 2 1 8 4 0 5 5 1 **Genital System** Epididymis Histiocytic sarcoma Penis Preputial gland Μ + + + + + + Prostate + + + Seminal vesicle + + + ++ + Testes Interstitial cell, adenoma Hematopoietic System Bone marrow Hemangiosarcoma x Lymph node Lymph node, bronchial MM + Μ + + Μ + ΜM Lymph node, mandibular Μ + + + ММ + ΜM + + + ΜM + Μ + Μ + + Lymph node, mesenteric ММ + + + +. + + M + + + + 4 ┺ + ++ + + Lymph node, mediastinal + + + M + Μ Α + + + Μ + Μ ММ + + + + M M+ Spleen + Hemangiosarcoma х Thymus **Integumentary System** Mammary gland Skin ++ + + + M ++ + + + + Prepuce, histiocytic sarcoma х х Subcutaneous tissue, histiocytic sarcoma Musculoskeletal System Bone + + + + + + ++ + + + + + + + + + ++ + + + + + + **Nervous System** Brain + + + + + + + + + + + + + + + +**Respiratory System** Larynx Lung Alveolar/bronchiolar adenoma Х x ХХ х Alveolar/bronchiolar adenoma, multiple Alveolar/bronchiolar carcinoma Hepatocellular carcinoma, metastatic, хх liver X Х X Nose + + + Trachea **Special Senses System** Harderian gland + + х Adenoma X х х Carcinoma

Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nitromethane: 0 ppm (continued) 7 7 Number of Days on Study 3 4 Total **Carcass ID Number** 3 3 3 4 5 0 0 0 1 1 2 2 3 3 4 0 0 1 1 2 3 4 2 2 4 Tissues/ 0 5 8 4 0 3 6 7 6 7 5 6 2 7 9 4 5 1 4 1 4 3 2 8 0 Tumors **Genital System** Epididymis 50 Histiocytic sarcoma 2 Penis 1 Preputial gland 49 Prostate + + + 49 + + + + + ++ + + ++ + + + + + 49 Seminal vesicle + + + + + + + + + + + ++ + + + Testes +50 + + + +++ Interstitial cell, adenoma х х 2 **Hematopoietic System** Bone marrow 49 Hemangiosarcoma 1 Lymph node 3 + M M M M + + M M M M + M +Lymph node, bronchial + M M M ++ M M +26 М + Lymph node, mandibular + M + +40 + + + + + + + + + + + + + + + + + + + + Lymph node, mesenteric + + ++ + + + + + + + + + + + + + + + 47 + + + + +. + + + + M M + Lymph node, mediastinal + + + + + M M M M + + + + 35 + + + Spleen 49 + Hemangiosarcoma 1 Thymus I + + + + M + I + + + + + M + + + M M + M M M + + 33 **Integumentary System** Mammary gland 49 Skin Prepuce, histiocytic sarcoma 1 Subcutaneous tissue, histiocytic sarcoma Х 2 **Musculoskeletal System** Bone 50 **Nervous System** Brain 50 **Respiratory System** Larynx 50 + + + + + + + 50 Lung + + + + ť + + хх х х Alveolar/bronchiolar adenoma 9 2 Alveolar/bronchiolar adenoma, multiple хх Alveolar/bronchiolar carcinoma х х 2 Hepatocellular carcinoma, metastatic, liver 6 Nose 50 + + + +49 Trachea + + + + +**Special Senses System** Harderian gland 49 + + + + ++ + + + + + + Adenoma х 9 хх Х хх Carcinoma 1

 TABLE C2
 Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nitromethane: 0 ppm (continued)

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Number of Days on Stud	dy		÷	4 4 1	4 4 9	4 9 0	5 0 3	5 0 3	5 3 4	5 4 5	5 7 6	5 8 1	6 0 9	6 2 3	6 5 3	6 5 3	6 5 3	6 5 3	6 6 5	7 0 1	7 1 4	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 · 4		
Carcass ID Number	· · · · ·	 -		0 1 3	0 4 2	0 3 1	0 1 8	0 2 [.] 4	0 1 0	0 1 5	0 3 3	0 4 7	0 3 6	0 4 6	0 0 2	0 1 2	0 3 9	0 4 8	0 4 5	0 4 1	0 1 9	0 2 3	0 0 1	0 0 8	0 0 9	0 2 0	0 2 7	0 2 9		 -
Urinary System Kidney Urinary bladder				++	+ +	+ A	 +	· +	• +	• +	· +	+ +	+ A	+ +	+ +	+++	++	+ +	+ +	++	++	+ +	++	++	+	+	+	+		
Systemic Lesions Multiple organs Histiocytic sarcoma Lymphoma malignant	<u> </u>			_ +	+	+ x	• +	+	• +	. +	+	+	+	+	+	+	+ X	+	+	+	+	+ X	+	+	+	+	+	+		

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Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nitromethane: 0 ppm (continued) 7 7777 77 7 7 7 77 7 7 7 7 7 7 7 7 7 7 7 77 Number of Days on Study 3 3 3 3 3 3 3 3 3 4 4 4 4 4 5 5 5 5 5 5 5 5 5 5 6 6 6 6 6 6 6 7 7 7 0 Total **Carcass ID** Number 3 3 3 4 5 0 0 0 1 1 2 2 3 3 4 0 0 1 1 2 3 4 2 2 4 Tissues/ 3 6 7 6 7 5 6 2 7 9 4 5 2 8 0 0 5 8 4 0 1 4 1 4 Tumors 3 **Urinary System** 50 Kidney + 48 Urinary bladder + + Systemic Lesions 50 Multiple organs Histiocytic sarcoma х 3 Lymphoma malignant х Х 3

TABLE C2 Individual A

Individual Animal Tumor Pat	holo	gy of	Ma	le 1	Mie	ce i	n t	he	2-	Ye	ar	In	ha	lat	ion	S	ud	y (of l	Nit	roi	ne	tha	ne	:	188	3 p	pm	1			
			3	4	4	4	5	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7					
Number of Days on Study			2	4	7	8	7	4	5	6	7	0	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3					
			0	8	9	4	8	6	9	5	9	7	1	1	8	1	4	4	4	4	4	4	5	5	5	5	5					
			2	2	2	2	2	2	2	2	2	2	2	2	2	Ż	2	2	2	2	2	2	2	2	2	2	2					-
Carcass ID Number			- À	1	4	1	4	4	3	2	3	3	0	2	1	2	0	0	0	2	3	4	0	0	1	1	1			,		
	•		2	4	0	0	4	8	9	6	5	2	5	0	8	4	1	6	8	1	7	5	3	7	1	2	6					
							·											i														-
Alimentary System			• .		·																											
Esophagus	. '	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	· +	+	+	+	+	+	+	+	+	+	+			•		
Galibladder			+	+	+	A	+	+	+	+	+	+	+	+	+	- A	+	+	+	, +	+	+	+	• +	+	+	+					
Intestine large, colon	÷ 1		+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+		· ·		÷.,	,
Intestine large, recum			· +	· +	- -		+ +	+ +	+ +	т -	- -	- -	- -	- -	- -	т 4	т -	. T _			т -	. -	т 	т -	Ŧ							
Intestine small duodenum			+	+	+	Ā	+	+	+	+	+	+	+	+	+	A	+	+	+	+	· •	+	+	+	· +	+	+					
Intestine small jejunum			+	+	+	Ā	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	4				1	
Intestine small, ileum			· +	+	+	Ā	÷	+	+	+	+	+	+	+	+	Å	+	+	+	_+-	·+	+	+	+	+	+	+					
Liver			+	+	+	+	+	+	+	+	+	+	+	+	+	· +	+	+	+	+	+	+	·+	+	+	+	·+					
Hemangiosarcoma														х			•				Ċ				X							
Hepatocellular carcinoma				х						х			х	х											х	х	X	.*				
Hepatocellular carcinoma, multiple								Х																								
Hepatocellular adenoma																		X				х										
Hepatocellular adenoma, multiple								-													Х					•	х				-	
Squamous cell carcinoma, metastatic stomach, forestomach	,														x										· ·	·						
Pancreas			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	+	+	÷					•
Adenoma												•																•				
Salivary glands			+	+	М	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	.+	+	.+	+	+					
Stomach, forestomach			+	+	+	+	+	+	+	+	+	+	+	+	• +	+	+	+	+	+	+	+	• +	+	+	+	+					
Squamous cell carcinoma							,								Х						·			•								
Squamous cell papilloma																									•							
Stomach, glandular			+	+	+	A	+	+	+	+	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	•				
Tooth									·			+											•		•							
Cardiovascular System																	-														:	5
Heart			+	+	+	+	+	+	+	+	•+	· +	+	+	+	+	+	÷	4	+	· +	·+	+	+	+	+	+					
																			• •				-					<u> </u>				-
Endocrine System																													•			
Adrenal cortex			+	+	+	+	+	,+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Capsule, adenoma									-		•										•											
Adrenal medulla			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Islets, pancreatic			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +					
Adenoma Depathurgid gland		•					à.	м		M	X							,	Å				м	м	м	×	т					
Paramyroid gland			· +	+	+	NI -	ivi	IVI -	+	IVI	IVI.	+	+	+	+	+	+	+	+	+	+	- -	TAT 1	111	NI 	т -	ц. Ц	۰.				
Thuraly gland			т Т	- -	- -	Ŧ	- -	т +	- -	+	+ +		- -		+ +	- -	+	+	+	+	- -	+	+	+	+	+	+					
Follicular cell, carcinoma			•	'	. '	ŀ	•	'	'	•			•	. '	•			'	'					•		x	,				•	
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None Several Body System																																
Conital System		· · · · ·	,			.,	· ·																					<u>.</u>			<u> </u>	-
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Denis		•	 		· *	+	т	T	r.	т	т			ſ	'	'	'		•	•			'		'		'					
Preputial gland				• +	+	+	+	+	+	+	∴ ∔	+	·+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+					
Prostate			. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Seminal vesicle			+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		•			
Testes			+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Interstitial cell, adenoma																Х								1								
· · · · · · · · · · · · · · · · · · ·		· · · ·																					•					<u> </u>				
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Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nitromethane: 188 ppm (continued) 7 .7 7 7 7 7 7 7 7777777 7 7 7 7 7 7 7 7 7 Number of Days on Study 5 5 5 5 5 5 5 5 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 2 2 2 2 2 2 2 2 Total **Carcass ID Number** 1 2 2 3 3 3 4 4 0 0 0 1 1 2 3 3 4 5 1 2 2 2 3 4 4 Tissues/ 7 8 0 3 4 1 9 2 4 9 3 9 5 1 8 7 0 5 2 3 9 6 3 6 7 Tumors **Alimentary System** Esophagus 50 + + + + ++ + + + + Gallbladder 47 Μ Intestine large, colon 49 + + + ++ + Intestine large, rectum 49 4 + + + + + + + + + + + Intestine large, cecum 48 + + + + 4 + + + 4 4 + + 4 4 + Intestine small, duodenum 48 + + + Intestine small, jejunum + + + 49 Intestine small, ileum 48 + Liver 50 + Hemangiosarcoma 2 Hepatocellular carcinoma х Х Х Х х 12 Hepatocellular carcinoma, multiple х 2 Hepatocellular adenoma х х х х х х 10 Х х Hepatocellular adenoma, multiple х х 4 Squamous cell carcinoma, metastatic, stomach, forestomach 1 Pancreas 50 Adenoma Х 1 Salivary glands 49 + + + + + + + + + + + + + + + + + + + Stomach, forestomach 50 Squamous cell carcinoma 1 Squamous cell papilloma Х 1 Stomach, glandular 48 + Tooth 3 **Cardiovascular System** Heart 50 + + + + + + + ++ + + + + + + + + + + + + + + +**Endocrine** System Adrenal cortex 50 + + + + + Capsule, adenoma х 1 Adrenal medulla + + + + 50 Islets, pancreatic 50 Adenoma 3 Parathyroid gland M M + 34 ++ M + Μ + + + + Μ + + + + Μ + M + + Pituitary gland 50 + + + + + + ++ + + + + + + + ++ + ++ Thyroid gland + 50 + + ++ + + + + + + + + Follicular cell, carcinoma 1 **General Body System** , None **Genital System** Epididymis 50 Penis 2 Preputial gland 50 Prostate 50 + ++ ++ + + + + ++ + + + + + + + + Seminal vesicle 49 + + + + + + + + + +++ + + ++ + ++ + + + + Testes 50 Interstitial cell, adenoma 1

TABLE C2

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Individual Animal Tumor Path	olog	y 01		lle	IVII	ce	in 1	tne	2-	xe	ar	In	nai	ati	on	S	ua	уc	1 10	NIC	roi	ne	tna	ne	: .	199	s pj	pm	(conti	nued	0
		•	3	4	4	4	5	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7				
Number of Days on Study			2	4	- 7	8	7	4	5	6	7	0	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3				
			0	8	9	4	8	6	9	5	9	7	1	1	8	1	4	4	4	4	4	4	5	5	5	5	5				
······································			2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2				
Carcass ID Number	· •		4	1	4	1	4	4	3	2	3	3	0	2	1	2.	0	0	0	2	3	4	0	0	1	1	1				
•			2	4	0	0	4	8	9	6	5	2	5	0	8	4	1	6	8	1	7	5	3	7	1	2	6				
Hematopoietic System						·		_			_			_											_						-
Bone marrow			-		⊢ +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Hemangiosarcoma						•	•	•	·		•	•		•	•	•	•	·	•	•		•	•		•	'	·				
I ymph node		· .														-			·					•							
Lymph node bronchial							-	ъ	т.	<u>т</u>	т	х		м	м	- -	'n	L.	+	т.	÷	л.	Т		м	м	м	•			
Lymph node, mondibular			1	4 7 4 1	г IV 4 Ъ	1 -	Ť	T M	· -		Ţ	111	IVI	IAT	IVI	Τ.	141	-	T N	- T	Ţ	- T	- 7	T	IVI.	IVI	IVĮ				
Lymph node, manufoular		•	n	/1 N	л IV	a +	· .+	M	+	+	+	+	+	+	+	+	+	+	M	+	. + 	+	+	+	+	+	+				
Lympn node, mesenteric					+ +	- +	· +	+	+	Μ	+	+	M	+	+	+	+	+	M	+	M	+	+	+	+	+	+				
Lymph node, mediastinal	. *		· N	1 -	+ +	- M	M	+	+	+	, +	+	÷	+	+	+	+	м	+	+	+	+	Μ	+	+	+	+				
Spleen	• •		-	+ -	+ +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Hemangiosarcoma																															
Thymus	••		+	+ -1	⊦ N	1 M	M	М	M	+	+	М	÷	+	М	+	+	+	-+	+	+	Μ	+	+	М	+	+	_			
Integumentary System										. •	_																				
Mammary gland			. N	ΛN	ΛN	1 M	I M	Μ	Μ	М	М	М	М	Μ	М	Μ	Μ	Μ	M	Μ	Μ	Μ	Μ	Μ	Μ	Μ	M				
Skin			-	+ +	+ +	- +	+	+	+	+	+	+	+	+	+	+	+	М	+	+	+	+	÷	+	+	+	+.				
Musculoskeletal System								_								•		·			-		_								-
Bone				⊢ ⊣	⊦ +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
							· ·					· ·		_																	_
Nervous System																															
Brain			-	+ +	⊦_+	- +	+	+	+	+	. +	+	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+		•		
Respiratory System																															
Larynx				+ +	F 4	+ +	+	+	+	+	+	+	+	+	+	Α	+	+	+	+	+	+	+	` +	+	+	+				
Lung			-	⊢ ⊣	⊦ +	- +	+	+	+	·+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Alveolar/bronchiolar adenoma								х							X		X						х			х	Х				
Alveolar/bronchiolar carcinoma																			Х		•										
Hepatocellular carcinoma, metastatic,																														•	
liver																														•	
Nose	:		-	⊢ ⊣	+ +	- +	+	+	+	+	+	+	+	÷	.+	Α	·+	+	+	+	+	+	+	+	+	+	+				
Trachea			-	+ +	+ +	+ +	+	+	+	+	+	+	+	÷	+	A	+	+	+	+	+	+	+	+	+	+	+				
Special Senses System	<u> </u>							_															_	•							-
Eve																															
Harderian gland			-	+ +	+ +	- +	. +	+	+	+	+	+	+	+	+	+	+	+	.+	+	+	+	+	+	+	+	+				
Adenoma					, . ζ	•	x	•	x	•	•	x	x	•	•	•		÷	•								x				
Adenoma multiple					•		~		~			**	~	x.																	
Carcinoma												•		"		•		х													
T	<u> </u>													_											•	_		·			_
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Urethra						+	•																								
Urinary bladder			-	+ -	+ -	- +	• +	+	+	+	+	+	+	+	+	+	+	+	+	.+	+	+	+	. +	+	+	+				
Systemic Lesions															•																
Multiple organs	•		-	+ -	+ +	+ +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		•		
Lymphoma malignant					Х	ζ.	•				Х					Х															
																															_

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TABLE C2

Systemic Lesions Multiple organs Lymphoma malignant		+	+	, +	+	+	+	+	+	+	X +	+	+	+	+	+	- +	+ +	+ -	+	+	+	+	+	+		¢ 20	,
Urethra Urinary bladder		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	+ -	+ ·	+	+	+	+	+	+	,	05 I	
U rinary System Kidney		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	+ •	+ ·	+	+	+	+	+	+		20	
Adenoma, multiple Carcinoma			x													x			x							•	.I 7	
smonsbA						•																					9	
Harderian gland		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	+ •	+	+	+	+	+	+	+		05	•
Special Senses System			+											,													l	
Ттасћеа		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ +	+ •	+	+	+	+	+	+	+		67	
əsoN		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	+ •	+	+	+	+	+	+	+		67	
Hepatocellular carcinoma, metastatic,										л											•						L	
Alveolar/bronchiolar carcinoma		x														х											ε	
Alveolar/bronchiolar adenoma						Х		X											х				•	х			01	
rung Anyr		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	r +	+ •	+	+	+	+	+	+	+		20	
Mespiratory System		Ţ	т	т	Ŧ	т	т	т	т	т	т	т	Ŧ	т	Ŧ	т		Τ '	т	T	т	Ŧ	T	Ŧ	Ŧ	÷	0V	
Nervous System Brain		+	+	+	+	+	+	+	+	+	+	÷	+	+	+	÷		+ •	+	+	+	+	+	+	+		ک 0	
Musculoskeletal System Bone	×	+	+	+	+	+	+	+	+	+	.+	+	+	+	+	+	+ +	+ ·	+	+	+	+	+	+	+		٥۶	
Zkin		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ +	+ •	.+	+	+	+	+	+	+		67	
Mammary gland Mammary gystem		M	M	M	M	М	M	M	M	W	IWI	W	М	M	М	М	NN	M	M	M	W	М	W	M	M			
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smoorsoignsmeH			•	т	,	т	.'	'		<i>y</i> 1			71	'	УĽ	1	X	×.	• .	•	м	1	r	,	т		I	
Zpleen		+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	+ +	+	+	+	+	+	+	+	+		05	
Lymph node, mediastinal		+	+	W	+	+	+	M	W	+	+	+	W	+	W	М	N +	+ 1	+	+	+	+	+	M	+		LE	
Lymph node, mesenteric		+	+	+	+	+	+	+	+	+	• +	+	+	+	+	+	+ +	+	+	+	+	+	+	+	+		97	
Lymph node, mandibular		M	+	+	+	+	+	M	. M	Ņ	· +	+	+	+	+	+	F M		+	+	+	+	+	+ TAT	+		68	
Lympn node Dronchial		N	М	+	N	м	Ŧ	м	Ŧ	. +	1	n	Ŧ	Ŧ	N	Ŧ	N +		+	м	Ŧ	N	м	N	Ŧ		9C	
Hemangiosarcoma																	x		x								z	
Bone marrow		+	+	+	+	+	+	+	+	+	• +	+	+	+	+	+	+ +	+	+	+	+	+	+	+	+		٥ <u>۶</u>	
meteric System		-																					_					
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Carcass ID Number		I	z	Z	ε	ε	ε	4	• •	0_0) ()	C	l	I	τ	٤	3 4	ς	I	τ	ζ	τ	ε	t	Þ	ssiΤ	/sər	
		2	z	Z	2	Z	2	2	ς ζ	: 7	5 2	: 7	2	2	7	5	<u>z</u> z	Z	z	Ζ	2	2	2	Z	7	L	otal	
<u> </u>		ç	ς	ς	ς	ς	S	ς) Ş	9	9	9	9	9	9	9	99	9	L	L	L	L	L	L	L			
Number of Days on Study		с С	2 3	s E	2 E	ς ε	ς ε	ς ε	2 2 3	9 ; E	9 5 E	9 : E	9 E	9 E	9 E	9 E	99 88	9 E	L E	L E	L E	L E	L E	L E	L E			

Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nitromethane: 188 ppm (continued)

59I

Individual Animal Tumor Patl	hology	y of l	Mal	le I	Aic	e i	n t	he	2-	Ye	ar	In	hal	ati	ion	St	ud	y o	of l	Nit	roi	ne	tha	ine	: 3	375	5 pj	om			
Number of Days on Study			3 3	3 7	4 3	4 9	5 2	5 3	5 4	5 6	5 7	5 8	5 8	5 9	6 4	6 5	6 7	6 9	7	7 0	7 2	7 3	7 3	7 3	7 3	7	7 3		1		
			1	7	6	8	0	4	1	3	6	1	1	2	5	5	9	3	5	7	6	3	4	4	4	4	4				
			4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	.4	4				-
Carcass ID Number			3 7.	4 2	3 3	2 3	4 6	0 2	1 9	3 4	3 8	2 9	3 9	3 1·	4 7	4 8	5 0	0΄ 5	2 1	2 8	4 5	0 8	0 7	1 0	1 7	2 2	3 5				
Alimentary System	<u> </u>	<u> </u>																			·		<u></u>		_	<u> </u>					
Esophagus			+	+	+ M	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+ M	+	+	• +	+	+	+	÷			· .	
Intestine large colon			+	+	A	+	+	+	A	+ +	+	т +	+	+	+	+	+	+	+	+	+	+		+	+	+	+				
Intestine large, rectum			+	+	+	+	+	+	A	+	+	+	+	+	+	Å	+	+	+	+	+	M	+	+	+	+	+				
Intestine large, cecum			+	+	Α	`+	+	+	Α	+	+	.+	+	+	+	Α	+	+	.+	+	+	+	+	+	+	+	+	• • •			
Intestine small, duodenum		·.	•+	+	Α	+	+	+	Α	+.	+	+	+	+	°+	·A	+	+	+	+	+	+	+	+	Α	+	+`				
Intestine small, jejunum			+	+	Α	+	+	`+	Α	+	+	+	+	+	+	Α	+	÷	+	+	, +	+	+	+	+	+	+		•	•	
Intestine small, ileum			+	+	Α	+	÷	+	Á	+	+	+	+	+	+	A	+	+	+	Α	+	+	+	+	+	+	+				
Liver			+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷				
Hepatocellular carcinoma				x		x	x .		x	x					x	x										х					
Hepatocellular carcinoma, multiple					· ·		••			••	х		х					;					• .								
Hepatocellular adenoma		;												x				х	X			х				х				ŝ.	
Hepatocellular adenoma, multiple					х					•												v			· · ·		÷		•		
Misciocytic salcollia Mesentery								+		Â.	+	+										^ +								÷	
Fat histiocytic sarcoma								•		x		•										x				~					
Pancreas			· +	+	+	+	÷	+	А	+	+	+	+	+	+	+.	+	+	· +	+	+	+	+	+	+	+	+				•
Histiocytic sarcoma										x										,		х						,			
Salivary glands			· +	+	+	+	÷	+	+	+	. +	÷	÷	÷	+	+	+	+	+	+	+	+	+	+	+	+	+				
Stomach, forestomach	si,		_ +	· +	+	÷	+`	+	+	Ĩ+	+	+	+	+	+	+	+	· +	.+	+	- +	+	+	+	+	+	+				
Histiocytic sarcoma	-						·			х																					
Stomach, glandular			+	+	Å	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+,	+			•.	
Histiocytic sarcoma										х							. •													· .	• •
1000	•				_																										
Cardiovascular System			۰.				-															• •									
Heart			<u> </u>	+	.+	+	+	+	+	<u>+</u>	+	+	+	+	+	+	+	+	+	· +	+	+	+	+	+	+	+				
Endocrine System												•															•				
Adrenal cortex			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	.+	+	+	Μ	+	+	.+	. +	· +		- () - () - () - ()		
Bilateral, capsule, adenoma Capsule, adenoma																											X				
Adrenal medulla	•		· +	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+		•		
Pheochromocytoma complex			•					Х									•			-											
Islets, pancreatic		· • •	, +	• +	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Parathyroid gland	١	-	· +	+	+	M	M	+	M	+	M	+	M	+	+	+	+	+	M	+	+	+	M	+	M	+	+				
Pitukary glano Pars intermedia adenoma			+	+	+	N	Ŧ	+	+	+	Ŧ	-†-	Ŧ	+	+	+	+	I	+	+	IVI	+	+		+	. .		· •		-	
Thyroid gland	•		· . +	+	·+	+	+	+	А	+	+	+	+	+	+	+	+	+	+	+	+	+	·+	+	4	·+	+			<i>,</i>	
	<u> </u>																											,			
General Body System	÷.,	•																											· · ·	,	
None		· .				_		_					_				. '					_									
Genital System	•			_		-	_																						•	`	
Epididymis			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	, +	+				
Penis	$\{t_i\}_{i \in \mathbb{N}}$,								+				+				+				ŀ		.,		.1		-		
Prostate	1997 - L		+ -	· +	+	+	+	+	+	+ ⊥	+	+	+	+	+ м	+	+	+	IVI ⊥	+	+	+	· + +	++	+	+	++				
Histiocytic sarcoma		•	-1-	Ţ	Ŧ	Ŧ	Ŧ	T	л	x	Ŧ	т	Ŧ	٣	141	т	т	-	т	т	·T'	т	τ.	т,	F		r				
	an ta mata	<u> </u>			•		· . ·	• •		**		_			_									,							_
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166

Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nitromethane: 375 ppm (continued)

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· · · · · ·	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	.3	
	4	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	
	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	Total
Carcass ID Number	3	0	0	2	3	0	0	1	1	1	1	2	2	2	2	4	0	1	1	1	3	4	4	4	.4	Tissues/
	6	1	4	0	2	3	6	2	4	5	8	4	5	6	7	3	9	1	3	6	0	0	1	4	9	Tumors
Alimentary System												•	_							_						
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	49
Gallbladder	М	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	М	+	+	+	+	+	+	+	+	43
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	÷	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small jejunum	.+	+	+	+	+	+	+	+	+	+	+	+	+	4	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	46
Liver	· -	ــــــــــــــــــــــــــــــــــــ		, ,					_	, _		Ļ	1	ـــ			, ,				, 	_	_			50
Uemangiosarcoma	Т	т	Ţ	v	т	т	v	т	Ŧ	т	т		.1	т	т	.1	т	т		1-	Т	т	-1	т	т	50 7
Henningiosarcoma				л			Λ																			2
Hepatocenular carcinoma																										°
Hepatocellular carcinoma, multiple														••												2
Hepatocellular adenoma			Х	х	Х							х		Х		х									х	12
Hepatocellular adenoma, multiple																										1
Histiocytic sarcoma																				Х						3
Mesentery							+																			6
Fat, histiocytic sarcoma																										. 2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Stomach glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	· +	+	· 48
Histiocytic sarcoma	•	'			'	'		,			'				•	•		•						•	•	1
Tooth								Ъ																		1
Cardiovascular System				• •														`								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, capsule, adenoma																										1
Capsule, adenoma							х																			1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma complex																										1
Islets, pancreatic	+	· +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	· +	+	+	49
Parathyroid gland	+	+	M	(+	+	+	+	+	+	+	+	+	+	+	М	+	+	+	+	+	Μ	(+	+	+	м	38
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	46
Pars intermedia, adenoma																									x	1
Thyroid gland	+	4	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4	+	+	. +	+	· +	49
·		•	·	'			•			<u>.</u>								•								
General Body System																	•						•••			
None													_													
Genital System	••••					•															-		_		-	· · ·
Epididymis	+	• +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	• +	+	+	50
Penis			,			-																				3
Preputial gland	+	• +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	• +	· +	• +	49
Prostate	, -+		• +	.	+	+	+	+	+	+	+	+	+	+	+	+	+	M	. +	4	• +	• +	+	.	· +	47
Histiocytic sarcoma	1	•	'	•	•	•		•		•	•	•			•	•	•				'		·	•	•	1
					_																					

Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nitromethane: 375 ppm (continued)

					_	_	_				_					_		_						_		_		_		
Number of Days on Study			3 3 1	3 7 7	4 3 6	4 9 8	5 2 0	5 3 4	5 4 1	5 6 3	5 7 6	5 8 1	5 8 1	5 9 2	6 4 5	6 5 5	6 7 9	6 9 3	7 0 5	7 0 7	7 2 6	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4			
Carcass ID Number			4 3 7	4 4 2	4 3 3	4 2 3	4 4 6	4 0 2	4 1 9	4 3 4	4 3 8	4 2 9	4 3 9	4 3 1	4 4 7	4 4 8	4 5 0	4 0 5	4 2 1	4 2 8	4 4 5	4 0 8	4 0 7	4 1 0	4 1 7	4 2 2	4 3 5			
Genital System (continued)																														
Seminal vesicle			+	+	+	+	+	+	Μ	+	+	+	+	+	+-	+	+	+	+	+	+	+	+	+	+	+	+			
Histiocytic sarcoma			Т	т	т	т			т.	X ⊥	т	т	т	т	æ	Ŧ	т	<u>т</u>	Т	<u>т</u>	Т	<u>т</u>	т		т	Ŧ	т			
Interstitial cell, adenoma			'			I	'	•	'	'	'	•		'	I	'	'	•			'	1	:	1	x	ı	•			•
Hematopoietic System																		,	_			-								
Bone marrow			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	·+	+	+	+	+	+	+			
Lymph node															+	,		v					v							
Histiocytic sarcoma			+	+	+	M	+	M	+	+ x	+	M	+	Ŧ	M	+	+	IVI	Ŧ	.+	+	M	IVI	+	+	M	IVI			
Lymph node, mandibular			м	+	+	м	+	+	+	+	+	÷	+	·+	м	Ň	+	+	+	М	+	М	+	+	+	÷	+			
Lymph node, mesenteric			+	+	+	+	+	М	М	+	+	+	+	+	+	+	+	+	+	+	+	М	+	+	+	+	+			
Histiocytic sarcoma										Х																		·	-	
Lymph node, mediastinal			М	+	М	+	Μ	+	M	+	M	М	М	+	Μ	М	Μ	+	+	М	+	+	+	+	·+	+	+			
Histiocytic sarcoma						•	,			X	. 1							ı	-	ų,							,	•		
Hemangiosarcoma			Ŧ	+	+	+	Ŧ	Ŧ	Ŧ	+	-	4-	Ŧ	+	Ŧ	Ŧ	+	Ť	Ŧ	Ŧ	Ŧ	+	Ŧ	+	Ŧ	+	Ŧ			
Histiocytic sarcoma																														
Thymus		۰.	+	+	Ŧ	Μ	+	Μ	+	+	+	+	+	М	Μ	+	+	Μ	М	Μ	+	I	М	+	+	+	М			
Integumentary System																									<u>, , , , , , , , , , , , , , , , , , , </u>					
Mammary gland	-		М	Μ	М	Μ	Μ	Μ	Μ	Μ	М	М	М	М	Μ	Μ	Μ	М	Μ	M	Μ	M	Μ	М	Μ	Μ	Μ			· * .
Skin			+	+	+	+	+	+	, +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Subcutaneous tissue, hemangiosarcoma				_					<u></u>															•	_			<u></u>		•
Musculoskeletal System																•												•		<i>r</i>
Bone			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Nervous System																														
Brain		·	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Carcinoma, metastanc, harderian gland		·										_	_				<u>х</u>											<u> </u>		
Respiratory System																				• • •							1.			
Larynx		·	+	+	+	+	+	+.	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +			• /
Lung			+	+	+	.+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ v			
Alveolat/bronchiolat adenoma multiple																				,						÷				
Alveolar/bronchiolar carcinoma																							х			х			۰.	
Carcinoma, metastatic, harderian gland																	х		•						. ·			•	·	•
Hepatocellular carcinoma, metastatic,	•			-							_		_									•				•. •			•	
liver				Х		X					Х		X		•							v					•			•
Histiocytic sarcoma Mediactinum, histicautia sarcoma					۰ ب					v												X						•	. •	
Nose	· · .		+	+	÷	÷	+	+	+	л +	+	+	·+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Carcinoma, metastatic, harderian gland			•		•	•	•	•	•		•	•	,	•	•	•	x	•	•	•		•		·						
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TABLE C2 Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nitromethane: 375 ppm (continued) 77 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 Number of Days on Study 3 3 3 3 3 3 3 33 33 3 3 3 3 3 3 3 3 3 3 3 3 3 3 7 55 55 6 6 6 6 6 6 6 6 66 6 7 7 7 7 7 77 7 4 4 4 4 4 4 4 4 4 4 4 4 Total **Carcass ID** Number 3 0 0 2 3 0 0 1 1 1 1 2 2 2 2 4 0 1 1 1 3 4 4 4 4 Tissues/ 6 1 4 0 2 3 6 2 4 5 8 4 5 6 7 3 9 1 3 6 0 0 1 4 9 Tumors Genital System (continued) Seminal vesicle 49 Histiocytic sarcoma 1 Testes 50 Interstitial cell, adenoma 1 **Hematopoietic System** Bone marrow 50 Lymph node 1 Lymph node, bronchial 24 M M M + M M M M M M M M M M + MHistiocytic sarcoma 1 37 Lymph node, mandibular + + + M ++ MM + M + + MM +Μ + + + + + + 47 Lymph node, mesenteric + + + + + + + + + + + + ++ + + + + + Histiocytic sarcoma х 2 36 Lymph node, mediastinal M + + Histiocytic sarcoma 1 50 Spleen + + + + + х Hemangiosarcoma 1 Histiocytic sarcoma 1 х 33 M + M M + + I + + + M + M + + +Thymus + + + + M + ++ Integumentary System. Mammary gland Skin + + 49 + + + I + + + + + + + + +Subcutaneous tissue, hemangiosarcoma Х 1 **Musculoskeletal System** 50 Bone + + + + + + + + + + + + + + + + + + + + + + + **Nervous System** Brain 50 Carcinoma, metastatic, harderian gland 1 **Respiratory System** Larynx 49 50 Lung + х х х хх х х Alveolar/bronchiolar adenoma 8 х Alveolar/bronchiolar adenoma, multiple Х Alveolar/bronchiolar carcinoma 3 Carcinoma, metastatic, harderian gland 1 Hepatocellular carcinoma, metastatic, liver 4 1 Histiocytic sarcoma 1 Mediastinum, histiocytic sarcoma 50 Nose Carcinoma, metastatic, harderian gland 1 49 Trachea

Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nitromethane: 375 ppm (continued)

Number of Days on Study Carcass ID Number		 1	3 3 3 7 1 7 4 4 3 4	3 4 7 3 7 6 1 4 1 3	4 9 8 4 4 2	5 2 0 4 4	5 <u>3</u> 4 4 02	5 4 1 4 1 9	5 6 3 4 3	5 7 6 4 3 8	5 8 1 4 2 9	5 8 1 4 3 9	5 9 2 4 3	6 4 5 4 4 7	6 5 5 4 4 8	6 7 9 4 5 0	6 9 3 4 0 5	7 0 5 4 2	7 0 7 4 2 8	7 2 6 4 4 5	7 3 3 4 0 8	7 3 4 4 0 7	7 3 4 4 1	7 3 4 4 1. 7	7 3 4 2 2	7 3 4 4 3 5	-			
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Urinary System Kidney Renal tubule, adenoma Urinary bladder	· .	·		+ ·		- + - +	- +	A	++	+	· +	+	+	+	+	++	+	++	+ X +	+	++	+	+	+	· +	· +	•		· ·	
Systemic Lesions Multiple organs Histiocytic sarcoma Lymphoma malignant			+ -	+ -	+ +	- +	- +	+	+ X	+	+	+	+	+	+	+	+	. +	+ x	+	+ X	+	+	. +		+		-		

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Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nitromethane: 375 ppm (continued) Number of Days on Study 4 4 4 Total **Carcass ID** Number 3 0 0 2 3 0 0 1 1 1 1 2 2 2 2 4 0 1 1 1 3 4 4 4 4 Tissues/ 6 1 4 0 2 3 6 2 4 5 8 4 5 6 7 3 9 1 3 6 0 0 1 4 9 Tumors **Special Senses System** Eye 3 Harderian gland 50 Adenoma хххх х х хххх 18 x Adenoma, multiple 1 Carcinoma Х Х 6 Urinary System Kidney 49 Renal tubule, adenoma 1 Urinary bladder 49 Systemic Lesions Multiple organs 50 Histiocytic sarcoma х 3 Lymphoma malignant х 2

Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nitromethane: 750 ppm 3 4 4 5 5 5 56 6 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7 Number of Days on Study 9 0 9 5 8 990 7 34 56 7 7 8 9 9 9 0 2 3 3 3 3 3 6 7 1 6 5 6 9 2 9 9 5 1 99 8 9 99 4 6 4 4 4 4 6 666 6 66 **Carcass ID Number** 4 3 3 1 0 0 0 0 1 0 0 4 2 2 4 3 3 0 0 1 2 2 1 4 4 9 2 7 59 1 5 2 6 8 0 16 1 3 3 9 6 4 1 2 3 6 7 8 **Alimentary System** Esophagus Gallbladder A M Intestine large, colon + Α + + + A + + + ++ + + + Intestine large, rectum A + A I +Intestine large, cecum A + + + 4 + A + + A ÷ + + + A Intestine small, duodenum Α + + Μ + + A + + A Intestine small, jejunum Α + ++ + Α + +Α + Α + 4 + Intestine small, ileum A + А + Α Liver + + + + + + + +Hepatocellular carcinoma х х х х Hepatocellular carcinoma, multiple х x х Hepatocellular adenoma Х Х х Hepatocellular adenoma, multiple х ХХ х Mesentery Pancreas + + + + + + + + Α + + + + + Salivary glands Α + + + + + + + + + + + Stomach, forestomach Α + А Squamous cell papilloma Stomach, glandular + A + + + + + + +Cardiovascular System Heart + + + + + + + + + + + ++ + **Endocrine System** Adrenal cortex + M ++ Adenoma Capsule, adenoma Adrenal medulla + M M+ + + + + Pheochromocytoma benign Islets, pancreatic Adenoma х Parathyroid gland M + + + + + M ++ M + + MM +Μ + + Μ + Μ + Pituitary gland + Ι + + + + + + + + + + + + + + + I A Thyroid gland + + + Μ + + + + + + + + + + + Follicular cell, adenoma **General Body System** None **Genital System** Epididymis Penis Preputial gland MA + + + Prostate + Μ + + + + + + + + Ι А Seminal vesicle Α + + + + Α + + Α + + + + + + + + + + 4 + Testes + \pm Interstitial cell, adenoma

Number of Days on Study 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 <th></th> <th></th> <th>7</th> <th>1 '</th> <th>7</th> <th></th>			7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	1 '	7	
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intestine large, rectum++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++<	Intestine large, colon		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +		+	+	48
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ntestine small, duodenum + + + + + + + + + + + + + + + + + + +	ntestine large, cecum		+	+	+	+	+	+	+	+	+	+	Ŧ	+	+	+	+	+	+	+	+	+	+	+	+		+	+	46
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Stomach, forestomach + + + + + + + + + + + + + + + + + + +	Salivary glands		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• -	+ •	+	+	49
Squamous cell papilloma X X Stomach, glandular + + + + + + + + + + + + + + + + + + +	Stomach, forestomach		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		⊢ ·	+	+	48
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Islets, pancreatic + + + + + + + + + + + + + + + + + + +	Pheochromocytoma benign								х																				1
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	Penis Preputial gland Prostate Seminal vesicle		+++	+ +	- +	- 4 - 4	- + - +	· +	- + - +	+	• + • +	+	· + · +	++	++	++	++	+.+	++	+	· +	++	· +		⊦ - ⊦ -	+ +	++	м +	46

Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Nitromethane: 750 ppm (continued)

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Hematopoietic System		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
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Lymph node, mandibular]	I	A	+	+	+	+	+	+	I	+	+	+	+	+	+	÷	+	+	Μ	+	+	Μ	+	+	. +				
Lymph node, mesenteric		+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	.+	+	+	+	+	+	+	+		۰.		
Lymph node, mediastinal		+	+	М	+	+	+	+	М	+	+	+	+	М	M	+	+	+	+	+	+	+	M	М	+	+	•			
Spleen		+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		•		
Histiocytic sarcoma										• •				• •																
Thymus		+	+	м	+	+	+	+	+	M	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+				
Integumentary System																			• •											
Mammary gland	1	M	M	M	M	M	M	Μ	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M				
Skin		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+				
Musculoskeletal System																			1	~										
Bone		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	, i			
Nervous System					_			_			_									·										
Brain		+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Resniratory System							_	_		-		_			_	-						_			_			-		
Larvnx		+	Α	+	+	+	+	+	+	+	+	м	+	+	+	+	+	+	+	+	+	+	+	+	+	, +				
Lung		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Alveolar/bronchiolar adenoma				Х	•					Х									Х			Х	X							
Alveolar/bronchiolar adenoma, multiple						v	v	v										v			v									
Alveolar/bronchiolar carcinoma						л	л	~										. ^			Λ	-								
Carcinoma, metastatic, harderian gland							х								х															
Hepatocellular carcinoma, metastatic, liver					х				Х										,											
Nose		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			•	
Carcinoma, metastatic, harderian gland				-		+	-		<u>т</u>	-	Ŧ		+	т	Х 	÷		-		т	+	ъ	+	т	+	+				
		+	A	_				-	Ŧ	т	- -		т		-	т		Ť	+				-	-	-				•	
Special Senses System																													•.	•
Harderian gland		+	А	+	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Adenoma				X	X	X		X		X		x				х		х	Х		Х				Х	х			•	
Adenoma, multiple									Х								X			Х			Х							
Carcinoma							х								v															
Carcinoma, multiple		_		_							_			_	X	_	_		_					•					`	
Urinary System				_			-						•					• ·							_					
Kidney		+	A	+	+	+	+	+	+	+	+	+	.+	+	+	+	+	+	+	+	+	+	+	+	÷	+				
Ureter Urinary bladder		+	А	++	+	+	+	+	+	+	А	+	+	+	+	+	+	+	. +	+	+	+	+	+	+	+				
																		<u> </u>										_		
Systemic Lesions		••							•							۰.			۰.							,				
Multiple organs		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	+	+	+	+	+	+	+	Ŧ				
Lymphoma malignant											х																		, . .	
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Individual Animal Tumor Pathology	y of	Mal	le I	Mie	ce	in '	the	2-	·¥e	ear	Ir	iha	lat	ion	I S	tud	ly	of	Nii	tro	me	eth	an	e:		750) p	pm (continued)
		7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	•	3 4	3 4	3 4	3 4	3 5	3 5	3 5	3 5	3 5	3 5	3 6	3 6	6	3 6	3 6	3	3	3 7	3 7	3	3	7	5 7	3 7	3 7	3 7	
	<u> </u>	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	;	6	6	6	Total
Carcass ID Number		3	3	4	4	0	1	1	2	2	2	1	2	3	4	5	1	1	1	2	2	3	3	3	3	4	4	Tissues/
······································															_									, 	-			
Hematopoletic System Bone marrow Lymph node		+	+	+	+	÷	+	+	+	• +	+	• +	+	• +	+	+	+	+	+	+	• +		F -	ł	+	+	+	50 2
Lymph node, bronchial		+	Μ	(+	Μ	(+	+	Μ	: +	• +	Μ	1+	• +	• +	+	Μ	+	M	(+	Μ	I M	1 N	A 1	M	М	Μ	Μ	28
Lymph node, mandibular Lymph node, mesenteric Histiocytic sarcoma		+	+	+	М +	[+ +	+	+ +	+ +	· +	+	• +	• +	• M • +	(+ +	+ +	+	+	++	+ +	· + + X		+ ·	+ +	+ +	+ +	+ +	43 49 1
Lymph node, mediastinal		+	+	+	+	+	+	М	: +	• +	+	• +	M	1 +	+	Μ	M	[+	+	+	+		⊦ -	ł	+	+	+	40
Spleen Histocytic sercome		+	+	+	+	+	+	+	+	+	+	• +	+	• +	+	+	+	+	+	+	+ v		+ -	ł	+	+	+	49
Thymus		+	Μ	[+	+	+	М	M	. +	• +	+	• +	M	1 +	+	+	+	+	+	+	+	. N	1.	ł	М	+	+	40
Integumentary System																												
Mammary gland Skin		м +	- H	м +	ім +	м +	ім +	м +	. M +	1 M - +	+	1 M • +	· +	1 M	м +	- M +	. м +	• +	ім +	1 M	. <u>№</u>	1 M 	νι ⊦I	NI	м +	м +	м +	48
Musculoskeletal System Bone		+	+	+	+	+	+	+	+		+	- +	· +	- +	 _ +	+	+	• +	· +		• +		+ -	+	+	+	+	50
Nervous System								·									_											· ·
Brain		+	+	+	+	+	+	+	+	- +	+	• +	· +	• +	+	+	+	· +	+	+	• +		+ -	+ 	+	+	+	49
Respiratory System																												40
Larynx Lung		++	· +	+ +	· +	+	· +	++	+ +	· +	· +	· + · +	· + · +	- + - +	+ +	++	+	• +	· +	· +	• +		+ - + -	+ +	++	++	+	48 50
Alveolar/bronchiolar adenoma		X	x					·	•			x		•	·	•		•				2		ĸ	x		•	11
Alveolar/bronchiolar adenoma, multiple Alveolar/bronchiolar carcinoma		x			Х			x									x					,	, , , , , , , , , , , , , , , , , , ,	ĸ				10
Alveolar/bronchiolar carcinoma, multiple Carcinoma, metastatic, harderian gland							X															•		-				1 2 2
Nose		+	+	+	+	+	+	+	+	• +	· +	- +	• +	• +	+	+	+	• +	• +	• +	• +		+ -	⊦	+	+	+	50
Carcinoma, metastatic, harderian gland														÷.														1
Trachea		+	+	+	+	+	+	+	+-	• +	+	• +	· +	+ •	+	+	+	+	+	+	+	• -	+ -	+	+	+	+	49
Special Senses System																												
Eye Harderian gland		-	<u>н</u>			+			-			. т	. ц			<u>т</u>	+		<u> </u>			_	ь.	1	Т	т		5
Adenoma		x	· •	x	· •	X	x	T	x	X	x		· •	· •	· •	т	т	X	·	. x	x		Γ. ζ	T	x	x	т	25
Adenoma, multiple			Х		Х												Х											7
Carcinoma Carcinoma, multiple								Х				Х			Х													4
Urinary System						_			<u> </u>																			
Kidney		+	+	+	+	+	+	+	+	• +	+	- +	+	- +	+	+	+	+	+	+	• +		+ •	+	+	+	+	49
Ureter Urinary bladder		+	+	+	+	+	+	+	+	- +	• +	- +	• 4	- +	+	+	+	· +	• +	• +	· +		+ ·	ł	+	+	+	1 48
Systemic Lesions											_												_					
Multiple organs		+	+	+	• +	+	+	+	+	• +	+	- +	• +	• +	+	+	+	• +	• +	+	• + •		+ •	ł	+	+	+	50
Lymphoma malignant																					Х	•						1
																								_				

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Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Nitromethane

Adrenal Cortex: Adenoma 5/49 (10%) 1/50 (2%) 2/49 (4%) 5/48 (10%) Oreall rate ⁴ 16.1% 2.8% 6.7% 16.4% Adjusted rate ⁴ 16.1% 2.8% 6.7% 16.4% Terminal rate ⁶ 5/31 (16%) 1/36 (3%) 2/30 (7%) 4/28 (14%) Terminal rate ⁶ P-0.0210 P=0.0210 P=0.2260 P=0.276 Life table test ⁶ P=0.336 P=0.071N P=0.2260N P=0.620 Cochran Armitage test ⁷ P=0.389 P=0.098N P=0.218N P=0.617 Harderian Cland: Adenoma Overail rate 26.6% 22.8% 51.9% 75.5% Adjusted rate 26.6% 22.8% 51.9% 75.5% Terminal rate 75.0 (64%) Adjusted rate 26.6% 22.8% 51.9% 75.5% 448 52.0 497 Life table test P<0.001 P=0.505 P=0.019 P<0.001 Declost 497 Life table test P<0.001 P=0.505 P=0.019 P<0.001 Declost	4		··· · .)	0.ppm	188 ppm	375 ppm	750 ppm
Adventor Correll and $\frac{1}{2}$ (14%) (10%) (15%) (15%) (24%) (24%) (54%) (10%) Adjusted rate $\frac{1}{2}$ (15%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17%) (17	Advanal Contava Ad	enoma					·
Octamination Discretion Discretion Discretion Discretion Terminal rate 151 % 2.5% 6.7% 16.4% Terminal rate 5/31 (15%) 1/36 (3%) 2/30 (7%) 4/28 (14%) Terminal rate 9/30 (15%) 734 (17) 734 (17) 649 Life table test ⁶ P=0.324 P=0.071N P=0.220N P=0.620 Cochran-Arminage test P=0.389 P=0.218N P=0.617 Harderian Gland: Adenoma 7/31 (23%) 10/50 (20%) 19/50 (38%) 32/50 (64%) Adjusted rate 2/50 (13%) 10/50 (20%) 19/50 (38%) 32/50 (64%) Terminal rate 2/50 (38%) 10/50 (20%) 19/50 (38%) 32/50 (64%) Terminal rate 2/50 (38%) 10/50 (20%) 19/50 (38%) 32/50 (64%) Terminal rate 2/50 (38%) 10/50 (20%) 19/50 (28%) 10/29 (66%) Terminal rate 2/50 (10%) 4/35 (11%) 13/30 (43%) 10/29 (66%) Terminal rate P<0.001	Aurenar Cortex. Au	enoma	5/	10 (10%)	1/50 (2%)	2/49 (4%)	5/48 (10%)
Adjusted rate 5/31 (16%) 1/36 (3%) 2/37 (7%) 4/28 (14%) First incidence (days) 734 (7) 734 (7) 734 (7) 649 Life table test P=0.324 P=0.071N P=0.220N P=0.576 Logistic regression test P=0.336 P=0.071N P=0.220N P=0.576 Cochran-Arminge test P=0.389 P=0.098N P=0.218N P=0.617 Harderian Gland: Adenoma Overall rate 26.6% 22.8% 51.19% 75.5% Overall rate 26.6% 22.8% 51.19% 75.5% 75.5% First incidence (days) 545 448 20.035 P=0.001 P<0.001	Adjusted rate ^b		16	1%	2.8%	67%	16 4%
First indicate (days) 734 (T) 734 (T) 734 (T) 734 (T) 734 (T) 734 (T) 649 649 649 107 Life table test P=0.324 P=0.071N P=0.26N P=0.620 Cohran-Armitage test P=0.389 P=0.018 P=0.218N P=0.617 Harderian Gland: Adenoma 0/50 (18%) 10/50 (20%) 19/50 (38%) 32/50 (64%) Adjusted rate 26.6% 22.8% 51.9% 75.5% Terminal rate 0/50 (18%) 10/50 (20%) 19/50 (38%) 32/50 (64%) Adjusted rate 26.6% 22.8% 51.9% 75.5% Terminal rate 0/50 (18%) 10/50 (20%) 19/29 (66%) 35.5% 15.9% 74.001 P=0.023 P<0.001	Terminal rate ^C	· · · · · · · · · · · · · · · · · · ·	5/	31 (16%)	1/36 (3%)	2/30 (7%)	4/28 (14%)
Life table test $P=0.324$ $P=0.071N$ $P=0.226N$ $P=0.576$ Logistic regression test ^d $P=0.356$ $P=0.071N$ $P=0.226N$ $P=0.576$ Cochran-Armitage test $P=0.356$ $P=0.071N$ $P=0.226N$ $P=0.520$ Fisher exact test $P=0.389$ $P=0.226N$ $P=0.520$ $P=0.620$ Overall rate 950 (18%) $10/50$ (20%) $19/50$ (38%) $32/50$ (64%) Adjusted rate 26.6% 22.8% 51.9% 75.5% Terminal rate $7/31$ (23%) 475 (11%) $19/50$ (38%) $32/50$ (64%) Life table test $P<0.001$ $P=0.550$ $P=0.023$ $P<0.001$ Cochran-Armitage test $P<0.001$ $P=0.505$ $P=0.019$ $P<0.001$ Fisher exact test $P<0.001$ $P=0.500$ $P=0.022$ $P < 0.001$ Cochran-Armitage test $P<0.001$ $P=0.730$ $P=0.0108$ Terminal rate $1/50$ (2%) $1/50$ (2%) $3/30$ (10%) $3/329$ (10%) Adjusted rate 2.6% 2.8% 53 734 (T) 436 595	First incidence (days)	•	73	4 (T)	734 (T)	734 (T)	649
Adjustic regression test ^d $P=0.356$ $P=0.071N$ $P=0.226N$ $P=0.620$ Cochran-Armitage test ^d $P=0.389$ $P=0.098N$ $P=0.218N$ $P=0.617$ Harderian Gland: Adenoma 0verall rate 9/50 (18%) 10/50 (20%) 19/50 (38%) 32/50 (64%) Adjusted rate 26.6% 22.8% 51.9% 75.5% Terminal rate 9/50 (18%) 10/50 (20%) 19/50 (38%) 32/50 (64%) Tift incidence (days) 545 448 520 497 Life table test $P<0.001$ $P=0.55N$ $P=0.023$ $P<0.001$ Logistic regression test $P<0.001$ $P=0.500$ $P=0.022$ $P<0.001$ Harderian Gland: Carcinoma 0/50 (2%) 1/50 (2%) 1/50 (1%) 3/30 (10%) 3/329 (10%) Harderian Gland: Carcinoma 0/31 (0%) 1/36 (3%) 3/30 (10%) 3/329 (10%) 3/329 (10%) Usite table test $P=0.036$ $P=0.730N$ $P=0.060$ $P=0.108$ Logistic regression test $P=0.036$ $P=0.750N$ $P=0.060$ $P=$	Life table test ^d	- * • • •	P=	=0 324	P=0.071N	P=0.226N	P=0.576
Adjusted rate 2.6% 1.5% 1.5% 1.5% Fisher exact test P=0.389 P=0.098N P=0.218N P=0.617 Harderian Gland: Adenoma Overall rate 26.6% 22.8% 51.9% 75.5% Adjusted rate 26.6% 22.8% 51.9% 75.5% Terminal rate $7/31$ ($23.\%$) 4736 ($11.\%$) $13/30$ ($43.\%$) $19/29$ ($66.\%$) First incidence (days) 545 448 520 $9=0.023$ $P<0.001$ Life table test $P<0.001$ $P=0.050$ $P=0.022$ $P<0.001$ $P<0.001$ Cochran-Arminge test $P<0.001$ $P=0.500$ $P=0.022$ $P<0.001$ Harderian Gland: Carcinoma $0/31$ (0%) $1/36$ (3.5%) $3/30$ ($10.\%$) $3/32$ ($10.\%$) Adjusted rate 2.6% 2.8% 1.5% $5/50$ (10.9%) Terminal rate $1/50$ (2.5% $1/50$ (2.5%) $5/50$ ($10.\%$) Terminal rate $1/50$ (2.5%) $1/50$ (2.5% $5/50$ ($10.\%$) Life table test	Logistic regression test ^d		. P:	=0.356	P = 0.071N	P=0.226N	P=0.620
Fisher exact test P=0.098N P=0.218N P=0.617 Harderian Gland: Adenoma 0/50 (18%) 10/50 (20%) 19/50 (38%) 32/50 (64%) Overall rate 26.6% 22.8% 51.9% 75.5% Terminal rate 7/31 (23%) 4/36 (11%) 13/30 (43%) 19/29 (66%) Ife table test P<0.001	Cochran-Armitage test ^d		P	=0.389			
Harderian Gland: Adenoma 9/50 (18%) 10/50 (20%) 19/50 (38%) 32/50 (64%) Adjusted rate 26.6% 22.8% 51.9% 75.5% Terminal rate 7/31 (23%) 4/36 (11%) 13/30 (43%) 19/29 (66%) First incidence (days) 545 448 520 497 Life table test P<0.001	Fisher exact test ^d		-	0.000	P = 0.098N	P = 0.218N	P=0.617
Harderian Gland: Adenoma 9/50 (18%) 10/50 (20%) 19/50 (38%) 32/50 (64%) Overall rate 26.6% 22.8% 51.9% 75.5% Terminal rate 7/31 (23%) 4/36 (1%) 13/30 (43%) 19/29 (66%) First incidence (days) 545 448 520 497 Life table test P<0.001	A ISHOT DALLOT LOST	-					
Overall rate9/50 (18%)10/50 (20%)19/50 (38%)32/50 (64%)Adjusted rate26.6%22.8%51.9%75.5%Terminal rate7/31 (23%)4/36 (11%)13/30 (43%)19/29 (65%)First incidence (days)545448520497Life table test $P < 0.001$ $P = 0.555$ $P = 0.023$ $P < 0.001$ Logistic regression test $P < 0.001$ $P = 0.555$ $P = 0.019$ $P < 0.001$ Cochran-Armitage test $P < 0.001$ $P = 0.505$ $P = 0.022$ $P < 0.001$ Harderian Gland:Carcinoma $P = 0.500$ $P = 0.022$ $P < 0.001$ Overall rate2.6%2.8%16.5%14.7%Adjusted rate2.6%2.8%16.5%14.7%Terminal rate1/50 (2%)1/50 (2%)3/30 (10%)3/29 (10%)First incidence (days)653734 (T)436595Life table test $P = 0.036$ $P = 0.762N$ $P = 0.060$ $P = 0.108$ Logistic regression test $P = 0.036$ $P = 0.753N$ $P = 0.056$ $P = 0.102$ Harderian Gland:Adenoma or Carcinoma $P = 0.056$ $P = 0.012$ $P = 0.003$ $P < 0.001$ Harderian te10/50 (20%)11/50 (22%)25/50 (50%)37/50 (74%) $Adjusted rateCorban-Armitage testP = 0.001P = 0.003P < 0.001P < 0.001Life table testP < 0.001P = 0.003P < 0.003P < 0.001Logistic regression testP < 0.001P = 0.$	Harderian Gland: A	denoma	· .		,		
Adjusted rate 26.6% 22.8% 51.9% 75.5% Terminal rate $7/31$ (23%) $4/36$ (11%) $13/30$ (43%) $19/29$ (66%)First incidence ($days$) 545 448 520 497 Life table test $P < 0.001$ $P = 0.555N$ $P = 0.023$ $P < 0.001$ Logistic regression test $P < 0.001$ $P = 0.505$ $P = 0.019$ $P < 0.001$ Cohran-Armitage test $P < 0.001$ $P = 0.500$ $P = 0.022$ $P < 0.001$ Harderian Gland:Carcinoma $P = 0.021$ $P < 0.001$ Harderian Gland:Carcinoma $P = 0.303$ $P = 0.022$ $P < 0.001$ Harderian Gland:Carcinoma $P = 0.031$ $P = 0.032$ $P < 0.001$ Harderian Glays) 2.6% 2.8% 16.5% 14.7% Adjusted rate 2.6% 2.8% 16.5% 14.7% Terminal rate $0/31$ (0%) $1/36$ (3%) $3/30$ (10%) $3/29$ (10%)Logistic regression test $P = 0.031$ $P = 0.752N$ $P = 0.060$ $P = 0.104$ Cochran-Armitage test $P = 0.036$ $P = 0.752N$ $P = 0.062$ $P = 0.104$ Cochran-Armitage test $P = 0.036$ $P = 0.753N$ $P = 0.056$ $P = 0.104$ Logistic regression test $P < 0.001$ $P = 0.540N$ $25/50$ (50%) $37/50$ (74%)Adjusted rate $2/3\%$ $2/3\%$ $3/3\%$ $3/3\%$ Life table test $P < 0.001$ $P = 0.560$ $P = 0.001$ $P < 0.001$ Logistic regression test	Overall rate		· 9/:	50 (18%)	10/50 (20%)	19/50 (38%)	32/50 (64%)
Terminal rate 7/31 (23 %) 4/36 (11 %) 13/30 (43 %) 19/29 (66 %) First incidence (days) 545 448 520 497 Life table test P<0.001	Adjusted rate		26	.6%	22.8%	51.9%	75.5%
First incidence (days) 545 448 520 497 Life table test $P < 0.001$ $P = 0.555N$ $P = 0.023$ $P < 0.001$ Life table test $P < 0.001$ $P = 0.555N$ $P = 0.023$ $P < 0.001$ Cochran-Armitage test $P < 0.001$ $P = 0.022$ $P < 0.001$ Harderian Gland: Carcinoma $P < 0.001$ $P = 0.022$ $P < 0.001$ Overall rate 1/50 (2%) 1/50 (3%) 5/50 (12%) 5/50 (10%) Adjusted rate 2.6% 2.8% 16.5% 14.7% Terminal rate 0/31 (0%) 1/36 (3%) 3/30 (10%) 3/29 (10%) Life table test $P = 0.036$ $P = 0.762N$ $P = 0.062$ $P = 0.104$ Logistic regression test $P = 0.036$ $P = 0.753N$ $P = 0.056$ $P = 0.102$ Harderian Gland: Adenoma or Carcinoma $P = 0.036$ $P = 0.036$ $P = 0.038$ $S = 3.7\%$ Terminal rate 10/50 (20%) 11/50 (22%) 25/50 (50%) 37/50 (74%) Adjusted rate 2.84% 2.5.3% 63.2% 83.7\% Terminal rate 10/50 (20%) 11/5	Terminal rate		7/:	31 (23%)	4/36 (11%)	13/30 (43%)	19/29 (66%)
Life table test $P < 0.001$ $P = 0.555N$ $P = 0.023$ $P < 0.001$ Logistic regression test $P < 0.001$ $P = 0.505$ $P = 0.019$ $P < 0.001$ Fisher exact test $P < 0.001$ $P = 0.505$ $P = 0.022$ $P < 0.001$ Harderian Gland: Carcinoma $P = 0.500$ $P = 0.022$ $P < 0.001$ Harderian Gland: Carcinoma $1/50 (2\%)$ $1/50 (2\%)$ $6/50 (12\%)$ $5/50 (10\%)$ Adjusted rate 2.6% 2.8% 16.5% 14.7% Terminal rate $0/31 (0\%)$ $1/36 (3\%)$ $3/30 (10\%)$ $3/29 (10\%)$ First incidence (days) 653 734 (T) 436 595 Life table test $P = 0.031$ $P = 0.730N$ $P = 0.060$ $P = 0.108$ Cochran-Armitage test $P = 0.036$ $P = 0.753N$ $P = 0.056$ $P = 0.102$ Harderian Gland: Adenoma or Carcinoma V V V V Overall rate 28.4% 25.3% 63.2% 83.7% Adjusted rate 28.4% 25.3% 63.2% 83.7% Terminal rate $7/31 (23\%)$ $5/36 (14\%)$ $16/30 (33\%)$ $22/29 (76\%)$ Harderian Gland: Adenoma or Carcinoma V V V V Cochran-Armitage test $P = 0.001$ $P = 0.003$ $P < 0.001$ Harderian Elevel $P < 0.001$ $P = 0.506$ $P = 0.001$ $P < 0.001$ Life table test $P < 0.001$ $P = 0.500$ $P = 0.001$ $P < 0.001$ Logistic regression test $P < 0.001$ $P = 0.500$ <	First incidence (days)		54	5	448	520	497
Logistic regression test $P < 0.001$ $P = 0.505$ $P = 0.019$ $P < 0.001$ Cochran-Armitage test $P < 0.001$ $P = 0.500$ $P = 0.022$ $P < 0.001$ Harderian Gland: Carcinoma	Life table test		P	< 0.001	P=0.555N	P=0.023	P<0.001
Cochran-Armitage test $P < 0.001$ Fisher exact test $P = 0.500$ $P = 0.022$ $P < 0.001$ Harderian Gland: Carcinoma	Logistic regression test		P	< 0.001	P=0.505	P=0.019	P<0.001
Fisher exact test $P=0.500$ $P=0.022$ $P<0.001$ Harderian Gland: Carcinoma Overall rate $1/50$ (2%) $1/50$ (2%) $6/50$ (12%) $5/50$ (10%) Adjusted rate 2.6% 2.8% 16.5% 14.7% Terminal rate $0/31$ (0%) $1/36$ (3%) $3/30$ (10%) $3/29$ (10%) First incidence (days) 653 734 (T) 436 595 Life table test $P=0.031$ $P=0.750N$ $P=0.0622$ $P=0.108$ Logistic regression test $P=0.036$ $P=0.762N$ $P=0.0622$ $P=0.104$ Cochran-Armitage test $P=0.036$ $P=0.753N$ $P=0.056$ $P=0.102$ Harderian Gland: Adenoma or Carcinoma $P=0.753N$ $P=0.056$ $P=0.102$ Harderian tate $10/50$ (20%) $11/50$ (22%) $25/50$ (50%) $37/50$ (74%) Adjusted rate 28.4% 25.3% 63.2% 83.7% Terminal rate $10/50$ (20%) $11/50$ (22%) $25/50$ (50%) $37/50$ (74%) Life table test $P<0.001$ $P=0.506$ $P=0.001$ $P=0.001$ Logistic r	Cochran-Armitage test		P	< 0.001	1		•
Harderian Gland: CarcinomaOverall rate $1/50 (2\%)$ $1/50 (2\%)$ $6/50 (12\%)$ $5/50 (10\%)$ Adjusted rate 2.6% 2.8% 16.5% 14.7% Terminal rate $0/31 (0\%)$ $1/36 (3\%)$ $3/30 (10\%)$ $3/22 (10\%)$ First incidence (days) 653 $734 (T)$ 436 595 Life table test $P=0.031$ $P=0.730N$ $P=0.060$ $P=0.108$ Logistic regression test $P=0.036$ $P=0.762N$ $P=0.062$ $P=0.104$ Cochran-Armitage test $P=0.036$ $P=0.753N$ $P=0.056$ $P=0.102$ Harderian Gland:Adenoma or Carcinoma $P=0.753N$ $P=0.056$ $P=0.102$ Cortarl rate $10/50 (20\%)$ $11/50 (22\%)$ $25/50 (50\%)$ $37/50 (74\%)$ Adjusted rate 28.4% 25.3% 63.2% 83.7% Terminal rate $7/31 (23\%)$ $5/36 (14\%)$ $16/30 (53\%)$ $22/29 (76\%)$ First incidence (days) 545 448 436 497 Life table test $P < 0.001$ $P = 0.500$ $P = 0.001$ $P < 0.001$ Cochran-Armitage test $P < 0.001$ $P = 0.500$ $P = 0.001$ $P < 0.001$ Cochran-Armitage test $P < 0.001$ $P = 0.500$ $P = 0.001$ $P < 0.001$ Cochran-Armitage test $P < 0.001$ $P = 0.500$ $P < 0.001$ Cochran-Armitage test $P < 0.001$ $P < 0.001$ $P < 0.001$ Cochran-Armitage test $P = 0.500$ $P = 0.002$ $P < 0.001$ Cochran-Armitage test	Fisher exact test	· · · · · · · · · · · · · · · · · · ·			P=0.500	P=0.022	P<0.001
Overall rate $1/50 (2\%)$ $1/50 (2\%)$ $6/50 (12\%)$ $5/50 (10\%)$ Adjusted rate 2.6% 2.8% 16.5% 14.7% Terminal rate $0/31 (0\%)$ $1/36 (3\%)$ $3/30 (10\%)$ $3/29 (10\%)$ First incidence (days) 653 $734 (T)$ 436 595 Life table test $P=0.031$ $P=-0.730N$ $P=-0.060$ $P=-0.108$ Logistic regression test $P=0.036$ $P=-0.762N$ $P=-0.062$ $P=-0.104$ Cochran-Armitage test $P=0.036$ $P=-0.753N$ $P=-0.056$ $P=-0.102$ Harderian Gland: Adenoma or CarcinomaOverall rate 0 volspan="3">Overall rate $10/50 (20\%)$ $11/50 (22\%)$ $25/50 (50\%)$ $37/50 (74\%)$ Adjusted rate 28.4% 25.3% 63.2% 83.7% Terminal rate $7/31 (23\%)$ $5/36 (14\%)$ $16/30 (35\%)$ $22/29 (76\%)$ Pixt incidence (days)Life table testP<0.001	Harderian Gland: C	Carcinoma					
Adjusted rate 2.6% 2.8% 16.5% 14.7% Terminal rate $0/31 (0\%)$ $1/36 (3\%)$ $3/30 (10\%)$ $3/29 (10\%)$ First incidence (days) 653 $734 (T)$ 436 595 Life table test $P=0.031$ $P=0.730N$ $P=0.060$ $P=0.108$ Logistic regression test $P=0.036$ $P=0.762N$ $P=0.062$ $P=0.104$ Cochran-Armitage test $P=0.036$ $P=0.753N$ $P=0.062$ $P=0.102$ Harderian Ghand:Adenoma or Carcinoma $P=0.753N$ $P=0.056$ $P=0.102$ Overall rate $10/50 (20\%)$ $11/50 (22\%)$ $25/50 (50\%)$ $37/50 (74\%)$ Adjusted rate $7/31 (23\%)$ $5/36 (14\%)$ $16/30 (53\%)$ $22/29 (76\%)$ First incidence (days) 545 448 436 497 Life table test $P<0.001$ $P=0.500N$ $P=0.001$ $P<0.001$ Logistic regression test $P<0.001$ $P=0.506$ $P=0.001$ $P<0.001$ Logistic regression test $P<0.001$ $P=0.506$ $P=0.002$ $P<0.001$ Logistic regression test $P<0.001$ $P=0.500$ $P=0.002$ $P<0.001$ Cochran-Armitage test $P<0.001$ $P=0.500$ $P=0.002$ $P<0.001$ Life table test $P<0.001$ $P=0.500$ $P=0.002$ $P<0.001$ Logistic regression test $P<0.001$ $P=0.500$ $P=0.002$ $P<0.001$ Logistic regression test $P=0.435\%$ 38.9% 36.2% 52.5% Life table test $P=0.322$ $P=0.100$ <td>Overall rate</td> <td></td> <td>1/.</td> <td>50 (2%)</td> <td>1/50 (2%)</td> <td>6/50 (12%)</td> <td>5/50 (10%)</td>	Overall rate		1/.	50 (2%)	1/50 (2%)	6/50 (12%)	5/50 (10%)
Terminal rate $0/31 (0\%)$ $1/36 (3\%)$ $3/30 (10\%)$ $3/29 (10\%)$ First incidence (days) 653 $734 (T)$ 436 595 Life table test $P=0.031$ $P=0.730N$ $P=0.060$ $P=0.108$ Logistic regression test $P=0.036$ $P=0.762N$ $P=0.062$ $P=0.104$ Cochran-Arminage test $P=0.036$ $P=0.753N$ $P=0.056$ $P=0.102$ Harderian Gland:Adenoma or Carcinoma $P=0.753N$ $P=0.056$ $P=0.102$ Overall rate $10/50 (20\%)$ $11/50 (22\%)$ $25/50 (50\%)$ $37/50 (74\%)$ Adjusted rate 28.4% 25.3% 63.2% 83.7% Terminal rate $7/31 (23\%)$ $5/36 (14\%)$ $16/30 (53\%)$ $22/29 (76\%)$ First incidence (days) 545 448 436 497 Life table test $P < 0.001$ $P = 0.500$ $P = 0.001$ $P < 0.001$ Logistic regression test $P < 0.001$ $P = 0.506$ $P = 0.001$ $P < 0.001$ Cochran-Armitage test $P < 0.001$ $P = 0.500$ $P = 0.001$ $P < 0.001$ Cochran-Armitage test $P < 0.001$ $P = 0.500$ $P = 0.002$ $P < 0.001$ Cochran-Armitage test $11/31 (35\%)$ $14/50 (28\%)$ $13/50 (26\%)$ $17/50 (34\%)$ Adjusted rate $11/31 (35\%)$ $14/36 (39\%)$ $8/30 (27\%)$ $14/29 (48\%)$ First incidence (days) 449 $734 (T)$ 436 679 Liver: Hepatocellular Adenoma $P = 0.352$ $P = 0.196N$ $P = 0.300N$ $P = 0.522$	Adjusted rate	· · · · ·	2.	6%	2.8%	16.5%	14.7%
First incidence (days)653734 (T)436595Life table test $P=0.031$ $P=0.730N$ $P=0.060$ $P=0.108$ Logistic regression test $P=0.036$ $P=0.762N$ $P=0.062$ $P=0.104$ Cochran-Armitage test $P=0.036$ $P=0.753N$ $P=0.056$ $P=0.102$ Harderian Gland:Adenoma or Carcinoma $P=0.753N$ $P=0.056$ $P=0.102$ Overall rate10/50 (20%)11/50 (22%)25/50 (50%)37/50 (74%)Adjusted rate28.4%25.3%63.2%83.7%Terminal rate7/31 (23%)5/36 (14%)16/30 (53%)22/29 (76%)First incidence (days)545448436497Life table test $P<0.001$ $P=0.506$ $P=0.001$ $P<0.001$ Logistic regression test $P<0.001$ $P=0.506$ $P=0.002$ $P<0.001$ Cochran-Armitage test $P<0.001$ $P=0.500$ $P=0.002$ $P<0.001$ Fisher exact test $P=0.500$ $P=0.002$ $P<0.001$ Liver:Hepatocellular Adenoma $V/50$ (34%)14/50 (28%)13/50 (26%)17/50 (34%)Adjusted rate11/31 (35%)14/36 (39%) $8/30$ (27%)14/29 (48%)First incidence (days)449734 (T)436679Life table test $P=0.352$ $P=0.106N$ $P=0.522$ Logistic regression test $P=0.352$ $P=0.106N$ $P=0.521$ Logistic regression test $P=0.484$ $P=0.292N$ $P=0.261N$	Terminal rate		0/	31 (0%)	1/36 (3%)	3/30 (10%)	3/29 (10%)
Life table test $P=0.031$ $P=0.730N$ $P=0.060$ $P=0.108$ Logistic regression test $P=0.036$ $P=0.762N$ $P=0.062$ $P=0.104$ Cochran-Armitage test $P=0.036$ $P=0.753N$ $P=0.056$ $P=0.102$ Harderian Gland:Adenoma or Carcinoma $P=0.753N$ $P=0.056$ $P=0.102$ Overall rate10/50 (20%)11/50 (22%)25/50 (50%)37/50 (74%)Adjusted rate28.4%25.3%63.2%83.7%Terminal rate7/31 (23%)5/36 (14%)16/30 (53%)22/29 (76%)First incidence (days)545448436497Life table test $P<0.001$ $P=0.506$ $P=0.003$ $P<0.001$ Logistic regression test $P<0.001$ $P=0.506$ $P=0.001$ $P<0.001$ Cochran-Armitage test $P<0.001$ $P=0.500$ $P=0.002$ $P<0.001$ Fisher exact test $P<0.001$ $P=0.500$ $P=0.002$ $P<0.001$ Corearl rate17/50 (34%)14/50 (28%)13/50 (26%)17/50 (34%)Adjusted rate11/31 (35%)14/36 (39%) $8/30 (27\%)$ 14/29 (48%)First incidence (days)449734 (T)436679Life table test $P=0.352$ $P=0.196N$ $P=0.261N$ $P=0.562N$	First incidence (days)		65	3	734 (T)	436	595
Logistic regression test $P=0.036$ $P=0.762N$ $P=0.062$ $P=0.104$ Cochran-Armitage test $P=0.036$ $P=0.036$ $P=0.753N$ $P=0.056$ $P=0.102$ Harderian Gland: Adenoma or Carcinoma $P=0.753N$ $P=0.056$ $P=0.102$ Overall rateAdjusted rate 28.4% 25.3% 63.2% 83.7% Terminal rate $7/31$ (23%) $5/36$ (14%) $16/30$ (53%) $22/29$ (76%)First incidence (days) 545 448 436 497 Life table test $P<0.001$ $P=0.540N$ $P=0.003$ $P<0.001$ Logistic regression test $P<0.001$ $P=0.506$ $P=0.001$ $P<0.001$ Cochran-Armitage test $P<0.001$ $P=0.500$ $P=0.002$ $P<0.001$ Fisher exact test $P<0.001$ $P=0.500$ $P=0.002$ $P<0.001$ Cochran-Armitage test $P<0.001$ $P=0.500$ $P=0.002$ $P<0.001$ Fisher exact test $P=0.500$ $P=0.002$ $P<0.001$ $P<0.001$ Liver: Hepatocellular Adenoma $17/50$ (34%) $14/50$ (28%) $13/50$ (26%) $17/50$ (34%)Adjusted rate $11/31$ (35%) $14/36$ (39%) $8/30$ (27%) $14/29$ (48%)First incidence (days) 449 734 (T) 436 679 Life table test $P=0.352$ $P=0.196N$ $P=0.300N$ $P=0.522$ Logistic regression test $P=0.484$ $P=0.292N$ $P=0.261N$ $P=0.562N$	Life table test		P	=0.031	P=0.730N	P=0.060	P = 0.108
Cochran-Armitage test $P=0.036$ Fisher exact test $P=0.753N$ $P=0.056$ $P=0.102$ Harderian Gland: Adenoma or Carcinoma $10/50 (20\%)$ $11/50 (22\%)$ $25/50 (50\%)$ $37/50 (74\%)$ Overall rate $10/50 (20\%)$ $11/50 (22\%)$ $25/50 (50\%)$ $37/50 (74\%)$ Adjusted rate 28.4% 25.3% 63.2% 83.7% Terminal rate $7/31 (23\%)$ $5/36 (14\%)$ $16/30 (53\%)$ $22/29 (76\%)$ First incidence (days) 545 448 436 497 Life table test $P < 0.001$ $P = 0.540N$ $P = 0.003$ $P < 0.001$ Logistic regression test $P < 0.001$ $P = 0.506$ $P = 0.001$ $P < 0.001$ Cochran-Armitage test $P < 0.001$ $P = 0.506$ $P = 0.002$ $P < 0.001$ Fisher exact test $P < 0.001$ $P = 0.500$ $P = 0.002$ $P < 0.001$ Liver: Hepatocellular Adenoma $17/50 (34\%)$ $14/50 (28\%)$ $13/50 (26\%)$ $17/50 (34\%)$ Overall rate $11/31 (35\%)$ $14/36 (39\%)$ $8/30 (27\%)$ $14/29 (48\%)$ First incidence (days) 449 $734 (T)$ 436 679 Life table test $P = 0.352$ $P = 0.196N$ $P = 0.300N$ $P = 0.522$ Logistic regression test $P = 0.484$ $P = 0.292N$ $P = 0.261N$ $P = 0.562N$	Logistic regression test	•	· P=	=0.036	P=0.762N	P = 0.062	P=0.104
Fisher exact test $P=0.753N$ $P=0.056$ $P=0.102$ Harderian Gland: Adenoma or CarcinomaOverall rate10/50 (20%)11/50 (22%)25/50 (50%)37/50 (74%)Adjusted rate28.4%25.3%63.2%83.7%Terminal rate7/31 (23%)5/36 (14%)16/30 (53%)22/29 (76%)First incidence (days)545448436497Life table test $P<0.001$ $P=0.540N$ $P=0.003$ $P<0.001$ Logistic regression test $P<0.001$ $P=0.506$ $P=0.001$ $P<0.001$ Cochran-Armitage testP<0.001	Cochran-Armitage test		P	=0.036	•		
Harderian Gland: Adenoma or CarcinomaOverall rate $10/50 (20\%)$ $11/50 (22\%)$ $25/50 (50\%)$ $37/50 (74\%)$ Adjusted rate 28.4% 25.3% 63.2% 83.7% Terminal rate $7/31 (23\%)$ $5/36 (14\%)$ $16/30 (53\%)$ $22/29 (76\%)$ First incidence (days) 545 448 436 497 Life table test $P < 0.001$ $P = 0.540N$ $P = 0.003$ $P < 0.001$ Logistic regression test $P < 0.001$ $P = 0.506$ $P = 0.001$ $P < 0.001$ Cochran-Armitage test $P < 0.001$ $P = 0.506$ $P = 0.002$ $P < 0.001$ Fisher exact test $P < 0.001$ $P = 0.500$ $P = 0.002$ $P < 0.001$ Liver: Hepatocellular AdenomaOverall rate $17/50 (34\%)$ $14/50 (28\%)$ $13/50 (26\%)$ $17/50 (34\%)$ Adjusted rate $11/31 (35\%)$ $14/36 (39\%)$ $8/30 (27\%)$ $14/29 (48\%)$ First incidence (days) 449 $734 (T)$ 436 679 Life table test $P = 0.352$ $P = 0.196N$ $P = 0.300N$ $P = 0.522$ Logistic regression test $P = 0.484$ $P = 0.292N$ $P = 0.261N$ $P = 0.562N$	Fisher exact test				P=0.753N	P=0.056	P=0.102
Overall rate $10/50 (20\%)$ $11/50 (22\%)$ $25/50 (50\%)$ $37/50 (74\%)$ Adjusted rate 28.4% 25.3% 63.2% 83.7% Terminal rate $7/31 (23\%)$ $5/36 (14\%)$ $16/30 (53\%)$ $22/29 (76\%)$ First incidence (days) 545 448 436 497 Life table test $P < 0.001$ $P = 0.540N$ $P = 0.003$ $P < 0.001$ Logistic regression test $P < 0.001$ $P = 0.506$ $P = 0.001$ $P < 0.001$ Cochran-Armitage test $P < 0.001$ $P = 0.500$ $P = 0.002$ $P < 0.001$ Fisher exact test $P = 0.500$ $P = 0.002$ $P < 0.001$ Liver: Hepatocellular AdenomaOverall rateOverall rate $17/50 (34\%)$ $14/50 (28\%)$ $13/50 (26\%)$ $17/50 (34\%)$ Adjusted rate $11/31 (35\%)$ $14/36 (39\%)$ $8/30 (27\%)$ $14/29 (48\%)$ First incidence (days)Life table test $P = 0.352$ $P = 0.196N$ $P = 0.300N$ $P = 0.522$ Logistic regression test $P = 0.484$ $P = 0.292N$ $P = 0.261N$ $P = 0.562N$	Harderian Gland: A	Adenoma or Carcinoma	•			х	
Adjusted rate 28.4% 25.3% 63.2% 83.7% Terminal rate $7/31 (23\%)$ $5/36 (14\%)$ $16/30 (53\%)$ $22/29 (76\%)$ First incidence (days) 545 448 436 497 Life table test $P < 0.001$ $P = 0.540N$ $P = 0.003$ $P < 0.001$ Logistic regression test $P < 0.001$ $P = 0.506$ $P = 0.001$ $P < 0.001$ Cochran-Armitage test $P < 0.001$ $P = 0.500$ $P = 0.002$ $P < 0.001$ Fisher exact test $P = 0.500$ $P = 0.002$ $P < 0.001$ Coverall rateOverall rate $17/50 (34\%)$ $14/50 (28\%)$ $13/50 (26\%)$ $17/50 (34\%)$ Adjusted rate $11/31 (35\%)$ $14/36 (39\%)$ $8/30 (27\%)$ $14/29 (48\%)$ First incidence (days) 449 $734 (T)$ 436 679 Life table test $P = 0.352$ $P = 0.196N$ $P = 0.300N$ $P = 0.522$ Logistic regression test $P = 0.484$ $P = 0.292N$ $P = 0.261N$ $P = 0.562N$	Overall rate		10	/50 (20%)	11/50 (22%)	25/50 (50%)	37/50 (74%)
Terminal rate $7/31 (23\%)$ $5/36 (14\%)$ $16/30 (53\%)$ $22/29 (76\%)$ First incidence (days) 545 448 436 497 Life table test $P < 0.001$ $P = 0.540N$ $P = 0.003$ $P < 0.001$ Logistic regression test $P < 0.001$ $P = 0.506$ $P = 0.001$ $P < 0.001$ Cochran-Armitage test $P < 0.001$ $P = 0.506$ $P = 0.002$ $P < 0.001$ Fisher exact test $P < 0.001$ $P = 0.500$ $P = 0.002$ $P < 0.001$ Liver: Hepatocellular AdenomaOverall rate $17/50 (34\%)$ $14/50 (28\%)$ $13/50 (26\%)$ $17/50 (34\%)$ Adjusted rate $11/31 (35\%)$ $14/36 (39\%)$ $8/30 (27\%)$ $14/29 (48\%)$ First incidence (days) 449 $734 (T)$ 436 679 Life table test $P = 0.352$ $P = 0.196N$ $P = 0.300N$ $P = 0.522$ Logistic regression test $P = 0.484$ $P = 0.292N$ $P = 0.261N$ $P = 0.562N$	Adjusted rate		28	.4%	25.3%	63.2%	83.7%
First incidence (days) 545 448 436 497 Life table test $P < 0.001$ $P = 0.540N$ $P = 0.003$ $P < 0.001$ Logistic regression test $P < 0.001$ $P = 0.506$ $P = 0.001$ $P < 0.001$ Cochran-Armitage test $P < 0.001$ $P = 0.500$ $P = 0.002$ $P < 0.001$ Fisher exact test $P < 0.001$ $P = 0.500$ $P = 0.002$ $P < 0.001$ Liver: Hepatocellular AdenomaOverall rateOverall rate $17/50 (34\%)$ $14/50 (28\%)$ $13/50 (26\%)$ $17/50 (34\%)$ Adjusted rate $11/31 (35\%)$ $14/36 (39\%)$ $8/30 (27\%)$ $14/29 (48\%)$ First incidence (days) 449 $734 (T)$ 436 679 Life table test $P = 0.352$ $P = 0.196N$ $P = 0.300N$ $P = 0.522$ Logistic regression test $P = 0.484$ $P = 0.292N$ $P = 0.261N$ $P = 0.562N$	Terminal rate		· 7/	31 (23%)	5/36 (14%)	16/30 (53%)	22/29 (76%)
Life table test $P < 0.001$ $P = 0.540N$ $P = 0.003$ $P < 0.001$ Logistic regression test $P < 0.001$ $P = 0.506$ $P = 0.001$ $P < 0.001$ Cochran-Armitage test $P < 0.001$ $P = 0.500$ $P = 0.002$ $P < 0.001$ Fisher exact test $P = 0.500$ $P = 0.002$ $P < 0.001$ Liver: Hepatocellular AdenomaOverall rate $17/50 (34\%)$ $14/50 (28\%)$ $13/50 (26\%)$ $17/50 (34\%)$ Adjusted rate 44.2% 38.9% 36.2% 52.5% Terminal rate $11/31 (35\%)$ $14/36 (39\%)$ $8/30 (27\%)$ $14/29 (48\%)$ First incidence (days) 449 $734 (T)$ 436 679 Life table test $P = 0.352$ $P = 0.196N$ $P = 0.300N$ $P = 0.522$ Logistic regression test $P = 0.484$ $P = 0.292N$ $P = 0.261N$ $P = 0.562N$	First incidence (days)		54	5	448	436	497
Logistic regression test $P < 0.001$ $P = 0.506$ $P = 0.001$ $P < 0.001$ Cochran-Armitage test $P < 0.001$ $P = 0.500$ $P = 0.002$ $P < 0.001$ Fisher exact test $P = 0.500$ $P = 0.002$ $P < 0.001$ Liver: Hepatocellular AdenomaOverall rate $17/50 (34\%)$ $14/50 (28\%)$ $13/50 (26\%)$ $17/50 (34\%)$ Adjusted rate 44.2% 38.9% 36.2% 52.5% Terminal rate $11/31 (35\%)$ $14/36 (39\%)$ $8/30 (27\%)$ $14/29 (48\%)$ First incidence (days) 449 $734 (T)$ 436 679 Life table test $P = 0.352$ $P = 0.196N$ $P = 0.300N$ $P = 0.522$ Logistic regression test $P = 0.484$ $P = 0.292N$ $P = 0.261N$ $P = 0.562N$	Life table test	-	P	< 0.001	P=0.540N	P=0.003	P<0.001
Cochran-Armitage test $P < 0.001$ Fisher exact test $P = 0.500$ $P = 0.002$ $P < 0.001$ Liver: Hepatocellular Adenoma $17/50 (34\%)$ $14/50 (28\%)$ $13/50 (26\%)$ $17/50 (34\%)$ Overall rate $17/50 (34\%)$ $14/50 (28\%)$ $13/50 (26\%)$ $17/50 (34\%)$ Adjusted rate $11/31 (35\%)$ $14/36 (39\%)$ $8/30 (27\%)$ $14/29 (48\%)$ First incidence (days) 449 $734 (T)$ 436 679 Life table test $P = 0.352$ $P = 0.196N$ $P = 0.300N$ $P = 0.522$ Logistic regression test $P = 0.484$ $P = 0.292N$ $P = 0.261N$ $P = 0.562N$	Logistic regression test		P	< 0.001	P=0.506	P=0.001	P<0.001
Fisher exact test $P=0.500$ $P=0.002$ $P<0.001$ Liver: Hepatocellular AdenomaOverall rate $17/50$ (34%) $14/50$ (28%) $13/50$ (26%) $17/50$ (34%)Adjusted rate 44.2% 38.9% 36.2% 52.5% Terminal rate $11/31$ (35%) $14/36$ (39%) $8/30$ (27%) $14/29$ (48%)First incidence (days) 449 734 (T) 436 679 Life table test $P=0.352$ $P=0.196N$ $P=0.300N$ $P=0.522$ Logistic regression test $P=0.484$ $P=0.292N$ $P=0.261N$ $P=0.562N$	Cochran-Armitage test		P	< 0.001	• .	÷	
Liver: Hepatocellular AdenomaOverall rate $17/50 (34\%)$ $14/50 (28\%)$ $13/50 (26\%)$ $17/50 (34\%)$ Adjusted rate 44.2% 38.9% 36.2% 52.5% Terminal rate $11/31 (35\%)$ $14/36 (39\%)$ $8/30 (27\%)$ $14/29 (48\%)$ First incidence (days) 449 $734 (T)$ 436 679 Life table test $P=0.352$ $P=0.196N$ $P=0.300N$ $P=0.522$ Logistic regression test $P=0.484$ $P=0.292N$ $P=0.261N$ $P=0.562N$	Fisher exact test	4 			P=0.500	P=0.002	P<0.001
Liver: Hepatocellular AdenomaOverall rate17/50 (34%)14/50 (28%)13/50 (26%)17/50 (34%)Adjusted rate44.2%38.9%36.2%52.5%Terminal rate11/31 (35%)14/36 (39%)8/30 (27%)14/29 (48%)First incidence (days)449734 (T)436679Life table testP=0.352P=0.196NP=0.300NP=0.522Logistic regression testP=0.484P=0.292NP=0.261NP=0.562N	• •						
Overall rate $17/50 (34\%)$ $14/50 (28\%)$ $13/50 (26\%)$ $17/50 (34\%)$ Adjusted rate 44.2% 38.9% 36.2% 52.5% Terminal rate $11/31 (35\%)$ $14/36 (39\%)$ $8/30 (27\%)$ $14/29 (48\%)$ First incidence (days) 449 $734 (T)$ 436 679 Life table test $P=0.352$ $P=0.196N$ $P=0.300N$ $P=0.522$ Logistic regression test $P=0.484$ $P=0.292N$ $P=0.261N$ $P=0.562N$	Liver: Hepatocellula	ar Adenoma			1		•
Adjusted rate 44.2% 38.9% 36.2% 52.5% Terminal rate $11/31$ (35%) $14/36$ (39%) $8/30$ (27%) $14/29$ (48%)First incidence (days) 449 734 (T) 436 679 Life table test $P=0.352$ $P=0.196N$ $P=0.300N$ $P=0.522$ Logistic regression test $P=0.484$ $P=0.292N$ $P=0.261N$ $P=0.562N$	Overall rate	s.	17	/50 (34%)	14/50 (28%)	13/50 (26%)	17/50 (34%)
Terminal rate $11/31 (35\%)$ $14/36 (39\%)$ $8/30 (27\%)$ $14/29 (48\%)$ First incidence (days) 449 $734 (T)$ 436 679 Life table test $P=0.352$ $P=0.196N$ $P=0.300N$ $P=0.522$ Logistic regression test $P=0.484$ $P=0.292N$ $P=0.261N$ $P=0.562N$	Adjusted rate	•	44	.2%	38.9%	36.2%	52.5%
First incidence (days)449734 (T)436679Life table test $P=0.352$ $P=0.196N$ $P=0.300N$ $P=0.522$ Logistic regression test $P=0.484$ $P=0.292N$ $P=0.261N$ $P=0.562N$	Terminal rate		- 11	/31 (35%)	14/36 (39%)	8/30 (27%)	14/29 (48%)
Life table test $P=0.352$ $P=0.196N$ $P=0.300N$ $P=0.522$ Logistic regression test $P=0.484$ $P=0.292N$ $P=0.261N$ $P=0.562N$	First incidence (days)		44	19	734 (T)	436	679
Logistic regression test $P=0.484$ $P=0.292N$ $P=0.261N$ $P=0.562N$	Life table test		P	=0.352	P=0.196N	P=0.300N	P=0.522
	Logistic regression test		P	=0.484	P = 0.292N	P = 0.261N	P = 0.562N
Cochran-Armitage test P=0.490	Cochran-Armitage test		P	=0.490			D 0 0001
Fisher exact test $P=0.333N$ $P=0.257N$ $P=0.583N$	Fisher exact test	•			P=0.333N	P=0.257N	P=0.383N
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Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Nitromethane (continued)

	0 ppm	188 ppm	375 ppm	750 ppm	
Liver: Hepatocellular Carcinoma					
Overall rate	16/50 (32%)	14/50 (28%)	10/50 (20%)	9/50 (18%)	
Adjusted rate	35.6%	33.3%	21.9%	20.7%	
Terminal rate	5/31 (16%)	9/36 (25%)	1/30 (3%)	2/29 (7%)	
First incidence (days)	441	448	377	406	
Life table test	P=0.085N	P=0.297N	P=0.177N	P=0.104N	
Logistic regression test	P=0.032N	P=0.440	P=0.120N	P≈0.099N	
Cochran-Armitage test	P=0.051N				
Fisher exact test		P=0.414N	P=0.127N	P=0.083N	
Liver: Hepatocellular Adenoma or Carcinoma					,
Overall rate	29/50 (58%)	24/50 (48%)	22/50 (44%)	26/50 (52%)	•
Adjusted rate	60.6%	58.0%	48.4%	64.9%	
Terminal rate	13/31 (42%)	19/36 (53%)	8/30 (27%)	16/29 (55%)	
First incidence (days)	441	448	377	406	
Life table test	P=0.502N	P=0.119N	P=0.210N	P = 0.405N	
Logistic regression test	P=0.319N	P=0.268N	P=0.111N	P = 0.383N	
Cochran-Armitage test	P=0.360N				
Fisher exact test		P=0.212N	P=0.115N	P=0.344N	
Lung: Alveolar/bronchiolar Adenoma					
Overall rate	11/50 (22%)	10/50 (20%)	9/50 (18%)	12/50 (24%)	
Adjusted rate	30.8%	26.0%	30.0%	35.1%	
Terminal rate	8/31 (26%)	8/36 (22%)	9/30 (30%)	8/29 (28%)	
First incidence (days)	449	646	734 (T)	497	
Life table test	P=0.322	P=0.365N	P = 0.433N	P=0.456	
Logistic regression test	P=0.422	P=0.456N	P = 0.412N	P=0.511	•
Cochran-Armitage test	P = 0.430	D 0 0001	D 0 (00)1	D 0 500	
Fisher exact test		P=0.500N	P=0.402N	P=0.500	
Lung: Alveolar/bronchiolar Carcinoma					
Overall rate	2/50 (4%)	.3/50 (6%)	3/50 (6%)	11/50 (22%)	
Adjusted rate	0.5%	8.3%	10.0%	30.4%	
Terminal rate	2/31 (0%)	3/30 (8%) 724 (TD)	3/30 (10%)	6/29 (21%)	
First incidence (days)	734 (1) D < 0.001	734 (1) D=0.560	/34 (1) D=0.495	380 D=0.000	
Life table test	P<0.001	P=0.569	P=0.485	P=0.009	
Logistic regression test	P = 0.001	P=0.309	P=0.485	P=0.009	
Fisher exact test	P=0.001	P≈0.500	P = 0.500	P=0.007	
		1 = 0.500	1 = 0.500		
Lung: Alveolar/bronchiolar Adenoma or Carcinoma					
Overall rate	13/50 (26%)	13/50 (26%)	12/50 (24%)	20/50 (40%)	
Adjusted rate	36.8%	33.9%	40.0%	51.2%	
Terminal rate	10/31 (32%)	11/36 (31%)	12/30 (40%)	11/29 (38%)	
First incidence (days)	449	646	734 (T)	497 ·	
Life table test	P=0.032	P=0.427N	P=0.540N	P=0.099	
Logistic regression test	P=0.059	P=0.517N	P=0.515N	P=0.105	
Cocnran-Armitage test	P=0.063	D-0.600N	D_0 600N	B-0 101	
risher exact lest		r=0.390N	r=0.300m	r=0.101	

Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Nitromethane (continued)

		0 ppm	188 ppm	375 ppm	750 ppm
Pancreatic Islets: Adenoma					
Overall rate		1/40 (2%)	3/50 (6%)	0/49 (0%)	1/49 (2%)
Adjusted rate		2.2%	78%	0.0%	2 4%
Terminal rate		0/31 (0%)	2/36 (6%)	0/30 (0%)	0/29(0%)
First incidence (days)	• · · ·	534	679	e	632
Life table test		P=0.421N	P=0 356	P=0.500N	P = 0.747N
Logistic regression test		P=0.416N	P=0.300	P = 0.425N	P = 0.734
Cochran-Armitage test		P = 0.412N			
Fisher exact test			P=0.316	P=0.500N	P=0.753N
All Organs: Hemangiosarcoma	•			· .	
Overall rate	•	1/50 (2%)	4/50 (8%)	2/50 (4%)	0/50 (0%)
Adjusted rate		3.2%	10.6%	6.7%	0.0%
Terminal rate		1/31 (3%)	3/36 (8%)	2/30 (7%)	0/29 (0%)
First incidence (days)		734 (T)	721	734 (T)	<u> </u>
Life table test		P=0.231N	P=0.234	P=0.488	P=0.513N
Logistic regression test		P=0.222N	P=0.235	P=0.488	P=0.513N
Cochran-Armitage test		P=0.199N			
Fisher exact test			P=0.181	P=0.500	P=0.500N
All Organs: Histiocytic Sarcoma					· ·
Overall rate		3/50 (6%)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted rate		8.7%	0.0%	8.6%	3.4%
Terminal rate		1/31 (3%)	0/36 (0%)	1/30 (3%)	1/29 (3%)
First incidence (days)		^ð 653		563	.734 (T)
Life table test		P = 0.405N	P=0.101N	P=0.648	P=0.326N
Logistic regression test		P=0.373N	P=0.110N	P=0.659	P=0.297N
Cochran-Armitage test		P=0.372N			a the second second second second
Fisher exact test			P=0.121N	P=0.661N	P=0.309N
All Organs: Malignant Lymphoma					
Overall rate		3/50 (6%)	4/50 (8%)	2/50 (4%)	1/50 (2%)
Adjusted rate		8.4%	9.6%	6.3%	2.4%
Terminal rate		2/31 (6%)	1/36 (3%)	1/30 (3%)	0/29 (0%)
First incidence (days)		490	479	707	649
Life table test		P = 0.187N	P = 0.558	P = 0.511N	P = 0.315N
Logistic regression test	1	P = 0.162N	P=0.465	P = 0.501N	P=0.315N
Cochran-Armitage test		P = 0.162N			
Fisher exact test			P=0.500	P = 0.500N	P=0.309N
All Organs: Benign Neoplasms					
Overall rate		31/50 (62%)	31/50 (62%)	33/50 (66%)	43/50 (86%).
Adjusted rate	* · ·	74.9%	67.3%	84.3%	95.5%
Terminal rate		21/31 (68%)	21/36 (58%)	24/30 (80%)	27/29 (93%)
First incidence (days)		449	448	436	497 D. 0.020
Life table test		P=0.003	P=0.289N	P=0.364	P=0.020
Logistic regression test		P = 0.002	P = 0.521N	P=0.378	P=0.00/
Cochran-Armitage test		P=0.003	D 0 50001	D-0.419	D-0.006
Fisher exact test		,	P=0.382N	P=0.418	r=0.000

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Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Nitromethane (continued)

	0 ppm	188 ppm	375 ppm	750 ppm
All Organs: Malignant Neoplasms	<u> </u>			· · ·
Overall rate	22/50 (44%)	25/50 (50%)	24/50 (48%)	22/50 (44%)
Adjusted rate	48.3%	55.3%	51.9%	50.0%
Terminal rate	9/31 (29%)	16/36 (44%)	9/30 (30%)	9/29 (31%)
First incidence (days)	441	448	377	406
Life table test	P=0.489	P=0.559	P=0.403	P=0.556
Logistic regression test	P=0.407N	P = 0.145	P = 0.343	P=0.534
Cochran-Armitage test	P=0.472N			
Fisher exact test		P=0.344	P = 0.421	P=0.580N
All Organs: Benign or Malignant Neoplasms				
Overall rate	40/50 (80%)	39/50 (78%)	43/50 (86%)	46/50 (92%)
Adjusted rate	83.0%	81.2%	89.5%	95.8%
Terminal rate	23/31 (74%)	27/36 (75%)	25/30 (83%)	27/29 (93%)
First incidence (days)	441	448	377	406
Life table test	P=0.057	P=0.209N	P=0.322	P = 0.178
Logistic regression test	P=0.032	P=0.523N	P=0.211	P=0.070
Cochran-Armitage test	P=0.034			
Fisher exact test		P=0.500N	P=0.298	P=0.074

(T)Terminal sacrifice

Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, lung, and pancreatic islets; for other tissues, denominator is number of animals necropsied. b

Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

с Observed incidence at terminal kill

d Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table test regards neoplasms 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. For all tests, a negative trend or a lower incidence in an exposure group is indicated by N.

e Not applicable; no neoplasms in animal group

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TABLE C4a

Historical Incidence of Harderian Gland Neoplasms in Chamber Control Male B6C3F₁ Mice^a

Study	Adenoma	Carcinoma	Adenoma or Carcinoma	
Historical Incidence at Battell	e Pacific Northwest Labo	oratories		<u></u>
1,3-Butadiene	6/50	0/50	6/50	
Acetonitrile	5/50	0/50	5/50	
Allyl glycidyl ether	4/50	0/50	4/50	•
2-Chloroacetophenone	3/50	0/50	3/50	
<i>l</i> -Epinephrine Hydrochloride	2/50	0/50	2/50	
Chloroethane	, 2/50	2/50	4/50	
Hexachlorocyclopentadiene	7/50	0/50	7/50	•
o-Chloroberzalmalononitrile (CS2)	6/50	0/50	6/50	
Ozone	1/50	0/50	1/50	
Total	36/450 (8.0%)	2/450 (0.4%)	38/450 (8.4%)	
Standard deviation	4.2%	1.3%	4.0%	
Range	2%-14%	0%-4%	2%-14%	
Overall Historical Incidence				
Total	47/950 (5.0%)	2/950 (0.2%)	49/950 (5.2%)	
Standard deviation	4.5%	0.9%	4.5%	
Range	0%-14%	0%-4%	0%-14%	

^a Data as of 12 May 1995

TABLE C4b

Historical Incidence of Alveolar/bronchiolar Neoplasms in Chamber Control Male B6C3F, Mice^a

		Incidence in Contr	ols
Study	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle	Pacific Northwest Labor	ratories	
1,3-Butadiene	18/50	5/50	21/50
Acetonitrile	6/50	4/50	10/50
Allyl glycidyl ether	7/50	0/50	7/50
2-Chloroacetophenone	7/50	6/50	11/50
l-Epinephrine Hydrochloride	11/50	5/50	15/50
Chloroethane	3/50	2/50	5/50
Hexachlorocyclopentadiene	11/49	0/49	11/49
o-Chlorobenzalmalononitrile (CS2)	7/49	7/49	14/49
Ozone	6/50	8/50	14/50
Total	76/448 (17.0%)	37/448 (8.3%)	108/448 (24.1%)
Standard deviation	8.7%	5.8%	9.5%
Range	6%-36%	0%-16%	10%-42%
Overall Historical Incidence			
Total	141/947 (14.9%)	75/947 (7.9%)	205/947 (21.7%)
Standard deviation	7.0%	5.7%	8.0%
Range	6%-36%	0%-16%	10%-42%

^a Data as of 12 May 1995

Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Nitromethane^a

	ta en la composición de la composición Composición de la composición de la comp	0 ppm		188 ppm	3	75 ppm	750 ppm	
Disposition Summary							6 V	
Animals initially in study		50		. 50		50	50	
Farly deaths	10 1	50		50		50	50	
Moribund		14		11		16	16	
Natural deaths		5		3		4	5	
Survivors	<i></i>						-	
Terminal sacrifice		31		36		30	. 29	
Animals examined microscopically	••	50		50	• • •	50	50	۰.
			<u>`</u>					
Alimentary System								
Gallbladder		(43)		(47)	(4	(3)	(42)	
Degeneration, hvaline		1 (2%)						
Hyperplasia		1 (270)		1 (2%)				
Intestine large, cecum		(46)	ŕ í.	(48)	. (4	7)	(46)	
Hemorrhage						1 (2%)		
Intestine small, jejunum		(45)	•	(49)	(4	(7)	(46)	
Pever's patch, hyperplasia						1 (2%)		
Liver	N.	(50)		(50)	(5	50)	(50)	
Basophilic focus				1 (2%)		3 (6%)	1 (2%)	
Clear cell focus		2 (4%)		2 (4%)		2 (4%)	8 (16%)	
Eosinophilic focus		11 (22%)		8 (16%)		9 (18%)	11 (22%)	
Hematopoietic cell proliferation				2 (4%)				
Inflammation, chronic		•				2 (4%)	1 (2%)	
Mixed cell focus		1 (2%)						
Necrosis	. 1 h.e.	4 (8%)		3 (6%)		3 (6%)	2 (4%)	
Bile duct, cyst		1 (2%)				1 (2%)		
Bile duct, degeneration	•	1 (2%)				. ,		
Mesentery		(3)			1	(6)	(2)	
Fat, inflammation, chronic		· · .				1 (17%)		
Fat, necrosis		3 (100%)				3 (50%)	2 (100%)	
Pancreas		(49)		(50)	(4	19)	(49)	
Angiectasis							1 (2%)	
Atrophy		2 (4%)						
Basophilic focus				1 (2%)			· · · · ·	•
Cytoplasmic alteration				1 (2%)			en en en la service de la s	
Duct, cyst		1 (2%)				1 (2%)		
Stomach, forestomach		(49)		(50)	(:	50)	(48)	
Inflammation, suppurative						A (0.01)	1 (2%)	
Epithelium, hyperplasia				(10)		4 (8%)	1 (2%)	
Stomach, glandular		(48)		(48)	. (4	+8)	(48)	
Inflammation		1 10 11		1 (2%)				
Ulcer	, ´	1 (2%)		2 (4%)		(1)	•	÷.
Tooth		(3)	· .	(3)	<i>.</i> .	1 (100 07)		ų.
Developmental malformation		2 (67%)		2 (0/%)	.:	1 (100%)		
Dysplasia		1 (20.01)		1 (33%)			* * * ·	
Infiltration cellular, mast cell		1 (33%)						

^a Number of animals examined microscopically at the site and the number of animals with lesion

Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Nitromethane (continued)

an a	0 ppm	18	8 ppm	375	ppm	750	ppm
Cardiovascular System			<u></u>			<u></u>	
Heart	(50)	(50)		(50)		(50)	
Cardiomyopathy	20 (40%)) 20	(40%)	20	(40%)	19	(38%)
Mineralization				1	(2%)		
Artery, thrombosis				1	(2%)		
Atrium, thrombosis	1 (2%)						
Endothelium, hyperplasia				2	(4%)		
Endocrine System			<u></u>				
Adrenal cortex	(49)	(50)		(49)		(48)	
Degeneration	· ·			1	(2%)		
Degeneration, cystic				1	(2%)		
Hematopoietic cell proliferation	1 (2%)						
Hemorrhage				1	(2%)		
Hyperplasia	4 (8%)	4	(8%)	6	(12%)	6	(13%)
Hypertrophy	22 (45%)) 22	(44%)	19	(39%)	22	(46%)
Capsule, hyperplasia				2	(4%)	2	(4%)
Adrenal medulla	(49)	(50)		(49)		(47)	-
Hyperplasia	1 (2%)			1	(2%)	1	(2%)
Islets, pancreatic	(49)	(50)		(49)		(49)	
Hyperplasia	5 (10%)) 4	(8%)	3	(6%)	4	(8%)
Parathyroid gland	(41)	(34)		(38)		(37)	
Cyst				1	(3%)		
Pituitary gland	(47)	(50)		(46)		(47)	
Pars intermedia, hyperplasia		1	(2%)				
Inyroid gland	(50)	(50)		(49)	((48)	(0.07)
	9 (18%) 3	(6%)	2	(4%)	4	(8%)
General Body System	u						•
	· · ·						
Genital System							
Epididymis	(50)	(50)		(50)		(49)	
Granuloma sperm	1 (2%)	1	(2%)		(A M)	1	(2%)
Inflammation, suppurative				1	(2%)		
Penis	(1)	(2)	(100 %)	(3)	(000)	(1)	(100 %)
Inflammation, suppurative	1 (1009	6) <u>2</u>	(100%)	1	(33%)	1	(100%)
Cust	(49)	(50)	(6.01)	(49)	(4.07)	• (48)	(0.01)
Lysi Inflommation chaonic	5 (10%) 3	(0%) (6 <i>1</i> /2)	2	(4%)	4	(8%)
Inflammation, supportive	4 (0%)	3	(0%) (1%)	5	(10%)	4	(8%)
Rilateral cyst		1	(270)	1	(20)		
Prostate	(40)	(50)		(47)	(270)	(46)	
Hyperplasia	· · · · · · · · · · · · · · · · · · ·	(30)		(47)		(+0)	
Inflammation, supportive	1 (270)	·)	(4%)	1	(2%)	2	(4%)
Seminal vesicle	(49)	(40)	(+/0)	1 (40)	(270)	(47)	(470)
Hyperplasia	(*7)	(+9)		(و به) 1	(2%)	(+/)	
Inflammation	1 (2%)			· •	(* , 0)		
	1 (270)	(50)		(50)		(60)	
Testes	(50)	. (50)		(10)		יוור)	
Testes Atrophy	(50) 4 (8%)	· (50)	(4%)	(50)	(8%)	(50)	(8%)

Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Nitromethane (continued)

Hematopoletic System Bone marrow (49) (50) (50) (50) (50) Hyperplasia 1 (2%) 2 (4%) 4 (6%) 1 (2%) Hyperplasia 1 (3%) 2 (100%) 2 (100%) Event, hyperplasia 1 (4%) 1 (4%) 2 (100%) Lymph node, mandbular (40) (39) (37) (43) Hyperplasia 2 (3%) 1 (3%) 1 (3%) 4 (9%) Lymph node, mandbular (40) (39) (37) (44) Lymph node, mandbular (40) (39) (37) (43) Hyperplasia 2 (3%) 1 (3%) 1 (2%) 1 (2%) Lymph node, meandbular (45) 2 (4%) 1 (2%) 1 (2%) Hyperplasia 2 (5%) 1 (3%) 1 (2%) 1 (2%) Lymph node, meandbular (49) (30) (49) (49) Anglectasis 1 (2%) 1 (2%) 1 (3%) 1 (3%) Lymph node, meandbular (49) (49)		0 ppm	18	8 ppm	375	ppm	75	50 ppm
Bon marow (49) (50) (50) (50) (50) (12%) Hyperplasia 1 (2%) 2 (4%) 4 (6%) 1 (2%) Lyperplasia 1 (3%) 1 (4%) 1 (4%) Lyperplasia 1 (3%) 1 (3%) 4 (9%) Lyperplasia 1 (3%) 1 (4%) 1 (4%) Lyperplasia 1 (4%) 1 (4%) 1 (4%) Lyperplasia 1 (4%) 1 (4%) 1 (4%) Lyperplasia 2 (5%) 1 (3%) 1 (3%) 4 (9%) Lyperplasia 2 (5%) 1 (3%) 1 (3%) 4 (9%) Lyperplasia 1 (4%) 1 (4%) Lyperplasia 2 (5%) 1 (3%) 1 (3%) 4 (9%) Lyperplasia 3 (6%) 7 (15%) 2 (4%) 40% Lyperplasia 3 (6%) 7 (15%) 2 (4%) 40% Lyperplasia 3 (6%) 7 (15%) 2 (4%) 40% Hyperplasia 3 (6%) 7 (15%) 1 (3%) 4 (3%) Lyperplasia 3 (6%) 7 (15%) 1 (2%) 1 (2%) Hyperplasia 4 (2%) 1 (2%) 1 (2%) Hyperplasia 4 (2%) 1 (2%) 1 (2%) Hernatopoletic cell profiteration 8 (16%) 9 (13%) 11 (2%) 7 (14%) Hyperplasia 1 (3%) 1 (3%) 400 Necrosis 1 (2%) 1 (2%) 2 (4%) Humatopoletic cell profiteration 8 (16%) 9 (13%) 11 (2%) 2 (4%) Lipperplasia (13%) 1 (3%) 400 Necrosis 1 (3%) 1 (3%) 5 (16%) 3 (6%) Humatopoletic cell profiteration 8 (16%) 9 (12%) 2 (4%) Nuc Hernatopoletic cell profiteration 8 (16%) 9 (12%) 2 (4%) Nuc Hateprotection 9 (50) (50) (50) (50) Nuc Hernatopoletic cell profiteration 1 (2%) 1 (2%) 3 (6%) Hatemation, suppurative 6 (12%) 3 (6%) 8 (16%) 3 (6%) Hatemation, suppurative 1 (2%) 1 (2%) 1 (2%) Infrancot cellar, histocyte 1 (2%) 1 (2%) 3 (6%) (50) Hernothage (50) (50) (50) (50) (50) Hernothage (50) (50) (50) (50) Hernothage (50) (50) (50) (50) Hernothage (50) (50) (50) (50) (50) Hernothage (50) (50) (50) (50) Hernothage (50) (50) (50) (50) Hernothage (50) (50) (50) (50) (50) Hernothage (50) (50) (50) (50) (50) Hernothage (50) (50) (50) (50)	Hematopoietic System			· · · · ·			······································	
Angicensis 1 (2%) 2 (4%) 4 (8%) 1 (2%) Lymph note (3) (1) (1) (2) Line, hyperplasia 1 (100%) 2 (100%) Renal, hyperplasia 1 (100%) 2 (100%) Lymph note, bronchial (26) (26) (24) Lypph note, manifebraic (4%) 1 (4%) 1 (4%) Lypph note, manifebraic (25) 1 (3%) 4 (9%) Lymph note, meanifebraic (47) (46) (47) Lypph note, meanifebraic (47) (46) (47) Angicensis 3 (0%) 2 (4%) Congestion 1 (2%) Hyperplasia 2 (0%) 1 (3%) 1 (3%) 1 (3%) Hyperplasia 3 (0%) 7 (15%) 2 (4%) 1 (3%) Hyperplasia 2 (0%) 1 (2%) 1 (3%) 1 (3%) Hyperplasia 1 (2%) 1 (2%) 1 (3%) 1 (3%) Hyperplasia 2 (0%) 1 (2%) 1 (4%) 1 (3%) Inflammation, supportentive 5 (10%) 1 (2%) 2 (4%) 1 (3%) In	Bone marrow	(49)	(50)		(50)		(50)
Ityperplasia 1 (2.5) 2 (4.5) 4 (4.5) 1 (2.5) 2 (100.5) 1 (1) (1) (2) 2 (100.5) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20) 1 (20)	Angiectasis		ζγ				(* *	1 (2%)
	Hyperplasia	1 (2%)	2	(4%)	4	(8%)		1 (2%)
line, hyperplasia 1 (33%) 2 (100%) Lymp hode, bronchial (26) (26) (24) (28) Lymp hode, mandbular (40) (39) (37) (43) Lymp hode, mandbular (40) (39) (37) (43) Lymp hode, meandbular (40) (39) (37) (43) Lymp hode, meandbular (40) (39) (37) (43) Lymp hode, meandbular (47) (46) (47) (49) Angicetasis 3 (6%) 7 (15%) 2 (4%) 5 (10%) Lymp hode, meinstainal (35) (37) (30) (40) Hyperplasis 2 (6%) 1 (2%) 1 (2%) 7 (14%) Hyperplasis (33) (34) (33) (40) Angicetasis 1 (3%) 1 (3%) 1 (3%) 1 (3%) Fibrosis 1 (3%) 1 (3%) 1 (3%) 1 (3%) Heratopoietic cell poliferation 8 (16%) 9 (18%) 1 (2%) 7 (14%) Hyperplasia 1 (3%) 1 (3%) 1 (3%) 1 (3%) 1 (3%)	Lymph node	(3)	(1)		(1)		(2)
Renal, hyperplasia 1 (10%) Hyperplasia 1 (4%) 1 (4%) 1 (4%) Hyperplasia 1 (4%) 1 (4%) 1 (4%) Hyperplasia 2 (5%) 1 (3%) 1 (3%) 4 (9%) Hyperplasia 2 (5%) 1 (3%) 1 (3%) 4 (9%) Congestion 1 (2%) 1 (3%) 4 (9%) Hyperplasia 3 (6%) 7 (15%) 2 (4%) 5 (10%) Lymph node, meetine (47) (40) 1 (3%) 1 (3%) 1 (3%) Hyperplasia 2 (6%) 1 (3%) 1 (2%) 1 (3%) 1 (3%) 1 (3%) Spleen (49) (50) (50) (50) (49) 1 (2%) 7 (14%) Hyperplasis 1 (2%) 1 (2%) 7 (14%) 1 (3%) 1 (3%) 1 (3%) 1 (3%) 1 (3%) 1 (3%) 1 (3%) 1 (3%) 1 (3%) 1 (3%) 1 (3%) 1 (3%) 1 (3%) 1 (3%) 1 (3%) 1 (3%) 1 (3%) 1 (3%) 1 (3%) 1 (3%) 1 (3%) 1 (3%) 1 (3%) 1 (3%) 1 (3%) 1 (3%) 1 (3%) <td>Iliac, hyperplasia</td> <td>1 (33%</td> <td>6)</td> <td></td> <td></td> <td></td> <td></td> <td>2 (100%)</td>	Iliac, hyperplasia	1 (33%	6)					2 (100%)
	Renal, hyperplasia				1	(100%)		· · ·
Hyperplasia 1 (4%) 1 (4%) T (4%) Hyperplasia 2 (5%) 1 (3%) 1 (3%) 4 (9%) Hyperplasia 2 (5%) 1 (3%) 1 (3%) 4 (9%) Angicctasis 3 (6%) 2 (4%) 1 (2%) 5 (10%) Congestion 1 (2%) 5 (10%) 1 (3%) 4 (9%) Hyperplasia 3 (6%) 7 (15%) 2 (4%) 5 (10%) Lymph node, meanstrainal (35) (37) (36) (40) Hyperplasia 2 (6%) 1 (3%) 1 (3%) 1 (3%) Spleen (49) (30) (50) (49) (49) Fibrosis, focal 1 (2%) 1 (2%) 7 (14%) Hyperplasia, lymphoid 1 (2%) 1 (2%) 7 (14%) Hyperplasia, lymphoid 1 (3%) 1 (3%) 1 (3%) Integumentary System 2 (4%) 3 (6%) 3 (6%) Stan (49) (49) (49) (48) Infarmation, suppurative 5 (10%) 1 (2%) 2 (4%) 1 (6%) Nervous System 1 (2%) 2 (4%)	Lymph node, bronchial	(26)	(26)		(24)		(28)
	Hyperplasia	1 (4%)) 1	(4%)	1	(4%)		
Hyperplasia 2 (5%) 1 (3%) 1 (3%) 4 (9%) Anglectasis 3 (6%) 2 (4%) (49) Congestion 3 (6%) 7 (15%) 2 (4%) 5 (10%) Hyperplasia 3 (6%) 7 (15%) 2 (4%) 5 (10%) Lymph node, mediastinal (35) (37) (36) (40) Lymph node, mediastinal (35) (37) (36) (49) Anglectasis 1 (2%) 1 (2%) (49) (49) Fibrosis, focal 1 (2%) 1 (2%) 7 (14%) Hyperplasia, lomphoid 2 (4%) 1 (3%) 1 (3%) Thymus (33) (34) (33) (40) Necrosis 1 (3%) 1 (3%) 1 (3%) Infarmation, suppurative 5 (10%) 1 (2%) 2 (4%) Prepue, inflammation, suppurative 5 (10%) 1 (2%) 2 (4%) Inflammation, suppurative 6 (12%) 3 (6%) 5 (10%) Horornage (50) (50) (50) (50) Inflammation, suppurative 1 (2%) 1 (2%) 1 (2%)	Lymph node, mandibular	(40)	(39)		(37)		(43)
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Hyperplasia	2 (5%)) 1	(3%)	1	(3%)		4 (9%)
Angiectasis 3 (6%) 2 (4%) 1 (2%) Hyperplasia 3 (6%) 7 (15%) 2 (4%) 5 (10%) Lymph node, mediastinal (35) (37) (36) (40) Lymph node, mediastinal (26%) 1 (3%) 1 (2%) (49) Angiectasis 1 (2%) 1 (2%) (49) (49) Angiectasis 1 (2%) 1 (2%) 7 (14%) Fibrosis, focal 1 (2%) 7 (14%) 1 (3%) Hyperplasia, lymphoid 2 (4%) 33 (40) (40) Necrosis 1 (3%) 1 (3%) 1 (3%) 1 (3%) Infarumation, suppurative 5 (10%) 1 (2%) 2 (4%) 3 (6%) Musculoskeletal System 5 (10%) 1 (2%) 2 (4%) 3 (6%) Nore	Lymph node, mesenteric	(47)	(46)		(47)		(49)
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Angiectasis	3 (6%)) 2	(4%)				
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Lymph node, mediastinal (35) (37) (36) (40) Hyperphasia 2 (6%) 1 (3%) 1 (3%) 1 (3%) Spleen (49) (50) (50) (49) Angiectasis 1 (2%) 1 (2%) 1 (2%) Fibrosis 1 (2%) 1 (2%) 1 (2%) Hematopoietic cell proliferation 8 (16%) 9 (18%) 11 (22%) 7 (14%) Hyperphasia, lymphoid 2 (4%) 3 (33) (40) 1 (3%) Necrosis 1 (3%) 1 (3%) 1 (3%) 1 (3%) Inflammation, suppurative 5 (10%) 1 (2%) 2 (4%) 3 (6%) Musculoskeletal System 500 (50) (50) (50) 46% Inflammation, suppurative 5 (10%) 1 (2%) 2 (4%) 46% Musculoskeletal System 500 (50) (50) (50) (50) Larynx 1 (2%) 2 (4%) 1 (2%) 1 (2%) 1 (2%) Inflaramation, suppurative 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) Larynx (50) <	Hyperplasia	3 (6%)) 7	(15%)	· 2	(4%)	:	5 (10%)
Hyperplasia 2 (6%) 1 (3%) 1 (3%) Spleen (49) (50) (50) (49) Angiectasis 1 (2%) 1 (2%) 1 (2%) Fibrosis 1 (2%) 1 (2%) 1 (2%) Fibrosis 1 (2%) 1 (2%) 7 (14%) Hematopoletic cell proliferation 8 (16%) 9 (18%) 11 (22%) 7 (14%) Hyperplasia, lymphoid 2 (4%) 3 (34) (33) (40) Necrosis 1 (3%) 1 (3%) 1 (3%) 1 (3%) Inflammation, suppurative 5 (10%) 1 (2%) 2 (4%) 7 (14%) Prepue, inflammation, suppurative 5 (10%) 1 (2%) 2 (4%) 3 (6%) Musculoskeletal System 500 (50) (50) (50) (50) Respiratory System 1 (2%) 2 (4%) 1 (2%) 1 (2%) 1 (2%) Inflammation, suppurative 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) Inflammation, suppurative 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%)	Lymph node, mediastinal	(35)	(37)		(36)	• • •	. (40)
	Hyperplasia	2 (6%)) 1	(3%)				1 (3%)
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Perivascular, inflammation, chronic 2 (4%)	Alveolar epithelium, hyperplasia	I (2%)) 1	(2%)	3	(0%)		1 (2%)
rerivascular, inflammation, chronic 2 (4%)	Mediastinum, inflammation, chronic	A (4.00)	`				· · ·	1 (270)
	rerivascular, inflammation, chronic	2 (4%))					

TABLE C5

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Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Nitromethane (continued)

	0 ppm	188 ppm	375 ppm	750 ppm
Respiratory System (continued)				
Nose	(50)	(49)	(50)	(50)
Inflammation, suppurative	1 (2%)	5 (10%)	3 (6%)	1 (2%)
Nasolacrimal duct, inflammation.		- (,-)	- ()	- ()
suppurative	2 (4%)	3 (6%)	10 (20%)	10 (20%)
Olfactory epithelium, atrophy, focal	3 (6%)	8 (16%)		
Olfactory epithelium, degeneration		10 (20%)	50 (100%)	50 (100%)
Olfactory epithelium, metaplasia		1 (2%)	41 (82%)	49 (98%)
Respiratory epithelium, degeneration,				
hyaline	5 (10%)	5 (10%)	50 (100%)	50 (100%)
Respiratory epithelium, metaplasia,	• •	. ,	. ,	
squamous		2 (4%)		
Trachea	(49)	(49)	(49)	(49)
Metaplasia, squamous			1 (2%)	
Special Senses System			· · · · · · · · · · · · · · · · · · ·	
Eye		(1)	(3)	(5)
Inflammation			3 (100%)	4 (80%)
Harderian gland	(49)	(50)	(50)	(49)
Hyperplasia	2 (4%)	2 (4%)	6 (12%)	2 (4%)
Urinary System				· · · · · · · · · · · · · · · · · · ·
Kidney	(50)	(50)	(49)	(49)
Amyloid deposition			1 (2%)	
Hydronephrosis	4 (8%)	1 (2%)	3 (6%)	
Inflammation, suppurative	1 (2%)	4 (8%)	2 (4%)	2 (4%)
Metaplasia, osseous	1 (2%)	4 (8%)	1 (2%)	1 (2%)
Nephropathy	35 (70%)	34 (68%)	33 (67%)	41 (84%)
Cortex, cyst		1 (2%)	1 (2%)	
Pelvis, necrosis				1 (2%)
Renal tubule, hyperplasia	2 (4%)	5 (10%)	2 (4%)	3 (6%)
Renal tubule, mineralization			2 (4%)	
Ureter				(1)
Inflammation, suppurative				1 (100%)
Necrosis				1 (100%)
Urethra		(1)		
Inflammation, suppurative		1 (100%)		
Urinary bladder	(48)	(50)	(49)	(48)
Calculus, gross observation	1 (2%)			
Inflammation, chronic			1 (2%)	
Inflammation, suppurative	1 (2%)	4 (8%)	2 (4%)	3 (6%)
Transitional epithelium, hyperplasia		1 (2%)		2 (4%)

APPENDIX D SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF NITROMETHANE

Table D1	Summary of the Incidence of Neoplasms in Female Mice	
	in the 2-Year Inhalation Study of Nitromethane	188
TABLE D2	Individual Animal Tumor Pathology of Female Mice	
	in the 2-Year Inhalation Study of Nitromethane	192
TABLE D3	Statistical Analysis of Primary Neoplasms in Female Mice	
	in the 2-Year Inhalation Study of Nitromethane	214
TABLE D4a	Historical Incidence of Harderian Gland Neoplasms	
	in Chamber Control Female B6C3F ₁ Mice	219
TABLE D4b	Historical Incidence of Hepatocellular Neoplasms	
	in Chamber Control Female B6C3F ₁ Mice	220
TABLE D4c	Historical Incidence of Alveolar/bronchiolar Neoplasms	
	in Chamber Control Female B6C3F ₁ Mice	221
TABLE D5	Summary of the Incidence of Nonneoplastic Lesions in Female Mice	
	in the 2-Year Inhalation Study of Nitromethane	222

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Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Nitromethane^a

Disposition Summary Animals initially in study 5 Early deaths 5 Accidental deaths 1 Moribund 1 Natural deaths 5 Survivors 0 Died last week of study 7 Terminal sacrifice 2 Animals examined microscopically 5 Alimentary System 6 Gallbladder (40)	50 2 6 7 25 50	50 17 5 1 27 50 (45) (45) (48) (46) (43) (45)	50 22 24 50 (45) (47) 1 ((47) 1 ((47)	0 1 0 3 6 0 (2%)	50 12 2 36 50 (46) (50)
Animals initially in study 5 Early deaths 6 Accidental deaths 7 Moribund 1 Natural deaths 7 Died last week of study 7 Terminal sacrifice 2 Animals examined microscopically 5 Alimentary System (40)	00 2 6 7 25 50	50 17 5 1 27 50 (45) (48) (46) (43) (45)	50 22 50 (45) (47) 1 ((47) 1 ((47)	0 1 0 3 6 0 (2%)	50 12 2 36 50 (46) (50)
Early deaths Accidental deaths Moribund 1 Natural deaths Survivors Died last week of study Terminal sacrifice 2 Animals examined microscopically 5 Alimentary System Gallbladder (40)	2 6 7 25 50	17 5 1 27 50 (45) (48) (46) (43) (45)	2 2 5 (45) (47) 1 (47) 1 (47)	1 0 3 6 0 (2%)	12 2 36 50 (46) (50)
Accidental deaths 1 Moribund 1 Natural deaths 1 Survivors 1 Died last week of study 1 Terminal sacrifice 2 Animals examined microscopically 5 Alimentary System 6 Gallbladder (40)	2 6 7 25 50	17 5 1 27 50 (45) (48) (46) (43) (45)	2 2 5 (45) (47) 1 (47) (47)	1 0 3 6 0 (2%)	12 2 36 50 (46) (50)
Moribund 1 Natural deaths 1 Survivors 1 Died last week of study 1 Terminal sacrifice 2 Animals examined microscopically 5 Alimentary System (40) Gallbladder (40)	6 7 5 50	17 5 1 27 50 (45) (48) (46) (43) (45)	2: 2: 5: (45) (47) 1 ((47)	0 3 6 0 (2%)	12 2 36 50 (46) (50)
Natural deaths Survivors Died last week of study Terminal sacrifice Animals examined microscopically S Alimentary System Gallbladder (40)	7 25 50	5 1 27 50 (45) (48) (46) (43) (45)	2/ 5/ (45) (47) 1 ((47)	3 6 0 (2%)	2 36 50 (46) (50)
Survivors Died last week of study Terminal sacrifice 2 Animals examined microscopically 5 Alimentary System Gallbladder (40)	25 50	1 27 50 (45) (48) (46) (43) (45)	2/ 5/ (45) (47) 1 ((47)	6 0 (2%)	36 50 (46) (50)
Died last week of study Terminal sacrifice 2 Animals examined microscopically 5 Alimentary System Gallbladder (40)	25	1 27 50 (45) (48) (46) (43) (45)	2 5 (45) (47) 1 (47) (47)	6 0 (2%)	36 50 (46) (50)
Terminal sacrifice 2 Animals examined microscopically 5 Alimentary System 6 Gallbladder (40)	5	27 50 (45) (48) (46) (43) (45)	(45) (47) (47) (47)	6 0 (2%)	36 50 (46) (50)
Animals examined microscopically 5 Alimentary System Gallbladder (40)		50 (45) (48) (46) (43) (45)	5((45) (47) 1 ((47)	0 (2%)	50 (46) (50)
Alimentary System Gallbladder (40)		(45) (48) (46) (43) (45)	(45) (47) 1 (47)	(2%)	(46) (50)
Alimentary System Gallbladder (40)	•	(45) (48) (46) (43)	(45) (47) 1 (47)	(2%)	(46) (50)
Gallbladder (40)		(45) (48) (46) (43)	(45) (47) 1 (47)	(2%)	(46) (50)
Tatasting laws salar (40)		(48) (46) (43)	(47) 1 ((47)	(2%)	(50)
Intestine large, colon (49)		(46) (43) (45)	1 (47)	(2%)	
Leiomyoma		(46) (43)	(47)		
Intestine large, cecum (49)		(43)			(50)
Intestine small, duodenum (48)		(45)	(45)		(49)
Intestine small, jejunum (47)		(45)	(47)		(48)
Intestine small, ileum (47)		(46)	(46)	;	(49)
Liver (50)		(49)	(49)		(50)
Hemangiosarcoma 2	(4%)		2 ((4%)	
Hepatocellular carcinoma 7	(14%)	14 (29%)	8 ((16%)	11 (22%)
Hepatocellular carcinoma, multiple 3	(6%)			·	1 (2%)
Hepatocellular adenoma 11	(22%)	12 (24%)	13 ((27%)	22 (44%)
Hepatocellular adenoma, multiple 3	(6%)	13 (27%)	4.((8%)	13 (26%)
Hepatocholangiocarcinoma 1	(2%)				
Histiocytic sarcoma 1	(2%)		2 ((4%)	
Mesentery (7)		(14)	(8)		(11)
Hemangioma		1 (7%)			1 (9%)
Hemangiosarcoma		i in an	1 ((13%)	
Hepatocellular carcinoma, metastatic, liver		1 (7%)			
Sarcoma		1 (7%)			
Sarcoma, metastatic, skin 1	(14%)				(4)
Oral mucosa (1)					(1)
Hepatocholangiocarcinoma, metastatic, liver 1	(100%)			•	(50)
Pancreas (50)		(48)	(48)	10.01	(50)
Histiocytic sarcoma		(10)		(2%)	(60)
Salivary glands (49)		(48)	(49)		(50)
Hemangiosarcoma		1 (2%)			(60)
Stomach, forestomach (50)		(48)	(49)		(50)
Squamous cell papilloma 1	(2%)	1 (2%)	(40)		2 (4%)
Stomach, glandular (49)		(48)	(48)		(50)
Adenoma		1 (2%)			
Cardiovascular System					
Heart (50)		(50)	(50)	н. На страната с	(50)
Henatocellular carcinoma metastatic liver		1 (2%)	(20)		
Henatocholangiocarcinoma metastatic liver 1	(2%)	- (-,0)			
Histiocytic sarcoma	(2%)		1	(2%)	
Pericardium, hepatocellular carcinoma	~~~~		-		
metastatic, liver		1 (2%)			

Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Nitromethane (continued)

	0 ppm	ı	18	8 ppm	375	ppm	750	ppm
Endocrine System								
Adrenal cortex	(50)		(48)		(49)		(50)	
Capsule, adenoma	1 (29	%)	. ,		1	(2%)	1	(2%)
Adrenal medulla	(50)		(48)		(49)		(49)	
Pheochromocytoma benign					1	(2%)		
Bilateral, pheochromocytoma benign					1	(2%)		
Islets, pancreatic	(50)		(48)		(47)		(50)	
Adenoma							1	(2%)
Parathyroid gland	(33)		(34)		(33)		(34)	
Carcinoma	1 (39	%)						
Pituitary gland	(50)		(46)		(48)		(50)	· · ·
Pars distalis, adenoma	9 (18	3%)	10	(22%)	8	(17%)	4	(8%)
Pars intermedia, adenoma			1	(2%)		· ·		
Thyroid gland	(50)		(48)		(48)		(50)	(a , a)
Follicular cell, adenoma	4 (89	%)	1	(2%)	1	(2%)	1	(2%)
General Body System None								
Genital System								<u> </u>
Ovary	(47)		(47)		(48)		(48)	
Cystadenocarcinoma			. ,				1	(2%)
Cystadenoma	2 (49	%)	1	(2%)			• 3	(6%)
Granulosa cell tumor benign			2	(4%)				
Histiocytic sarcoma	1 (29	%)						• , •
Luteoma							1	(2%)
Teratoma benign							1	(2%)
Uterus	(50)		(49)		(49)		(50)	
Adenoma	1 (29	%)	1	(2%)			1	(2%)
Deciduoma benign			1	(2%)				
Hemangioma	2 (4)	%)	5	(10%)				
Histiocytic sarcoma	1 (2)	%)	_		1	(2%)		
Polyp stromal	4 (8	%)	2	(4%)	1	(2%)	3	(6%)
Vagina	(1)							•
Histiocytic sarcoma	1 (10	00%)					•	¢
Hematopoietic System				-				
Bone marrow	(50)		(48)		(49))	(50)	· · · ·
Hemangiosarcoma	1 (2	%)			2	(4%)		
Histiocytic sarcoma	1 (2	%)						
Mast cell tumor malignant	1 (2	%)						(a m)
Sarcoma, metastatic, skin							1	(2%)
Lymph node	(8)		(6)		(5))	(6)	
Lymph node, bronchial	(39)		(36)		(40))	(40)	
Hepatocellular carcinoma, metastatic, liver		<i>M</i> >	2	(6%)				
Hepatocnolangiocarcinoma, metastatic, liver	1 (3	70)			(20)		(40)	
Lympn node, mandibular	(43)	Ø7 \	(34)	ł	(38)	(43)	
HISUOCYUC SARCOMA	1 (2	70)	140			(3%)	(40)	
Histiocytic sarcoma	(48)	%)	(40)	,	(46	(2%)	(48)	

Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Nitromethane (continued)

	0 ppm	188 ppm	375 ppm	750 ppm
Hematonoietic System (continued)		······································		
Lymph node mediastinal	(38)	(37)	(35)	(41)
Carcinoma metastatic barderian gland	(50)	(57)	(33)	(41)
Henatocellular carcinoma metastatic liver		1 (3%)	1 (570)	
Henatocholangiocarcinoma, metastatic liver	1 (3%)	1 (570)		•
Histiocytic sarcoma	1 (570)		1 (3%)	
Soleen	(50)	(48)	· (40)	(50)
Hemangiosarcoma	(50)	1 (2%)	1 (2%)	(50)
Histiocytic sarcoma		x (270)	2(4%)	
Mast cell tumor malignant	1 (2%)		2 (470)	
Thymus	(43)	(39)	(41)	(47)
Henatocellular carcinoma metastatic liver	(1 (3%)	(41)	(47)
Henatocholangiocarcinoma metastatic liver	1 (2%)	1 (370)		•
Mast cell timor malignant	1(2%)			
Thymoma benign	1(2%)			
Thymoma bonign	1 (270)			
				·····
Intommontory System				
Manual And	(50)	(48)	(40)	(50)
Adamama	(50)	(48)	(49)	(50)
Adenoma	0 (40)	0 (49)	1(2%)	
Carcinoma	2 (4%)	2 (4%)	2 (4%)	(50)
Skin	(49)	(47)	(50)	(50)
Squamous cell carcinoma			.1 (2%)	
Subcutaneous tissue, hemangiosarcoma			2 (4%)	0 (177)
Subcutaneous tissue, sarcoma	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Musculoskeletal System				
Rone	(50)	(50)	(50)	(50)
Hemangiosarcoma	(50)	(30)	2 (4%)	(55)
Osteosarcoma		1 (270)	1 (2%)	
Nervous System		· · · · · · · · · · · · · · · · · · ·		
Brain	(50)	(50)	(49)	(50)
				· · · · · · · · · · · · · · · · · · ·
Respiratory System				
Larynx	(49)	(48)	(49)	(50)
Lung	(50)	(50)	(49)	(50)
Alveolar/bronchiolar adenoma	3 (6%)	2 (4%)	2 (4%)	8 (16%)
Alveolar/bronchiolar adenoma, multiple	, ,	1 (2%)		1 (2%)
Alveolar/bronchiolar carcinoma		3 (6%)	5 (10%)	
Alveolar/bronchiolar carcinoma, multiple	94	,	- (3 (6%)
Carcinoma, metastatic harderian gland		· · · · · · · · · · · · · · · · · · ·	2 (4%)	
Hepatocellular carcinoma metastatic liver	2 (4%)	5 (10%)	- (170)	3 (6%)
Hepatocholangiocarcinoma metastatic liver	1 (2%)	- (1070)		- (-,-)
Histiocytic sarcoma	1 (2%)		2 (4%)	
Osteosarcoma metastatic hone	- (=,0)	.*	1 (2.%)	
Sarcoma, metastatic, skin				1 (2%)
	*			

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Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Nitromethane (continued)

	0 ppm	188 ppm	375 ppm	750 ppm
Respiratory System (continued)				
Lung (continued)	(50)	(50)	(49)	(50)
Mediastinum, hemangioma	1 (2%)			
Mediastinum, hemangiosarcoma	1 (2%)			
Mediastinum, hepatocellular carcinoma,				
metastatic, liver		2 (4%)		
Mediastinum, hepatocholangiocarcinoma,				
metastatic, liver	1 (2%)			
Mediastinum, mast cell tumor malignant	1 (2%)			
Nose	(50)	(49)	(50)	(50)
Snecial Senses System	<u></u>			
Harderian gland	(49)	(49)	(50)	(50)
Adenoma	4 (8%)	6 (12%)	15 (30%)	16 (32%)
Adenoma, multiple	1 (2%)	1(2%)	1 (2%)	3(6%)
Carcinoma	1 (2%)	2 (4%)	4 (8%)	2(4%)
Carcinoma, multiple	· ,			1 (2%)
Urinary System			· · · · · · · · · · · · · · · · · · ·	
Kidney	(50)	(48)	(49)	(50)
Hepatocholangiocarcinoma metastatic liver	1 (2%)	(+0)	(42)	(50)
Histiocytic sarcoma	(270)		2 (4%)	
Osteosarcoma, metastatic, bone			1(2%)	
Urinary bladder	(49)	(47)	(47)	(49)
Histiocytic sarcoma	(12)		1 (2%)	
Systemic Lesions	·····			
Multiple organs ^b	(50)	(50)	(50)	(50)
Histiocytic sarcoma	2 (4%)	(50)	3 (6%)	(30)
Lymphoma malignant	9 (18%)	7 (14%)	7 (14%)	7 (14%)
Neonlasm Summary				
Total animals with primary peoplesms ^C	38	15	12	16
Total primary peoplasms	30	40	43	40 110
Total animals with benign neonlasms	31	7.) 20	32	110
Total benign neoplasms	48	57 67	55	40 87
Total animals with malignant neonlasme	76	02 7A	<u> </u>	. 04 .
Total malignant neoplasms	35	24	40 47	21
Total animals with metastatic peoplasms	4	5	3	20 4
	-		•	

^a Number of animals examined microscopically at the site and the number of animals with neoplasm

^b Number of animals examined intersecopeanly at the site that the

^c Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE D2

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+: Tissue examined microscopically A: Autolysis precludes examination M: Missing tissue I: Insufficient tissue X: Lesion present Blank: Not examined

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TABLE D2

Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nitromethane: 0 ppm (continued) 7 7 7 7 7 77 7 777 Number of Days on Study 3 3 3 3 3 5 5 5 5 6 6 66 77 777 5 5 5 6 4 4 4 4 4 4 4 5 1 1 1 1 1 1 1 1 1 Total 4 4 1 1 1 2 2 2 4 4 2 2 2 4 4 0 0 0 2 3 **Carcass ID** Number 0 0 1 2 3 Tissues/ 3 8 9 4 9 4 5 5 7 8 0 1 9 0 7 3 6 7 3 9 2 6 9 5 4 Tumors **Alimentary System** 48 Esophagus + + Μ Gallbladder 40 м м ĩ + 4 4 4 4 + + 49 Intestine large, colon 50 Intestine large, rectum 49 Intestine large, cecum Intestine small, duodenum 48 47 Intestine small, jejunum Intestine small, ileum 47 + + + 4 + M + + + Liver 50 2 Hemangiosarcoma х Hepatocellular carcinoma х х х 7 Hepatocellular carcinoma, multiple 3 х х ххх Х 11 Hepatocellular adenoma Х Hepatocellular adenoma, multiple Х х 3 Hepatocholangiocarcinoma 1 Histiocytic sarcoma 1 Mesentery 7 + Sarcoma, metastatic, skin 1 Oral mucosa 1 Hepatocholangiocarcinoma, metastatic, liver 1 Pancreas 50 Salivary glands 49 + Stomach, forestomach 50 + ++ + + Squamous cell papilloma X 1 Stomach, glandular +49 Cardiovascular System 50 Heart Hepatocholangiocarcinoma, metastatic, liver 1 Histiocytic sarcoma 1 **Endocrine** System Adrenal cortex 50 Capsule, adenoma х 1 Adrenal medulla 50 + Islets, pancreatic 50 ++ + + + Parathyroid gland MM М + М + + + Μ 1 + Μ M + М Μ ++ + М + Μ 33 м + Carcinoma X 1 Pituitary gland 50 + 9 Pars distalis, adenoma Х X X х х Х Thyroid gland + + 50 + х Follicular cell, adenoma х 4 **General Body System** None

Individual Animal Tumor Pathology	of Fer	nal	le]	Mic	ce i	in t	he	2-`	Yea	ar	Inl	nal	ati	on	Sti	udy	y o	f N	Nitı	ron	net	ha	ne	. () pj	pm (conti	nued)
Number of Days on Study	3	 3 7 6	3	4	436	4 3 6	5 7 4	5 7 6	5 9 7	6 0 0	6 1 7	6 1 8	6 3 2	6 3 2	6 5 7	6 6 3	6 6 7	6 6 7	6 8 1	6 9 1	692	6 9 2	7 0 7	7 0 7	7 1 6			
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Carcass ID Number	1 1 1	1 0 7	1 3 1	1 1 6	1 3 7	1 3 8	1 0 1	1 3 0	1 1 3	1 2 2	1 3 2	1 3 6	1 1 0	1 5 0	1 2 8	1 0 4	1 0 5	1 3 3	1 4 6	1 1 4	1 4 1	1 4 8	1 1 2	1 4 2	1 3 5			
Genital System																					~~~					· · ·		è
Clitoral gland	+)	1	- M	I M	IМ	М	м	+	+	+	÷	+	+	+	+	.+	+	+	+	+	+	+	+	+			
Ovary	+	+	1	- +	• +	+	+	+	+	+	+	+	+	+	I	I	+	+	+	+	+	+	+	+	+			
Cystadenoma								Х						Х														
Histiocytic sarcoma																					х							•
Uterus	- +	+	+	- +	· +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
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Histiocytic sarcoma																												
Hematopoietic System					·																	<u> </u>	-					· .
Bone marrow	+	- +	+	- +	+	+	+	+	+	+	+	+	.+	+	+	+	+	+	+	+	+	+	+	+	+			
Hemangiosarcoma																												
Histiocytic sarcoma														•							х							
Mast cell tumor malignant																				Х								
Lymph node				+	+				+	+		+												+				
Lymph node, bronchial Hepatocholangiocarcinoma, metastatic,	+	- M	1 +	- +	+	M	М	+	М	+	+	+	+	+	+	+	+	+	M	+	+	М	+	+	M			
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Lymph node, mandibular	-+	- +	}	- M	I +	+	+	.+	+	+	+	÷	М	÷	+	,+	+	+	+	Μ	+ v	Μ	+	+	+		,	
Lymph node mesenteric	+		4	- +	+	+	+	+	+	+	+	+	÷	+-	+	+	· +	+	+	+	л +	+	+	+	+	÷ .		
Histiocytic sarcoma						•	•	•		•	•	•	•			•			•		x					,		
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Hepatocholangiocarcinoma, metastatic,																									. '			
liver											х																	
Spleen	+	- H		- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷			
Mast cell tumor malignant																				х								
Thymus	+	• +	• +	- +	. +	+	+	+	+.	+	+	+	+	+	+	+	+	+	м	+	м	+	м	+	I			
Hepatocholangiocarcinoma, metastatic,											v																	
Mast cell tumor malignant	,										л									x	, ·	. •						
Thymoma benign														х														
																					~~~							
Integumentary System						·		,																				
Mammary gland	+	- +	- +	- +	+	+	+	+	+	+	+	+	·+	+	+	+	+	+	+	+	+	+	+	+	+			
Carcinoma													·	L	-		x		-1-	-	+			н.	т			
Subcutaneous tissue, sarcoma	7	+	- 1	- +	• •	А.	т	Ŧ	т	Ŧ	т	Ŧ	Ŧ	Ŧ	т	<b>T</b>	. •	т	Ŧ	Ŧ	Τ.	x	т ,	Ţ	τ.			
Musculoskeletal System			<u> </u>							<u>.</u>									<u> </u>					~~~				
Bone	.+	• 4	+	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Nervous System																												,
Brain	+	- +	- +	- +	+	+	+	+	+	t	+	+	÷	+	+	+	+	+	+	+′	' <b>+</b>	+	+	+	+			
										~~~																		

TABLE D2

Individual Animal Tumor Pathology	of Fe	m	ale	e N	/lic	e i	in 1	the	2-	Ye	ar	In	hal	lati	on	St	ud	y a	fr	liti	ron	net	ha	ne	; () p	pm (continued)
Number of Days on Study	3	- 7 5	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	. 7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	1 (3)	1 0 8	1 1 9	1 2 4	1 3 9	1 4 4	1 4 5	1 1 5	1 1 7	1 1 8	1 2 0	1 2 1	1 2 9	1 4 0	1 4 7	1 2 3	1 2 6	1 2 7	1 4 3	1 4 9	1 0 2	1 0 6	1 0 9	1 2 5	1 3 4	Total Tissues/ Tumors
Genital System Clitoral gland Ovary Cystadenoma Histiocytic sarcoma Uterus Adenoma Hemangioma Histiocytic sarcoma Polyp stromal Vagina		++ ++ +	++++		 · I · +	- M + - +	1 + - + - +	- + - +	+ - + X	 · + · +	- +	- +	- + - +	· + · +	+++++	 + +	M + +	+++++++++++++++++++++++++++++++++++++++		+++ +	 + +	++++	+++++	+++++	++ + X	+++++	39 47 2 1 50 1 2 1 4 1
Histocytic sarcoma Hematopoietic System Bone marrow Hemangiosarcoma Histiocytic sarcoma Mast cell tumor malignant Lymph node Lymph node, bronchial		• +	++	++	 - + - +	- +	 	- +	- +	- + - +	- 4	- + + +	- + . N	 +	+	+	+	+	+ M	+	+	+ M	+	+ x +	+	+	50 1 1 1 8 4 39
Hepatocholangiocarcinoma, metastatic, liver Lymph node, mandibular Histiocytic sarcoma Lymph node, mesenteric Histiocytic sarcoma Lymph node, mediastinal Hepatocholangiocarcinoma, metastatic, liver		+ +	++++	+ + +	- + - + - N	+ + 11 -+	+ 4 ⊦ 4	- + - +	- M - +	1 + · + · +	 	- +	- + - +	· + · M	+ (+ +	+	+ M +	+++++	M + +	+ + M	+ +	M + M	+ + +	+++++	+ + +	+ + M	1 43 1 48 1 1 38
Spieen Mast cell tumor malignant Thymus Hepatocholangiocarcinoma, metastatic, liver Mast cell tumor malignant Thymoma benign		+	+	+	- +		⊢ ⊣ ⊢ ⊣		- +	- +		⊦ +	- + - N	· +	• +	+	+ M	+	+ M	+	+	+	+	+	+	• +	1 43 1 1 1
Integumentary System Mammary gland Carcinoma Skin Subcutaneous tissue, sarcoma		 + +	++	+	 - +	 	 	 	- + - +	- +		 + +	- +	 - +	· +	· +	++	+ +	+ X +	+	+++	++	++	+ +	 + +	· +	50 2 49 1
Musculoskeletal System Bone		+	+	+	- +				- +			 ⊦ +	+		· +		+	+	+	+	+	+	+	+	+	• +	50
Nervous System Brain		+	+	 +	- +					+			+	 · +		· +	+	+	+	+		 +		+	+		50

195

Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nitromethane: 0 ppm (continued)

																												`	
Number of Days on Study			3 0 1	3 7 6	3 8 5	4 0 1	4 3 6	4 3 6	5 7 4	5 7 6	5 9 7	6 0 9	6 1 7	6 1 _, 8	6 3 2	6 3 2	6 5 7	6 6 3	6 6 7	6 6 7	6 8 1	6 9 3	6 9 3	6 9 3	7 0 7	7 0 7	7 1 6		
Carcass ID Number	;		1 1 1	1 0 7	1 3 1	1 1 6	1 3 7	1 3 8	1 0 1	1 3 0	1 1 3	1 2 2	1 3 2	1 3 6	1 1 0	1 5 0	1 2 8	1 0 4	1 0 5	1 3 3	1 4 6	1 1 4	1 4 1	1 4 8	1 1 2	1 4 2	1 3 5	×	
Respiratory System Larynx Lung Alveolar/bronchiolar adenoma Henatocellular carrinoma metastatic			 + +	++	++	++	I +	++	+++	+ +	++	++	++	+ +	++	+++	+ +	++	++	++	++	++	++	+ +	++	+++	+ + X		 ·
 Hepatocentular caremonia, metastatic, liver Histiocytic sarcoma Mediastinum, hemangioma Mediastinum, hemangiosarcoma 		. •								X			X		s				-	•	x		x	• .					
Mediastinum, hepatocholangiocarcinon metastatic, liver Mediastinum, mast cell tumor maligna Nose Trachea	ma, ant		++	· + · +	+++	++	+++++	+++	, + +	+++	+++	+++	x + +	+++	+++	+++++++++++++++++++++++++++++++++++++++	++++	+ +	+++	+ +	+ +	x + +	++	+++	+++	+ +	+ +		•
Special Senses System Harderian gland Adenoma Adenoma, multiple Carcinoma			"+ "	• +	+	+	+	+	+	+	,+	* x	+	+	+		+	+ x	+	+ x	+	+	+	+	+	+ X	+		
Urinary System Kidney Hepatocholangiocarcinoma, metastatic liver Urinary bladder	 2,		+ +	· +	+	+	+	++	++	++	++	++	+ x +	++	++	++	++	+	++	+	+	+	++	+	++	+	+		
Systemic Lesions Multiple organs Histiocytic sarcoma Lymphoma malignant			+	 +	+ . x	+ x	+	+	+	+	+ x	+ x	+	+ x	+	+	+	+	+ x	+	+	+	+ X	+	+	+ x	+		

TABLE D2

Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nitromethane: 0 ppm (continued) 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 Number of Days on Study 4 4 4 4 4 5 5 5 5 5 5 5 5 6 6 6 6 6 7 7 7 7 7 4 4 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 Total **Carcass ID Number** 0 0 2 3 4 4 1 12 2 2 4 2 2 2 4 4 Ò 0 0 2 3 Tissues/ 1 1 4 3 8 9 4 9 4 5 5 7 8 0 1 9 0 73 6 73 9 2 954 6 Tumors **Respiratory** System Larynx 49 + + + + + + + Lung + 50 + + + + Alveolar/bronchiolar adenoma х x 3 Hepatocellular carcinoma, metastatic, liver 2 Hepatocholangiocarcinoma, metastatic, liver 1 Histiocytic sarcoma 1 Mediastinum, hemangioma Х 1 х Mediastinum, hemangiosarcoma 1 Mediastinum, hepatocholangiocarcinoma, metastatic, liver 1 Mediastinum, mast cell tumor malignant 1 Nose 50 Trachea 50 **Special Senses System** Harderian gland 49 Adenoma х 4 Adenoma, multiple х 1 Carcinoma 1 **Urinary System** Kidney 50 Hepatocholangiocarcinoma, metastatic, liver 1 Urinary bladder 49 + + + + + + + + + + + I + + Systemic Lesions Multiple organs 50 x Histiocytic sarcoma 2 Lymphoma malignant х х 9

TABLE D2Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nitromethane:188 ppm

· · · · · · · · · · · · · · · · · · ·		1.11	•													_			_			•	_			'				 	_
			3	3	4	4	4	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	. 7.	7	. 7	. 7	,			
Number of Days on Study			4	. 5	1	2	4	3	5	6	6	6	7	8	3	3	4	5	5	6	6	9	9	3	3	3	3				
	:		5	7	6	6	5 1	4	5	4	9	9	9	1	7	9	6	3	6	3	5	3	3	1	4	4	4	Ļ			
			3		3	3		3		3	3	3	3	3.	3	3	3	3	3	3	3	3	3	3	3	3	3			 	
Carcase ID Number			1	2	3			1	0	1	1	3	2	2	0	1	1	1	3	1	2	1	3	1	2	2	3	2			
Carcass ID Indinder				0		7	1	6		1	2	1	0	4	4	3	5	0	5	0	7	5	2	7	2	2	7	,			
<u></u>						. ,			0					. 4	. 4				5	0		5				. 2	. '	•	• •	 	
Alimentary System	~																														
Esophagus			÷		- +	+ +	+ -	+ +		+ +	- +	- +	·A	+	· A	+	+	+	+	+	+	+	+	+	-	+ +	+ +	ł			
Galibladder			4	⊦ -	⊢ +	+ +	+ -	+ +	- A	A	. +	- +	• +	+	A	Α	+	+	+	+	+	+	+	+		+ +		+			
Intestine large, colon			+	+' -	+ +	+ +	+ -	+ +		+ +	- +	- +	·A	+	A	+	+	+	+	+	+	+	+	+	•	+ +	۲.۲	+			
Intestine large, rectum			-	- ۱	+ +	+ +	+ -	+ +		⊦ A	. +	• +	· A	+	A	Α	+	+	+	+	+	+	+	+	-	+ +		+	,		. 3
Intestine large, cecum			-	+ -	+ +	+ +	+ -	+ • +	- A	A	. +	- +	·A	+	A	+	+	+	+	+	+	+	+	+	-	۲۱	+ +	ł			
Intestine small, duodenum			-	+ -	+ +	+ +	+ -	+ +	- A	M	1+	- M	I A	+	A	Α	+	+	+	+	+	+	+	+	-	+ +	+ +	÷	۰.		
Intestine small, jejunum			-	⊦ -	H. H	+ +	+ -	+ +	⊢ A	A A	. +	- +	·A	. +	A	Α	+	+	+	+	+	+	+	+	•	+ +		+ ,			
Intestine small, ileum			• +	+ -	+ +	+ +	+ -	+ +	F A	\ +	- +	- +	·A	+	A	Α	+	+	+	+	+	+	+	+	-	+ +	+ - +	+ :			
Liver			+	+ -	+ +	+ +	+ -	+ +	+ +	+ +	- +	- +	• +	+	A	+	+	+	+	+	+	+	+	+	-	H. H	Η	+			
Hepatocellular carcinoma								X	X	X	X		Х	X		Х	Х		. •,												
Hepatocellular adenoma	4									·X	[Х					х		Х							X	ζ.				
Hepatocellular adenoma, multiple								X	ζ.									Х					Х	X			Х	K			
Mesentery						-	۲.							+			+									-	F			ς.	
Hemangioma				•																											
Hepatocellular carcinoma, metastatic,	,																														
liver																	Х														
Sarcoma																															
Pancreas			-	+ •	+ -	+ +	+ -	+ +	+ -	+ +	+ +	- +	·A	. +	À	· +	+	+	+	+	+	+	+	+	-	+ +		+			
Salivary glands				+ •	+ -	+ - +	+ -	+ +	+ -	+ +	+ +	- +	- A	+	·A	+	+	+	+	+	+	+	+	• +		+- +	+ -	+	,		
Hemangiosarcoma																												. ,			,
Stomach, forestomach		· ·	-	+ •	+ -	+ +	+ •	+ +	F 4	+ +	- +	- +	- A	+	A	+	+	+	+	÷	+	+	+	• +		+ +	۰. ۲	+			
Squamous cell papilloma																											· 3	ĸ			
Stomach, glandular				+ •	+ -	+ +	+ •	+ +	+ -	+ +	- +		- A	+	· A	. +	+	+	+	+	+	+	+	• +		+ +	+ -	ł			
Adenoma	2.5																			۰.	÷.										
																			~~~				÷.,		-					 	
Cardiovascular System																															
Blood vessel	•				t									•																	
Heart			-	+ -	+ •	+ -	+ •	+ -	+ -	+ +	- +	- +	- +	· +	• +	+	+	+	+	+	+	+	+	• +	•	+		+			
Hepatocellular carcinoma, metastatic	,																														
liver																	X														
Pericardium, hepatocellular carcinom	ia,																•••														
metastatic, liver	• •													• ,			X														
Endocrine System											-			,																	;
Adrenal cortex				+ •	+ -	+ -	+ •	+ -	+ -	+ +	- 4	+ -1	- A	. +	- A	+	+	+	+	+	+	+	+	• +		+ +	+ -	+			-
Adrenal medulla	~			+ •	+ •	+ •	+ -	+ -	+ -	+ +	⊢ -1	⊢ -1	- A	. +	- A	+	+	+	+	+	+	+	+	. +		+ +	⊢ -	ł			
Islets, pancreatic	1.5			+ •	+ •	+ -	+ •	+ -	+ -	+ +	+ 4	+ +	- A	. +	- A	+	+	+	+	+	+	+	+	- +		+ +	+ +	+			
Parathyroid gland			N	<b>N</b> .	+ +	+ -	+ -	+ N	4 1	MN	ΛŇ	1 -	- M	1 +	• M	[+	+	+	+	+	+	+	M	1 +	. ,	+ ' +	+ -	+			
Pituitary gland				+ .	+ 1	м	+ -	+ -	+ -	+ +	F 4	F 4	- A	. +	- A	+	+	+	+	+	+	+	+	• +		+ -	+ -	+			
Pars distalis adenoma																,	-		x	,			x			2	ζ				
Pars intermedia, adenoma																						х						•			*
Thyroid gland				+ •	+ •	+ -	+ •	+ -	+ -	+ +	+ +	+ +	- A	. +	- A	+	+	+	+	+	+	+	• +	· +		+ -	+ -	+			
Follicular cell adenoma								-	-					x				,	-		-		-						_		
· · · · · · · · · · · · · · · · · · ·		• •		`				,							_												_			 	

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Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nitromethane: 188 ppm (continued)

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· · · ·	7	1	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7		
Number of Days on Study	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	-3		
	4	ł	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7		
· · ·		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	Tc	otal
Carcass ID Number	4	F	0	0	2	2	3	3	4	4	4	5	0	0	0	1	1	2	4	4	0	2	2	3	3	4	Tissu	es/
	7	1	1	3	1	5	2	4	0	3	6	0	2	5	6	8	9	6	2	4	9	3	8	6	9	8	Tum	ors
Alimentary System		-													<u></u>										·			
Esophagus		÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	+		48
Gallbladder		+	÷	+	+	+	+	+	+	+	+	. +	+	+	+	÷	+	+	÷	+	+	+	, +	+	Ň	- -		45
Intestine large, colon	· .	+	, +	+	+	+	+	+	+	+	, +	· +	+	+	+	+	+	, +	+	+	+	+	+	+	+	+		49
Intestine large rectum		Ļ	+	+	<u>ب</u>	+	+	.+	+	+	+	. <b>.</b>	+	+	+	+	+	+	+	+	+	+	+		+	- -		46
Intestine large cecum		+	+	, +	+	+	+	+	+	+	4	· +	•	, +	+	+	+	+	+	+	+	+	+	+	+	+		46
Intestine small duodenum			÷	- -	, 	+		י ב			- -		, +	، ــــــــــــــــــــــــــــــــــــ	м	+	ب	+	, ,	, ,	, 		، ــــــــــــــــــــــــــــــــــــ		1	1		13
Intestine small jejunum		+	, +	, +	- -	, +	+	, +	, +	+	, -		, +	- -	- -	+	ب	, +	, +	4	+	+	- -	+	, ,	- -		45
Intestine small ileum		1 	т Т	- -	т 	 بد	т Т	т 	г -		T L	۲ ـــــ	т Т	т -	т —	1-	T L	-1 -1	-	т —	1	- ب	Ŧ	т 	т 	т 		45
Liver		T L	т 	т 	т 	т 	т 4	т -	т -	т 	т 1		т 	т -	т -	т 		т 	т 	т 	т 	т 		т 				40
Uenatocallular corainomo		T V	т	т	Ŧ	т	т	. <b>T</b>	т	v	т	- т	Ŧ	Ŧ	v	т	v	v	-	т	т	т	т	т	v	т		47
Hepatocentular carcinoma	-	^				v				л	v	v			л		л	л			v			v	A V	v		14
Hepatocellular adenoma			v		v	л			v		л	л	v		v	v			v		л	v		л	л	л		12
Meantaine			<u>л</u>		<b>.</b>				<u>л</u>				х		<u>х</u>	х			л			<u>х</u>						13
Mesentery		+	+		+	+			+	+					+					+	+	+						14
Hemangioma	4	7																										1
Hepatocellular carcinoma, metastatic,																												
liver																												1
Sarcoma	2	K																										1
Pancreas		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Salivary glands	• •	+	+	+	+	+	+	+	+	+	+	· +	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Hemangiosarcoma															Х													1
Stomach, forestomach		t	+	+	+	+	+	+	+	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•	48
Squamous cell papilloma																												1
Stomach, glandular		+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Adenoma														Х														1
Cardiovascular System																												
Blood vessel																												1
Heart		+	+	+	+	+	+	+	+	+	+	· +	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hepatocellular carcinoma, metastatic,																												
liver																										•. •		1
Pericardium, hepatocellular carcinoma,																												
metastatic, liver																												1
Endocrine System		-																										
Adrenal cortex		÷	+	+	+	+	+	+	+		-	<b>.</b>		4	+	+	+	+	+	4	+	+	+	+	+	+		48
Adrenal medulla		+	-	, +	+	+	, _	, 	, 		L	, , ,	, 					, 1		, ,	ــــ					- -		40
Islets nancreatic		+	+	ب	г -	г —	- ب	т Ц	т -		τ ر	ד د .	יד- נ	т Ц	т -	т -	т Т	т -	т –	T L	т -	т - т	т Т	т -	т 	т 		18
Parathyroid gland		г +		т 1	Ť	T M	т -	т 	- -	÷۲ بر	т 	т .т	Ť	т 	т Т	M	т -	M	M	T M	т -	т -	T M	т Т	т . м	T L		34
Pituitary gland		Т	т -	т ,	т 	141	. <del>.</del>	Ť	-		- T - ,	1	T*	+	<b>T</b>	141	Ť	141	141	171	- T	- T*	141	+	141	. т ( т		54 16
Pare distalie adenome		т	v	T V	+	Ŧ	+ v	+	+	+	4	+	+ v	+ v	+	+	+	+	+	+ v	+	+	+ v	+	IVI	+		40
ano unitario, autificialia Dara intermedia, adaptere			л	л			л						А	л						л			л					10
Thuroid aland						,			,				,											۰.		,		1 40
Follioular cell adenomo		т	Ŧ	+	+	+	+	+	+	+	+	• +	+	+	Ŧ	+	+	+	+	+	+	+	+	+	+	+	•	40
Fonculai cen, adenoma																												1

199

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Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nitromethane: 188 ppm (continued)

												_				_							_					
Number of Days on Study		3 4 5	3 5 7	4 1 6	4 2 6	4 4 1	5 3 4	5 5 5	5 6 4	5 6 9	5 6 9	5 7 9	5 8 1	6 3 7	6 3 9	6 4 6	6 5 3	6 5 6	6 6 3	6 6 5	6 9 3	6 9 3	7 3 1	7 3 4	7 3 4	7 3 4		
Carcass ID Number		3 1 4	3 3 0	3 3 8	3 0 7	3 4 1	3 1 6	3 0 8	3 1 1	3 1 2	3 3 1	3 2 9	3 2 4	3 0 4	3 1 3	3 4 5	3 4 9	3 3 5	3 1 0	3 2 7	3 1 5	3 3 3	3 1 7	3 2 0	3 2 2	3 3 7	•	
General Body System None																												
Genital System				-				<u> </u>		_	_		_	_		_		_		_		_			_			
Clitoral gland		+		· N	1+	+	+	м	+	м	+	А	+	м	+	+	+	+	+	м	м	+	+	+	+	+		
Ovary		+	• +	• +	• +	+	+	+	+	+	+	A	+	A	+	+	+	+	ī	+	+	+	+	+	+	+		
Cystadenoma	•	•			•		•	·		•		••	•	••	·	•		•	^	•		•.		·		•		
Granulosa cell tumor benign	•						•														х							
Uterus		+	• +	• +	• +	+	÷	+	+	+	+	+	+	А	+	+	+	+	+	+	+	+	+	+	+	+		
Adenoma						-				,														х				
Deciduoma benign										•															х			
Hemangioma										х					1							Х				Х	. •	
Polyp stromal																												· .
Homotopointin System			_											· ·				-									 <u></u>	
Rematopoletic System				· .														-1			· .					-		
Bone marrow		-	• +	• •	· •	Ŧ	Ŧ	Ŧ	т	Ŧ	Ŧ	A	т	А	т	т	т	Ŧ	- -	Ŧ	- -	Ŧ	- -	т	. +	Ŧ		
Lymph node	. •					L	м	-1-	-	л.	Т	M	1		-	т	м		+	т	-	-	· _	м	т м	-		
Hanatocellular carcinoma metastatic		4	· 1		1	-	141	7	7	т	-	141	-	л	-1	г	141	F	1	1	1	΄.	'	1.1				
liver									x							x												
Lymph node mandihular		N	1 N	ſ.↓		-	+	+	- -	+	+	Δ	+	Δ	+	+	+	м	м	+	+	м	+	+	м	+		
Lymph node, mesenteric		N	1 14		. м	, 1	+	+	+	+	, +	Δ	÷	м	+	+	+	+	+	+	+	+	+	+	+	+		
Lymph node, mediastinal		N	1 - 1 -	. v	( <del>-</del>	ัพ	· +	+	+	м́	+	Δ	м́	A	+	+	+	Ň	÷.	+	+	Ň	+	+	÷.	+		
Hepatocellular carcinoma, metastatic,			• •		• •	141		•							•	x			•	•	•					•		
Spleen		· .			+	+	+	+	+	+	+	Α	+	Α	+	+	+	+	+	+	+	+	+	·+	+	+		
Hemangiosarcoma						. '	'	•	·	•	·	••	•		·	•		·	•									
Thymus -		+	- +		- м	í +	+	+	м	+	+	м	+	Α	+	+	+	+	+	+	+	+	+	М	Ι	+		
Henatocellular carcinoma, metastatic,							-														,			•		1		
liver																х												
				_				<u>.</u>		-											-						 	
Integumentary System					. `							. :																
Mammary gland		+	+	- N	1 +	+	+	+	+	+	+	А	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Carcinoma											X														X			
Skin		+	- +	- N	1 +	· +	+	М	+	+	+	М	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Subcutaneous tissue, sarcoma								•		u		_		х	_													
Musculoskeletal System	-					1												_										-
Bone		-	+	- +	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Hemangiosarcoma																												•
Normous System	<u> </u>				_					<u> </u>	-					<u> </u>		<u> </u>	-								 	
Brain				ہ ۔	L L		<b>.</b>	+	+	+	+		+	+	.+	+	+	+	+	+	+	+	+	+	+	+		
			1	1		-1	т ^е					T															 	

Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nitromethane: 188 ppm (continued)

Number of Days on Study	7 3 4	7 3 5	7 3 6	7 3 7																							
Carcass ID Number	 3 4 7	3 0 1	3 0 3	3 2 1	3 2 5	3 3 2	3 3 4	3 4 0	3 4 3	3 4 6	3 5 0	3 0 2	3 0 5	3 0 6	3 1 8	3 1 9	3 2 6	3 4 2	3 4 4	3 0 9	3 2 3	3 2 8	3 3 6	3 3 9	34	3 4 8	Total Tissues/ Tumors
General Body System None	 																	4 <u>7</u>									
Genital System	 						·																				
Clitoral gland	+	+	+	м	M	м	+	м	+	+	+	+	+	+	м	м	+	+	4	+	+	+	+	• +		+	37
Ovary	+	+	+	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+			+	47
Cystadenoma							•			·	•				·	x	•	•	•	•	•	•	•			•	1
Granulosa cell tumor benign													x														2
Uterus	+	+	+		+	+	+	+	+	+	+	+	4	+	+	+	+	+	+	+	÷	+	-4			÷	49
Adenoma	'	'		1	,		'		'	,	'	'	•	r	I.	1		.1	.1	г	т	Ŧ	т	F		Г	1
Deciduoma benign																											1
Hemangioma									v											v							5
Polyn stromal						v			л						v					л							2
						~						_											_				2
Hematopoietic System																											
Bone marrow	+	+	+	• +	+	+	+	+	+	÷	.+	+	+	+	+	+	+	+	+	+	+	+	+	• +	•	+	48
Lymph node	+																				+						6
Lymph node, bronchial	+	Μ	( +	• +	M	+	+	Μ	M	M	+	+	Μ	+	+	Μ	М	+	+	+	+	+	· +	• +		+	36
Hepatocellular carcinoma, metastatic, liver																											2
Lymph node, mandibular	+	+	M	1+	+	М	+	+	Μ	+	+	Μ	M	M	+	М	Μ	+	+	+	4	• +	• +	- +	-	+	34
Lymph node; mesenteric	+	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	.+	+	+	+	+	+	+	+	• +		+	46
Lymph node, mediastinal	+	Μ	[ +	• +	I	+	÷	+	+	+	+	Μ	: +	+	+	+	+	+	+	+	` <b>+</b>	• +	-+	- N	1	+	37
Hepatocellular carcinoma, metastatic, liver																											1
Spleen	+	+	- +	- +	· +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	. 4	- +		+	48
Hemangiosarcoma														x	•		·	•	•		•	•					.0
Thymus	+	+	+	- +	• +	+	+	м	м	i +	+	+	м	· +	+	м	+	+	+	+	+		N	1 4		+	39
Hepatocellular carcinoma, metastatic, liver				•	•	·	•			• •	•	·						•		•		•	1,		÷		1
	 									_																	·
Integumentary System																											
Mammary gland	+	+	- +	- +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +		- +	-	+	48
Carcinoma																											2
Skin	+	+	· +	- +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	1	- +	-	+	47
Subcutaneous tissue, sarcoma																											1
Musculoskeletal System	 		-															•	_								
Bone	+	· -+	- 4	- +	+ -	+	+	+	+	+	+	• +	+	+	+	+	+	+	+	+	• +	- +		- 4	-	+	50
Hemangiosarcoma										·				X													1
Norvous System	 							· · ·																			
Drain																,	,	,									<b>6</b> 0
Diam	+	• +		r 4	- +	• +	+	+	• +	• +	• +	• +	• +	+	+	+	+	+	+	• +	• +	- +		+	F	+	50

TABLE D2

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Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nitromethane: 188 ppm (continued)

Number of Days on Study		3 4 5	3 5 7	4 1 6	4 2 6	4 4 1	5 3 4	5 5 5	5 6 4	5 6 9	5 6 9	5 7 9	5 8 1	6 3 7	6 3 9	6 4 6	6 5 3	6 5 6	6 6 3	6 6 5	6 9 3	6 9 3	7 3 1	7 3 4	7 3 4	7 3 4			
Carcass ID Number		3 1 4	3 3 0	3 3 8	3 0 7	3 4 1	3 1 6	3 0 8	3 1 1	3 1 2	3 3 1	3 2 9	3 2 4	3 0 4	3 1 3	3 4 5	3 4 9	3 3 5	3 1 0	3 2 7	3 1 5	3 3 3	3 1 7	3 2 0	3 2 2	3 3 7		 	_
Respiratory System Larynx Lung Alveolar/bronchiolar adenoma Alveolar/bronchiolar adenoma, multiple Alveolar/bronchiolar carcinoma Hepatocellular carcinoma, metastatic.	 	++	+++	++	+ +	++	+ + X	++	+++	++	+++++++++++++++++++++++++++++++++++++++	A +	++	A +	+ + X	+++	++	+++	++	+++	++	++	++	+ + X	+ + X	+++			
liver Mediastinum, hepatocellular carcinoma, metastatic, liver Nose Trachea	•	+++	+++	++	+++	+ +	+ +	x + +	X X + +	x + +	+: +	+ A	, + +.	A A	+ +	X X + +	+	+++	+ +	+++	+++++++++++++++++++++++++++++++++++++++	+++++++++++++++++++++++++++++++++++++++	++	++	++	++			
Special Senses System Eye Harderian gland Adenoma Adenoma, multiple Carcinoma		+	·+	+	+	+	+	+	+	+	+	+		- -	+ X	+ X	+	+	+ X	÷+	+	+ + X	. +	+	: +	+			-
<b>Urinary System</b> Kidney Urinary bladder	 	++	++	+ +	+++	++	÷ + +	+ +	++++	+ +	+ +	A A	++	A A	+++	+ +	++	+ *	+++	+ +	+++++++++++++++++++++++++++++++++++++++	++	+ +	+ +	++	++++	÷	-	
Systemic Lesions Multiple organs Lymphoma malignant		+	+	+ x	+	+	+	+	+	+	+	+	+ x	+	+	+	+	+	+ X	+	+	+	+	+	+ X	+			

 Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nitromethane: 188 ppm (continued)

	 																_			_			_				
Number of Days on Study	 7 3 4	7 3 5	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7																		
Carcass ID Number	 3 4 7	3 0 1	3 0 3	3 2 1	3 2 5	3 3 2	3 3 4	3 4 0	3 4 3	3 4 6	3 5 0	3 0 2	3 0 5	3 0 6	3 1 8	3 1 9	3 2 6	3 4 2	3 4 4	3 0 9	3 2 3	3 2 8	3 3 6	3 3 9	3 4 8	Total Tissues/ Tumors	
Respiratory System													-		_			_									_
Larynx Lung Alveolar/bronchiolar adenoma Alveolar/bronchiolar adenoma, multiple Alveolar/bronchiolar carcinoma Hantstocallular carcinoma	+	+ +	+ +	+ +	+ + x	+ +	+ +	+ +	+ +	+ +	++	+ +	+ + X	+ +	++	++	+ +	48 50 2 1 3									
liver Mediastinum, hepatocellular carcinoma, metastatic, liver									1				-	.1.										x		, 5 2 10	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Special Senses System Eye Harderian gland Adenoma Adenoma, multiple Carcinoma	+	+	+	+ x	+ _x	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+ X	+ x	+	+	+	+	+	1 49 6 1 2	
Urinary System Kidney Urinary bladder	++	++	++	++	+	++	+ I	+ +	++	+	+++	+ +	++	+ +	+ +	++	+ +	++	++	++	++	++	++	.+ +	+++	48 47	
Systemic Lesions Multiple organs Lymphoma malignant	 +	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+ x	+	+	+	+	50 7	_

0 . 2 4 5 5 5 6 6 6 6 6 6 6 6 6 6 7 7 7 6 6 6 6 7 7 Number of Days on Study 9 6 946 7 0 0 0 3 3 3 4 5 78 0 9 1 2 6 6 2 3 3 9 6 88 8 2 9 1 7 7 6 3 5 5 9 0 3 3 6 28 1734 5 5 55 5 5 5 5 5 5 5 5 5 5 5 55 5 5 5 5 5 5 5 5 **Carcass ID Number** 0 4 1 1 1 3 1 2 2 2 14 4 0 0 1 4 3 0 3 2 3 0 3 0 0 9 7 6 0 9 4 7 2 6 7 1 1 6 3 8 5 2 1 8 2 3 5 7 4 **Alimentary System** Esophagus + + + + + Α + +. + + + + + + Gallbladder Α 4 + + + . + Α + + Intestine large, colon + Α + Α + ++ Μ Leiomyoma x Intestine large, rectum Α Intestine large, cecum Α Intestine small, duodenum A + + A + A + + м + Intestine small, jejunum Α + + А + Α + + + + + + + + + Intestine small, ileum Μ A + + +A + A + + + Liver + + + + + А + + + + + Hemangiosarcoma х Hepatocellular carcinoma Х х Hepatocellular adenoma х х Х ххх Х Hepatocellular adenoma, multiple х Histiocytic sarcoma х х Mesentery Hemangiosarcoma Pancreas Μ м Histiocytic sarcoma Salivary glands Stomach, forestomach + A + + ++ + + + + + + + Stomach, glandular + ÷ Α + A + + + + + + + + + + Cardiovascular System Blood vessel Heart + Histiocytic sarcoma x **Endocrine System** Adrenal cortex M Capsule, adenoma Adrenal medulla Pheochromocytoma benign Bilateral, pheochromocytoma benign Islets, pancreatic Μ М Μ Parathyroid gland м Μ + Μ Μ м м Pituitary gland + Pars distalis, adenoma Х Thyroid gland + Follicular cell, adenoma **General Body System** None **Genital System** Clitoral gland + Μ + ММ + Μ M + Ovary + I + A + + + + + + + + + + + + Uterus + + + Α + Histiocytic sarcoma x Polyp stromal

Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nitromethane: 375 ppm

#### TABLE D2

Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nitromethane: 375 ppm (continued)

		_					_	_				_													_			
Number of Days on Study	-	7 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7		
Carcass ID Number	:	5 :	5 0 9	5 1 4	5 1 9	5 2 7	5 3 9	5 4 2	5 0 2	5 1 3	5 2 0	5 2 1	5 3 4	5 3 6	5 4 1	5 4 3	5 1 5	5 2 3	5 2 5	5 2 8	5 3 0	5 3 5	5 4 4	5 4 6	5 4 8	5 5 0	Total Tissues/ Tumors	
Alimentary System							<u> </u>																					
Esophagus		+	+	+	+	+	+	+	+	+	+	+	+	Ŧ	+	+	+	+	+	+	+	+	+	+	+	+	49	
Gallbladder		+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	М	+	+	+	+	Μ	+	45	
Intestine large, colon		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
Leiomyoma																											1	
Intestine large, rectum		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
Intestine large, cecum		ł	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
Intestine small, duodenum		+	+	+	+	+	÷	÷	+	+	+	+	+	+	÷	+	+	I	+	+	+	+	+	+	+	+	45	
Intestine small, jejunum		+	+	+	+	+	+	+	+	+	+	+	+	+.	÷	+	+	+	+	+	+	+	+	+	+	+	47	
Intestine small, ileum		+	+.	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	· +	46	2
Liver		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Hemangiosarcoma																	х										· 2	
Hepatocellular carcinoma					х	Х					Х											Х			Х	$\mathbf{X}^{\cdot}$	8	
Hepatocellular adenoma				Х	х							Х							х				Х	X			13	
Hepatocellular adenoma, multiple		X											Х													х	4	
Histiocytic sarcoma																											2	
Mesentery		+						+		+		+			+												8	
Hemangiosarcoma															х												1	•
Pancreas		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Histiocytic sarcoma																				Х							1	
Salivary glands		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	49	1
Stomach, forestomach		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- 49	۲.
Stomach, glandular		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Cardiovascular System			_																									
Blood vessel															+												2	
Heart		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	)
Histiocytic sarcoma																											1	
Endocrine System			-																			_						
Adrenal cortex		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	49	)
Capsule, adenoma																Х											1	
Adrenal medulla		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. 49	)
Pheochromocytoma benign																										Х	1	
Bilateral, pheochromocytoma benign																							Х				. 1	
Islets, pancreatic		+	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	÷	+	+	47	,
Parathyroid gland		+	+	М	+	Μ	+	+	+	Μ	M	+	М	Μ	+	+	+	+	М	+	+	Μ	M	: +	Μ	[ + ]	33	1
Pituitary gland		+	+	М	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	• +	48	5
Pars distalis, adenoma									х	Х			х	х		х					х					х	· . 8	5
Thyroid gland		+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	3
Follicular cell, adenoma																						х					1	
General Body System None															<b>.</b>				<del>,</del>								. <u></u> .	
Genital System			_										_															
Clitoral gland		+	М	+	+	+	м	+	+	м	M	. +	М	+	+	+	+	+	+	+	+	+	+	+	- +	·м	. 39	)
Ovary		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	· +	· +	• +	• +	• +	48	3
Uterus		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4	+		+	· +	<u>+</u>	• +	49	)
Histiocytic sarcoma		•	•	•	•	•	•	•	·	•	•	•	•	•	•	•	·	•	•				,			•	1	l
Polyp stromal							х																				]	l
* •																												

Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nitromethane: 375 ppm (continued)

				-	_	_					· · · ·				_			~~~			~~~	• • •								_
		. 0	2	4	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7				
Number of Days on Study		6	9	9	4	6	7	0	0	0	3	3	3	4	5	6	6	7	8	9	9	1	2	2	3	3				
		9	6	8	8	8	2	2	8	9	1	7	7	6	3	5	5	9	0	3	3	6	1	7	3	4				
		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	•			
Carcass ID Number		0	4	1	1	<u></u> 1	3	1	2	2	2	1	4	4	0	0	1	4	3	0	3	2	3	0	3	0				
		7	0	6	0	7	1	2	9	4	6	1	9	7	6	3	8	5	2	1	8	2	3	5	7	4				
Hematonoietic System																	-													
Bone marrow		L.	Ъ	л.	Т	Т	· <b>λ</b>	Т	Ŧ	Т	+	Т	L.	Ŧ	т	Т	т	Ŧ	ъ	1	i	+		Ŧ		+				
Hemangiosarroma		Ŧ	т	т	Ŧ	v	n	т	Τ.	<b>–</b>	Ŧ	Ŧ	. –	Ŧ	т	Ŧ	Ŧ	т	т	т	÷	Ŧ	Ŧ	Ŧ	Ŧ	Ŧ				
Lymph pode						л								-1-	-						<u>^</u>									
Lymph node bronchiel			м	L	1					L	м	L		T	- -			r		+	-		м	м	м					
Lymph node, mandibular		T M	т. ТМ	T L	т 	т _	A .	т	T	т 	111	т 	т 	т -	т 	т -	Ť	<u>т</u>	т M	1	- -	포	111	M	1.1	. I .L				
Lymph note, manufoliai		141		,	1	ŕ	Л	141	т	т	v	Т.	Т.	т	T	Ŧ	Т.	Т.	141	Т.	г	ч.	г	141	т	. т				
Lumph node mesonteric		ملہ	ц.	м	<u>т</u>	<u>н</u>	۸		٨	ц.	<u>л</u>	л.	л.	ц.						-		-	Ľ.	<u>т</u>	<u>т</u>	-		. •		
Lymph node, mesenteric		т	т	IVI	т	т	A	т	A	Ŧ	т	т	Ŧ	Ŧ	т	т	Ŧ	т	т	т		т	Ŧ	т	т	т				
Lymph node, mediastinal		м		м	м		٨		м			м	.1	3.6		.1	1	<b>.</b>	<b>.</b>	.د	-1.	.د	. I.	-1-						
Lymph node, mediastinal		IVI	IVI	IVI	IVI	Ŧ	А	Ŧ	11/1	<del>`</del> +	Ŧ	IVI	Ŧ	IVI	Ŧ	Ŧ	IVI	Ŧ	+	Ŧ	<u>т</u>	Ŧ	Ŧ	Ŧ	Ŧ	Ŧ				
Histiocytic sarcoma											x																			
Spleen		+	+	+	+	+	М	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	.+				
Hemangiosarcoma																					х									
Histiocytic sarcoma						•					х														X					
Thymus		+	+	+	+	М	А	+	+	I	+	+	+	+	+	+	+	+.	+	+	+	+	Μ	Μ	Μ	+				
Integumentomy System				~~~						÷							÷					·								
Menunentary System			,							,	,	,			r.		,						,			۰,				
		+	Ŧ	Ŧ	. <b>†</b>	Ŧ	. A	Ŧ	Ŧ	Ŧ	Ŧ	Ť	Ŧ	Ŧ	+ v	Ŧ	Ŧ	Ŧ	Ŧ	+	Ŧ	Ŧ	+	Ŧ	+	Ŧ				
Adenoma		•			v										л			v												
Carcinoma				,	л ,	ı.	1.	1.	а.	ь.								A.		1		. 1.		-		-				
		+	Ŧ	Ŧ	Τ.	т	T	Ŧ	T	т	T	T	Τ.	Ŧ	Ŧ	Ŧ	Ŧ	T	т	. <b>T</b>	Ŧ	v	т	т	т	T				
Subautanacua tissua hamangiosarrooma																					v	Λ								
Subcutaneous tissue, nemangiosarcoma																					л	v								
Subcutaneous issue, sarcoina																														
Musculoskeletal System																												•		•
Bone		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	+	+				
Hemangiosarcoma						Х															X									
Osteosarcoma						•													X						·					
Nervous System														_																
Brain		+	÷	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+		-		. 1
Spinal cord		÷						•																						
Besniratory System						•																								
Longra		د	ـد	.د.	ىد	<u>ـ</u> ـ	۸	j.	ـد	<u>ا</u>	بد	÷	Ŧ	÷	۰	÷	Ŧ	÷	Ŧ	Ŧ	+	÷	+	+	+	+			• •	
Larynx		т 1	- T		+ +	т -	A	т -	. — —	+ +	т -			т Т	т -	т -	+ +	т +	+	÷	- -	4	, +	+	, +					
Alveolar/bronchieler adeneme		. т	т	v		Ŧ	A	v	r		r	'	r	F	•	,	'	'	,	'	'		. '	. '	'	'				
Alveolar/bronchiolar agenoma				Å				Y								x				x										
Carcinoma metactatic harderian aland							• •	л								~				~										
Histioovtie sarcoma											x								•						x				,	
Osteosarcoma metastatic hone											л								x						~1					
Nose		L.	_د .	٦	<u> </u>	ـ	<u>ـ</u> ــ	<u>ـ</u> د	ـد	+	Ł	4	+	+	+	+	+	÷	4	÷	.+	+	+	+	+	+				
Trachen	•			+	- <del>-</del>	4	Δ	+	+	+	+	+	+	+	+	+	+	, +	, +	+	+	+	+	+	+	+				
TIAUNUA		਼ਾ	Ţ		· • •		A	1	T	ч.	Т.			.'	'	•		•					•		•					

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#### TABLE D2

Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nitromethane: 375 ppm (continued)

		_	_	_	_			_	_	_	_			-	_	-		_	_	_	_	_	_	_	_	
Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 7										
Carcass ID Number	5 0 8	5 0 9	5 1 4	5 1 9	5 2 7	5 3 9	5 4 2	5 0 2	5 1 3	5 2 0	5 2 1	5 3 4	5 3 6	5 4 1	5 4 3	5 1 5	5 2 3	5 2 5	5 2 8	5 3 0	5 3 5	5 4 4	5 4 6	5 4 8	5 5 0	Total Tissues/ Tumors
Hematopoietic System														<u> </u>					_							
Bone marrow Hemangiosarcoma	+	+	- +	• +	- +	• +	• +	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49 2 5
Lymph node, bronchial	. +	+	- 4		- M	[ +	• +	+	+	+	+	+	+	м	+	+	+	+	+	+	+	+	+	+	+	40
Lymph node, mandibular Histiocytic sarcoma	+	+	- +	N	1 +	• +	·M	+	M	+	+	Ņ	+	+	+	+	+	+	М	+	M	+	M	+	+	38 1
Lymph node, mesenteric Histiocytic sarcoma	+	+	- +		~ +	+	M	+	+	+	÷	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	46 1
Lymph node, mediastinal Carcinoma, metastatic, harderian gland Histiocytic sarcoma	М	+	- +		- +	·M	1 +	+ X	+	+	+	+	М	+	+	+	М	+	+	+	м	+	+	I	+	35 1 1
Spleen Hemangiosarcoma Histiocytic sarcoma	+	+	- +		- +	• +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49 1 2 .
Thymus	+	+	- +	• -	- +	• +	• +	М	+	+	+	+	+	М	+	+	+	+	+	+	+	+	Μ	+	+	41
Integumentary System Mammary gland Adenoma	+	+	- +	• •	- +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Carcinoma Skin Squamous cell carcinoma Subcutaneous tissue, hemangiosarcoma Subcutaneous tissue, sarcoma	+	4	- 4		- +	• +	• +	+	+	+ x	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	2 50 1 2 1
Musculoskeletal System Bone Hemangiosarcoma Osteosarcoma	+ +	 +	- +	 	- +	+	· +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 2 1
Nervous System Brain Spinal cord	+	+	- +		 ⊦ +	- +	· +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49 1
Respiratory System																				_						
Larynx Lung Alveolar/bronchiolar adenoma Alveolar/bronchiolar carcinoma Carcinoma, metastatic, harderian gland Histiocytic sarcoma	++	+ + X X	- + - + :	  X	+ + + +	· +	· +·	+ + X	+	+ +	+ +	+ +	+ +	++	+ +	+ +	++	+ +	+ +	+ +	++	+ +	+ +	+ +	+ +	49 49 2 5 2 2
Osteosarcoma, metastatic, bone																										1
Nose Trachea	++	+ +	- + - +	• •	⊦ + ⊦ +	• +	· + · +	++	+++++++++++++++++++++++++++++++++++++++	++	++	++	++	++	++	++	++	++	++	++	++	+ +	++	++	++	50 49

#### TABLE D2-

Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nitromethane: 375 ppm (continued)

		 	_													_													 
Number of Days on Study			0 6 9	2 9 6	4 9 8	5 4 8	5 6 8	5 7 2	6 0 2	6 0 8	6 0 9	6 3 1	6 3 7	6 3 7	6 4 6	6 5 3	6 6 5	6 6 5	6 7 9	6 8 0	6 9 3	6 9 3	7 1 6	7 2 1	7 2 7	7 3 3	7 3 4	 	
Carcass ID Number			5 0 7	5 4 0	5 1 6	5 1 0	5 1 7	5 3 1	5 1 2	5 2 9	5 2 4	5 2 6	5 1 1	5 4 9	5 4 7	5 0 6	5 0 3	5 1 8	5 4 5	5 3 2	5 0 1	5 3 8	5 2 2	5 3 3	5 0 5	5 3 7	5 0 4		
Special Senses System Eye Harderian gland Adenoma Adenoma, multiple Carcinoma			+	+	+ X	+++	+	+	+ x	+ X	+	+	+ X	+	+	+ X	+ X	- +	+ x	+	+ x	+ X	+		+	+ X	+		 
Urinary System Kidney Histiocytic sarcoma Osteosarcoma, metastatic, bone Urinary bladder Histiocytic sarcoma	· · ·		+	+	+	++	+	A	+	+ A	+ +	+ x +	+	+ +	++	++	+ +	+	+	+ X +	+	+	+	+`+	+	· + X · + X	+		
Systemic Lesions Multiple organs Histiocytic sarcoma Lymphoma malignant			+	+	+	+	+	+	+	+	+ x	+ X	+	+	+	, + X	+	+	+ x	+	+	+	+	+ x	• +	+ X	+		

#### TABLE D2

Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nitromethane: 375 ppm (continued)

		_	_		-	_		-	_				_		_	_	_				_					_		
Number of Days on Study	7 3 4	3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 7	× .										
Carcass ID Number	5 ( 8	; ) }	5 : 0 : 9 :	5 1 4	5 1 9	5 2 7	5 3 9	5 4 2	5 0 2	5 1 3	5 2 0	5 2 1	5 3 4	5 3 6	5 4 1	5 4 3	5 1 5	5 2 3	5 2 5	5 2 8	5 3 0	5 3 5	5 4 4	5 4 6	5 4 8	5 5 0	Ta Tissu Tum	otal les/ lors
Special Senses System Eye Harderian gland Adenoma Adenoma, multiple Carcinoma		÷	+ x	+	+	+ x	+	+	+ x	+	+ X	+ + X X		+ + {	+	+ x	+ x	+ x	+	+	+ x	+	+	+	+	+		1 50 15 1 4
Urinary System Kidney Histiocytic sarcoma Osteosarcoma, metastatic, bone Urinary bladder Histiocytic sarcoma		+	+	+	+	+	+	+ +	+	• +	+ +	+ +		+ +	• +	+ +	+	+	+	+	+	+	+	+	++	+	-	49. 2 1 47 1
Systemic Lesions Multiple organs Histiocytic sarcoma Lymphoma malignant		+	+	+	+	+	+	+	+	• +	• +	+ +	 - 	+ + K	• +	· +	+	+	+ x	+ x	+	+	+	+	+	+ x		50 3 7

Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nitromethane: 750 ppm

																				_											
Number of Days on Study		÷	0	4	5	5 5	6	6	6	6	6 0	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7				
rumber of Days of Study			1	2 6	3	3	3	2	5 8	3 7	7	9	6	1	2	2	э Л	3 ⊿	3 1	3	3 1	3	3	3	3	5	3				
								<u></u>		<i></i>	, 	<u>_</u>	<u> </u>							-											
_			7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7				
Carcass ID Number			3 3	1 9	4 4	2 4	3 1	3 8	0 9	2. 9	0 4	2 8	0 3	0 1	1 5	3 5	0 8	1 4	1 6	1 8	2 1	2 3	3 4	4 2	4 5	0 5	1 2				
Alimentary System										-																					
Esophagus			+	+	+	+	м	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Gallbladder			À	+	+	+	+	+	r	+	+	+	+	+	Ň	+	+	+	÷	м	+	+	+	+	+	+	+				
Intestine large, colon			+	+	+	+	4	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	, +				
Intestine large, rectum			Á	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Intestine large, cecum			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	+		÷ +		
Intestine small, duodenum			A	+	+	+	+	+	+	+	+	+	+	÷.	+	+	+	+	+	+	+	+	+	+	+	+	+				
Intestine small, jejunum			A	+	+	+	À	+	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	, +				
Intestine small_ileum			A	+	+	+	+	+	+	÷	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Liver			+	+	+	, +	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Hepatocellular carcinoma				x	x	•	x	x	x	•	x	x		x	x	•	•	•		•	'		'	•			•				
Henatocellular carcinoma multiple				••				••				••			· .	x															
Hepatocellular adenoma				x	x						x	x		x				x	x	x		1					·Y				
Hepatocellular adenoma multiple							x					**		~			x		Δ	Λ			x	x	x	٠x	~				
Mesentery	•						4	·			+				Ŧ		4						~	+	~						
Hemangioma							'				x				•		,							•							
Oral mucosa											**																				
Pancreas			4	+	+	+	+	+	÷	+	+	+	Ŧ.	+	+	+	+	+	∔	+	+	+	+	+	+	+	+		•		
Salivary glands			, .+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+			·	
Stomach forestomach	•		+	+	+	+	+	+	+	, +	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+				
Squamous cell papilloma			•	'			'	'	,	,		'	'		•	•		•	'	•	•	•	•		•		. '				
Stomach, glandular			· +	+	+	÷	+	+	+	+ '	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	· +	+				
Cardiovasoular System	<del></del>																														
Heart			·	т	-1-	4		ъ	-	+	+		+	+	+	÷	+	+	Ŧ	÷	+	Ŧ	+	+		+	÷				
			· · ·		· · ·			· · · · ·																÷							
Endocrine System																												4			
Adrenal cortex			+	+	+	+	+	+	+.	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Capsule, adenoma																											•			·	· ·
Adrenal medulla			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+				
Islets, pancreatic			+	+	≁	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	<b>,</b> +	+				1.4.4
Adenoma								Х																							•
Parathyroid gland			+	+	+	М	+	+	М	+	+	+	+	М	+	+	+	+	М	+	+	+	М	М	+	М	+				
Pituitary gland			+	+	+	+	Ή	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Pars distalis, adenoma																X															
Thyroid gland			÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+				· ·
Follicular cell, adenoma																													,	t	•
General Body System	·		<u></u>																				_								
None																										·					
Conital System		<u>`</u>		<u></u>																											
Cliteral aland			,			,		,		,	,	14	,	J		<b>.</b>	M	т	. ر		۱.	ب	м	۸.	24	T	л.				
Cilitoral gland			+	M	+	+	+	.+	+	+	+	IVI	+	+	+	+	IVI 1	1 	+	+	+	+	141	111	IVI IVI	1	+ _				
Cultura de no constrain como			+	+	+-	+	+	+	Ŧ	T: V	+	+	+	+	Ŧ	Ŧ	+	7	+	Ŧ	<b>-</b> T	Ŧ	Ŧ	т	т	Ŧ	Ŧ				
Cystadenocarcinoma										л	v								v	y					. *						
Lutama									v		л								A	А											
Luteoma			v						л																						
I tratoma benign			A J	بد	ـــ	.J.,	+	-	+	+	ᄮ	Ŧ	+	٦	Ŧ	+	+	÷	Ŧ	Ŧ	+	Ŧ	+	+	Ł	Ŧ	∓				
Adenoma			+	T	т	r	Ŧ	т	·	T	۲	-r-	۰r	т	г	r	r	C	r	Г	1	Γ.	1	•	ч.	7'					
Polyn stromal															x								x								
i olyp suomai	****														~							•									

#### TABLE D2

3- ----

Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nitromethane: 750 ppm (continued)

				_				_						_		_	_									
Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 [.] 6	7 3 6	7 3 7																			
Carcass ID Number	7 1 7	7 4 0	7 4 3	7 4 6	7 0 6	7 0 7	7 1 0	7 1 1	7 2 0	7 2 6	7 2 7	7 3 0	7 3 2	7 3 9	7 4 7	7 5 0	7 0 2	7 1 3	7 2 2	7 2 5	7 3 6	7 3 7	7 4 1	7 4 8	7 4 9	Total Tissues/ Tumors
Alimentary System			_					-					_		_			_								
Esophagus	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma							x															x				11
Hepatocellular carcinoma, multiple																										1
Henatocellular adenoma			x	•						x	x	x	x		x	x			x		x	x	x	x	x	22
Henatocellular adenoma multiple	x	x		x					x					x	••			x		x						13
Mesentery	**	+		4				+		+							+									11
Hemangioma				'				•																		1
Oral mucosa																							+			1
Pancreas	+	+	+	+	+	Ŧ	Ŧ	+	+	+	÷	+	+	+	+	Ŧ	Ŧ	+	+	+	+	Ŧ	+	+	Ŧ	50
Salivary glands			, 上	, _	, ⊥	, 	, _	, ,	, 	, +	, 上	, +	, _	, -	, +	- -	, 1	+	, _	, _	, ,	, ,	, -	÷	, 1	50
Stomach forestomach	_	-	т -	1	-	т -	т —	т Т			т -	, 	1	т Ц	1		т. Т.	+	- <b>T</b>	т Т	1	т 	а —	Т.	л Ц	50
Squamous cell nanilloma		•	'	'	•	'	x	'	x	'	•	'		,	•	·	•	'	•	'	•	•	•			20
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System													-													
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																						<u> </u>				
Adrenal cortex	<b>ب</b> د	Ъ	ىد	Ŧ	Ŧ	ᆂ	Ŧ	Ŧ	Ŧ	-	Ъ	+	÷	Ъ	÷	т	Ŧ	Ъ	ـ	+	<u>ـ</u> ـ	Ŧ	L.	Ŧ	Ŧ	50
Cansule adenoma	т.	т	т	Ŧ	т	т	т	т	т	т	т	ч.	т	т	т	v	т	т	т	т.	т	т	Τ-	т	Ŧ	50
Adrenal medulla	1		-	<b>.</b>	т.	-	л.	+	-	. L	-	-		+	н.	^ _		-	+	-		Т	ц.	1	+	40
Islets nancreatic	т 1	т -		т 	т 	т 	т 	т Т	т 	т 	т -	т 	т 	т -	т Т	Ť	т Т	т 	т -	т -	т -	т 	т 1	т -	т _	50
Adenoma	т	Ŧ	т	т	т	т	т	т	т	т	т	Ŧ	т	т	т	т	т	т	т	Ŧ	т	т	т	т	т	50
Parathyroid gland	.د	т	м		4	м		м			L.		м	м	-	Т.	-	л.	ъ	-	м	1	м	м		24
Pituitonu gland	T L	1	141			IVI	т .ь	IAT	т 			т Т	141	141	т 	Ť	т 	т 	- -	т 	141	- T - L	141	11	T L	50
Pare distalis adenoma	Ŧ	т	· •	Ŧ	т	т	т	v	Ŧ	т	т	т	т	т	т	т	т	т	т	т	т	т	v	v	Ŧ	50
Thuroid aland			,	,	,	,		<u>,</u>		,	,	,	,	,	,	,	,	,	,	,	,	,	<u>,</u>	Â,	,	50
Follicular cell, adenoma	т	т	-	т	т	т	т	т	т	x	Ŧ	т	т	т	Ŧ	Ŧ	Ŧ	Ŧ	Ŧ	Ŧ	T	т	Ŧ	т	Ŧ	1
Canaral Body System			·																							
None																										
Genital System																										
Clitoral gland	r	. 1			_	а	л	-			Ŀ		л	R.4		34	14		L	_1	_1	<b>1</b> 4	J.	L	ı.	26
	1	+	+	M	+	+	+	+	+	+	+	+	+	171	+	141	1.11	+	+	+	+	IVI	+	+	+	00
Cystadenocarcinomo	+	T		Ŧ	Ŧ	Ŧ	Ŧ	-1-	Ŧ	Ŧ	Ŧ	IVI	т	Ŧ	Ŧ	Ŧ	Ŧ	Ŧ	141	Ŧ	Ŧ	Ŧ	Ŧ	Ŧ	Ŧ	40
Cystadenoma																										1
Cystauchonia Luteomo		·																								3
Lucoma																										1
Letatoma benign			•																							1
Adenoma	+	- +-	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Aucionia Polyn strongt	v																							х		1
rotyp stromat	X																									3

Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nitromethane: 750 ppm (continued)

			_											•		•															
Number of Days on Study			0 5 1	4 2 6	5 0 3	5 5 3	6 0 3	6 3 2	6 3 8	6 5 7	6 8 7	6 9 9	7 0 6	7 1 6	7 2 1	7 2 9	7 3 4	7 3 5	7 3 5												
Carcass ID Number			7 3 3	7 1 9	7 4 4	7 2 4	7 3 1	7 3 8	7 0 9	7 2 9	7 0 4	7 2 8	7 0 3	7 0 1	7 1 5	7 3 5	7 0 8	7 1 4	7 1 6	7 1 8	7 2 1	7 2 3	7 3 4	7 4 2	7 4 5	7 0 5	7 1 2				
Hematopoietic System														_							,				-	-					
Bone marrow			+	+	+	+	+	+	+	+	·+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•			
Sarcoma, metastatic, skin						х															-			-							
Lymph node						+	+									+															
Lymph node, bronchial	· ·		Μ	+	+	М	+	+	+	+	М	+	+	М	+	+	+	+	M	М	+	М	М	М	+	+	+				
Lymph node, mandibular			+	+	+	+	+	М	М	+	+	+	+	+	+	+	+	+	+	+	+	Μ	+	+	+	+	· +				
Lymph node, mesenteric			Μ	+	+	+	+	+	+	+	÷	+	+	÷	÷	+	+	+	+	+	+	+	+	+	+	+	+				
Lymph node, mediastinal	-		+	+	Μ	М	+	÷	М	+	+	+	+	+	+	+	+	+	+	+	М	+	Μ	+	+	+	+				
Spleen			• +	+	+	.+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Thymus			Μ	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	М	+	М	+	+	+				
Integumentary System														-			-														
Mammary gland	•.		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				·
Skin			+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Subcutaneous tissue, sarcoma			•	•		x		•	x	·	•	•	•	•			•	,	•	·	••	•		•		•					
Musculoskeletal System Bone			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	 +	+		-		
		<u></u>																													
Nervous System																															
Brain	,		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Respiratory System																															
Larynx			+	+	+	+	+	+	+	+	+	+	+	+	+	+	Ή	+	+	+	+	+	+	+	+	+	•+				
Lung			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Alveolar/bronchiolar adenoma				Х											Х																
Alveolar/bronchiolar adenoma, mult	iple															Х								~							
Alveolar/bronchiolar carcinoma, mu	ltiple				Х									х																	
Hepatocellular carcinoma, metastatic	,																				~										
liver						-	х	х								X															
Sarcoma, metastatic, skin						X																					,				
Nose	-		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
	•		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Special Senses System									_							•															
Harderian gland			+	+	+	+	+	+	+	+	+	+	.+	+	+	+	+	+	+	+	+	+	+	÷.	+	+	+				
Adenoma		,			Х						х	х		х				х	х	х											
Adenoma, multiple															Х																
Carcinoma													ł											·							
Carcinoma, multiple				,																							х				
Urinary System				_	Ŷ																	_		_			;				
Kidney			+	+	+	+	.+	+	+	+	+	+	+	+	+	·+	+	+	+	+	+	+	+	+	+	+	+			,	
Urinary bladder			Å	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Systemic Lesions																										-					
Multiple organs			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Lymphoma malignant							Х						Х			Х	X										•				
#### Lesions in Female Mice

#### TABLE D2

Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Nitromethane: 750 ppm (continued)

					_								_													_	
Number of Days on Study	7		7	7 3	7 3	7 3	7 3	73	7 3	7 3	73	7 3	73	7 3	7 3	7 3	7 3	7 3 7	7 3	7 3	7 3	737	7 3	737	7 3 7	7 3	
			> 7	5 7	5 7	7	7	7	7	7	7	7	7	7	7	7	6 7	7	7	7	7	7	7	7	7	7	Total
Carcass ID Number	1	(	4 )	4 3	4 6	0 6	0 7	1 0	1 1	2 0	2 6	2 7	3 0	3 2	3 9	4 7	5 0	0 2	1 3	2 2	2 5	3 6	3 7	4 1	4 8	4 9	Tissues/ Tumors
Hematopoietic System																	-						_				
Bone marrow	-	F	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, skin																											1
Lymph node		r						+				,				+	,	+	,						,		6
Lymph node, bronchiai			+	+	+	+	+	+	+ M	+	+	+	+	+	MI -	+ M	+	+	+	+	+	+ M	+	+	+	+ M	40
Lymph node, manufoular	_	г -	- -	- -	+	- -	- -	+	141	+		- -	+	+	T	+	+ +	+	+	т 4	+	-+	+	- -+	+	-	45
Lymph node, mediastinal	N	A.	+	+	+	+	พ่	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	'n	+	41
Spleen	-	F .	+	+	+	+	+	+	+	.+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	-	ŀ	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																											
Mammary gland		۲	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin Subcutaneous tissue, sarcoma	-	F	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 2
Musculoskeletal System Bone	-	 ŀ	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																											
Brain	-	⊦	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System				-																							
Larynx	-	t	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	-	⊦	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma											х	х	х		х				х			х					8
Alveolar/bronchiolar carcinoma multiple										x																	. 3
Hepatocellular carcinoma, metastatic.										~																	
liver																											3
Sarcoma, metastatic, skin																											1
Nose		ł	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System											_									_							
Harderian gland	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	2	K				х			X	х						х	د د	•			х	v	х	v	Х	Х	16
Adenoma, multiple			v			v																х		λ			3
Carcinoma, multiple			Λ			Λ																					1
Urinary System			-									_				_								_			
Kidney		ł	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	. <u></u>	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions														_				_									
Multiple organs		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma mangnant								х								X							Х				. /

Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Nitromethane

	х -	0 ppm	188 ppm	375 ppm	750 ppm
Harderian Clande Adenomo				· · · · · · · · · · · · · · · ·	
Overall merc ^a		5/50 (100)	7/50 (1496)	16/50 (22%)	10/50 (28%)
Adjusted mtab		16.0%	7/30 (14%)	10/30 (32.70)	15/50 (58 %)
Aujusted rate		10.0%	21.470 A/39 (1402)	43.1% 7/36 (37%)	4J.770 14/26 (20%)
First incidence (dous)		2/23 (8%)	4/28 (14%)	1120 (2170)	14/30 (39%) 503
First incluence (days)		D-0.009	039 D-0 412	470 D-0.016	DU3
Life table test		P = 0.008	P≈0.413	P = 0.010	P = 0.020
Logistic regression test		P < 0.001	P=0.380	F≈0.008	F=0.003
Cochran-Armitage test		P<0.001	D-0 290	P-0.006	B<0.001
Fisher exact test		<i>x</i>	F=0.380	r-0.000	F < 0.001
Harderian Gland: Carcinoma	н. 				
Overall rate		1/50 (2%)	2/50 (4%)	4/50 (8%)	3/50 (6%)
Adjusted rate	,	2.9%	6.7%	14.1%	8.3%
Terminal rate		0/25 (0%)	1/28 (4%)	3/26 (12%)	3/36 (8%)
First incidence (days)		663	693	679	734 (T)
Life table test		P=0.364	P=0.506	P=0.195	P=0.425
Logistic regression test		P=0.305	P=0.501	P=0.194	P=0.365
Cochran-Armitage test		P=0.221			· · · · · · · · · · · · · · · · · · ·
Fisher exact test	-		P=0.500	P=0.181	P=0.309
Harderian Gland: Adenoma or Ca	rcinoma		•		·
Overall rate		6/50 (12%)	9/50 (18%)	20/50 (40%)	21/50 (42%)
Adjusted rate		18.4%	27.1%	53.5%	50.8%
Terminal rate		2/25 (8%)	5/28 (18%)	10/26 (38%)	16/36 (44%)
First incidence (days)		609	639	498	503
Life table test		P=0.010	P=0.324	P=0.005	P = 0.019
Logistic regression test		P<0.010	P=0.175	P = 0.002	P = 0.002
Cochran_Armitage test	•	P<0.001			
Fisher exact test		1 (0.001	P=0.288	P=0.001	P<0.001
			, ¹ · · ·	· ·	
Liver: Hepatocellular Adenoma	\$				· · · · · ·
Overall rate		14/50 (28%)	25/49 (51%)	17/49 (35%)	35/50 (70%)
Adjusted rate		45.5%	68.6%	49.0%	83.1%
Terminal rate		9/25 (36%)	17/28 (61%)	10/26 (38%)	29/36 (81%)
First incidence (days)		597	534	498	426
Life table test		P=0.022	P=0.048	P=0.395	P=0.009
Logistic regression test		P<0.001	P=0.013	P=0.364	P<0.001
Cochran-Armitage test		P<0.001			
Fisher exact test			P=0.016	P = 0.308	P<0.001
				· ·	and the second se
Liver: Hepatocellular Carcinoma		10/50 (00)	14/40 (000)	9/40 (160)	12(50 (24%)
Overall rate	. [.]	10/50 (20%)	14/49 (29%)	8/49 (10%) 26 60	12/3U (2470) 25.6%
Adjusted rate		29.1%	33.1%	20.0%	23.0%
Terminal rate		3/25 (12%)	0/28 (21%)	0/20 (23%) 549	4/50 (070) A26
First incidence (days)	· ·	5/0	JJ4 D=0.200	240 D-0 263N	420 B-0 405N
Life table test	· · · · · ·	P = 0.322N	P=0.296	P=0.302N	P = 0.4951N P = 0.200
Logistic regression test		P=0.329	F=0.132	P=0.3631	r =0.200
Cochran-Armitage test	11 A	P=0.505	B-0 234	B-0.416N	P-0.405
Fisher exact test	7		r ÷v.224	r 0.41014	1-0.405

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Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Nitromethane (continued)

· · ·	0 ppm	188 ppm	375 ppm	750 ppm
		<u></u>	· · · · · · · · · · · · · · · · · · ·	
Liver: Hepatocellular Adenoma or Car	cinoma	0440 (000)	00140 (45.01)	10.150 (00.01)
Overall rate	19/50 (38%)	34/49 (69%)	22/49 (45%)	40/50 (80%)
Adjusted rate	24.0%	82.4%	02.0%	80.9%
First insidence (daus)	10/25 (40%)	21/28 (75%)	14/20 (54%)	30/30 (83%)
Life table test	5/0 D-0.005	0.019 D=0.019	490 D-0.420	420 R0.022
Life table test	P=0.093	P = 0.018	P = 0.420 P = 0.369	P = 0.032
Cochran-Armitage test	P = 0.001	r < 0.001	r -0.508	F < 0.001
Fisher evact test	P < 0.001	P = 0.002	P = 0.311	P<0.001
		r = 0.002	1-0.511	F < 0.001
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	3/50 (6%)	3/50 (6%)	2/49 (4%)	9/50 (18%)
Adjusted rate	11.5%	10.7%	4.3%	22.7%
Terminal rate	2/25 (8%)	3/28 (11%)	0/26 (0%)	6/36 (17%)
First incidence (days)	716	734 (T)	498	426
Life table test	P=0.065	P = 0.610N	P = 0.466N	P=0.186
Logistic regression test	P=0.022	P = 0.632N	P=0.514N	P=0.083
Cochran-Armitage test	P=0.018	<b>D</b>	<b>b a a a b b b b b b b b b b</b>	<b>N</b> 0.044
Fisher exact test		P=0.661N	P=0.510N	P=0.061
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	0/50 (0%)	3/50 (6%)	5/49 (10%)	3/50 (6%)
Adjusted rate	0.0%	8.3%	15.0%	7.2%
Terminal rate	0/25 (0%)	1/28 (4%)	2/26 (8%)	1/36 (3%)
First incidence (days)	e	534	602	503
Life table test	P=0.264	P=0.134	P=0.041	P = 0.178
Logistic regression test	P=0.149	P=0.119	P=0.033	P=0.110
Cochran-Armitage test	P=0.159			
Fisher exact test		P=0.121	P = 0.027	P=0.121
Lung: Alveolar/bronchiolar Adenoma o	r Carcinoma			
Overall rate	3/50 (6%)	6/50 (12%)	6/49 (12%)	12/50 (24%)
Adjusted rate	11.5%	18.5%	16.8%	28.7%
Terminal rate	2/25 (8%)	4/28 (14%)	2/26 (8%)	7/36 (19%)
First incidence (days)	716	534	498	426
Life table test	P = 0.042	P=0.293	P=0.280	P = 0.066
Logistic regression test	P≈0.007	P=0.243	P=0.238	P=0.015
Cochran-Armitage test	P=0.007			
Fisher exact test		P=0.243	P=0.233	P=0.011
Mammary Gland: Adenoma or Carcino	oma			
Overall rate	2/50 (4%)	2/50 (4%)	3/50 (6%)	0/50 (0%)
Adjusted rate	6.8%	5.9%	7.6%	0.0%
Terminal rate	1/25 (4%)	1/28 (4%)	0/26 (0%)	0/36 (0%)
First incidence (days)	667	569	548	
Life table test	P=0.151N	P=0.685N	P=0.517	P=0.179N
Logistic regression test	P = 0.208N	P=0.695N	P=0.497	P=0.217N
Cochran-Armitage test	P=0.199N			
Fisher exact test		P=0.691N	P=0.500	P=0.247N

Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Nitromethane (continued)

. •	1	0 ppm	188 ppm	375 ppm	750 ppm	
Ovary: Cystadenoma				<u></u>	· · · · · · · · · · · · · · · · · · ·	
Overall rate		2/47 (4%)	1/47 (2%)	0/48 (0%)	3148 (6%)	
Adjusted rate		4.9%	3.6%	0.0%	81%	
Terminal rate	,	0/24 (0%)	1/28 (4%)	0/26 (0%)	2/34 (6%)	
First incidence (days)	, t	576	734 (T)	-	687	
Life table test		P=0.433	P = 0.491N	P = 0.232N	P=0.609	
Logistic regression test		P = 0.354	P = 0.502N	P=0.236N	P=0.505	
Cochran-Armitage test		P = 0.345			1-0.505	
Fisher exact test			P = 0.500N	P = 0.242N	P=0.510	
				1 0.0.2.	1-0.510	
Ovary: Cystadenoma or Cysta	denocarcinoma				· ·	
Overall rate		2/47 (4%)	1/47 (2%)	0/48 (0%)	4/48 (8%)	
Adjusted rate		4.9%	3.6%	0.0%	10.3%	
Terminal rate		0/24 (0%)	1/28 (4%)	0/26 (0%)	2/34 (6%)	
First incidence (days)		576	734 (T)	-	657	
Life table test		P=0.247	P=0.491N	P = 0.232N	P=0.453	
Logistic regression test		P = 0.174	P=0.502N	P=0.236N	P=0.338	•
Cochran-Armitage test		P = 0.171	·	1997 - E. S. S.		•
Fisher exact test			P=0.500N	P=0.242N	P=0.349	
Pituitary Gland (Pars Distalis):	Adenoma				· , ·	
Overall rate		9/50 (18%)	10/46 (22%)	8/48 (17%)	4/50 (8%)	
Adjusted rate		30.3%	33.9%	32.0%	10.8%	
Terminal rate		6/25 (24%)	8/27 (30%)	8/25 (32%)	3/36 (8%)	
First incidence (days)		597	656	734 (T)	729	
Life table test	4 1	P=0.014N	P=0.544	P=0.494N	P=0.036N	
Logistic regression test	•	P=0.019N	P=0.456	P = 0.470N	P=0.063N	
Cochran-Armitage test		P = 0.064 N				
Fisher exact test			P=0.419	P=0.537N	P=0.117N	
Thyroid Gland (Follicular Cell)	: Adenoma					· ·
Overall rate		4/50 (8%)	1/48 (2%)	1/48 (2%)	1/50 (2%)	
Adjusted rate	4	12.2%	2.6%	4.0%	2.8%	
Terminal rate	and the second sec	2/25 (8%)	0/28 (0%)	1/25 (4%)	1/36 (3%)	
First incidence (days)		385	581	734 (T)	734 (T)	
Life table test		P=0.096N	P=0.177N	P=0.180N	P=0.116N	
Logistic regression test	1.	P = 0.144N	P=0.196N	P=0.196N	P=0.198N	
Cochran-Armitage test		P=0.134N				
Fisher exact test		· · · *	P=0.194N	P=0.194N	P=0.181N	· · · 4
Uterus: Hemangioma		• •			· .	1
Overall rate		2/50 (4%)	5/50 (10%)	0/50 (0%)	0/50 (0%)	1.1
Adjusted rate		6.3%	15.7%	0.0%	0.0%	÷
Terminal rate		1/25 (4%)	3/28 (11%)	0/26 (0%)	0/36 (0%)	
First incidence (days)		597	569	· · · · · · · · · · · · · · · · · · ·	· · · · · · · · · · · · · · · · · · ·	
Life table test	1	P=0.034N	P=0.239	P=0.230N	P = 0.191N	
		D 0.049N	P-0.217	P-0 239N	D-0 242N	
Logistic regression test		P=0.048IN	r≈0.21/	r -0.2001	r - 0.2421	
Logistic regression test Cochran-Armitage test		P = 0.048N P = 0.052N	F=0.217	r = 0.256N	P=0.2421	

# Lesions in Female Mice

## TABLE D3

n Hogy

Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Nitromethane (continued)

Uterus: Stromal Polyp           Overall rate $4/50 (8\%)$ $2/50 (4\%)$ $1/50 (2\%)$ $3/50 (6\%)$ Adjusted rate $14.0\%$ $7.1\%$ $3.8\%$ $8.0\%$ Terminal rate $3/25 (12\%)$ $2/28 (7\%)$ $1/26 (4\%)$ $2/36 (6\%)$ First incidence (days) $576$ $734 (T)$ $734 (T)$ $721$ Life table test         P=0.308N         P=0.299N         P=0.169N         P=0.327N           Logistic regression test         P=0.361N         P=0.333N         P=0.166N         P=0.341N           Cochran-Armitage test         P=0.456N         Fisher exact test         P=0.309N         P=0.181N         P=0.500N           All Organs: Hemangioma         Overall rate $1/50 (6\%)$ $6/50 (12\%)$ $0/50 (0\%)$ $1/50 (2\%)$ Overall rate $2/25 (8\%)$ $4/28 (14\%)$ $0/26 (0\%)$ $0/36 (0\%)$ First incidence (days) $597$ $569$ $ 687$ Life table test         P=0.044N         P=0.275         P=0.115N         P=0.215N           Logistic regression test         P=0.064N         P=0.243         P=0.121N         P	
Overall rate $4/50 (8\%)$ $2/50 (4\%)$ $1/50 (2\%)$ $3/50 (6\%)$ Adjusted rate $14.0\%$ $7.1\%$ $3.8\%$ $8.0\%$ Terminal rate $3/25 (12\%)$ $2/28 (7\%)$ $1/26 (4\%)$ $2/36 (6\%)$ First incidence (days) $576$ $734 (T)$ $734 (T)$ $721$ Life table testP=0.308NP=0.299NP=0.169NP=0.327NLogistic regression testP=0.361NP=0.333NP=0.166NP=0.431NCochran-Armitage testP=0.456NP=0.339NP=0.181NP=0.500NAll Organs: Hemangioma $3/50 (6\%)$ $6/50 (12\%)$ $0/50 (0\%)$ $1/50 (2\%)$ Adjusted rate $10.2\%$ $19.0\%$ $0.0\%$ $2.4\%$ Terminal rate $2/25 (8\%)$ $4/28 (14\%)$ $0/26 (0\%)$ $0/36 (0\%)$ First incidence (days) $597$ $569$ $ 687$ Life table testP=0.064NP=0.275P=0.115NP=0.215NLogistic regression testP=0.077N $F=0.243$ P=0.116NP=0.292NCochran-Armitage testP=0.077N $F=0.243$ P=0.121NP=0.309NAll Organs: Hemangiosarcoma $P=0.775$ P=0.121NP=0.309NAll Organs: Hemangiosarcoma $P=0.6\%$ $1/50 (2\%)$ $5/50 (10\%)$ $0/50 (0\%)$	
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Cochran-Armitage test         P=0.077N           Fisher exact test         P=0.243         P=0.121N         P=0.309N           All Organs: Hemangiosarcoma         Verall rate         4/50 (8%)         1/50 (2%)         5/50 (10%)         0/50 (0%)	
Fisher exact test       P=0.243       P=0.121N       P=0.309N         All Organs: Hemangiosarcoma       4/50 (8%)       1/50 (2%)       5/50 (10%)       0/50 (0%)         Overall rate       4/50 (8%)       1/50 (2%)       5/50 (10%)       0/50 (0%)	
All Organs:         Hemangiosarcoma           Overall rate         4/50 (8%)         1/50 (2%)         5/50 (10%)         0/50 (0%)	
Overall rate         4/50 (8%)         1/50 (2%)         5/50 (10%)         0/50 (0%)	
Adjusted rate 15.1% 3.6% 16.2% 0.0%	
Terminal rate         3/25 (12%)         1/28 (4%)         3/26 (12%)         0/36 (0%)	
First incidence (days) 707 734 (T) 568 -	
Life table test $P=0.063N$ $P=0.152N$ $P=0.526$ $P=0.028N$	
Logistic regression test $P=0.081N$ $P=0.160N$ $P=0.533$ $P=0.031N$	
Cochran-Armitage test P=0.114N	
Fisher exact test $P=0.181N$ $P=0.500$ $P=0.059N$	
All Organs: Hemangioma or Hemangiosarcoma	
Overall rate 7/50 (14%) 7/50 (14%) 5/50 (10%) 1/50 (2%)	
Adjusted rate 24.7% 22.4% 16.2% 2.4%	
Terminal rate $5/25 (20\%)$ $5/28 (18\%)$ $3/26 (12\%)$ $0/36 (0\%)$	
Prist incluence (days)         597         569         568         687           0.00001         0.00001         0.00001         0.00001         0.00001         0.00001	
Life table test $P=0.006N$ $P=0.556N$ $P=0.352N$ $P=0.011N$	
Logistic regression test $P \approx 0.01$ N $P \approx 0.012$ N $P \approx 0.34$ / N $P \approx 0.020$ N	
Fisher exact test $P=0.019N$ $P=0.613N$ $P=0.380N$ $P=0.030N$	
All Organse Missionatio Sancorro	
AN OT BAND. THE MORAN SALCONNA One will not a 2150 (70) 2150 (70) 2150 (70) 2150 (70) 2150 (70)	
$\frac{1}{2} \frac{1}{2} \frac{1}$	
Aujusteu rate $1.1\%$ $0.0\%$ $9.1\%$ $0.0\%$ Torminal rate $1/25/(4\%)$ $0/25/(0\%)$ $1/25/(4\%)$ $0/25/(0\%)$	
I Clininal Iaic $1/20 (4\%)$ $0/20 (0\%)$ First insidence (days)       602       631	
$\frac{1}{1}$ In the fact $D=0.221 M$ $D=0.221 M$ $D=0.524 M$ $D=0.172 M$	
Longitic regression fact $D = 0.261N$ $T = 0.22N$ $D = 0.522$ $D = 0.201N$	
P=0.2010 r = 0.2010 r = 0.2010 r = 0.2210 r = 0.2210 r = 0.2210 r = 0.2010	
Fisher exact test $P=0.247N$ $P=0.500$ $P=0.247N$	

Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Nitromethane (continued)

	0 ppm	188 ppm	375 ppm	750 ppm
All Organs: Malignant Lymphoma				
Overall rate	9/50 (18%)	7/50 (14%)	7/50 (14%)	7/50 (14%)
Adjusted rate	23.4%	20.7%	21.3%	17.5%
Ferminal rate	2/25 (8%)	4/28 (14%)	3/26 (12%)	4/36 (11%)
First incidence (days)	385	416	609	603
Life table test	P=0.196N	P=0.382N	P=0.368N	P=0.223N
Logistic regression test	P=0.389N	P=0.397N	P=0.404N	P=0.440N
Cochran-Armitage test	P=0.369N			· · ·
Fisher exact test		P=0.393N	P=0.393N	P=0.393N
All Organs: Benign Neoplasms		•		
Overall rate	31/50 (62%)	39/50 (78%)	33/50 (66%)	43/50 (86%)
Adjusted rate	78.8%	95.1%	86.2%	91.4%
Terminal rate	17/25 (68%)	26/28 (93%)	21/26(81%)	32/36 (89%)
First incidence (days)	385	534	498	51
( ife table test	P=0.422N	P = 0.208	P = 0.522	P=0.533
Logistic regression test	P=0.041	P=0.043	P=0.512	P=0.011
Cochran-Armitage test	P = 0.014	1 0.015	1 0.012	
Fisher evact test	1 0.011	P≈0.063	P = 0.418	P=0.006
i Biler exact test				
All Organs: Malignant Neoplasms			•	•
Overall rate	26/50 (52%)	24/50 (48%)	28/50 (56%)	21/50 (42%)
Adjusted rate	61.1%	56.6%	67.4%	42.9%
Terminal rate	9/25 (36%)	11/28 (39%)	13/26 (50%)	8/36 (22%)
First incidence (days)	385	416	548	426
Life table test	P=0.048N	P=0.385N	P=0.515	P=0.055N
Logistic regression test	P = 0.404N	P=0.398N	P=0.462	P=0.520N
Cochran-Armitage test	P=0.215N			2
Fisher exact test		P=0.421N	P=0.421	P = 0.212N
All Organs: Benjon or Malignant Neonlasms				· · ·
Averall rate	38/50 (76%)	45/50 (90%)	43/50 (86%)	46/50 (92%)
Adjusted rate	86.2%	100.0%	97.7%	92.0%
Terminal rate	19/25 (76%)	28/28 (100%)	25/26 (96%)	32/36 (89%)
First incidence (days)	385	416	498	51
Life table test	P=0.157N	P = 0.288	P=0.368	P=0.286N
Line while wat	P=0.070	P = 0.040	P = 0.198	P = 0.040
Cochran. Armitage test	P = 0.070			
cooman-mininage tost	· - 0.027	D 0.054	D-0.154	D=0.027

(T)Terminal sacrifice

^a Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, ovary, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.

^b Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

^c Observed incidence at terminal kill

^d Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table test regards neoplasms 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. For all tests, a negative trend or a lower incidence in an exposure group is indicated by N.

^e Not applicable; no neoplasms in animal group

# TABLE D4a

Historical Incidence of Harderian Gland Neoplasms in Chamber Control Female B6C3F1 Mice^a

	,	Incidence in Cont	rols
Study	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle	Pacific Northwest Labo	ratories	
1,3-Butadiene	8/50	0/50	8/50
Acetonitrile	3/49	0/49	3/49
Allyl glycidyl ether	0/50	0/50	0/50
2-Chloroacetophenone	0/50	0/50	0/50
l-Epinephrine Hydrochloride	1/50	1/50	2/50
Chloroethane	2/49	0/49	2/49
Hexachlorocyclopentadiene	4/49	1/49	5/49
o-Chlorobenzalmalononitrile (CS2)	2/50	2/50	4/50
Ozone	1/50	2/50	3/50
Total	21/447 (4.7%)	6/447 (1.3%)	27/447 (6.0%)
Standard deviation	5.0%	1.7%	5.0%
Range	0%-16%	0%-4%	0%-16%
Overall Historical Incidence			
Total	26/941 (2.8%)	6/941 (0.6%)	32/941 (3.4%)
Standard deviation	4.0%	1.4%	4.4%
Range	0%-16%	0%-4%	0%-16%
-			

^a Data as of 12 May 1995

# TABLE D4b

Historical Incidence of Hepatocellular Neoplasms in Chamber Control Female B6C3F₁ Mice^a

Study	A Jamiana				
	Adenoma	Carcinoma	Adenoma or Carcinoma		
Historical Incidence at Battelle	Pacific Northwest	Laboratories			
1,3-Butadiene	11/49	4/49	15/49		
Acetonitrile	4/49	7/49	9/49		
Allyl glycidyl ether	1/50	5/50	6/50		
2-Chloroacetophenone	4/50	8/50	12/50		
<i>l</i> -Epinephrine Hydrochloride	2/50	1/50	3/50		
Chloroethane	0/49	3/49	3/49		·.
Hexachlorocyclopentadiene	5/49	4/49	9/49		
o-Chlorobenzalmalononitrile (CS2)	4/50	7/50	11/50	•	
Ozone	20/50	15/50	27/50		· ·
Total	51/446 (11.4%)	54/446 (12.1%)	95/446 (21.3%)		
Standard deviation	12.4%	8.1%	14.8%		
Range	0%-40%	2%-30%	6%-54%		
Ū				4	
<b>Overall Historical Incidence</b>	· .	λ.	· .	. ,	, ¹
Total	114/937 (12.2%)	103/937 (11.0%)	200/937 (21.3%)		
Standard deviation	9.7%	6.7%	11.9%		. ·
Range	0%-40%	0%-30%	3%-54%		

^a Data as of 12 May 1995

# TABLE D4c

Historical Incidence of Alveolar/bronchiolar Neoplasms in Chamber Control Female B6C3F1 Mice^a

		Incidence in Cont	rols	
Study	Adenoma	Carcinoma	Adenoma or Carcinoma	٠
listorical Incidence at Battelle	Pacific Northwest Labor	ratories		
,3-Butadiene	4/50	0/50	4/50	
cetonitrile	7/49	1/49	8/49	
Allyl glycidyl ether	0/50	0/50	0/50	
-Chloroacetophenone	4/50	3/50	6/50	,
Epinephrine Hydrochloride	3/50	2/50	5/50	
Chloroethane	2/49	3/49	5/49	
Iexachlorocyclopentadiene	4/48	3/48	7/48	
-Chlorobenzalmalononitrile (CS2)	4/50	1/50	5/50	
Dzone	4/50	2/50	6/50	
Total	32/446 (7.2%)	15/446 (3.4%)	46/446 (10.3%)	
Standard deviation	3.8%	2.4%	4.6%	
Range	0%-14%	0%-6%	0%-16%	
Dverall Historical Incidence				
Total	61/939 (6.5%)	38/939 (4.1%)	97/939 (10.3%)	
Standard deviation	3.2%	. 3.2%	3.7%	
Range	0%-14%	0%-12%	0%-16%	

^a Data as of 12 May 1995

Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Nitromethane^a

	0 ppm	188 ppm	375 ppm	750 ppm
Disposition Summary			· · · · · · · · · · · · · · · · · · ·	
Animals initially in study	50	50	50	50
Early deaths	· · · · · · · · · · · · · · · · · · ·			
Accidental deaths	. 2		1	
Moribund	16	17	20	12
Natural deaths	7	5	3	2
Survivors		,	1	
Died last week of study		1		
Terminal sacrifice	25	27	26	36
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(48)	(48)	(49)	(49)
Epithelium, hyperplasia	1 (2%)			1 (2%)
Gallbladder	(40)	(45)	(45)	(46)
Inflammation, chronic		1 (2%)		
Inflammation, suppurative		1 (2%)	1 (2%)	
Intestine large, cecum	(49)	(46)	(47)	(50)
Diverticulum	. ,			1 (2%)
Muscularis, hyperplasia	1 (2%)			
Intestine small, duodenum	(48)	(43)	(45)	(49)
Cyst	1 (2%)			•
Peyer's patch, hyperplasia		1 (2%)		
Intestine small, jejunum	(47)	(45)	(47)	(48)
Epithelium, hyperplasia				1 (2%)
Liver	(50)	(49)	(49)	(50)
Angiectasis				1 (2%)
Basophilic focus	1 (2%)		11 (00.01)	1(2%)
Eosinophilic focus	4 (8%)	7 (14%)	11(22%)	15(30%)
Hematopoietic cell proliferation	2 (4%)	4 (8%)	2 (4%)	2(4%)
Inflammation, chronic	1 (2%)	3(0%)	1 (2%)	1(2%)
Mixed cell focus	· · · · · · · · · · · · · · · · · · ·	2(4%)	1 (2%)	1 (270)
Necrosis	2 (4%)	2 (4%)	5 (0%)	1 (2%)
Pile dust sust		1 (2%)		1 (270)
Contributor deconstruction fatty	1 (394)	1 (2%)		
Centrilobular, degeneration, rany	1 (2%)	3 (6%)		
Masantany	(7)	(14)	(8)	(11)
Hemorrhage	(1)	1 (7%)		
Inflammation suppurative		- (* /*)	1 (13%)	
Fat hemorrhage	· .		1 (13%)	•
Fat, necrosis	6 (86%)	11 (79%)	5 (63%)	10 (91%)
Fat. thrombosis		1 (7%)		
Pancreas	(50)	(48)	(48)	(50)
Atrophy	2 (4%)	2 (4%)	1 (2%)	2 (4%)
Basophilic focus	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Necrosis				1 (2%)
Duct, cyst			1 (2%)	2 (4%)
Duct, inflammation, suppurative	•			1 (2%)

^a Number of animals examined microscopically at the site and the number of animals with lesion

Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Nitromethane (continued)

	0 ppm	188 ppm	375 ppm	750 ppm
Alimentary System (continued)				
Salivary glands	(49)	(48)	(49)	(50)
Atrophy			1 (2%)	
Stomach, forestomach	(50)	(48)	(49)	(50)
Angiectasis				1 (2%)
Inflammation, suppurative	1 (2%)	1 (2%)	· · · · ·	
Ulcer	3 (6%)			1 (2%)
Epithelium, hyperplasia	1 (2%)	4 (8%)	3 (6%)	1 (2%)
Stomach, glandular	(49)	(48)	(48)	(50)
Degeneration, hyaline				1 (2%)
Inflammation		1 (2%)	1 (2%)	
Ulcer	1 (2%)		1 (2%)	1 (2%)
Cardiovascular System		<u>x 1 1.0 - 1</u>		
Blood vessel		(1)	(2)	
Aorta, mineralization		1 (100%)	1 (50%)	
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	13 (26%)	23 (46%)	19 (38%)	18 (36%)
Mineralization	1 (2%)			
Thrombosis	- ()			1 (2%)
Artery, inflammation	1 (2%)			
Endothelium, hyperplasia	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(48)	(49)	(50)
Degeneration cystic	1 (2%)	(40)	(+>)	3 (6%)
Hypernlasia	1 (2,0)	1 (2%)		2(4%)
Hypertrophy	2 (4%)	4 (8%)	5 (10%)	3 (6%)
Capsule, hyperplasia	- (,	2 (4%)	- (,	2 (4%)
Adrenal medulla	(50)	(48)	(49)	(49)
Hyperplasia	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Islets, pancreatic	(50)	(48)	(47)	(50)
Hyperplasia			1 (2%)	1 (2%)
Parathyroid gland	(33)	(34)	(33)	(34)
Cyst		1 (3%)		
Pituitary gland	(50)	(46)	(48)	(50)
Pars distalis, angiectasis		1 (2%)		
Pars distalis, hyperplasia	11 (22%)	20 (43%)	11 (23%)	18 (36%)
Pars intermedia, hyperplasia	1 (2%)			
Pars intermedia, hypertrophy	•	1 (2%)		
Thyroid gland	(50)	(48)	(48)	(50)
Follicular cell, hyperplasia	5 (10%)	4 (8%)	3 (6%)	5 (10%)

None

÷.

Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Nitromethane (continued)

	· 0 ]	ppm	18	8 ppm	375	5 ppm		750	) ppm	
Genital System										
Ovary	(47)		(47)		(49)			(40)		
Angiectasis	(47)	(0%)	(47)	(19)	(48)	$(\mathbf{n}, \mathbf{n})$		(48)		
Atrophy	14	(30%)	16	(470) (240'')	. 14	(270)		12	(779)	
Cvet	14	(30%)	10	(34%)	14	(29%)		13	(27%)	
Hyperplasia tubular	13	(28%)	14	(30%)		(33%)		13	(2/70)	•
Thrombosis	5	(0%)	2	(470)	2	(470)			$(\mathbf{n}, \mathbf{n})$	
Bilateral cyst	. 1	(270)	1	$(2 \alpha)$				1	(2%)	
Granulosa call hyperplasia			1	(270)					-	
Interstitial cell, hyperplasia			1	(270)		$(\mathcal{D}, \mathcal{O})$				
Interstitiat Cen, hyperplasia	(50)		(40)			(2%)		(50)		
Adenomyosia	(30)		(49)		(49)	(2.7)		(30)		
Angiectasis	2	(49)	2	(40)	1	(2%)				
Hemorrhage	. 2	(4%)	2	(4%)	4	(8%)				•
Hudromotro	· .			(0.01)	1	(2%)				
Hydrometra	. 3	(6%)	4	(8%)	5	(10%)		. 10	(20%)	
Hyperplasia, cystic	. 4	(8%)	6	(12%)	. 3	(6%)		2	(4%)	
Inflammation, suppurative								1	(2%)	8 - 1 L
Thrombosis			1	(2%)	2	(4%)				
Myometrium, hyperplasia		-			1	(2%)				·
Hematopoietic System										
Bone marrow	(50)		(48)		(49)			(50)		
Hyperplasia			3	(6%)					۰.	
Infiltration cellular, mast cell	1	(2%)		()						
Lymph node	(8)	(,	(6)		(5)			(6)		•
Ectasia	1	(13%)	(-)		(*)	· * .				
Hyperplasia			•		1	(20%)		•		
Iliac, hematopoietic cell proliferation					. 1	(20%)				
Iliac, hyperplasia			2	(33%)	-	()		1	(17%)	
Pancreatic, hyperplasia				(00/10)				1	(17%)	
Renal, hematopoietic cell proliferation					1	(20%)		, -	(1, ,0)	
Renal, hyperplasia			2	(33%)	i	(20%)		2	(33%)	
Lymph node, bronchial	(39)		(36)	(00 / 0 /	(40)	(20,0)		(40)	(00%)	
Hyperplasia	4	(10%)	5	(14%)	3	(8%)		2	(5%)	
Lymph node, mandibular	(43)	(10,0)	(34)	(1470)	(38)	(0,0)		(43)	(370)	
Hematopoietic cell proliferation	(10)		(34)	(3%)	(55)			(45)		
Hypernlasia	1	(2%)	- 1	(3%)	5	(13%)		5	(12%)	
Lymph node mesenteric	(48)	(270)	(46)	(370)	(46)	(1570)		(48)	(12/0)	· .
Angiectasis	(40)	(2%)	(40)		. (40)	(2%)		(40)	(4%)	
Congestion	· · 1	(2%)	. 1	(29)	•	(270)		2	(470)	
Hunemlasia		(2 %)	0	(2, n)	2	(70)		~ ^	(90%)	•
Infiltration cellular mast cell	1	(13%)	9	(20%)	3	(170)		4	(0%)	
I worth node mediastinal	(29)	(2%)	. (27)		(25)		1.1.1	(41)		
Lympin houe, mediasunai	(38)	(160)	(37)	(1492)	(33)	(00)		(41)	(50)	1.1
Spleen		(10%)	. (49)	(1470)	. 3	(970)		(50)	(3%)	•
Angiastagia	(50)		(48)		(49)	$(\mathbf{D} \mathbf{d})$		(50)		
Anglectasis	10	(200)		$(2\pi d)$	1	(2%)		.10	(24.00)	
Humanopoletic cell proliteration	10	(20%)	13	(2170)	10	(20%)		12	(24%)	
Hyperplasia, lymphold		(10%)	10	(21%)	0	(12%)		8	(10%)	· .
Inflitration cellular, mast cell	1	(2%)	(00)							
1 nymus	(43)	(2.27)	(39)	(F. M)	(41)	1.0		(47)		
Atrophy	1	(2%)	2	(5%)	2	(5%)		-		
Hyperplasia, lymphoid	3	(7%)	2	(5%)	6	(15%)		5	(11%)	
Infiltration cellular, mast cell	1	(2%)		(a. at )						
Necrosis			1	(3%)				1	(2%)	

Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Nitromethane (continued)

· · · · ·	0 ppm	188 ppm	375 ppm	750 ppm
Integumentary System				
Mammary gland	(50)	(48)	(49)	(50)
Hyperplasia	(40)	(47)	(50)	2 (4%)
SKIN Cyst epithelial inclusion	(49)	(47)	(30)	(30) 1 (2%)
Inflammation chronic	1 (2%)		· · ·	1 (270)
Inflammation, suppurative	1 (2%)	1 (2%)	1 (2%)	
Musculoskeletal System	<u> </u>			
Bone	(50)	(50)	(50)	(50)
Arthrosis	1 (2%)			
Fibrous osteodystrophy Hyperostosis	17 (34%)	18 (36%)	18 (36%) 1 (2%)	12 (24%)
Nervous System			<u></u>	<u></u>
Brain	(50)	(50)	(49)	(50)
Meninges, infiltration cellular,				×
mononuclear cell		2 (4%)	1 (2%)	
Respiratory System	······································	······································		· .
Larynx	(49)	(48)	(49)	(50)
Inflammation, suppurative		1 (2%)		
Metaplasia, squamous		1 (2%)		·
Lung	(50)	(50)	(49)	(50)
Hemorrhage	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Inflammation children in the starting	3 (494)	1 (2%)	0 (12%)	4 (8%)
Pigmentation, temosiderin	2 (470)		1(270)	1 (2%)
Alveolar epithelium, hyperplasia	3 (6%)	1 (2%)	5(10%)	1(2%)
Bronchus, infiltration cellular, mixed cell	1 (2%)			- (
Mediastinum, hemorrhage, focal	1 (2%)			• -
Mediastinum, infiltration cellular, mast cell	1 (2%)			
Mediastinum, inflammation, chronic				1 (2%)
Mediastinum, necrosis		1 (2%)		
Perivascular, inflammation, chronic		1 (2%)		1 (2%)
Nose	(50)	(49)	(50)	(50)
Inflammation, chronic, local	2 (194)		1 (276)	1 (2%)
Glands, hyperplasia	2 (470)		<b>+</b> (678)	1 (2%)
Nasolacrimal duct, inflammation.				- (270)
suppurative	1 (2%)		3 (6%)	3 (6%)
Olfactory epithelium, atrophy, focal	2 (4%)	6 (12%)		
Olfactory epithelium, degeneration		22 (45%)	50 (100%)	50 (100%)
Olfactory epithelium, metaplasia		2 (4%)	46 (92%)	48 (96%)
Respiratory epithelium, degeneration,		AA (00 M)	<b>P</b>	
nyaline Recointory epithelium motorlasia	16 (32%)	39 (80%)	50 (100%)	50 (100%)
solution control and the solution of the solut			1 (2%)	
syaamous			· (270)	

Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Nitromethane (continued)

· · · · ·	0 ppm	188 ppm	375 ppm	750 ppm
Special Senses System				
Eye	•	(1)	(1)	
Inflammation		1 (100%)	1 (100%)	
Harderian gland	(49)	(49)	(50)	(50)
Fibrosis, focal				1 (2%)
Hyperplasia	3 (6%)	2 (4%)	5 (10%)	1 (2%)
· · · · · · · · · · · · · · · · · · ·		ŕ		
Urinary System	•			
Kidney	(50)	(48)	(49)	(50)
Amyloid deposition		1 (2%)		*
Hydronephrosis			1 (2%)	
Metaplasia, osseous	1 (2%)	2 (4%)	3 (6%)	1 (2%)
Nephropathy	12 (24%)	5 (10%)	7 (14%)	7 (14%)
Renal tubule, degeneration		,		1 (2%)
Renal tubule, mineralization		1 (2%)	1 (2%)	
Urinary bladder	(49)	(47)	(47)	(49)
Inflammation, suppurative	1 (2%)	2 (4%)	•	
Transitional epithelium, hyperplasia		1 (2%)		
	•	•		

# APPENDIX E GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL									
CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS									
MOUSE PER	RIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOL	229							
<b>RESULTS</b> .		230							
Table E1	Mutagenicity of Nitromethane in Salmonella typhimurium	231							
TABLE E2	Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells								
	by Nitromethane	232							
TABLE E3	Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells								
	by Nitromethane	233							
Table E4	Frequency of Micronuclei in Peripheral Blood Erythrocytes of Mice								
	Following Treatment with Nitromethane by Inhalation for 13 Weeks	234							

# **GENETIC TOXICOLOGY**

# SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Mortelmans *et al.* (1986). Nitromethane was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It 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. Top agar supplemented with *l*-histidine and *d*-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and five doses of nitromethane. The high dose was limited by experimental design to 10,000  $\mu$ g/plate. All trials were repeated.

In this assay, a positive response is defined as a reproducible, dose-related increase in histidineindependent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants that is not dose related, not reproducible, or not of sufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment. There is no minimum percentage or fold increase required for a chemical to be judged positive or weakly positive.

# CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1987). Nitromethane was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), 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-substituted DNA. Each test consisted of concurrent solvent and positive controls and of three doses of nitromethane. In the absence of toxicity, the high dose was limited to approximately 5,000  $\mu$ g/mL. A single flask per dose was used, and tests yielding equivocal or positive results were repeated.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 26 hours with nitromethane in McCoy's 5A medium. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing nitromethane was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 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 nitromethane, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no nitromethane and 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. All slides were scored blind and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.*, 1987). 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

#### **Genetic Toxicology**

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. An increase of 20% or greater at any single dose was considered weak evidence of activity; increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend (P < 0.005) in the absence of any responses reaching 20% above background led to a call of equivocal.

**Chromosomal Aberrations Test:** In the Abs test without S9, cells were incubated in McCoy's 5A medium with nitromethane for 11.5 hours; Colcemid was added, and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with nitromethane and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 11.5 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.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype  $(21 \pm 2 \text{ chromosomes})$ . All slides were scored blind and those from a single test were read by the same person. Two hundred first-division metaphase cells were scored at each dose level. 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).

Chromosomal aberration data are presented as percentages of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted on both the dose response curve and individual dose points. For a single trial, a statistically significant ( $P \le 0.05$ ) difference for one dose point and a significant trend ( $P \le 0.015$ ) were considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive. A positive trend test in the absence of a statistically significant increase at any one dose resulted in an equivocal call (Galloway *et al.*, 1987). Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological information available to the reviewers.

# MOUSE PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOL

A detailed discussion of this assay can be found in MacGregor *et al.* (1990). Peripheral blood samples were obtained from male and female  $B6C3F_1$  mice at the end of the 13-week toxicity study. Smears were immediately prepared and fixed in absolute methanol and were later stained with a chromatin-specific fluorescent dye mixture of Hoechst 33258/pyronin Y (MacGregor *et al.*, 1983) and coded. Slides were scanned to determine the frequency of micronuclei in 2,000 normochromatic erythrocytes (NCEs) in each animal per dose group. The criteria of Schmid (1976) were used to define micronuclei, with the additional requirement that the micronuclei exhibit the characteristic fluorescent emissions of DNA (blue with 360 nm and orange with 510 nm ultraviolet illumination); the minimum size limit was approximately one-twentieth the diameter of the NCE cell.

The results were tabulated as the mean of the pooled results from all animals within a treatment group, plus or minus the standard error of the mean. The frequency of micronucleated cells among NCEs was analyzed by a statistical software package that tested for increasing trend over exposure groups with a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each exposure group and the control group (Margolin *et al.*, 1990). In the presence of excess binomial variation, as detected by a binomial dispersion test, the binomial variance of the Cochran-Armitage test was adjusted upward in proportion to the excess variation. In the micronucleus test, an individual trial is considered positive if the trend test P value is less than or equal to 0.025 or if the P value for any exposure group is less than or equal to 0.025 divided by the number of exposed groups. A final call of positive for micronucleus induction is preferably based on reproducibly positive trials (as noted above). Ultimately, the final call is

determined by the scientific staff after considering the results of statistical analyses, the reproducibility of any effects observed, and the magnitudes of those effects.

# RESULTS

Nitromethane was not mutagenic *in vitro* or *in vivo*. Nitromethane (100 to 10,000  $\mu$ g/plate) was negative for induction of mutations in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 when tested with or without induced S9 enzymes (Table E1; Mortelmans *et al.*, 1986). No induction of SCEs (Table E2) or Abs (Table E3) was observed in cultured CHO cells treated with up to 5,000  $\mu$ g/mL nitromethane. Nitromethane administered by inhalation for 13 weeks at concentrations up to 1,500 ppm did not induce increased frequencies of micronucleated erythrocytes in the peripheral blood of male or female mice (Table E4).

#### Table E1

	$\begin{array}{r} +10\% \text{ r:} \\ \hline \text{Trial 1} \\ \\ 55 \pm 2.3 \\ 86 \pm 5.5 \\ 88 \pm 2.1 \\ 88 \pm 0.6 \\ 91 \pm 10.3 \\ 84 \pm 5.7 \\ \hline \text{Negative} \\ 738 \pm 28.9 \end{array}$	amster S9           Trial 2 $104 \pm 6.8$ $113 \pm 7.5$ $111 \pm 0.6$ $101 \pm 8.7$ $105 \pm 10.0$ $120 \pm 3.2$	$\begin{array}{c} +10\% \text{ ha}\\ \hline \\ \mathbf{Trial 1}\\ 54 \pm 1.7\\ 92 \pm 11.4\\ 93 \pm 4.4\\ 85 \pm 4.3\\ 90 \pm 6.7\\ 96 \pm 5.5\\ \end{array}$	$\begin{array}{c} & \\ \hline \\ \hline$	$ \begin{array}{r} -59 \\ \hline      \hline     \hline      \hline           $	Strain Dose (µg/plate) TA100 0 100 333.3 1,000 3,333.3
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	Trial 1 $55 \pm 2.3$ $86 \pm 5.5$ $88 \pm 2.1$ $88 \pm 0.6$ $91 \pm 10.3$ $84 \pm 5.7$ Negative $738 \pm 28.9$	Trial 2 $104 \pm 6.8$ $113 \pm 7.5$ $111 \pm 0.6$ $101 \pm 8.7$ $105 \pm 10.0$ $120 \pm 3.2$	Trial 1 $54 \pm 1.7$ $92 \pm 11.4$ $93 \pm 4.4$ $85 \pm 4.3$ $90 \pm 6.7$ $96 \pm 5.5$	Trial 2 $82 \pm 2.8$ $104 \pm 2.2$ $106 \pm 10.3$ $92 \pm 4.5$ $101 \pm 11.3$ 127 + 9.1	Trial 1 $64 \pm 1.9$ $70 \pm 2.3$ $74 \pm 3.2$ $64 \pm 1.8$ $60 \pm 4.2$	(µg/plate) TA100 0 100 333.3 1,000 3,333.3
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	$55 \pm 2.3 \\ 86 \pm 5.5 \\ 88 \pm 2.1 \\ 88 \pm 0.6 \\ 91 \pm 10.3 \\ 84 \pm 5.7 \\ Negative \\ 738 \pm 28.9 \\ \end{cases}$	$104 \pm 6.8 \\ 113 \pm 7.5 \\ 111 \pm 0.6 \\ 101 \pm 8.7 \\ 105 \pm 10.0 \\ 120 \pm 3.2 \\ 105 \pm 10.0 \\ 120 \pm 3.2 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 10$	$54 \pm 1.7 \\92 \pm 11.4 \\93 \pm 4.4 \\85 \pm 4.3 \\90 \pm 6.7 \\96 \pm 5.5$	$82 \pm 2.8 \\104 \pm 2.2 \\106 \pm 10.3 \\92 \pm 4.5 \\101 \pm 11.3 \\127 + 9.1$	$\begin{array}{r} 64 \pm 1.9 \\ 70 \pm 2.3 \\ 74 \pm 3.2 \\ 64 \pm 1.8 \\ 60 \pm 4.2 \end{array}$	TA100 0 100 333.3 1,000 3,333.3
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$86 \pm 5.5 \\ 88 \pm 2.1 \\ 88 \pm 0.6 \\ 91 \pm 10.3 \\ 84 \pm 5.7 \\ Negative \\ 738 \pm 28.9 \\ \end{cases}$	$ \begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	$92 \pm 11.4 93 \pm 4.4 85 \pm 4.3 90 \pm 6.7 96 \pm 5.5$	$104 \pm 2.2 \\ 106 \pm 10.3 \\ 92 \pm 4.5 \\ 101 \pm 11.3 \\ 127 + 9.1$	$70 \pm 2.3 \\ 74 \pm 3.2 \\ 64 \pm 1.8 \\ 60 \pm 4.2 \\ 150 \pm 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 10$	100 333.3 1,000 3,333.3
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$88 \pm 2.1 \\88 \pm 0.6 \\91 \pm 10.3 \\84 \pm 5.7 \\$ Negative 738 \pm 28.9	$ \begin{array}{r} 111 \pm 0.6 \\ 101 \pm 8.7 \\ 105 \pm 10.0 \\ 120 \pm 3.2 \end{array} $	$93 \pm 4.4 \\ 85 \pm 4.3 \\ 90 \pm 6.7 \\ 96 \pm 5.5$	$106 \pm 10.3 \\92 \pm 4.5 \\101 \pm 11.3 \\127 + 9.1$	$74 \pm 3.2 \\ 64 \pm 1.8 \\ 60 \pm 4.2 \\ 67 \pm 610 \\ 60 \pm 610 $	333.3 1,000 3,333.3
1,000 $64 \pm 1.8$ $92 \pm 4.5$ $85 \pm 4.3$ $101 \pm 8.7$ $88 \pm 0.6$ $94 \pm 5.5$ 3,333.3 $60 \pm 4.2$ $101 \pm 11.3$ $90 \pm 6.7$ $105 \pm 10.0$ $91 \pm 10.3$ $101 \pm 8.4$ $10,000$ $27 \pm 15.3^{\circ}$ $127 \pm 9.1$ $96 \pm 5.5$ $120 \pm 3.2$ $84 \pm 5.7$ $99 \pm 6.1$ Trial summary Positive controlNegative $222 \pm 20.9$ Negative $461 \pm 5.9$ Negative $2,168 \pm 100.8$ Negative $1,720 \pm 67.7$ Negative $738 \pm 28.9$ Negative $577 \pm 26.1$ TA15350 $7 \pm 1.5$ $7 \pm 1.2$ $19 \pm 2.6$ $8 \pm 2.9$ $10 \pm 2.8$ $8 \pm 0.6$ $5 \pm 0.9$ $9 \pm 1.2$ $13 \pm 2.8$ $333.3$ $9 \pm 1.2$ $19 \pm 1.3$ $1.3$ $5 \pm 1.0$ $10 \pm 1.5$ $8 \pm 0.6$ $10 \pm 1.5$ $9 \pm 2.0$ $13 \pm 2.8$ $3,333.3$ $10 \pm 1.2$ $12 \pm 2.7$ $20 \pm 3.0$ $4 \pm 2.0$ $4 \pm 2.0$ $12 \pm 1.8$ $1.5$ $6 \pm 0.6$ $10 \pm 1.9$ $10,000$ $5 \pm 2.0$ $23 \pm 1.5$ $5 \pm 1.5$ $14 \pm 3.1$ $11 \pm 1.0$ $14 \pm 1.3$ $10,000$ $5 \pm 2.0$ $23 \pm 1.5$ $5 \pm 1.5$ $14 \pm 3.1$ $11 \pm 1.0$ $14 \pm 1.3$ $13.6$ $458 \pm 19.8$ $322 \pm 52.9$ $421 \pm 16.5$ $332 \pm 24.6$ $332 \pm 24.6$ $392 \pm 23.1$ Trial summary Positive control $8 \pm 1.2$ $248 \pm 13.6$ $458 \pm 19.8$ $2.6$ $4 \pm 1.5$ $11 \pm 0.9$ $3 \pm 2.6$ $6 \pm 0.7$ $4 \pm 1.5$ TA1537 $0$ $3 \pm 1.3$ $8 \pm 2.6$ $4 \pm 1.5$ $11 \pm 0.9$ $3 \pm 2.6$ $6 \pm 0.7$ $4 \pm 1.5$ $100$ $3 \pm 1.3$ $7 \pm 0.9$ $5 \pm 0.9$ <	$88 \pm 0.6 91 \pm 10.3 84 \pm 5.7 Negative 738 \pm 28.9$	$ \begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	$92 \pm 4.5$ 101 ± 11.3 127 + 9.1	$64 \pm 1.8$ $60 \pm 4.2$	1,000 3,333.3
3,333.3 10,000 $60 \pm 4.2$ $27 \pm 15.3^{c}$ $101 \pm 11.3$ $127 \pm 9.1$ $90 \pm 6.7$ $96 \pm 5.5$ $100$ $120 \pm 3.2$ $91 \pm 10.3$ $84 \pm 5.7$ $101 \pm 8.4$ $99 \pm 6.1$ Trial summary Positive controldNegative $222 \pm 20.9$ Negative $461 \pm 5.9$ Negative $2,168 \pm 100.8$ Negative $1,720 \pm 67.7$ Negative $738 \pm 28.9$ Negative $577 \pm 26.1$ TA1535 $100$ $333.3$ $9 \pm 1.2$ $7 \pm 1.2$ $100$ $7 \pm 1.5$ $23 \pm 2.0$ $19 \pm 2.6$ $19 \pm 2.6$ $13 \pm 2.9$ $6 \pm 2.3$ $11 \pm 1.5$ $11 \pm 1.5$ $10 \pm 2.8$ $5 \pm 0.9$ Negative $13 \pm 2.8$ $5 \pm 0.9$ Negative $13 \pm 2.8$ $5 \pm 0.9$ Negative $13 \pm 2.8$ $12 \pm 2.0$ $10 \pm 1.2$ $12 \pm 2.7$ $12 \pm 2.0$ $10 \pm 1.2$ $12 \pm 2.7$ $12 \pm 2.0$ $12 \pm 2.0$ 	91 ± 10.3 84 ± 5.7 Negative 738 ± 28.9	$105 \pm 10.0$ $120 \pm 3.2$	$90 \pm 6.7$ $96 \pm 5.5$	$101 \pm 11.3$ $127 \pm 9.1$	$60 \pm 4.2$	3,333.3
10,000 $27 \pm 15.3^{\circ}$ $127 \pm 9.1$ $96 \pm 5.5$ $120 \pm 3.2$ $84 \pm 5.7$ $99 \pm 6.1$ Trial summary Positive control ^d Negative $222 \pm 20.9$ Negative $461 \pm 5.9$ Negative $2,168 \pm 100.8$ Negative $1,720 \pm 67.7$ Negative $738 \pm 28.9$ Negative $577 \pm 26.1$ TA15350 $7 \pm 1.5$ $7 \pm 1.2$ $100$ $7 \pm 1.5$ $23 \pm 2.0$ $19 \pm 2.6$ $6 \pm 2.3$ $8 \pm 2.9$ $11 \pm 1.5$ $10 \pm 2.8$ $8 \pm 0.6$ $5 \pm 0.9$ $9 \pm 1.2$ $13 \pm 2.8$ $333.3$ $9 \pm 1.2$ $9 \pm 1.2$ $10 \pm 1.2$ $19 \pm 2.6$ $11 \pm 2.0$ $8 \pm 2.9$ 	84 ± 5.7 Negative 738 ± 28.9	$120 \pm 3.2$	$96 \pm 5.5$	$127 \pm 9.1$		10.000
Trial summary Positive controlNegative $222 \pm 20.9$ Negative $461 \pm 5.9$ Negative $2,168 \pm 100.8$ Negative $1,720 \pm 67.7$ Negative $738 \pm 28.9$ Negative 	Negative 738 ± 28.9				$27 \pm 15.3^{\circ}$	10,000
Positive control ^d $222 \pm 20.9$ $461 \pm 5.9$ $2,168 \pm 100.8$ $1,720 \pm 67.7$ $738 \pm 28.9$ $577 \pm 26.1$ TA15350 $7 \pm 1.2$ $23 \pm 2.0$ $6 \pm 2.3$ $11 \pm 1.5$ $8 \pm 0.6$ $9 \pm 1.2$ 100 $7 \pm 1.5$ $19 \pm 2.6$ $8 \pm 2.9$ $10 \pm 2.8$ $5 \pm 0.9$ $13 \pm 2.8$ 333.3 $9 \pm 1.2$ $19 \pm 1.3$ $5 \pm 1.0$ $10 \pm 1.5$ $6 \pm 1.5$ $13 \pm 2.1$ 1,000 $10 \pm 1.2$ $21 \pm 2.0$ $4 \pm 1.0$ $11 \pm 3.2$ $5 \pm 0.9$ $9 \pm 2.0$ 3,333.3 $12 \pm 2.7$ $20 \pm 3.0$ $4 \pm 2.0$ $12 \pm 1.8$ $6 \pm 0.6$ $10 \pm 1.9$ 10,000 $5 \pm 2.0$ $23 \pm 1.5$ $5 \pm 1.5$ $14 \pm 3.1$ $11 \pm 1.0$ $14 \pm 1.3$ Trial summaryNegativeNegativeNegativeNegativeNegativePositive control $248 \pm 13.6$ $458 \pm 19.8$ $322 \pm 52.9$ $421 \pm 16.5$ $332 \pm 24.6$ $392 \pm 23.1$ TA15370 $8 \pm 1.2$ $8 \pm 2.6$ $4 \pm 1.5$ $11 \pm 0.9$ $6 \pm 2.2$ $12 \pm 2.2$ 100 $3 \pm 1.3$ $7 \pm 0.9$ $5 \pm 0.9$ $13 \pm 2.6$ $6 \pm 0.7$ $4 \pm 1.5$ $333.3$ $4 \pm 0.7$ $7 \pm 1.2$ $4 \pm 0.7$ $12 \pm 3.2$ $5 \pm 0.6$ $4 \pm 1.5$ $1,000$ $3 \pm 1.5$ $8 \pm 1.0$ $2 \pm 0.0$ $13 \pm 2.6$ $6 \pm 1.0$ $5 \pm 0.3$ $3,33.3$ $1 \pm 1.0$ $9 \pm 1.7$ $5 \pm 1.8$ $15 \pm 2.1$ $6 \pm 0.9$ $3 \pm 0.6$ $1,000$ $3 \pm 1.5$ $8 \pm 1.0$ $2 \pm 0.0$ $13 \pm 2.6$ $6 $	738 ± 28.9	Negative	Negative	Negative	Negative	Trial summary
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		1,720 ± 67.7	$2,168 \pm 100.8$	461 ± 5.9	$222 \pm 20.9$	Positive control ^d
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	8 ± 0.6	$11 \pm 1.5$	$6 \pm 2.3$	$23 \pm 2.0$	$7 \pm 1.2$	TA1535 0
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$5 \pm 0.9$	$10 \pm 2.8$	$8 \pm 2.9$	$19 \pm 2.6$	$7 \pm 1.5$	100
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$6 \pm 1.5$	$10 \pm 1.5$	$5 \pm 1.0$	$19 \pm 1.3$	$9 \pm 1.2$	333.3
3,333.3 10,000 $12 \pm 2.7$ $5 \pm 2.0$ $20 \pm 3.0$ $23 \pm 1.5$ $4 \pm 2.0$ 	$5 \pm 0.9$	$11 \pm 3.2$	$4 \pm 1.0$	$21 \pm 2.0$	$10 \pm 1.2$	1,000
10,000 $5 \pm 2.0$ $23 \pm 1.5$ $5 \pm 1.5$ $14 \pm 3.1$ $11 \pm 1.0$ $14 \pm 1.3$ Trial summary Positive controlNegative $248 \pm 13.6$ Negative $458 \pm 19.8$ Negative $322 \pm 52.9$ Negative $421 \pm 16.5$ Negative $332 \pm 24.6$ Negative $392 \pm 23.1$ TA15370 $3\pm 1.3$ $8 \pm 1.2$ $\pm 1.3$ $8 \pm 2.6$ $\pm 1.2$ $4 \pm 1.5$ $11 \pm 0.9$ $11 \pm 0.9$ $6 \pm 2.2$ $6 \pm 2.2$ $12 \pm 2.2$ 100 $3\pm 1.3$ $7 \pm 0.9$ $\pm 0.9$ $5 \pm 0.9$ $13 \pm 2.6$ $6 \pm 0.7$ $4 \pm 1.5$ $1,000$ $3\pm 1.5$ $8 \pm 1.0$ $\pm 1.5$ $2 \pm 0.0$ $13 \pm 2.6$ $6 \pm 1.0$ $5 \pm 0.3$ $5 \pm 0.3$ $5 \pm 0.3$ $1,000$ $3\pm 1.5$ $8 \pm 1.0$ $\pm 1.7$ $2 \pm 0.0$ $\pm 1.8$ $15 \pm 2.1$ $1.8$ $6 \pm 0.9$ $3 \pm 0.7$ $2 \pm 0.6$ $10,000$ $1 \pm 0.7$ $7 \pm 3.0$ $6 \pm 1.2$ $12 \pm 1.9$ $3 \pm 0.7$ $3 \pm 0.7$ $2 \pm 0.6$	6 ± 0.6	$12 \pm 1.8$	$4 \pm 2.0$	$20 \pm 3.0$	$12 \pm 2.7$	3,333.3
Trial summary Positive controlNegative $248 \pm 13.6$ Negative $458 \pm 19.8$ Negative $322 \pm 52.9$ Negative $421 \pm 16.5$ Negative $332 \pm 24.6$ Negative $332 \pm 24.6$ Negative $392 \pm 23.1$ TA15370 $8 \pm 1.2$ $8 \pm 2.6$ $4 \pm 1.5$ $11 \pm 0.9$ $6 \pm 2.2$ $12 \pm 2.2$ 100 $3 \pm 1.3$ $7 \pm 0.9$ $5 \pm 0.9$ $13 \pm 2.6$ $6 \pm 0.7$ $4 \pm 1.5$ 333.3 $4 \pm 0.7$ $7 \pm 1.2$ $4 \pm 0.7$ $12 \pm 3.2$ $5 \pm 0.6$ $4 \pm 1.5$ 1,000 $3 \pm 1.5$ $8 \pm 1.0$ $2 \pm 0.0$ $13 \pm 2.6$ $6 \pm 1.0$ $5 \pm 0.3$ 3,333.3 $1 \pm 1.0$ $9 \pm 1.7$ $5 \pm 1.8$ $15 \pm 2.1$ $6 \pm 0.9$ $3 \pm 0.6$ 10,000 $1 \pm 0.7$ $7 \pm 3.0$ $6 \pm 1.2$ $12 \pm 1.9$ $3 \pm 0.7$ $2 \pm 0.6$	$11 \pm 1.0$	$14 \pm 3.1$	$5 \pm 1.5$	$23 \pm 1.5$	$5 \pm 2.0$	10,000
Positive control $248 \pm 13.6$ $458 \pm 19.8$ $322 \pm 52.9$ $421 \pm 16.5$ $332 \pm 24.6$ $392 \pm 23.1$ <b>TA1537</b> 0 $8 \pm 1.2$ $8 \pm 2.6$ $4 \pm 1.5$ $11 \pm 0.9$ $6 \pm 2.2$ $12 \pm 2.2$ 100 $3 \pm 1.3$ $7 \pm 0.9$ $5 \pm 0.9$ $13 \pm 2.6$ $6 \pm 0.7$ $4 \pm 1.5$ 333.3 $4 \pm 0.7$ $7 \pm 1.2$ $4 \pm 0.7$ $12 \pm 3.2$ $5 \pm 0.6$ $4 \pm 1.5$ 1,000 $3 \pm 1.5$ $8 \pm 1.0$ $2 \pm 0.0$ $13 \pm 2.6$ $6 \pm 1.0$ $5 \pm 0.3$ 3,333.3 $1 \pm 1.0$ $9 \pm 1.7$ $5 \pm 1.8$ $15 \pm 2.1$ $6 \pm 0.9$ $3 \pm 0.6$ 10,000 $1 \pm 0.7$ $7 \pm 3.0$ $6 \pm 1.2$ $12 \pm 1.9$ $3 \pm 0.7$ $2 \pm 0.6$	Negative	Negative	Negative	Negative	Negative	Trial summary
TA15370 $8 \pm 1.2$ $8 \pm 2.6$ $4 \pm 1.5$ $11 \pm 0.9$ $6 \pm 2.2$ $12 \pm 2.2$ 100 $3 \pm 1.3$ $7 \pm 0.9$ $5 \pm 0.9$ $13 \pm 2.6$ $6 \pm 0.7$ $4 \pm 1.5$ 333.3 $4 \pm 0.7$ $7 \pm 1.2$ $4 \pm 0.7$ $12 \pm 3.2$ $5 \pm 0.6$ $4 \pm 1.5$ 1,000 $3 \pm 1.5$ $8 \pm 1.0$ $2 \pm 0.0$ $13 \pm 2.6$ $6 \pm 1.0$ $5 \pm 0.3$ 3,333.3 $1 \pm 1.0$ $9 \pm 1.7$ $5 \pm 1.8$ $15 \pm 2.1$ $6 \pm 0.9$ $3 \pm 0.6$ 10,000 $1 \pm 0.7$ $7 \pm 3.0$ $6 \pm 1.2$ $12 \pm 1.9$ $3 \pm 0.7$ $2 \pm 0.6$	$332 \pm 24.6$	421 ± 16.5	$322 \pm 52.9$	458 ± 19.8	$248 \pm 13.6$	Positive control
100 $3 \pm 1.3$ $7 \pm 0.9$ $5 \pm 0.9$ $13 \pm 2.6$ $6 \pm 0.7$ $4 \pm 1.5$ 333.3 $4 \pm 0.7$ $7 \pm 1.2$ $4 \pm 0.7$ $12 \pm 3.2$ $5 \pm 0.6$ $4 \pm 1.5$ 1,000 $3 \pm 1.5$ $8 \pm 1.0$ $2 \pm 0.0$ $13 \pm 2.6$ $6 \pm 1.0$ $5 \pm 0.3$ 3,333.3 $1 \pm 1.0$ $9 \pm 1.7$ $5 \pm 1.8$ $15 \pm 2.1$ $6 \pm 0.9$ $3 \pm 0.6$ 10,000 $1 \pm 0.7$ $7 \pm 3.0$ $6 \pm 1.2$ $12 \pm 1.9$ $3 \pm 0.7$ $2 \pm 0.6$	$6 \pm 2.2$	11 ± 0.9	4 ± 1.5	8 ± 2.6	8 ± 1.2	TA1537 0
333.3 $4 \pm 0.7$ $7 \pm 1.2$ $4 \pm 0.7$ $12 \pm 3.2$ $5 \pm 0.6$ $4 \pm 1.5$ 1,000 $3 \pm 1.5$ $8 \pm 1.0$ $2 \pm 0.0$ $13 \pm 2.6$ $6 \pm 1.0$ $5 \pm 0.3$ 3,333.3 $1 \pm 1.0$ $9 \pm 1.7$ $5 \pm 1.8$ $15 \pm 2.1$ $6 \pm 0.9$ $3 \pm 0.6$ 10,000 $1 \pm 0.7$ $7 \pm 3.0$ $6 \pm 1.2$ $12 \pm 1.9$ $3 \pm 0.7$ $2 \pm 0.6$	6 ± 0.7	$13 \pm 2.6$	5 ± 0.9	7 ± 0.9	$3 \pm 1.3$	100
1,000 $3 \pm 1.5$ $8 \pm 1.0$ $2 \pm 0.0$ $13 \pm 2.6$ $6 \pm 1.0$ $5 \pm 0.3$ 3,333.3 $1 \pm 1.0$ $9 \pm 1.7$ $5 \pm 1.8$ $15 \pm 2.1$ $6 \pm 0.9$ $3 \pm 0.6$ 10,000 $1 \pm 0.7$ $7 \pm 3.0$ $6 \pm 1.2$ $12 \pm 1.9$ $3 \pm 0.7$ $2 \pm 0.6$	$5 \pm 0.6$	$12 \pm 3.2$	$4 \pm 0.7$	$7 \pm 1.2$	4 ± 0.7	333.3
3,333.3 $1 \pm 1.0$ $9 \pm 1.7$ $5 \pm 1.8$ $15 \pm 2.1$ $6 \pm 0.9$ $3 \pm 0.6$ 10,000 $1 \pm 0.7$ $7 \pm 3.0$ $6 \pm 1.2$ $12 \pm 1.9$ $3 \pm 0.7$ $2 \pm 0.6$	6 ± 1.0	$13 \pm 2.6$	$2 \pm 0.0$	8 ± 1.0	$3 \pm 1.5$	1,000
10,000 1 $\pm$ 0.7 7 $\pm$ 3.0 6 $\pm$ 1.2 12 $\pm$ 1.9 3 $\pm$ 0.7 2 $\pm$ 0.6	6± 0.9	$15 \pm 2.1$	$5 \pm 1.8$	9 ± 1.7	$1 \pm 1.0$	3,333.3
	$3 \pm 0.7$	$12 \pm 1.9$	$6 \pm 1.2$	$7 \pm 3.0$	1 ± 0.7	10,000
Trial summary Negative Negative Negative Negative Negative Negative	Negative	Negative	Negative	Negative	Negative	Trial summary
Positive control $530 \pm 132.9$ $431 \pm 20.9$ $152 \pm 22.0$ $510 \pm 10.7$ $298 \pm 20.9$ $221 \pm 31.0$	$298 \pm 20.9$	$510 \pm 10.7$	$152 \pm 22.0$	431 ± 20.9	530 ± 132.9	Positive control
<b>TA98</b> 0 $26 \pm 4.4$ $28 \pm 1.5$ $24 \pm 3.5$ $40 \pm 1.9$ $21 \pm 2.6$ $48 \pm 4.3$	$21 \pm 2.6$	40 ± 1.9	$24 \pm 3.5$	28 ± 1.5	$26 \pm 4.4$	TA <b>98</b> 0
100 19 $\pm$ 0.3 37 $\pm$ 0.3 28 $\pm$ 1.5 43 $\pm$ 6.2 33 $\pm$ 4.2 48 $\pm$ 3.6	$33 \pm 4.2$	$43 \pm 6.2$	$28 \pm 1.5$	$37 \pm 0.3$	$19 \pm 0.3$	100
333.3 17 $\pm$ 4.9 34 $\pm$ 4.3 32 $\pm$ 4.4 33 $\pm$ 5.6 25 $\pm$ 5.8 43 $\pm$ 2.0	$25 \pm 5.8$	$33 \pm 5.6$	$32 \pm 4.4$	34 ± 4.3	17 ± 4.9	333.3
1,000 16 $\pm$ 2.6 31 $\pm$ 2.8 27 $\pm$ 1.8 44 $\pm$ 1.3 30 $\pm$ 4.7 47 $\pm$ 4.5	$30 \pm 4.7$	$44 \pm 1.3$	$27 \pm 1.8$	$31 \pm 2.8$	$16 \pm 2.6$	1,000
3,333.3 21 $\pm$ 2.6 25 $\pm$ 2.6 33 $\pm$ 2.9 41 $\pm$ 0.9 26 $\pm$ 5.5 37 $\pm$ 3.1	$26 \pm 5.5$	$41 \pm 0.9$	$33 \pm 2.9$	$25 \pm 2.6$	$21 \pm 2.6$	3,333.3
10,000 16 $\pm$ 1.5 30 $\pm$ 5.2 26 $\pm$ 2.7 36 $\pm$ 5.7 26 $\pm$ 0.9 39 $\pm$ 1.2	$26 \pm 0.9$	36 ± 5.7	$26 \pm 2.7$	$30 \pm 5.2$	16 ± 1.5	10,000
Trial summary Negative Negative Negative Negative Negative Negative	Negative	Negative	Negative	Negative	Negative	Trial summary
Positive control $837 \pm 116.2$ $777 \pm 23.2$ $1,733 \pm 92.8$ $1,598 \pm 76.2$ $458 \pm 13.6$ $511 \pm 35.6$	-	$1508 \pm 762$	1.733 + 92.8	777 ± 23.2	837 ± 116.2	Positive control

Mutagenicity of Nitromethane in Salmonella typhimurium^a

^a The study was performed at SRI International. The detailed protocol and these data are presented in Mortelmans et al. (1986).

^b Revertants are presented as mean  $\pm$  standard error from three plates.

^c Slight toxicity

^d The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA1537), and 4-nitro-o-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

232
434

# TABLE E2

Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Nitromethane^a

Compound	Dose (μg/mL)	Total Cells	No. of Chromo- somes	No. of SCEs	SCEs/ Chromo- some	SCEs/ Cell	Hrs in BrdU	Relative Change of SC Chromosom (%)	CEs/ ie ^b
		 					•		
Summary: Negative									
Distilled water		50	1,048	349	0.33	7.0	26.0	<u>с</u>	. *
Mitomycin-C	0.001	50	1,050	534	0.50	10.7	26.0	52.72	· ·
	0.004	10	209	186	0.88	18.6	26.0	167.24	-
Nitromethane	497	50	1,049	374	0.35	7.5	26.0	7.06	
	1,655	50	1.049	394	0.37	7.9	26.0	12.79	
· · · · · · · · · · · · · · · · · · ·	4,965	50	1,052	411	0.39	8.2	26.0	17.32	
					P=0.010 ^c			•••	
+ 50		•							
Summary: Negative							,		
Distilled water		50	1,053	428	0.40	8.6	26.0		
								•	
Cyclophosphamide	0.125	50	1,051	647	0.61	12.9	26.0	51.46	
	0.500	10	210	241	1.14	24.1	26.0	182.35	
Nitromethane	497	50	1.050	407	0.38	8.1	26.0	-4.64	
	1.655	50	1.052	383	0.36	7.7	26.0	-10.43	
	4,965	50	1,051	381	0.36	7.6	26.0	-10.81	
		•			P=0.967				

^a The study was performed at SITEK Research Laboratories. A detailed description of the protocol is presented in Galloway *et al.* (1987). SCE=sister chromatid exchange; BrdU=bromodeoxyuridine.

^b SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells

^c Significance of SCEs/chromosome tested by the linear regression trend test versus log of the dose

#### TABLE E3

Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Nitromethane^a

		-59					+ \$9		
Dose (µg/mL)	Total Cells	No. of Abs	Abs/ Cell	Cells with Abs (%)	Dose (µg/mL)	Total Cells	No. of Abs	Abs/ Cell	Cells with Abs (%)
Harvest time: 13.5 Summary: Negativ	i hours e				Harvest time: 13.5 h Summary: Negative	ours			
Distilled water					Distilled water				
	200	6	0.03	3.0	4	200	3	0.02	1.5
ditomycin-C					Cyclophosphamide				
0.4	25	10	0.40	32.0	20	25	51	2.04	68.0
Vitromethane					Nitromethane				
1,077	200	0	0.00	0.0	1,077	200	5	0.03	2.5
2,316	200	3	0.02	1.5	2,316	200	2	0.01	1.0
4,980	200	3	0.02	1.5	4,980	200	6	0.03	3.0
				P=0.782 ^b					P=0.249

а The study was performed at SITEK Research Laboratories. The detailed protocol is presented in Galloway et al. (1987). Abs=aberrations. Significance of percent cells with aberrations tested by the linear regression trend test versus log of the dose

b

Dose (ppm)	Total NCEs	Micronucleated NCEs	Micronucleated NCEs/ Total NCEs ^b (%)	P Value ^c
Male			· · ·	
0	103,800	54	$0.052 \pm 0.0076$	
94	106,300	85	$0.080 \pm 0.0078$	0.006
188	105,175	64	$0.061 \pm 0.0064$	0.198
375	106,925	72	$0.067 \pm 0.0111$	0.075
750	106,075	68	$0.064 \pm 0.0076$	0.125
1,500	105,850	74	0.070 ± 0.0066	0.049
Trend test	æ	· .	$P = 0.273^{d}$	
			· · · · · · · · · · · · · · · · · · ·	•
Female		<i>•</i>		· • •
0	106,400	58	$0.055 \pm 0.0071$	
94	106,625	39	$0.037 \pm 0.0062$	0.974
188	106,700	43	$0.040 \pm 0.0068$	0.934
375	104,750	41	$0.039 \pm 0.0031$	0.949
750	106,200	58	$0.055 \pm 0.0056$	0.496
1,500	108,075	53	$0.049 \pm 0.0064$	0.711
Trend test			P=0.186	

## TABLE E4

Frequency of Micronuclei in Peripheral Blood Erythrocytes of Mice Following Treatment with Nitromethane by Inhalation for 13 Weeks^a

^a The study was performed at SRI International. The detailed protocol is presented in MacGregor *et al.* (1990); NCE=normochromatic erythrocyte.

^b Mean  $\pm$  standard error

^c Pairwise comparisons; significant at P<0.005

^d Significance of micronucleated NCEs/total NCEs tested by a one-tailed trend test; significant at P<0.025

# APPENDIX F ORGAN WEIGHTS AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE F1	Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats	
	in the 16-Day Inhalation Study of Nitromethane	236
TABLE F2	Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats	
	in the 13-Week Inhalation Study of Nitromethane	237
TABLE F3	Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice	
	in the 16-Day Inhalation Study of Nitromethane	238
Table F4	Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice	
	in the 13-Week Inhalation Study of Nitromethane	239

Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 16-Day Inhalation Study of Nitromethane^a

n         5         5         5         5         5         5           Male         Necropsy body wt         218 $\pm 3$ 225 $\pm 5$ 223 $\pm 6$ 215 $\pm 7$ 206 $\pm 4$ 192 $\pm 4^{**}$ Heart         Absolute         0.700 $\pm$ 0.018         0.710 $\pm$ 0.016         0.706 $\pm$ 0.014         0.680 $\pm$ 0.021         0.640 $\pm$ 0.017*         0.650 $\pm$ 0.016*           Relative         3.21 $\pm$ 0.05         3.16 $\pm$ 0.05         3.17 $\pm$ 0.09         3.17 $\pm$ 0.03         0.849 $\pm$ 0.017*         0.650 $\pm$ 0.016*           Absolute         0.852 $\pm$ 0.014         0.878 $\pm$ 0.011         0.904 $\pm$ 0.029         4.05 $\pm$ 0.037         0.880 $\pm$ 0.016         0.880 $\pm$ 0.022           Absolute         8.922 $\pm$ 0.201         9.950 $\pm$ 0.250         9.794 $\pm$ 0.033         9.988 $\pm$ 0.63**         48.49 $\pm$ 0.03**           Liver         Absolute         1.214 $\pm$ 0.025         1.402 $\pm$ 0.098         1.244 $\pm$ 0.034         1.844 $\pm$ 0.017**         1.192 $\pm$ 0.027         1.196 $\pm$ 0.027           R Testis         1.242 $\pm$ 0.032         1.279 $\pm$ 0.041         1.220 $\pm$ 0.039         1.227 $\pm$ 0.020         1.238 $\pm$ 0.05*         1.622 $\pm$ 0.32           R Testis         1.362 $\pm$ 0.042         1.79 $\pm$ 0.041         1.220 $\pm$ 0.039         1.238 $\pm$ 0.040         0.	, ()	0 ppm	94 ppm	188 ppm	375 ppm	750 ppm	1,500 ppm
Male           Necropsy body wt $218 \pm 3$ $225 \pm 5$ $223 \pm 6$ $215 \pm 7$ $206 \pm 4$ $192 \pm 4^{**}$ Heart         Absolute $0.700 \pm 0.018$ $0.710 \pm 0.016$ $0.706 \pm 0.014$ $0.680 \pm 0.021$ $0.640 \pm 0.017^*$ $0.650 \pm 0.016^*$ Relative $3.21 \pm 0.05$ $3.16 \pm 0.05$ $3.17 \pm 0.09$ $3.17 \pm 0.03$ $3.10 \pm 0.02^*$ $3.38 \pm 0.04^*$ Absolute $0.822 \pm 0.014$ $0.878 \pm 0.011$ $0.904 \pm 0.029$ $0.870 \pm 0.037$ $0.884 \pm 0.016^*$ $0.880 \pm 0.022$ Liver $3.91 \pm 0.02$ $3.91 \pm 0.02$ $3.91 \pm 0.02$ $3.92 \pm 0.144 \pm 0.027^*$ $4.05 \pm 0.037$ $9.282 \pm 0.144 \pm 9.322 \pm 0.346$ Liver $8.922 \pm 0.2101$ $9.950 \pm 0.250$ $9.794 \pm 0.303$ $9.988 \pm 0.333$ $9.088 \pm 0.032 \pm 0.144 \pm 9.322 \pm 0.346$ Liver $40.98 \pm 0.55$ $44.29 \pm 0.71^*$ $1.844 \pm 0.034^*$ $1.844 \pm 0.037^*$ $1.192 \pm 0.025$ $1.232 \pm 0.346$ Ling $40.22 \pm 0.34$ $5.77 \pm 0.15$ $6.73 \pm 0.75$ $1.056 \pm 0.070$ $6.22 \pm 0.32$ Absolute $1.224 \pm 0.032$ $1.238 \pm 0.025$ <th>n</th> <th>5</th> <th>5</th> <th>5</th> <th>5</th> <th>. 5</th> <th>5</th>	n	5	5	5	5	. 5	5
Necropsy body wt 218 $\pm 3$ 225 $\pm 5$ 223 $\pm 6$ 215 $\pm 7$ 206 $\pm 4$ 192 $\pm 4^{**}$ Heart Relative 0.700 $\pm$ 0.018 0.710 $\pm$ 0.016 0.706 $\pm$ 0.014 0.680 $\pm$ 0.021 0.640 $\pm$ 0.017 0.650 $\pm$ 0.016 $\pm$ 0.318 $\pm$ 0.04 Relative 3.21 $\pm$ 0.05 3.16 $\pm$ 0.05 3.17 $\pm$ 0.09 0.870 $\pm$ 0.037 0.854 $\pm$ 0.016 0.880 $\pm$ 0.022 Relative 3.91 $\pm$ 0.02 3.91 $\pm$ 0.02 0.878 $\pm$ 0.011 0.904 $\pm$ 0.029 0.870 $\pm$ 0.037 0.854 $\pm$ 0.016 0.880 $\pm$ 0.022 Relative 3.91 $\pm$ 0.02 3.91 $\pm$ 0.02 4.052 $\pm$ 0.017 4.14 $\pm$ 0.024 4.054 $\pm$ 0.027 4.584 $\pm$ 0.088 $\pm$ 0.022 0.870 $\pm$ 0.037 0.854 $\pm$ 0.016 0.880 $\pm$ 0.022 0.216 Relative 3.91 $\pm$ 0.02 0.250 9.794 $\pm$ 0.303 9.988 $\pm$ 0.393 9.028 $\pm$ 0.144 9.022 4.58 $\pm$ 0.080 $\pm$ 0.999 $\pm$ 0.850 $\pm$ 0.650 $\pm$ 0.122 0.21 0.950 $\pm$ 0.250 9.794 $\pm$ 0.303 9.988 $\pm$ 0.393 9.028 $\pm$ 0.144 9.022 4.58 $\pm$ 0.089 $\pm$ 0.999 $\pm$ 0.850 $\pm$ 0.650 $\pm$ 0.450 $\pm$ 0.660 $\pm$ 0.450 $\pm$ 0.660 $\pm$ 0.450 $\pm$ 0.670 $\pm$ 0.452 $\pm$ 0.027 1.196 $\pm$ 0.070 Relative 5.58 $\pm$ 0.10 6.222 $\pm$ 0.32 1.279 $\pm$ 0.041 1.220 $\pm$ 0.039 1.277 $\pm$ 0.020 1.238 $\pm$ 0.025 1.203 $\pm$ 0.344 Relative 5.71 $\pm$ 0.15 5.70 $\pm$ 0.17 5.46 $\pm$ 0.06 5.73 $\pm$ 0.15 6.01 $\pm$ 0.09 6.27 $\pm$ 0.20 $\pm$ 1.70 $\pm$ 0.017 Relative 0.088 $\pm$ 0.012 1.70 $\pm$ 0.06 1.62 $\pm$ 0.10 1.63 $\pm$ 0.020 1.340 $\pm$ 0.010 0.284 $\pm$ 0.014** 1.484 $\pm$ 0.017** 1.148 $\pm$ 0.04 1.48 $\pm$ 0.010 0.118 $\pm$ 0.001 0.018 $\pm$ 0.001 0.019 $\pm$ 0.001 0.020 $\pm$ 0.001 0.01 $\pm$ 0.002 $\pm$ 0.001 0.01 $\pm$ 0.001 0.020 $\pm$ 0.001 0.01 $\pm$ 0.001 0.020 $\pm$ 0.001 0.01 $\pm$ 0.002 $\pm$ 0.001 0.01 $\pm$ 0.001 0.01 $\pm$ 0.002 $\pm$ 0.001 0.01 $\pm$ 0.001 0.020 $\pm$ 0.001 0.01 $\pm$ 0.000 0.020 $\pm$ 0.001 0.01 $\pm$ 0.002 $\pm$ 0.002 $\pm$ 0.002 $\pm$ 0.002 $\pm$ 0.003 0.003 0.003 0.003 0.003 0.003 0.003 0.004 0.003 0.004 0.004 0.48	Male						
Necropsy body wi 218 $\pm 3$ 225 $\pm 5$ 223 $\pm 6$ 215 $\pm 7$ 206 $\pm 4$ 192 $\pm 4^{**}$ Heart Absolute 0.700 $\pm 0.018$ 0.710 $\pm 0.016$ 0.706 $\pm 0.014$ 0.680 $\pm 0.021$ 0.640 $\pm 0.017^*$ 0.650 $\pm 0.016^*$ Relative 3.21 $\pm 0.05$ 3.16 $\pm 0.05$ 3.17 $\pm 0.09$ 3.17 $\pm 0.03$ 3.10 $\pm 0.02$ 3.38 $\pm 0.04$ Absolute 3.17 $\pm 0.03$ 3.10 $\pm 0.02$ 3.38 $\pm 0.04$ Relative 3.91 $\pm 0.02$ 3.91 $\pm 0.08$ 4.055 0.05 4.055 4.037 0.854 $\pm 0.014$ 0.880 $\pm 0.022$ Absolute 3.91 $\pm 0.02$ 3.91 $\pm 0.08$ 4.250 9.794 $\pm 0.303$ 9.988 $\pm 0.393$ 9.028 $\pm 0.144$ 9.322 $\pm 0.346$ Relative 40.98 $\pm 0.55$ 1.402 $\pm 0.098$ 1.244 $\pm 0.034$ 1.844 $\pm 0.017^{**}$ 1.192 $\pm 0.02^{*}$ 1.196 $\pm 0.070$ Relative 40.98 $\pm 0.55$ 1.402 $\pm 0.098$ 1.244 $\pm 0.034$ 1.844 $\pm 0.017^{**}$ 1.192 $\pm 0.027$ 1.196 $\pm 0.070$ Relative 5.58 $\pm 0.10$ 6.22 $\pm 0.34$ 5.57 $\pm 0.06$ 8.63 $\pm 0.30^{**}$ 5.79 $\pm 0.11$ 6.22 $\pm 0.32$ Absolute 1.244 $\pm 0.032$ 1.279 $\pm 0.041$ 1.220 $\pm 0.039$ 1.227 $\pm 0.020$ 1.238 $\pm 0.025$ 1.203 $\pm 0.034$ Relative 5.71 $\pm 0.15$ 5.70 $\pm 0.17$ 5.464 $\pm 0.06$ 5.73 $\pm 0.15$ 6.01 $\pm 0.09$ 6.27 $\pm 0.204$ Thymus 0.369 $\pm 0.025$ 0.332 $\pm 0.011$ 0.363 $\pm 0.024$ 0.394 $\pm 0.020$ 0.344 $\pm 0.010$ 0.224 $\pm 0.014^{**}$ Relative 1.70 $\pm 0.12$ 1.70 $\pm 0.06$ 1.62 $\pm 0.101$ 1.63 $\pm 0.001$ 0.019 $\pm 0.001$ 0.024 $\pm 0.010$ Relative 1.70 $\pm 0.012$ 0.018 $\pm 0.002$ 0.016 $\pm 0.001$ 0.018 $\pm 0.001$ 0.019 $\pm 0.001$ 0.020 $\pm 0.001$ Relative 0.08 $\pm 0.00$ 0.08 $\pm 0.01$ 0.07 $\pm 0.00$ 3.50 $\pm 0.03$ 3.50 $\pm 0.04$ 3.86 $\pm 0.05^{**}$ Absolute 0.48 $\pm 0.001$ 0.018 $\pm 0.002$ 0.616 $\pm 0.011$ 0.512 $\pm 0.009$ 0.502 $\pm 0.009$ 0.528 $\pm 0.011$ Relative 3.42 $\pm 0.06$ 3.51 $\pm 0.08$ 3.41 $\pm 0.08$ 3.50 $\pm 0.03$ 3.50 $\pm 0.04$ 4.88 $\pm 0.05^{**}$ Absolute 0.612 $\pm 0.022$ 0.616 $\pm 0.019$ 0.634 $\pm 0.013$ 0.614 $\pm 0.007$ 0.636 $\pm 0.009$ 0.528 $\pm 0.0111$ Absolute 0.644 $\pm 0.34$ 4.			<b>225</b> 5				100
Heart         Or 00 $\pm$ 0.018         Or 00 $\pm$ 0.016         Or 00 $\pm$ 0.017         Or 00 $\pm$ 0.016         Or 00 $\pm$ 0.017         Or 00 $\pm$ 0.017         Or 00 $\pm$ 0.016         Or 00 $\pm$ 0.017         Or 00 $\pm$ 0.017         Or 00 $\pm$ 0.016         Or 00 $\pm$ 0.017         Or 00 $\pm$ 0.017         Or 00 $\pm$ 0.016         Or 00 $\pm$ 0.017         Or 00 $\pm$ 0.017         Or 00 $\pm$ 0.012         Or 00 $\pm$ 0.017         Or 00 $\pm$ 0.017         Or 00 $\pm$ 0.016         Or 00 $\pm$ 0.016         Or 00 $\pm$ 0.016         Or 00 $\pm$ 0.017         Or 00 $\pm$ 0.016         Or 00 $\pm$ 0.017         Or 00 $\pm$ 0.01         Or 00 $\pm$ 0.01 <tho 00="" <math="">\pm 0.01         &lt;</tho>	Necropsy body wt	$218 \pm 3$	$225 \pm 5$	$223 \pm 6$	$215 \pm 7$	$206 \pm 4$	192 ± 4**
Absolute $0.700 \pm 0.018$ $0.710 \pm 0.016$ $0.706 \pm 0.014$ $0.680 \pm 0.021$ $0.640 \pm 0.017^*$ $0.650 \pm 0.017^*$ $0.854 \pm 0.016$ $0.850 \pm 0.027$ $3.18 \pm 0.012^*$ $3.38 \pm 0.040^*$ Absolute $0.952 \pm 0.201$ $9.950 \pm 0.250$ $9.794 \pm 0.033$ $9.988 \pm 0.393$ $9.028 \pm 0.144$ $9.322 \pm 0.346$ Relative $40.98 \pm 0.55$ $44.29 \pm 0.71^{**}$ $43.87 \pm 0.66^{**}$ $46.50 \pm 0.68^{**}$ $43.84 \pm 0.63^{**}$ $48.49 \pm 0.99^{**}$ Ling       Absolute $1.214 \pm 0.025$ $1.402 \pm 0.098$ $1.244 \pm 0.034$ $1.844 \pm 0.017^{**}$ $1.192 \pm 0.027$ $1.196 \pm 0.070$ R tarive $5.58 \pm 0.10$ $6.22 \pm 0.34$ $5.57 \pm 0.06$ $8.63 \pm 0.39^{**}$ $5.79 \pm 0.071$ $1.202 \pm 0.032$ $1.279 \pm 0.027$ $1.203 \pm 0.027$ $1.203 \pm 0.027$ $1.203 \pm 0.027$ R tarive $5.71 \pm 0.13$ $5.70 \pm 0.11$ $0.363 \pm 0.024$ $0.349 \pm 0.020$ $0.340 \pm 0.010$ $0.284 \pm 0.014^{**}$ Horant       Absolute $0$	Heart				:		
Relative Absolute $3.21 \pm 0.05$ $3.16 \pm 0.05$ $3.17 \pm 0.09$ $3.17 \pm 0.03$ $3.10 \pm 0.02$ $3.38 \pm 0.04$ Absolute Relative $0.852 \pm 0.014$ $0.878 \pm 0.011$ $0.904 \pm 0.029$ $0.870 \pm 0.037$ $0.854 \pm 0.016$ $0.880 \pm 0.022$ Absolute $8.922 \pm 0.201$ $9.950 \pm 0.250$ $9.794 \pm 0.033$ $9.988 \pm 0.337$ $9.028 \pm 0.144$ $9.322 \pm 0.346$ Relative $40.98 \pm 0.55$ $44.29 \pm 0.025$ $1.442 \pm 0.034$ $1.844 \pm 0.017^{**}$ $1.192 \pm 0.027$ $1.196 \pm 0.070$ Absolute $1.214 \pm 0.025$ $1.402 \pm 0.098$ $1.234 \pm 0.034$ $5.57 \pm 0.06$ $8.63 \pm 0.30^{**}$ $5.79 \pm 0.11$ $6.22 \pm 0.32$ R Testis         Absolute $1.242 \pm 0.032$ $1.279 \pm 0.041$ $1.202 \pm 0.039$ $1.227 \pm 0.020$ $1.238 \pm 0.025$ $1.203 \pm 0.034$ R Testis         Absolute $0.369 \pm 0.025$ $0.382 \pm 0.011$ $0.363 \pm 0.024$ $0.349 \pm 0.020$ $0.349 \pm 0.020$ $0.340 \pm 0.010$ $0.284 \pm 0.014^{***}$ Absolute $0.369 \pm 0.025$ $0.382 \pm 0.011$ $0.363 \pm 0.024$ $0.349 \pm 0.020$ $0.340 \pm 0.010$ <th< td=""><td>Absolute</td><td>$0.700 \pm 0.018$</td><td>0.710 ± 0.016</td><td>$0.706 \pm 0.014$</td><td>$0.680 \pm 0.021$</td><td>0.640 ± 0.017*</td><td>$0.650 \pm 0.016*$</td></th<>	Absolute	$0.700 \pm 0.018$	0.710 ± 0.016	$0.706 \pm 0.014$	$0.680 \pm 0.021$	0.640 ± 0.017*	$0.650 \pm 0.016*$
R. Kidney       0.852 $\pm$ 0.014       0.878 $\pm$ 0.011       0.904 $\pm$ 0.029       0.870 $\pm$ 0.037       0.854 $\pm$ 0.016       0.880 $\pm$ 0.022         Absolute       3.91 $\pm$ 0.02       3.91 $\pm$ 0.08       4.05 $\pm$ 0.05       4.05 $\pm$ 0.07       4.14 $\pm$ 0.02*       4.58 $\pm$ 0.08**         Liver       Absolute       8.922 $\pm$ 0.201       9.950 $\pm$ 0.250       9.794 $\pm$ 0.303       9.988 $\pm$ 0.393       9.028 $\pm$ 0.144       9.322 $\pm$ 0.346         Relative       40.98 $\pm$ 0.55       44.29 $\pm$ 0.71**       43.87 $\pm$ 0.66**       46.50 $\pm$ 0.68**       43.84 $\pm$ 0.63**       48.84 $\pm$ 0.07*         Inig       Absolute       1.214 $\pm$ 0.022       1.402 $\pm$ 0.098       1.244 $\pm$ 0.034       1.844 $\pm$ 0.01**       1.192 $\pm$ 0.027       1.196 $\pm$ 0.070         Relative       5.78 $\pm$ 0.10       6.22 $\pm$ 0.34       5.57 $\pm$ 0.06       8.63 $\pm$ 0.30**       5.79 $\pm$ 0.11       6.22 $\pm$ 0.32         R. Testis       Absolute       0.369 $\pm$ 0.025       0.382 $\pm$ 0.011       0.363 $\pm$ 0.024       0.349 $\pm$ 0.020       0.340 $\pm$ 0.010       0.284 $\pm$ 0.014**         Absolute       0.369 $\pm$ 0.025       0.382 $\pm$ 0.011       0.363 $\pm$ 0.024       0.349 $\pm$ 0.020       0.340 $\pm$ 0.010       0.284 $\pm$ 0.014***         Thyroid Gland       Absolute       0.018 $\pm$ 0.001       0.018 $\pm$ 0.012       0.502 $\pm$	Relative	$3.21 \pm 0.05$	$3.16 \pm 0.05$	$3.17 \pm 0.09$	$3.17 \pm 0.03$	$3.10 \pm 0.02$	$3.38 \pm 0.04$
Absolute       0.852 ± 0.014       0.878 ± 0.01       0.904 ± 0.029       0.870 ± 0.037       0.854 ± 0.016       0.880 ± 0.022         Relative       3.91 ± 0.02       3.91 ± 0.02       3.91 ± 0.02       4.05 ± 0.05       4.05 ± 0.07       4.14 ± 0.02*       4.58 ± 0.08**         Liver       Absolute       8.922 ± 0.201       9.950 ± 0.250       9.794 ± 0.303       9.968 ± 0.393       9.028 ± 0.144       9.322 ± 0.346         Absolute       1.214 ± 0.025       1.402 ± 0.098       1.244 ± 0.034       1.844 ± 0.017**       1.192 ± 0.027       1.196 ± 0.070         Relative       5.58 ± 0.10       6.22 ± 0.34       5.57 ± 0.06       8.63 ± 0.30**       5.79 ± 0.11       6.22 ± 0.32         Absolute       1.242 ± 0.032       1.279 ± 0.017       5.46 ± 0.06       5.73 ± 0.15       6.01 ± 0.09       6.27 ± 0.20*         Thymus       Absolute       0.369 ± 0.025       0.382 ± 0.011       0.363 ± 0.024       0.349 ± 0.020       0.340 ± 0.010       0.284 ± 0.014***         Thymus       0.08 ± 0.001       0.018 ± 0.002       0.016 ± 0.001       0.018 ± 0.001       0.024 ± 0.010       0.48 ± 0.014         Absolute       0.09 ± 0.01       0.018 ± 0.002       0.016 ± 0.001       0.018 ± 0.001       0.018 ± 0.001       0.018 ± 0.001       0.018 ± 0.001       0.022 ± 0	R. Kidney				•		· · · · · · · · · · · · · · · · · · ·
Relative $3.91 \pm 0.02$ $3.91 \pm 0.03$ $4.05 \pm 0.05$ $4.05 \pm 0.07$ $4.14 \pm 0.02^{*}$ $4.58 \pm 0.08^{**}$ Absolute $8.922 \pm 0.201$ $9.950 \pm 0.250$ $9.794 \pm 0.303$ $9.988 \pm 0.393$ $9.028 \pm 0.144$ $9.322 \pm 0.346$ Ling $43.87 \pm 0.66^{**}$ $43.84 \pm 0.63^{**}$ $43.84 \pm 0.62^{**}$ $1.92 \pm 0.027$ $1.196 \pm 0.070$ $6.22 \pm 0.32$ R Testis $Absolute$ $1.242 \pm 0.032$ $1.277 \pm 0.041$ $1.220 \pm 0.039$ $1.227 \pm 0.020$ $1.238 \pm 0.025$ $1.203 \pm 0.034$ Absolute $0.369 \pm 0.025$ $0.382 \pm 0.011$ $0.363 \pm 0.024$ $0.349 \pm 0.020$ $0.340 \pm 0.010$ $0.284 \pm 0.014^{**}$ $0.48 \pm 0.04$ $1.48 \pm 0.04$ <th< td=""><td>Absolute</td><td>$0.852 \pm 0.014$</td><td>$0.878 \pm 0.011$</td><td>$0.904 \pm 0.029$</td><td>$0.870 \pm 0.037$</td><td>$0.854 \pm 0.016$</td><td>$0.880 \pm 0.022$</td></th<>	Absolute	$0.852 \pm 0.014$	$0.878 \pm 0.011$	$0.904 \pm 0.029$	$0.870 \pm 0.037$	$0.854 \pm 0.016$	$0.880 \pm 0.022$
Liver Absolute 8.922 $\pm 0.201$ 9.950 $\pm 0.250$ 9.794 $\pm 0.303$ 9.988 $\pm 0.393$ 9.028 $\pm 0.144$ 9.322 $\pm 0.346$ 48.49 $\pm 0.55$ 44.29 $\pm 0.71^{**}$ 43.87 $\pm 0.66^{**}$ 45.50 $\pm 0.68^{**}$ 43.84 $\pm 0.65^{**}$ 48.49 $\pm 0.99^{**}$ 48.49 $\pm 0.09^{**}$ 5.88 $\pm 0.10$ 5.22 $\pm 0.34$ 5.57 $\pm 0.06^{**}$ 6.65 $\pm 0.06^{**}$ 5.79 $\pm 0.11$ 6.22 $\pm 0.32$ 1.203 $\pm 0.034$ 8.64 $\pm 0.017^{**}$ 1.192 $\pm 0.027$ 1.196 $\pm 0.070$ 6.22 $\pm 0.32$ 1.279 $\pm 0.041$ 1.220 $\pm 0.039$ 1.227 $\pm 0.020$ 1.238 $\pm 0.025$ 1.203 $\pm 0.034$ Relative 5.71 $\pm 0.15$ 5.70 $\pm 0.17$ 5.46 $\pm 0.06$ 5.73 $\pm 0.15$ 6.01 $\pm 0.09$ 6.27 $\pm 0.20^{*}$ Thymus 0.369 $\pm 0.025$ 0.382 $\pm 0.011$ 0.363 $\pm 0.024$ 0.349 $\pm 0.020$ 0.340 $\pm 0.010$ 0.284 $\pm 0.014^{**}$ Relative 1.70 $\pm 0.12$ 1.70 $\pm 0.06$ 1.62 $\pm 0.01$ 1.65 $\pm 0.020$ 0.340 $\pm 0.010$ 0.284 $\pm 0.014^{**}$ Relative 0.018 $\pm 0.001$ 0.018 $\pm 0.002$ 0.016 $\pm 0.001$ 0.018 $\pm 0.001$ 0.028 $\pm 0.001$ 0.028 $\pm 0.011$ 0.008 $\pm 0.001$ 0.018 $\pm 0.001$ 0.019 $\pm 0.001$ 0.028 $\pm 0.001$ 0.029 $\pm 0.011$ 0.10 $\pm 0.009^{*}$ 7.1000 0.18 $\pm 0.001$ 0.019 $\pm 0.001$ 0.020 $\pm 0.001$ 0.10 $\pm 0.009^{*}$ 7.148 $\pm 0.04^{**}$ Relative 0.08 $\pm 0.00$ 0.08 $\pm 0.01$ 0.07 $\pm 0.00$ 0.08 $\pm 0.00$ 0.09 $\pm 0.01$ 0.10 $\pm 0.009^{*}$ 7.148 $\pm 0.04^{**}$ 1.15 $\pm 0.08$ 1.512 $\pm 0.099^{*}$ 0.502 $\pm 0.001$ 0.10 $\pm 0.009^{*}$ 0.528 $\pm 0.011$ Relative 3.42 $\pm 0.06$ 3.51 $\pm 0.08$ 3.41 $\pm 0.08$ 3.50 $\pm 0.03$ 3.50 $\pm 0.04$ 3.86 $\pm 0.009^{*}$ 4.82 $\pm 0.061^{*}$ Absolute 0.612 $\pm 0.022$ 0.616 $\pm 0.019$ 0.634 $\pm 0.013$ 0.614 $\pm 0.007$ 0.666 $\pm 0.009$ 4.82 $\pm 0.009^{*}$ 4.31 $\pm 0.08$ 4.19 $\pm 0.004$ 4.44 $\pm 0.06$ 4.82 $\pm 0.009^{*}$ Absolute 4.20 $\pm 0.132$ 4.572 $\pm 0.537$ 4.0.187 5.750 $\pm 0.160^{*}$ 5.832 $\pm 0.067^{*}$ 6.204 $\pm 0.118^{**}$ Relative 3.555 $\pm 0.85$ 6.872 $\pm 0.25$ 3.788 $\pm 0.187$ 3.750 $\pm 0.160^{*}$ 5.832 $\pm 0.067^{*}$ 6.204 $\pm 0.118^{**}$ Relative 5.240 $\pm 0.182^{*}$ 5.672 $\pm 0.042^{*}$ 6.573 $\pm 0.109^{*}$ 6.204 $\pm 0.118^{**}$ 7.203 1.199^{*} 1.099^{*} 4.31	Relative	$3.91 \pm 0.02$	$3.91 \pm 0.08$	$4.05 \pm 0.05$	$4.05 \pm 0.07$	$4.14 \pm 0.02*$	4.58 ± 0.08**
Absolute $8.922 \pm 0.201$ $9.930 \pm 0.250$ $9.794 \pm 0.303$ $9.936 \pm 0.393$ $9.322 \pm 0.144$ $9.322 \pm 0.144$ $9.322 \pm 0.340$ Lung $40.98 \pm 0.55$ $44.29 \pm 0.71^{**}$ $43.87 \pm 0.66^{**}$ $46.50 \pm 0.68^{**}$ $43.84 \pm 0.01^{**}$ $43.84 \pm 0.025$ $1.192 \pm 0.027$ $1.196 \pm 0.070$ Relative $5.58 \pm 0.10$ $6.22 \pm 0.34$ $5.57 \pm 0.06$ $8.63 \pm 0.30^{**}$ $5.79 \pm 0.11$ $6.22 \pm 0.32$ R. TestisAbsolute $1.242 \pm 0.032$ $1.279 \pm 0.041$ $1.220 \pm 0.039$ $1.227 \pm 0.020$ $1.238 \pm 0.025$ $1.203 \pm 0.034$ Relative $5.71 \pm 0.15$ $5.70 \pm 0.17$ $5.46 \pm 0.06$ $5.73 \pm 0.15$ $6.01 \pm 0.09$ $6.27 \pm 0.20^{*}$ Thyming $0.369 \pm 0.025$ $0.382 \pm 0.011$ $0.363 \pm 0.024$ $0.349 \pm 0.020$ $0.340 \pm 0.010$ $0.284 \pm 0.014^{**}$ Absolute $0.369 \pm 0.025$ $0.382 \pm 0.011$ $0.363 \pm 0.024$ $0.349 \pm 0.020$ $0.340 \pm 0.010$ $0.284 \pm 0.014^{**}$ Absolute $0.018 \pm 0.001$ $0.018 \pm 0.002$ $0.016 \pm 0.001$ $0.018 \pm 0.001$ $0.019 \pm 0.001$ $0.020 \pm 0.001$ Relative $0.08 \pm 0.001$ $0.052 \pm 0.012$ $0.502 \pm 0.009$ $0.522 \pm 0.001$ $0.10 \pm 0.00^{*}$ Relative $0.498 \pm 0.012$ $0.520 \pm 0.012$ $0.502 \pm 0.014$ $0.512 \pm 0.029$ $0.528 \pm 0.011$ Relative $0.498 \pm 0.012$ $0.520 \pm 0.012$ $0.502 \pm 0.009$	Liver	0.000 + 0.001	0.050 1.0.050	0 704 1 0 202	0.000 1.0.202	0.028 1.0.144	0 202 + 0 246
Relative $40.36 \pm 0.33$ $41.29 \pm 0.174$ $43.37 \pm 0.367$ $40.30 \pm 0.037$ $1.192 \pm 0.027$ $1.196 \pm 0.070$ R restisAbsolute $1.242 \pm 0.032$ $1.279 \pm 0.041$ $1.220 \pm 0.039$ $1.227 \pm 0.020$ $1.238 \pm 0.025$ $1.203 \pm 0.034$ Relative $5.71 \pm 0.15$ $5.70 \pm 0.17$ $5.46 \pm 0.06$ $5.73 \pm 0.15$ $6.01 \pm 0.09$ $6.27 \pm 0.20^{\circ}$ Thymus $0.369 \pm 0.025$ $0.382 \pm 0.011$ $0.363 \pm 0.024$ $0.349 \pm 0.020$ $0.340 \pm 0.010$ $0.284 \pm 0.014^{**}$ Relative $1.70 \pm 0.025$ $0.382 \pm 0.011$ $0.363 \pm 0.024$ $0.349 \pm 0.020$ $0.340 \pm 0.010$ $0.284 \pm 0.014^{**}$ Absolute $0.018 \pm 0.001$ $0.018 \pm 0.001$ $0.018 \pm 0.001$ $0.019 \pm 0.001$ $0.020 \pm 0.001$ Absolute $0.08 \pm 0.00$ $0.08 \pm 0.00$ $0.09 \pm 0.01$ $0.020 \pm 0.001$ Retative $3.42 \pm 0.06$ $3.51 \pm 0.08$ $3.41 \pm 0.08$ $3.50 \pm 0.003$ $3.50 \pm 0.001$ Retative $3.42 \pm 0.06$ $3.51 \pm 0.001$ $0.512 \pm 0.009$ $0.528 \pm 0.011$ Retative $3.42 \pm 0.06$ $3.51 \pm 0.08$ $3.41 \pm 0.08$ $3.50 \pm 0.03$ Retative $3.42 \pm 0.022$ $0.616 \pm 0.019$ $0.634 \pm 0.013$ $0.614 \pm 0.007$ $0.636 \pm 0.007$ Re	Absolute	$8.922 \pm 0.201$	$9.950 \pm 0.250$	$9.794 \pm 0.303$	9.988 ± 0.393	$9.028 \pm 0.144$	$9.322 \pm 0.340$
$\begin{array}{c} Ling \\ Absolute \\ Relative \\ Relative \\ R. Testis \\ Absolute \\ S.71 \pm 0.15 \\ S.70 \pm 0.10 \\ S.70 \pm 0.11 \\ S.70 \pm 0.11 \\ S.70 \pm 0.025 \\ S.70 \pm 0.01 \\ S.70 \pm 0.11 \\ S.46 \pm 0.06 \\ S.73 \pm 0.10 \\ S.73 \pm 0.15 \\ S.73 \pm 0.15 \\ S.73 \pm 0.10 \\ S.73 \pm 0.15 \\ S.73 \pm 0.10 \\ S.73 \pm 0.15 \\ S.73 \pm 0.10 \\ S.73 \pm 0.15 \\ S.73 \pm 0.15 \\ S.73 \pm 0.10 \\ S.73 \pm 0.15 \\ S.73 \pm 0.020 \\ S.73 \pm 0.10 \\ S.73 \pm 0.15 \\ S.73 \pm 0.10 \\ S.73 \pm 0.15 \\ S.73 \pm 0.10 \\ S.73 \pm 0.00 \\ S.40 \pm 0.001 \\ S.40 \pm 0.00$	Relative	40.98 ± 0.55	$44.29 \pm 0.71^{++}$	43.8/ ± 0.00**	40.30 ± 0.08**	43.84 ± 0.03**	48.49 ± 0.99**
Absolute1.24 $\pm$ 0.0221.602 $\pm$ 0.0391.24 $\pm$ 0.0321.752 $\pm$ 0.0271.752 $\pm$ 0.0341.752 $\pm$ 0.0271.752 $\pm$ 0.0271.752 $\pm$ 0.0241.752 $\pm$ 0.0271.752 $\pm$ 0.0271.752 $\pm$ 0.0241.752 $\pm$ 0.0241.752 $\pm$ 0.2041.752 $\pm$ 0.204 <t< td=""><td>Abcolute</td><td>$1.214 \pm 0.025$</td><td>1 402 ± 0.008</td><td>1 244 ± 0.034</td><td>1 844 + 0 017**</td><td>$1102 \pm 0.027$</td><td>$1.196 \pm 0.070$</td></t<>	Abcolute	$1.214 \pm 0.025$	1 402 ± 0.008	1 244 ± 0.034	1 844 + 0 017**	$1102 \pm 0.027$	$1.196 \pm 0.070$
R. Testis Absolute1.242 $\pm 0.032$ 1.279 $\pm 0.041$ 1.220 $\pm 0.039$ 1.227 $\pm 0.020$ 1.238 $\pm 0.025$ 1.203 $\pm 0.034$ Relative5.71 $\pm 0.15$ 5.70 $\pm 0.17$ 5.46 $\pm 0.06$ 5.73 $\pm 0.15$ 6.01 $\pm 0.09$ 6.27 $\pm 0.20^{\circ}$ Thymus Absolute0.369 $\pm 0.025$ 0.382 $\pm 0.011$ 0.363 $\pm 0.024$ 0.349 $\pm 0.020$ 0.340 $\pm 0.010$ 0.284 $\pm 0.014^{**}$ Relative1.70 $\pm 0.12$ 1.70 $\pm 0.06$ 1.62 $\pm 0.10$ 1.63 $\pm 0.02$ 0.340 $\pm 0.010$ 0.284 $\pm 0.014^{**}$ Absolute0.018 $\pm 0.001$ 0.018 $\pm 0.002$ 0.016 $\pm 0.001$ 0.018 $\pm 0.001$ 0.019 $\pm 0.001$ 0.202 $\pm 0.001$ Absolute0.018 $\pm 0.001$ 0.018 $\pm 0.002$ 0.016 $\pm 0.001$ 0.018 $\pm 0.001$ 0.020 $\pm 0.001$ 0.10 $\pm 0.00^{*}$ FemaleNecropsy body wt146 $\pm 2$ 148 $\pm 3$ 147 $\pm 2$ 146 $\pm 2$ 143 $\pm 2$ 137 $\pm 3$ Heart Absolute0.498 $\pm 0.012$ 0.520 $\pm 0.012$ 0.502 $\pm 0.014$ 0.512 $\pm 0.009$ 0.502 $\pm 0.009$ 0.528 $\pm 0.011$ R kidative3.42 $\pm 0.06$ 3.51 $\pm 0.08$ 3.41 $\pm 0.08$ 3.50 $\pm 0.03$ 3.50 $\pm 0.04$ 3.86 $\pm 0.05^{**}$ R kidative4.20 $\pm 0.13$ 4.15 $\pm 0.05$ 4.31 $\pm 0.08$ 4.19 $\pm 0.04$ 4.44 $\pm 0.06$ 4.82 $\pm 0.10^{**}$ Absolute0.612 $\pm 0.022$ 0.616 $\pm 0.019$ 0.634 $\pm 0.013$ 0.614 $\pm 0.007$ 0.635 $\pm 0.007$ 6.606 $\pm 0.009$ Relative3.595 $\pm 0.86$ 36.87 $\pm 0.62$ 37.88 $\pm 0.82$ 39.28 $\pm 1.09^{**}$ 40.72 $\pm 0.22^{**}$	Relative	$1.214 \pm 0.023$	$6.22 \pm 0.098$	$1.244 \pm 0.054$ 5 57 + 0.06	$8.63 \pm 0.30**$	$5.79 \pm 0.11$	$6.22 \pm 0.32$
Absolute Absolute $1.242 \pm 0.032$ $1.279 \pm 0.041$ $1.220 \pm 0.039$ $1.227 \pm 0.020$ $1.238 \pm 0.025$ $1.203 \pm 0.034$ Relative $5.71 \pm 0.15$ $5.70 \pm 0.17$ $5.46 \pm 0.06$ $5.73 \pm 0.15$ $6.01 \pm 0.09$ $6.27 \pm 0.20^{\circ}$ Thymus $Absolute$ $0.369 \pm 0.025$ $0.382 \pm 0.011$ $0.363 \pm 0.024$ $0.349 \pm 0.020$ $0.340 \pm 0.010$ $0.284 \pm 0.014^{**}$ Relative $1.70 \pm 0.12$ $1.70 \pm 0.06$ $1.62 \pm 0.10$ $1.63 \pm 0.08$ $1.65 \pm 0.06$ $1.48 \pm 0.04$ Thyroid Gland Absolute $0.018 \pm 0.001$ $0.018 \pm 0.002$ $0.016 \pm 0.001$ $0.018 \pm 0.001$ $0.020 \pm 0.001$ $0.020 \pm 0.001$ Relative $0.08 \pm 0.00$ $0.08 \pm 0.01$ $0.07 \pm 0.00$ $0.08 \pm 0.00$ $0.09 \pm 0.01$ $0.10 \pm 0.00^{\circ}$ Female       Necropsy body wt $146 \pm 2$ $148 \pm 3$ $147 \pm 2$ $146 \pm 2$ $143 \pm 2$ $137 \pm 3$ Heart       Absolute $0.498 \pm 0.012$ $0.520 \pm 0.012$ $0.502 \pm 0.003$ $3.50 \pm 0.03$ $3.50 \pm 0.04$ $3.86 \pm 0.05^{**}$ R. Kidney $A_{20} \pm 0.13$ $4.15 \pm 0.05$ $4.31 \pm 0.08$ $3.51 \pm 0.09$	R Testis	5.50 T 0.10	0.22 1 0.34	5.57 <u>1</u> 0.00	0.05 1 0.50		
Relative Relative $5.71 \pm 0.15$ $5.70 \pm 0.17$ $5.46 \pm 0.06$ $5.73 \pm 0.15$ $6.01 \pm 0.09$ $6.27 \pm 0.20^{*}$ Thymus Absolute Relative $0.369 \pm 0.025$ $0.382 \pm 0.011$ $0.363 \pm 0.024$ $0.349 \pm 0.020$ $0.340 \pm 0.010$ $0.284 \pm 0.014^{**}$ Thymus Absolute Relative $1.70 \pm 0.12$ $1.70 \pm 0.06$ $1.62 \pm 0.10$ $1.63 \pm 0.08$ $0.010$ $0.284 \pm 0.014^{**}$ Thyroid Gland Absolute Relative $0.018 \pm 0.001$ $0.018 \pm 0.002$ $0.016 \pm 0.001$ $0.018 \pm 0.001$ $0.019 \pm 0.001$ $0.020 \pm 0.001$ Retative $0.08 \pm 0.00$ $0.08 \pm 0.01$ $0.07 \pm 0.00$ $0.08 \pm 0.00$ $0.09 \pm 0.01$ $0.020 \pm 0.001$ FemaleNecropsy body wt $146 \pm 2$ $148 \pm 3$ $147 \pm 2$ $146 \pm 2$ $143 \pm 2$ $137 \pm 3$ Heart Absolute Relative $0.498 \pm 0.012$ $0.520 \pm 0.012$ $0.502 \pm 0.014$ $0.512 \pm 0.009$ $0.502 \pm 0.009$ $0.528 \pm 0.011$ Absolute Relative $0.498 \pm 0.012$ $0.520 \pm 0.012$ $0.502 \pm 0.014$ $0.512 \pm 0.009$ $0.502 \pm 0.009$ $0.528 \pm 0.011$ Absolute Relative $0.612 \pm 0.022$ $0.616 \pm 0.019$ $0.634 \pm 0.013$ $0.614 \pm 0.007$ $0.636 \pm 0.007$ $0.660 \pm 0.009$ Relative Liver Absolute Relative $5.240 \pm 0.182$ $5.778 \pm 0.187$ $5.750 \pm 0.160^{*}$ $5.832 \pm 0.067^{*}$ $6.204 \pm 0.118^{**}$ Lung Absolute Relative $0.968 \pm 0.058$ $0.950 \pm 0.046$ $1.010 \pm 0.025$ $0.962 \pm 0.020$ $0.906 \pm 0.011$ $0.928 \pm 0.042$ Lung	Absolute	1.242 + 0.032	1.279 + 0.041	1.220 + 0.039	1.227 + 0.020	1.238 + 0.025	$1.203 \pm 0.034$
Thymus Absolute Relative 1.70 $\pm$ 0.025 0.382 $\pm$ 0.011 0.363 $\pm$ 0.024 1.63 $\pm$ 0.020 1.63 $\pm$ 0.010 1.65 $\pm$ 0.06 1.65 $\pm$ 0.06 1.65 $\pm$ 0.00 1.65 $\pm$ 0.00 1.65 $\pm$ 0.00 1.65 $\pm$ 0.00 1.65 $\pm$ 0.00 1.65 $\pm$ 0.00 1.65 $\pm$ 0.00 0.019 $\pm$ 0.001 0.019 $\pm$ 0.001 0.019 $\pm$ 0.001 0.019 $\pm$ 0.001 0.020 $\pm$ 0.001 0.10 $\pm$ 0.00* Female Necropsy body wt 146 $\pm$ 2 148 $\pm$ 3 147 $\pm$ 2 146 $\pm$ 2 143 $\pm$ 2 137 $\pm$ 3 Heart Absolute 0.498 $\pm$ 0.012 0.520 $\pm$ 0.012 0.520 $\pm$ 0.014 0.512 $\pm$ 0.009 0.522 $\pm$ 0.009 0.522 $\pm$ 0.009 0.528 $\pm$ 0.011 3.50 $\pm$ 0.04 3.50 $\pm$ 0.04 3.56 $\pm$ 0.05** R. Kidney Absolute 0.612 $\pm$ 0.022 0.616 $\pm$ 0.019 0.634 $\pm$ 0.013 0.614 $\pm$ 0.007 0.636 $\pm$ 0.007 0.636 $\pm$ 0.007 0.660 $\pm$ 0.009 Relative 4.20 $\pm$ 0.182 5.472 $\pm$ 0.193 5.578 $\pm$ 0.187 5.750 $\pm$ 0.160* 5.832 $\pm$ 0.067* 6.204 $\pm$ 0.118** Absolute 0.968 $\pm$ 0.058 0.950 $\pm$ 0.046 1.010 $\pm$ 0.025 0.962 $\pm$ 0.020 0.906 $\pm$ 0.011 0.928 $\pm$ 0.042 6.77 $\pm$ 0.23 Thymus Absolute 0.281 $\pm$ 0.008 0.317 $\pm$ 0.011 0.321 $\pm$ 0.012 0.318 $\pm$ 0.008 0.313 $\pm$ 0.015 0.286 $\pm$ 0.014 Relative 1.93 $\pm$ 0.06 2.17 $\pm$ 0.00 0.11 $\pm$ 0.001 0.016 $\pm$ 0.001 Relative 0.013 $\pm$ 0.001 0.016 $\pm$ 0.001 0.015 $\pm$ 0.001 0.016 $\pm$ 0.001 0.015 $\pm$ 0.001 0.016 $\pm$ 0.001 0.015 $\pm$ 0.001 0.016 $\pm$ 0.001	Relative	$5.71 \pm 0.15$	$5.70 \pm 0.17$	$5.46 \pm 0.06$	$5.73 \pm 0.15$	$6.01 \pm 0.09$	$6.27 \pm 0.20*$
Absolute Relative $0.369 \pm 0.025$ $1.70 \pm 0.12$ $0.382 \pm 0.011$ $1.70 \pm 0.06$ $0.363 \pm 0.024$ $1.62 \pm 0.10$ $0.349 \pm 0.020$ $1.63 \pm 0.08$ $0.340 \pm 0.010$ $1.65 \pm 0.06$ $0.284 \pm 0.014^{**}$ $1.48 \pm 0.04$ Thyroid Gland Absolute Relative $0.018 \pm 0.001$ $0.08 \pm 0.00$ $0.018 \pm 0.002$ $0.08 \pm 0.01$ $0.016 \pm 0.001$ $0.07 \pm 0.00$ $0.019 \pm 0.001$ $0.08 \pm 0.01$ $0.020 \pm 0.001$ $0.09 \pm 0.01$ $0.020 \pm 0.001$ $0.09 \pm 0.01$ FemaleNecropsy body wt $146 \pm 2$ $148 \pm 3$ $147 \pm 2$ $146 \pm 2$ $143 \pm 2$ $137 \pm 3$ Heart Absolute Relative $0.498 \pm 0.012$ $3.42 \pm 0.06$ $0.502 \pm 0.014$ $3.51 \pm 0.08$ $0.512 \pm 0.009$ $3.50 \pm 0.03$ $0.502 \pm 0.009$ $3.50 \pm 0.04$ $0.528 \pm 0.011$ $3.86 \pm 0.05*$ R. Kidney, Absolute Relative $0.612 \pm 0.022$ $4.20 \pm 0.13$ $0.616 \pm 0.013$ $4.15 \pm 0.05$ $0.634 \pm 0.013$ $4.31 \pm 0.08$ $0.614 \pm 0.007$ $4.19 \pm 0.04$ $0.636 \pm 0.009$ $4.44 \pm 0.06$ $4.82 \pm 0.10*$ Liver Absolute Relative $5.240 \pm 0.182$ $5.95 \pm 0.86$ $5.578 \pm 0.187$ $36.87 \pm 0.62$ $5.750 \pm 0.160*$ $5.832 \pm 0.067*$ $6.204 \pm 0.118**$ $4.530 \pm 0.53**$ Lung Absolute Relative $0.968 \pm 0.058$ $0.950 \pm 0.046$ $0.912 \pm 0.022$ $0.962 \pm 0.020$ $0.906 \pm 0.011$ $0.928 \pm 0.042$ $6.77 \pm 0.23$ $0.313 \pm 0.016$ $0.77 \pm 0.23$ $0.286 \pm 0.014$ $0.77 \pm 0.23$ Thyrous Absolute Relative $0.281 \pm 0.008$ $0.317 \pm 0.011$ $0.321 \pm 0.012$ $0.318 \pm 0.006$ $2.15 \pm 0.012$ $0.014 \pm 0.001$ $0.014 \pm 0.001$ $0.015 \pm 0.001$ <br< td=""><td>Thymus</td><td></td><td></td><td></td><td>_</td><td></td><td>. —</td></br<>	Thymus				_		. —
Relative $1.70 \pm 0.12$ $1.70 \pm 0.06$ $1.62 \pm 0.10$ $1.63 \pm 0.08$ $1.65 \pm 0.06$ $1.48 \pm 0.04$ Thyroid Gland Absolute $0.018 \pm 0.001$ $0.018 \pm 0.002$ $0.016 \pm 0.001$ $0.018 \pm 0.001$ $0.018 \pm 0.001$ $0.019 \pm 0.001$ $0.020 \pm 0.001$ Relative $0.08 \pm 0.00$ $0.08 \pm 0.01$ $0.07 \pm 0.00$ $0.018 \pm 0.001$ $0.019 \pm 0.001$ $0.020 \pm 0.001$ Relative $0.08 \pm 0.00$ $0.08 \pm 0.01$ $0.07 \pm 0.00$ $0.08 \pm 0.00$ $0.09 \pm 0.01$ $0.10 \pm 0.00^*$ FemaleNecropsy body wt $146 \pm 2$ $148 \pm 3$ $147 \pm 2$ $146 \pm 2$ $143 \pm 2$ $137 \pm 3$ Heart Absolute $0.498 \pm 0.012$ $0.520 \pm 0.012$ $0.502 \pm 0.014$ $0.512 \pm 0.009$ $0.502 \pm 0.009$ $0.528 \pm 0.011$ R kidney Absolute $0.612 \pm 0.022$ $0.616 \pm 0.019$ $0.634 \pm 0.013$ $0.614 \pm 0.007$ $0.636 \pm 0.007$ $0.660 \pm 0.009$ Relative $4.20 \pm 0.13$ $4.15 \pm 0.05$ $4.31 \pm 0.08$ $4.19 \pm 0.04$ $4.44 \pm 0.06$ $4.82 \pm 0.10^{**}$ Liver Absolute $5.240 \pm 0.182$ $5.472 \pm 0.193$ $5.578 \pm 0.187$ $5.750 \pm 0.160^{**}$ $5.832 \pm 0.067^{**}$ $6.204 \pm 0.118^{**}$ Absolute $0.968 \pm 0.058$ $0.950 \pm 0.046$ $1.010 \pm 0.025$ $0.962 \pm 0.020$ $0.906 \pm 0.011$ $0.928 \pm 0.042$ Absolute $0.968 \pm 0.058$ $0.317 \pm 0.011$ $0.321 \pm 0.012$ $0.318 \pm 0.008$ $0.313 \pm 0.015$ $0.286 \pm 0.014$ Relative $1.93 \pm 0.06$ $2.15 \pm 0.09$ $2.18 \pm 0.06$ $2.17 \pm 0.06$	Absolute	$0.369 \pm 0.025$	$0.382 \pm 0.011$	$0.363 \pm 0.024$	$0.349 \pm 0.020$	0.340 ± 0.010	0.284 ± 0.014**
Thyroid Gland Absolute 0.018 $\pm$ 0.001 0.018 $\pm$ 0.002 0.016 $\pm$ 0.001 0.018 $\pm$ 0.001 0.019 $\pm$ 0.001 0.020 $\pm$ 0.001 Relative 0.08 $\pm$ 0.00 0.08 $\pm$ 0.01 0.07 $\pm$ 0.00 0.08 $\pm$ 0.00 0.09 $\pm$ 0.01 0.10 $\pm$ 0.00* Female Necropsy body wt 146 $\pm$ 2 148 $\pm$ 3 147 $\pm$ 2 146 $\pm$ 2 143 $\pm$ 2 137 $\pm$ 3 Heart Absolute 0.498 $\pm$ 0.012 0.520 $\pm$ 0.012 0.502 $\pm$ 0.014 0.512 $\pm$ 0.009 0.502 $\pm$ 0.009 0.528 $\pm$ 0.011 Relative 3.42 $\pm$ 0.06 3.51 $\pm$ 0.08 3.41 $\pm$ 0.08 3.50 $\pm$ 0.03 3.50 $\pm$ 0.04 3.86 $\pm$ 0.05** R. Kidney Absolute 0.612 $\pm$ 0.022 0.616 $\pm$ 0.019 0.634 $\pm$ 0.013 0.614 $\pm$ 0.007 0.636 $\pm$ 0.007 0.660 $\pm$ 0.009 Relative 4.20 $\pm$ 0.13 4.15 $\pm$ 0.05 4.31 $\pm$ 0.08 4.19 $\pm$ 0.04 4.44 $\pm$ 0.06 4.82 $\pm$ 0.10** Liver Absolute 5.240 $\pm$ 0.182 5.472 $\pm$ 0.193 5.578 $\pm$ 0.187 5.750 $\pm$ 0.160* 5.832 $\pm$ 0.067* 6.204 $\pm$ 0.118** Relative 3.95 $\pm$ 0.86 36.87 $\pm$ 0.62 37.88 $\pm$ 0.82 39.28 $\pm$ 1.09** 40.72 $\pm$ 0.22** 45.30 $\pm$ 0.53** Lung Absolute 0.968 $\pm$ 0.058 0.950 $\pm$ 0.046 1.010 $\pm$ 0.025 0.962 $\pm$ 0.020 0.906 $\pm$ 0.011 0.928 $\pm$ 0.042 Relative 1.93 $\pm$ 0.06 2.15 $\pm$ 0.02 10.313 $\pm$ 0.012 0.318 $\pm$ 0.028 $\pm$ 0.011 0.928 $\pm$ 0.042 Relative 1.93 $\pm$ 0.06 2.15 $\pm$ 0.09 2.18 $\pm$ 0.012 0.318 $\pm$ 0.008 0.313 $\pm$ 0.13 0.22** 45.30 $\pm$ 0.53** Thymus Absolute 0.013 $\pm$ 0.008 0.317 $\pm$ 0.011 0.321 $\pm$ 0.012 0.318 $\pm$ 0.008 0.313 $\pm$ 0.013 0.286 $\pm$ 0.014 Absolute 0.013 $\pm$ 0.001 0.016 $\pm$ 0.001 0.014 $\pm$ 0.002 0.014 $\pm$ 0.001 0.015 $\pm$ 0.001 0.016 $\pm$ 0.001 Relative 0.09 $\pm$ 0.01 0.016 $\pm$ 0.001 0.014 $\pm$ 0.002 0.014 $\pm$ 0.001 0.015 $\pm$ 0.001 0.016 $\pm$ 0.001 Relative 0.09 $\pm$ 0.01 0.016 $\pm$ 0.001 0.014 $\pm$ 0.002 0.014 $\pm$ 0.001 0.015 $\pm$ 0.001 0.016 $\pm$ 0.001	Relative	$1.70 \pm 0.12$	1.70 ± 0.06	$1.62 \pm 0.10$	$1.63 \pm 0.08$	$1.65 \pm 0.06$	$1.48 \pm 0.04$
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FemaleNecropsy body wt $146 \pm 2$ $148 \pm 3$ $147 \pm 2$ $146 \pm 2$ $143 \pm 2$ $137 \pm 3$ Heart Absolute $0.498 \pm 0.012$ $0.520 \pm 0.012$ $0.502 \pm 0.014$ $0.512 \pm 0.009$ $0.502 \pm 0.009$ $0.528 \pm 0.011$ Relative $3.42 \pm 0.06$ $3.51 \pm 0.08$ $3.41 \pm 0.08$ $3.50 \pm 0.03$ $3.50 \pm 0.04$ $3.86 \pm 0.05^{**}$ R. Kidney, Absolute $0.612 \pm 0.022$ $0.616 \pm 0.019$ $0.634 \pm 0.013$ $0.614 \pm 0.007$ $0.636 \pm 0.007$ $0.660 \pm 0.009$ Relative $4.20 \pm 0.13$ $4.15 \pm 0.05$ $4.31 \pm 0.08$ $4.19 \pm 0.04$ $4.44 \pm 0.06$ $4.82 \pm 0.10^{**}$ Liver Absolute $5.240 \pm 0.182$ $5.472 \pm 0.193$ $5.578 \pm 0.187$ $5.750 \pm 0.160^{**}$ $5.832 \pm 0.067^{**}$ $6.204 \pm 0.118^{**}$ Relative $35.95 \pm 0.86$ $36.87 \pm 0.62$ $37.88 \pm 0.82$ $39.28 \pm 1.09^{***}$ $40.72 \pm 0.22^{***}$ $45.30 \pm 0.53^{***}$ Lung Absolute $0.968 \pm 0.058$ $0.950 \pm 0.046$ $1.010 \pm 0.025$ $0.962 \pm 0.020$ $0.906 \pm 0.011$ $0.928 \pm 0.042$ Relative $1.93 \pm 0.06$ $2.15 \pm 0.09$ $2.18 \pm 0.008$ $0.313 \pm 0.015$ $0.286 \pm 0.014$ Relative $1.93 \pm 0.06$ $2.15 \pm 0.09$ $2.18 \pm 0.002$ $0.014 \pm 0.001$ $0.015 \pm 0.001$ $0.016 \pm 0.001$ Relative $1.93 \pm 0.001$ $0.016 \pm 0.001$ $0.014 \pm 0.002$ $0.014 \pm 0.001$ $0.015 \pm 0.001$ $0.016 \pm 0.001$ Relative $0.013 \pm 0.001$ $0.016 \pm 0.001$ $0.014 \pm 0.002$ $0.014 \pm 0.001$ $0.015 \pm 0.001$ <	Relative	$0.08 \pm 0.00$	$0.08 \pm 0.01$	$0.07 \pm 0.00$	$0.08 \pm 0.00$	$0.09 \pm 0.01$	$0.10 \pm 0.00*$
Necropsy body wt $146 \pm 2$ $148 \pm 3$ $147 \pm 2$ $146 \pm 2$ $143 \pm 2$ $137 \pm 3$ Heart Absolute $0.498 \pm 0.012$ $0.520 \pm 0.012$ $0.502 \pm 0.014$ $0.512 \pm 0.009$ $0.502 \pm 0.009$ $0.528 \pm 0.011$ Relative $3.42 \pm 0.06$ $3.51 \pm 0.08$ $3.41 \pm 0.08$ $3.50 \pm 0.03$ $3.50 \pm 0.04$ $3.86 \pm 0.05^{**}$ R. Kidney Absolute $0.612 \pm 0.022$ $0.616 \pm 0.019$ $0.634 \pm 0.013$ $0.614 \pm 0.007$ $0.636 \pm 0.007$ $0.660 \pm 0.009$ Relative $4.20 \pm 0.13$ $4.15 \pm 0.05$ $4.31 \pm 0.08$ $4.19 \pm 0.04$ $4.44 \pm 0.06$ $4.82 \pm 0.10^{**}$ Liver Absolute $5.240 \pm 0.182$ $5.472 \pm 0.193$ $5.578 \pm 0.187$ $5.750 \pm 0.160^{**}$ $5.832 \pm 0.067^{**}$ $6.204 \pm 0.118^{***}$ Relative $3.59 \pm 0.86$ $36.87 \pm 0.62$ $37.88 \pm 0.82$ $39.28 \pm 1.09^{***}$ $40.72 \pm 0.22^{***}$ $45.30 \pm 0.53^{***}$ Lung Absolute $0.968 \pm 0.058$ $0.950 \pm 0.046$ $1.010 \pm 0.025$ $0.962 \pm 0.020$ $0.906 \pm 0.011$ $0.928 \pm 0.042$ Absolute $0.281 \pm 0.008$ $0.317 \pm 0.011$ $0.321 \pm 0.012$ $0.318 \pm 0.008$ $0.313 \pm 0.015$ $0.286 \pm 0.014$ Relative $1.93 \pm 0.06$ $2.15 \pm 0.09$ $2.18 \pm 0.06$ $2.17 \pm 0.06$ $2.19 \pm 0.12$ $2.10 \pm 0.13$ Thyroid Gland Absolute $0.013 \pm 0.001$ $0.016 \pm 0.001$ $0.014 \pm 0.001$ $0.015 \pm 0.001$ $0.016 \pm 0.001$ Relative $0.09 \pm 0.01$ $0.11 \pm 0.001$ $0.014 \pm 0.001$ $0.015 \pm 0.001$ $0.016 \pm 0.001$	Female						
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Absolute $0.498 \pm 0.012$ $0.520 \pm 0.012$ $0.502 \pm 0.014$ $0.512 \pm 0.009$ $0.502 \pm 0.009$ $0.528 \pm 0.011$ Relative $3.42 \pm 0.06$ $3.51 \pm 0.08$ $3.41 \pm 0.08$ $3.50 \pm 0.03$ $3.50 \pm 0.04$ $3.86 \pm 0.05^{**}$ R. Kidney $Absolute$ $0.612 \pm 0.022$ $0.616 \pm 0.019$ $0.634 \pm 0.013$ $0.614 \pm 0.007$ $0.636 \pm 0.007$ $0.660 \pm 0.009$ Relative $4.20 \pm 0.13$ $4.15 \pm 0.05$ $4.31 \pm 0.08$ $4.19 \pm 0.04$ $4.44 \pm 0.06$ $4.82 \pm 0.10^{**}$ Liver $Absolute$ $5.240 \pm 0.182$ $5.472 \pm 0.193$ $5.578 \pm 0.187$ $5.750 \pm 0.160^{**}$ $5.832 \pm 0.067^{**}$ $6.204 \pm 0.118^{***}$ Relative $3.59 \pm 0.86$ $36.87 \pm 0.62$ $37.88 \pm 0.82$ $39.28 \pm 1.09^{***}$ $40.72 \pm 0.22^{**}$ $45.30 \pm 0.53^{***}$ Lung $Absolute$ $0.968 \pm 0.058$ $0.950 \pm 0.046$ $1.010 \pm 0.025$ $0.962 \pm 0.020$ $0.906 \pm 0.011$ $0.928 \pm 0.042$ Relative $6.64 \pm 0.34$ $6.40 \pm 0.23$ $6.87 \pm 0.14$ $6.57 \pm 0.11$ $6.33 \pm 0.13$ $6.77 \pm 0.23$ Thymus $Absolute$ $0.281 \pm 0.008$ $0.317 \pm 0.011$ $0.321 \pm 0.012$ $0.318 \pm 0.008$ $0.313 \pm 0.015$ $0.286 \pm 0.014$ Relative $1.93 \pm 0.06$ $2.15 \pm 0.09$ $2.18 \pm 0.06$ $2.17 \pm 0.06$ $2.19 \pm 0.12$ $2.10 \pm 0.13$ Thyroid Gland $0.013 \pm 0.001$ $0.016 \pm 0.001$ $0.014 \pm 0.002$ $0.014 \pm 0.001$ $0.015 \pm 0.001$ $0.016 \pm 0.001$ Relative $0.09 \pm 0.01$ $0.11 \pm 0.00$ $0.014 \pm 0.002$ $0.014 \pm 0.00$	Heart	•			•		
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R. Kidney       Absolute $0.612 \pm 0.022$ $0.616 \pm 0.019$ $0.634 \pm 0.013$ $0.614 \pm 0.007$ $0.636 \pm 0.007$ $0.660 \pm 0.009$ Relative $4.20 \pm 0.13$ $4.15 \pm 0.05$ $4.31 \pm 0.08$ $4.19 \pm 0.04$ $4.44 \pm 0.06$ $4.82 \pm 0.10^{**}$ Liver       Absolute $5.240 \pm 0.182$ $5.472 \pm 0.193$ $5.578 \pm 0.187$ $5.750 \pm 0.160^*$ $5.832 \pm 0.067^*$ $6.204 \pm 0.118^{**}$ Relative $35.95 \pm 0.86$ $36.87 \pm 0.62$ $37.88 \pm 0.82$ $39.28 \pm 1.09^{**}$ $40.72 \pm 0.22^{**}$ $45.30 \pm 0.53^{**}$ Lung       Absolute $0.968 \pm 0.058$ $0.950 \pm 0.046$ $1.010 \pm 0.025$ $0.962 \pm 0.020$ $0.906 \pm 0.011$ $0.928 \pm 0.042$ Relative $0.281 \pm 0.008$ $0.317 \pm 0.011$ $0.321 \pm 0.012$ $0.318 \pm 0.008$ $0.313 \pm 0.015$ $0.286 \pm 0.014$ Relative $1.93 \pm 0.06$ $2.15 \pm 0.09$ $2.18 \pm 0.006$ $2.17 \pm 0.06$ $2.19 \pm 0.12$ $2.10 \pm 0.13$ Thyroid Gland $0.013 \pm 0.001$ $0.016 \pm 0.001$ $0.014 \pm 0.002$ $0.014 \pm 0.001$ $0.015 \pm 0.001$ $0.016 \pm 0.001$ Relative $0.09 \pm 0.01$ $0.11 \pm 0.00$ $0.014 \pm 0.001$ <t< td=""><td>Relative</td><td>$3.42 \pm 0.06$</td><td>$3.51 \pm 0.08$</td><td>$3.41 \pm 0.08$</td><td>$3.50 \pm 0.03$</td><td>$3.50 \pm 0.04$</td><td>3.86 ± 0.05**</td></t<>	Relative	$3.42 \pm 0.06$	$3.51 \pm 0.08$	$3.41 \pm 0.08$	$3.50 \pm 0.03$	$3.50 \pm 0.04$	3.86 ± 0.05**
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Liver Absolute $5.240 \pm 0.182$ $5.472 \pm 0.193$ $5.578 \pm 0.187$ $5.750 \pm 0.160^*$ $5.832 \pm 0.067^*$ $6.204 \pm 0.118^{**}$ Relative $35.95 \pm 0.86$ $36.87 \pm 0.62$ $37.88 \pm 0.82$ $39.28 \pm 1.09^{**}$ $40.72 \pm 0.22^{**}$ $45.30 \pm 0.53^{**}$ Lung Absolute $0.968 \pm 0.058$ $0.950 \pm 0.046$ $1.010 \pm 0.025$ $0.962 \pm 0.020$ $0.906 \pm 0.011$ $0.928 \pm 0.042$ Relative $6.64 \pm 0.34$ $6.40 \pm 0.23$ $6.87 \pm 0.14$ $6.57 \pm 0.11$ $6.33 \pm 0.13$ $6.77 \pm 0.23$ Thymus Absolute $0.281 \pm 0.008$ $0.317 \pm 0.011$ $0.321 \pm 0.012$ $0.318 \pm 0.008$ $0.313 \pm 0.015$ $0.286 \pm 0.014$ Relative $1.93 \pm 0.06$ $2.15 \pm 0.09$ $2.18 \pm 0.06$ $2.17 \pm 0.06$ $2.19 \pm 0.12$ $2.10 \pm 0.13$ Thyroid Gland Absolute $0.013 \pm 0.001$ $0.016 \pm 0.001$ $0.014 \pm 0.002$ $0.014 \pm 0.001$ $0.015 \pm 0.001$ $0.016 \pm 0.001$	Relative	$4.20 \pm 0.13$	$4.15 \pm 0.05$	$4.31 \pm 0.08$	$4.19 \pm 0.04$	$4.44 \pm 0.06$	$4.82 \pm 0.10$ **
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Relative $35.95 \pm 0.86$ $36.87 \pm 0.62$ $37.88 \pm 0.82$ $39.28 \pm 1.09^{44}$ $40.72 \pm 0.22^{44}$ $43.30 \pm 0.33^{44}$ Lung Absolute $0.968 \pm 0.058$ $0.950 \pm 0.046$ $1.010 \pm 0.025$ $0.962 \pm 0.020$ $0.906 \pm 0.011$ $0.928 \pm 0.042$ Relative $6.64 \pm 0.34$ $6.40 \pm 0.23$ $6.87 \pm 0.14$ $6.57 \pm 0.11$ $6.33 \pm 0.13$ $6.77 \pm 0.23$ Thymus Absolute $0.281 \pm 0.008$ $0.317 \pm 0.011$ $0.321 \pm 0.012$ $0.318 \pm 0.008$ $0.313 \pm 0.015$ $0.286 \pm 0.014$ Relative $1.93 \pm 0.06$ $2.15 \pm 0.09$ $2.18 \pm 0.06$ $2.17 \pm 0.06$ $2.19 \pm 0.12$ $2.10 \pm 0.13$ Thyroid Gland Absolute $0.013 \pm 0.001$ $0.016 \pm 0.001$ $0.014 \pm 0.002$ $0.014 \pm 0.001$ $0.015 \pm 0.001$ $0.016 \pm 0.001$ Relative $0.09 \pm 0.01$ $0.11 \pm 0.00$ $0.10 \pm 0.01$ $0.09 \pm 0.00$ $0.11 \pm 0.01$ $0.12 \pm 0.01$	Absolute	$5.240 \pm 0.182$	$5.472 \pm 0.193$	$5.578 \pm 0.187$	$5.750 \pm 0.160*$	$5.832 \pm 0.067*$	$6.204 \pm 0.118^{++}$
Lung Absolute $0.968 \pm 0.058$ $0.950 \pm 0.046$ $1.010 \pm 0.025$ $0.962 \pm 0.020$ $0.906 \pm 0.011$ $0.928 \pm 0.042$ Relative $6.64 \pm 0.34$ $6.40 \pm 0.23$ $6.87 \pm 0.14$ $6.57 \pm 0.11$ $6.33 \pm 0.13$ $6.77 \pm 0.23$ Thymus Absolute $0.281 \pm 0.008$ $0.317 \pm 0.011$ $0.321 \pm 0.012$ $0.318 \pm 0.008$ $0.313 \pm 0.015$ $0.286 \pm 0.014$ Relative $1.93 \pm 0.06$ $2.15 \pm 0.09$ $2.18 \pm 0.06$ $2.17 \pm 0.06$ $2.19 \pm 0.12$ $2.10 \pm 0.13$ Thyroid Gland Relative $0.013 \pm 0.001$ $0.016 \pm 0.001$ $0.014 \pm 0.002$ $0.014 \pm 0.001$ $0.015 \pm 0.001$ $0.016 \pm 0.001$ Relative $0.09 \pm 0.01$ $0.11 \pm 0.00$ $0.10 \pm 0.01$ $0.09 \pm 0.00$ $0.11 \pm 0.01$ $0.12 \pm 0.01$	Relative	35.95 ± 0.86	$36.87 \pm 0.62$	$37.88 \pm 0.82$	39.28 ± 1.09**	$40.72 \pm 0.22^{**}$	45.30 ± 0.53**
Absolute $0.968 \pm 0.038$ $0.900 \pm 0.046$ $1.010 \pm 0.023$ $0.962 \pm 0.026$ $0.962 \pm 0.011$ $0.926 \pm 0.011$ $0.926 \pm 0.011$ Relative $6.64 \pm 0.34$ $6.40 \pm 0.23$ $6.87 \pm 0.14$ $6.57 \pm 0.11$ $6.33 \pm 0.13$ $6.77 \pm 0.23$ ThymusAbsolute $0.281 \pm 0.008$ $0.317 \pm 0.011$ $0.321 \pm 0.012$ $0.318 \pm 0.008$ $0.313 \pm 0.015$ $0.286 \pm 0.014$ Relative $1.93 \pm 0.06$ $2.15 \pm 0.09$ $2.18 \pm 0.06$ $2.17 \pm 0.06$ $2.19 \pm 0.12$ $2.10 \pm 0.13$ Thyroid Gland $Absolute$ $0.013 \pm 0.001$ $0.016 \pm 0.001$ $0.014 \pm 0.002$ $0.014 \pm 0.001$ $0.015 \pm 0.001$ $0.016 \pm 0.001$ Relative $0.09 \pm 0.01$ $0.11 \pm 0.00$ $0.10 \pm 0.01$ $0.09 \pm 0.00$ $0.11 \pm 0.01$ $0.12 \pm 0.01$	Lung	0.069 0.069	50 050 L 0 046	1 010 + 0 025	$0.962 \pm 0.020$	$0.906 \pm 0.011$	$0.928 \pm 0.042$
Relative $0.04 \pm 0.04$ $0.14 \pm 0.02$ $0.01 \pm 0.14$ $0.01 \pm 0.12$ $0.01 \pm 0.12$ $0.01 \pm 0.12$ Thymus Absolute $0.281 \pm 0.008$ $0.317 \pm 0.011$ $0.321 \pm 0.012$ $0.318 \pm 0.008$ $0.313 \pm 0.015$ $0.286 \pm 0.014$ Relative $1.93 \pm 0.06$ $2.15 \pm 0.09$ $2.18 \pm 0.06$ $2.17 \pm 0.06$ $2.19 \pm 0.12$ $2.10 \pm 0.13$ Thyroid Gland Relative $0.013 \pm 0.001$ $0.016 \pm 0.001$ $0.014 \pm 0.002$ $0.014 \pm 0.001$ $0.015 \pm 0.001$ $0.016 \pm 0.001$ Relative $0.09 \pm 0.01$ $0.11 \pm 0.00$ $0.10 \pm 0.01$ $0.09 \pm 0.00$ $0.11 \pm 0.01$ $0.12 \pm 0.01$	Aosolute	$0.908 \pm 0.038$	$-0.930 \pm 0.040$ 6.40 ± 0.23	$6.87 \pm 0.025$	$6.57 \pm 0.020$	$6.33 \pm 0.13$	$6.77 \pm 0.23$
Invince Absolute $0.281 \pm 0.008$ $0.317 \pm 0.011$ $0.321 \pm 0.012$ $0.318 \pm 0.008$ $0.313 \pm 0.015$ $0.286 \pm 0.014$ Relative $1.93 \pm 0.06$ $2.15 \pm 0.09$ $2.18 \pm 0.06$ $2.17 \pm 0.06$ $2.19 \pm 0.12$ $2.10 \pm 0.13$ Thyroid Gland Absolute $0.013 \pm 0.001$ $0.016 \pm 0.001$ $0.014 \pm 0.002$ $0.014 \pm 0.001$ $0.015 \pm 0.001$ $0.016 \pm 0.001$ Relative $0.09 \pm 0.01$ $0.11 \pm 0.00$ $0.10 \pm 0.01$ $0.09 \pm 0.00$ $0.11 \pm 0.01$ $0.12 \pm 0.01$	Thymus	0.04 ± 0.34	0.40 <u>T</u> 0.23	0.0% T 0.14	0.57 ± 0.11	0.55 T 0.15	5.17 <u>T</u> 0.55
Relative $1.93 \pm 0.06$ $2.15 \pm 0.09$ $2.18 \pm 0.06$ $2.17 \pm 0.06$ $2.19 \pm 0.12$ $2.10 \pm 0.13$ Thyroid GlandAbsolute $0.013 \pm 0.001$ $0.016 \pm 0.001$ $0.014 \pm 0.002$ $0.014 \pm 0.001$ $0.015 \pm 0.001$ $0.016 \pm 0.001$ Relative $0.09 \pm 0.01$ $0.11 \pm 0.00$ $0.10 \pm 0.01$ $0.09 \pm 0.00$ $0.11 \pm 0.01$	Absolute	$0.281 \pm 0.008$	0.317 + 0.011	0.321 + 0.012	0.318 + 0.008	$0.313 \pm 0.015$	$0.286 \pm 0.014$
Thyroid Gland AbsoluteAbsolute $0.013 \pm 0.001$ $0.016 \pm 0.001$ $0.014 \pm 0.002$ $0.014 \pm 0.001$ $0.015 \pm 0.001$ $0.016 \pm 0.001$ Relative $0.09 \pm 0.01$ $0.11 \pm 0.00$ $0.10 \pm 0.01$ $0.09 \pm 0.00$ $0.11 \pm 0.01$ $0.12 \pm 0.01$	Relative	$1.93 \pm 0.06$	$2.15 \pm 0.09$	$2.18 \pm 0.06$	$2.17 \pm 0.06$	$2.19 \pm 0.12$	$2.10 \pm 0.13$
Absolute $0.013 \pm 0.001$ $0.016 \pm 0.001$ $0.014 \pm 0.002$ $0.014 \pm 0.001$ $0.015 \pm 0.001$ $0.016 \pm 0.001$ Relative $0.09 \pm 0.01$ $0.11 \pm 0.00$ $0.10 \pm 0.01$ $0.09 \pm 0.00$ $0.11 \pm 0.01$ $0.12 \pm 0.01$	Thyroid Gland	T 0.00	<b>_</b>			. –	
Relative $0.09 \pm 0.01$ $0.11 \pm 0.00$ $0.10 \pm 0.01$ $0.09 \pm 0.00$ $0.11 \pm 0.01$ $0.12 \pm 0.01$	Absolute	$0.013 \pm 0.001$	$0.016 \pm 0.001$	0.014 ± 0.002	$0.014 \pm 0.001$	0.015 ± 0.001	$0.016 \pm 0.001$
	Relative	$0.09 \pm 0.01$	$0.11 \pm 0.00$	$0.10 \pm 0.01$	$0.09 \pm 0.00$	$0.11 \pm 0.01$	$0.12 \pm 0.01$

* Significantly different ( $P \le 0.05$ ) from the control group by Williams' or Dunnett's test

** P≤0.01

^a Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Inhalation Study of Nitromethane^a

	0 ppm	94 ppm	188 ppm	375 ppm	750 ppm	1,500 ppm
n	10	10	10	10	10	10
Male	·	s.				
Necropsy body wt	338 ± 7	328 ± 7	346 ± 4	341 ± 4	331 ± 4	299 ± 11**
Heart						
Absolute	$0.941 \pm 0.020$	$0.900 \pm 0.023$	$0.943 \pm 0.015$	$0.936 \pm 0.012$	$0.952 \pm 0.013$	$0.913 \pm 0.025$
Relative	$2.78 \pm 0.03$	$2.74 \pm 0.03$	$2.72 \pm 0.03$	$2.75 \pm 0.03$	$2.88 \pm 0.02$	$3.07 \pm 0.06^{**}$
R. Kidney				_		
Absolute	$1.098 \pm 0.038$	$1.040 \pm 0.024$	$1.130 \pm 0.024$	$1.114 \pm 0.018$	$1.103 \pm 0.020$	$1.094 \pm 0.031$
Relative	$3.24 \pm 0.06$	$3.17 \pm 0.05$	$3.27 \pm 0.07$	$3.27 \pm 0.05$	$3.33 \pm 0.05$	3.68 ± 0.09**
Liver						
Absolute	11.518 ± 0.403	10.881 ± 0.462	11.898 ± 0.306	11.984 ± 0.113	12.010 ± 0.433	10.334 ± 0.454
Relative	33.99 ± 0.66	$33.05 \pm 0.76$	$34.34 \pm 0.65$	$35.23 \pm 0.55$	$36.23 \pm 1.08$	$34.52 \pm 0.42$
Lung						
Absolute	$1.708 \pm 0.053$	1.758 ± 0.063	$1.859 \pm 0.057$	1.667 ± 0.044	1.631 ± 0.035	1.533 ± 0.061*
Relative	$5.05 \pm 0.11$	5.36 ± 0.16	5.38 ± 0.17	4.89 ± 0.09	4.93 ± 0.09	$5.13 \pm 0.08$
R. Testis						
Absolute	$1.358 \pm 0.031$	1.293 ± 0.027	1.333 ± 0.020	$1.326 \pm 0.019$	$1.265 \pm 0.037$	1.245 ± 0.028*
Relative	$4.01 \pm 0.05$	3.95 ± 0.06	$3.85 \pm 0.05$	3.89 ± 0.04	$3.82 \pm 0.10$	$4.21 \pm 0.16$
Thymus						
Absolute	$0.345 \pm 0.013$	$0.331 \pm 0.016$	$0.351 \pm 0.012$	0.340 ± 0.018	$0.323 \pm 0.016$	0.278 ± 0.011**
Relative	$1.02 \pm 0.03$	$1.00 \pm 0.03$	$1.01 \pm 0.03$	$1.00 \pm 0.05$	$0.98 \pm 0.05$	$0.93 \pm 0.03$
Thyroid Gland						
Absolute	$0.020 \pm 0.001$	$0.018 \pm 0.001$	$0.022 \pm 0.002$	0.019 ± 0.002	$0.020 \pm 0.001$	$0.025 \pm 0.001^{\circ}$
Relative	$0.06 \pm 0.00$	$0.05 \pm 0.00$	$0.06 \pm 0.01$	$0.05 \pm 0.00$	$0.06 \pm 0.00$	$0.08 \pm 0.01^{**0}$
Female						
Necropsy body wt	188 ± 5	198 ± 3	199 ± 3	200 ± 5	195 ± 4	178 ± 3
Heart						
Absolute	$0.583 \pm 0.015$	$0.613 \pm 0.007$	$0.627 \pm 0.013$	$0.622 \pm 0.017$	$0.614 \pm 0.010$	$0.614 \pm 0.012$
Relative	$3.11 \pm 0.04$	$3.10 \pm 0.04$	$3.15 \pm 0.04$	$3.12 \pm 0.05$	$3.16 \pm 0.04$	$3.45 \pm 0.05^{**}$
R. Kidney						-
Absolute	0.619 ± 0.016	$0.655 \pm 0.011$	$0.642 \pm 0.017$	0.659 ± 0.017	0.668 ± 0.013	$0.643 \pm 0.010$
Relative	$3.30 \pm 0.05$	$3.31 \pm 0.04$	$3.22 \pm 0.06$	$3.31 \pm 0.07$	$3.44 \pm 0.06$	$3.62 \pm 0.08 * *$
Liver						
Absolute	$6.342 \pm 0.205$	6.773 ± 0.095	7.028 ± 0.258	7.042 ± 0.175*	6.707 ± 0.172	$6.623 \pm 0.193$
Relative	$33.74 \pm 0.54$	$34.25 \pm 0.50$	35.30 ± 1.07	$35.36 \pm 0.62$	$34.50 \pm 0.60$	37.15 ± 0.62**
Lung						
Absolute	$1.051 \pm 0.025$	$1.102 \pm 0.018$	$1.052 \pm 0.056$	$1.092 \pm 0.023$	$1.098 \pm 0.018$	$1.049 \pm 0.024$
Relative	5.60 ± 0.07	$5.58 \pm 0.12$	5.29 ± 0.27	5.49 ± 0.09	$5.66 \pm 0.10$	5.89 ± 0.08
Thymus						
Absolute	$0.242 \pm 0.008$	$0.263 \pm 0.008$	$0.280 \pm 0.011*$	$0.256 \pm 0.008$	$0.253 \pm 0.009$	$0.239 \pm 0.009$
Relative	$1.29 \pm 0.03$	$1.33 \pm 0.03$	$1.41 \pm 0.05$	$1.28 \pm 0.04$	1.30 ± 0.04	$1.34 \pm 0.05$
Thyroid Gland						
Absolute	$0.018 \pm 0.001$	$0.016 \pm 0.002$	$0.021 \pm 0.002$	$0.017 \pm 0.001$	$0.018 \pm 0.001$	$0.018 \pm 0.001$
Relative	$0.10 \pm 0.01$	$0.08 \pm 0.01$	$0.10 \pm 0.01$	$0.09 \pm 0.01$	$0.09 \pm 0.00$	$0.10 \pm 0.01$

* Significantly different ( $P \le 0.05$ ) from the control group by Williams' or Dunnett's test

** P≤0.01

a Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean  $\pm$  standard error). b n=9

Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 16-Day Inhalation Study of Nitromethane^a

n         5         5         5         5         5         5           Male           Necropsy body wt         27.4 $\pm$ 0.6         29.0 $\pm$ 1.0         28.9 $\pm$ 0.6         27.7 $\pm$ 0.9         29.2 $\pm$ 0.7         28.6 $\pm$ 0.2           Heart         Absolute         0.136 $\pm$ 0.009         0.134 $\pm$ 0.006         0.138 $\pm$ 0.007         0.136 $\pm$ 0.007         0.128 $\pm$ 0.007         0.278 $\pm$ 0.006         Relative         1.042 $\pm$ 0.26         9.85 $\pm$ 0.20         9.62 $\pm$ 0.28 $\pm$ 0.012         0.284 $\pm$ 0.007         0.278 $\pm$ 0.006         Note         9.73 $\pm$ 0.11         9.72 $\pm$ 0.19         1.752 $\pm$ 0.081 $\pm$ 1.680 $\pm$ 0.053 $\pm$ 0.027         7.28 $\pm$ 0.077         7.32 $\pm$ 0.012         1.526 $\pm$ 0.025         7.24 $\pm$ 0.27         7.20 $\pm$ 0.07         7.13 $\pm$ 0.05           Ling         Absolute         0.200 $\pm$ 0.004         0.212 $\pm$ 0.012         0.202 $\pm$ 0.005         0.210 $\pm$ 0.005         0.210 $\pm$ 0.005         0.210 $\pm$ 0.005         0.210 $\pm$ 0.007         7.13 $\pm$ 0.15           Relative         7.31 $\pm$ 0.2	· · ·	0 ppm	94 ppm	188 ppm	375 ppm	750 ppm	1,500 ppm
MaleNecropsy body wi $27.4 \pm 0.6$ $29.0 \pm 1.0$ $28.9 \pm 0.6$ $27.7 \pm 0.9$ $29.2 \pm 0.7$ $28.6 \pm 0.2$ Heart Absolute $0.136 \pm 0.009$ $0.134 \pm 0.006$ $0.138 \pm 0.006$ $0.128 \pm 0.007$ $0.136 \pm 0.007$ $0.128 \pm 0.007$ Ridiney Relative $4.94 \pm 0.22$ $4.62 \pm 0.013$ $0.278 \pm 0.007$ $0.282 \pm 0.012$ $0.284 \pm 0.007$ $0.128 \pm 0.006$ Absolute Relative $0.286 \pm 0.012$ $0.286 \pm 0.013$ $0.278 \pm 0.007$ $0.282 \pm 0.012$ $0.284 \pm 0.007$ $0.278 \pm 0.007$ Liver Absolute $1.376 \pm 0.044$ $1.538 \pm 0.083$ $1.552 \pm 0.045$ $1.526 \pm 0.078$ $1.752 \pm 0.081^{**}$ Absolute Relative $0.200 \pm 0.004$ $0.212 \pm 0.012$ $0.202 \pm 0.006$ $0.200 \pm 0.005$ $0.210 \pm 0.005$ Absolute Relative $0.200 \pm 0.004$ $0.212 \pm 0.012$ $0.202 \pm 0.006$ $0.200 \pm 0.005$ $0.210 \pm 0.005$ Absolute Relative $0.200 \pm 0.004$ $0.212 \pm 0.012$ $0.202 \pm 0.006$ $0.200 \pm 0.005$ $0.210 \pm 0.005$ Absolute Relative $0.113 \pm 0.003$ $0.112 \pm 0.003$ $0.112 \pm 0.001$ $0.113 \pm 0.001$ Absolute Relative $0.47 \pm 0.003$ $0.112 \pm 0.003$ $0.112 \pm 0.001$ $0.113 \pm 0.001$ Absolute Relative $0.47 \pm 0.002$ $0.114 \pm 0.002$ $0.112 \pm 0.001$ $0.113 \pm 0.001$ Absolute Relative $0.113 \pm 0.002$ $0.114 \pm 0.002$ $0.112 \pm 0.004$ $0.114 \pm 0.002$ Absolute Relative $0.112 \pm 0.002$ $0.118 \pm 0.002$ $0.114 \pm 0.002$ $0.112 \pm 0.004$ $0.$	n	5	. 5	5	5	5	5
Neuropsy body wt $27.4 \pm 0.6$ $29.0 \pm 1.0$ $28.9 \pm 0.6$ $27.7 \pm 0.9$ $29.2 \pm 0.7$ $28.6 \pm 0.2$ Heart Absolute $4.04 \pm 0.22$ $4.62 \pm 0.08$ $4.77 \pm 0.14$ $4.60 \pm 0.07$ $0.136 \pm 0.007$ $0.128 \pm 0.006$ $0.128 \pm 0.007$ $0.136 \pm 0.007$ $0.128 \pm 0.007$ $0.284 \pm 0.007$ $0.278 \pm 0.012$ $0.284 \pm 0.037$ $0.278 \pm 0.012$ $0.208 \pm 0.017$ $0.278 \pm 0.081^{ser}$ $1.538 \pm 0.063$ $1.552 \pm 0.045$ $1.526 \pm 0.078$ $1.752 \pm 0.081^{ser}$ $1.680 \pm 0.053^{ser}$ Absolute $0.200 \pm 0.004$ $0.212 \pm 0.012$ $0.202 \pm 0.006$ $0.200 \pm 0.005$ $0.210 \pm 0.005$ $7.24 \pm 0.27$ $7.20 \pm 0.07$ $7.13 \pm 0.15$ R. Testis $0.113 \pm 0.003$ $0.113 \pm 0.003$ $0.112 \pm 0.001$ $0.113 \pm 0.001$ Absolute $0.1047 \pm 0.003$ $0.046 \pm 0.004$ $0.044 \pm 0.003$ $0.037 \pm 0.003$ $0.124 \pm 0.011$ $1.59 \pm 0.10$ $1.64 \pm 0.17$ $1.84 \pm 0.08$ Hearive $1.73 \pm 0.11$ $1.69 \pm 0.022$ $0.114 \pm 0.002$ $0.112 \pm 0.002$	Male				•		
Heart Absolute Relative Absolute Relative Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute Absolute	Necropsy body wt	$27.4 \pm 0.6$	$29.0 \pm 1.0$	$28.9 \pm 0.6$	$27.7 \pm 0.9$	29.2 ± 0.7	$28.6 \pm 0.2$
Absolute Relative $0.136 \pm 0.009$ $4.94 \pm 0.22$ $0.134 \pm 0.006$ $4.62 \pm 0.08$ $0.138 \pm 0.006$ $4.77 \pm 0.14$ $0.128 \pm 0.007$ $4.66 \pm 0.13$ $0.136 \pm 0.007$ $4.66 \pm 0.16$ $0.136 \pm 0.007$ $4.67 \pm 0.19$ $0.128 \pm 0.006$ $4.47 \pm 0.19$ Absolute Relative $0.286 \pm 0.012$ $0.42 \pm 0.26$ $0.286 \pm 0.013$ $9.85 \pm 0.20$ $0.278 \pm 0.007$ $9.62 \pm 0.28*$ $0.284 \pm 0.007$ $0.282 \pm 0.012$ $9.73 \pm 0.11$ $0.278 \pm 0.006$ $9.73 \pm 0.11$ $0.278 \pm 0.007$ $9.73 \pm 0.11$ $0.278 \pm 0.007$ $9.72 \pm 0.011$ $0.278 \pm 0.007$ $9.72 \pm 0.017$ $0.278 \pm 0.007$ $9.73 \pm 0.11$ $0.278 \pm 0.007$ $1.752 \pm 0.081**$ $1.680 \pm 0.053**$ $58.99 \pm 1.138**$ $58.72 \pm 1.61**$ Ling Absolute Relative $0.200 \pm 0.004$ $0.201 \pm 0.001$ $0.212 \pm 0.006$ $0.200 \pm 0.005$ $0.200 \pm 0.005$ $0.204 \pm 0.007$ $7.11 \pm 0.017$ $0.113 \pm 0.001$ $3.89 \pm 0.16$ $0.110 \pm 0.003$ $3.89 \pm 0.16$ $0.112 \pm 0.001$ $3.83 \pm 0.04$ $0.113 \pm 0.001$ $3.83 \pm 0.04$ $0.113 \pm 0.001$ $3.83 \pm 0.04$ $0.94 \pm 0.04$ Thymus Absolute Relative $0.047 \pm 0.002$ $1.73 \pm 0.11$ $0.114 \pm 0.002$ $1.53 \pm 0.11$ $0.112 \pm 0.004$ $1.53 \pm 0.10$ $0.114 \pm 0.002$ $1.53 \pm 0.10$ $0.112 \pm 0.004$ $0.114 \pm 0.002$ $0.114 \pm 0.002$ $4.54 \pm 0.22$ $0.114 \pm 0.002$ Heart Absolute Relative $0$	Heart	•					
Relative R. Kidney Absolute $4.94 \pm 0.22$ $4.62 \pm 0.08$ $4.77 \pm 0.14$ $4.60 \pm 0.13$ $4.65 \pm 0.16$ $4.47 \pm 0.19$ R. Kidney Absolute $0.286 \pm 0.012$ $0.286 \pm 0.013$ $0.278 \pm 0.007$ $0.282 \pm 0.012$ $0.284 \pm 0.007$ $0.278 \pm 0.006$ Relative $10.42 \pm 0.26$ $9.85 \pm 0.20$ $9.62 \pm 0.28^*$ $10.16 \pm 0.15$ $9.73 \pm 0.11$ $9.72 \pm 0.19$ Liver Absolute $1.376 \pm 0.044$ $1.538 \pm 0.083$ $1.552 \pm 0.045$ $1.526 \pm 0.078$ $1.752 \pm 0.081^{**}$ $1.680 \pm 0.053^{**}$ Relative $50.15 \pm 0.67$ $52.99 \pm 2.14$ $53.63 \pm 0.53$ $54.96 \pm 1.53^*$ $59.39 \pm 1.38^{**}$ $58.72 \pm 1.61^{**}$ Ling Absolute $0.200 \pm 0.004$ $0.212 \pm 0.012$ $0.202 \pm 0.005$ $0.210 \pm 0.005$ $0.204 \pm 0.005$ R. Testis $7.31 \pm 0.27$ $7.29 \pm 0.20$ $7.00 \pm 0.25$ $7.24 \pm 0.27$ $7.20 \pm 0.001$ $0.113 \pm 0.001$ R. Testis $0.113 \pm 0.003$ $0.112 \pm 0.003$ $0.112 \pm 0.003$ $0.112 \pm 0.003$ $0.113 \pm 0.001$ $0.113 \pm 0.001$ Relative $1.73 \pm 0.11$ $1.50 \pm 0.13$ $1.51 \pm 0.11$ $1.35 \pm 0.10$ $1.64 \pm 0.17$ $1.84 \pm 0.08$ FemaleNecropsy body wt $23.3 \pm 0.2$ $23.7 \pm 0.3$ $23.6 \pm 0.3$ $23.8 \pm 0.4$ $24.7 \pm 0.4^*$ $24.0 \pm 0.4$ Absolute $0.112 \pm 0.002$ $0.118 \pm 0.002$ $0.114 \pm 0.002$ $4.12 \pm 0.04$ $0.114 \pm 0.002$ Relative $4.81 \pm 0.07$ $4.98 \pm 0.06$ $4.84 \pm 0.08$ $4.71 \pm 0.07$ $4.55 \pm 0.22$ $4.75$	Absolute	0.136 + 0.009	0.134 + 0.006	0.138 + 0.006	0.128 + 0.007	0.136 + 0.007	0.128 + 0.006
R. Kidney       0.286 $\pm$ 0.012       0.286 $\pm$ 0.013       0.278 $\pm$ 0.007       0.282 $\pm$ 0.007       0.278 $\pm$ 0.006         Relative       10.42 $\pm$ 0.26       9.85 $\pm$ 0.20       9.62 $\pm$ 0.28*       10.16 $\pm$ 0.15       9.73 $\pm$ 0.11       9.72 $\pm$ 0.09         Liver       Absolute       50.15 $\pm$ 0.67       52.99 $\pm$ 2.14       53.63 $\pm$ 0.53       54.96 $\pm$ 1.53*       59.93 $\pm$ 1.38**       58.72 $\pm$ 1.61**         Ling       Absolute       0.200 $\pm$ 0.004       0.212 $\pm$ 0.012       0.202 $\pm$ 0.006       0.200 $\pm$ 0.005       0.210 $\pm$ 0.005       0.204 $\pm$ 0.005         R. Testis       7.31 $\pm$ 0.27       7.29 $\pm$ 0.20       7.00 $\pm$ 0.25       7.24 $\pm$ 0.27       7.20 $\pm$ 0.01       0.113 $\pm$ 0.001         R. Testis       0.113 $\pm$ 0.003       0.113 $\pm$ 0.003       0.112 $\pm$ 0.003       0.112 $\pm$ 0.001       0.113 $\pm$ 0.001         R. Testis       0.047 $\pm$ 0.011       3.92 $\pm$ 0.13       3.89 $\pm$ 0.16       3.88 $\pm$ 0.04       3.94 $\pm$ 0.04         Absolute       0.477 $\pm$ 0.003       0.466 $\pm$ 0.044 $\pm$ 0.03       0.037 $\pm$ 0.10       0.647 $\pm$ 0.004       0.647 $\pm$ 0.003       0.047 $\pm$ 0.003       0.047 $\pm$ 0.004       0.633 $\pm$ 0.002         Relative       1.73 $\pm$ 0.11       1.60 $\pm$ 0.13       1.51 $\pm$ 0.11       1.35 $\pm$ 0.10       1.64 $\pm$ 0.17       1.84 $\pm$ 0.08	Relative	$4.94 \pm 0.22$	$4.62 \pm 0.08$	$4.77 \pm 0.14$	$4.60 \pm 0.13$	$4.65 \pm 0.16$	$4.47 \pm 0.19$
Absolute Relative $0.286 \pm 0.012$ $10.42 \pm 0.26$ $0.286 \pm 0.013$ $9.85 \pm 0.20$ $0.278 \pm 0.007$ $9.62 \pm 0.28* \pm 0.012$ $9.62 \pm 0.28*$ $0.16 \pm 0.15$ $1.16 \pm 0.15$ $0.73 \pm 0.11$ $9.73 \pm 0.11$ $0.278 \pm 0.006$ $9.73 \pm 0.11$ Absolute Relative $1.376 \pm 0.044$ $1.538 \pm 0.083$ $20.99 \pm 2.14$ $5.55 \pm 0.045$ $1.526 \pm 0.078$ $5.9.96 \pm 1.53*$ $1.752 \pm 0.081**$ $1.680 \pm 0.053**$ $59.93 \pm 1.38**$ Lung Absolute $0.200 \pm 0.004$ $0.212 \pm 0.012$ $0.202 \pm 0.002$ $0.005$ $0.202 \pm 0.005$ $0.210 \pm 0.005$ $0.210 \pm 0.007$ $0.210 \pm 0.005$ $7.24 \pm 0.27$ $0.210 \pm 0.005$ $7.24 \pm 0.27$ $0.210 \pm 0.005$ $7.24 \pm 0.27$ $0.210 \pm 0.007$ $7.13 \pm 0.15$ R. Testis Absolute $0.113 \pm 0.003$ $0.113 \pm 0.003$ $0.112 \pm 0.003$ $0.112 \pm 0.011$ $0.112 \pm 0.001$ $3.98 \pm 0.16$ $0.112 \pm 0.001$ $3.89 \pm 0.04$ Absolute Market $0.113 \pm 0.003$ $0.112 \pm 0.11$ $0.033$ $3.92 \pm 0.13$ $0.389 \pm 0.16$ $3.83 \pm 0.04$ $3.38 \pm 0.04$ Absolute Market $0.047 \pm 0.003$ $1.73 \pm 0.11$ $0.046 \pm 0.004$ $1.51 \pm 0.11$ $0.033$ $1.55 \pm 0.10$ $0.047 \pm 0.004$ $1.64 \pm 0.17$ Absolute Market Absolute $0.112 \pm 0.002$ $1.73 \pm 0.11$ $0.114 \pm 0.002$ $1.51 \pm 0.11$ $0.112 \pm 0.004$ $1.55 \pm 0.22$ $0.114 \pm 0.005$ FemaleNecropsy body wt $23.3 \pm 0.2$ $23.7 \pm 0.3$ $23.7 \pm 0.3$ $23.6 \pm 0.3$ $23.6 \pm 0.3$ $23.8 \pm 0.4$ $24.7 \pm 0.4^*$ $24.0 \pm 0.4$ Heart Absolute Relative $0.112 \pm 0.002$ $1.98 \pm 0.002$ $0.114 \pm 0.002$ $4.84 \pm 0.02$	R. Kidney						· · ·
Relative Liver $10.42 \pm 0.26$ $9.85 \pm 0.20$ $9.62 \pm 0.28^*$ $10.16 \pm 0.15$ $9.73 \pm 0.11$ $9.72 \pm 0.19$ Liver Absolute $1.376 \pm 0.044$ $1.538 \pm 0.083$ $1.552 \pm 0.045$ $1.526 \pm 0.078$ $1.752 \pm 0.081^{***}$ $1.680 \pm 0.053^{***}$ Relative Lung Absolute $0.200 \pm 0.004$ $0.212 \pm 0.012$ $0.202 \pm 0.006$ $0.200 \pm 0.005$ $0.210 \pm 0.005$ $0.210 \pm 0.005$ $0.204 \pm 0.005$ Relative Relative $7.31 \pm 0.27$ $7.29 \pm 0.20$ $7.00 \pm 0.25$ $7.24 \pm 0.27$ $7.20 \pm 0.01$ $0.113 \pm 0.003$ Relative Relative $0.113 \pm 0.003$ $0.112 \pm 0.003$ $0.112 \pm 0.003$ $0.112 \pm 0.001$ $0.113 \pm 0.001$ Absolute Relative $0.113 \pm 0.003$ $0.112 \pm 0.003$ $0.107 \pm 0.003$ $0.047 \pm 0.004$ $0.94 \pm 0.004$ Thymus Absolute $0.047 \pm 0.003$ $0.046 \pm 0.004$ $0.044 \pm 0.003$ $0.037 \pm 0.003$ $0.047 \pm 0.004$ $0.053 \pm 0.002$ Relative $1.73 \pm 0.11$ $1.60 \pm 0.13$ $1.51 \pm 0.11$ $1.35 \pm 0.10$ $1.64 \pm 0.17$ $1.84 \pm 0.08$ FemaleNecropsy body wt $23.3 \pm 0.2$ $23.7 \pm 0.3$ $23.6 \pm 0.3$ $23.8 \pm 0.4$ $24.7 \pm 0.4*$ $24.0 \pm 0.4$ Heart Absolute Relative $0.112 \pm 0.002$ $0.118 \pm 0.002$ $0.114 \pm 0.002$ $0.112 \pm 0.002$ $0.112 \pm 0.004$ $0.114 \pm 0.005$ Relative $8.33 \pm 0.07$ $4.98 \pm 0.08$ $4.84 \pm 0.08$ $4.71 \pm 0.07$ $4.55 \pm 0.22$ $4.75 \pm 0.16$ Kidney Absolute Relative $0.194 \pm 0.002$ $0.196 \pm 0.002$ $0.1$	Absolute	$0.286 \pm 0.012$	$0.286 \pm 0.013$	$0.278 \pm 0.007$	$0.282 \pm 0.012$	$0.284 \pm 0.007$	0.278 ± 0.006
Liver Absolute 1.376 $\pm$ 0.044 1.538 $\pm$ 0.083 1.552 $\pm$ 0.045 1.526 $\pm$ 0.078 1.752 $\pm$ 0.081** 1.680 $\pm$ 0.053** Relative 2.015 $\pm$ 0.67 52.99 $\pm$ 2.14 53.63 $\pm$ 0.53 54.96 $\pm$ 1.53* 59.93 $\pm$ 1.38* 58.72 $\pm$ 1.61** Lung Absolute 0.200 $\pm$ 0.004 0.212 $\pm$ 0.012 0.202 $\pm$ 0.006 0.200 $\pm$ 0.005 0.210 $\pm$ 0.005 0.204 $\pm$ 0.005 Relative 7.31 $\pm$ 0.27 7.29 $\pm$ 0.20 7.00 $\pm$ 0.25 7.24 $\pm$ 0.27 7.20 $\pm$ 0.07 7.13 $\pm$ 0.15 Absolute 0.113 $\pm$ 0.003 0.113 $\pm$ 0.003 0.112 $\pm$ 0.003 0.110 $\pm$ 0.003 0.112 $\pm$ 0.001 0.113 $\pm$ 0.001 Relative 4.12 $\pm$ 0.11 3.92 $\pm$ 0.13 3.89 $\pm$ 0.16 3.98 $\pm$ 0.16 3.83 $\pm$ 0.04 3.94 $\pm$ 0.04 Thymus Absolute 0.047 $\pm$ 0.003 0.046 $\pm$ 0.004 0.044 $\pm$ 0.003 0.37 $\pm$ 0.003 0.047 $\pm$ 0.004 0.53 $\pm$ 0.002 Relative 1.73 $\pm$ 0.11 1.60 $\pm$ 0.13 1.51 $\pm$ 0.11 1.35 $\pm$ 0.10 1.64 $\pm$ 0.17 1.84 $\pm$ 0.08 Female Necropsy body wt 23.3 $\pm$ 0.2 23.7 $\pm$ 0.3 23.6 $\pm$ 0.3 23.8 $\pm$ 0.4 24.7 $\pm$ 0.4* 24.0 $\pm$ 0.4 Heart Absolute 0.112 $\pm$ 0.002 0.118 $\pm$ 0.002 0.114 $\pm$ 0.002 0.112 $\pm$ 0.004 0.114 $\pm$ 0.005 Relative 4.81 $\pm$ 0.07 4.98 $\pm$ 0.08 4.84 $\pm$ 0.08 4.71 $\pm$ 0.07 4.55 $\pm$ 0.22 4.75 $\pm$ 0.16 R. Kidney Absolute 0.194 $\pm$ 0.002 0.196 $\pm$ 0.002 0.198 $\pm$ 0.006 0.192 $\pm$ 0.004 0.196 $\pm$ 0.022 0.202 $\pm$ 0.007 Relative 1.146 $\pm$ 0.020 1.256 $\pm$ 0.035* 1.338 $\pm$ 0.037** 1.364 $\pm$ 0.047** 1.442 $\pm$ 0.020** 1.410 $\pm$ 0.044** Relative 49.24 $\pm$ 0.96 53.00 $\pm$ 1.40* 56.77 $\pm$ 1.15** 57.28 $\pm$ 1.56** 58.44 $\pm$ 1.18** 58.70 $\pm$ 0.99* Liver Absolute 0.198 $\pm$ 0.020 0.190 $\pm$ 0.003 0.196 $\pm$ 0.007 0.200 $\pm$ 0.008 0.190 $\pm$ 0.004 Relative 8.50 $\pm$ 0.30 8.02 $\pm$ 0.08 8.31 $\pm$ 0.27 $\pm$ 0.40 8.10 $\pm$ 0.44 $\pm$ 0.202** 1.410 $\pm$ 0.044** Relative 49.24 $\pm$ 0.96 53.00 $\pm$ 1.40* 56.77 $\pm$ 1.15** 57.28 $\pm$ 1.56** 58.44 $\pm$ 1.18** 58.70 $\pm$ 0.99* Lung Absolute 0.198 $\pm$ 0.027 0.190 $\pm$ 0.003 0.196 $\pm$ 0.007 0.200 $\pm$ 0.008 0.190 $\pm$ 0.004 Relative 8.50 $\pm$ 0.30 8.02 $\pm$ 0.08 8.31 $\pm$ 0.27 8.42 $\pm$ 0.40 8.10 $\pm$ 0.34 7.93 $\pm$ 0.22 Thymus Absolute 0.065 $\pm$ 0.020 0.064 $\pm$ 0.020 0.072 $\pm$ 0.001 0.064 $\pm$ 0	Relative	$10.42 \pm 0.26$	$9.85 \pm 0.20$	9.62 ± 0.28*	$10.16 \pm 0.15$	9.73 ± 0.11	9.72 ± 0.19
Absolute Relative $1.376 \pm 0.044$ $1.538 \pm 0.083$ $1.552 \pm 0.045$ $5.250 \pm 0.078$ $1.752 \pm 0.081^{**}$ $1.680 \pm 0.053^{**}$ Ling Absolute $0.200 \pm 0.004$ $0.212 \pm 0.012$ $0.202 \pm 0.006$ $0.200 \pm 0.005$ $0.210 \pm 0.005$ $0.210 \pm 0.005$ $0.204 \pm 0.005$ Relative $7.31 \pm 0.27$ $7.29 \pm 0.20$ $7.00 \pm 0.25$ $7.24 \pm 0.27$ $7.20 \pm 0.007$ $7.13 \pm 0.15$ Absolute $0.113 \pm 0.003$ $0.112 \pm 0.003$ Relative $4.12 \pm 0.11$ $3.92 \pm 0.13$ $3.89 \pm 0.16$ $3.98 \pm 0.16$ $3.83 \pm 0.04$ $3.94 \pm 0.04$ Thymus $0.47 \pm 0.003$ $0.046 \pm 0.004$ $0.044 \pm 0.003$ $0.037 \pm 0.003$ $0.047 \pm 0.004$ $0.053 \pm 0.002$ Relative $1.73 \pm 0.11$ $1.60 \pm 0.13$ $1.51 \pm 0.11$ $1.35 \pm 0.10$ $1.64 \pm 0.17$ $1.84 \pm 0.08$ FemaleNecropsy body wt $23.3 \pm 0.2$ $23.7 \pm 0.3$ $23.6 \pm 0.3$ $23.8 \pm 0.4$ $24.7 \pm 0.4^*$ $24.0 \pm 0.4$ Heart Absolute $0.112 \pm 0.002$ $0.118 \pm 0.002$ $0.114 \pm 0.002$ $0.112 \pm 0.004$ $0.114 \pm 0.005$ Riditive $4.81 \pm 0.07$ $4.98 \pm 0.08$ $4.84 \pm 0.08$ $4.71 \pm 0.07$ $4.55 \pm 0.22$ $4.75 \pm 0.16$ R. Kidney Absolute $0.194 \pm 0.002$ $0.196 \pm 0.002$ $0.198 \pm 0.006$ $0.192 \pm 0.004$ $0.196 \pm 0.002$ $0.202 \pm 0.007$ Relative $1.466 \pm 0.020$ $1.256 \pm 0.035^*$ $1.338 \pm 0.037^{**}$ $1.364 \pm 0.047^{*$	Liver						
Relative $50.15 \pm 0.67$ $52.99 \pm 2.14$ $53.63 \pm 0.53$ $54.96 \pm 1.53^*$ $59.93 \pm 1.38^{**}$ $58.72 \pm 1.61^{**}$ LungAbsolute $0.200 \pm 0.004$ $0.212 \pm 0.012$ $0.202 \pm 0.006$ $0.200 \pm 0.005$ $0.210 \pm 0.005$ $0.210 \pm 0.005$ $0.204 \pm 0.005$ Relative $7.31 \pm 0.27$ $7.29 \pm 0.20$ $7.00 \pm 0.25$ $7.24 \pm 0.27$ $7.20 \pm 0.07$ $7.13 \pm 0.15$ R. Testis $0.113 \pm 0.003$ $0.112 \pm 0.003$ $0.112 \pm 0.003$ $0.110 \pm 0.003$ $0.112 \pm 0.001$ $0.113 \pm 0.001$ Relative $4.12 \pm 0.11$ $3.92 \pm 0.13$ $3.89 \pm 0.16$ $3.98 \pm 0.16$ $3.83 \pm 0.04$ $3.94 \pm 0.04$ Thymus $0.047 \pm 0.003$ $0.046 \pm 0.004$ $0.044 \pm 0.003$ $0.037 \pm 0.003$ $0.047 \pm 0.004$ $0.053 \pm 0.002$ Relative $1.73 \pm 0.11$ $1.60 \pm 0.13$ $1.51 \pm 0.11$ $1.35 \pm 0.10$ $1.64 \pm 0.17$ $1.84 \pm 0.08$ FemaleNecropsy body wt $23.3 \pm 0.2$ $23.7 \pm 0.3$ $23.6 \pm 0.3$ $23.8 \pm 0.4$ $24.7 \pm 0.4^*$ $24.0 \pm 0.4$ Heart $Absolute$ $0.112 \pm 0.002$ $0.118 \pm 0.002$ $0.114 \pm 0.002$ $0.112 \pm 0.004$ $0.114 \pm 0.005$ R. Kidney $A.81 \pm 0.07$ $4.98 \pm 0.08$ $4.84 \pm 0.08$ $4.71 \pm 0.07$ $4.55 \pm 0.22$ $4.75 \pm 0.16$ R. Kidney $A.19 \pm 0.002$ $0.196 \pm 0.002$ $0.198 \pm 0.006$ $0.192 \pm 0.004$ $0.196 \pm 0.002$ $0.202 \pm 0.007$ R. Kidney $A.33 \pm 0.07$ $8.27 \pm 0.12$ $8.40 \pm 0.17$ $8.07 \pm 0.11$ $7.95 \pm 0.19$ $8.4$	Absolute	1.376 ± 0.044	$1.538 \pm 0.083$	$1.552 \pm 0.045$	$1.526 \pm 0.078$	1.752 ± 0.081**	1.680 ± 0.053**
Lung Absolute 0.200 $\pm$ 0.004 0.212 $\pm$ 0.012 7.29 $\pm$ 0.20 Relative 7.31 $\pm$ 0.27 7.29 $\pm$ 0.20 R. Testis Absolute 0.113 $\pm$ 0.003 0.113 $\pm$ 0.003 0.112 $\pm$ 0.003 0.110 $\pm$ 0.003 0.112 $\pm$ 0.001 0.113 $\pm$ 0.001 Relative 1.12 $\pm$ 0.11 3.92 $\pm$ 0.13 3.89 $\pm$ 0.16 3.98 $\pm$ 0.16 3.83 $\pm$ 0.04 3.94 $\pm$ 0.04 Thymus 0.047 $\pm$ 0.003 0.046 $\pm$ 0.004 0.044 $\pm$ 0.003 0.037 $\pm$ 0.003 0.047 $\pm$ 0.004 0.053 $\pm$ 0.002 Relative 1.73 $\pm$ 0.11 1.60 $\pm$ 0.13 1.51 $\pm$ 0.11 1.35 $\pm$ 0.10 1.64 $\pm$ 0.17 1.84 $\pm$ 0.08 Female Necropsy body wt 2.3.3 $\pm$ 0.2 2.3.7 $\pm$ 0.3 2.3.6 $\pm$ 0.3 2.3.8 $\pm$ 0.4 24.7 $\pm$ 0.4* 24.0 $\pm$ 0.4 Heart Absolute 0.112 $\pm$ 0.002 0.118 $\pm$ 0.002 0.114 $\pm$ 0.002 0.112 $\pm$ 0.004 0.196 $\pm$ 0.004 0.114 $\pm$ 0.005 Relative 4.81 $\pm$ 0.07 4.98 $\pm$ 0.08 4.84 $\pm$ 0.08 4.71 $\pm$ 0.004 0.196 $\pm$ 0.022 $\pm$ 0.007 Relative 8.33 $\pm$ 0.07 8.27 $\pm$ 0.12 8.40 $\pm$ 0.17 8.07 $\pm$ 0.11 7.95 $\pm$ 0.19 8.42 $\pm$ 0.20 Relative 1.146 $\pm$ 0.020 1.256 $\pm$ 0.035* 1.338 $\pm$ 0.04 0.192 $\pm$ 0.004 0.196 $\pm$ 0.002 0.202 $\pm$ 0.007 Relative 1.146 $\pm$ 0.020 1.256 $\pm$ 0.035* 1.338 $\pm$ 0.037** 1.364 $\pm$ 0.047*** 1.442 $\pm$ 0.020** 1.410 $\pm$ 0.004 Relative 4.9.24 $\pm$ 0.96 53.00 $\pm$ 1.40* 56.77 $\pm$ 1.15** 57.28 $\pm$ 1.56** 58.44 $\pm$ 1.18** 58.70 $\pm$ 0.90* Lung Absolute 0.198 $\pm$ 0.007 0.190 $\pm$ 0.003 0.196 $\pm$ 0.007 0.200 $\pm$ 0.007 0.200 $\pm$ 0.008 0.190 $\pm$ 0.004 Relative 1.146 $\pm$ 0.027 0.190 $\pm$ 0.003 0.196 $\pm$ 0.007 0.200 $\pm$ 0.008 0.190 $\pm$ 0.004 Relative 2.50 $\pm$ 0.19 $\pm$ 0.002 0.196 $\pm$ 0.007 0.200 $\pm$ 0.007 0.200 $\pm$ 0.008 0.190 $\pm$ 0.004 Relative 2.50 $\pm$ 0.19 $\pm$ 0.007 0.190 $\pm$ 0.003 0.196 $\pm$ 0.007 0.200 $\pm$ 0.008 0.190 $\pm$ 0.004 Relative 2.50 $\pm$ 0.30 8.02 $\pm$ 0.08 8.31 $\pm$ 0.22 8.42 $\pm$ 0.40 8.10 $\pm$ 0.34 7.93 $\pm$ 0.22 Thymus Absolute 0.198 $\pm$ 0.007 0.190 $\pm$ 0.003 0.196 $\pm$ 0.007 0.200 $\pm$ 0.008 0.190 $\pm$ 0.004 Relative 2.80 $\pm$ 0.11 2.69 $\pm$ 0.07 3.06 $\pm$ 0.07 2.68 $\pm$ 0.13 2.57 $\pm$ 0.13 2.83 $\pm$ 0.03	Relative	50.15 ± 0.67	52.99 ± 2.14	53.63 ± 0.53	54.96 ± 1.53*	59.93 ± 1.38**	58.72 ± 1.61**
Absolute Relative $0.200 \pm 0.004$ $7.31 \pm 0.27$ $0.212 \pm 0.012$ $7.29 \pm 0.20$ $0.202 \pm 0.005$ $7.00 \pm 0.25$ $0.200 \pm 0.005$ $7.24 \pm 0.27$ $0.005$ $7.20 \pm 0.07$ $0.204 \pm 0.005$ $7.24 \pm 0.27$ $0.005$ $7.20 \pm 0.07$ $0.204 \pm 0.005$ $7.24 \pm 0.27$ $0.200 \pm 0.005$ $7.24 \pm 0.27$ $0.007$ $7.20 \pm 0.07$ $0.113 \pm 0.003$ $7.13 \pm 0.15$ Absolute Relative $0.113 \pm 0.003$ $1.12 \pm 0.11$ $0.112 \pm 0.003$ $3.92 \pm 0.13$ $0.112 \pm 0.003$ $3.98 \pm 0.16$ $0.112 \pm 0.001$ $3.98 \pm 0.16$ $0.112 \pm 0.001$ $3.83 \pm 0.04$ $0.113 \pm 0.001$ $3.94 \pm 0.04$ Thymus Absolute Relative $0.047 \pm 0.003$ $1.73 \pm 0.11$ $0.046 \pm 0.004$ $1.60 \pm 0.13$ $0.037 \pm 0.003$ $1.51 \pm 0.11$ $0.047 \pm 0.004$ $1.35 \pm 0.10$ $0.047 \pm 0.004$ $1.64 \pm 0.17$ $0.053 \pm 0.002$ $1.64 \pm 0.17$ FemaleNecropsy body wt Absolute Absolute $0.112 \pm 0.002$ $0.118 \pm 0.002$ $0.118 \pm 0.002$ $0.114 \pm 0.002$ $0.114 \pm 0.002$ $0.112 \pm 0.004$ $0.112 \pm 0.004$ $0.114 \pm 0.005$ $4.75 \pm 0.22$ Absolute Absolute Absolute $0.194 \pm 0.002$ $0.196 \pm 0.002$ $0.196 \pm 0.002$ $0.114 \pm 0.002$ $0.198 \pm 0.004$ $0.196 \pm 0.002$ $0.192 \pm 0.004$ $0.114 \pm 0.002$ $0.196 \pm 0.002$ $0.192 \pm 0.004$ $0.192 \pm 0.004$ $0.114 \pm 0.005$ $4.75 \pm 0.12$ Riditive Relative Liver Absolute Absolute Relative $0.196 \pm 0.002$ $0.198 \pm 0.003$ $0.192 \pm 0.004$ $0.196 \pm 0.002$ $0.196 \pm 0.007$ $0.200 \pm 0.004$ $0.196 \pm 0.002$ $0.202 \pm 0.007$ $0.198 \pm 0.007$ Absolute Relative<	Lung						
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R. Testis Absolute0.113 $\pm 0.003$ 0.113 $\pm 0.003$ 0.112 $\pm 0.003$ 0.110 $\pm 0.003$ 0.112 $\pm 0.001$ 0.113 $\pm 0.001$ Relative4.12 $\pm 0.11$ 3.92 $\pm 0.13$ 3.89 $\pm 0.16$ 3.98 $\pm 0.16$ 3.88 $\pm 0.04$ 3.94 $\pm 0.04$ Thymus Absolute0.047 $\pm 0.003$ 0.046 $\pm 0.004$ 0.044 $\pm 0.003$ 0.037 $\pm 0.003$ 0.047 $\pm 0.004$ 0.053 $\pm 0.002$ Relative1.73 $\pm 0.11$ 1.60 $\pm 0.13$ 1.51 $\pm 0.11$ 1.35 $\pm 0.10$ 1.64 $\pm 0.17$ 1.84 $\pm 0.08$ FemaleNecropsy body wt23.3 $\pm 0.2$ 23.7 $\pm 0.3$ 23.6 $\pm 0.3$ 23.8 $\pm 0.4$ 24.7 $\pm 0.4^*$ 24.0 $\pm 0.4$ Heart AbsoluteAbsolute0.112 $\pm 0.002$ 0.118 $\pm 0.002$ 0.114 $\pm 0.002$ 0.112 $\pm 0.002$ 0.114 $\pm 0.005$ Relative4.81 $\pm 0.07$ 4.98 $\pm 0.08$ 4.84 $\pm 0.08$ 4.71 $\pm 0.07$ 4.55 $\pm 0.22$ 4.75 $\pm 0.16$ R. Kidney Absolute0.194 $\pm 0.002$ 0.196 $\pm 0.002$ 0.198 $\pm 0.006$ 0.192 $\pm 0.004$ 0.196 $\pm 0.002$ 0.202 $\pm 0.007$ Relative8.33 $\pm 0.07$ 8.27 $\pm 0.12$ 8.40 $\pm 0.17$ 8.07 $\pm 0.11$ 7.95 $\pm 0.19$ 8.42 $\pm 0.26$ Liver Absolute1.146 $\pm 0.020$ 1.256 $\pm 0.035^*$ 1.338 $\pm 0.037^{**}$ 1.364 $\pm 0.047^{**}$ 1.410 $\pm 0.044^{**}$ Relative4.90 $\pm 0.007$ 0.190 $\pm 0.003$ 0.196 $\pm 0.007$ 0.200 $\pm 0.007$ 0.200 $\pm 0.008$ 0.190 $\pm 0.004$ Relative0.198 $\pm 0.007$ 0.190 $\pm 0.003$ 0.196 $\pm 0.007$ 0.200 $\pm 0.00$	Relative	$7.31 \pm 0.27$	$7.29 \pm 0.20$	$7.00 \pm 0.25$	$7.24 \pm 0.27$	$7.20 \pm 0.07$	$7.13 \pm 0.15$
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Thymus Absolute 0.047 $\pm$ 0.003 0.046 $\pm$ 0.004 0.044 $\pm$ 0.003 0.037 $\pm$ 0.003 0.047 $\pm$ 0.004 0.053 $\pm$ 0.002 Relative 1.73 $\pm$ 0.11 1.60 $\pm$ 0.13 1.51 $\pm$ 0.11 1.35 $\pm$ 0.10 1.64 $\pm$ 0.17 1.84 $\pm$ 0.08 Female Necropsy body wt 2.3.3 $\pm$ 0.2 2.3.7 $\pm$ 0.3 23.6 $\pm$ 0.3 23.8 $\pm$ 0.4 24.7 $\pm$ 0.4* 24.0 $\pm$ 0.4 Heart Absolute 0.112 $\pm$ 0.002 0.118 $\pm$ 0.002 0.114 $\pm$ 0.002 0.112 $\pm$ 0.002 0.112 $\pm$ 0.004 0.114 $\pm$ 0.005 Relative 4.81 $\pm$ 0.07 4.98 $\pm$ 0.08 4.84 $\pm$ 0.08 4.71 $\pm$ 0.07 4.55 $\pm$ 0.22 4.75 $\pm$ 0.16 R. Kidney Absolute 0.194 $\pm$ 0.002 0.196 $\pm$ 0.002 0.198 $\pm$ 0.006 0.192 $\pm$ 0.004 0.196 $\pm$ 0.002 0.202 $\pm$ 0.007 Relative 1.146 $\pm$ 0.020 1.256 $\pm$ 0.035* 1.338 $\pm$ 0.037** 1.364 $\pm$ 0.047** 1.442 $\pm$ 0.020** 1.410 $\pm$ 0.044** Relative 4.9.24 $\pm$ 0.96 53.00 $\pm$ 1.40* 56.77 $\pm$ 1.15** 57.28 $\pm$ 1.56** 58.44 $\pm$ 1.18** 58.70 $\pm$ 0.90** Lung Absolute 0.198 $\pm$ 0.007 0.190 $\pm$ 0.003 0.196 $\pm$ 0.007 0.200 $\pm$ 0.008 0.190 $\pm$ 0.004 7.93 $\pm$ 0.202 $\pm$ 0.004 Absolute 0.198 $\pm$ 0.007 0.190 $\pm$ 0.003 0.196 $\pm$ 0.007 0.200 $\pm$ 0.008 0.190 $\pm$ 0.004 Relative 8.50 $\pm$ 0.30 8.02 $\pm$ 0.08 8.31 $\pm$ 0.22 8.42 $\pm$ 0.40 8.10 $\pm$ 0.34 7.93 $\pm$ 0.22 Thymus Absolute 0.65 $\pm$ 0.002 0.664 $\pm$ 0.002 0.72 $\pm$ 0.001 0.664 $\pm$ 0.004 0.633 $\pm$ 0.003 0.688 $\pm$ 0.003 Relative 2.80 $\pm$ 0.11 2.69 $\pm$ 0.07 3.06 $\pm$ 0.07 2.68 $\pm$ 0.13 2.57 $\pm$ 0.13 2.83 $\pm$ 0.13	Relative	$4.12 \pm 0.11$	$3.92 \pm 0.13$	$3.89 \pm 0.16$	$3.98 \pm 0.16$	$3.83 \pm 0.04$	$3.94 \pm 0.04$
Absolute Relative $0.047 \pm 0.003$ $0.046 \pm 0.004$ $0.044 \pm 0.003$ $0.037 \pm 0.003$ $0.047 \pm 0.004$ $0.053 \pm 0.002$ FemaleNecropsy body wt $23.3 \pm 0.2$ $23.7 \pm 0.3$ $23.6 \pm 0.3$ $23.8 \pm 0.4$ $24.7 \pm 0.4^*$ $24.0 \pm 0.4$ Heart Absolute $0.112 \pm 0.002$ $0.118 \pm 0.002$ $0.114 \pm 0.002$ $0.112 \pm 0.002$ $0.112 \pm 0.004$ $0.114 \pm 0.005$ Relative $4.81 \pm 0.07$ $4.98 \pm 0.08$ $4.84 \pm 0.08$ $4.71 \pm 0.07$ $4.55 \pm 0.22$ $4.75 \pm 0.16$ R. Kidney Absolute $0.194 \pm 0.002$ $0.196 \pm 0.002$ $0.198 \pm 0.006$ $0.192 \pm 0.004$ $0.196 \pm 0.002$ $0.202 \pm 0.007$ Relative $8.33 \pm 0.07$ $8.27 \pm 0.12$ $8.40 \pm 0.17$ $8.07 \pm 0.11$ $7.95 \pm 0.19$ $8.42 \pm 0.26$ Liver Absolute $1.146 \pm 0.020$ $1.256 \pm 0.035*$ $1.338 \pm 0.037**$ $1.364 \pm 0.047**$ $1.442 \pm 0.020**$ $1.410 \pm 0.044**$ Absolute $0.198 \pm 0.007$ $0.190 \pm 0.003$ $0.196 \pm 0.007$ $0.200 \pm 0.007$ $0.200 \pm 0.008$ $0.190 \pm 0.004$ Lung Absolute $0.198 \pm 0.007$ $0.190 \pm 0.003$ $0.196 \pm 0.007$ $0.200 \pm 0.008$ $0.190 \pm 0.004$ Absolute $0.065 \pm 0.002$ $0.064 \pm 0.002$ $0.072 \pm 0.001$ $0.064 \pm 0.004$ $0.063 \pm 0.003$ $0.068 \pm 0.003$ Relative $2.80 \pm 0.11$ $2.69 \pm 0.07$ $3.06 \pm 0.07$ $2.68 \pm 0.13$ $2.57 \pm 0.13$ $2.83 \pm 0.13$	Thymus	0.045 0.000	0.046 + 0.004	0.044 + 0.000	0.007 0.000	0.047 + 0.004	0.050 1.0.000
Relative $1.73 \pm 0.11$ $1.60 \pm 0.13$ $1.31 \pm 0.11$ $1.33 \pm 0.10$ $1.64 \pm 0.17$ $1.64 \pm 0.07$ FemaleNecropsy body wt $23.3 \pm 0.2$ $23.7 \pm 0.3$ $23.6 \pm 0.3$ $23.8 \pm 0.4$ $24.7 \pm 0.4^*$ $24.0 \pm 0.4$ Heart Absolute $0.112 \pm 0.002$ $0.118 \pm 0.002$ $0.114 \pm 0.002$ $0.112 \pm 0.002$ $0.112 \pm 0.004$ $0.114 \pm 0.005$ Relative $4.81 \pm 0.07$ $4.98 \pm 0.08$ $4.84 \pm 0.08$ $4.71 \pm 0.07$ $4.55 \pm 0.22$ $4.75 \pm 0.16$ R. Kidney Absolute $0.194 \pm 0.002$ $0.196 \pm 0.002$ $0.198 \pm 0.006$ $0.192 \pm 0.004$ $0.196 \pm 0.002$ $0.202 \pm 0.007$ Relative $8.33 \pm 0.07$ $8.27 \pm 0.12$ $8.40 \pm 0.17$ $8.07 \pm 0.11$ $7.95 \pm 0.19$ $8.42 \pm 0.26$ Liver Absolute $1.146 \pm 0.020$ $1.256 \pm 0.035^*$ $1.338 \pm 0.037^{**}$ $1.364 \pm 0.047^{**}$ $1.442 \pm 0.020^{**}$ $1.410 \pm 0.044^{**}$ Relative $49.24 \pm 0.96$ $53.00 \pm 1.40^*$ $56.77 \pm 1.15^{**}$ $57.28 \pm 1.56^{**}$ $58.44 \pm 1.18^{**}$ $58.70 \pm 0.90^{**}$ Lung Absolute $0.198 \pm 0.007$ $0.190 \pm 0.003$ $0.196 \pm 0.007$ $0.200 \pm 0.008$ $0.190 \pm 0.004$ Relative $8.50 \pm 0.30$ $8.02 \pm 0.08$ $8.31 \pm 0.22$ $8.42 \pm 0.40$ $8.10 \pm 0.34$ $7.93 \pm 0.22$ Thymus Absolute $0.065 \pm 0.002$ $0.064 \pm 0.002$ $0.072 \pm 0.001$ $0.064 \pm 0.003$ $0.068 \pm 0.003$ Relative $2.80 \pm 0.11$ $2.69 \pm 0.07$ $3.06 \pm 0.07$ $2.68 \pm 0.13$ $2.57 \pm 0.13$ $2.83 \pm 0.13$ </td <td>Absolute</td> <td>$0.047 \pm 0.003$</td> <td>$0.046 \pm 0.004$</td> <td>$0.044 \pm 0.003$</td> <td>$0.037 \pm 0.003$</td> <td>$0.04/\pm0.004$</td> <td>$0.053 \pm 0.002$</td>	Absolute	$0.047 \pm 0.003$	$0.046 \pm 0.004$	$0.044 \pm 0.003$	$0.037 \pm 0.003$	$0.04/\pm0.004$	$0.053 \pm 0.002$
FemaleNecropsy body wt $23.3 \pm 0.2$ $23.7 \pm 0.3$ $23.6 \pm 0.3$ $23.8 \pm 0.4$ $24.7 \pm 0.4^*$ $24.0 \pm 0.4$ Heart Absolute $0.112 \pm 0.002$ $0.118 \pm 0.002$ $0.114 \pm 0.002$ $0.112 \pm 0.002$ $0.112 \pm 0.002$ $0.114 \pm 0.005$ R. Kidney Absolute $4.81 \pm 0.07$ $4.98 \pm 0.08$ $4.84 \pm 0.08$ $4.71 \pm 0.07$ $4.55 \pm 0.22$ $4.75 \pm 0.16$ R. Kidney Absolute $0.194 \pm 0.002$ $0.196 \pm 0.002$ $0.198 \pm 0.006$ $0.192 \pm 0.004$ $0.196 \pm 0.002$ $0.202 \pm 0.007$ Relative $8.33 \pm 0.07$ $8.27 \pm 0.12$ $8.40 \pm 0.17$ $8.07 \pm 0.11$ $7.95 \pm 0.19$ $8.42 \pm 0.26$ Liver Absolute $1.146 \pm 0.020$ $1.256 \pm 0.035^*$ $1.338 \pm 0.037^{**}$ $1.364 \pm 0.047^{**}$ $1.442 \pm 0.020^{**}$ $1.410 \pm 0.044^{**}$ Relative $4.9.24 \pm 0.96$ $53.00 \pm 1.40^*$ $56.77 \pm 1.15^{**}$ $57.28 \pm 1.56^{**}$ $58.44 \pm 1.18^{**}$ $58.70 \pm 0.90^{**}$ Lung Absolute $0.198 \pm 0.007$ $0.190 \pm 0.003$ $0.196 \pm 0.007$ $0.200 \pm 0.007$ $0.200 \pm 0.008$ $0.190 \pm 0.004$ Relative $8.50 \pm 0.30$ $8.02 \pm 0.08$ $8.31 \pm 0.22$ $8.42 \pm 0.40$ $8.10 \pm 0.34$ $7.93 \pm 0.22$ Thymus Absolute $0.065 \pm 0.002$ $0.064 \pm 0.002$ $0.072 \pm 0.001$ $0.064 \pm 0.004$ $0.063 \pm 0.003$ $0.068 \pm 0.003$ Relative $2.80 \pm 0.11$ $2.69 \pm 0.07$ $3.06 \pm 0.07$ $2.68 \pm 0.13$ $2.57 \pm 0.13$ $2.83 \pm 0.13$	Relative	$1.73 \pm 0.11$	$1.60 \pm 0.13$	$1.51 \pm 0.11$	$1.35 \pm 0.10$	1.04 ± 0.17	$1.64 \pm 0.06$
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Absolute Relative $4.81 \pm 0.07$ $4.98 \pm 0.08$ $4.84 \pm 0.08$ $4.71 \pm 0.07$ $4.55 \pm 0.22$ $4.75 \pm 0.16$ R. Kidney Absolute $0.194 \pm 0.002$ $0.196 \pm 0.002$ $0.198 \pm 0.006$ $0.192 \pm 0.004$ $0.196 \pm 0.002$ $0.202 \pm 0.007$ Relative $8.33 \pm 0.07$ $8.27 \pm 0.12$ $8.40 \pm 0.17$ $8.07 \pm 0.11$ $7.95 \pm 0.19$ $8.42 \pm 0.26$ Liver Absolute $1.146 \pm 0.020$ $1.256 \pm 0.035^*$ $1.338 \pm 0.037^{**}$ $1.364 \pm 0.047^{**}$ $1.442 \pm 0.020^{**}$ $1.410 \pm 0.044^{**}$ Relative $49.24 \pm 0.96$ $53.00 \pm 1.40^*$ $56.77 \pm 1.15^{**}$ $57.28 \pm 1.56^{**}$ $58.44 \pm 1.18^{**}$ $58.70 \pm 0.90^{**}$ Lung Absolute $0.198 \pm 0.007$ $0.190 \pm 0.003$ $0.196 \pm 0.007$ $0.200 \pm 0.007$ $0.200 \pm 0.008$ $0.190 \pm 0.004$ Relative $8.50 \pm 0.30$ $8.02 \pm 0.08$ $8.31 \pm 0.22$ $8.42 \pm 0.40$ $8.10 \pm 0.34$ $7.93 \pm 0.22$ Thymus Absolute $0.065 \pm 0.002$ $0.064 \pm 0.002$ $0.072 \pm 0.001$ $0.064 \pm 0.004$ $0.063 \pm 0.003$ $0.068 \pm 0.003$ Relative $2.80 \pm 0.11$ $2.69 \pm 0.07$ $3.06 \pm 0.07$ $2.68 \pm 0.13$ $2.57 \pm 0.13$ $2.83 \pm 0.13$	Absolute	$0.112 \pm 0.002$	$0.118 \pm 0.002$	0.114 + 0.002	0.112 + 0.002	0.112 + 0.004	0.114 + 0.005
R. Kidney Absolute0.194 $\pm 0.002$ 0.196 $\pm 0.002$ 0.198 $\pm 0.006$ 0.192 $\pm 0.004$ 0.196 $\pm 0.002$ 0.202 $\pm 0.007$ Relative8.33 $\pm 0.07$ 8.27 $\pm 0.12$ 8.40 $\pm 0.17$ 8.07 $\pm 0.11$ 7.95 $\pm 0.19$ 8.42 $\pm 0.26$ Liver Absolute1.146 $\pm 0.020$ 1.256 $\pm 0.035^*$ 1.338 $\pm 0.037^{**}$ 1.364 $\pm 0.047^{**}$ 1.442 $\pm 0.020^{**}$ 1.410 $\pm 0.044^{**}$ Relative49.24 $\pm 0.96$ 53.00 $\pm 1.40^*$ 56.77 $\pm 1.15^{**}$ 57.28 $\pm 1.56^{**}$ 58.44 $\pm 1.18^{**}$ 58.70 $\pm 0.90^{**}$ Lung Absolute0.198 $\pm 0.007$ 0.190 $\pm 0.003$ 0.196 $\pm 0.007$ 0.200 $\pm 0.007$ 0.200 $\pm 0.008$ 0.190 $\pm 0.004$ Relative8.50 $\pm 0.30$ 8.02 $\pm 0.08$ 8.31 $\pm 0.22$ 8.42 $\pm 0.40$ 8.10 $\pm 0.34$ 7.93 $\pm 0.22$ Thymus Absolute0.065 $\pm 0.002$ 0.064 $\pm 0.002$ 0.072 $\pm 0.001$ 0.064 $\pm 0.004$ 0.063 $\pm 0.003$ 0.068 $\pm 0.003$ Relative2.80 $\pm 0.11$ 2.69 $\pm 0.07$ 3.06 $\pm 0.07$ 2.68 $\pm 0.13$ 2.57 $\pm 0.13$ 2.83 $\pm 0.13$	Relative	$4.81 \pm 0.07$	$4.98 \pm 0.08$	$4.84 \pm 0.08$	$4.71 \pm 0.07$	$4.55 \pm 0.22$	$4.75 \pm 0.16$
Absolute Relative $0.194 \pm 0.002$ $8.33 \pm 0.07$ $0.196 \pm 0.002$ $8.27 \pm 0.12$ $0.198 \pm 0.006$ $8.40 \pm 0.17$ $0.192 \pm 0.004$ $8.07 \pm 0.11$ $0.196 \pm 0.002$ $7.95 \pm 0.19$ $0.202 \pm 0.007$ $8.42 \pm 0.26$ Liver Absolute $1.146 \pm 0.020$ $49.24 \pm 0.96$ $1.256 \pm 0.035^*$ $53.00 \pm 1.40^*$ $1.338 \pm 0.037^{**}$ $56.77 \pm 1.15^{**}$ $1.364 \pm 0.047^{**}$ $57.28 \pm 1.56^{**}$ $1.442 \pm 0.020^{**}$ $58.44 \pm 1.18^{**}$ $1.410 \pm 0.044^{**}$ $58.70 \pm 0.90^{**}$ Lung Absolute $0.198 \pm 0.007$ $0.198 \pm 0.007$ $0.190 \pm 0.003$ $8.02 \pm 0.08$ $0.196 \pm 0.007$ $8.31 \pm 0.22$ $0.200 \pm 0.008$ $8.42 \pm 0.40$ $0.190 \pm 0.008$ $8.10 \pm 0.34$ $0.190 \pm 0.004$ $7.93 \pm 0.22$ Thymus Absolute Relative $0.065 \pm 0.002$ $2.80 \pm 0.11$ $0.064 \pm 0.002$ $2.69 \pm 0.07$ $0.072 \pm 0.001$ $3.06 \pm 0.07$ $0.064 \pm 0.003$ $2.68 \pm 0.13$ $0.063 \pm 0.003$ $2.57 \pm 0.13$ $0.068 \pm 0.003$ $2.83 \pm 0.13$	R. Kidney	···· <b>±</b> ····		• – •			
Relative $8.33 \pm 0.07$ $8.27 \pm 0.12$ $8.40 \pm 0.17$ $8.07 \pm 0.11$ $7.95 \pm 0.19$ $8.42 \pm 0.26$ LiverAbsolute $1.146 \pm 0.020$ $1.256 \pm 0.035^*$ $1.338 \pm 0.037^{**}$ $1.364 \pm 0.047^{**}$ $1.442 \pm 0.020^{**}$ $1.410 \pm 0.044^{**}$ Relative $49.24 \pm 0.96$ $53.00 \pm 1.40^*$ $56.77 \pm 1.15^{**}$ $57.28 \pm 1.56^{**}$ $58.44 \pm 1.18^{**}$ $58.70 \pm 0.90^{**}$ LungAbsolute $0.198 \pm 0.007$ $0.190 \pm 0.003$ $0.196 \pm 0.007$ $0.200 \pm 0.007$ $0.200 \pm 0.008$ $0.190 \pm 0.004$ Relative $8.50 \pm 0.30$ $8.02 \pm 0.08$ $8.31 \pm 0.22$ $8.42 \pm 0.40$ $8.10 \pm 0.34$ $7.93 \pm 0.22$ Thymus $Absolute$ $0.065 \pm 0.002$ $0.064 \pm 0.002$ $0.072 \pm 0.001$ $0.064 \pm 0.004$ $0.063 \pm 0.003$ $0.068 \pm 0.003$ Relative $2.80 \pm 0.11$ $2.69 \pm 0.07$ $3.06 \pm 0.07$ $2.68 \pm 0.13$ $2.57 \pm 0.13$ $2.83 \pm 0.13$	Absolute	$0.194 \pm 0.002$	$0.196 \pm 0.002$	0.198 ± 0.006	0.192 ± 0.004	0.196 ± 0.002	$0.202 \pm 0.007$
Liver Absolute $1.146 \pm 0.020$ $1.256 \pm 0.035^*$ $1.338 \pm 0.037^{**}$ $1.364 \pm 0.047^{**}$ $1.442 \pm 0.020^{**}$ $1.410 \pm 0.044^{**}$ Relative $49.24 \pm 0.96$ $53.00 \pm 1.40^*$ $56.77 \pm 1.15^{**}$ $57.28 \pm 1.56^{**}$ $58.44 \pm 1.18^{**}$ $58.70 \pm 0.90^{**}$ Lung Absolute $0.198 \pm 0.007$ $0.190 \pm 0.003$ $0.196 \pm 0.007$ $0.200 \pm 0.007$ $0.200 \pm 0.008$ $0.190 \pm 0.004$ Relative $8.50 \pm 0.30$ $8.02 \pm 0.08$ $8.31 \pm 0.22$ $8.42 \pm 0.40$ $8.10 \pm 0.34$ $7.93 \pm 0.22$ Thymus Absolute $0.065 \pm 0.002$ $0.064 \pm 0.002$ $0.072 \pm 0.001$ $0.064 \pm 0.004$ $0.063 \pm 0.003$ $0.068 \pm 0.003$ Relative $2.80 \pm 0.11$ $2.69 \pm 0.07$ $3.06 \pm 0.07$ $2.68 \pm 0.13$ $2.57 \pm 0.13$ $2.83 \pm 0.13$	Relative	$8.33 \pm 0.07$	8.27 ± 0.12	8.40 ± 0.17	$8.07 \pm 0.11$	7.95 ± 0.19	$8.42 \pm 0.26$
Absolute Relative $1.146 \pm 0.020$ $49.24 \pm 0.96$ $1.256 \pm 0.035^*$ $53.00 \pm 1.40^*$ $1.338 \pm 0.037^{**}$ $56.77 \pm 1.15^{**}$ $1.364 \pm 0.047^{**}$ $57.28 \pm 1.56^{**}$ $1.442 \pm 0.020^{**}$ $58.44 \pm 1.18^{**}$ $1.410 \pm 0.044^{**}$ $58.70 \pm 0.90^{**}$ Lung Absolute $0.198 \pm 0.007$ $0.198 \pm 0.30$ $0.190 \pm 0.003$ $8.02 \pm 0.08$ $0.196 \pm 0.007$ $8.31 \pm 0.22$ $0.200 \pm 0.007$ $8.42 \pm 0.40$ $0.200 \pm 0.008$ $8.10 \pm 0.34$ $0.190 \pm 0.004$ $7.93 \pm 0.22$ Thymus Relative $0.065 \pm 0.002$ $2.80 \pm 0.11$ $0.064 \pm 0.002$ $2.69 \pm 0.07$ $0.072 \pm 0.001$ $3.06 \pm 0.07$ $0.064 \pm 0.003$ $2.68 \pm 0.13$ $0.063 \pm 0.003$ $2.57 \pm 0.13$ $0.068 \pm 0.003$ $2.83 \pm 0.13$	Liver	· · · · ·				•	
Relative $49.24 \pm 0.96$ $53.00 \pm 1.40^*$ $56.77 \pm 1.15^{**}$ $57.28 \pm 1.56^{**}$ $58.44 \pm 1.18^{**}$ $58.70 \pm 0.90^{**}$ LungAbsolute $0.198 \pm 0.007$ $0.190 \pm 0.003$ $0.196 \pm 0.007$ $0.200 \pm 0.007$ $0.200 \pm 0.008$ $0.190 \pm 0.004$ Relative $8.50 \pm 0.30$ $8.02 \pm 0.08$ $8.31 \pm 0.22$ $8.42 \pm 0.40$ $8.10 \pm 0.34$ $7.93 \pm 0.22$ ThymusAbsolute $0.065 \pm 0.002$ $0.064 \pm 0.002$ $0.072 \pm 0.001$ $0.064 \pm 0.004$ $0.063 \pm 0.003$ $0.068 \pm 0.003$ Relative $2.80 \pm 0.11$ $2.69 \pm 0.07$ $3.06 \pm 0.07$ $2.68 \pm 0.13$ $2.57 \pm 0.13$ $2.83 \pm 0.13$	Absolute	$1.146 \pm 0.020$	$1.256 \pm 0.035*$	1.338 ± 0.037**	1.364 ± 0.047**	1.442 ± 0.020**	$1.410 \pm 0.044 **$
Lung Absolute $0.198 \pm 0.007$ $0.190 \pm 0.003$ $0.196 \pm 0.007$ $0.200 \pm 0.007$ $0.200 \pm 0.008$ $0.190 \pm 0.004$ Relative $8.50 \pm 0.30$ $8.02 \pm 0.08$ $8.31 \pm 0.22$ $8.42 \pm 0.40$ $8.10 \pm 0.34$ $7.93 \pm 0.22$ Thymus Absolute $0.065 \pm 0.002$ $0.064 \pm 0.002$ $0.072 \pm 0.001$ $0.064 \pm 0.004$ $0.063 \pm 0.003$ $0.068 \pm 0.003$ Relative $2.80 \pm 0.11$ $2.69 \pm 0.07$ $3.06 \pm 0.07$ $2.68 \pm 0.13$ $2.57 \pm 0.13$ $2.83 \pm 0.13$	Relative	49.24 ± 0.96	53.00 ± 1.40*	56.77 ± 1.15**	57.28 ± 1.56**	58.44 ± 1.18**	58.70 ± 0.90**
Absolute Relative $0.198 \pm 0.007$ $0.190 \pm 0.003$ $0.196 \pm 0.007$ $0.200 \pm 0.007$ $0.200 \pm 0.008$ $0.190 \pm 0.004$ Relative $8.50 \pm 0.30$ $8.02 \pm 0.08$ $8.31 \pm 0.22$ $8.42 \pm 0.40$ $8.10 \pm 0.34$ $7.93 \pm 0.22$ Thymus Absolute $0.065 \pm 0.002$ $0.064 \pm 0.002$ $0.072 \pm 0.001$ $0.064 \pm 0.004$ $0.063 \pm 0.003$ $0.068 \pm 0.003$ Relative $2.80 \pm 0.11$ $2.69 \pm 0.07$ $3.06 \pm 0.07$ $2.68 \pm 0.13$ $2.57 \pm 0.13$ $2.83 \pm 0.13$	Lung						0.400 . 0.004
Relative $8.50 \pm 0.30$ $8.02 \pm 0.08$ $8.31 \pm 0.22$ $8.42 \pm 0.40$ $8.10 \pm 0.34$ $7.93 \pm 0.22$ Thymus Absolute $0.065 \pm 0.002$ $0.064 \pm 0.002$ $0.072 \pm 0.001$ $0.064 \pm 0.004$ $0.063 \pm 0.003$ $0.068 \pm 0.003$ Relative $2.80 \pm 0.11$ $2.69 \pm 0.07$ $3.06 \pm 0.07$ $2.68 \pm 0.13$ $2.57 \pm 0.13$ $2.83 \pm 0.13$	Absolute	0.198 ± 0.007	$0.190 \pm 0.003$	$0.196 \pm 0.007$	$0.200 \pm 0.007$	$0.200 \pm 0.008$	$0.190 \pm 0.004$
Inymus Absolute $0.065 \pm 0.002$ $0.064 \pm 0.002$ $0.072 \pm 0.001$ $0.064 \pm 0.004$ $0.063 \pm 0.003$ $0.068 \pm 0.003$ Relative $2.80 \pm 0.11$ $2.69 \pm 0.07$ $3.06 \pm 0.07$ $2.68 \pm 0.13$ $2.57 \pm 0.13$ $2.83 \pm 0.13$	Relative	$8.50 \pm 0.30$	$8.02 \pm 0.08$	$8.31 \pm 0.22$	$8.42 \pm 0.40$	$8.10 \pm 0.34$	$7.93 \pm 0.22$
Absolute $0.005 \pm 0.002$ $0.064 \pm 0.002$ $0.072 \pm 0.001$ $0.064 \pm 0.004$ $0.003 \pm 0.003$ $0.068 \pm 0.003$ Relative $2.80 \pm 0.11$ $2.69 \pm 0.07$ $3.06 \pm 0.07$ $2.68 \pm 0.13$ $2.57 \pm 0.13$ $2.83 \pm 0.13$	Thymus	0.000	0.000	0.070 \ 0.001		0.062 1 0.002	0.049 1.0.002
Keizuve $2.00 \pm 0.11$ $2.09 \pm 0.07$ $3.00 \pm 0.07$ $2.00 \pm 0.13$ $2.37 \pm 0.13$ $2.65 \pm 0.13$	Absolute	$0.005 \pm 0.002$	$0.064 \pm 0.002$	$0.0/2 \pm 0.001$	$0.004 \pm 0.004$	$0.003 \pm 0.003$	$0.000 \pm 0.003$
	Kelauve	$2.00 \pm 0.11$	2.09 ± 0.07	3.00 <u>T</u> 0.07	2.00 ± 0.15	2.37 ± 0.13	2.05 T 0.15

* Significantly different ( $P \le 0.05$ ) from the control group by Williams' or Dunnett's test

^a Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

^{**} P≤0.01

Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Inhalation Study of Nitromethane^a

	0 ppm	94 ppm	188 ppm	375 ppm	750 ppm	1,500 ppm
n	10	10	10	10	10	10
Male						
Necropsy body wt	$36.1 \pm 0.5$	$35.9 \pm 0.5$	$35.5 \pm 0.8$	36.3 ± 0.6	$35.2 \pm 0.4$	34.7 ± 0.5
Heart						
Absolute	$0.148 \pm 0.003$	$0.153 \pm 0.003$	$0.147 \pm 0.002$	$0.151 \pm 0.002$	$0.148 \pm 0.003$	$0.149 \pm 0.002$
Relative	$4.10 \pm 0.07$	4.26 ± 0.06	$4.16 \pm 0.07$	$4.17 \pm 0.09$	$4.20 \pm 0.10$	$4.30 \pm 0.06$
R. Kidney	_		. –			_
Absolute	$0.294 \pm 0.009$	$0.329 \pm 0.006 **$	$0.322 \pm 0.005*$	$0.332 \pm 0.007 **$	0.339 ± 0.007**	$0.315 \pm 0.008$
Relative	$8.15 \pm 0.20$	$9.15 \pm 0.11 **$	$9.10 \pm 0.15^{**}$	$9.15 \pm 0.20^{**}$	$9.63 \pm 0.20 **$	$9.08 \pm 0.18 **$
Liver	_	_	_	_		_
Absolute	$1.633 \pm 0.040$	$1.700 \pm 0.023$	$1.678 \pm 0.031$	$1.731 \pm 0.027$	1.789 ± 0.029*	$1.724 \pm 0.053$
Relative	$45.27 \pm 0.89$	$47.32 \pm 0.38$	$47.39 \pm 0.78$	47.70 ± 0.60*	50.79 ± 0.72**	49.62 ± 0.99**
Lung	_			_	_	-
Absolute	$0.240 \pm 0.008$	$0.251 \pm 0.007$	$0.234 \pm 0.007$	$0.241 \pm 0.005$	$0.237 \pm 0.004$	$0.234 \pm 0.006$
Relative	$6.65 \pm 0.20$	$6.98 \pm 0.13$	$6.59 \pm 0.10$	$6.65 \pm 0.14$	$6.73 \pm 0.11$	$6.75 \pm 0.17$
R. Testis						
Absolute	$0.126 \pm 0.003$	$0.123 \pm 0.002$	$0.124 \pm 0.004$	$0.127 \pm 0.003$	$0.127 \pm 0.003$	$0.126 \pm 0.003$
Relative	$3.51 \pm 0.08$	$3.43 \pm 0.09$	$3.51 \pm 0.10$	$3.50 \pm 0.09$	$3.61 \pm 0.09$	$3.63 \pm 0.06$
Thymus		. –				
Absolute	$0.042 \pm 0.002$	$0.042 \pm 0.002$	$0.041 \pm 0.002$	$0.045 \pm 0.004$	$0.041 \pm 0.003$	$0.039 \pm 0.002$
Relative	1.18 ± 0.05	1.17 ± 0.07	1.17 ± 0.07	$1.24 \pm 0.09$	$1.16 \pm 0.09$	1.11 ± 0.06
Female						
Necropsy body wt	$31.1 \pm 0.7$	$31.5 \pm 0.7$	$32.8 \pm 0.7$	34.2 ± 0.8**	$31.5 \pm 0.5$	30.4 ± 0.5
Heart						
Absolute	$0.132 \pm 0.003$	$0.129 \pm 0.002$	0.132 + 0.002	0.129 + 0.006	$0.130 \pm 0.003$	$0.134 \pm 0.002$
Relative	$4.25 \pm 0.09$	$4.11 \pm 0.10$	$4.03 \pm 0.05$	$3.77 \pm 0.16^{**}$	$4.12 \pm 0.07$	$4.41 \pm 0.07$
R. Kidney					. –	_
Absolute	$0.210 \pm 0.007$	$0.221 \pm 0.005$	$0.228 \pm 0.005*$	$0.232 \pm 0.005*$	0.231 ± 0.006*	$0.230 \pm 0.006*$
Relative	$6.75 \pm 0.18$	$7.03 \pm 0.15$	$6.97 \pm 0.15$	$6.80 \pm 0.17$	$7.33 \pm 0.21*$	7.57 ± 0.15**
Liver						
Absolute	$1.536 \pm 0.033$	$1.590 \pm 0.030$	$1.604 \pm 0.044$	$1.639 \pm 0.037$	$1.563 \pm 0.041$	$1.575 \pm 0.050$
Relative	49.49 ± 0.99	50.64 ± 1.15	48.89 ± 0.72	47.97 ± 0.95	49.52 ± 0.76	51.77 ± 1.25
Lung						<b>x</b>
Absolute	$0.233 \pm 0.005$	$0.239 \pm 0.004$	0.248 ± 0.013	$0.244 \pm 0.003$	$0.245 \pm 0.015$	$0.227 \pm 0.005$
Relative	$7.50 \pm 0.13$	$7.62 \pm 0.19$	$7.55 \pm 0.33$	$7.15 \pm 0.11$	7.76 ± 0.44	$7.47 \pm 0.14$
Thymus						
Absolute	$0.055 \pm 0.002$	$0.053 \pm 0.004$	$0.063 \pm 0.002$	$0.060 \pm 0.003$	$0.057 \pm 0.002$	$0.061 \pm 0.002$
Datation	$1.79 \pm 0.00$	1 60 1 0 12	1.01 1.0.05	1 75 1 0 06	1 91 1 0 09	2 00 1 0 08

* Significantly different (P  $\leq$  0.05) from the control group by Williams' or Dunnett's test

** P≤0.01

^a Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

# APPENIDIX G HIEMATOLOGY AND CLINICAL CHIEMISTRY RESULTS

 TABLE G1
 Hematology and Clinical Chemistry Data for Rats

 in the 13-Week Inhalation Study of Nitromethane
 242

# TABLE G1

Hematology and Clinical Chemistry Data for Rats in the 13-Week Inhalation Study of Nitromethane^a

		0 ppm	94 ppm	188 ppm	375 ppm	750 ppm	1,500 ppm
M		·			<u></u>		
He	matology						
					•		
n							
	Day 3	10	10	10	10	10	10
	Day 23	6	8	9	10	10	10
	Week 13	10	10	10	10	10	10
	Hematocrit (%)					· .	
	Dev 2	$36.7 \pm 0.5$	363 ± 03	35 2 + 0 2*	33 1 + 0 3**	· 317 ± 0.2**	37 3 + 0.2**
	Day 3	$30.7 \pm 0.3$	$30.5 \pm 0.5$	$33.2 \pm 0.2$	$37.6 \pm 0.4*$	$34.0 \pm 0.4**$	$32.3 \pm 0.2$
•	Wash 12	$40.7 \pm 0.3$	$46.6 \pm 0.1$	$46.1 \pm 0.4$	116±03**	$42^{5} \pm 0.4^{**}$	$30.2 \pm 0.4$
	Hemoglobin (g/dI)	$40.5 \pm 0.1$	40.0 <u>+</u> 0.4	40.1 <u>+</u> 0.4	44.0 <u>1</u> 0.5	42.5 <u>1</u> 0.4	
	Day 3	$130 \pm 0.2$	$13.5 \pm 0.1$	$13.3 \pm 0.1*$	12.6 + 0.1**	-122 + 0.1**	$12.4 \pm 0.1**$
	Day 3	$15.9 \pm 0.2$ 15.2 $\pm 0.2$	$15.5 \pm 0.1$	$15.5 \pm 0.1$	$14.3 \pm 0.1*$	$12.2 \pm 0.1$ $13.2 \pm 0.1**$	$11.9 \pm 0.1$
	Waak 12	$15.5 \pm 0.2$	$10.1 \pm 0.3$	$15.0 \pm 0.1$	$14.5 \pm 0.1$	$13.2 \pm 0.1$	$13.4 \pm 0.2**$
	Fruthroauter (10 ⁶ / ₁₀ I)	$15.5 \pm 0.1$	$13.4 \pm 0.1$	$15.2 \pm 0.1$	14.0 T 0.1	$14.5 \pm 0.1^{\circ}$	$15.4 \pm 0.2$
•	Eryunocytes (10 $/\mu L$ )	$7.75 \pm 0.10$	7 58 + 0.08	7 38 + 0 08**	$7.16 \pm 0.07**$	$6.97 \pm 0.04 **$	$6.94 \pm 0.06**$
	Day 3	$8.74 \pm 0.06$	$7.36 \pm 0.08$	$7.38 \pm 0.08$	$9.36 \pm 0.00*$	$0.97 \pm 0.04$	$7.77 \pm 0.11$
	Waak 12	$0.12 \pm 0.03$	$9.37 \pm 0.10^{\circ}$	$9.00 \pm 0.07$	$9.72 \pm 0.02**$	$10.10 \pm 0.00**$	$0.41 \pm 0.11**$
	Nucleoted eruthrocutes (	$9.12 \pm 0.03$	9.45 <u>T</u> 0.00 ¹¹	$9.55 \pm 0.08$	$9.72 \pm 0.00$	10.10 ± 0.09	7.41 ± 0.11
	Day 2	$0.11 \pm 0.03$	$0.17 \pm 0.05$	$0.10 \pm 0.03$	$0.08 \pm 0.03$	$0.05 \pm 0.02$	$0.06 \pm 0.02$
	Day 3	$0.11 \pm 0.03$	$0.17 \pm 0.03$	$0.19 \pm 0.03$	$0.05 \pm 0.03$	$0.05 \pm 0.02$	$0.00 \pm 0.02$ 0.12 ± 0.03*
	Wook 12	$0.01 \pm 0.01$	$0.03 \pm 0.02$	$0.03 \pm 0.02$	$0.05 \pm 0.02$ 0.11 ± 0.03	$0.04 \pm 0.02$	$0.12 \pm 0.03$
	Mean cell volume (fl.)	$0.05 \pm 0.02$	$0.04 \pm 0.02$	0.05 ± 0.05	0.11 ± 0.05	0.00 1 0.05	0.27 ± 0.07
	Day 2	472 + 03	470 + 03	$47.7 \pm 0.4$	$46.2 \pm 0.1*$	$45.5 \pm 0.2**$	463 + 02**
	Day 3 Day 23	$47.2 \pm 0.3$	$47.9 \pm 0.3$	$47.7 \pm 0.4$	$40.2 \pm 0.1$ $40.2 \pm 0.3**$	$375 \pm 0.2**$	$391 \pm 0.2$
	Week 12	$40.3 \pm 0.3$	$40.0 \pm 0.2$	$48.4 \pm 0.2**$	$45.2 \pm 0.3$	$42.0 \pm 0.6**$	41.6 + 0.3**
	Mean cell hemoglohin (	ng)	49.5 ± 0.2	40.4 1 0.2	10.0 ± 0.1	1210 1 010	11.0 T 0.0
	Dav 3	$17.9 \pm 0.1$	$178 \pm 01$	$18.1 \pm 0.1$	$17.6 \pm 0.0^*$	$17.5 \pm 0.1*$	$17.9 \pm 0.1$
	Day 23	$17.5 \pm 0.2$	$17.2 \pm 0.1$	$16.7 \pm 0.1^{**}$	$15.3 \pm 0.1**$	$14.5 \pm 0.0**$	$15.3 \pm 0.1**$
	Week 13	$168 \pm 0.0$	$163 \pm 0.1**$	$16.0 \pm 0.0**$	$15.2 \pm 0.1**$	$14.1 \pm 0.2^{**}$	$14.3 \pm 0.1**$
	Mean cell hemoglobin c	oncentration (g/dL)	1010 1 010			· · ·	. — .
	Day 3	$37.8 \pm 0.2$	$37.3 \pm 0.1$	$37.8 \pm 0.1$	38.1 + 0.1	38.4 + 0.2*	$38.6 \pm 0.1 **$
	Day 23	$37.5 \pm 0.2$	$37.3 \pm 0.1$	$37.3 \pm 0.2$	$38.2 \pm 0.3$	38.8 ± 0.2*	$39.3 \pm 0.2^{**}$
	Week 13	$33.0 \pm 0.1$	$33.0 \pm 0.1$	$33.0 \pm 0.1$	$33.2 \pm 0.1$	$33.6 \pm 0.1 **$	$34.3 \pm 0.3^{**}$
	Platelets $(10^3/\mu L)$			. –			
	Dav 3	663.6 + 15.5	741.9 ± 13.8**	708.2 ± 13.5**	732.7 ± 17.8**	781.2 ± 10.5**	870.6 ± 16.3**
	Day 23	$643.8 \pm 44.1$	$663.4 \pm 8.8$	$675.0 \pm 16.0$	704.8 ± 19.2	878.4 ± 22.5**	1,325.2 ± 24.0**
	Week 13	$538.3 \pm 7.5$	527.8 ± 16.7	539.2 ± 5.7	578.7 ± 6.1**	625.0 ± 9.2**	817.4 ± 32.9**
	Leukocytes $(10^3/\mu L)$						•
	Day 3	$7.22 \pm 0.24$	8.24 ± 0.28	7.96 ± 0.46	$7.22 \pm 0.35$	7.70 ± 0.31	$7.17 \pm 0.32$
	Day 23	$5.46 \pm 0.61$	$7.19 \pm 0.45$	$6.91 \pm 0.44$	5.45 ± 0.48	5.87 ± 0.52	5.46 ± 0.36
	Week 13	$8.65 \pm 0.29$	$8.71 \pm 0.46$	8.20 ± 0.34	$8.42 \pm 0.46$	8.79 ± 0.37	$9.84 \pm 0.26$
	Segmented neutrophils (	$(10^{3}/\mu L)$			4 .		
, i	Day 3	$1.10 \pm 0.10$	$0.90 \pm 0.07$	$0.94 \pm 0.11$	$0.96 \pm 0.08$	$0.82 \pm 0.12$	$0.90 \pm 0.15$
	Day 23	$0.84 \pm 0.05$	$0.74 \pm 0.09$	0.84 ± 0.12	$0.76 \pm 0.10$	$0.52 \pm 0.10$	$0.54 \pm 0.08$
	Week 13	$1.90 \pm 0.12$	$1.63 \pm 0.21$	$1.96 \pm 0.14$	$1.57 \pm 0.17$	1.29 ± 0.21	$1.64 \pm 0.18$
	Lymphocytes $(10^3/\mu L)$		ê				
	Day 3	$5.82 \pm 0.27$	$6.90 \pm 0.28$	6.47 ± 0.46	$6.04 \pm 0.30$	$6.53 \pm 0.25$	$6.03 \pm 0.23$
	Day 23	$4.45 \pm 0.56$	$6.19 \pm 0.41$	$5.73 \pm 0.36$	$4.55 \pm 0.39$	$5.15 \pm 0.44$	$4.78 \pm 0.32$
	NY 1 10	<pre>&lt; 0.00</pre>	6 60 1 0 01		6 05 1 0 00	C 0 C + 0 45	7 07 1 0 26**

# Hematology and Clinical Chemistry

# Table G1

Hematology and Clinical Chemistry Data for Rats in the 13-Week Inhalation Study of Nitromethane (continued)

	0 ppm	94 ppm	188 ppm	375 ppm	750 ppm	1,500 ppm
Male (continued)		· · · ·				
Hematology (continued)						
1						
Day 3	10	10	10	10	10	10
Day 23	6	8	9	10	10	10
Week 13	10	10	10	10	10	10
Monocytes $(10^3/\mu L)$						
Day 3	$0.28 \pm 0.04$	$0.39 \pm 0.07$	$0.53 \pm 0.11$	$0.21 \pm 0.05$	$0.33 \pm 0.06$	$0.23 \pm 0.04$
Day 23	$0.16 \pm 0.05$	$0.37 \pm 0.07$ $0.24 \pm 0.07$	$0.31 \pm 0.07$	$0.13 \pm 0.05$	$0.19 \pm 0.04$	0.14 + 0.03
Week 13	$0.47 \pm 0.08$	$0.43 \pm 0.05$	$0.43 \pm 0.07$	$0.43 \pm 0.05$	$0.47 \pm 0.09$	$0.35 \pm 0.06$
Eosinophils $(10^3/\mu L)$	3.17 I 0.00	0.10 1 0.00	0.15 1 0.07	0.10 - 0.00	5 <u>-</u> 0.05	0.00 T 0.00
Dav 3	0.02 + 0.01	$0.05 \pm 0.02$	0.02 + 0.01	0.01 + 0.01	0.02 + 0.01	0.01 + 0.01
Day 23	0.01 + 0.01	$0.04 \pm 0.01$	$0.02 \pm 0.01$	$0.00 \pm 0.00$	0.01 + 0.01	$0.00 \pm 0.00$
Week 13	0.02 + 0.02	$0.03 \pm 0.01$	$0.04 \pm 0.02$	$0.06 \pm 0.03$	$0.07 \pm 0.03$	0.04 + 0.02
Methemoglobin (g/dL)	5.02 <u>+</u> 0.02	0.00 1 0.01	0.01 - 0.02	0.00 <u>-</u> 0.05		<u>.</u>
Day 3	$0.16 \pm 0.02^{b}$	$0.14 \pm 0.02^{b}$	$0.19 \pm 0.02^{c}$	0.34 + 0.02**	$0.21 + 0.03^{*d}$	$0.22 + 0.02^{*c}$
Day 23	0.08 + 0.01	0.06 + 0.01	$0.08 \pm 0.01$	$0.16 \pm 0.06$	$0.15 \pm 0.01*$	0.28 + 0.02 **
Week 13	$0.15 \pm 0.01$	$0.17 \pm 0.02$	$0.17 \pm 0.01*$	$0.17 \pm 0.01*$	$0.21 \pm 0.01 **$	0.41 ± 0.09**
Clinical Chemistry						
1						
Day 3	10	10	10	10	10	10
Day 23	6	8	9	10	10	9
Week 13	10	10	10	10	10	10
Urea nitrogen (mg/dL)						
Day 3	$15.5 \pm 0.5$	$17.0 \pm 0.5$	$15.6 \pm 0.5$	$15.7 \pm 0.4$	$14.2 \pm 0.3$	12.9 ± 0.3**
Day 23	$13.8 \pm 0.6$	$16.4 \pm 0.8$	$14.4 \pm 0.6$	$15.4 \pm 0.5$	$12.5 \pm 0.4$	$12.2 \pm 0.5$
Week 13	$22.6 \pm 0.7$	$23.0 \pm 1.0$	$22.5 \pm 0.6$	$23.1 \pm 0.7$	$22.2 \pm 0.7$	19.4 ± 0.5**
Creatinine (mg/dL)	L					
Day 3	$0.62 \pm 0.02^{\circ}$	$0.64 \pm 0.02$	$0.61 \pm 0.02$	$0.65 \pm 0.02$	0.78 ± 0.03**	$1.05 \pm 0.03^{**}$
Day 23	$0.82 \pm 0.02$	$0.76 \pm 0.02$	$0.87 \pm 0.02$	$0.82 \pm 0.03$	$0.85 \pm 0.03$	$0.94 \pm 0.04$
Week 13	$0.84 \pm 0.03$	$0.83 \pm 0.03$	$0.82 \pm 0.04$	$0.84 \pm 0.03$	$0.78 \pm 0.04$	$0.71 \pm 0.04$
Total protein (g/dL)	n h					
Day 3	$6.3 \pm 0.0^{\circ}$	$6.3 \pm 0.1$	$6.4 \pm 0.1$	$6.6 \pm 0.1$	$6.2 \pm 0.1$	$6.4 \pm 0.1$
Day 23	$7.3 \pm 0.1$	$7.0 \pm 0.1$	$7.1 \pm 0.1$	$7.4 \pm 0.2$	$7.0 \pm 0.1*$	$6.5 \pm 0.1$ **
Week 13	$7.2 \pm 0.1$	$7.2 \pm 0.1$	$7.4 \pm 0.1$	$7.3 \pm 0.1$	$7.2 \pm 0.1$	$6.8 \pm 0.1$
Albumin (g/dL)					4.0	
Day 3	$4.1 \pm 0.1^{\circ}$	$4.1 \pm 0.1$	$4.3 \pm 0.1$	$4.6 \pm 0.1^{**}$	$4.3 \pm 0.1$	$4.4 \pm 0.1$
Day 23	$4.9 \pm 0.1$	$4.9 \pm 0.1$	$5.0 \pm 0.1$	$4.9 \pm 0.1$	$4.8 \pm 0.0$	$4.5 \pm 0.1^{**}$
Week 13	$4.5 \pm 0.1$	$4.6 \pm 0.1$	$4.6 \pm 0.1$	$4.6 \pm 0.1$	$4.6 \pm 0.1$	$4.6 \pm 0.1$
Globulin (g/dL)	aa ka th			20.011	10,004+	0.0 1.0.0**
Day 3	$2.2 \pm 0.1^{\circ}$	$2.2 \pm 0.0$	$2.0 \pm 0.1$	$2.0 \pm 0.1^*$	1.9 ± 0.0 [∓] *	$2.0 \pm 0.0^{**}$
Day 23	$2.4 \pm 0.1$	$2.1 \pm 0.1$	$2.0 \pm 0.1$ *	$2.5 \pm 0.1$	$2.2 \pm 0.1$	$2.0 \pm 0.1^*$
Week 13	$2.7 \pm 0.1$	$2.5 \pm 0.1$	$2.8 \pm 0.1$	$2.7 \pm 0.1$	$2.6 \pm 0.1$	$2.2 \pm 0.1^*$

# TABLE G1

Hematology and Clinical Chemistry Data for Rats in the 13-Week Inhalation Study of Nitromethane (continued)

	0 ppm	94 ppm	188 ppm	375 ppm	750 ppm	1,500 ppm
fale (continued)	· · · · · · · · · · · · · · · · · · ·					
linical Chemistry (continu	ied)			·		
				•		
Day 3	10	10	10	10	10	10
Day 23	6	8	9	10	10	9 .
Week 13	10	10	10	- 10	10	10
Alanine aminotransfera	ise (IU/L)	,			•	
Day 3	41 ± 3:	$41 \pm 2$	$41 \pm 1$	34 ± 1*	32 ± 1**	31 ± 1**
Day 23	$39 \pm 2$	$42 \pm 5$	$41 \pm 2$	$41 \pm 3$	$34 \pm 1*$	33 ± 1* '
Week 13	$57 \pm 5$	$72 \pm 6$	$73 \pm 7$	$63 \pm 3$	$60 \pm 4$	$40 \pm 1*$
Alkaline phosphatase (	IU/L)		· · · ·	··· <b></b> ·	-	. –
Day 3	883 ± 19	971 ± 25	995 ± 18	943 ± 16	811 ± 20	779 ± 22
Day 23	$645 \pm 25$	$631 \pm 15$	$625 \pm 11$	$667 \pm 27$	$572 \pm 16*$	523 ± 20**
Week 13	$359 \pm 14$	$346 \pm 12$	$334 \pm 8$	$371 \pm 19$	$365 \pm 12$	$333 \pm 12$
Creatine kinase (IU/L)		_		_		
Day 3	$526 \pm 24^{b}$	• 442 ± 14*	443 ± 33*	429 ± 22*	416 ± 86**	231 ± 13**
Day 23	$255 \pm 43$	$482 \pm 74$	$512 \pm 39^{c}$	$430 \pm 85^{b}$	$244 \pm 44$	$167 \pm 14^{c}$
Week 13	$200 \pm 25$	$214 \pm 22$	$172 \pm 19$	177 ± 23	$200 \pm 28$	$122 \pm 14$
Sorbitol dehydrogenase	e (IU/L)			·	1. S.	
Day 3	8 ± 1	9 ± 1	$10 \pm 0$	$10 \pm 1*$	8 ± 1	6±0
Day 23	$12 \pm 1$	$13 \pm 1$	$13 \pm 1$	$12 \pm 1$	$10 \pm 1$	9 ± 1*
Week 13	11 ± 1	$13 \pm 1$	$13 \pm 1$	$13 \pm 1$	$12 \pm 1$	8 ± 0 ·
Bile acids (µmol/L)	·					1
Day 3	$11.8 \pm 2.9^{c}$	$9.4 \pm 0.8$	$7.8 \pm 1.5^{b}$	$9.1 \pm 1.6^{c}$	$8.2 \pm 1.0$	$8.4 \pm 1.0^{b}$
Day 23	$\cdot$ 13.1 ± 4.5	$9.6 \pm 2.0$	$8.6 \pm 2.1$	$10.6 \pm 2.3^{b}$	7.8 ± 2.5	$3.6 \pm 0.7^{**}$
Week 13	$7.0 \pm 2.5$	$5.3 \pm 0.6^{b}$	8.7 ± 1.9 ^b	4.9 ± 0.4	$4.5 \pm 0.9^{\circ}$	8.4 ± 2.3 ^b
Thyroid-stimulating ho	ormone (ng/mL)	¢				· · ·
Day 23	$0.7 \pm 0.2^{e}$	$0.5 \pm 0.1^{r}$	$1.2 \pm 0.2$	$1.5 \pm 0.3^{\circ}$	$1.0 \pm 0.2$	$0.7 \pm 0.1$
Week 13	$3.7 \pm 0.8$	$2.5 \pm 0.4$	$4.1 \pm 0.6$	$3.3 \pm 0.5$	$3.3 \pm 0.4$	$3.0 \pm 0.5$
Triiodothyronine (ng/d	IL)					
Day 23	$116 \pm 7^{e}$	$105 \pm 5$	$105 \pm 3$	$91 \pm 4^{**c}$	95 ± 4*	$92 \pm 10^{*}$
Week 13	$123 \pm 8$	$134 \pm 12$	$125 \pm 6$	138 ± 4	$137 \pm 8$	$134 \pm 8$
Thyroxine (µg/dL)	· · · ·					
Day 23	$5.4 \pm 0.2$	$5.2 \pm 0.2$	$5.2 \pm 0.2^{\circ}$	$4.4 \pm 0.2^{*2}$	$5.0 \pm 0.2$	$4.4 \pm 0.2^{**}$
Week 13	$4.9 \pm 0.3$	$5.2 \pm 0.3$	$5.1 \pm 0.2$	$5.3 \pm 0.2$	$5.2 \pm 0.1$	5.9 ± 0.3**
Free thyroxine (ng/dL)	)			o o i o stath		
Day 23	$1.3 \pm 0.1$	$1.2 \pm 0.1^{1}$	$1.2 \pm 0.1$	$0.9 \pm 0.1^{**0}$	$1.1 \pm 0.1*$	$1.0 \pm 0.1*$
Week 13	$1.4 \pm 0.1$	$1.4 \pm 0.1$	$1.2 \pm 0.1$	$1.2 \pm 0.1$	$1.3 \pm 0.0$	$1.5 \pm 0.1$

# Table G1

Hematology and Clinical Chemistry Data for Rats in the 13-Week Inhalation Study of Nitromethane (continued)

	0 ppm	94 ppm	188 ppm	375 ppm	750 ppm	1,500 ppm	
Female						· · · ·	
Hematology							
n							
n Dav 3	10	10	10	10	10	10	
Day 23	10	10	10	10	10	-8	
Week 13	10	10	10	10	10	10	
Hematocrit (%)					·		
Day 3	$38.9 \pm 0.6$	$38.7 \pm 0.3$	$38.1 \pm 0.4$	36.7 ± 0.3**	36.0 ± 0.3**	36.6 ± 0.4**	
Day 23	$42.6 \pm 0.3$	$40.5 \pm 0.9^{**}$	$41.1 \pm 0.5^*$	37.9 ± 0.4**	35.2 ± 0.3**	31.7 ± 0.2**	
Week 13	$46.8 \pm 0.3$	$46.6 \pm 0.4$	44.7 ± 0.4**	44.4 ± 0.5**	40.7 ± 0.4**	$37.8 \pm 0.4^{**}$	
Hemoglobin (g/dL)							
Day 3	$14.9 \pm 0.2$	$14.9 \pm 0.1$	$14.6 \pm 0.2$	$14.0 \pm 0.1$ **	$13.7 \pm 0.1^{**}$	$14.1 \pm 0.2^{**}$	
Day 23	$16.2 \pm 0.1$	$15.4 \pm 0.3^{**}$	$15.6 \pm 0.2^*$	$14.5 \pm 0.1$ **	$13.5 \pm 0.1$ **	$12.5 \pm 0.1^{**}$	
Week 13	$16.0 \pm 0.1$	$15.8 \pm 0.1$	$15.3 \pm 0.1^{**}$	$15.3 \pm 0.1^{**}$	$14.1 \pm 0.1^{\pm \pm}$	$13.4 \pm 0.2^{\ddagger \ddagger}$	
Erythrocytes $(10^{\circ}/\mu L)$	0.00 + 0.15	0.40 1.0.07	0.04 + 0.11	0.10 + 0.00		0.14 1 0.11*	
Day 3	$8.39 \pm 0.15$	$8.42 \pm 0.07$	$8.34 \pm 0.11$	$8.10 \pm 0.09$	$7.87 \pm 0.07$	$8.14 \pm 0.11^{\circ}$	
Day 23 Week 12	$9.03 \pm 0.00$	$8.80 \pm 0.18$	$9.35 \pm 0.09$	$9.32 \pm 0.09$	$9.14 \pm 0.09$	$8.10 \pm 0.00$	
Week 15 Nucleated emuthroquited	$8.71 \pm 0.05$	8.91 ± 0.00	8.92 ± 0.09	$9.42 \pm 0.07^{++}$	9.24 ± 0.07**	$0.51 \pm 0.10$	
Day 3	$0.07 \pm 0.03$	$0.06 \pm 0.03$	0.08 ± 0.02	$0.07 \pm 0.03$	$0.04 \pm 0.02$	$0.02 \pm 0.02$	
Day 3 Day 23	$0.07 \pm 0.03$	$0.00 \pm 0.03$	$0.03 \pm 0.02$ $0.02 \pm 0.02$	$0.07 \pm 0.03$	$0.04 \pm 0.02$	$0.02 \pm 0.02$	
Week 13	$0.00 \pm 0.00$	$0.03 \pm 0.02$ 0.07 ± 0.02	$0.02 \pm 0.02$	$0.05 \pm 0.02$	$0.22 \pm 0.09$	$0.30 \pm 0.11 $	
Mean cell volume (fL)	0.05 1 0.01	0.07 1 0.02	0.07 1 0.01	0.00 1 0.01		0.00 1 0.11	
Dav 3	46.5 + 0.2	$45.8 \pm 0.2*$	$45.6 \pm 0.3^*$	45.3 ± 0.2**	45.7 ± 0.2**	45.0 ± 0.2**	
Day 23	$47.0 \pm 0.0$	$45.8 \pm 0.2^{**}$	$43.9 \pm 0.2^{**}$	$40.6 \pm 0.2^{**}$	$38.4 \pm 0.2^{**}$	38.8 ± 0.2**	
Week 13	$53.9 \pm 0.2$	$52.4 \pm 0.2^{**}$	$50.1 \pm 0.3^{**}$	47.2 ± 0.2**	$44.2 \pm 0.5^{**}$	$44.4 \pm 0.4^{**}$	
Mean cell hemoglobin	(pg)						
Day 3	$17.7 \pm 0.1$	$17.7 \pm 0.1$	$17.5 \pm 0.1$	17.3 ± 0.1**	17.4 ± 0.1**	$17.3 \pm 0.1^{**}$	
Day 23	$18.0 \pm 0.1$	$17.4 \pm 0.1 **$	$16.7 \pm 0.1^{**}$	$15.6 \pm 0.1 **$	· 14.8 ± 0.1**	$15.3 \pm 0.1^{**}$	
Week 13	$18.3 \pm 0.1$	$17.7 \pm 0.1**$	$17.1 \pm 0.1 **$	$16.2 \pm 0.1$ **	$15.3 \pm 0.1 $ **	$15.7 \pm 0.1^{**}$	
Mean cell hemoglobin	concentration (g/dL)	x					
Day 3	$38.1 \pm 0.1$	$38.4 \pm 0.1$	$38.4 \pm 0.1$	$38.1 \pm 0.1$	$38.1 \pm 0.1$	$38.6 \pm 0.1^{**}$	
Day 23	$38.0 \pm 0.2$	$38.1 \pm 0.2$	$38.0 \pm 0.2$	$38.2 \pm 0.2$	$38.4 \pm 0.2$	$39.5 \pm 0.2^{**}$	
Week 13	$34.1 \pm 0.2$	$33.9 \pm 0.2$	$34.2 \pm 0.2$	$34.4 \pm 0.2$	$34.7 \pm 0.2$	$35.4 \pm 0.2^{**}$	
Platelets $(10^{-7} \mu L)$		50/ 0 · 16 0+		(17 0 1 17 0		(04 ( ) 17 (	
Day 3	$669.7 \pm 26.8$	$586.2 \pm 15.3^{*}$	$609.0 \pm 26.4$	$637.9 \pm 17.9$	$668.0 \pm 15.8$	$624.0 \pm 1/.0$	
Day 25 Week 12	$649.2 \pm 12.7$	$628.9 \pm 14.4$	$637.2 \pm 12.0$	$098.7 \pm 14.0$	$611.9 \pm 14.4^{++}$	$1,1/9.0 \pm 10.3^{++}$	
Leukoovtes (10 ³ /I)	554.2 ± 1.1	$500.0 \pm 10.8$	$528.4 \pm 10.2$	000.0 ± 11./**	009.9 ± 10.8++	$703.0 \pm 32.0^{++}$	
Day 3	$9.26 \pm 0.32$	$9.98 \pm 0.32$	$10.43 \pm 0.23*$	$9.78 \pm 0.24$	$9.83 \pm 0.24$	8.02 + 0.26	
Day 23	$635 \pm 0.27$	$9.93 \pm 0.52$ 6 57 ± 0.43	$6.20 \pm 0.35$	$6.19 \pm 0.25$	$5.90 \pm 0.20$	$6.25 \pm 0.50$	
Week 13	$9.56 \pm 0.67$	$7.99 \pm 0.29$	$8.08 \pm 0.51$	$10.28 \pm 0.80$	$9.95 \pm 0.73$	$10.60 \pm 0.82$	
Segmented neutrophil	$(10^{3}/\mu L)$	7.77 <u>T</u> 0.27	0.00 1 0.01	10.20 <u>T</u> 0.00	100 T 000	10:00 1 0:00	
Day 3	$0.90 \pm 0.07$	$0.84 \pm 0.13$	$0.77 \pm 0.13$	$0.78 \pm 0.07^{b}$	$0.64 \pm 0.09$	$0.49 \pm 0.08^{**}$	
Day 23	$0.72 \pm 0.09$	$0.54 \pm 0.05$	$0.85 \pm 0.08$	$0.67 \pm 0.10$	$0.43 \pm 0.07$	$0.47 \pm 0.11$	
Week 13	$1.25 \pm 0.17$	$1.30 \pm 0.13$	$1.22 \pm 0.13$	$1.64 \pm 0.33$	$1.84 \pm 0.19$	$1.63 \pm 0.21$	
Lymphocytes (10 ³ /µL	) –	—		-			
Day 3	8.14 ± 0.34	8.91 ± 0.35	9.35 ± 0.28	$8.75 \pm 0.32^{b}$	8.93 ± 0.21	7.36 ± 0.26	
	5 20 1 0 27	572 + 0.38	5 09 + 0 28	5 20 + 0 19	5 25 ± 0 28	5 51 + 0.45	
Day 23	$5.39 \pm 0.27$	$3.75 \pm 0.56$	$3.08 \pm 0.38$	$5.30 \pm 0.18$	$5.25 \pm 0.20$	$5.51 \pm 0.45$	

Nitromethane, NTP TR 461

TABLE G1 Hematology and Clinical Chemistry Data for Rats in the 13-Week Inhalation Study of Nitromethane (continued)

	0 ppm	94 ppm	188 ppm	375 ppm	750 ppm	1,500 ppm
Female (continued)	· · · · · · · · · · · · · · · · · · ·	·····	<u></u>			
Hematology (continued)						• • •
(continued)						
n						
Day 3	10	10	10	10	10	10
Day 23	10	10	10	10	10	8
Week 13	10	10	10	10	10	10
Monocytes $(10^3/\mu L)$		•				· · · ·
Day 3	$0.20 \pm 0.06$	$0.21 \pm 0.04$	$0.26 \pm 0.05$	$0.20 \pm 0.04^{b}$	$0.23 \pm 0.04$	$0.12 \pm 0.03$
Day 23	$0.23 \pm 0.04$	$0.26 \pm 0.06$	$0.23 \pm 0.03$	$0.19 \pm 0.03$	$0.19 \pm 0.05$	$0.23 \pm 0.05$
Week 13	$0.33 \pm 0.12$	$0.16 \pm 0.04$	$0.17 \pm 0.05$	$0.23 \pm 0.06$	$0.26 \pm 0.09$	$0.22 \pm 0.05$
Eosinophils $(10^3/\mu L)$						· · ·
Day 3	$0.02 \pm 0.01$	$0.01 \pm 0.01$	$0.05 \pm 0.02$	$0.05 \pm 0.02^{b}$	$0.03 \pm 0.02$	$0.06 \pm 0.02$
Day 23	$0.02 \pm 0.01$	$0.04 \pm 0.01$	$0.04 \pm 0.01$	$0.03 \pm 0.01$	$0.03 \pm 0.01$	$0.04 \pm 0.04$
Week 13	$0.02 \pm 0.01$	$0.06 \pm 0.02$	$0.04 \pm 0.02$	$0.07 \pm 0.03$	$0.02 \pm 0.02$	$0.06 \pm 0.03$
Methemoglobin (g/dL)						
Day 3	$0.20 \pm 0.03$	$0.27 \pm 0.10$	$0.17 \pm 0.04$	$0.10 \pm 0.02*$	$0.11 \pm 0.01$	$0.16 \pm 0.01$
Day 23	$0.09 \pm 0.01$	$0.10 \pm 0.01^{6}$	$0.12 \pm 0.01*$	$0.12 \pm 0.01^{**}$	$0.19 \pm 0.01 **$	$0.35 \pm 0.01^{**}$
Week 13	$0.20 \pm 0.01$	$0.20 \pm 0.01$	$0.20 \pm 0.01$	$0.21 \pm 0.01$	$0.25 \pm 0.01$ **	$0.40 \pm 0.04^{**}$
	· .					,
Clinical Chemistry		'		× , -		· · · · · · · · · · · · · · · · · · ·
ennical enclinistry						
n						
Day 3	10	10	. 10	10	10	10
Day 23	10	9	10	10	10	8
Week 13	10	10	10	10	10	10
Urea nitrogen (mg/dL)			~			
Day 3	$21.3 \pm 0.6$	17.8 ± 0.6**	_ 17.2 ± 0.5**	$16.6 \pm 0.5 **$	$16.9 \pm 0.4 **$	$17.5 \pm 0.6**$
Day 23	$14.3 \pm 0.6$	$14.0 \pm 0.4$	$14.7 \pm 0.2$	$13.7 \pm 0.5$	$14.7 \pm 0.4$	$16.0 \pm 0.8$
Week 13	$22.6 \pm 0.8$	$23.3 \pm 1.0$	$21.9 \pm 1.0$	$22.7 \pm 1.1$	$22.6 \pm 0.8$	$22.2 \pm 0.8$ ,
Creatinine (mg/dL)						
Day 3	$0.61 \pm 0.04$	0.79 ± 0.02**	0.75 ± 0.04**	$0.66 \pm 0.02*$	$0.73 \pm 0.03*$	$0.99 \pm 0.04 **$
Day 23	$0.77 \pm 0.03$	$0.70 \pm 0.02$	$0.73 \pm 0.03$	$0.71 \pm 0.04$	$0.82 \pm 0.04$	$1.28 \pm 0.09^{**}$
Week 13	$0.78 \pm 0.03$	$0.79 \pm 0.03$	$0.75 \pm 0.02$	$0.79 \pm 0.02$	$0.73 \pm 0.02$	$0.74 \pm 0.02$
Total protein (g/dL)	•	<i>:</i>				~
Day 3	$6.6 \pm 0.1$	$6.2 \pm 0.1*$	$6.5 \pm 0.1$	$6.7 \pm 0.1$	$6.5 \pm 0.1$	$6.4 \pm 0.1$
Day 23	$7.2 \pm 0.1$	$6.8 \pm 0.1$	$7.2 \pm 0.1$	$7.1 \pm 0.1$	$7.0 \pm 0.1$	$6.5 \pm 0.1$
Week 13	$7.4 \pm 0.1$	$7.4 \pm 0.1$	$7.7 \pm 0.1$	$7.2 \pm 0.3$	$7.5 \pm 0.1$	$7.0 \pm 0.1$
Albumin (g/dL)		10.01		45101	45 + 0.0	$17 \pm 01$
Day 3	$4.5 \pm 0.1$	$4.2 \pm 0.1$	$4.4 \pm 0.1$	$4.5 \pm 0.1$	$4.5 \pm 0.0$	$4.7 \pm 0.1$
Day 23	$4.9 \pm 0.1$	$4.6 \pm 0.1^{*}$	$4.8 \pm 0.1$	$4.8 \pm 0.1$	$4.9 \pm 0.1$	$4.7 \pm 0.1$
Week 13	$5.1 \pm 0.1$	$5.1 \pm 0.1$	$5.4 \pm 0.1$	$5.0 \pm 0.2$	$5.5 \pm 0.1$	4.7 I U.I
Globulin (g/dL)		20 / 01	21401	23 + 0.0	$20 \pm 01$	$18 \pm 0.0*$
Day 3	$2.1 \pm 0.1$	$2.0 \pm 0.1$	$2.1 \pm 0.1$	$2.3 \pm 0.0$	$2.0 \pm 0.1$ 21 + 0.1	$1.0 \pm 0.0$
Day 23	$2.3 \pm 0.1$	$2.2 \pm 0.1$	$2.4 \pm 0.0$	$2.5 \pm 0.1$	$2.1 \pm 0.1$ $2.2 \pm 0.1$	$2.1 \pm 0.1$
week 13	$2.3 \pm 0.1$	2.4 ± 0.1	2.2 1 0.1	2.1 <u>1</u> 0.1	2.2 1 0.1	

#### Hematology and Clinical Chemistry

#### Table G1

Hematology and Clinical Chemistry Data for Rats in the 13-Week Inhalation Study of Nitromethane (continued)

	0 ppm	94 ppm	188 ppm	375 ppm	750 ppm	1,500 ppm
					÷	
e <b>male</b> (continued)			.e		Pr	·
linical Chemistry (continu	ed)					
Day 3	10	10	10	10	10	10
Day 23	10	9	10	10	10	8
Week 13	10	10	10	10	10	10
Alanine aminotransfera	se (IU/L)					
Day 3	$34 \pm 1$	$37 \pm 1$	$33 \pm 1$	36 ± 1	$34 \pm 1$	$32 \pm 1^{b}$
Day 23	29 ± 2	$30 \pm 1$	$31 \pm 1$	$31 \pm 1$	¹ 28 ± 1	$26 \pm 1$
Week 13	$51 \pm 3$	47 ± 4	53 ± 7	$46 \pm 5$	' ' 38 ± 2*	38 ± 4**
Alkaline phosphatase (I	IU/L)	_	—	-	-	-
Day 3	$762 \pm 36$	706 ± 21	718 ± 24	747 ± 20	678 ± 22	643 ± 23**
Day 23	$415 \pm 15$	$479 \pm 9$	$416 \pm 6$	$388 \pm 11$	$403 \pm 15$	368 ± 7*
Week 13	348 + 15	354 + 17	327 + 19	317 + 27	332 ± 9	322 + 12
Creatine kinase (IU/L)	-	· -	_	-	-	-
Dav 3	366 + 45	357 + 9 ^b	434 + 51	416 + 23	398 ± 34	302 + 32
Day 23	$502 \pm 178^{b}$	$364 \pm 62$	$333 \pm 43$	$316 \pm 55$	$193 \pm 20*$	$207 \pm 25$
Week 13	$191 \pm 29$	$181 \pm 19$	$120 \pm 11$	$173 \pm 19$	$145 \pm 27$	$128 \pm 19$
Sorbitol dehydrogenase	e (IU/L)	-	-	-	<del></del>	-
Day 3	$10 \pm 1$	$11 \pm 0$	8 ± 1	$10 \pm 1$	$10 \pm 1$	$10 \pm 0$
Day 23	$13 \pm 0$	$12 \pm 1$	$12 \pm 1$	$12 \pm 0$	$11 \pm 1^{**}$	$11 \pm 1^{**}$
Week 13	10 + 1	11 + 1	10 + 1	10 + 1	8 ± 0*	9 ± 1*
Bile acids (µmol/L)	-		- <b>-</b>		-	-
Day 3	$9.8 \pm 1.2^{c}$	$8.2 \pm 1.1^{b}$	$10.4 \pm 2.3^{d}$	$8.7 \pm 2.2^{d}$	$9.0 \pm 0.8$	7.7 ± 1.6
Day 23	$10.6 \pm 1.3$	$11.3 \pm 1.4^{c}$	$7.2 \pm 1.4^{b}$	$7.6 \pm 2.2$	$8.6 \pm 2.4$	$10.9 \pm 4.0$
Week 13	$13.4 \pm 2.8$	$7.7 \pm 1.8$	$13.7 \pm 3.7$	$9.2 \pm 1.9$	$16.5 \pm 4.4$	22.9 ± 5.5
Thyroid-stimulating ho	rmone (ng/mL)	_	_	_		
Day 23	$0.1 \pm 0.1^{g}$	$0.5 \pm 0.2^{e}$	$0.5 \pm 0.1^{c}$	$0.4 \pm 0.2^{f}$	$0.6 \pm 0.1^{*b}$	$0.5 \pm 0.1^{f}$
Week 13	$1.7 \pm 0.2$	$2.1 \pm 0.3$	$1.7 \pm 0.2$	$1.6 \pm 0.3^{b}$	$2.0 \pm 0.3$	$1.7 \pm 0.2$
Triiodothyronine (ng/d	L)	—	. —	-	÷ —	
Day 23	$110 \pm 5$	$107 \pm 6$	109 ± 7	96 ± 5	92 ± 4*	85 ± 3**
Week 13	$150 \pm 12$	$148 \pm 12$	$163 \pm 10$	$152 \pm 14$	148 ± 10	$136 \pm 12$
Thyroxine (µg/dL)	-	-	-	_	_	-
Day 23	$4.8 \pm 0.2$	$4.6 \pm 0.2$	4.1 ± 0.3*	3.6 ± 0.1**	3.3 ± 0.2**	3.2 ± 0.2**
Week 13	$4.6 \pm 0.4$	$4.1 \pm 0.3$	$4.3 \pm 0.2$	$4.0 \pm 0.2$	$3.7 \pm 0.2$	$4.0 \pm 0.3$
Free thyroxine (ng/dL)	j —	—	— .	-		-
Day 23	$0.9 \pm 0.1^{c}$	$1.1 \pm 0.1^{c}$	$0.9 \pm 0.1$	$0.7 \pm 0.0^{b}$	$0.5 \pm 0.1$ **	0.5 ± 0.0**
Week 13	0.9 + 0.1	$07 \pm 01$	$0.7 \pm 0.1$	$0.7 \pm 0.1$	$0.6 \pm 0.1$	$07 \pm 01$

* Significantly different ( $P \le 0.05$ ) from the control group by Dunn's or Shirley's test

** P≤0.01

^a Mean  $\pm$  standard error. Statistical tests were performed on unrounded data.

b n=9

c n=8

¹ n=7

e n=5

 $f_{n=6}$ 

 $g_{n=4}$ 

d
# APPENDIX H REPRODUCTIVE TISSUE EVALUATIONS AND ESTROUS CYCLE CHARACTERIZATION

Table H1	Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization	
	for Rats in the 13-Week Inhalation Study of Nitromethane	250
Table H2	Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization	
	for Mice in the 13-Week Inhalation Study of Nitromethane	251

	0 ppm	375 ppm	750 ppm	1,500 ppm
Male			· · · · · · · · · · · · · · · · · · ·	<u> </u>
n	10	. 10	10	10
Weights (g)				· ·
Necronsy hody wt	338 + 7	341 + 4	331 + 4	299 + 11**
L. cauda	$0.207 \pm 0.004$	$0.210 \pm 0.004$	$0.204 \pm 0.006$	$0.177 \pm 0.009**$
L. epididymis	$0.467 \pm 0.009$	$0.468 \pm 0.006$	$0.204 \pm 0.000$	$0.412 \pm 0.013**$
L. testis	$1.39 \pm 0.03$	$1.36 \pm 0.01$	$1.34 \pm 0.02$	$1.29 \pm 0.02^{**}$
Spermatid measurements				
Spermatid heads (10 ⁷ /g testis)	$9.21 \pm 0.46$	$9.23 \pm 0.50$	$9.35 \pm 0.45$	10.73 + 0.50
Spermatid heads (10 ⁷ /testis)	$12.87 \pm 0.78$	$12.55 \pm 0.73$	$12.54 \pm 0.60$	13.79 + 0.63
Spermatid count	. –		-	<b>-</b>
(mean/10 ⁻⁴ mL suspension)	64.33 ± 3.89	62.75 ± 3.63	62.68 ± 3.02	68.95 ± 3.14
Epididymal spermatozoal measurements		• *		<u>.</u>
Motility (%)	94.57 ± 1.30	92.16 ± 1.90	87.11 ± 1.88**	76.43 ± 2.78**
Concentration	- :			
(10 ⁶ /g cauda epididymal tissue)	449 ± 45	483 ± 24	434 ± 35	380 ± 42
•				
Female	• .			
n	10	10	10	10
	. 10	10	10	10
Necronsy body wt (a)	188 ± 5	200 ± 5	$105 \pm 4$	178 ± 3
Estrous cycle length (days)	$4.89 \pm 0.07^{b}$	$4.75 \pm 0.16^{\circ}$	$5.00 \pm 0.14^{b}$	$5.00 \pm 0.15$
Estrous stages (% of cycle)	4.07 T 0.07	4.75 T 0.10	5.00 T 0.14	5.00 I 0.15
Diestrus	30.8	26.7	35.8	30.0
Proestrus	15.8	13.3	16.7	12.5
Estrus	23.3	23.3	25.8	26.7
Metestrus	14.2	11.7	11.7	14.2
Uncertain diagnoses	15.8	25.0	10.0	16.7

#### TABLE H1

Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Rats in the 13-Week Inhalation Study of Nitromethane^a

** Significantly different (P≤0.01) from the control group by Williams' or Dunnett's test (body and tissue weights) or by Shirley's test (motility)

Weights, spermatid and epididymal spermatozoal measurements, and estrous cycle lengths are presented as mean ± standard error.
 Differences from the control group for spermatid measurements, epididymal spermatozoal concentration, and estrous cycle length are not significant by Dunn's test. By multivariate analysis of variance, exposed females do not differ significantly from the control females in the relative length of time spent in the estrous stages.

^b Estrous cycle was longer than 12 days or unclear in 1 of 10 animals.

^c Estrous cycle was longer than 12 days or unclear in 2 of 10 animals.

### TABLE H2

Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Mice in the 13-Week Inhalation Study of Nitromethane^a

	0 ppm	375 ppm	750 ppm	1,500 ppm
Male				
n	10	10	10	10
Weights (g)				
Necropsy body wt	$36.1 \pm 0.5$	$36.3 \pm 0.6$	$35.2 \pm 0.4$	$34.7 \pm 0.5$
L. cauda	$0.020 \pm 0.001$	$0.019 \pm 0.001$	$0.020 \pm 0.001$	$0.018 \pm 0.001$
L. epididymis	$0.049 \pm 0.002$	$0.047 \pm 0.002$	$0.050 \pm 0.002$	$0.050 \pm 0.003$
L. testis	$0.118 \pm 0.003$	$0.121 \pm 0.002$	$0.117 \pm 0.003$	$0.121 \pm 0.001$
Spermatid measurements				
Spermatid heads (10 ⁷ /g testis)	$22.53 \pm 0.46$	$20.45 \pm 0.62$	$21.22 \pm 0.83$	$21.82 \pm 0.81$
Spermatid heads (10 ⁷ /testis)	$2.65 \pm 0.06$	$2.46 \pm 0.06$	$2.48 \pm 0.10$	$2.64 \pm 0.10$
Spermatid count				
(mean/10 ⁻⁴ mL suspension)	82.80 ± 1.89	76.85 ± 1.80	77.43 ± 3.11	82.58 ± 3.14
Epididymal spermatozoal measurements				
Motility (%)	93.50 ± 0.46	85.09 ± 1.21**	86.47 ± 1.17**	82.41 ± 1.30**
Concentration				
(10 ⁶ /g cauda epididymal tissue)	1,106 ± 84	1,035 ± 95	1,048 ± 85	1,244 ± 138
Female				
n	10	10	10	10
Necropsy body wt (g)	$31.1 \pm 0.7$	$34.2 \pm 0.8$	$31.5 \pm 0.5$	$30.4 \pm 0.5$
Estrous cycle length (days)	$4.00 \pm 0.00^{\circ}$	$4.33 \pm 0.14^{*d}$	$4.50 \pm 0.21*$	$4.71 \pm 0.26^{**e}$
Estrous stages ^b (% of cycle)				_
Diestrus	25.0	16.7	25.8	25.0
Proestrus	10.0	17.5	20.8	15.0
Estrus	33.3	25.8	23.3	24.2
Metestrus	9.2	13.3	17.5	16.7
Uncertain diagnoses	22.5	26.7	12.5	19.2

* Significantly different ( $P \le 0.05$ ) from the control group by Shirley's test

** P≤0.01

^a Weights, spermatid and epididymal spermatozoal measurements, and estrous cycle lengths are presented as mean ± standard error. Differences from the control group for weights, spermatid measurements, and epididymal spermatozoal concentration are not significant by Dunn's or Dunnett's test.

^b Evidence shows that females exposed to 750 or 1,500 ppm differ significantly (Wilk's Criterion, P≤0.05) from the control females in the relative length of time spent in the estrous stages. Exposed females spent more time in metestrus and proestrus and less time in estrus than control females.

^c Estrous cycle was longer than 12 days or unclear in 2 of 10 animals.

^d Estrous cycle was longer than 12 days or unclear in 1 of 10 animals.

^e Estrous cycle was longer than 12 days or unclear in 3 of 10 animals.

# APPENDIX I NEUROBEHAVIORAL EVALUATION RESULTS

Table I1	Neurobehavior Data for Rats in the 13-Week Inhalation Study	
	of Nitromethane	254

253

### TABLE I1

Neurobehavior Data for Rats in the 13-Week Inhalation Study of Nitromethane^a

0 ppm	94 ppm	188 ppm	375 ppm	750 ppm	1,500 ppm
	· · · · · · · · · · · · · · · · · · ·	e	· · · · · · · · · · · · · · · · · · ·		
10	10	10	10	10	10
		· · ·			
0.617 ± 0.025	0.554 ± 0.015	0.583 ± 0.037	0.592 ± 0.021	0.568 ± 0.029	0.471 ± 0.024**
$0.433 \pm 0.020$	0.399 ± 0.026	0.407 ± 0.020	0.378 ± 0.023	$0.382 \pm 0.017$	0.213 ± 0.020**
$2.90 \pm 0.40$	$2.22 \pm 0.24$	$2.51 \pm 0.24$	$2.67 \pm 0.31$	$2.93 \pm 0.33$	$2.31 \pm 0.39$
					1. K. 1.
61.85 ± 14.42 ^b	69.80 ± 6.43	65.37 ± 7.15	42.13 ± 4.00	38.98 ± 4.54 ^b	42.57 ± 4.53
	· · · ·				•
$42.82 \pm 2.74^{b}$	47.92 ± 2.08	40.93 ± 2.61	40.25 ± 2.66	38.35 ± 1.63 ^b	48.88 ± 3.12
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	· · ·	· .	1		
$0.598 \pm 0.020$	$0.633 \pm 0.021$	$0.700 \pm 0.011$ **	$0.619 \pm 0.029$	0.585 ± 0.019	$0.632 \pm 0.018$
$0.403 \pm 0.018$	$0.425 \pm 0.011$	$0.435 \pm 0.014$	$0.419 \pm 0.013$	$0.333 \pm 0.019^{**}$	0.209 ± 0.015**
$2.67 \pm 0.16$	$3.10 \pm 0.36$	$3.08 \pm 0.33$	$3.09 \pm 0.27$	$2.71 \pm 0.32$	$1.79 \pm 0.26$
			,	1	
29.88 + 3.49	43.82 ± 7.00*	38:67 ± 2.25	32.92 ± 3.47	24.47 ± 1.25	27.17 ± 2.39
		-	<del>-</del> .		
39.13 + 1.22	42.20 + 1.50	$38.17 \pm 1.75$	42.44 + 2.78	37.28 ± 2.41	39.90 ± 2.06
	0 ppm 10 $0.617 \pm 0.025$ $0.433 \pm 0.020$ $2.90 \pm 0.40$ $61.85 \pm 14.42^{b}$ $42.82 \pm 2.74^{b}$ $0.598 \pm 0.020$ $0.403 \pm 0.018$ $2.67 \pm 0.16$ $29.88 \pm 3.49$ $39.13 \pm 1.22$	0 ppm94 ppm1010 $0.617 \pm 0.025$ $0.433 \pm 0.020$ $2.90 \pm 0.40$ $0.554 \pm 0.015$ $0.399 \pm 0.026$ $2.22 \pm 0.24$ $61.85 \pm 14.42^b$ $47.92 \pm 2.08$ $69.80 \pm 6.43$ $42.82 \pm 2.74^b$ $47.92 \pm 2.08$ $0.598 \pm 0.020$ $0.403 \pm 0.018$ $2.67 \pm 0.16$ $0.425 \pm 0.011$ $3.10 \pm 0.36$ $29.88 \pm 3.49$ $43.82 \pm 7.00^*$ $39.13 \pm 1.22$	0 ppm94 ppm188 ppm101010 $0.617 \pm 0.025$ $0.433 \pm 0.020$ $2.90 \pm 0.40$ $0.554 \pm 0.015$ $0.399 \pm 0.026$ $2.22 \pm 0.24$ $0.583 \pm 0.037$ $0.407 \pm 0.020$ $2.51 \pm 0.24$ $61.85 \pm 14.42^b$ 	0 ppm94 ppm188 ppm375 ppm10101010 $0.617 \pm 0.025$ $0.433 \pm 0.020$ $2.90 \pm 0.40$ $0.554 \pm 0.015$ $2.22 \pm 0.24$ $0.583 \pm 0.037$ $0.407 \pm 0.020$ $2.51 \pm 0.24$ $0.592 \pm 0.021$ $0.378 \pm 0.023$ $2.67 \pm 0.31$ $61.85 \pm 14.42^{b}$ $42.82 \pm 2.74^{b}$ $69.80 \pm 6.43$ $47.92 \pm 2.08$ $65.37 \pm 7.15$ $40.93 \pm 2.61$ $40.25 \pm 2.66$ $0.598 \pm 0.020$ $0.403 \pm 0.018$ $2.67 \pm 0.16$ $0.633 \pm 0.021$ $0.425 \pm 0.011$ $3.10 \pm 0.36$ $0.700 \pm 0.011^{**}$ $3.08 \pm 0.33$ $0.619 \pm 0.029$ $0.419 \pm 0.013$ $3.09 \pm 0.27$ $29.88 \pm 3.49$ $43.82 \pm 7.00^{*}$ $38.67 \pm 2.25$ $32.92 \pm 3.47$ $39.13 \pm 1.22$ $42.20 \pm 1.50$ $38.17 \pm 1.75$ $42.44 \pm 2.78$	0 ppm94 ppm188 ppm375 ppm750 ppm101010101010 $0.617 \pm 0.025$ $0.433 \pm 0.020$ $2.90 \pm 0.40$ $0.554 \pm 0.015$ $2.22 \pm 0.24$ $0.583 \pm 0.037$ $0.407 \pm 0.020$ $2.51 \pm 0.24$ $0.592 \pm 0.021$ $2.67 \pm 0.31$ $0.568 \pm 0.029$ $0.382 \pm 0.017$ $2.93 \pm 0.33$ $61.85 \pm 14.42^{b}$ $42.82 \pm 2.74^{b}$ $69.80 \pm 6.43$ $47.92 \pm 2.08$ $65.37 \pm 7.15$ $40.93 \pm 2.61$ $40.25 \pm 2.66$ $40.25 \pm 2.66$ $38.35 \pm 1.63^{b}$ $0.598 \pm 0.020$ $0.403 \pm 0.018$ $2.67 \pm 0.16$ $0.619 \pm 0.029$ $3.10 \pm 0.36$ $0.585 \pm 0.019$ $0.435 \pm 0.014$ $3.08 \pm 0.33$ $0.619 \pm 0.029$ $0.419 \pm 0.013$ $3.09 \pm 0.27$ $0.585 \pm 0.019$ $2.71 \pm 0.32$ $29.88 \pm 3.49$ $43.82 \pm 7.00^*$ $38.67 \pm 2.25$ $32.92 \pm 3.47$ $24.47 \pm 1.25$ $24.47 \pm 1.25$ $37.28 \pm 2.41$

* Significantly different (P $\leq$ 0.05) from the control group by Williams' or Dunnett's test

** P≤0.01

^a Mean  $\pm$  standard error

 $b_{n=9}$ 

## APPENDIX J

## CHIEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

PROCUREME	nt and Characterization of Nitromethane	256
VAPOR GENE	eration and Exposure System	257
VAPOR CON	CENTRATION MONITORING	258
CHAMBER A'	IMOSPHERE CHARACTERIZATION	258
Figure J1	Infrared Absorption Spectrum of Nitromethane	261
FIGURE J2	Nuclear Magnetic Resonance Spectrum of Nitromethane	262
Figure J3	Nitromethane Vapor Generator	263
Figure J4a	Nitromethane Vapor Generation and Delivery System for the 16-Day Studies	264
FIGURE J4b	Nitromethane Vapor Generation and Delivery System	
	for the 13-Week and 2-Year Studies	265
FIGURE J5	Nitromethane Inhalation Exposure Chamber	266
FIGURE J6a	Nitromethane Exposure Suite for the 16-Day Studies	267
FIGURE J6b	Nitromethane Exposure Suite for the 13-Week and 2-Year Studies	268
Table J1	Summary of Chamber Concentrations in the 16-Day Inhalation Studies	
	of Nitromethane	269
TABLE J2	Summary of Chamber Concentrations in the 13-Week Inhalation Studies	
	of Nitromethane	269
TABLE J3	Summary of Chamber Concentrations in the 2-Year Inhalation Studies	
	of Nitromethane	270
FIGURE J7	Monthly Mean Concentration and Standard Deviation in the 94 ppm	
	Rat Exposure Chamber in the 2-Year Inhalation Study of Nitromethane	271
FIGURE J8	Monthly Mean Concentration and Standard Deviation in the 188 ppm	
	Rat Exposure Chamber in the 2-Year Inhalation Study of Nitromethane	272
FIGURE J9	Monthly Mean Concentration and Standard Deviation in the 375 ppm	
	Rat Exposure Chamber in the 2-Year Inhalation Study of Nitromethane	273
FIGURE J10	Monthly Mean Concentration and Standard Deviation in the 188 ppm	
	Mouse Exposure Chamber in the 2-Year Inhalation Study of Nitromethane	274
FIGURE J11	Monthly Mean Concentration and Standard Deviation in the 375 ppm	
	Mouse Exposure Chamber in the 2-Year Inhalation Study of Nitromethane	275
FIGURE J12	Monthly Mean Concentration and Standard Deviation in the 750 ppm	
	Mouse Exposure Chamber in the 2-Year Inhalation Study of Nitromethane	276

## CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

## **PROCUREMENT AND CHARACTERIZATION OF NITROMETHANE**

Nitromethane was obtained from W.R. Grace and Company (Lexington, MA) in three lots. Lot 1F 13 06 was used during the 16-day studies and the beginning of the 13-week studies; lot 1-H-0501, which was received in two shipments (batches 2 and 3), was used throughout the remainder of the 13-week studies and at the beginning of the 2-year studies. Lot 1-H-1004 was used throughout the remainder of the 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on the analyses performed in support of the nitromethane studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a clear, colorless liquid, was identified as nitromethane by infrared, ultraviolet/visible, and nuclear magnetic resonance spectrometry. All spectra were consistent with those expected for the structure and with the literature spectra (*Sadtler Standard Spectra*) of nitromethane. The infrared and nuclear magnetic resonance spectra are presented in Figures J1 and J2. The boiling point and density of the chemical were also consistent with literature references (*Merck Index*, 1983).

The purity of each lot was determined by elemental analysis, Karl Fischer water analysis, functional group titration, and gas chromatography. For indirect iodometric titration, aqueous nitromethane samples were reacted with hypochlorite in 0.25 N sodium hydroxide and then cooled; the excess hypochlorite was reacted with potassium iodide in an acidic medium, and the liberated iodine was titrated with 0.1 N sodium thiosulfate to the starch endpoint. Gas chromatography was performed with a flame ionization detector. Two systems were used:

- A) 80/100 Carbopack C/0.1% SP-1000 glass column, with an oven temperature program of 50° C for 5 minutes, then 50° to 225° C at 10° C per minute, and a nitrogen carrier gas at a flow rate of 70 mL/minute and
- B) DB-Wax fused silica column with an oven temperature program of 40° C for 5 minutes, then 40° to 230° C at 10° C per minute, a helium carrier gas at a flow rate of 10 mL/minute, and a nitrogen makeup gas at a flow rate of 25 mL/minute (20 mL/minute for lot 1-H-1004).

For lot 1F 13 06, elemental analyses of carbon and hydrogen agreed with the theoretical values for nitromethane, but results for nitrogen were low. Karl Fischer water analysis indicated  $0.022\% \pm 0.004\%$  water. Functional group titration indicated a purity of  $100\% \pm 1\%$ . Both gas chromatographic systems indicated one major peak and one impurity with an area greater than 0.1% relative to the major peak. The area of the impurity peak indicated by system A was 0.62% relative to the major peak; the area of the impurity peak indicated by system B was 0.52% relative to the major peak. The overall purity of lot 1F 13 06 was determined to be approximately 99%.

Additional analyses of lot 1F 13 06 were performed with gas chromatography/mass spectrometry to identify the impurity indicated by gas chromatography. The gas chromatograph system included an 80/100 Carbopack C/0.1% SP-1000 column with an oven temperature program of 40° C for 4 minutes, then 40° to 220° C at 10° C per minute, and a helium carrier gas at a flow rate of 30 mL/minute. The mass spectrum of the impurity was consistent with that of propionitrile; an additional impurity observed in the sample was identified as 2-nitropropane. The quantity of propionitrile was determined with gas chromatography by system A described under the purity analyses, but with a final temperature of 200° C

#### Chemical Characterization and Generation of Chamber Concentrations

and with cyclohexane as an internal standard; a concentration of  $0.400\% \pm 0.001\%$  propionitrile was determined. The quantity of 2-nitropropane, determined with the same gas chromatographic system but with cyclohexanone as an internal standard, was determined to be  $0.017\% \pm 0.000\%$ .

For lot 1-H-0501 (batch 2), the supplier indicated a purity of 99.3% for the bulk chemical, with 0.27%nitroethane present as a contaminant. Elemental analyses of carbon and hydrogen by the analytical chemistry laboratory agreed with the theoretical values for nitromethane, but results for nitrogen were low. Karl Fischer water analysis indicated  $0.018\% \pm 0.003\%$  water. Functional group titration indicated a purity of 98.9%  $\pm$  0.8%. Gas chromatography with system A indicated one major peak and three impurities with a combined area of 1.69% relative to the major peak; the major impurity was identified as propionitrile. System B indicated one major peak and two impurities with a combined area of 1.49% relative to the major peak. Batch 3 of lot 1-H-0501 was also analyzed with gas chromatographic system A; one major peak and three impurities with a total peak area 1.71% relative to the major peak were identified, with the major impurity identified as propionitrile. Major peak comparisons of batch 2 with lot 1F 13 06 and of batch 3 with batch 2 were performed with gas chromatography with a flame ionization detector, 10% SP-1000 on 80/100 Supelcoport glass column, a nitrogen carrier gas at 70 mL/minute, an oven temperature program of 80° C for 4 minutes, then 80° to 130° C at 10° C per minute, and tridecane as an internal standard. The results indicated a purity of 99.3%  $\pm$  0.3% for batch 2 of lot 1-H-0501 relative to lot 1F 13 06 and a purity of 99.5% + 0.5% for batch 3 relative to batch 2. The overall purity of lot 1-H-0501 was determined to be approximately 98%.

For lot 1-H-1004, the supplier indicated a 99% purity of the bulk chemical, with nitroethane (0.25%) and 2-nitropropane (0.03%) present as contaminants. Elemental analyses of carbon and hydrogen by the analytical chemistry laboratory agreed with the theoretical values for nitromethane, but results for nitrogen were low. Karl Fischer water analysis indicated  $0.086\% \pm 0.006\%$  water. Functional group titration indicated a purity of 97.8%  $\pm 0.5\%$ . Gas chromatography with system A indicated one major peak and three impurities with a combined area of 1.5% relative to the major peak; the major impurity was identified as propionitrile. System B indicated one major peak and three impurities with a combined area of 1.9% relative to the major peak. Major peak comparison of lot 1-H-1004 with lot 1F 13 06 by gas chromatography by the system described for major peak comparisons of lot 1-H-0501, but with an isothermal oven temperature of 80° C, indicated a purity of 100.3%  $\pm 0.9\%$  for lot 1-H-1004 relative to lot 1F 13 06. The overall purity of lot 1-H-1004 was determined to be approximately 98%.

Accelerated stability studies of lots 1F 13 06 and 1-H-0501 of the bulk chemical were conducted with the gas chromatography system described for the major peak comparisons of lot 1-H-0501, but with an isothermal oven temperature of 80° C for lot 1F 13 06. Nitromethane was determined to be stable as a bulk chemical when stored in Teflon[°]-lined amber glass bottles, protected from light, for up to 2 weeks at temperatures up to 60° C. To ensure stability, the bulk chemical was stored in the original shipping containers (metal drums and amber glass bottles) at room temperature; lot 1F 13 06 was stored under a nitrogen headspace. Stability was monitored by the study laboratory throughout the studies with gas chromatography; no degradation of the bulk chemical was detected.

### VAPOR GENERATION AND EXPOSURE SYSTEM

Nitromethane was held in a stainless-steel reservoir under a nitrogen blanket; a MasterFlex variable-speed peristaltic pump head (Cole-Parmer, Inc., Chicago, IL) was used to pump nitromethane through a liquid distribution manifold of stainless steel tubing to heated-wick vaporizers (Figure J3). Before and during the 16-day studies, the rubber tubing in the peristaltic pump used to deliver nitromethane to the generation system was analyzed for suitability by testing for flexibility, size, appearance, and weight loss on drying; no deterioration was noted. Nitromethane cycled through and held in the tubing was also analyzed for

purity and for the presence of phthalates by gas chromatography; results indicated that the sample had a purity of greater than 99%, and no phthalates were detected. The tubing was replaced immediately before the 16-day studies began and every 2 weeks during the 13-week and 2-year studies.

During the 16-day studies, single vaporizers were used for each of the 750 and 1,500 ppm chambers, and a third vaporizer was located in the vapor distribution system that supplied the 94, 188, and 375 ppm chambers (Figure J4a). During the 13-week and 2-year studies, one set of dual vaporizers supplied nitromethane vapor to all chambers (Figure J4b). Each vaporizer consisted of a stainless-steel cylinder covered with a glass fiber wick from which the liquid nitromethane was vaporized (Decker *et al.*, 1982). An 80-watt heater and two temperature-sensing elements were located within the cylinder. One sensing element was connected to a remote temperature controller that maintained the generator at approximately 84° to 91° C; the second element allowed monitoring of the vaporizer and was connected to an alarm that automatically shut off the flow of nitromethane to the vaporizer if the temperature exceeded 120° C. Vapor was generated by drawing filtered air across the vaporizer and into the vapor distribution line.

The vapor-laden air was transferred through the distribution line, where it was diluted with HEPA- and charcoal-filtered air, to the inhalation chambers; three-way valves mounted in the chamber inlet ducts allowed nitromethane vapors to be diverted to the exhaust until a stable concentration of nitromethane was built up in the distribution line. At each chamber, air moving through the chamber inlet duct was further diluted with HEPA- and charcoal-filtered air to the appropriate nitromethane concentration for the chamber with a metered three-way valve. Diagrams of the inhalation exposure chambers and exposure suites are shown in Figures J5, J6a, and J6b. The study laboratory designed the inhalation exposure chamber (Harford Systems Division of Lab Products, Inc., Aberdeen, MD) so that uniform vapor concentrations could be maintained throughout the chamber with the catch pans in place. The total active mixing volume of each chamber was 1.7 m³. A small particle detector (Type CN, Gardner Associates, Schenectady, NY) was used with and without animals in the exposure chambers to ensure that nitromethane vapor, and not aerosol, was produced. No particle counts above the minimum resolvable level (approximately 200 particles/cm³) were detected.

## VAPOR CONCENTRATION MONITORING

Chamber concentrations were monitored with an on-line gas chromatograph. The monitor was coupled with the inhalation chambers by a computer-controlled 12-port stream select valve. Each chamber was sampled approximately every 36 minutes. The gas chromatograph calibration was checked daily against a commercial standard of nitromethane in nitrogen. Additionally, the gas chromatograph was calibrated by a comparison of chamber concentration data to data from grab samples analyzed by an off-line gas chromatograph; the grab samples were collected in bubblers containing dimethylformamide. The volumes of gas were sampled at a constant flow rate ensured by a calibrated critical orifice. The off-line gas chromatograph was calibrated with gravimetrically prepared nitromethane standards.

Summaries of the chamber concentrations for the 16-day, 13-week, and 2-year studies are in Tables J1 through J3. The monthly mean exposure concentrations for the 2-year study chambers are presented in Figures J7 through J12.

### CHAMBER ATMOSPHERE CHARACTERIZATION

Buildup and decay rates for chamber concentrations were determined with and without animals present in the chambers. At a chamber airflow rate of 15 air changes per hour, the theoretical value for the time to achieve 90% of the target concentration after the beginning of vapor generation ( $T_{so}$ ) and the time for the chamber concentration to decay to 10% of the target concentration after vapor generation was terminated

#### **Chemical Characterization and Generation of Chamber Concentrations**

 $(T_{10})$  was approximately 12.5 minutes. Room air was changed 12 to 18 times per hour during all studies. During the 16-day and 13-week studies, the mean  $T_{90}$  value with and without animals in the chambers was 11 minutes, ranging from 10 to 13 minutes during the 16-day studies and from 6 to 13 minutes during the 13-week studies.  $T_{10}$  ranged from 11 to 14 minutes during the 16-day studies and from 11 to 15 minutes during the 13-week studies. During the 2-year studies,  $T_{90}$  ranged from 11 to 14 minutes without animals and from 5 to 17 minutes with animals in the chambers;  $T_{10}$  ranged from 13 to 16 minutes without animals and from 13 to 19 minutes with animals. A  $T_{90}$  value of 12 minutes was selected for all studies.

The uniformity of vapor concentration in the inhalation exposure chambers without animals was evaluated before each of the studies began; concentration uniformity with animals present in the chambers was also measured once during the 16-day studies, twice during the 13-week studies, and approximately every 90 days during the 2-year studies. Vapor concentration was determined with the on-line gas chromatograph, with the 12-port sampling valve disabled to allow continuous monitoring from a single line; samples were taken from several positions in each chamber. Chamber concentration uniformity was maintained throughout the 16-day, 13-week, and 2-year studies.

The persistence of nitromethane in the chamber following exposure was determined by monitoring overnight the concentration in the 1,500 ppm chamber in the 16-day and 13-week studies, the 375 ppm chamber in the 2-year rat study, and the 750 ppm chamber in the 2-year mouse study, with and without animals present. During the 16-day studies, the chamber concentration decreased to less than 1% of the target concentration within 100 minutes after the nitromethane flow was shut off. In the 13-week studies, the concentration decreased to 1% of the target concentration within 55 minutes with no animals present and within 100 to 140 minutes with animals present. Approximately 1.5 ppm nitromethane was detected in the chamber the morning after testing during the 16-day and 13-week studies. In the 2-year rat study, the time for the concentration to decrease to 1% of the target concentration ranged from 112 to 315 minutes. In the 2-year mouse study, the concentration decreased to 1% of the target concentration ranged from 112 to within 89 to 178 minutes.

Nitromethane from the vapor generator reservoir was tested for stability during all studies with gas chromatography, with a nitromethane standard as a reference. Results indicated that nitromethane was stable in the reservoir for at least 61 days. Because nitromethane was flash vaporized, the most likely type of decomposition resulting from the generation system would be thermal; these degradation products would include nitric acid, nitrous acid, methanol, formaldehyde, and formic acid. Stability was monitored by testing nitromethane samples collected from the generator reservoir, vapor distribution line, and exposure chambers for nitrous and nitric acid during the 16-day studies and for formaldehyde, methanol, and other volatile compounds during the 13-week studies. During the 16-day studies, samples collected from the vapor distribution line and the 94 and 1,500 ppm exposure chambers, with and without animals, were monitored for nitrous and nitric acid by analyzing bubbler samples with ion chromatography. Blanks from the control chamber were used to correct organic carbon measurements for the amount of carbon as carbon dioxide present in the bubblers. No more than 0.2% nitrate and 0.3% nitrite were detected in any sample.

During the 13-week studies, samples from the vapor distribution line and the unoccupied 94 and 1,500 ppm chambers were tested for formaldehyde. Samples were collected in adsorbent particulate tubes coated with N-benzylethanolamine; the reactivity between the formaldehyde and nitromethane in the tubes confounded attempts to measure formaldehyde but made the presence of free formaldehyde in the chambers unlikely. Bubbler samples collected from the vapor distribution line before and after exposure periods and from the occupied and unoccupied 94 and 1,500 ppm chambers were tested for methanol and other degradation products by gas chromatography/headspace analysis during the 13-week studies. In all reservoir and chamber samples (except some reservoir samples that were apparently contaminated during

sample preparation), methanol was below the limit of detection, with a bubbler collection efficiency of approximately 85%. These results indicated that no degradation of nitromethane occurred as a result of vapor generation during the studies.

The concentration of the impurity 2-nitropropane was monitored during all studies. During the 16-day studies, samples from the 1,500 ppm exposure chamber with and without animals were collected on adsorbent tubes; during the 13-week and 2-year studies, bubbler samples were collected from the distribution line and the 94 and 1,500 ppm (13-week) or 94 and 750 ppm (2-year) exposure chambers with and without animals. During the 13-week and 2-year studies, concentrations of nitroethane and propionitrile were also monitored. At the beginning of the 2-year studies, a third impurity present in the bulk chemical was identified as isooxazole with gas chromatography/mass spectrometry; the concentration of isooxazole was also monitored during the 2-year studies. In all studies, impurities in the samples were quantitated versus gravimetrically prepared standards by gas chromatography; the amount of each impurity detected in all distribution line and exposure chamber samples was the same as that detected in the reservoir, indicating that the impurities were neither concentrated nor dispersed by the generation system.



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Chemical Characterization and Generation of Chamber Concentrations

261



FIGURE J2 Nuclear Magnetic Resonance Spectrum of Nitromethane





### FIGURE J4a Nitromethane Vapor Generation and Delivery System for the 16-Day Studies



FICURE 14b Nitromethane Vapor Generation and Delivery System for the 13-Week and 2-Year Studies

Chemical Characterization and Generation of Chamber Concentrations





FIGURE J5 Nitromethane Inhalation Exposure Chamber



FIGURE J6a Nitromethane Exposure Suite for the 16-Day Studies

267



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FIGURE J6b Nitromethane Exposure Suite for the 13-Week and 2-Year Studies

### Chemical Characterization and Generation of Chamber Concentrations

### TABLE J1

Summary of Chamber Concentrations in the 16-Day Inhalation Studies of Nitromethane

Target Concentration (ppm)	Total Number of Readings	Average Concentration ^a (ppm)
Rat Chambers		
<b>94</b>	95	94 ± 3
188	97	$187 \pm 6$
375	92	$377 \pm 10$
750	92	752 ± 34
1,500	90	1,510 ± 30
Mouse Chambers		
94	97	94 ± 3
188	100	186 ± 7
375	94	$377 \pm 10$
750	94	$750 \pm 25$
1.500	92	$1,510 \pm 31$

^a Mean  $\pm$  standard deviation

Table J2

Summary of Chamber Concentrations in the 13-Week Inhalation Studies of Nitromethane

Target Concentration (ppm)	Total Number of Readings	Average Concentration ^a (ppm)
Rat Chambers		
94	974	$94 \pm 6$
188	938	$187 \pm 10$
375	951	373 ± 19
750	971	748 ± 37
1,500	969	$1,500 \pm 58$
Mouse Chambers		
94	988	93.6 ± 5.5
188	951	187 ± 10
375	963	373 ± 19
750	984	748 ± 37
1,500	982	$1,500 \pm 58$

^a Mean  $\pm$  standard deviation

270
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## TABLE J3

Target Concentration (ppm)	Total Number of Readings	Average Concentration ^a (ppm)
Rat Chambers	· · · · · · · · · · · · · · · · · · ·	
<b>.</b> 94	5,791	94 ± 4
188	5,775	188 ± 7
375	5,575	$375 \pm 10$
Mouse Chambers		
188	5,543	189 ± 5
375	5,623	$376 \pm 11$
750	5,672	$753 \pm 18$
· · · ·		

^a Mean  $\pm$  standard deviation





""Exp



### FIGURE J8

Monthly Mean Concentration and Standard Deviation in the 188 ppm Rat Exposure Chamber in the 2-Year Inhalation Study of Nitromethane





Monthly Mean Concentration and Standard Deviation in the 375 ppm Rat Exposure Chamber in the 2-Year Inhalation Study of Nitromethane 273



### FIGURE J10

Monthly Mean Concentration and Standard Deviation in the 188 ppm Mouse Exposure Chamber in the 2-Year Inhalation Study of Nitromethane

Concentrat: on (ppm) *. 3^{66, 1}2 *. 678×22. Sol Toles برد. برد. ⁸ 13F 13F Aug 49 -^урд – °, • • • • ^%, ₽9_ ₽⁰0 ⁰0 -^уел 99 -^бөб У@_-Ar_{@A} \$@ _ 20 °& -×, 90 -°un 9⊕ -°, v, ⊗⊕ _ ⁷ℓ₀ \$⊕.. S₆ 90 -°, °& -¹∕3_ \$∲ -0 0 0 0 Sen 9, -⁶6 9, _ ¹0, 9₁ -1301 - 91 -⁵UN 87 -St. . ⁷¹L 91 -Summary Mean & Std Dev

### FIGURE J11

Monthly Mean Concentration and Standard Deviation in the 375 ppm Mouse Exposure Chamber in the 2-Year Inhalation Study of Nitromethane 275

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Monthly Mean Concentration and Standard Deviation in the 750 ppm Mouse Exposure Chamber in the 2-Year Inhalation Study of Nitromethane

## APPENDIX K

# INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIHI-07 RAT AND MOUSE RATION

Table K1	Ingredients of NIH-07 Rat and Mouse Ration	278
TABLE K2	Vitamins and Minerals in NIH-07 Rat and Mouse Ration	278
TABLE K3	Nutrient Composition of NIH-07 Rat and Mouse Ration	279
Table K4	Contaminant Levels in NIIH-07 Rat and Mouse Ration	280

### TABLE K1 Ingredients of NIH-07 Rat and Mouse Ration^a

Ingredients ^b			Percent by Weight				
· · · · ·					·		
Ground #2 yellow shelled corn	ł.		•		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% pr	otein)				4.00		
Corn gluten meal (60% protein)					3.00	•	<i>:</i>
Soy oil		. · · · · ·			2.50		
Dried brewer's yeast			. *		2.00		
Dry molasses					1.50		
Dicalcium phosphate					1.25		
Ground limestone		C .			0.50		
Salt					0.50		
Premixes (vitamin and mineral)		1			0.25		

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

#### TABLE K2

### Vitamins and Minerals in NIH-07 Rat and Mouse Ration^a

	Amount	Source	
·		· · · · · · · · · · · · · · · · · · ·	^
Vitamins	· · · .		
Α	5.500.000 IU	Stabilized vitamin A palmitate or acetate	
Da	4,600,000 IU	D-activated animal sterol	•
-3 K2	2.8 g	Menadione	
$d - \alpha$ -Tocophervi 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

### Feed Analyses

## Table K3

### Nutrient Composition of NIH-07 Rat and Mouse Ration

	Mean ± Standard		Number of Samples	
Nutrient	Deviation	Range		
Protein (% by weight)	23.29 ± 0.52	22.2 - 24.0	25	
Crude fat (% by weight)	$5.27 \pm 0.14$	5.00 - 5.60	25	
Crude fiber (% by weight)	$3.57 \pm 0.41$	2.60 - 4.30	25	
Ash (% by weight)	$6.38 \pm 0.16$	6.11 - 6.63	25	
Amino Acids (% of total diet)			•	
Arginine	$1.280 \pm 0.083$	1.110 1.390	11	
Cystine	$0.308 \pm 0.071$	0.181 — 0.400	11	
Glycine	$1.158 \pm 0.048$	1.060 — 1.220	11	
Histidine	$0.584 \pm 0.027$	0.531 — 0.630	11	
Isoleucine	$0.917 \pm 0.033$	0.867 — 0.965	11	
Leucine	$1.975 \pm 0.051$	1.850 - 2.040	11	
Lysine	$1.274 \pm 0.049$	1,200 — 1.370	11	
Methionine	$0.437 \pm 0.109$	0.306 — 0.699	11	
Phenylalanine	$0.999 \pm 0.120$	0.665 — 1.110	11	
Threonine	$0.904 \pm 0.058$	0.824 0.985	11	
Tryptophan	$0.218 \pm 0.153$	0.107 — 0.671	11	
Tyrosine	$0.685 \pm 0.094$	0.564 — 0.794	11	
Valine	$1.086 \pm 0.055$	0.962 — 1.170	11	
Essential Fatty Acids (% of total	diet)			
Linoleic	$2.407 \pm 0.227$	1.830 — 2.570	10	
Linolenic	$0.259 \pm 0.065$	0.100 — 0.320	10	
Vitamins			,	
Vitamin A (IU/kg)	$7,009 \pm 2,131$	4,180 - 12,140	25	
Vitamin D (IU/kg)	$4,450 \pm 1,382$	3,000 — 6,300	4	
α-Tocopherol (ppm)	$36.12 \pm 9.15$	22.5 — 48.9	10	
Thiamine (ppm)	$18.72 \pm 2.42$	15.0 - 28.0	25	
Riboflavin (ppm)	$7.83 \pm 0.92$	6.10 - 9.00	11	
Niacin (ppm)	$98.64 \pm 25.5$	65.0 — 150.0	10	
Pantothenic acid (ppm)	$30.55 \pm 3.52$	23.0 - 34.6	11	
Pyridoxine (ppm)	$9.11 \pm 2.53$	5.60 - 14.0	11	
Folic acid (ppm)	$2.46 \pm 0.63$	1.80 - 3.70	11	
Biotin (ppm)	$0.268 \pm 0.047$	0.190 - 0.354	11	
Vitamin B ₁₂ (ppb)	$40.5 \pm 19.1$	10.6 - 65.0	11	
Choline (ppm)	2,991 ± 382	2,300 3,430	10	
Minerals		· · · · · · · · ·	· ·	
Calcium (%)	$1.18 \pm 0.10$	1.00 - 1.49	25	
Phosphorus (%)	$0.93 \pm 0.04$	0.85 - 1.00	25	
Potassium (%)	$0.886 \pm 0.063$	0.772 - 0.971	9	
Chloride (%)	$0.529 \pm 0.087$	0.380 - 0.635	<b>y</b>	
Sodium (%)	$0.316 \pm 0.033$	0.238 - 0.371	11	
wiagnesium (%)	$0.100 \pm 0.010$	0.146 - 0.181	10	
	0.272 I 0.039 350 5 ± 87 3	255 0 523 0	11	
Mangapese (nnm)	$330.5 \pm 61.5$ 97 48 $\pm$ 5 14	81 7 <u>90 4</u>	11	
Zinc (nnm)	$50.3 \pm 10.2$	46.1 81.6	11	
Copper (ppm)	11.81 + 2.50	8.09 15.4	11	
Iodine (ppm)	$3.54 \pm 1.19$	1.52 - 5.83	10	
and an and the state of the sta	2.2. I I.I.			
Chromium (ppm)	1.66 + 0.46	0.85 — 2.09	11	

### TABLE K4

## Contaminant Levels in NIH-07 Rat and Mouse Ration^a

	Mean ± Standard		Number of Samples	
	Deviation ^b	Range		
Contaminants		· · ·		
Arsenic (ppm)	$0.36 \pm 0.18$	0.10 - 0.70	25	
Cadmium (ppm)	$0.08 \pm 0.05$	0.05 - 0.20	25	
Lead (ppm)	$0.28 \pm 0.23$	0.10 - 1.00	25	
Mercury (ppm)	$0.03 \pm 0.01$	0.02 - 0.50	25	
Selenium (ppm)	$0.36 \pm 0.12$	0.05 - 0.60	25	
Aflatoxins (ppm) ^c	<5.0		24	
Nitrate nitrogen (ppm) ^d	$14.35 \pm 4.41$	5.70 21.0	25	
Nitrite nitrogen (ppm) ^d	$0.22 \pm 0.18$	0.10 0.70	25	
BHA (ppm) ^e	$1.88 \pm 1.94$	1.00 - 10.0	25	
BHT (ppm) ^e	$1.60 \pm 1.58$	1.0 - 8.00	25	
Aerobic plate count (CFU/g)	40,360 ± 25,193	4,100 110,000	25	
Coliform (MPN/g)	<3		25	
Escherichia coli (MPN/g)	<3		25	
Salmonella (MPN/g)	Negative		25	
Total nitrosoamines (ppb) ^f	$7.78 \pm 2.63$	4.80 - 16.50	25	
N-Nitrosodimethylamine (ppb) ^f	$5.81 \pm 1.98$	3.80 - 13.0	25	
N-Nitrosopyrrolidine (ppb) ^f	$1.97 \pm 1.13$	1.00 — 4.30	25	
Pesticides (ppm)				
α-BHC	< 0.01	· · ·	25	
β-ΒΗC	< 0.02		25	
γ-ΒΗC	< 0.01		25	
δ-BHC	<0.01		25	
Heptachlor	<0.01		25	
Aldrin	< 0.01		25	
Heptachlor epoxide	<0.01		25	
DDE	< 0.01	· .	25	
DDD	<0.01		25	
DDT	< 0.01		25	
HCB	<0.01		25	
Mirex	<0.01		25	
Methoxychlor	< 0.05		25	
Dieldrin	<0.01	•	25	
Endrin	< 0.01		25	
Telodrin	<0.01		25	
Chlordane	< 0.05		25	
Toxaphene	<0.10		25	
Estimated PCBs	<0.20		25	
Ronnel	<0.01		25	
Ethion	< 0.02		25	
Trithion	< 0.05		25	
Diazinon	<0.10		25	
Methyl parathion	< 0.02		25	
Ethyl parathion	< 0.02		25	
Malathion	$0.27 \pm 0.27$	0.05 - 1.00	25	
Endosulfan I	< 0.01		25	
Endosulfan II	< 0.01		25	
Endosulfan sulfate	< 0.03		25	

^a CFU = colony-forming units; MPN = most probable number; BHC = hexachlorocyclohexane or benzene hexachloride

^b For values less than the limit of detection, the detection limit is given as the mean.

^c No aflatoxin measurement was recorded for the lot milled on 2 October 1989.

^d Sources of contamination: alfalfa, grains, and fish meal

e Sources of contamination: soy oil and fish meal

f All values were corrected for percent recovery.

# AIPPENIDIX L SENTINEL ANIMAL PROGRAM

 Methods
 282

 Results
 284

## SENTINEL ANIMAL PROGRAM

## **METHODS**

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

Serum samples were collected from randomly selected rats and mice during the 13-week and 2-year studies. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to Microbiological Associates, Inc. (Bethesda, MD), for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the studies are also listed.

#### Method and Test

**Time of Analysis** 

### RATS

13-Week Study ELISA PVM (pneumonia virus of mice) RCV/SDA (rat coronavirus/sialodacryoadenitis virus) Sendai

Hemagglutination Inhibition H-1 (Toolan's H-1 virus) KRV (Kilham rat virus)

2-Year Study ELISA

> Mycoplasma arthritidis Mycoplasma pulmonis PVM RCV/SDA Sendai

Immunofluorescence Assay RCV/SDA

Hemagglutination Inhibition

H-1 KRV 13 weeks 13 weeks

13 weeks

13 weeks 13 weeks

24 months 24 months 6, 12, 18, and 24 months 6, 12, 18, and 24 months 6, 12, 18, and 24 months

12 months

6, 12, 18, and 24 months 6, 12, 18, and 24 months

#### Sentinel Animal Program

## MICE 13-Week Study ELISA Ectromelia virus GDVII (mouse encephalomyelitis virus) MVM (minute virus of mice) Mouse adenoma virus MHV (mouse hepatitis virus) PVM Reovirus 3 Sendai Immunofluorescence Assay EDIM (epizootic diarrhea of infant mice) LCM (lymphocytic choriomeningitis virus)

Hemagglutination Inhibition

K (papovavirus) Polyoma virus

2-Year Study ELISA Ectromelia virus EDIM GDVII LCM Mouse adenoma virus Mouse adenoma virus-FL MHV *M. arthritidis M. pulmonis* PVM Reovirus 3 Sendai

Immunofluorescence Assay EDIM GDVII MVM Mouse adenoma virus-FL MHV Sendai

Hemagglutination Inhibition K MVM Polyoma virus 13 weeks 13 weeks

13 weeks 13 weeks

13 weeks 13 weeks

6, 12, 18, and 24 months 12, 18, and 24 months 6, 12, 18, and 24 months 6, 12, 18, and 24 months 6 months 12, 18, and 24 months 6, 12, 18, and 24 months 18 and 24 months 18 and 24 months 6, 12, 18, and 24 months

6, 12, and 18 months
24 months
6 and 12 months
24 months
12 months
24 months

6, 12, 18, and 24 months 18 and 24 months 6, 12, 18, and 24 months

## RESULTS

One rat had a positive titer to *M. arthritidis* at the end of the 2-year study. Further evaluation of the serum positive for *M. arthritidis* by immunoblot and Western blot procedures indicated that the positive titer may have been due to cross reaction with antibodies of nonpathogenic *Mycoplasma* or other agents. Only a single sample was positive, and there were no clinical findings or histopathologic changes of *M. arthritidis* infection in the animal with the positive titer. Accordingly, the *M. arthritidis*-positive titer was considered to be a false positive.

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## DEPARTMENT OF HEALTH & HUMAN SERVICES

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