NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 331

TOXICOLOGY AND CARCINOGENESIS STUDIES OF MALONALDEHYDE, SODIUM SALT (3-HYDROXY-2-PROPENAL, SODIUM SALT)

(CAS NO. 24382-04-5)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

NATIONAL TOXICOLOGY PROGRAM

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

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NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

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IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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Public Health Service
National Institutes of Health

NOTE TO THE READER

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

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

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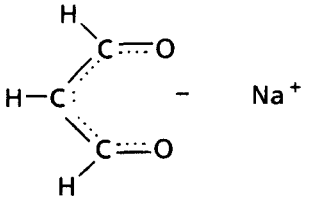
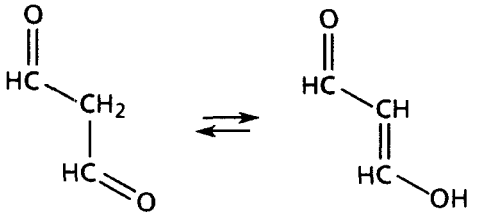


MALONALDEHYDE, SODIUM SALT

CAS No. 24382-04-5

$C_3H_3O_2Na$ Molecular weight 94.04

Synonyms: malonaldehyde, enol, sodium salt; propanedial, sodium; 3-hydroxy-2-propenal, sodium salt; sodium β-oxyacrolein



Malonaldehyde **Enol tautomer**

CAS No. 542-78-9

$C_3H_4O_2$ Molecular weight 72.06

ABSTRACT

Malonaldehyde occurs as a natural metabolic byproduct of prostaglandin biosynthesis and as an end product of polyunsaturated lipid peroxidation. Toxicology and carcinogenesis studies of malonaldehyde were conducted by administering the chemical as malonaldehyde, sodium salt, a stabilized form of malonaldehyde, in distilled water by gavage to groups of F344/N rats and B6C3F$_1$ mice of each sex for 14 days, 13 weeks, and 2 years. The study material was 63%-79% malonaldehyde, sodium salt, 22%-38% water, and 1% or less other impurities. The water content was taken into account when the dose mixtures were prepared.

Fourteen-Day and Thirteen-Week Studies: In the 14-day studies, groups of five rats and five mice of each sex were dosed with 250, 500, 750, 1,000, or 1,500 mg/kg malonaldehyde, sodium salt. Controls were untreated. Rats and mice that received 1,500 mg/kg malonaldehyde, sodium salt, did not survive to the end of the 14-day studies. No compound-related gross lesions were seen in the dosed animals.

In the 13-week studies, groups of 10 males and 10 females of each species were administered 0, 30, 60, 125, 250, or 500 mg/kg malonaldehyde, sodium salt. Nine of 10 male rats, 10/10 female rats, 3/10 male mice, and 1/10 female mice that received 500 mg/kg malonaldehyde, sodium salt, died before the

end of the studies. Body weights were reduced by more than 15% in rats receiving 250 or 500 mg/kg and in mice receiving 500 mg/kg.

Compound-related nonneoplastic lesions were present in the stomach, testis, and kidney of rats and in the pancreas, stomach, and testis of mice. Focal and multifocal erosive lesions were observed in the gastric mucosa of the glandular stomach in the 500 mg/kg groups of male and female rats. Dilatation of the gastric glands of the stomach mucosa occurred in the 500 mg/kg male mice. Lesions of the kidney included membranous glomerular nephropathy in the 250 and 500 mg/kg male rats and the 125, 250, and 500 mg/kg female rats and mineralization in the 250 and 500 mg/kg male rats and the 60, 125, 250, and 500 mg/kg female rats. Degeneration of the testicular germinal epithelium was observed in male rats and male mice receiving 250 and 500 mg/kg. Atrophy of the exocrine pancreas was seen in the 125, 250, and 500 mg/kg male and the 250 and 500 mg/kg female mice.

Based on these results, 2-year studies of malonaldehyde, sodium salt, were conducted by exposing groups of 50 F344/N rats of each sex at doses of 0, 50, or 100 mg/kg, administered 5 days per week for 103 weeks. Doses of 0, 60, or 120 mg/kg were administered on the same schedule to groups of 50 male and 50 female $B6C3F_1$ mice.

Body Weight and Survival in the Two-Year Studies: Final mean body weights at the end of the study were reduced by 26% and 36% for high dose male and female rats compared with those for the vehicle controls. The final mean body weight of high dose male mice was 92% that of the vehicle controls. The final mean body weights of low dose male mice, low dose rats, and all groups of female mice were comparable to those of the vehicle controls.

The survival of high dose male and female rats was significantly lower than that of the vehicle controls, with survival declining rapidly after week 76 for high dose males and after week 59 for high dose females (survival--male: vehicle control, 37/50; low dose, 33/50; high dose, 15/50; female: 37/50; 37/50; 14/50). Survival of all groups of male mice was low (male: 24/50; 20/50; 14/50; female: 41/50; 38/50; 30/50). Survival of the high dose group of male mice was significantly lower than that of the vehicle controls; no other significant differences in survival were observed between any groups of mice.

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: The incidences of a variety of nonneoplastic lesions were increased in dosed rats of each sex, primarily in the high dose male and female rat groups. These lesions were ulceration and inflammation of the glandular stomach; epithelial hyperplasia of the forestomach; inflammation of the cornea, retinal atrophy, and cataracts of the crystalline lens; focal lipoid degeneration of the adrenal cortex; and diffuse pancreatic atrophy. Cytoplasmic vacuolization and cystic degeneration in the liver occurred at increased incidences in the high dose rat groups; in addition, the incidences of bile duct hyperplasia and bile duct fibrosis were increased in the high dose female and male rat groups, respectively. Bone marrow hematopoietic hyperplasia, hematopoiesis of the spleen, and ultimobranchial cysts of the thyroid gland occurred with increased incidences in high dose female rats.

The incidences of thyroid gland follicular cell adenomas or carcinomas (combined) were significantly increased in high dose male (vehicle control, 4/50; low dose, 8/49; high dose, 13/50) and female (2/50; 1/50; 7/50) rats. Follicular cell hyperplasia of the thyroid gland also occurred at an increased incidence in high dose female rats (10/50; 10/50; 26/50) but not in male rats (9/50; 7/49; 7/50). The incidence of pancreatic islet cell adenomas was increased in low dose male rats (0/49; 9/50; 1/49). Adenomas and adenomas or carcinomas (combined) of the anterior pituitary gland occurred at significantly lower incidences in high dose rats than those in vehicle controls (combined incidence--male: 20/47; 14/49; 8/49; female: 18/49; 10/49; 2/48).

Nonneoplastic lesions that occurred at increased incidences in dosed mice included atrophy of the pancreatic acinus and dilatation of the uterus. Depigmentation of hair shafts and change of coat color from agouti to gray were observed in high dose mice. No compound-related neoplasms were observed in dosed mice.

Genetic Toxicology: Malonaldehyde, sodium salt, was not mutagenic in the *Salmonella typhimurium*/microsome assay when tested at doses of up to 10,000 μg/plate in a preincubation protocol using the excision-repair deficient strains TA98, TA100, TA1535, and TA1537 with or without S9 metabolic activation. The chemical induced forward mutations in mouse L5178Y lymphoma cells in the absence of S9; it was not tested with S9. Malonaldehyde, sodium salt, was not mutagenic in the *Drosophila melanogaster* sex-linked recessive lethal mutagenicity test in which adult male flies were exposed either by feeding or by abdominal injection. In cytogenetic assays with cultured Chinese hamster ovary (CHO) cells, malonaldehyde, sodium salt, produced a dose-related increase in the frequency of sister chromatid exchanges both in the presence and absence of rat liver S9; no increase in the number of chromosomal aberrations was observed in CHO cells in the absence or presence of S9.

Audit: The data, documents, and pathology materials from the 2-year studies of malonaldehyde, sodium salt, have been audited. The audit found no special circumstances or significant deficiencies in the conduct or documentation of the studies which needed to be taken into consideration for reporting purposes.

Conclusions: Under the conditions of these 2-year gavage studies, there was *clear evidence of carcinogenic activity** for male and female F344/N rats administered malonaldehyde, sodium salt, as shown by the increased incidences of follicular cell adenomas or carcinomas (combined) of the thyroid gland. Pancreatic islet cell adenomas were also observed at an increased incidence in low dose male rats. There was *no evidence of carcinogenic activity* for $B6C3F_1$ mice administered 60 or 120 mg/kg malonaldehyde, sodium salt, in distilled water by gavage 5 days per week for 2 years.

Chemically related increased incidences of nonneoplastic lesions included ulcers and inflammation of the glandular stomach and epithelial hyperplasia of the forestomach; corneal inflammation, retinal atrophy, and cataracts of the crystalline lens; and cystic degeneration of the liver, bile duct fibrosis, and bile duct hyperplasia in rats. Most of these nonneoplastic lesions as well as the thyroid gland follicular cell neoplasms occurred primarily in the high dose rat groups, in which survival and final body weights were reduced in high dose male and female rats. Increased incidences of atrophy of the pancreatic acinus and pigmentation loss in hair shafts were seen in high dose mice.

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*Explanation of Levels of Evidence of Carcinogenic Activity is on page 9.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 12-13.

SUMMARY OF THE TWO-YEAR GAVAGE AND GENETIC TOXICOLOGY STUDIES OF MALONALDEHYDE, SODIUM SALT

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Doses (mg/kg)			
0, 50, or 100 in distilled water, 5 d/wk	0, 50, or 100 in distilled water, 5 d/wk	0, 60, or 120 in distilled water, 5 d/wk	0, 60, or 120 in distilled water, 5 d/wk
Survival rates in the 2-year study			
37/50; 33/50; 15/50	37/50; 37/50; 14/50	24/50; 20/50; 14/50	41/50; 38/50; 30/50
Nonneoplastic effects			
Ulcers and inflammation of the glandular stomach; epithelial hyperplasia of the forestomach; corneal inflammation, retinal atrophy, cataracts of the crystalline lens; cystic degeneration of the liver; bile duct fibrosis; bile duct hyperplasia	Ulcers and inflammation of the glandular stomach; epithelial hyperplasia of the forestomach; corneal inflammation, retinal atrophy, cataracts of the crystalline lens; cystic degeneration of the liver; bile duct hyperplasia	Atrophy of the pancreatic acinus; pigmentation loss in hair shafts	Atrophy of the pancreatic acinus; pigmentation loss in hair shafts; dilatation of the uterus
Neoplastic effects			
Thyroid gland follicular cell adenomas or carcinomas (combined) (4/50; 8/49; 13/50); pancreatic islet cell adenomas (0/49; 9/50; 1/49)	Thyroid gland follicular cell adenomas or carcinomas (combined) (2/50; 1/50; 7/50)	None	None
Other considerations			
Decrease in incidence of anterior pituitary gland adenomas or carcinomas (combined) (20/47;14/49; 8/49)	Decrease in incidence of anterior pituitary gland adenomas or carcinomas (combined) (18/49;10/49; 2/48)		
Level of evidence of carcinogenic activity			
Clear evidence	Clear evidence	No evidence	No evidence

Genetic toxicology

Salmonella (gene mutation)	Mouse L5178Y/TK$^{+/-}$ (gene mutation)	CHO Cells in Vitro		Drosophila
		SCE	Aberration	Sex-linked Rec. Lethals
Negative with and without S9	Positive without S9; no test with S9	Positive with and without S9	Negative with and without S9	Negative

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

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

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

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

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

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Malonaldehyde, Sodium Salt, is based on the 13-week studies that began in October 1978 and ended in January 1979 and on the 2-year studies that began in February 1980 and ended in February 1982 at Battelle Columbus Laboratories (Columbus, Ohio).

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The members of the Peer Review Panel who evaluated the draft Technical Report on malonaldehyde, sodium salt, on March 4, 1987, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF MALONALDEHYDE, SODIUM SALT

On March 4, 1987, the draft Technical Report on the toxicology and carcinogenesis studies of malonaldehyde, sodium salt, received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. J.W. Spalding, NIEHS, began the discussion by reviewing the experimental design, results, and proposed conclusions (clear evidence of carcinogenic activity for male or female rats, no evidence of carcinogenic activity for male or female mice).

Dr. Hughes, a principal reviewer, agreed with the conclusions for male and female mice. He proposed that the conclusions for male and female rats be changed to some evidence of carcinogenic activity because he felt that the maximum tolerated dose was exceeded in rats, possibly perturbing the endocrine axis and perhaps leading to endocrine tumor response through an indirect mechanism, because the total incidence of adenomas and carcinomas of the thyroid gland was low, because both short-term studies and initiation/promotion studies yielded mixed results, and because there was not a dose response for pancreatic islet cell tumors in male rats. Dr. Spalding pointed out that thyroid gland neoplasms are uncommon and the incidences in male and female rats at the top dose were well above the historical control range. Commenting on the inconsistencies in the short-term studies and initiation/promotion data cited, Dr. Spalding said that pre-1980 studies used mixtures of malonaldehyde and intermediates in its synthesis which had mutational activity. Dr. J. Huff, NIEHS, commented that the conclusions for rats were based on the thyroid gland neoplasia, not on the low dose effect for pancreatic tumors.

As a second principal reviewer, Dr. Popp agreed with the conclusions. He agreed with Dr. Hughes that the maximum tolerated dose had been exceeded for high dose male and female rats but felt that the implications were unclear. He suggested that the lower incidence of rats with pituitary gland neoplasms in high dose groups was probably due to reduced survival and was not a primary effect of the chemical, whereas the nonneoplastic eye lesions probably were chemically related. Dr. Spalding agreed that the eye lesions were chemically related and said that the discussion would be expanded.

As a third principal reviewer, Dr. Gallo agreed with the conclusions but noted that when the maximum tolerated dose is exceeded, interpretation of either positive or negative findings is sometimes difficult. He added, however, that based on the 13-week studies, the doses selected for the 2-year studies were appropriate. Since the chemical is an intermediate in the biosynthesis of prostaglandins, he suggested that the toxicity may override control mechanisms in the synthetic pathway. Dr. Gallo thought that the rationale for deciding to study malonaldehyde was weak.

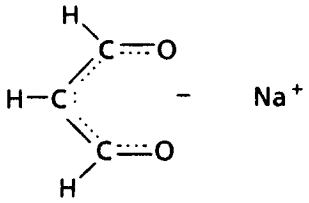
In other discussion, Dr. Sivak proposed that a statement be included for the rat studies which indicates reduced survival and body weight gain in top dose groups. Dr. Hooper requested that all the genetic toxicology data be organized into a summary table to help the reader draw conclusions about the mutagenic activity of the malonaldehyde salt (see page 8 and Appendix E).

Dr. Hughes moved that the Technical Report on malonaldehyde, sodium salt, be accepted with the conclusions as written for mice, no evidence of carcinogenic activity, but with the conclusions for rats changed to some evidence of carcinogenic activity, along with a statement that the maximum tolerated dose had been exceeded. Dr. Sivak asked that the statement be amended to replace the expression maximum tolerated dose with a description of the biologic alterations themselves, i.e., that there was decreased survival and a greater than 10% decrease in body weight gain in high dose groups. Dr. Hughes agreed. Dr. Gallo seconded the amended motion, and after considerable discussion, it was defeated by six votes to one (Dr. Hughes). Dr. Gallo moved that the Technical Report be accepted with the conclusions as written for mice, no evidence of carcinogenic activity, and for rats, clear evidence of carcinogenic activity, with Dr. Sivak's amendment. Dr. Sivak seconded the amended motion, and it was approved by six votes to one (Dr. Hughes).

I. INTRODUCTION

Occurrence
Toxicity and Metabolism
Carcinogenicity Studies
Genetic Toxicology
Study Rationale

I. INTRODUCTION

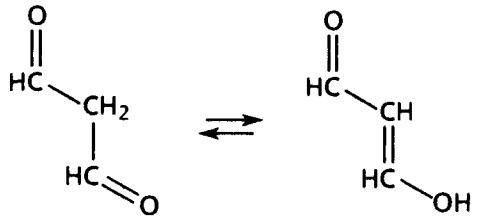


MALONALDEHYDE, SODIUM SALT

CAS No. 24382-04-5

$C_3H_3O_2Na$ Molecular weight 94.04

Synonyms: malonaldehyde, enol, sodium salt; propanedial, sodium; 3-hydroxy-2-propenal, sodium salt; sodium β-oxyacrolein



Malonaldehyde **Enol tautomer**

CAS No. 542-78-9

$C_3H_4O_2$ Molecular weight 72.06

Malonaldehyde is a three-carbon dialdehyde that in dilute aqueous solution exists in equilibrium with its enol form (Mashio and Kimura, 1960). Malonaldehyde exists in stable form as the enolate sodium salt (Huttel, 1941) and can be prepared from either 1,1,3,3-tetraethoxypropane or 1,1,3,3-tetramethoxypropane by acid hydrolysis.

Occurrence

Malonaldehyde occurs as a natural byproduct of the cyclooxygenase reaction in prostaglandin biosynthesis (Draper et al., 1986) and is formed as an end product of polyunsaturated lipid peroxidation (Bernheim et al., 1948; Hamberg and Samuelsson, 1967; Diczfalusy et al., 1977). The relative content of malonaldehyde in foods has been associated with oxidative rancidity; detection of malonaldehyde at low or minimal levels has been used for many years as a measure of the wholesomeness and freshness of foods. The reaction of malonaldehyde with 2-thiobarbituric acid to form a chromogen of extremely high absorptivity is the basis of a sensitive method for the qualitative measurement of malonaldehyde in food and food products (Crawford et al., 1965).

Two surveys have been conducted in North America to measure the malonaldehyde content of food items. In a study of 96 samples of fresh meat and fish obtained from supermarkets in Ontario, Canada, Siu and Draper (1978) found that the malonaldehyde content ranged from 0.14 μg/g in cooked ham to 10.05 μg/g in cooked chicken. The levels of malonaldehyde found by the Canadian study were somewhat lower than those described in a study by Shamberger et al. (1977), who reported that malonaldehyde levels ranged from 1 to 14 μg/g of tissue in food items

obtained from Cleveland, Ohio, supermarkets and that cooking of the meat resulted in small decreases or twofold to fivefold increases in malonaldehyde content. Assuming that the average U.S. citizen consumes 120 g of meat daily (NAS, 1981), and based on the malonaldehyde content of cooked meat reported by Shamberger et al. (1974), it is estimated that the amount of malonaldehyde ingested per person per day through meat consumption alone could range from 240 to 1,200 µg from beef or turkey to 3,600 µg from chicken.

The impact, if any, of malonaldehyde on human health at these concentrations is not known. However, reports on the potential mutagenic and carcinogenic character (Shamberger et al., 1974) of this chemical have suggested the desirability of minimizing its occurrence during storage, marketing, and preparation of food.

Malonaldehyde in the presence of nitrite has been reported to facilitate the formation of nitrosamines from dimethylamine, diethylamine, piperidine, pyrrolidine, and morpholine (Kikugawa et al., 1980), although it is not clear whether malonaldehyde's stimulation of nitrosamine formation is much greater than that observed for the unsaturated fatty acids from which malonaldehyde is derived (Goutefongea et al., 1977).

Toxicity and Metabolism

The mean LD_{50} value for malonaldehyde, sodium salt, administered by gavage was determined to be 632 mg/kg body weight in male Wistar rats (Crawford et al., 1965). The mean LD_{50} value for malonaldehyde administered by gavage to female Swiss mice was 606 mg/kg body weight (Apaja, 1980).

After intubation of two male Wistar rats with [1,3-^{14}C]malonaldehyde (approximately 27.5 µg/kg), 84%-96% of the radiolabel was eliminated in 12 hours (Siu and Draper, 1982). Between 60% and 70% of the total dose was expired as [^{14}C]carbon dioxide, 9%-17% was recovered in the urine, and 5%-15%, in the feces. In vitro studies with [1,3-^{14}C]malonaldehyde demonstrated that malonaldehyde is metabolized primarily in the mitochondria. The probable pathway of malonaldehyde metabolism involves oxidation by mitochondrial aldehyde dehydrogenase followed by decarboxylation to produce carbon dioxide and acetate.

Malonaldehyde reacts readily with sulfhydryl and amino groups of proteins (Shin et al., 1972). It produces intramolecular and intermolecular linkages that result in the inactivation and polymerization of enzymes (Chio and Tappel, 1969). It can react with the nitrogenous bases of DNA (Brooks and Klamerth, 1968; Reiss et al., 1972) and thus inhibit DNA, RNA, and protein synthesis (Bird and Draper, 1980).

Carcinogenicity Studies

Groups of 50 female ICR Swiss mice were exposed for 12 months to a preparation of malonaldehyde, sodium salt (greater than 98% pure), in drinking water (acidified to pH 4 to prevent malonaldehyde polymerization) at concentrations calculated to provide a daily dose of 0, 0.1, 1, or 10 mg/kg (Bird et al., 1982a). There was no significant increase in tumors observed at any site in the dosed animals. Compound-related lesions were confined to the liver, but the total liver lesions were not dose dependent. The liver lesions included anisokaryosis, changes in cytoplasmic volume of hepatocytes, hepatocellular nodular hyperplasia (control, 0/48; 0.1 mg/kg, 1/49; 1 mg/kg, 2/50; 10 mg/kg, 2/48), and hepatomas (0/48; 0/49; 2/50; 0/48).

A malonaldehyde preparation of undefined purity administered to 25 animals in each dose group for 100 weeks in drinking water at concentrations of 1,250, 2,500, or 5,000 ppm did not increase the tumor incidence in male or female Swiss mice (Apaja, 1980). More males than females died at all three concentrations. At the highest concentration, there were no surviving males at week 80, and only one female survived to the end of the study. In a two-stage dermal carcinogenesis study, application of a single dose of either 6 or 12 mg of malonaldehyde in acetone to the backs of female Swiss mice (30 mice per dose group) was followed 3 weeks later by the application (5 days per week) of 0.1% croton oil for 27 weeks (Shamberger et al., 1974). Fifty-two percent of the dosed mice developed keratoacanthomas; the first tumors were seen at 11 weeks.

The interpretation of these results is confounded because the malonaldehyde preparation used in this study was of undefined purity and the doses of 6 and 12 mg are estimates based on the assumption that malonaldehyde was the only hydrolysis product of 1,1,3,3-tetramethoxypropane. Marnett and Tuttle (1980) subsequently demonstrated that the acid hydrolysis of 1,1,3,3-tetramethoxypropane also produces several reactive chemical intermediate species, such as β-methoxyacrolein and 3,3-dimethoxypropionaldehyde, which are 20-30 times more mutagenic than the pure form of malonaldehyde or malonaldehyde, sodium salt.

In a later two-stage dermal carcinogenicity study of 28-52 weeks' duration, purified malonaldehyde, sodium salt, in acetone:dimethyl sulfoxide (80:20) was found to be inactive as a tumor initiator, promoter, or complete carcinogen for male and female SENCAR mice (40 mice per dose group) (Fischer et al., 1983). Doses of malonaldehyde, sodium salt, ranging from 20 to 500 µg were administered as single applications in studies to detect activity as an initiator or a complete carcinogen, and the same doses were administered in repetitive applications in a study designed to detect promoter activity. Benzo[*a*]pyrene served as a positive control for tumor initiation and as the complete carcinogen in this study, whereas 12-*O*-tetradecanoyl phorbol-13-acetate was used as the positive control for promotion. However, the highest dose (500 µg) of malonaldehyde used in these studies was tenfold less than the lowest dose applied in the study reported by Shamberger et al. (1974). Malonaldehyde, sodium salt, was also inactive in the in vitro Chinese hamster V-79 cell metabolic cooperation assay for promoters (Fischer et al., 1983).

Genetic Toxicology

Malonaldehyde was first shown to be mutagenic in several excision-repair-competent frameshift mutant strains of Salmonella in the absence of exogenous metabolic activation (Mukai and Goldstein, 1976; Shamberger et al., 1979). The tester strain D3052 was the most sensitive to malonaldehyde activity in both studies. However, the purity of malonaldehyde in these studies was undefined. In the earlier study (Mukai and Goldstein, 1976), malonaldehyde was generated by the acid hydrolysis of 1,1,3,3-tetramethoxypropane, and the hydrolysate was used directly as the source of malonaldehyde; the quantification of malonaldehyde was based on the amount of starting material 1,1,3,3-tetramethoxypropane and on the assumption that the reaction went to completion with malonaldehyde as the only end product. In the Shamberger et al. study (1979), neither the source nor method of malonaldehyde preparation was given, although in an earlier in vivo study reported by the same laboratory (Shamberger et al., 1974), malonaldehyde was prepared from 1,1,3,3-tetramethoxypropane in the manner described above. Subsequent studies (Marnett and Tuttle, 1980; Basu and Marnett, 1983) demonstrated that the product of 1,1,3,3-tetramethoxypropane hydrolysis included substantial amounts of reactive intermediates such as β-methoxyacrolein and 3,3-dimethoxypropionaldehyde, which were 125-160 and 105-135 times more active, respectively, as Salmonella mutagens than was malonaldehyde. Therefore, the mutagenic activity attributed to malonaldehyde in the earlier investigations is suspect. The mutagenicity of a highly purified preparation of malonaldehyde, sodium salt, in Salmonella strain D3052 was confirmed by Marnett and Tuttle (1980), although the magnitude of response was much less than that reported by the earlier investigators. Malonaldehyde was also found to be inactive in Salmonella strains TA98, TA100, TA1535, and TA1538, which are deficient in excision-repair capability. These observations confirmed the earlier studies of Mukai and Goldstein (1976) and Shamberger et al. (1979).

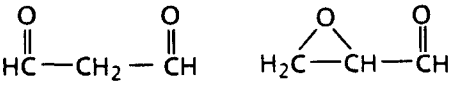
In a later study, further confirmation of the mutagenicity of malonaldehyde, sodium salt, in Salmonella came from the results of plate incorporation assays (Basu and Marnett, 1983) which demonstrated a dose-dependent increase in revertant colonies of the excision-repair-competent frameshift mutant strain D3052 over a dose range of 0-20 µmol/plate. The mutation frequency was low, about 5 revertants/µmol of malonaldehyde. A similar mutation frequency in two recently developed excision-repair-competent *Salmonella typhimurium* strains TA102 and TA104, which are base-substitution mutants that are highly sensitive to carbonyl compounds,

was observed after exposure to malonaldehyde, sodium salt, in a liquid preincubation procedure without S9 metabolic activation (Marnett et al., 1985). Malonaldehyde, sodium salt, was also reported to be an effective mutagen through base substitution in repair-competent *Escherichia coli* H/r30 but not in *E. coli* strains that were repair deficient (Yonei and Furui, 1981). The mutagenicity of malonaldehyde, sodium salt, was not observed by NTP in *S. typhimurium* assays with a preincubation protocol with the excision-repair-deficient strains TA98, TA100, TA1535, or TA1537 with or without Aroclor 1254-induced liver S9 from male Sprague Dawley rats or Syrian hamsters (Mortelmans et al., 1986; Table E1). These results reported by the NTP do confirm the earlier observations of Marnett and Tuttle (1980) that Salmonella tester strains that are deficient in excision-repair capability are not sensitive to malonaldehyde.

In NTP tests with mouse L5178Y lymphoma cells, malonaldehyde, sodium salt, induced forward mutations at the TK locus over a concentration range of 125-1,000 μg/ml in the absence of S9; it was not tested with S9 (Table E2). Yau (1979) also reported the induction of mutations in mouse L5178Y cells by malonaldehyde (undetermined purity and generated from the acid hydrolysis of tetramethoxypropane) within a concentration range of 10-100 μM and in the absence of exogenous metabolic activation. Feeding malonaldehyde (unspecified purity) to Drosophila larvae at a dose that resulted in 50% lethality induced a low frequency of somatic mosaicism that was detected in adult wing and eye tissue but did not induce sex-linked recessive lethal mutations (Szabad et al., 1983). Likewise, in NTP tests, no induction of sex-linked recessive lethal mutations was seen in Drosophila when malonaldehyde, sodium salt, was fed to adult males at a concentration of 25,000 ppm or injected as a 10,000-ppm solution (Woodruff et al., 1985; Table E5). Dose-related increases in micronuclei and chromosomal aberrations were observed in cultured rat skin fibroblast cells treated with 10^{-4} to 10^{-2} M concentrations of malonaldehyde, sodium salt, generated by acid hydrolysis of tetramethoxypropane and judged to be approximately 98% pure (Bird et al., 1982b). In NTP cytogenetic assays with cultured Chinese hamster ovary (CHO) cells, malonaldehyde, sodium salt, produced a clear dose-related increase in the frequency of sister chromatid exchanges both in the presence and absence of Aroclor 1254-induced male Sprague Dawley rat liver S9. No increase in chromosomal aberrations was observed in CHO cells after treatment with up to 409 μg/ml of malonaldehyde, sodium salt, in the absence of S9 or up to 3,270 μg/ml in the presence of S9 (Tables E3 and E4).

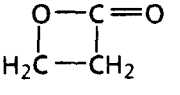
Study Rationale

Malonaldehyde was nominated by the NCI for toxicology and carcinogenesis studies because of reports in the literature that this byproduct of lipid peroxidation of polyunsaturated fatty acids was mutagenic in bacteria (Mukai and Goldstein, 1976) and active as an initiator in a two-stage dermal carcinogenicity study in rodents (Shamberger et al., 1974). Further, malonaldehyde (I) has a structural resemblance to two known carcinogens, glycidaldehyde (II) and β-propiolactone (III) (Van Duuren et al , 1963). The oral route of administration was chosen for the present studies because human exposure to exogenous malonaldehyde is through the diet



I

II



III

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF MALONALDEHYDE, SODIUM SALT

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Study Design

Source and Specifications of Animals

Animal Maintenance

Clinical Examinations and Pathology

Statistical Methods

PROCUREMENT AND CHARACTERIZATION OF MALONALDEHYDE, SODIUM SALT

3-Hydroxy-2-propenal, sodium salt (referred to in this report as malonaldehyde, sodium salt), was synthesized at the Midwest Research Institute (MRI) (Kansas City, Missouri) by the hydrolysis of 1,1,3,3-tetramethoxypropane. The starting material was obtained in 14 lots from Aldrich Chemical Company (Table 1). Each lot was converted to malonaldehyde, sodium salt, by mixing it with 1.0 N hydrochloric acid and stirring for 3 hours under nitrogen at 0° C. After storage for 48 hours under nitrogen at 5° C, sodium hydroxide was added to produce a reaction mixture with a pH of 10 which was maintained at 0° C. Malonaldehyde, sodium salt, was precipitated from the reaction mixture by the addition of acetone, separated by suction filtration, and dried in a desiccator over sodium hydroxide.

The study material was characterized by elemental analysis, ultraviolet/visible and nuclear magnetic resonance spectroscopy, and Karl Fischer water analysis. The nuclear magnetic resonance spectrum agreed with that expected for the structure of malonaldehyde enolate for all the batches prepared (Figure 1). The nuclear magnetic resonance spectra did not detect the presence of 3,3-dimethoxypropionaldehyde or methoxyacrolein, which are potential toxic impurities in the study material. Table 2 presents a summary of the analysis for each batch of study material. The analytical reports for the analyses performed in support of the malonaldehyde, sodium salt, studies are on file at NIEHS.

Stability studies of the bulk malonaldehyde, sodium salt, were run for 3 weeks at −20° C. Purity analysis by ultraviolet spectroscopy (266 nm) established that no degradation of the chemical occurred. Further confirmation of the stability of the bulk material during the toxicity studies (storage at −20° C) was obtained by Karl Fischer water analysis and ultraviolet spectroscopic analysis. No notable degradation was seen over the course of the studies.

TABLE 1. IDENTITY AND SOURCE OF 1,1,3,3-TETRAMETHOXYPROPANE LOTS USED IN THE PREPARATION OF MALONALDEHYDE, SODIUM SALT, FOR THE GAVAGE STUDIES

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Lot Number		
JHW11	JHW11, DE 112778, DE 112978	DE 122078, DC80-23, GB32880, GB80-80-2A, GB80-80-5G, GB80-80-5F, GB80-80-8, GB80-80-9-11, KK80-160-12, LK80-160-13, GO-80-160-20
Date of Initial Use		
Rats--8/24/78; mice--8/21/78	10/24/78, 12/19/78, 1/9/79	DE 122078: 3/17/80; DC80-23: 4/14/80; GB32880: 5/1/80; GB80-80-2A: 5/5/80; GB80-80-5G: 5/19/80; GB80-80-5F: 7/10/80; GB80-80-8: 8/6/80; GB80-80-9-11: rats--9/18/80, mice--10/2/80; KK80-160-12: rats--12/18/80, mice--1/22/81; LK80-160-13: rats--6/4/81, mice--5/6/81; GO-80-160-20: 9/21/81
Supplier		
Aldrich Chemical Co. (Milwaukee, WI)	Same as 14-d studies	Same as 14-d studies

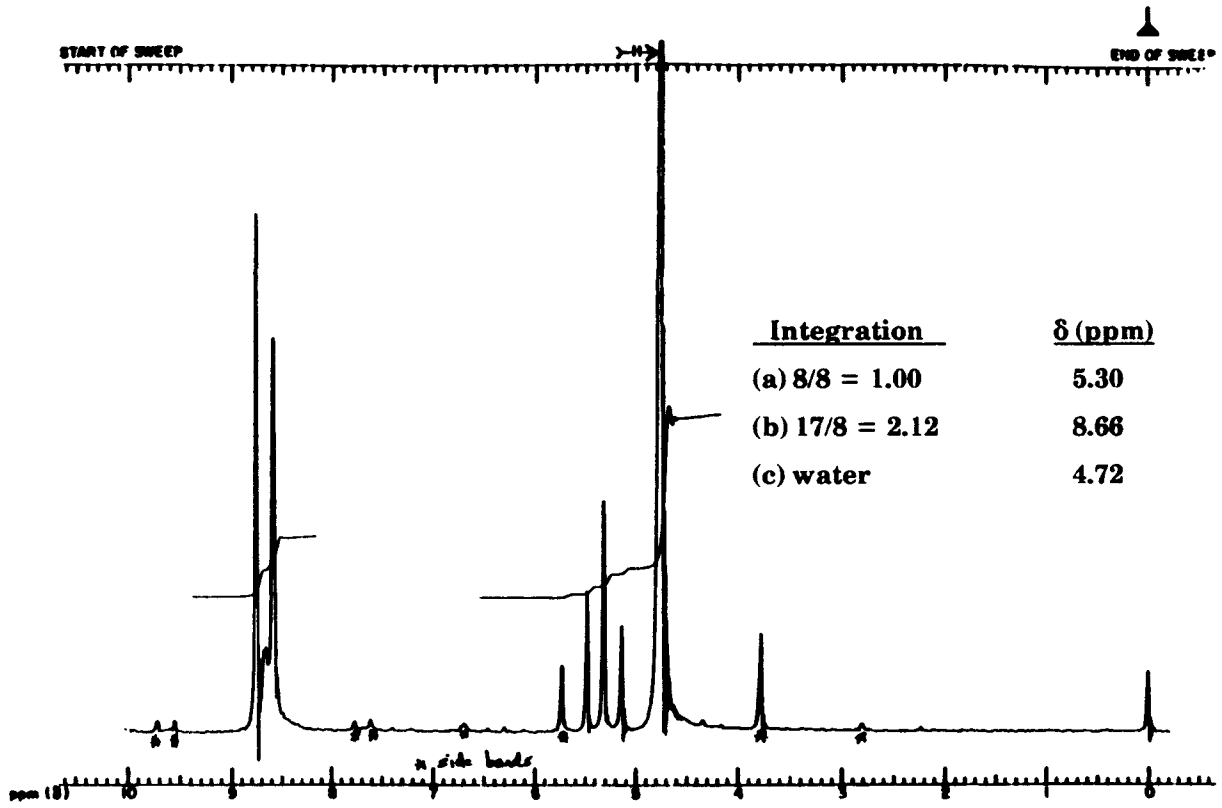


FIGURE 1. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF MALONALDEHYDE, SODIUM SALT
(LOT NO. LK80-160-13)

TABLE 2. SUMMARY OF RESULTS OF PURITY ANALYSIS OF THE LOTS USED IN THE GAVAGE STUDIES OF MALONALDEHYDE, SODIUM SALT

Lot No. of Starting Material	Malonaldehyde, Sodium Salt (percent) (a)	Water (percent) (b)	Chloride (percent) (c)	Acetone (percent) (d)
JHW11	70.1 ± 1.4	30.0 ± 0.0	--	0.8
DE 112778	68.9 ± 0.5	30.6 ± 0.5	0.28	Trace
DE 112978	70.3 ± 0.3	31.5 ± 1.1	0.74	Trace
DE 122078	76.4 ± 0.9	24.4 ± 0.3	0.69	--
DC80-23	78.9 ± 0.4	21.9 ± 0.4	0.28	--
GB32880	66.6 ± 1.5	32.2 ± 0.6	1.0	Trace
GB80-80-2A	64.3 ± 2.2	35.2 ± 0.8	0.1	--
GB80-80-5G	64.4 ± 1.3	37.3 ± 0.8	0.5	--
GB80-80-5F	64.8 ± 0.5	37.8 ± 0.9	0.5	--
GB80-80-8	63.4 ± 0.4	36.0 ± 0.2	0.87	--
GB80-80-9-11	65.6 ± 0.3	33.1 ± 0.9	0.76	--
KK80-160-12	63.4 ± 1.1	35.2 ± 0.3	0.3	--
LK80-160-13	71.2 ± 0.5	29.6 ± 0.5	0.2	--
GO-80-160-20	67.8 ± 1.0	35.0 ± 1.5	0.6	--

(a) Based on ultraviolet spectroscopic analysis at 266 nm; mean ± standard deviation.
(b) Karl Fischer titration; mean ± standard deviation.
(c) By elemental analysis
(d) By nuclear magnetic resonance spectroscopy

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

Dose mixtures were prepared by dissolving enough study material in distilled water to give the desired concentration (w/v) of anhydrous malonaldehyde, sodium salt (Table 3). Dose mixture stability studies by ultraviolet spectroscopy indicated that a solution of 1% malonaldehyde, sodium salt, in water was stable at −20° C for 7 days. Aliquots of formulated solutions of malonaldehyde, sodium salt, in water were stored at −20° C for no longer than 7 days in the 2-year studies.

Periodic analysis for malonaldehyde, sodium salt, in dose mixtures was performed by the study and analytical chemistry laboratories by the same spectrophotometric method to determine if the dose mixtures contained the correct concentrations of malonaldehyde, sodium salt. The results of analysis of one dose formulation (100 mg/ml) during the 13-week studies indicated that the concentration (99.6 mg/ml) was within specifications (±10% of the target concentration). During the 2-year studies, the dose mixtures were analyzed once every 2 months; concentrations varied from 53.5% to 127.1% of the target concentrations (Table 4). All dose mixtures except those mixed on 9/25/80 were within 91.0%-110.4% of the target concentrations. The dose mixtures prepared on 9/25/80 were outside of the specification limits and, therefore, not administered to the animals. The dose mixtures subsequently prepared on 9/26/80 were within specifications and were administered to the animals. Because 48/52 dose mixtures analyzed were within 10% of the target concentration, it is estimated that the dose mixtures were prepared within specifications 92% of the time. Results of periodic referee analysis performed by the analytical chemistry laboratory indicated variable agreement with the results from the study laboratory (Table 5).

TABLE 3. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF MALONALDEHYDE, SODIUM SALT

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation A stock solution was prepared by placing a weighed portion of malonaldehyde, sodium salt, in a graduated cylinder, adding distilled water to the proper volume, and mechanically stirring for 40 min. Dose mixtures were prepared by serial dilution of the stock solution	Similar to 14-d studies	Similar to 14-d studies
Maximum Storage Time 17 d	7 d	7 d
Storage Conditions −20° C in the dark; vials of dose mixture kept at room temperature for 30-60 min before gavage administration	Same as 14-d studies	Similar to 14-d studies

TABLE 4. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF MALONALDEHYDE, SODIUM SALT

Date Mixed	Concentration of Malonaldehyde, Sodium Salt, in Water for Target Concentration (mg/ml) (a)			
	10	12	20	24
02/21/80	10.6	12.5	19.85	25.15
04/10/80	9.5	12.15	19.85	24.0
06/05/80	9.75	13.25	20.5	24.35
08/07/80	10.0	11.9	19.8	25.2
09/25/80	(b) 6.1	(b) 8.4	(b) 10.7	(b) 30.5
09/26/80	(c) 10.1	(c) 12.5	(c) 19.9	(c) 24.8
11/20/80	10.7	12.5	18.6	24.2
01/29/81	9.71	11.39	19.96	24.66
03/12/81	10.3	12.9	20.5	26.2
05/14/81	9.8	13.0	20.4	22.8
07/09/81	9.8	12.6	19.2	24.3
09/17/81	9.7	12.0	20.3	24.6
11/06/81	9.8	11.8	19.6	24.0
01/08/82	9.1	11.4	18.8	24.2
Mean (mg/ml)	9.6	12.0	19.1	24.9
Standard deviation	1.14	1.22	2.59	1.85
Coefficient of variation (percent)	11.9	10.2	13.6	7.4
Range (mg/ml)	6.1-10.7	8.4-13.25	10.7-20.5	22.8-30.5
Number of samples	13	13	13	13

(a) Results of duplicate analysis
(b) Out of specifications, not administered to animals
(c) Remix, not included in the mean

TABLE 5. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF MALONALDEHYDE, SODIUM SALT

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (mg/ml)	
		Study Laboratory (a)	Referee Laboratory (b)
04/10/80	12	12.15	8.8
09/25/80	10	6.1	9.5
03/12/81	24	26.2	24.3
09/10/81	20	(c) 19.9	(c) 14.8
01/08/82	10	9.1	8.9

(a) Results of duplicate analysis
(b) Results of triplicate analysis
(c) Results from samples taken from animal room during dosing

FOURTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for 14 days (rats) and 17 days (mice) before the studies began. Groups of five males and five females of each species were administered 250, 500, 750, 1,000, or 1,500 mg/kg malonaldehyde, sodium salt, in distilled water by gavage for 14 consecutive days. (Dose mixtures were adjusted for water content in the bulk chemical; animals were actually given 360, 720, 1,080, 1,440, or 2,160 mg/kg of the bulk malonaldehyde, sodium salt.) Controls were untreated.

Rats and mice were housed five per cage. Feed and water were available ad libitum. Details of animal maintenance are presented in Table 6. Rats and mice were observed two times per day and weighed initially and at the end of the studies. A necropsy was performed on all animals.

THIRTEEN-WEEK STUDIES

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

Four- to five-week-old male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories, held for 17 days, and then assigned to cages according to a table of random numbers. Vehicle control and dosed groups were assigned to cages according to another table of random numbers.

Groups of 10 rats and 10 mice of each sex were administered 0, 30, 60, 125, 250, or 500 mg/kg malonaldehyde, sodium salt (anhydrous equivalent), in distilled water by gavage 5 days per week for 13 weeks.

Rats and mice were housed five per cage in polycarbonate cages. Feed and water were available ad libitum. Further experimental details are summarized in Table 6. Animals were checked two times per day; moribund animals were killed. Individual animal weights were recorded once per week.

At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 6.

TWO-YEAR STUDIES

Study Design

Groups of 50 male and 50 female rats were administered malonaldehyde, sodium salt, at doses equivalent to 0, 50, or 100 mg/kg anhydrous malonaldehyde, sodium salt, in distilled water by gavage 5 days per week for 103 weeks. Groups of 50 male and 50 female mice were administered 0, 60, or 120 mg/kg on the same schedule.

TABLE 6. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF MALONALDEHYDE, SODIUM SALT

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN		
Size of Study Groups		
5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses		
250, 500, 750, 1,000, or 1,500 mg/kg malonaldehyde, sodium salt, in distilled water by gavage; dose vol--10 ml/kg; controls were untreated	0, 30, 60, 125, 250, or 500 mg/kg malonaldehyde, sodium salt, in distilled water by gavage; dose vol -5 ml/kg	Rats--0, 50, or 100 mg/kg malonaldehyde, sodium salt, in distilled water by gavage; mice--0, 60, or 120 mg/kg; dose vol--5 ml/kg
Date of First Dose		
Rats--8/24/78; mice--8/21/78	10/24/78	Rats--2/18/80; mice--2/25/80
Date of Last Dose		
Rats--9/6/78, mice--9/3/78	1/22/79	Rats--2/5/82; mice--2/12/82
Duration of Dosing		
14 consecutive d	5 d/wk for 13 wk	5 d/wk for 102 wk
Type and Frequency of Observation		
Observed 2 × d; weighed initially and at the end of the studies	Observed 2 × d; weighed initially and 1 × wk thereafter	Observed 2 × d; weighed initially, 1 × wk for 13 wk, and 1 × mo thereafter
Necropsy and Histologic Examination		
Necropsy performed on all animals, histologic examination not performed	Necropsy performed on all animals; the following tissues examined histologically for vehicle control and high dose groups, for all animals dying before terminal kill, and for lower dose animals with compound-related lesions: adrenal glands, brain, colon, esophagus, femur, gallbladder (mice), heart, kidneys, liver, lungs and mainstem bronchi, mammary gland, mandibular lymph nodes, pancreas, parathyroids, pituitary gland, prostate/testes or ovaries/uterus, salivary glands, small intestine, stomach, thymus, thyroid gland, trachea, and urinary bladder	Necropsy and histologic examination performed on all animals; the following tissues were examined: adrenal glands, brain, cecum, colon, duodenum, esophagus, eyes, femur including marrow, gallbladder (mice), gross lesions, heart, kidneys, larynx, liver, lungs and mainstem bronchi, mammary gland, mandibular lymph nodes, pancreas, parathyroids, pituitary gland, prostate/testes or ovaries/uterus, salivary glands, skin, small intestine, spleen, stomach, thymus, thyroid gland, tissue masses, trachea, and urinary bladder
ANIMALS AND ANIMAL MAINTENANCE		
Strain and Species		
F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice
Animal Source		
Charles River Breeding Laboratories (Portage, MI)	Same as 14-d studies	Rats--Charles River Breeding Laboratories (Portage, MI); mice--Charles River Breeding Laboratories (Kingston, NY)
Study Laboratory		
Battelle Columbus Laboratories	Battelle Columbus Laboratories	Battelle Columbus Laboratories
Method of Animal Identification		
By cage	Toe clip	Toe clip and ear notch
Time Held Before Study		
Rats--14 d, mice--17 d	17 d	Rats--18 d; mice--20 d
Age When Placed on Study		
6 wk	7 wk	Rats--7 wk, mice--8 wk

TABLE 6. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF MALONALDEHYDE, SODIUM SALT (Continued)

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)		
Age When Killed		
8 wk	20 wk	Rats--111-112 wk; mice--112-113 wk
Necropsy Dates		
Rats--9/8/78; mice--9/5/78	Rats--1/23/79; mice--1/24/79	Rats--2/16/82-2/19/82; mice--2/22/82-2/25/82
Method of Animal Distribution		
Distributed according to tables of random numbers	Same as 14-d studies	Animals distributed to weight classes and then assigned to cages according to one table of random numbers and to groups according to another table
Feed		
Purina Lab Chow® pellets (Ralston Purina Co., St. Louis, MO); available ad libitum	Same as 14-d studies	NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA) except for week of 4/27/81 when Purina Lab Chow® was used; available ad libitum
Bedding		
Absorb-Dri (Lab Products, Inc., Garfield, NJ)	Same as 14-d studies	Same as 14-d studies
Water		
Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as 14-d studies	Same as 14-d studies
Cages		
Polycarbonate (Lab Products, Inc., Garfield, NJ)	Same as 14-d studies	Same as 14-d studies
Cage Filters		
Reemay spun-bonded polyester filters (Snow Filtration, Cincinnati, OH)	Same as 14-d studies	Same as 14-d studies
Animals per Cage		
5	5	5
Other Chemicals on Study in the Same Room		
None	None	None
Animal Room Environment		
Temp--20°-23° C; humidity--40%-60%; fluorescent light 12 h/d; 15 room air changes/h	Same as 14-d studies	Temp--17°-26° C; humidity--15%-63%; fluorescent light 12 h/d; 15 room air changes/h

Source and Specifications of Animals

The male and female F344/N rats and $B6C3F_1$ (C57BL/6N, female × C3H/HeN MTV^-, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the Carcinogenesis Program. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Rats were shipped to the study laboratory at 4 weeks of age and mice at 5 weeks of age. The rats were quarantined at the study laboratory for 18 days and the mice for 20 days. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rats were placed on study at 7 weeks of age and the mice at 8 weeks of age. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix F).

A quality control skin grafting program has been in effect since early 1978 to monitor the genetic integrity of the inbred mice used to produce the hybrid $B6C3F_1$ study animal. In mid-1981, data were obtained that showed incompatibility between the NIH C3H reference colony and the C3H colony from a Program supplier. In August 1981, inbred parental lines of mice were further tested for genetic integrity via isozyme and protein electrophoresis profiles that demonstrate phenotype expressions of known genetic loci.

The C57BL/6N mice were homogeneous at all loci tested. Eighty-five percent of the C3H mice monitored were variant at one to three loci, indicating some heterogeneity in the C3H line from this supplier. Nevertheless, the genome of this line is more homogeneous than that of randomly bred stocks.

Male mice from the C3H colony and female mice from the C57BL/6N colony were used as parents for the hybrid $B6C3F_1$ mice used in these studies. The influence of the potential genetic nonuniformity in the hybrid mice on these results is not known, but results of the studies are not affected because concurrent controls were included in each study.

Animal Maintenance

Rats and mice were housed five per cage. Feed and water were available ad libitum. Cages were not rotated during the studies (Figure 2). Details of animal maintenance are summarized in Table 6.

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded once per day for the first 20 months and once per month thereafter. Body weights by cage were recorded once per week for the first 13 weeks of the studies and once per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals including those found dead, unless they were excessively autolyzed or cannibalized, missexed, or found missing. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study.

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissues examined microscopically are listed in Table 6.

When the pathology evaluation was completed, the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assessment pathologist. The

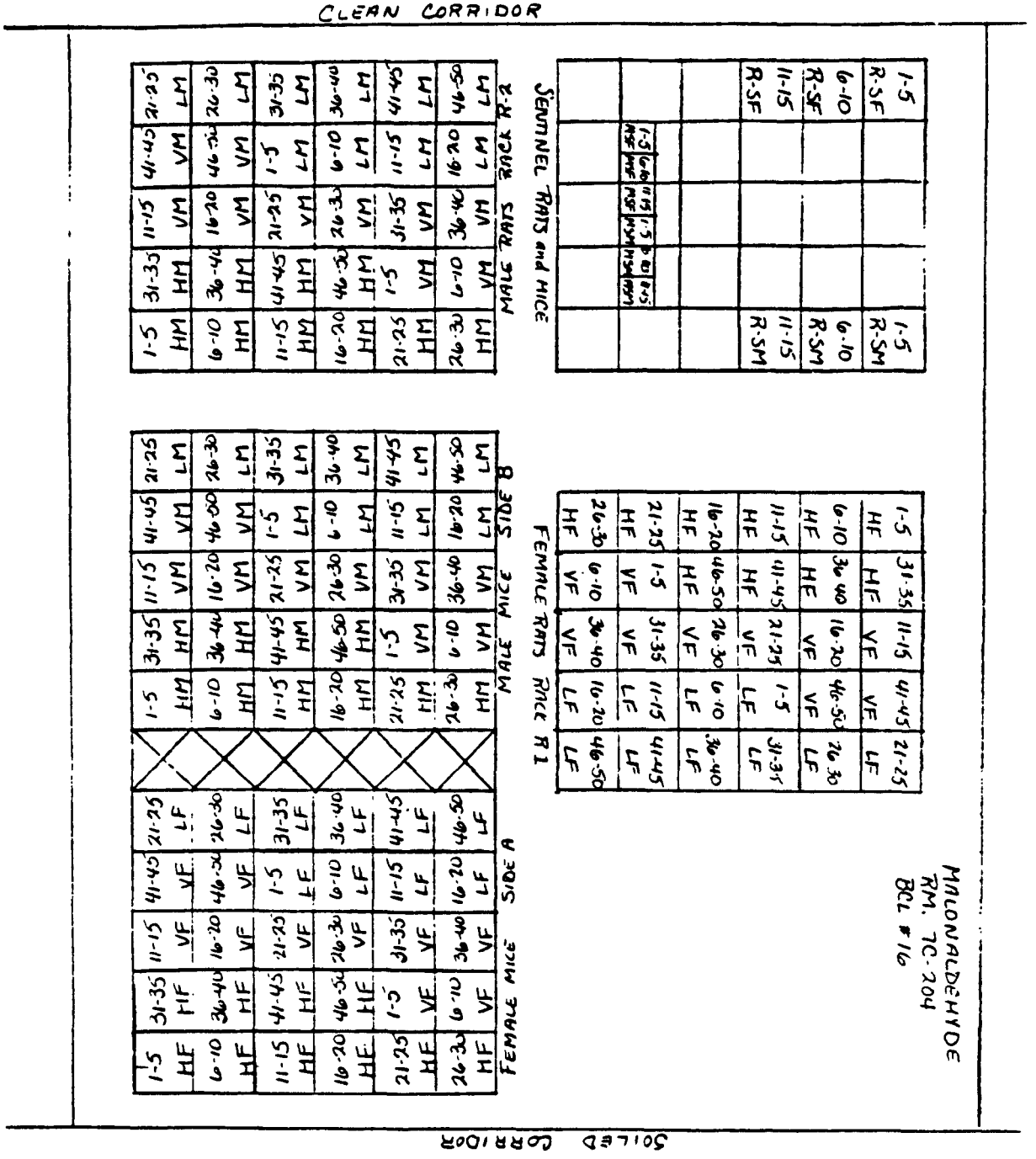


FIGURE 2. CAGE LOCATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF MALONALDEHYDE, SODIUM SALT

quality assessment report and slides were submitted to the Pathology Working Group (PWG) Chairperson, who reviewed all target tissues and those about which there was a disagreement between the laboratory and quality assessment pathologists.

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

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

Statistical Methods

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

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

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

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

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

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

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

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

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

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

III. RESULTS

RATS

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

FOURTEEN-DAY STUDIES

All rats that received 1,500 mg/kg malonaldehyde, sodium salt, 2/5 males and 3/5 females that received 1,000 mg/kg, and 1/5 males that received 750 mg/kg died before the end of the studies (Table 7). Final mean body weights of rats that received 750 or 1,000 mg/kg malonaldehyde, sodium salt, were 15% or 7% lower than that of the controls for males and 24% or 25% lower for females. All dosed animals had rough hair coats. By day 4, the color of the urine of all dosed animals was a shade similar to that of the study material. By day 11, all surviving rats at 750 and 1,000 mg/kg exhibited generalized body weakness. The tissues from animals in the 14-day studies were not examined microscopically.

THIRTEEN-WEEK STUDIES

Nine of 10 male rats and 10/10 female rats that received 500 mg/kg malonaldehyde, sodium salt, died before the end of the studies (Table 8). Final mean body weights of males that received 125, 250, or 500 mg/kg were 5%, 16%, or 39% lower than that of the vehicle controls. Final mean body weights of females that received 125 or 250 mg/kg were 5% or 14% lower than that of the vehicle controls.

During the course of the 13-week studies, the clinical signs preceding the early deaths or moribund termination in the highest dosed animals were rough hair coats, red exudate around the eyes, and impairment of hindleg motor ability to the extent of complete immobilization in some animals.

TABLE 7. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FOURTEEN-DAY GAVAGE STUDIES OF MALONALDEHYDE, SODIUM SALT

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial	Final	Change (b)	Final Weight Relative to Controls (percent)
MALE					
(c) 0	5/5	117	177	+60	
250	5/5	115	165	+50	93.2
500	5/5	123	178	+55	100.6
750	(d) 4/5	107	151	+44	85.3
1,000	(e) 3/5	124	165	+41	93.2
1,500	(f) 0/5	109	(g)	(g)	(g)
FEMALE					
(c) 0	5/5	98	141	+43	
250	5/5	102	136	+34	96.5
500	5/5	102	129	+27	91.5
750	5/5	97	107	+10	75.9
1,000	(h) 2/5	103	106	+3	75.2
1,500	(i) 0/5	102	(g)	(g)	(g)

(a) Number surviving/number in group
(b) Mean body weight change of the survivors
(c) Controls were untreated.
(d) Day of death: 15 (1 day after last dose)
(e) Day of death: 4,7
(f) Day of death: 4,4,5,6,8
(g) No data are reported due to the 100% mortality in this group.
(h) Day of death: 9,11,14
(i) Day of death: 3,4,5,7,7

TABLE 8. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF MALONALDEHYDE, SODIUM SALT

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	132 ± 4	331 ± 6	+199 ± 4	
30	10/10	137 ± 5	347 ± 2	+210 ± 5	105
60	10/10	139 ± 4	345 ± 10	+206 ± 8	104
125	10/10	142 ± 4	314 ± 6	+172 ± 5	95
250	10/10	139 ± 4	278 ± 8	+139 ± 9	84
500	(d) 1/10	138 ± 3	203 ± 0	+68 ± 0	61
FEMALE					
0	10/10	113 ± 1	195 ± 3	+82 ± 2	
30	10/10	107 ± 2	187 ± 4	+80 ± 2	96
60	10/10	105 ± 3	188 ± 3	+83 ± 1	96
125	10/10	110 ± 3	185 ± 6	+75 ± 3	95
250	10/10	112 ± 2	167 ± 4	+55 ± 4	86
500	(e) 0/10	110 ± 2	(f)	(f)	(f)

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Week of death: 3,6,7,8,8,8,8,10,12
(e) Week of death: 5,5,7,7,7,7,7,7,8,8
(f) No data are reported due to the 100% mortality in this group.

Compound-related lesions were present in the stomach, kidney, and testis, primarily in the two highest dose groups (Table 9). Lesions in the kidney consisted of thickenings in the glomerular tuft, which appeared to involve basement membranes and mesangial areas. The designation "membranous glomerular nephropathy" was given to the lesion for which evidence of thickening of Bowman's capsule or proliferation of visceral or parietal epithelium was present without associated inflammation. These kidney lesions occurred in nine males and eight females at 500 mg/kg, one male and nine females at 250 mg/kg, and six females at 125 mg/kg. Mild mineralization of the kidney was present in male rats from the two highest dose groups and in female rats from the four highest dose groups. Renal tubular pigmentation and/or basophilia occurred in several rats from the 500 mg/kg group. Renal tubular pigmentation was observed in 10 females in the 250 mg/kg group. Focal and multifocal erosive lesions were observed in the gastric mucosa of the glandular stomach in 500 mg/kg male and female rats. A diffuse degeneration of virtually all the testicular germinal epithelium was observed in 3/10 males that received 250 mg/kg and in 9/10 males that received 500 mg/kg; the lesions in the 250 mg/kg group were less severe than those in the 500 mg/kg group. Lymphoid depletion in the spleen, thymus, and mandibular lymph nodes occurred in the two highest male and female dose groups, and increased splenic extramedullary hematopoiesis and bone marrow hyperplasia were observed in the 500 mg/kg groups.

Dose Selection Rationale: Because of reduced weight gain and compound-related lesions in the bone marrow, spleen, lymph nodes, thymus, stomach, kidney, and testis at the higher doses in the 13-week studies, doses selected for rats for the 2-year studies were 50 and 100 mg/kg malonaldehyde, sodium salt, administered in distilled water by gavage 5 days per week.

TABLE 9. NUMBER OF RATS WITH LESIONS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF MALONALDEHYDE, SODIUM SALT

Site/Lesion	Dose (mg/kg) 0	60	125	250	500
MALE					
Number of rats examined	10	10	10	10	10
Stomach, gastric mucosa					
Erosion	0	0	0	0	5
Kidney					
Membranous glomerular nephropathy	0	0	0	1	9
Mineralization	0	0	0	6	9
Tubular pigmentation	0	0	0	0	4
Tubular basophilia	0	0	0	0	3
Bone marrow					
Hyperplasia	0	0	0	0	5
Spleen					
Lymphoid depletion, B-cell area	0	0	0	9	6
Lymphoid depletion	0	0	0	0	4
Extramedullary hematopoiesis	0	0	0	0	7
Mandibular lymph node					
Lymphoid depletion	0	0	0	0	2
Thymus					
Lymphocytic depletion	0	0	0	0	3
Testis, seminiferous tubules					
Degeneration	0	0	0	3	9
FEMALE					
Number of rats examined	10	10	10	10	10
Stomach, gastric mucosa					
Erosion	0	0	0	0	4
Kidney					
Membranous glomerular nephropathy	0	0	6	10	8
Mineralization	0	2	6	7	5
Tubular pigmentation	0	0	0	10	1
Tubular basophilia	0	0	0	0	6
Bone marrow					
Hyperplasia	0	0	0	0	4
Spleen					
Lymphoid depletion, B-cell area	0	0	0	10	7
Lymphoid depletion	0	0	0	0	3
Extramedullary hematopoiesis	0	0	0	0	9
Mandibular lymph node					
Lymphoid depletion	0	0	0	0	3
Thymus					
Lymphocytic depletion	0	0	0	0	5

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male rats were 10%-20% lower than those of the vehicle controls from week 33 to week 72 and 20%-26% lower from week 72 to the end of the study (Table 10 and Figure 3). Mean body weights of low dose male rats were 3%-7% lower than those of the vehicle controls from week 67 to the end of the study. Mean body weights of high dose female rats were 10%-20% lower than those of the vehicle controls from week 54 to week 72 and 21%-36% lower from week 72 to the end of the study. Mean body weights of low dose and vehicle control female rats were similar throughout the study. No compound-related clinical signs were observed.

TABLE 10. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF MALONALDEHYDE, SODIUM SALT

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	50 mg/kg Av. Wt. (grams)	50 mg/kg Wt. (percent of veh. controls)	50 mg/kg No. of Survivors	100 mg/kg Av. Wt. (grams)	100 mg/kg Wt. (percent of veh. controls)	100 mg/kg No. of Survivors
MALE								
0	111	50	115	104	50	112	101	50
1	171	50	170	99	50	171	100	50
2	199	50	198	99	50	200	101	50
3	219	50	219	100	50	223	102	50
4	234	50	238	102	50	240	103	50
5	250	50	255	102	50	259	104	50
6	264	50	265	100	50	267	101	50
7	267	50	269	101	50	271	101	50
8	280	50	281	100	50	279	100	50
9	293	50	294	100	50	295	101	50
10	304	50	305	100	50	305	100	50
11	309	50	310	100	50	302	98	50
12	318	50	317	100	50	307	97	50
13	324	50	321	99	50	313	97	50
16	342	50	340	99	50	328	96	50
20	359	50	358	100	50	344	96	50
25	391	50	388	99	50	367	94	50
29	396	50	402	102	50	367	93	50
33	408	50	401	98	50	369	90	50
37	420	50	417	99	50	378	90	50
41	425	50	423	100	50	372	88	49
46	431	50	432	100	50	383	89	48
50	448	50	445	99	50	391	87	48
54	453	50	442	98	50	385	85	48
59	460	49	447	97	50	381	83	48
63	457	48	447	98	50	368	81	47
67	460	48	448	97	50	375	82	47
72	469	48	452	96	50	367	78	46
76	459	48	427	93	48	350	76	45
78	456	48	424	93	48	351	77	43
81	455	44	429	94	47	345	76	37
85	452	43	427	94	46	353	78	32
90	462	39	445	96	42	347	75	27
94	461	39	445	97	40	341	74	23
99	448	37	434	97	36	334	75	19
103	447	37	430	96	33	332	74	15
FEMALE								
0	98	50	102	104	50	101	103	50
1	126	50	130	103	50	127	101	50
2	137	50	139	101	50	136	99	50
3	143	50	146	102	50	144	101	50
4	152	50	156	103	50	152	100	50
5	160	50	161	101	50	159	99	50
6	164	50	166	101	50	164	100	50
7	164	50	166	101	50	163	99	50
8	167	50	169	101	50	166	99	50
9	171	50	173	101	50	169	99	50
10	174	50	175	101	50	173	99	50
11	174	50	175	101	50	171	98	50
12	178	50	179	101	49	173	97	50
13	181	50	183	101	49	177	98	50
16	189	50	187	99	49	184	97	50
20	190	50	192	101	49	190	100	50
25	205	49	207	101	49	203	99	50
29	207	49	208	100	49	202	98	50
33	208	49	211	101	49	203	98	50
37	213	48	215	101	49	205	96	50
41	216	48	220	102	49	207	96	50
46	223	48	228	102	48	215	96	50
50	234	48	243	104	47	214	91	50
54	240	48	247	103	47	214	89	49
59	245	48	251	102	47	206	84	43
63	253	47	256	101	47	214	85	39
67	260	47	262	101	46	215	83	39
72	274	47	276	101	45	217	79	37
76	269	47	272	101	45	211	78	35
78	271	46	268	99	45	207	76	34
81	272	46	267	98	45	215	79	31
85	280	44	275	98	43	213	76	26
90	286	42	280	98	42	207	72	25
94	282	42	280	99	42	199	71	23
99	286	39	286	100	39	203	71	16
103	290	37	289	100	37	187	64	14

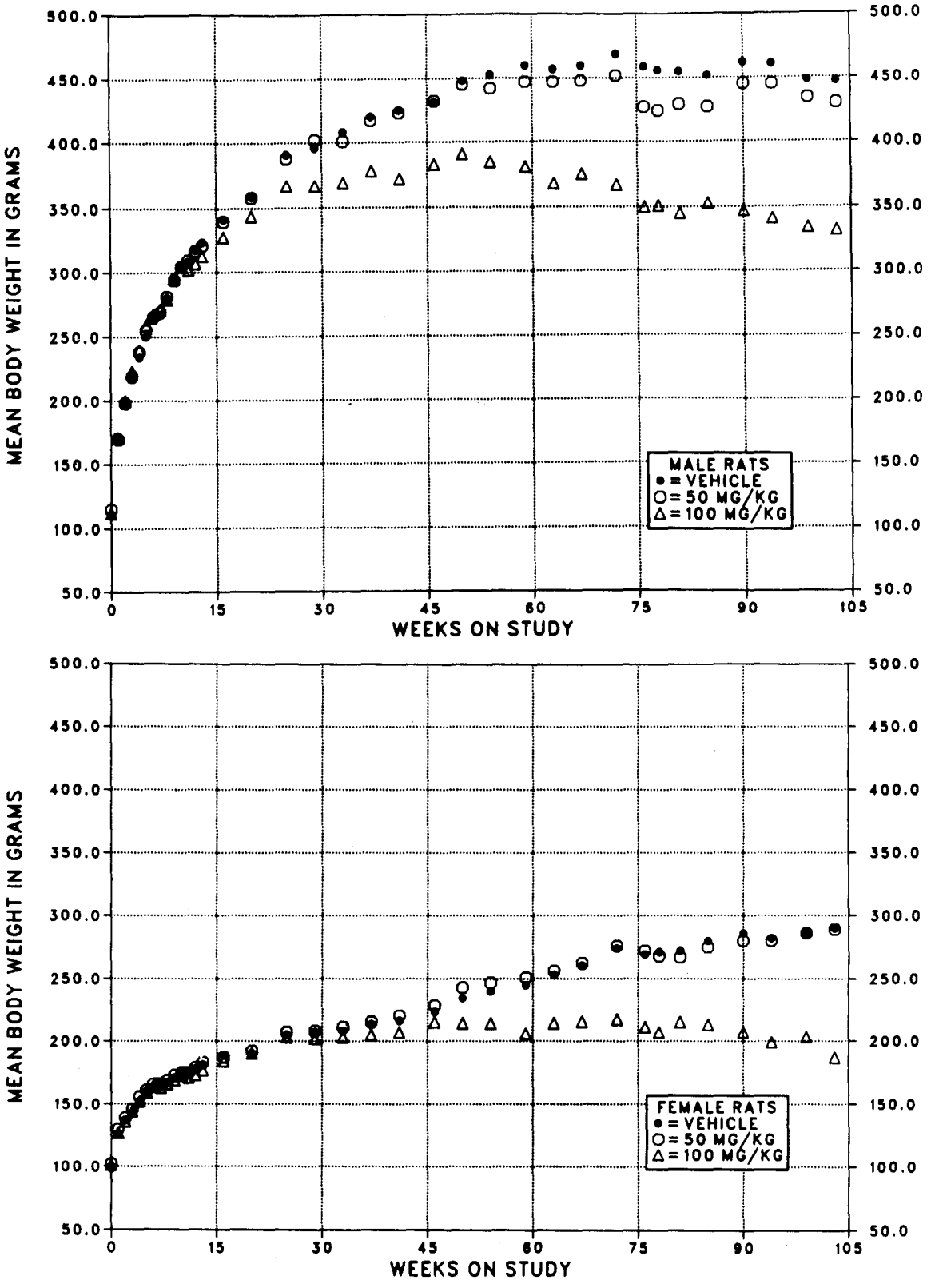


FIGURE 3. GROWTH CURVES FOR RATS ADMINISTERED MALONALDEHYDE, SODIUM SALT, IN WATER BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats administered malonaldehyde, sodium salt, at the doses used in these studies and for vehicle controls are shown in Table 11 and in the Kaplan and Meier curves in Figure 4. Survival of the high dose groups of both male (after week 88) and female (after week 68) rats was significantly lower than that of the vehicle controls.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the thyroid gland, pancreatic islets, pancreas, subcutaneous tissue, hematopoietic system (bone marrow, spleen, or multiple organs), adrenal gland, anterior pituitary gland, liver, stomach, and eye.

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

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

TABLE 11. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF MALONALDEHYDE, SODIUM SALT

	Vehicle Control	50 mg/kg	100 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	13	17	34
Accidentally killed	0	0	1
Killed at termination	37	33	15
Survival P values (c)	<0.001	0.633	<0.001
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	13	12	34
Accidentally killed	0	1	2
Killed at termination	37	37	14
Survival P values (c)	<0.001	0.846	<0.001

(a) Terminal-kill period: male--week 104; female--weeks 104-105
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

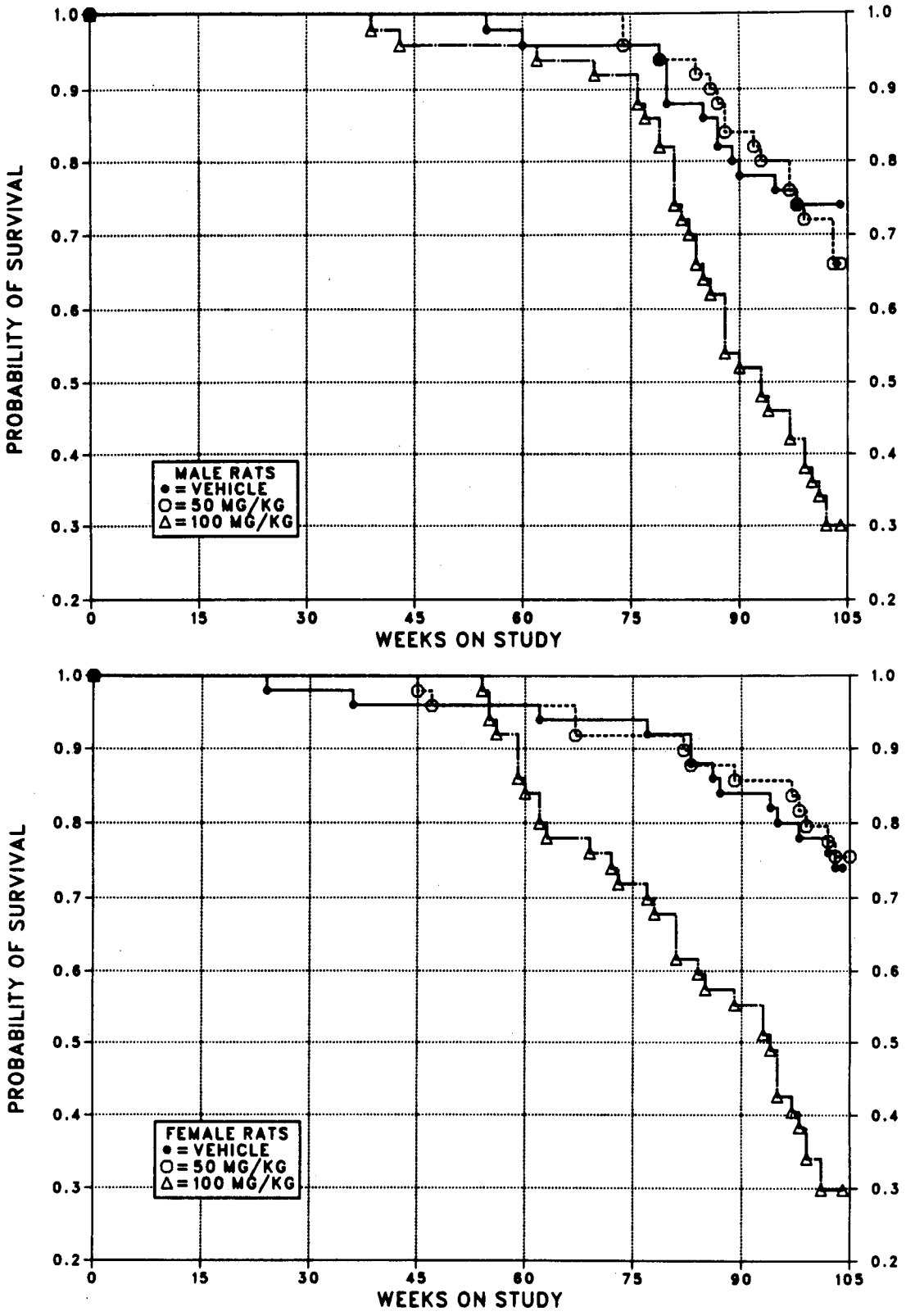


FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED MALONALDEHYDE, SODIUM SALT, IN WATER BY GAVAGE FOR TWO YEARS

Thyroid Gland: Follicular cell hyperplasia was observed at an increased incidence ($P<0.001$) in high dose female rats (Table 12). Hyperplasia was characterized by micropapillary folds of columnar cells or microfollicle formation on the wall of slightly enlarged follicles that did not compress adjacent structures.

Follicular cell adenomas, carcinomas, and adenomas or carcinomas (combined) in male and female rats occurred with positive trends (Table 12). The incidences of adenomas in high dose male and female rats and carcinomas in high dose male rats were significantly greater than those in the vehicle controls by the life table test; the incidences of follicular cell adenomas or carcinomas (combined) in high dose male and female rats were significantly ($P<0.05$) greater than those in the vehicle controls by the life table and incidental tumor tests. Two high dose male rats had bilateral follicular cell tumors: one had a bilateral carcinoma, and the second had an adenoma in one lobe and a carcinoma in the other lobe. A third high dose male had two adenomas in one lobe. Follicular cell adenomas were usually well-circumscribed masses consisting of variably sized follicles often with papillary fronds extending into the lumen. The follicular cell carcinomas (Figures 5-8) were more pleomorphic (Figure 7) and consisted of irregular follicular structures lined by anaplastic epithelial cells; a scirrhous response (Figure 7) was commonly seen with these tumors.

An increased incidence of thyroid gland follicular cell hyperplasia is often associated with an increased incidence of follicular cell adenomas and/or carcinomas. In this study, however, the increased incidence of follicular cell tumors in low and high dose male rats was not accompanied by increased follicular cell hyperplasia. However, in high dose female rats, a significant increase in follicular cell hyperplasia was associated with an increase in thyroid gland follicular cell tumors.

Ultimobranchial cysts occurred at an increased incidence ($P<0.001$) in high dose female rats (male: vehicle control, 0/50; low dose, 0/49; high dose, 2/50; female: 1/50; 0/50; 12/50). These embryologic remnants of the ultimobranchial bodies were unilocular or multilocular spaces lined by squamous epithelium.

TABLE 12. ANALYSIS OF THYROID GLAND FOLLICULAR CELL LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF MALONALDEHYDE, SODIUM SALT (a)

	Vehicle Control	50 mg/kg	100 mg/kg
MALE			
Hyperplasia			
Overall Rates	9/50 (18%)	7/49 (14%)	7/50 (14%)
Adenoma			
Overall Rates	3/50 (6%)	3/49 (6%)	9/50 (18%)
Adjusted Rates	7.3%	9.1%	34.4%
Terminal Rates	2/37 (5%)	3/33 (9%)	3/15 (20%)
Week of First Observation	55	104	81
Life Table Tests	P=0.003	P=0.618	P=0.007
Incidental Tumor Tests	P=0.026	P=0.618	P=0.068
Carcinoma			
Overall Rates	1/50 (2%)	5/49 (10%)	5/50 (10%)
Adjusted Rates	2.1%	13.3%	19.8%
Terminal Rates	0/37 (0%)	3/33 (9%)	2/15 (13%)
Week of First Observation	79	87	79
Life Table Tests	P=0.019	P=0.099	P=0.041
Incidental Tumor Tests	P=0.105	P=0.109	P=0.116
Adenoma or Carcinoma (b)			
Overall Rates	4/50 (8%)	8/49 (16%)	13/50 (26%)
Adjusted Rates	9.2%	22.0%	48.1%
Terminal Rates	2/37 (5%)	6/33 (18%)	5/15 (33%)
Week of First Observation	55	87	79
Life Table Tests	P<0.001	P=0.154	P<0.001
Incidental Tumor Tests	P=0.008	P=0.168	P=0.015
FEMALE			
Hyperplasia			
Overall Rates	10/50 (20%)	10/50 (20%)	26/50 (52%)
Adenoma			
Overall Rates	2/50 (4%)	0/50 (0%)	5/50 (10%)
Adjusted Rates	5.3%	0.0%	30.4%
Terminal Rates	1/37 (3%)	0/37 (0%)	4/14 (29%)
Week of First Observation	103		69
Life Table Tests	P=0.015	P=0.240N	P=0.020
Incidental Tumor Tests	P=0.069	P=0.240N	P=0.083
Carcinoma			
Overall Rates	0/50 (0%)	1/50 (2%)	2/50 (4%)
Adenoma or Carcinoma (c)			
Overall Rates	2/50 (4%)	1/50 (2%)	7/50 (14%)
Adjusted Rates	5.3%	2.7%	37.6%
Terminal Rates	1/37 (3%)	1/37 (3%)	4/14 (29%)
Week of First Observation	103	105	69
Life Table Tests	P=0.001	P=0.500N	P=0.003
Incidental Tumor Tests	P=0.026	P=0.500N	P=0.045

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table A3 (footnotes).
(b) Historical incidence in water gavage controls (mean ± SD): 2/144 (1% ± 1%); historical incidence in untreated controls (mean ± SD): 27/1,928 (1% ± 2%)
(c) Historical incidence in water gavage controls (mean ± SD): 4/146 (3% ± 3%); historical incidence in untreated controls (mean ± SD): 20/1,952 (1% ± 1%)

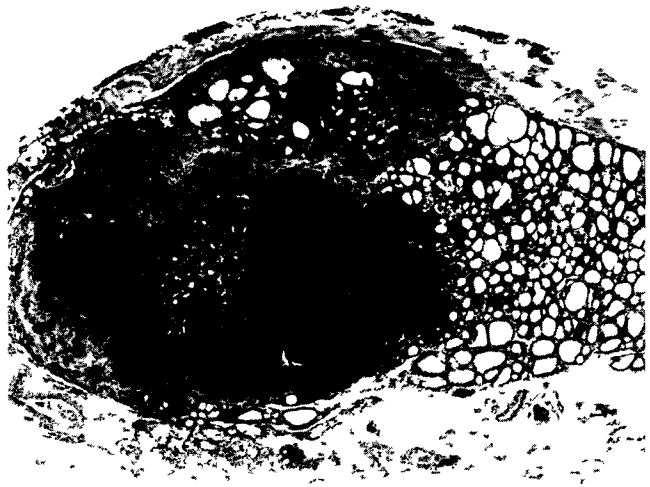


Figure 5 Photomicrograph of thyroid gland with a follicular cell carcinoma from a male rat given malonaldehyde, sodium salt Over half the normal tissue is replaced by neoplastic follicular epithelium Normal thyroid follicles containing colloid are present in the right hand portion of the gland H&E, magnification 9×

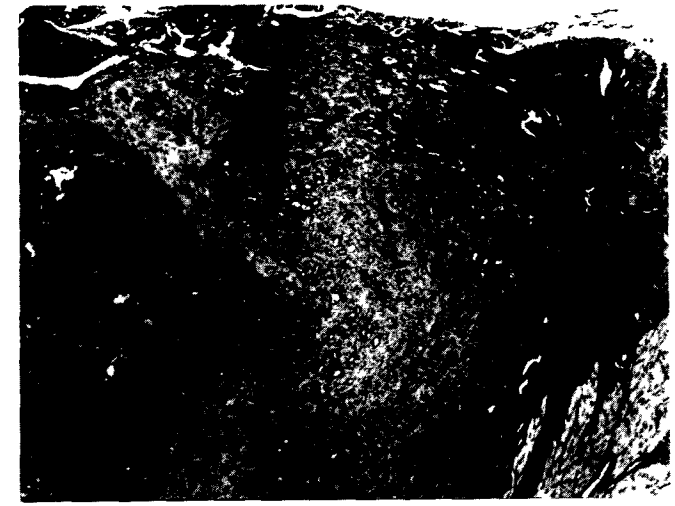


Figure 6 Photomicrograph of a thyroid follicular cell carcinoma that has totally obliterated the gland and invaded adjacent skeletal muscle H&E, magnification 9×

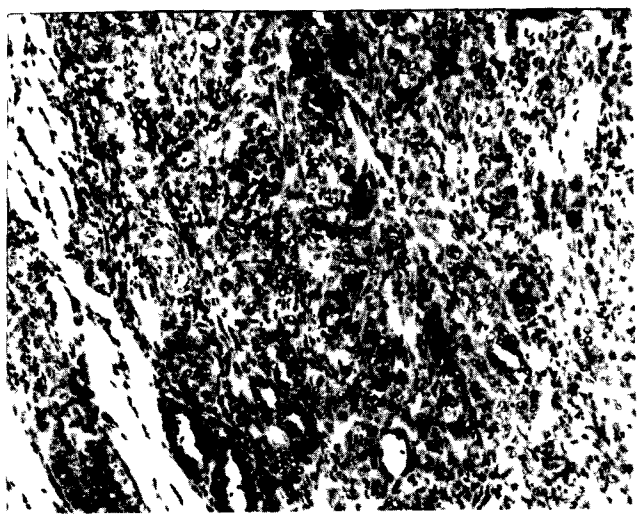


Figure 7 Photomicrograph of the thyroid follicular cell carcinoma shown in Figure 6 The neoplastic epithelium is arranged in pleomorphic tubular structures and is invading the adjacent muscle The neoplasm has elicited a scirrhous response characterized by the formation of collagenous connective tissue that is interspersed among the neoplastic follicular epithelium H&E, magnification 25×

Figure 8 Photomicrograph of a moderately well differentiated thyroid follicular cell carcinoma This neoplasm has not elicited a scirrhous response, and the follicular epithelium is arranged in tubular and follicle like structures H&E magnification 25×

Pancreatic Islets: The incidences of islet cell adenomas and adenomas or carcinomas (combined) in low dose male rats were significantly greater than those in the vehicle controls (Table 13) and exceeded the range for historical control males (0/50-7/49).

Pancreas: An increased incidence and severity of diffuse atrophy of the acinar pancreas occurred in dosed male and female rats (male: vehicle control, 8/49; low dose, 26/50; high dose, 38/49; female: 5/50; 27/50; 42/50). This lesion was characterized by reduction in the number of secretory granules and reduction in the size of pancreatic acini and lobules. This lesion was distinct from the spontaneously occurring focal atrophy that was also diagnosed and characterized by fibrosis and atrophy of a single lobule.

Subcutaneous Tissue: Although the incidence of fibromas, fibrosarcomas, or myxosarcomas (combined) was slightly increased in low dose male rats, it was not significantly different from that in the vehicle controls (vehicle control, 2/50; low dose, 7/50; high dose, 3/50).

Hematopoietic System:

Bone Marrow--The incidences of hematopoietic hyperplasia in high dose female rats and reticulum cell hyperplasia in low dose female rats were greater ($P<0.01$) than those in the vehicle controls (hematopoietic hyperplasia--male: vehicle control, 5/50; low dose, 2/50; high dose, 5/50; female: 2/50; 4/50; 11/50; reticulum cell hyperplasia--male: 5/50; 3/50; 1/50; female: 6/50; 19/50; 7/50).

Spleen--Hematopoiesis was observed at an increased incidence ($P<0.01$) in high dose female rats (male: vehicle control, 3/50; low dose, 4/50; high dose, 1/50; female: 1/50; 2/50; 9/50).

TABLE 13. ANALYSIS OF PANCREATIC ISLET CELL TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT

	Vehicle Control	50 mg/kg	100 mg/kg
Adenoma			
Overall Rates	0/49 (0%)	9/50 (18%)	1/49 (2%)
Adjusted Rates	0.0%	26.1%	6.7%
Terminal Rates	0/37 (0%)	8/33 (24%)	1/15 (7%)
Week of First Observation		97	104
Life Table Tests	P=0.092	P=0.002	P=0.320
Incidental Tumor Tests	P=0.138	P=0.002	P=0.320
Carcinoma			
Overall Rates	1/49 (2%)	0/50 (0%)	0/49 (0%)
Adenoma or Carcinoma (a)			
Overall Rates	1/49 (2%)	9/50 (18%)	1/49 (2%)
Adjusted Rates	2.7%	26.1%	6.7%
Terminal Rates	1/37 (3%)	8/33 (24%)	1/15 (7%)
Week of First Observation	104	97	104
Life Table Tests	P=0.169	P=0.006	P=0.548
Incidental Tumor Tests	P=0.235	P=0.009	P=0.548

(a) Historical incidence in water gavage controls (mean ± SD): 12/147 (8% ± 4%); historical incidence in untreated controls (mean ± SD): 102/1,913 (5% ± 4%)

Multiple Organs--Mononuclear cell leukemia in male rats occurred with a significant positive trend by life table analysis; the incidences in low and high dose males were not significantly different from that in vehicle controls and did not exceed the mean historical control incidence (Table 14).

Adrenal Gland: The incidence of lipoid degeneration of the adrenal gland cortex was significantly ($P<0.05$) increased in high dose male rats (vehicle control, 12/50; low dose, 13/50; high dose, 23/50) and in high dose female rats (19/50; 20/50; 30/50).

Pheochromocytomas in male rats occurred with a significant positive trend; the incidence in the high dose group was significantly greater than that in the vehicle controls by the life table test but not by the incidental tumor test (Table 15), which is the more appropriate test for this generally nonfatal tumor.

Anterior Pituitary Gland: Adenomas and adenomas or carcinomas (combined) in male and female rats occurred with significant negative trends, and the incidences in the high dose groups were significantly lower than those in the vehicle controls by the incidental tumor test (Table 16).

TABLE 14. ANALYSIS OF MONONUCLEAR CELL LEUKEMIA IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (a)

	Vehicle Control	50 mg/kg	100 mg/kg
Overall Rates	7/50 (14%)	10/50 (20%)	11/50 (22%)
Adjusted Rates	15.2%	23.7%	34.9%
Terminal Rates	1/37 (3%)	3/33 (9%)	0/15 (0%)
Week of First Observation	55	74	79
Life Table Tests	P=0.039	P=0.306	P=0.067
Incidental Tumor Tests	P=0.245N	P=0.503	P=0.272N

(a) Historical incidence of leukemia in water gavage controls (mean ± SD): 74/150 (49% ± 11%); historical incidence in untreated controls (mean ± SD): 583/1,977 (29% ± 12%)

TABLE 15. ANALYSIS OF ADRENAL GLAND LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT

	Vehicle Control	50 mg/kg	100 mg/kg
Medullary Focal Hyperplasia			
Overall Rates	18/50 (36%)	21/50 (42%)	16/50 (32%)
Pheochromocytoma (a)			
Overall Rates	5/50 (10%)	6/50 (12%)	8/50 (16%)
Adjusted Rates	13.5%	16.8%	40.0%
Terminal Rates	5/37 (14%)	5/33 (15%)	5/15 (33%)
Week of First Observation	104	74	76
Life Table Tests	P=0.014	P=0.430	P=0.016
Incidental Tumor Tests	P=0.048	P=0.427	P=0.055

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

TABLE 16. ANALYSIS OF ANTERIOR PITUITARY GLAND TUMORS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF MALONALDEHYDE, SODIUM SALT

	Vehicle Control	50 mg/kg	100 mg/kg
MALE			
Adenoma			
Overall Rates	20/47 (43%)	14/49 (29%)	7/49 (14%)
Adjusted Rates	50.8%	38.3%	30.7%
Terminal Rates	16/35 (46%)	11/33 (33%)	3/15 (20%)
Week of First Observation	80	93	84
Life Table Tests	P=0.175N	P=0.189N	P=0.242N
Incidental Tumor Tests	P=0.010N	P=0.080N	P=0.016N
Carcinoma			
Overall Rates	0/47 (0%)	0/49 (0%)	1/49 (2%)
Adenoma or Carcinoma (a)			
Overall Rates	20/47 (43%)	14/49 (29%)	8/49 (16%)
Adjusted Rates	50.8%	38.3%	36.5%
Terminal Rates	16/35 (46%)	11/33 (33%)	4/15 (27%)
Week of First Observation	80	93	84
Life Table Tests	P=0.264N	P=0.189N	P=0.357N
Incidental Tumor Tests	P=0.022N	P=0.080N	P=0.039N
FEMALE			
Adenoma			
Overall Rates	16/49 (33%)	10/49 (20%)	2/48 (4%)
Adjusted Rates	39.8%	26.2%	14.3%
Terminal Rates	13/37 (35%)	8/36 (22%)	2/14 (14%)
Week of First Observation	83	102	104
Life Table Tests	P=0.032N	P=0.147N	P=0.060N
Incidental Tumor Tests	P=0.005N	P=0.146N	P=0.015N
Carcinoma			
Overall Rates	2/49 (4%)	0/49 (0%)	0/48 (0%)
Adenoma or Carcinoma (b)			
Overall Rates	18/49 (37%)	10/49 (20%)	2/48 (4%)
Adjusted Rates	43.7%	26.2%	14.3%
Terminal Rates	14/37 (38%)	8/36 (22%)	2/14 (14%)
Week of First Observation	83	102	104
Life Table Tests	P=0.013N	P=0.074N	P=0.034N
Incidental Tumor Tests	P=0.001N	P=0.068N	P=0.004N

(a) Historical incidence in water gavage controls (mean ± SD): 51/150 (34% ± 9%); historical incidence in untreated controls (mean ± SD): 428/1,861 (23% ± 11%)
(b) Historical incidence in water gavage controls (mean ± SD): 72/143 (50% ± 2%); historical incidence in untreated controls (mean ± SD): 931/1,952 (48% ± 11%)

Liver: Cystic degeneration, cytoplasmic vacuolization, bile duct hyperplasia, and bile duct fibrosis occurred with increased incidences and/or severity in male and female rats (Table 17). Cystic degeneration (also referred to as spongiosis hepatis) consists of focal multilocular cystic formations containing granular material or, occasionally, erythrocytes. The cytoplasmic vacuolization affected randomly distributed clusters of hepatocytes and probably represents lipid accumulation within the cells. Bile duct hyperplasia and fibrosis occur spontaneously in aged rats, and the lesions in dosed rats were qualitatively similar. In affected rats, some of the portal triads in sections of the liver contained increased numbers of bile ducts or ductules surrounded by dense collagenous connective tissue.

Stomach: Acute and chronic inflammation, necrotizing inflammation characterized by epithelial necrosis and erosion of the glandular mucosa, and ulcers were observed at increased incidences in the glandular stomach of dosed male rats and high dose female rats (Table 18). Epithelial hyperplasia was observed at increased incidences in the forestomach near the junction with the glandular stomach in dosed male and high dose female rats.

Eye: Corneal inflammation in high dose male and female rats and retinal atrophy and cataracts of the crystalline lens were observed at increased incidences in dosed male and female rats (Table 19). The incidences of eye lesions in the dosed groups were not related to the rack position, e.g., top row and outside columns of rack versus inside (see Figure 2). Cages were not rotated on racks during the studies.

The increased incidences of stomach and eye lesions in dosed rats are compound related and appear to occur in response to the toxicity of the compound.

TABLE 17. NUMBER OF RATS WITH LESIONS OF THE LIVER IN THE TWO-YEAR GAVAGE STUDIES OF MALONALDEHYDE, SODIUM SALT

Site/Lesion	Male			Female		
	Vehicle Control	50 mg/kg	100 mg/kg	Vehicle Control	50 mg/kg	100 mg/kg
Number of liver examined	50	50	50	50	50	50
Cytoplasmic vacuolization	7	7	12	6	6	18
Cystic degeneration	13	26	24	0	0	5
Bile duct hyperplasia (a)	50 (2.5)	45 (2.9)	50 (3.5)	17 (1.6)	15 (2.1)	35 (2.6)
Bile duct fibrosis (a)	4 (1.3)	8 (1.7)	28 (2.1)	1	0	1

(a) Mean grade of severity of hyperplasia or fibrosis for affected rats is given in parentheses: minimal = 1, mild = 2, moderate = 3, and marked = 4.

TABLE 18. NUMBER OF RATS WITH LESIONS OF THE STOMACH IN THE TWO-YEAR GAVAGE STUDIES OF MALONALDEHYDE, SODIUM SALT

Site/Lesion	Male			Female		
	Vehicle Control	50 mg/kg	100 mg/kg	Vehicle Control	50 mg/kg	100 mg/kg
Number of stomachs examined	50	49	50	50	50	50
Glandular stomach						
Inflammation	1	4	(a) 7	1	2	3
Inflammation, necrotizing	1	(a) 7	4	0	1	(b) 9
Ulcer	0	(a) 5	(b) 15	1	2	(b) 19
Forestomach						
Epithelial hyperplasia	3	8	(b) 18	4	5	(b) 18
Squamous cell papilloma	0	1	1	1	0	1

(a) $P<0.05$ vs. vehicle controls
(b) $P<0.01$ vs. vehicle controls

TABLE 19. NUMBER OF RATS WITH LESIONS OF THE EYE IN THE TWO-YEAR GAVAGE STUDIES OF MALONALDEHYDE, SODIUM SALT

Site/Lesion	Male			Female		
	Vehicle Control	50 mg/kg	100 mg/kg	Vehicle Control	50 mg/kg	100 mg/kg
Number of rats examined	50	50	50	50	50	50
Corneal inflammation	2	2	(a) 19	2	2	(a) 25
Retinal atrophy	5	9	(a) 24	3	(a) 31	(a) 30
Crystalline lens cataract	4	(a) 14	(a) 19	4	(a) 26	(a) 31

(a) $P<0.01$ vs. vehicle controls

FOURTEEN-DAY STUDIES

All mice that received 1,500 mg/kg malonaldehyde, sodium salt, 4/5 males that received 1,000 mg/kg, and 5/5 males that received 750 mg/kg died before the end of the studies (Table 20). The final mean body weights of males that received 500 or 1,000 mg/kg were 18% or 23% lower than that of the controls. The final mean body weight of females that received 1,000 mg/kg was 16% lower than that of the controls.

After 8 days, the urine of all dosed mice was nearly the same shade of yellow as the dose mixture. Male mice that received 750 mg/kg or more and female mice that received 1,500 mg/kg had rough hair coats and were inactive. No compound-related effects were observed at necropsy.

THIRTEEN-WEEK STUDIES

Three of 10 male mice and 1/10 female mice that received 500 mg/kg and 1/10 males and 1/10 females that received 125 mg/kg died before the end of the studies (Table 21). The final mean body weights of mice that received 500 mg/kg were 38% lower than that of the vehicle controls for males and 18% lower for females.

TABLE 20. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FOURTEEN-DAY GAVAGE STUDIES OF MALONALDEHYDE, SODIUM SALT

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
(d) 0	5/5	25.4	27.4	+2.0	
250	5/5	26.6	26.0	−0.6	94.9
500	5/5	27.8	22.4	−5.4	81.8
750	(e) 0/5	23.6	(f)	(f)	(f)
1,000	(g) 1/5	24.8	21.0	−3.8	76.6
1,500	(h) 0/5	24.8	(f)	(f)	(f)
FEMALE					
(d) 0	5/5	19.6	20.8	+1.2	
250	5/5	19.4	19.0	−0.4	91.3
500	5/5	20.0	19.8	−0.2	95.2
750	5/5	20.6	20.0	−0.6	96.2
1,000	5/5	18.6	17.4	−1.2	83.7
1,500	(i) 0/5	18.8	(f)	(f)	(f)

(a) Number surviving/number initially in the group
(b) Initial mean group body weight
(c) Mean body weight change of the survivors
(d) Controls were untreated.
(e) Day of death: 7,7,7,8,13
(f) No data are reported due to the 100% mortality in this group.
(g) Day of death: 10,10,11,11
(h) Day of death: 4,4,4,5,6
(i) Day of death: 7,7,7,8,8

TABLE 21. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF MALONALDEHYDE, SODIUM SALT

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	22.9 ± 0.5	34.1 ± 0.7	+11.2 ± 0.8	
30	10/10	24.4 ± 0.5	35.6 ± 0.7	+11.2 ± 0.4	104.4
60	10/10	23.7 ± 0.8	33.6 ± 0.8	+9.9 ± 0.8	98.5
125	(d) 9/10	25.3 ± 0.5	34.1 ± 0.9	+8.7 ± 0.7	100.0
250	10/10	23.9 ± 0.6	34.2 ± 1.0	+10.3 ± 1.0	100.3
500	(e) 7/10	23.4 ± 0.6	21.0 ± 1.0	−2.9 ± 1.3	61.6
FEMALE					
0	10/10	18.8 ± 0.4	26.0 ± 0.7	+7.2 ± 0.7	
30	10/10	19.1 ± 0.4	25.3 ± 0.5	+6.2 ± 0.5	97.3
60	10/10	19.1 ± 0.4	24.9 ± 0.6	+5.8 ± 0.4	95.8
125	(d) 9/10	18.9 ± 0.3	25.1 ± 0.6	+6.1 ± 0.6	96.5
250	10/10	19.1 ± 0.3	25.3 ± 1.0	+6.2 ± 0.7	97.3
500	(f) 9/10	18.8 ± 0.4	21.4 ± 0.5	+2.7 ± 0.4	82.3

(a) Number surviving/number initially in the group
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Week of death: 9
(e) Week of death: 7,11,13
(f) Week of death: 1

Compound-related lesions were observed in the pancreas, stomach, and testis (Table 22). Lesions in the pancreas diagnosed as exocrine atrophy were characterized by an accumulation of adipose tissue in the interstitium, with a reduced amount of normal-appearing pancreatic acinar tissue. This lesion was present in most mice at 250 and 500 mg/kg and in one male at 125 mg/kg. Mild dilatation of the gastric glands was observed in six males in the 500 mg/kg group. Degeneration of the germinal epithelium was observed in the testis of 2/10 males that received 500 mg/kg and 9/10 males that received 250 mg/kg. Lesions in lymphoid organs included lymphoid depletion. Increased splenic extramedullary hematopoiesis was present in three males in the 500 mg/kg group.

TABLE 22. NUMBER OF MICE WITH LESIONS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF MALONALDEHYDE, SODIUM SALT

Site/Lesion	Dose (mg/kg) 0	60	125	250	500
MALE					
Number of mice examined	10	10	10	10	10
Pancreas					
Exocrine atrophy	0	0	1	10	8
Spleen					
Lymphoid depletion	0	0	0	0	6
Extramedullary hematopoiesis	0	0	0	0	3
Mandibular lymph node					
Lymphoid depletion	0	0	0	0	3
Stomach mucosa, gastric glands					
Dilatation	0	0	0	0	6
Testis, germinal epithelium					
Degeneration	0	0	0	9	2
FEMALE					
Number of mice examined	10	10	10	10	10
Pancreas					
Exocrine atrophy	0	0	0	8	9
Spleen					
Lymphoid depletion	0	0	0	0	1
Extramedullary hematopoiesis	0	0	0	0	0
Mandibular lymph node					
Lymphoid depletion	0	0	0	0	0
Stomach mucosa, gastric glands					
Dilatation	0	0	0	0	0

Dose Selection Rationale: Because of compound-related lesions in the pancreas, spleen, lymph nodes, stomach, and testis, doses selected for mice for the 2-year studies were 60 and 120 mg/kg malonaldehyde, sodium salt, administered in distilled water by gavage 5 days per week.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed and vehicle control male mice were comparable throughout most of the study (Table 23 and Figure 9). After week 93, mean body weights of the high dose male group were lower than those of the vehicle controls. Mean body weights of dosed female mice were greater than those of the vehicle controls throughout most of the study. Hair color of high dose mice changed from wild agouti to gray during the studies. Eczema, alopecia, rough hair coat, skin wounds, and genital inflammation or infection observed in all groups of male mice were considered to be a consequence of fighting.

TABLE 23. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF MALONALDEHYDE, SODIUM SALT

Weeks on Study	Vehicle Control		60 mg/kg			120 mg/kg		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors
MALE								
1	27 9	50	28 9	104	50	29 2	105	50
2	29 2	50	29 6	101	50	29 1	100	50
3	31 0	50	30 9	100	50	30 3	98	50
4	31 5	50	31 2	99	50	29 8	95	50
5	31 7	50	31 6	100	50	30 3	96	50
6	32 5	50	31 9	98	50	30 9	95	50
8	34 2	50	32 4	95	50	33 1	97	50
9	35 1	50	34 4	98	50	33 3	95	50
10	33 6	50	31 8	95	50	31 6	94	50
11	35 3	50	32 9	93	50	32 3	92	50
12	36 0	49	34 9	97	50	33 7	94	50
13	36 5	49	33 5	92	50	34 9	96	50
17	37 9	49	36 7	97	50	38 1	101	50
21	38 9	48	37 5	96	49	39 6	102	50
26	40 9	48	41 0	100	49	42 8	105	50
30	41 3	48	41 3	100	49	43 4	105	50
33	42 1	48	43 3	103	49	44 6	106	50
38	42 2	48	42 4	100	49	44 0	104	50
42	40 7	47	41 9	103	48	42 5	104	50
46	42 0	47	42 7	102	45	43 3	103	50
50	43 6	47	44 7	103	45	44 0	101	50
54	43 7	47	41 6	95	45	42 8	98	50
58	44 4	47	44 3	100	45	44 1	99	50
63	43 2	45	44 2	102	42	44 0	102	50
67	43 2	45	44 0	102	42	42 9	99	48
71	43 9	45	45 1	103	41	43 8	100	46
76	42 7	45	43 1	101	41	42 8	100	44
80	43 7	43	44 3	101	38	42 7	98	44
84	43 0	39	42 4	99	33	41 5	97	43
89	41 9	36	41 9	100	33	40 1	96	35
93	42 6	35	43 6	102	31	40 1	94	25
98	40 0	29	40 8	102	24	37 1	93	17
104	39 8	24	39 7	100	20	36 6	92	14
FEMALE								
1	20 8	50	20 7	100	50	20 4	98	50
2	20 7	50	20 8	100	50	21 5	104	50
3	21 9	50	22 6	103	50	22 2	101	50
4	22 4	50	22 4	100	50	22 4	100	50
5	22 6	50	22 6	100	50	23 0	102	50
6	23 1	50	22 9	99	50	23 6	102	50
8	23 3	50	24 6	106	50	23 2	100	50
9	23 8	50	24 6	103	50	24 6	103	50
10	23 8	50	22 8	96	50	23 8	100	50
11	25 0	50	23 5	94	50	24 8	99	50
12	25 5	50	24 4	96	50	24 3	95	50
13	25 9	50	25 1	97	50	25 4	98	50
17	25 7	50	26 3	102	50	26 9	105	50
21	26 8	50	26 6	99	50	27 5	103	50
26	29 4	50	29 6	101	50	30 0	102	50
30	29 0	50	29 5	102	50	30 9	107	50
33	30 2	50	31 9	106	50	33 7	112	50
38	30 9	50	31 7	103	49	33 6	109	50
42	29 2	50	30 5	104	49	32 6	112	50
46	30 4	50	32 3	106	49	35 3	116	50
50	31 7	49	34 2	108	49	36 9	116	50
54	32 8	49	33 5	102	49	37 3	114	49
58	33 4	49	35 8	107	49	37 7	113	49
63	33 8	49	35 7	106	49	39 1	116	49
67	34 4	49	36 7	107	48	40 2	117	49
71	36 8	49	39 5	107	48	41 7	113	49
76	36 2	48	39 3	109	47	41 0	113	48
80	36 6	47	38 9	106	46	41 8	114	46
84	37 0	46	39 1	106	44	40 8	110	42
89	37 7	46	41 5	110	44	40 6	108	41
93	40 4	43	43 0	106	44	37 8	94	38
98	36 6	42	38 5	105	42	35 6	97	32
104	35 9	41	37 5	104	38	35 7	99	30

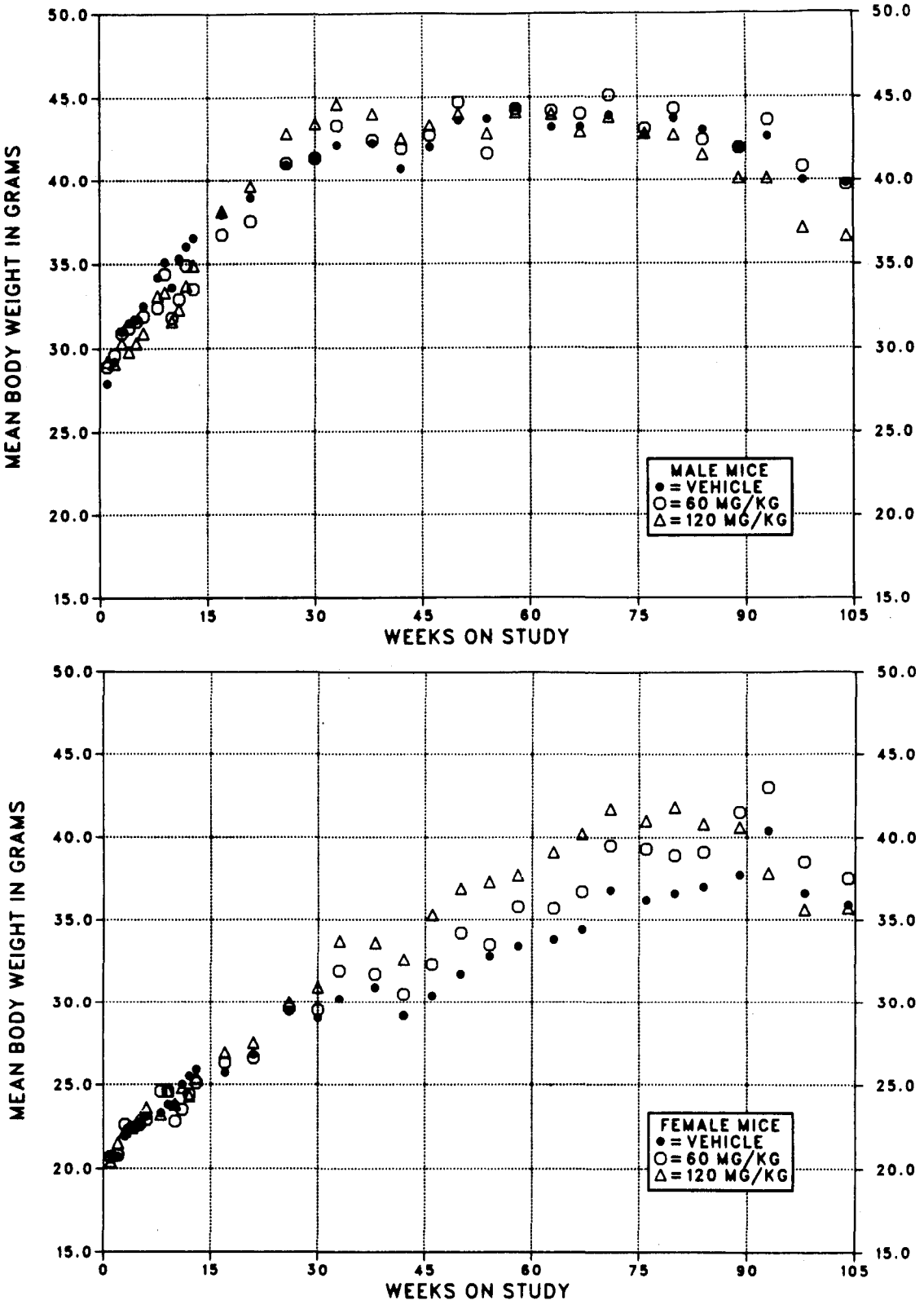


FIGURE 9. GROWTH CURVES FOR MICE ADMINISTERED MALONALDEHYDE, SODIUM SALT, IN WATER BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice administered malonaldehyde, sodium salt, at the doses used in these studies and for vehicle controls are shown in Table 24 and in the Kaplan and Meier curves in Figure 10. The survival of the high dose group of male mice was significantly lower than that of the vehicle controls after week 92. No other significant differences in survival were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the skin, pancreatic acinus, and uterus.

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

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

TABLE 24. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF MALONALDEHYDE, SODIUM SALT

	Vehicle Control	60 mg/kg	120 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	23	28	36
Accidentally killed	3	2	0
Killed at termination	23	19	14
Died during termination period	1	1	0
Survival P values (c)	0.014	0.333	0.017
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	9	11	13
Accidentally killed	0	1	(d) 7
Killed at termination	41	38	30
Survival P values (c)	0.297	0.787	0.368

(a) Terminal-kill period: male--week 104; female--weeks 104-105
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.
(d) During week 94, five high dose female mice in one cage died from drowning because of a malfunction of the water-dispensing system.

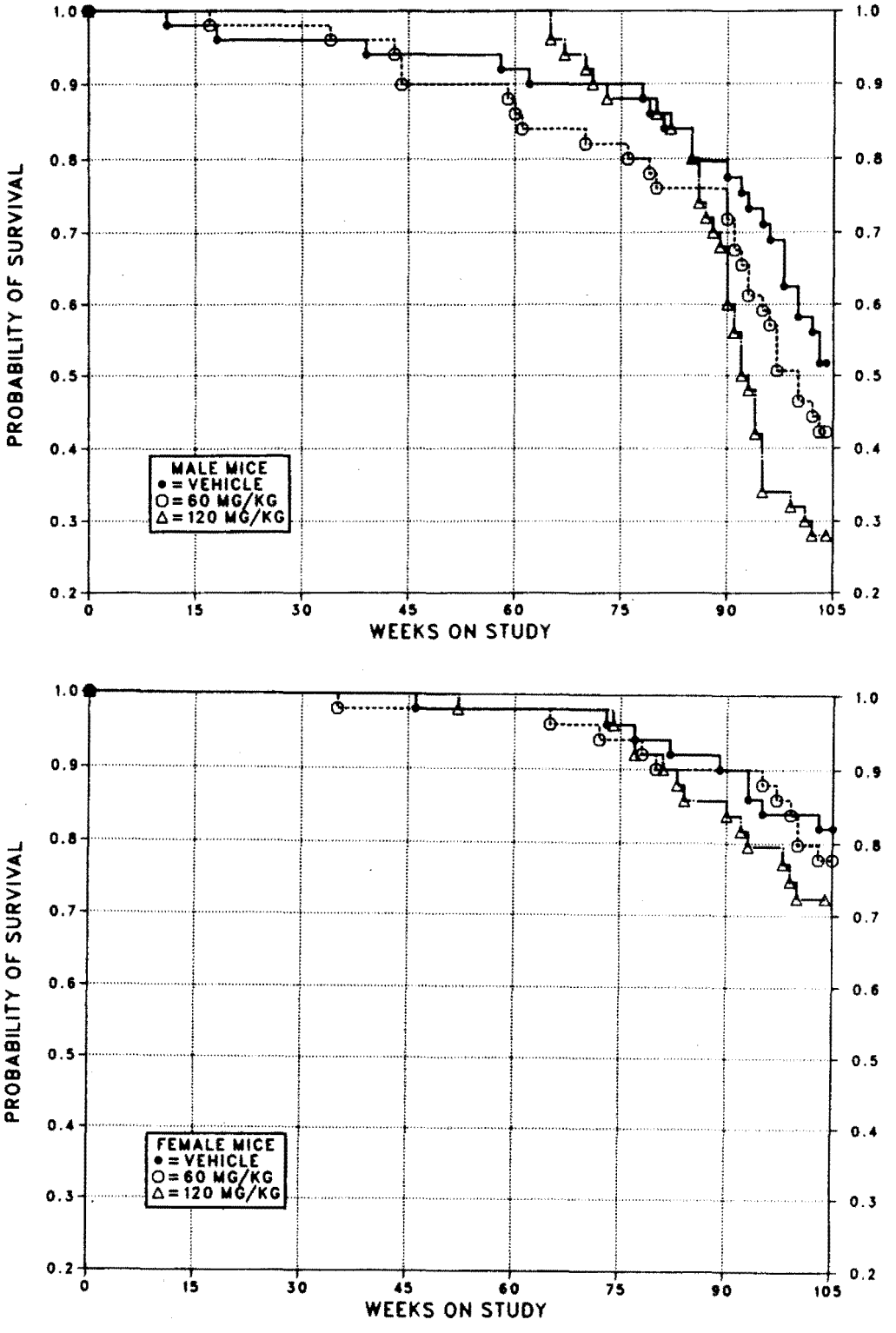


FIGURE 10. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED MALONALDEHYDE, SODIUM SALT, IN WATER BY GAVAGE FOR TWO YEARS

At no site was an increased incidence of neoplasms observed in dosed mice. A significant increase in the incidence of nonneoplastic lesions occurred at the following sites:

Skin: An increased incidence ($P<0.001$) of pigmentation loss (listed as pigmentation, NOS, in Table C4) in hair shafts was observed in high dose mice (male: vehicle control, 0/50; low dose, 1/50; high dose, 31/50; female: 2/50; 0/50; 27/50).

Pancreatic Acinus: Atrophy was observed at increased incidences ($P<0.001$) in dosed mice (male: vehicle control, 5/43; low dose, 18/43; high dose, 31/45; female: 8/47; 26/50; 41/48).

Uterus: Dilatation was observed at increased incidences ($P<0.001$) in dosed female mice (vehicle control, 0/49; low dose, 12/48; high dose, 16/47.

IV. DISCUSSION AND CONCLUSIONS

Results of Thirteen-Week Studies
Two-Year Studies in Rats
Two-Year Studies in Mice
Genetic Toxicology
Audit
Conclusions

Malonaldehyde, sodium salt, was studied for potential toxicity and carcinogenicity in male and female F344/N rats and B6C3F$_1$ mice. The chemical was administered by gavage in distilled water. Since 1/5 male rats and 5/5 male mice that received 750 mg/kg malonaldehyde, sodium salt, did not survive to the end of the 14-day studies, doses for rats and mice in the 13-week studies were set at 0, 30, 60, 125, 250, and 500 mg/kg.

Results of Thirteen-Week Studies

Nine of 10 male rats and 10/10 female rats that received 500 mg/kg malonaldehyde, sodium salt, did not survive to the end of the 13-week studies. The final mean body weights of male and female rats that received 125 and 250 mg/kg were lower than those of vehicle controls at the end of 13 weeks. The final mean body weight of male rats administered 500 mg/kg was 61% that of vehicle controls. Both male and female rats had compound-related lesions in the stomach and kidney; these lesions occurred primarily in the two highest dose groups. Male rats at the two highest doses also had lesions of the testis. Although degeneration of the testicular germinal epithelium is frequently observed in moribund or debilitated rats, this lesion occurred in three male rats receiving 250 mg/kg, and all animals in this group survived until the end of the study. Thus, the testicular degeneration may have been compound related. The hyperplastic changes observed in the bone marrow and the spleen (hematopoiesis) may be secondary to the acute inflammatory changes associated with necrosis and erosion in the glandular stomach. Lymphoid depletion in the spleen, thymus, and mandibular lymph nodes is frequently observed in moribund or debilitated rats, and it may not be a primary, compound-related lesion.

Three of 10 male mice and 1/10 female mice that received 500 mg/kg died before the end of the 13-week studies. The final mean body weights of male and female mice that received 500 mg/kg were lower than those of the vehicle controls. Atrophy of the exocrine pancreas occurred in most mice in the two highest dose groups. Other lesions occurred in the stomach, spleen, and lymph nodes of male mice in the highest dose group and in the testis of the two highest dose groups. Based on these results, the doses of malonaldehyde, sodium salt, selected for the 2-year studies were 50 and 100 mg/kg for rats and 60 and 120 mg/kg for mice, administered in distilled water by gavage, 5 days per week.

Two-Year Studies in Rats

Survival and weight gains were poor in high dose rats. Survival of the high dose groups of male rats (after week 88) and female rats (after week 68) was significantly reduced compared with that of the vehicle controls. A 10% reduction in mean body weight was observed in the high dose groups as early as 33 and 54 weeks. Mean body weights of high dose males and females were 26% and 36% lower than those of vehicle controls at the end of the studies. The final mean body weight of low dose males was 4% lower than that of the vehicle controls, and the survival rate was 8% lower. Mean body weights and survival rates of low dose female rats were similar to those of vehicle controls throughout the study. No compound-related clinical signs were observed.

The incidences of thyroid gland follicular cell adenomas were increased in high dose rats (see Table 12). The occurrence of bilateral follicular cell neoplasms in two high dose male rats is an unusual finding and provides additional support for a compound-related effect. It should also be noted that the incidence of combined adenomas and carcinomas in the male rat vehicle controls (8%) was greater than the historical incidence (1.4%) in water gavage controls in three other studies at Battelle Columbus Laboratories and greater than the overall historical incidence (1.4%) in all untreated controls (Table A4). Follicular cell hyperplasia and ultimobranchial cysts occurred at increased incidences in high dose female rats; the incidences of these nonneoplastic lesions in dosed male rats were not markedly different from those in vehicle controls. Although follicular cell hyperplasia is a lesion that often precedes or is associated with the appearance of thyroid gland follicular cell neoplasms, analyses of thyroid tumor and follicular cell hyperplasia incidences in previous NTP/NCI studies indicate that there is no general pattern of correlation. Among four structurally related chemicals, 4,4'-thiodianiline (NCI, 1978),

4,4'-methylenedianiline dihydrochloride (NTP, 1983), 4,4'-oxydianiline (NCI, 1980), and C.I. Basic Red 9 monohydrochloride (NTP, 1986), which all induced thyroid follicular cell tumors in both male and female rats, there was no consistent correlation between the induction of tumors and an increase in follicular cell hyperplasia. However, most of the positive correlations did occur at the highest doses.

The incidence of pancreatic islet cell adenomas or carcinomas (combined) in low dose male rats was significantly greater than that in vehicle controls (vehicle control, 1/49; low dose, 9/50; high dose, 1/49). Although the combined incidence of fibromas, fibrosarcomas, or myxosarcomas was slightly increased in low dose male rats (2/50; 7/50; 3/50), it was not significantly different from that in the vehicle controls. Since this increase was observed only at the low dose, with no significant dose-response trend evident, it was not considered to be related to the administration of malonaldehyde, sodium salt.

The incidences of bone marrow hematopoietic hyperplasia in high dose female rats (vehicle control, 2/50; low dose, 4/50; high dose, 11/50) and reticulum cell hyperplasia in low dose female rats (6/50; 19/50; 7/50) were greater than those in the vehicle controls. Hematopoiesis of the spleen occurred at an increased incidence in high dose female rats (1/50; 2/50; 9/50). This increased hematopoiesis in some animals may be related to the inflammation and erosion that occurred in the glandular stomach. Mononuclear cell leukemia in male rats (7/50; 10/50; 11/50) occurred with a significant positive trend by the life table test, but the incidence in dosed males was not significantly different from that in vehicle controls. The historical incidence of leukemia in male water gavage control rats at Battelle Columbus Laboratories and in all untreated controls is 49% and 29%, respectively; both of these values are greater than the 22% incidence for the high dose group in the present studies; therefore, this is probably not a chemically related effect.

Pheochromocytomas of the adrenal gland in male rats occurred with a significant positive trend; the incidence (16%) in the high dose group was significantly greater than that in the vehicle controls by the life table test but not by the more appropriate incidental tumor test. Adenomas or carcinomas (combined) of the anterior pituitary gland in male and female rats occurred with significant negative trends; the incidences in the male and female high dose groups, 16% and 4%, respectively, were significantly lower than those in the vehicle controls, 43% and 37%. The decrease in the incidences of anterior pituitary gland neoplasms in the high dose groups of male and female rats cannot be explained by reduced survival because the decrease is still observed when the incidences in animals of the same age are compared at the end of the studies. The conclusion is that the reduced incidence of anterior pituitary gland neoplasms is chemically related.

Compound-related nonneoplastic lesions were observed in the liver. Cystic degeneration was observed at increased incidences in dosed male rats and high dose female rats (male: vehicle control, 13/50; low dose, 26/50; high dose, 24/50; female: 0/50; 0/50; 5/50). Cytoplasmic vacuolization and bile duct hyperplasia were observed at increased incidences and/or severity in high dose female rats. Bile duct fibrosis was seen at an increased incidence and/or severity in dosed male rats (4/50; 8/50; 28/50).

The dose-related increase in diffuse pancreatic acinar atrophy in male and female rats may be secondary to debilitation, reduced feed consumption, or reduced weight gain in dosed animals.

Inflammation, necrotizing inflammation, and ulcers were observed at increased incidences in the glandular stomach of dosed male rats and high dose female rats. The presence of focal epithelial necrosis, erosion, and ulceration, fibroplasia, scarring, and chronic inflammation suggests a process of repeated injury and healing of the glandular mucosa. Since these lesions occur at the site of compound administration by water gavage, they are probably an indication of chronic malonaldehyde toxicity. Epithelial hyperplasia occurring near the junction of the glandular stomach and forestomach was observed at increased incidences in the forestomach of dosed male rats and high dose female rats. Squamous cell papillomas were observed in one animal in the low and high dose groups of male

rats and in the vehicle control and high dose groups of female rats.

Corneal inflammation in high dose male and female rats and retinal atrophy and cataracts of the crystalline lens were observed at increased incidences in dosed male and female rats. These eye lesions occurred in 28%-48% of dosed male and 50%-62% of dosed female rats. Although the cage positions were not changed during the course of the study, the increased incidences of eye lesions in the dosed groups were not related to the rack position of the cages (top row and outside columns of rack vs. inside). When the cages and rack positions of the individual animals with eye lesions were identified (see Figure 2), it was clear that the eye lesions occurred at similar incidences whether the animals were located on the top and outside positions or on the interior positions of the rack; therefore, the increased incidences of eye lesions were considered to be chemically related.

The increased incidences of thyroid follicular cell tumors and of most of the nonneoplastic lesions were observed in high dose rats, groups in which malonaldehyde, sodium salt, toxicity was indicated by reduced survival rates of 59% and 62% and by a reduction of 26% and 36% of final body weights in the high dose male and female rat groups, respectively.

Two-Year Studies in Mice

Malonaldehyde, sodium salt, was administered to mice by gavage at 60 mg/kg and 120 mg/kg for 2 years. No significant differences in survival were observed between any groups of female mice. Survival in all male groups was similar at 89 weeks, but at the end of the study, high dose male mice showed reduced ($P = 0.017$) survival relative to that of the vehicle controls. Mean body weights of dosed and vehicle control male mice were comparable throughout most of the study, but after week 93, the mean body weights of the high dose male group were 6%-8% lower than those of vehicle controls. Mean body weights of dosed female mice were greater than those of the vehicle controls throughout most of the study. The only compound-related clinical sign was the change in hair color from wild agouti to gray in high dose mice.

There was no increase in the incidences of neoplasms at any site in dosed mice. Several nonneoplastic lesions appeared to be compound related. The incidence of depigmentation of hair shafts was markedly increased in high dose male and female mice vs. that in vehicle controls. An increase in the incidences of pancreatic acinar cell atrophy was dose related in male and female mice. Dilatation of the uterus was observed at increased incidences in dosed female mice.

The increase in the number of natural deaths and of animals killed because they were moribund in high dose male mice and the increased incidences of nonneoplastic lesions in dosed mice are indicative of the chronic toxic effects produced by malonaldehyde, sodium salt, at the doses used in these studies. Even though there was poor survival in all groups of males at the end of the study (vehicle control, 24/50; low dose, 20/50; high dose, 14/50), the study was not considered to be inadequate because there was no evidence of even marginal neoplastic lesions seen in the dosed groups of either male or female mice; survival of the male mice was 50% or more in all groups (35/50; 31/50; 25/50) at week 93, after which the rate of deaths accelerated; the mice were housed five per cage, and clinical observations indicated fighting and bite wounds, a relatively common occurrence for group-housed $B6C3F_1$ mice. (Currently, all mice in NTP 2-year studies are housed individually.) Thus, this long-term study, although somewhat reduced in biologic and statistical sensitivity, is considered to be adequate for assessment of carcinogenicity.

Genetic Toxicology

Malonaldehyde, sodium salt, exhibited genetic toxicity in two of five assays sponsored by the NTP (Appendix E). The chemical induced forward mutations in mouse L5178Y lymphoma cells in the absence of an exogenous metabolic activation component; it was not tested with S9 in this assay. In the cytogenetic assays that detect chromosomal damage in cultured Chinese hamster ovary (CHO) cells, malonaldehyde, sodium salt, increased the frequency of sister chromatid exchanges, both in the presence and absence of rat liver S9; no increase in chromosomal aberrations was observed in CHO cells in the presence or absence of rat liver S9. No

induction of sex-linked recessive lethal mutations was seen in Drosophila after exposure to malonaldehyde.

Malonaldehyde, sodium salt, was not mutagenic in any of the four *Salmonella typhimurium* strains (TA98, TA100, TA1535, or TA1538) used routinely in the NTP-sponsored Salmonella/microsome assay. These results confirmed earlier reports by Marnett and Tuttle (1980), who also observed that malonaldehyde, sodium salt, was inactive in these strains. This inactivity can be attributed to the fact that these mutant tester strains are all deficient in excision-repair capability, which has been shown to be a requirement for the expression of malonaldehyde-induced mutagenicity in Salmonella (Mukai and Goldstein, 1976; Marnett and Tuttle, 1980).

Independent studies of the genetic toxicity of malonaldehyde have yielded mixed results. Mukai and Goldstein (1976) were the first to report the mutagenicity of malonaldehyde preparations in Salmonella but only in those tester strains that retained excision-repair capability; the tester strain D3052 was the most sensitive to malonaldehyde. These results were later confirmed by Shamberger et al. (1979). In both of these studies, as in most investigations concerned with malonaldehyde toxicity conducted through 1980, the malonaldehyde preparations were of undefined purity and contained the more reactive intermediates, such as β-ethoxyacrolein, β-methoxyacrolein, and 3,3-dimethoxypropionaldehyde, which along with malonaldehyde are the products of the acid hydrolysis of the tetraalkoxypropanes (Marnett and Tuttle, 1980). The quantification of malonaldehyde in these hydrolysates was based on the amount of starting material and on the assumption that malonaldehyde was the only end product of the reaction. Thus, interpretation of these earlier studies is confounded because no consideration was given to the mutagenic activity contributed by the active intermediates and no further purification of malonaldehyde from the hydrolysis mixture was performed. Marnett and Tuttle (1980) were the first to report that the reaction intermediates produced by tetraalkoxypropane hydrolysis were more potent Salmonella mutagens than the pure malonaldehyde, sodium salt. These investigators also confirmed that malonaldehyde was mutagenic only in those Salmonella tester strains that retained excision-repair capability.

Audit

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

IV. DISCUSSION AND CONCLUSIONS

Conclusions

Under the conditions of these 2-year gavage studies, there was *clear evidence of carcinogenic activity** for male and female F344/N rats administered malonaldehyde, sodium salt, as shown by the increased incidences of follicular cell adenomas or carcinomas (combined) of the thyroid gland. Pancreatic islet cell adenomas were also observed at an increased incidence in low dose male rats. There was *no evidence of carcinogenic activity* for $B6C3F_1$ mice administered 60 or 120 mg/kg malonaldehyde, sodium salt, in distilled water by gavage 5 days per week for 2 years.

Chemically related increased incidences of nonneoplastic lesions included ulcers and inflammation of the glandular stomach and epithelial hyperplasia of the forestomach; corneal inflammation, retinal atrophy, and cataracts of the crystalline lens; and cystic degeneration of the liver, bile duct fibrosis, and bile duct hyperplasia in rats. Most of these nonneoplastic lesions as well as the thyroid gland follicular cell neoplasms occurred primarily in the high dose rat groups, in which survival and final body weights were reduced in high dose male and female rats. Increased incidences of atrophy of the pancreatic acinus and pigmentation loss in hair shafts were seen in high dose mice.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 9.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 12-13.

V. REFERENCES

V. REFERENCES

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APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT

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TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Papilloma, NOS	1 (2%)		
Squamous cell papilloma	1 (2%)	1 (2%)	2 (4%)
Squamous cell carcinoma			1 (2%)
Sebaceous adenoma		1 (2%)	1 (2%)
Sebaceous adenocarcinoma	1 (2%)		
Keratoacanthoma	3 (6%)	3 (6%)	3 (6%)
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma	1 (2%)	6 (12%)	2 (4%)
Fibrosarcoma		1 (2%)	1 (2%)
Myxosarcoma	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Squamous cell carcinoma, metastatic			1 (2%)
Alveolar/bronchiolar carcinoma		1 (2%)	2 (4%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, histiocytic type		1 (2%)	1 (2%)
Leukemia, mononuclear cell	7 (14%)	10 (20%)	11 (22%)
CIRCULATORY SYSTEM			
None			
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(50)
Squamous cell papilloma			1 (2%)
#Liver	(50)	(50)	(50)
Neoplastic nodule	1 (2%)	2 (4%)	1 (2%)
Hepatocellular carcinoma	2 (4%)		2 (4%)
#Pancreas	(49)	(50)	(49)
Acinar cell adenoma	1 (2%)		
#Forestomach	(50)	(49)	(50)
Squamous cell papilloma		1 (2%)	1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Tubular cell adenocarcinoma			1 (2%)
#Urinary bladder	(47)	(46)	(49)
Transitional cell papilloma	1 (2%)		
ENDOCRINE SYSTEM			
#Anterior pituitary	(47)	(49)	(49)
Carcinoma, NOS			1 (2%)
Adenoma, NOS	20 (43%)	14 (29%)	7 (14%)
#Adrenal	(50)	(50)	(50)
Cortical adenoma		1 (2%)	3 (6%)
#Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma	5 (10%)	6 (12%)	8 (16%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Thyroid	(50)	(49)	(50)
Follicular cell adenoma	3 (6%)	3 (6%)	9 (18%)
Follicular cell carcinoma	1 (2%)	5 (10%)	5 (10%)
C-cell adenoma	10 (20%)	11 (22%)	2 (4%)
C-cell carcinoma	2 (4%)	4 (8%)	
#Parathyroid	(42)	(37)	(42)
Adenoma, NOS	2 (5%)	4 (11%)	1 (2%)
#Pancreatic islets	(49)	(50)	(49)
Islet cell adenoma		9 (18%)	1 (2%)
Islet cell carcinoma	1 (2%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Fibroadenoma	2 (4%)	1 (2%)	
*Preputial gland	(50)	(50)	(50)
Adenoma, NOS	3 (6%)	1 (2%)	
Adenocarcinoma, NOS		1 (2%)	
Sebaceous adenoma	1 (2%)		
#Testis	(50)	(50)	(50)
Interstitial cell tumor	40 (80%)	45 (90%)	36 (72%)
*Epididymis	(50)	(50)	(50)
Leiomyosarcoma	1 (2%)		
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Carcinoma, NOS, invasive			1 (2%)
Choroid plexus papilloma	1 (2%)		
SPECIAL SENSE ORGANS			
None			
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Tunica vaginalis	(50)	(50)	(50)
Mesothelioma, NOS	2 (4%)		2 (4%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Mesothelioma, NOS	2 (4%)		3 (6%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	2	10	19
Moribund sacrifice	11	7	15
Terminal sacrifice	37	33	15
Dosing accident			1

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	49	49	47
Total primary tumors	116	132	108
Total animals with benign tumors	47	48	46
Total benign tumors	95	107	77
Total animals with malignant tumors	16	19	22
Total malignant tumors	16	23	25
Total animals with secondary tumors##			2
Total secondary tumors			2
Total animals with tumors uncertain benign or malignant	5	2	6
Total uncertain tumors	5	2	6

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

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT: VEHICLE CONTROL

ANIMAL NUMBER	0 1 0	0 3 3	0 2 8	0 1 4	0 3 1	0 3 7	0 1 2	0 0 2	0 0 4	0 2 9	0 3 2	0 1 5	0 4 7	0 0 1	0 0 3	0 0 5	0 0 6	0 0 7	0 0 8	0 0 9	0 1 1	0 1 3	0 1 6	0 1 7	0 1 8
WEEKS ON STUDY	0 5 5	0 6 0	0 7 9	0 8 0	0 8 0	0 8 0	0 8 5	0 8 7	0 8 7	0 8 9	0 9 0	0 9 5	0 9 8	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS																							X		
Squamous cell papilloma																									
Sebaceous adenocarcinoma																									
Keratoacanthoma																		X							
Subcutaneous tissue	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Myxosarcoma		X																							
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	−	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	−	+	−	−	+
Thymus	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	−	+	−	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule															X										
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																									
Esophagus	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS				X						X	X		X			X	X		X		X	X			
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																		X							
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma	X													X											
Follicular cell carcinoma			X																						
C cell adenoma																X			X						
C cell carcinoma																	X								
Parathyroid	+	+	−	+	+	−	−	+	+	+	+	+	−	−	+	+	−	+	+	+	+	+	+	+	+
Adenoma, NOS																							X		
Pancreatic islets	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	+	N	N	N	+	N	+	N	N	N	N	N	N	N	N	N	N	+	N	+	N	+
Fibroadenoma																							X		
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor			X			X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X
Prostate	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS													X												
Sebaceous adenoma																						X			
Epididymis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leiomyosarcoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Choroid plexus papilloma																									
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS										X															
Leukemia, mononuclear cell	X				X		X	X	X		X										X				

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

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

ANIMAL NUMBER	0019	0020	0021	0022	0023	0024	0025	0026	0027	0030	0034	0035	0036	0038	0039	0040	0041	0042	0043	0044	0045	0046	0048	0049	0050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Papilloma, NOS																	X									1
Squamous cell papilloma																										1
Sebaceous adenocarcinoma																							X			1
Keratoacanthoma					X					X																3
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma								X																		1
Myxosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Thymus	+	−	+	+	+	−	+	+	−	−	−	+	+	+	+	+	+	+	+	−	+	+	+	−	−	37
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										1
Hepatocellular carcinoma																X	X									2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinar cell adenoma																X										1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	47
Transitional cell papilloma			X																							1
ENDOCRINE SYSTEM																										
Pituitary	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS	X			X	X						X	X	X	X				X		X			X	X		20
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma	X											X		X									X			5
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma												X														3
Follicular cell carcinoma																										1
C cell adenoma			X							X				X	X	X			X	X					X	10
C cell carcinoma																			X							2
Parathyroid	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Adenoma, NOS					X																					2
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell carcinoma																				X						1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	+	N	N	N	N	N	N	N	+	+	+	+	N	N	+	+	N	N	N	N	N	N	*50
Fibroadenoma															X											2
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X			X	40
Prostate	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	47
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS															X				X							3
Sebaceous adenoma																										1
Epididymis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leiomyosarcoma	X																									1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Choroid plexus papilloma								X																		1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS			X								X															2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, NOS												X														2
Leukemia, mononuclear cell																										7

* Animals necropsied

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

ANIMAL NUMBER	023	028	016	045	010	002	032	038	009	003	021	033	043	022	025	029	039	001	004	005	006	007	008	011	012
WEEKS ON STUDY	074	074	079	084	086	087	088	088	092	093	097	097	098	099	103	103	103	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma								X																	
Sebaceous adenoma																									
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma															X									X	
Fibrosarcoma							X																		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																						X			
Trachea	+	–	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+
Thymus	+	–	+	+	–	+	+	+	+	+	+	–	+	+	–	+	–	+	+	–	–	+	–	+	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	–	–	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS										X	X						X		X						
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																			X						
Pheochromocytoma	X																			X				X	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																			X						
Follicular cell carcinoma						X					X													X	
C cell adenoma												X							X	X					
C cell carcinoma													X												
Parathyroid	–	–	+	+	+	+	+	+	–	–	–	+	+	+	–	+	+	+	–	–	+	+	+	–	+
Adenoma, NOS			X		X																				
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma												X													
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	+	+	+	+	N	+	N	N	+	+	N	+	N	+	N	+	+	N	+	+	N	N
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor	X	X	X	X	X	X	X		X		X	X	X		X	X	X	X	X	X		X	X	X	X
Prostate	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
Adenocarcinoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, histiocytic type						X																			
Leukemia, mononuclear cell		X	X								X	X	X	X	X					X					

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

ANIMAL NUMBER	0 1 3	0 1 4	0 1 5	0 1 7	0 1 8	0 1 9	0 2 0	0 2 4	0 2 6	0 2 7	0 3 0	0 3 1	0 3 4	0 3 5	0 3 6	0 3 7	0 4 0	0 4 1	0 4 2	0 4 4	0 4 6	0 4 7	0 4 8	0 4 9	0 5 0	TOTAL TISSUES TUMORS
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																										1
Sebaceous adenoma					X																					1
Keratoacanthoma										X								X							X	3
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma	X				X						X											X				6
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	45
Thymus	−	+	+	+	−	+	+	+	+	+	+	+	+	+	−	−	+	+	−	+	+	+	+	−	+	35
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule							X															X				2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																			X							1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS					X		X	X		X			X					X				X	X	X	X	14
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																										1
Pheochromocytoma		X								X			X													6
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma						X										X										3
Follicular cell carcinoma								X				X														5
C cell adenoma	X	X	X								X		X	X			X				X					11
C cell carcinoma											X					X	X									4
Parathyroid	−	+	+	+	+	+	−	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	37
Adenoma, NOS																			X						X	4
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma		X			X		X		X		X		X				X							X		9
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	+	+	N	N	+	N	+	+	N	+	N	N	+	+	+	+	N	N	+	N	+	N	*50
Fibroadenoma													X													1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	45
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	48
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS	X																									1
Adenocarcinoma, NOS								X																		1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, histiocytic type																										1
Leukemia, mononuclear cell										X														X		10

* Animals necropsied

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

ANIMAL NUMBER	0004	0034	0007	0110	0441	0448	0512	0532	0538	0606	0808	0845	0847	0925	0921	0941	0935	0919	0905	0916	0917	0933	0943	0928	0115
WEEKS ON STUDY	0339	0443	0662	0770	0766	0766	0777	0779	0779	0781	0881	0881	0881	0882	0883	0884	0884	0885	0886	0888	0888	0888	0888	0890	0993
INTEGUMENTARY SYSTEM																									
Skin	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N
Squamous cell papilloma																									
Squamous cell carcinoma				X																					
Sebaceous adenoma			X																						
Keratoacanthoma												X													
Subcutaneous tissue	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N
Fibroma																									
Fibrosarcoma												X													
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic				X																					
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	–	–	–	+	–	–	–	–	+	+	+	+	+	+	–	–	+	+	+	+	–	+	+	+	+
Thymus	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	+	+	+	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																									
Salivary gland	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	+	–	+	–	+	–	+	+	+	+	+	+	+	+	–	+	–	–	–	+	+	+	+	+	+
Large intestine	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma																									
Urinary bladder	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS																	X				X				X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma		X																		X					X
Pheochromocytoma					X											X									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma											X		X		X			X	X						
Follicular cell carcinoma								X				X				X									
C cell adenoma																									
Parathyroid	+	+	+	+	–	+	+	–	+	–	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+
Adenoma, NOS																									
Pancreatic islets	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	+	N	N	N	N	N	N	+	N	N	+	N	+	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor				X					X	X	X		X	X	X	X		X		X		X	X	X	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																									
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS																								X	
Malignant lymphoma, histiocytic type												X													
Leukemia, mononuclear cell									X		X	X								X			X	X	

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

ANIMAL NUMBER	0050	0003	0133	0422	0227	0336	0330	0226	0220	0229	0001	0002	0009	0111	0118	0222	0223	0241	0331	0331	0337	0440	0444	0446	0449	TOTAL: TISSUES
WEEKS ON STUDY	0993	0994	0997	0997	0999	0999	1000	1001	1002	1002	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma														X		X										2
Squamous cell carcinoma																										1
Sebaceous adenoma																										1
Keratoacanthoma																		X					X			3
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																					X		X			2
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic																										1
Alveolar/bronchiolar carcinoma											X			X												2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	39
Thymus	+	−	+	+	−	−	+	−	−	+	+	−	+	−	+	+	−	−	−	+	−	+	+	+	−	32
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	X	N	N	N	N	*50
Squamous cell papilloma																										1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule														X												1
Hepatocellular carcinoma													X			X										2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																				X						1
Small intestine	+	+	−	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenocarcinoma													X													1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS																						X				1
Adenoma, NOS		X																X	X						X	7
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																										3
Pheochromocytoma							X					X	X								X	X	X			8
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma								X					X						X					X		9
Follicular cell carcinoma																		X		X						5
C cell adenoma																					X	X				2
Parathyroid	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	42
Adenoma, NOS																			X							1
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma																			X							1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	+	+	N	+	N	+	+	N	N	N	+	+	N	+	N	N	N	+	N	N	+	+	+	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		36
Prostate	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																						X				1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS								X							X											2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, NOS												X						X								3
Malignant lymphoma, histiocytic type																										1
Leukemia, *mononuclear cell*	X	X		X					X	X																11

* Animals necropsied

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT

	Vehicle Control	50 mg/kg	100 mg/kg
Skin: Keratoacanthoma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	8 1%	9 1%	15 4%
Terminal Rates (c)	3/37 (8%)	3/33 (9%)	2/15 (13%)
Week of First Observation	104	104	81
Life Table Tests (d)	P=0 230	P=0 610	P=0 299
Incidental Tumor Tests (d)	P=0 271	P=0 610	P=0 355
Cochran Armitage Trend Test (d)	P=0 583		
Fisher Exact Test (d)		P=0 661	P=0 661
Skin: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	2 7%	2 3%	15 2%
Terminal Rates (c)	1/37 (3%)	0/33 (0%)	2/15 (13%)
Week of First Observation	104	88	70
Life Table Tests (d)	P=0 081	P=0 756	P=0 107
Incidental Tumor Tests (d)	P=0 163	P=0 719	P=0 151
Cochran Armitage Trend Test (d)	P=0 202		
Fisher Exact Test (d)		P=0 753	P=0 309
Skin: Papilloma or Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	5 4%	2 3%	15 2%
Terminal Rates (c)	2/37 (5%)	0/33 (0%)	2/15 (13%)
Week of First Observation	104	88	70
Life Table Tests (d)	P=0 188	P=0 518N	P=0 200
Incidental Tumor Tests (d)	P=0 304	P=0 555N	P=0 261
Cochran Armitage Trend Test (d)	P=0 399		
Fisher Exact Test (d)		P=0 500N	P=0 500
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	1/50 (2%)	6/50 (12%)	2/50 (4%)
Adjusted Rates (b)	2 7%	17 5%	13 3%
Terminal Rates (c)	1/37 (3%)	5/33 (15%)	2/15 (13%)
Week of First Observation	104	103	104
Life Table Tests (d)	P=0 092	P=0 044	P=0 205
Incidental Tumor Tests (d)	P=0 154	P=0 066	P=0 205
Cochran Armitage Trend Test (d)	P=0 417		
Fisher Exact Test (d)		P=0 056	P=0 500
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	1/50 (2%)	7/50 (14%)	3/50 (6%)
Adjusted Rates (b)	2 7%	19 4%	15 4%
Terminal Rates (c)	1/37 (3%)	5/33 (15%)	2/15 (13%)
Week of First Observation	104	88	81
Life Table Tests (d)	P=0 051	P=0 026	P=0 105
Incidental Tumor Tests (d)	P=0 136	P=0 035	P=0 139
Cochran Armitage Trend Test (d)	P=0 283		
Fisher Exact Test (d)		P=0 030	P=0 309
Subcutaneous Tissue: Fibroma, Fibrosarcoma, or Myxosarcoma			
Overall Rates (a)	2/50 (4%)	7/50 (14%)	3/50 (6%)
Adjusted Rates (b)	4 7%	19 4%	15 4%
Terminal Rates (c)	1/37 (3%)	5/33 (15%)	2/15 (13%)
Week of First Observation	60	88	81
Life Table Tests (d)	P=0 124	P=0 070	P=0 265
Incidental Tumor Tests (d)	P=0 302	P=0 088	P=0 396
Cochran Armitage Trend Test (d)	P=0 427		
Fisher Exact Test (d)		P=0 080	P=0 500

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	7/50 (14%)	10/50 (20%)	11/50 (22%)
Adjusted Rates (b)	15.2%	23.7%	34.9%
Terminal Rates (c)	1/37 (3%)	3/33 (9%)	0/15 (0%)
Week of First Observation	55	74	79
Life Table Tests (d)	P=0 039	P=0.306	P=0.067
Incidental Tumor Tests (d)	P=0.245N	P=0.503	P=0.272N
Cochran-Armitage Trend Test (d)	P=0.185		
Fisher Exact Test (d)		P=0.298	P=0.218
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	8 1%	6.1%	20.0%
Terminal Rates (c)	3/37 (8%)	2/33 (6%)	3/15 (20%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.216	P=0.552N	P=0.233
Incidental Tumor Tests (d)	P=0.216	P=0.552N	P=0.233
Cochran-Armitage Trend Test (d)	P=0.588		
Fisher Exact Test (d)		P=0.500N	P=0.661N
Pituitary Gland: Adenoma			
Overall Rates (a)	20/47 (43%)	14/49 (29%)	7/49 (14%)
Adjusted Rates (b)	50.8%	38.3%	30.7%
Terminal Rates (c)	16/35 (46%)	11/33 (33%)	3/15 (20%)
Week of First Observation	80	93	84
Life Table Tests (d)	P=0.175N	P=0.189N	P=0.242N
Incidental Tumor Tests (d)	P=0.010N	P=0.080N	P=0.016N
Cochran-Armitage Trend Test (d)	P=0 002N		
Fisher Exact Test (d)		P=0.112N	P=0.002N
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	20/47 (43%)	14/49 (29%)	8/49 (16%)
Adjusted Rates (b)	50.8%	38.3%	36.5%
Terminal Rates (c)	16/35 (46%)	11/33 (33%)	4/15 (27%)
Week of First Observation	80	93	84
Life Table Tests (d)	P=0.264N	P=0.189N	P=0.357N
Incidental Tumor Tests (d)	P=0 022N	P=0.080N	P=0.039N
Cochran-Armitage Trend Test (d)	P=0.003N		
Fisher Exact Test (d)		P=0.112N	P=0.005N
Adrenal Gland: Cortical Adenoma			
Overall Rates (a)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	0 0%	3.0%	8.8%
Terminal Rates (c)	0/37 (0%)	1/33 (3%)	0/15 (0%)
Week of First Observation		104	43
Life Table Tests (d)	P=0 028	P=0.477	P=0.085
Incidental Tumor Tests (d)	P=0.203	P=0.477	P=0.500
Cochran-Armitage Trend Test (d)	P=0.060		
Fisher Exact Test (d)		P=0.500	P=0.121
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	5/50 (10%)	6/50 (12%)	8/50 (16%)
Adjusted Rates (b)	13.5%	16.8%	40.0%
Terminal Rates (c)	5/37 (14%)	5/33 (15%)	5/15 (33%)
Week of First Observation	104	74	76
Life Table Tests (d)	P=0.014	P=0.430	P=0.016
Incidental Tumor Tests (d)	P=0.048	P=0.427	P=0.055
Cochran-Armitage Trend Test (d)	P=0.226		
Fisher Exact Test (d)		P=0.500	P=0.277

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	3/50 (6%)	3/49 (6%)	9/50 (18%)
Adjusted Rates (b)	7 3%	9 1%	34 4%
Terminal Rates (c)	2/37 (5%)	3/33 (9%)	3/15 (20%)
Week of First Observation	55	104	81
Life Table Tests (d)	P=0 003	P=0 618	P=0 007
Incidental Tumor Tests (d)	P=0 026	P=0 618	P=0 068
Cochran Armitage Trend Test (d)	P=0 034		
Fisher Exact Test (d)		P=0 651	P=0 061
Thyroid Gland: Follicular Cell Carcinoma			
Overall Rates (a)	1/50 (2%)	5/49 (10%)	5/50 (10%)
Adjusted Rates (b)	2 1%	13 3%	19 8%
Terminal Rates (c)	0/37 (0%)	3/33 (9%)	2/15 (13%)
Week of First Observation	79	87	79
Life Table Tests (d)	P=0 019	P=0 099	P=0 041
Incidental Tumor Tests (d)	P=0 105	P=0 109	P=0 116
Cochran Armitage Trend Test (d)	P=0 090		
Fisher Exact Test (d)		P=0 098	P=0 102
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	8/49 (16%)	13/50 (26%)
Adjusted Rates (b)	9 2%	22 0%	48 1%
Terminal Rates (c)	2/37 (5%)	6/33 (18%)	5/15 (33%)
Week of First Observation	55	87	79
Life Table Tests (d)	P<0 001	P=0 154	P<0 001
Incidental Tumor Tests (d)	P=0 008	P=0 168	P=0 015
Cochran Armitage Trend Test (d)	P=0 011		
Fisher Exact Test (d)		P=0 168	P=0 016
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	10/50 (20%)	11/49 (22%)	2/50 (4%)
Adjusted Rates (b)	27 0%	32 0%	13 3%
Terminal Rates (c)	10/37 (27%)	10/33 (30%)	2/15 (13%)
Week of First Observation	104	97	104
Life Table Tests (d)	P=0 296N	P=0 388	P=0 245N
Incidental Tumor Tests (d)	P=0 231N	P=0 440	P=0 245N
Cochran-Armitage Trend Test (d)	P=0 019N		
Fisher Exact Test (d)		P=0 479	P=0 014N
Thyroid Gland: C-Cell Carcinoma			
Overall Rates (a)	2/50 (4%)	4/49 (8%)	0/50 (0%)
Adjusted Rates (b)	5 4%	11 5%	0 0%
Terminal Rates (c)	2/37 (5%)	3/33 (9%)	0/15 (0%)
Week of First Observation	104	98	
Life Table Tests (d)	P=0 493N	P=0 295	P=0 452N
Incidental Tumor Tests (d)	P=0 353N	P=0 377	P=0 452N
Cochran Armitage Trend Test (d)	P=0 223N		
Fisher Exact Test (d)		P=0 329	P=0 247N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	11/50 (22%)	13/49 (27%)	2/50 (4%)
Adjusted Rates (b)	29 7%	36 7%	13 3%
Terminal Rates (c)	11/37 (30%)	11/33 (33%)	2/15 (13%)
Week of First Observation	104	97	104
Life Table Tests (d)	P=0 274N	P=0 296	P=0 191N
Incidental Tumor Tests (d)	P=0 161N	P=0 389	P=0 191N
Cochran Armitage Trend Test (d)	P=0 013N		
Fisher Exact Test (d)		P=0 385	P=0 007N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Parathyroid: Adenoma			
Overall Rates (a)	2/42 (5%)	4/37 (11%)	1/42 (2%)
Adjusted Rates (b)	6 1%	11 6%	7 7%
Terminal Rates (c)	2/33 (6%)	2/26 (8%)	1/13 (8%)
Week of First Observation	104	79	104
Life Table Tests (d)	P=0 495	P=0 275	P=0 676
Incidental Tumor Tests (d)	P=0 566N	P=0 266	P=0 676
Cochran Armitage Trend Test (d)	P=0 408N		
Fisher Exact Test (d)		P=0 279	P=0 500N
Pancreatic Islets: Islet Cell Adenoma			
Overall Rates (a)	0/49 (0%)	9/50 (18%)	1/49 (2%)
Adjusted Rates (b)	0 0%	26 1%	6 7%
Terminal Rates (c)	0/37 (0%)	8/33 (24%)	1/15 (7%)
Week of First Observation		97	104
Life Table Tests (d)	P=0 092	P=0 002	P=0 320
Incidental Tumor Tests (d)	P=0 138	P=0 002	P=0 320
Cochran Armitage Trend Test (d)	P=0 420		
Fisher Exact Test (d)		P=0 001	P=0 500
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Overall Rates (a)	1/49 (2%)	9/50 (18%)	1/49 (2%)
Adjusted Rates (b)	2 7%	26 1%	6 7%
Terminal Rates (c)	1/37 (3%)	8/33 (24%)	1/15 (7%)
Week of First Observation	104	97	104
Life Table Tests (d)	P=0 169	P=0 006	P=0 548
Incidental Tumor Tests (d)	P=0 235	P=0 009	P=0 548
Cochran Armitage Trend Test (d)	P=0 576		
Fisher Exact Test (d)		P=0 009	P=0 753
Preputial Gland: Adenoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	7 9%	3 0%	0 0%
Terminal Rates (c)	2/37 (5%)	1/33 (3%)	0/15 (0%)
Week of First Observation	98	104	
Life Table Tests (d)	P=0 147N	P=0 337N	P=0 293N
Incidental Tumor Tests (d)	P=0 065N	P=0 224N	P=0 103N
Cochran Armitage Trend Test (d)	P=0 060N		
Fisher Exact Test (d)		P=0 309N	P=0 121N
Preputial Gland: Adenoma or Sebaceous Adenoma			
Overall Rates (a)	4/50 (8%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	10 5%	3 0%	0 0%
Terminal Rates (c)	3/37 (8%)	1/33 (3%)	0/15 (0%)
Week of First Observation	98	104	
Life Table Tests (d)	P=0 081N	P=0 210N	P=0 213N
Incidental Tumor Tests (d)	P=0 035N	P=0 131N	P=0 077N
Cochran Armitage Trend Test (d)	P=0 026N		
Fisher Exact Test (d)		P=0 181N	P=0 059N
Preputial Gland: Adenoma, Sebaceous Adenoma, or Adenocarcinoma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	10 5%	6 1%	0 0%
Terminal Rates (c)	3/37 (8%)	2/33 (6%)	0/15 (0%)
Week of First Observation	98	104	
Life Table Tests (d)	P=0 127N	P=0 382N	P=0 213N
Incidental Tumor Tests (d)	P=0 065N	P=0 285N	P=0 077N
Cochran Armitage Trend Test (d)	P=0 037N		
Fisher Exact Test (d)		P=0 339N	P=0 059N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Testis: Interstitial Cell Tumor			
Overall Rates (a)	40/50 (80%)	45/50 (90%)	36/50 (72%)
Adjusted Rates (b)	90.8%	95.7%	97.1%
Terminal Rates (c)	33/37 (89%)	31/33 (94%)	14/15 (93%)
Week of First Observation	79	74	70
Life Table Tests (d)	P<0.001	P=0.076	P<0.001
Incidental Tumor Tests (d)	P=0.278	P=0.072	P=0.275
Cochran-Armitage Trend Test (d)	P=0.188N		
Fisher Exact Test (d)		P=0.131	P=0.242N
All Sites: Mesothelioma			
Overall Rates (a)	4/50 (8%)	0/50 (0%)	5/50 (10%)
Adjusted Rates (b)	10.3%	0.0%	27.2%
Terminal Rates (c)	3/37 (8%)	0/33 (0%)	3/15 (20%)
Week of First Observation	89		90
Life Table Tests (d)	P=0.127	P=0.075N	P=0.111
Incidental Tumor Tests (d)	P=0.304	P=0.085N	P=0.317
Cochran-Armitage Trend Test (d)	P=0.417		
Fisher Exact Test (d)		P=0.059N	P=0.500
All Sites: Benign Tumors			
Overall Rates (a)	47/50 (94%)	48/50 (96%)	46/50 (92%)
Adjusted Rates (b)	97.9%	97.9%	100.0%
Terminal Rates (c)	36/37 (97%)	32/33 (97%)	15/15 (100%)
Week of First Observation	55	74	43
Life Table Tests (d)	P<0.001	P=0.257	P<0.001
Incidental Tumor Tests (d)	P=0.335	P=0.433	P=0.408
Cochran-Armitage Trend Test (d)	P=0.417N		
Fisher Exact Test (d)		P=0.500	P=0.500N
All Sites: Malignant Tumors			
Overall Rates (a)	16/50 (32%)	19/50 (38%)	22/50 (44%)
Adjusted Rates (b)	34.5%	44.1%	68.6%
Terminal Rates (c)	8/37 (22%)	10/33 (30%)	7/15 (47%)
Week of First Observation	55	74	70
Life Table Tests (d)	P=0.003	P=0.305	P=0.005
Incidental Tumor Tests (d)	P=0.328	P=0.399	P=0.321
Cochran-Armitage Trend Test (d)	P=0.129		
Fisher Exact Test (d)		P=0.338	P=0.151
All Sites: All Tumors			
Overall Rates (a)	49/50 (98%)	49/50 (98%)	47/50 (94%)
Adjusted Rates (b)	98.0%	98.0%	100.0%
Terminal Rates (c)	36/37 (97%)	32/33 (97%)	15/15 (100%)
Week of First Observation	55	74	43
Life Table Tests (d)	P<0.001	P=0.329	P<0.001
Incidental Tumor Tests (d)	P=0.407N	P=0.736N	P=0.616N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Test (d)		P=0.753N	P=0.309N

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

TABLE A4a. HISTORICAL INCIDENCE OF THYROID GLAND FOLLICULAR CELL TUMORS IN MALE F344/N RATS (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence in Water Gavage Controls at Battelle Columbus Laboratories (b)			
Chlorpheniramine maleate	0/50	1/50	1/50
Tetrakis(hydroxymethyl)phosphonium chloride	0/47	0/47	0/47
Tetrakis(hydroxymethyl)phosphonium sulfate	0/47	1/47	1/47
TOTAL	0/144 (0.0%)	2/144 (1.4%)	2/144 (1.4%)
SD (c)	0.00%	1.19%	1.19%
Range (d)			
High	0/50	1/47	1/47
Low	0/50	0/47	0/47
Overall Historical Incidence in Untreated Controls			
TOTAL	(e) 16/1,928 (0.8%)	(f) 11/1,928 (0.6%)	(e,f) 27/1,928 (1.4%)
SD (c)	1.41%	0.91%	1.75%
Range (d)			
High	2/44	2/89	3/50
Low	0/50	0/50	0/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) No other water gavage studies are included in the historical data base.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes one cystadenoma and one papillary cystadenoma
(f) Includes one papillary adenocarcinoma

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

Study	Incidence in Controls	
	Adenoma	Adenoma or Carcinoma
Historical Incidence in Water Gavage Controls at Battelle Columbus Laboratories (b)		
Chlorpheniramine maleate	0/49	0/49
Tetrakis(hydroxymethyl)phosphonium chloride	0/50	0/50
Tetrakis(hydroxymethyl)phosphonium sulfate	3/50	3/50
TOTAL	3/149 (2 0%)	3/149 (2 0%)
SD (c)	3 46%	3 46%
Range (d)		
High	3/50	3/50
Low	0/50	0/50
Overall Historical Incidence in Untreated Controls		
TOTAL	28/1,950 (1 4%)	30/1,950 (1 5%)
SD (c)	1 81%	1 84%
Range (d)		
High	4/49	4/49
Low	0/50	0/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) No other water gavage studies are included in the historical data base
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals

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

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

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) No other water gavage studies are included in the historical data base.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE A4d. HISTORICAL INCIDENCE OF LEUKEMIA IN MALE F344/N RATS (a)

Study	Incidence in Controls
Historical Incidence in Water Gavage Controls at Battelle Columbus Laboratories (b)	
Chlorpheniramine maleate	25/50
Tetrakis(hydroxymethyl)phosphonium chloride	19/50
Tetrakis(hydroxymethyl)phosphonium sulfate	30/50
TOTAL	74/150 (49 3%)
SD (c)	11 02%
Range (d)	
High	30/50
Low	19/50
Overall Historical Incidence in Untreated Controls	
TOTAL	583/1,977 (29 5%)
SD (c)	11 59%
Range (d)	
High	30/50
Low	5/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) No other water gavage studies are included in the historical data base
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals

TABLE A4e. HISTORICAL INCIDENCE OF PANCREATIC ISLET CELL TUMORS IN MALE F344/N RATS (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence in Water Gavage Controls at Battelle Columbus Laboratories (b)			
Chlorpheniramine maleate	3/50	2/50	5/50
Tetrakis(hydroxymethyl)phosphonium chloride	2/49	0/49	2/49
Tetrakis(hydroxymethyl)phosphonium sulfate	4/48	1/48	5/48
TOTAL	9/147 (6.1%)	3/147 (2.0%)	12/147 (8.2%)
SD (c)	2.13%	2.00%	3.54%
Range (d)			
High	4/48	2/50	5/48
Low	2/49	0/49	2/49
Overall Historical Incidence in Untreated Controls			
TOTAL	63/1,913 (3.3%)	40/1,913 (2.1%)	102/1,913 (5.3%)
SD (c)	3.35%	2.54%	3.58%
Range (d)			
High	6/49	4/49	7/49
Low	0/88	0/50	0/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) No other water gavage studies are included in the historical data base.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE A4f. HISTORICAL INCIDENCE OF PITUITARY GLAND TUMORS IN MALE F344/N RATS (a)

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

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Includes adenoma, NOS, chromophobe adenoma, and acidophil adenoma.
(c) Includes carcinoma, NOS, and chromophobe carcinoma
(d) No other water gavage studies are included in the historical data base.
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.

TABLE A4g. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM TUMORS IN MALE F344/N RATS (a)

Study	Incidence in Controls		
	Fibroma (b)	Fibrosarcoma (c)	Fibroma or Fibrosarcoma (b,c)
Historical Incidence in Water Gavage Controls at Battelle Columbus Laboratories (d)			
Chlorpheniramine maleate	2/50	2/50	4/50
Tetrakis(hydroxymethyl)phosphonium chloride	0/50	1/50	1/50
Tetrakis(hydroxymethyl)phosphonium sulfate	0/50	3/50	3/50
TOTAL	2/150 (1.3%)	6/150 (4.0%)	8/150 (5.3%)
SD (e)	2.31%	2.00%	3.06%
Range (f)			
High	2/50	3/50	4/50
Low	0/50	1/50	1/50
Overall Historical Incidence in Untreated Controls			
TOTAL	110/1,977 (5.6%)	39/1,977 (2.0%)	148/1,977 (7.5%)
SD (e)	3.15%	2.72%	4.27%
Range (f)			
High	6/50	7/50	12/50
Low	0/50	0/50	0/49

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Includes neurofibroma
(c) Includes sarcoma, NOS, and neurofibrosarcoma
(d) No other water gavage studies are included in the historical data base.
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Inflammation, NOS	2 (4%)	5 (10%)	4 (8%)
Ulcer, NOS	1 (2%)		
Fibrosis	1 (2%)		
Hyperplasia, NOS	1 (2%)	1 (2%)	1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Epidermal inclusion cyst			2 (4%)
RESPIRATORY SYSTEM			
#Trachea	(50)	(47)	(49)
Inflammation, acute	1 (2%)		
Inflammation, chronic	1 (2%)		
#Lung	(50)	(50)	(50)
Congestion, NOS			1 (2%)
Hemorrhage		2 (4%)	1 (2%)
Inflammation, NOS	6 (12%)	3 (6%)	5 (10%)
Foreign material, NOS			1 (2%)
Pigmentation, NOS			1 (2%)
Alveolar macrophages	1 (2%)		
Hyperplasia, alveolar epithelium	3 (6%)	3 (6%)	1 (2%)
Metaplasia, osseous			1 (2%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(50)	(50)
Inflammation, granulomatous focal	1 (2%)		
Atrophy, NOS		1 (2%)	
Hyperplasia, hematopoietic	5 (10%)	2 (4%)	5 (10%)
Hyperplasia, reticulum cell	5 (10%)	3 (6%)	1 (2%)
#Spleen	(50)	(50)	(50)
Collapse		1 (2%)	
Congestion, NOS	1 (2%)	1 (2%)	
Fibrosis	2 (4%)	2 (4%)	2 (4%)
Necrosis, coagulative	1 (2%)		
Hemosiderosis	1 (2%)	1 (2%)	
Depletion, lymphoid			1 (2%)
Hematopoiesis	3 (6%)	4 (8%)	1 (2%)
#Mandibular lymph node	(46)	(45)	(39)
Dilatation/sinus	1 (2%)	2 (4%)	1 (3%)
Epidermal inclusion cyst		1 (2%)	
Hemorrhage			1 (3%)
Plasmacytosis	1 (2%)	1 (2%)	
#Mediastinal lymph node	(46)	(45)	(39)
Hemorrhage			1 (3%)
Inflammation, chronic diffuse	1 (2%)		
Plasmacytosis		1 (2%)	
#Pancreatic lymph node	(46)	(45)	(39)
Inflammation, granulomatous focal		1 (2%)	
#Lumbar lymph node	(46)	(45)	(39)
Hemorrhage		1 (2%)	
#Mesenteric lymph node	(46)	(45)	(39)
Dilatation/sinus		3 (7%)	1 (3%)
Inflammation, granulomatous	1 (2%)		2 (5%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Ileum	(49)	(46)	(40)
Hyperplasia, lymphoid		1 (2%)	
#Thymus	(37)	(35)	(32)
Cyst, NOS		1 (3%)	
CIRCULATORY SYSTEM			
#Brain	(50)	(50)	(50)
Thrombosis, NOS		1 (2%)	
#Heart	(50)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
#Heart/atrium	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)		1 (2%)
#Heart/ventricle	(50)	(50)	(50)
Thrombosis, NOS			1 (2%)
#Myocardium	(50)	(50)	(50)
Degeneration, NOS	47 (94%)	46 (92%)	42 (84%)
#Cardiac valve	(50)	(50)	(50)
Inflammation, acute focal			1 (2%)
DIGESTIVE SYSTEM			
#Salivary gland	(49)	(47)	(49)
Dilatation/ducts			1 (2%)
Focal cellular change	4 (8%)	2 (4%)	
Atrophy, NOS		1 (2%)	4 (8%)
#Liver	(50)	(50)	(50)
Abnormal curvature		1 (2%)	
Inflammation, acute		1 (2%)	
Inflammation, granulomatous	1 (2%)	2 (4%)	1 (2%)
Fibrosis, condensation	1 (2%)		
Degeneration, cystic	13 (26%)	26 (52%)	24 (48%)
Necrosis, coagulative	5 (10%)	1 (2%)	2 (4%)
Hyperchromatism	1 (2%)		
Cytoplasmic vacuolization	7 (14%)	7 (14%)	12 (24%)
Basophilic cyto change	28 (56%)	23 (46%)	7 (14%)
Focal cellular change	27 (54%)	24 (48%)	10 (20%)
Hyperplasia, nodular	1 (2%)		
Angiectasis	2 (4%)	1 (2%)	1 (2%)
#Bile duct	(50)	(50)	(50)
Fibrosis	4 (8%)	8 (16%)	28 (56%)
Pigmentation, NOS			1 (2%)
Hyperplasia, NOS	50 (100%)	45 (90%)	50 (100%)
#Pancreas	(49)	(50)	(49)
Dilatation/ducts	2 (4%)		1 (2%)
Cyst, NOS		1 (2%)	
Inflammation, chronic	1 (2%)	1 (2%)	
#Pancreatic duct	(49)	(50)	(49)
Hyperplasia, NOS	4 (8%)		
#Pancreatic acinus	(49)	(50)	(49)
Necrosis, focal	1 (2%)		
Focal cellular change	2 (4%)	1 (2%)	1 (2%)
Atrophy, focal	23 (47%)	21 (42%)	25 (51%)
Atrophy, diffuse	8 (16%)	26 (52%)	38 (78%)
Hyperplasia, NOS	2 (4%)	3 (6%)	7 (14%)
#Esophagus	(49)	(50)	(49)
Inflammation, chronic		1 (2%)	1 (2%)
Scar			1 (2%)
#Gastric fundal gland	(50)	(49)	(50)
Dilatation, NOS			1 (2%)
Hyperplasia, NOS		2 (4%)	6 (12%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Glandular stomach	(50)	(49)	(50)
Inflammation, NOS	1 (2%)	4 (8%)	7 (14%)
Ulcer, NOS		5 (10%)	15 (30%)
Inflammation, necrotizing	1 (2%)	7 (14%)	4 (8%)
#Forestomach	(50)	(49)	(50)
Inflammation, NOS		3 (6%)	1 (2%)
Ulcer, acute		3 (6%)	
Hyperplasia, epithelial	3 (6%)	8 (16%)	18 (36%)
#Jejunum	(49)	(46)	(40)
Inflammation, chronic	1 (2%)		
#Ileum	(49)	(46)	(40)
Inflammation, acute/chronic	1 (2%)		
Ulcer, healed	1 (2%)		
#Colon	(48)	(48)	(47)
Epidermal inclusion cyst	1 (2%)		
Parasitism	2 (4%)	3 (6%)	2 (4%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Cyst, NOS	2 (4%)		
Multiple cysts	1 (2%)		
Hemorrhagic cyst	1 (2%)		
Pyelonephritis, acute			1 (2%)
Nephropathy	50 (100%)	45 (90%)	47 (94%)
Nephrosis, NOS		4 (8%)	1 (2%)
Necrosis, coagulative		1 (2%)	
#Kidney/pelvis	(50)	(50)	(50)
Inflammation, acute			2 (4%)
#Urinary bladder	(47)	(46)	(49)
Calculus, gross observation only	1 (2%)	2 (4%)	
Mineralization		1 (2%)	
Hemorrhage	1 (2%)		
Inflammation, NOS		1 (2%)	4 (8%)
Hyperplasia, epithelial		2 (4%)	1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(47)	(49)	(49)
Colloid cyst	4 (9%)	1 (2%)	
Congestion, NOS		1 (2%)	
Pigmentation, NOS		1 (2%)	
Clear cell change		1 (2%)	
Atrophy, diffuse		1 (2%)	
Hyperplasia, chromophobe cell	9 (19%)	12 (24%)	6 (12%)
Angiectasis	1 (2%)	1 (2%)	1 (2%)
#Adrenal	(50)	(50)	(50)
Necrosis, coagulative			3 (6%)
#Adrenal cortex	(50)	(50)	(50)
Degeneration, cystic			1 (2%)
Degeneration, lipoid	12 (24%)	13 (26%)	23 (46%)
Necrosis, coagulative	2 (4%)		1 (2%)
Cytoplasmic vacuolization	13 (26%)	9 (18%)	5 (10%)
Eosinophilic cyto change	7 (14%)	6 (12%)	5 (10%)
Clear cell change	1 (2%)		
Hypertrophy, focal	1 (2%)	3 (6%)	1 (2%)
Hyperplasia, focal	14 (28%)	14 (28%)	16 (32%)
#Adrenal medulla	(50)	(50)	(50)
Hyperplasia, focal	18 (36%)	21 (42%)	16 (32%)
#Thyroid	(50)	(49)	(50)
Ultimobranchial cyst			2 (4%)
Follicular cyst, NOS	4 (8%)	5 (10%)	3 (6%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Thyroid (Continued)	(50)	(49)	(50)
Focal cellular change			2 (4%)
Hyperplasia, C-cell	39 (78%)	39 (80%)	27 (54%)
Hyperplasia, follicular cell	9 (18%)	7 (14%)	7 (14%)
#Parathyroid	(42)	(37)	(42)
Hyperplasia, NOS	2 (5%)	3 (8%)	6 (14%)
#Pancreatic islets	(49)	(50)	(49)
Atrophy, NOS		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Dilatation/ducts	2 (4%)	2 (4%)	
Galactocele	1 (2%)		
Hyperplasia, NOS		4 (8%)	2 (4%)
Hyperplasia, cystic	1 (2%)	4 (8%)	
Lactation		1 (2%)	1 (2%)
*Mammary duct	(50)	(50)	(50)
Hyperplasia, epithelial		1 (2%)	
*Preputial gland	(50)	(50)	(50)
Impaction, NOS	1 (2%)	1 (2%)	1 (2%)
Inflammation, NOS	3 (6%)	2 (4%)	
#Prostate	(47)	(48)	(49)
Cyst, NOS		2 (4%)	3 (6%)
Inflammation, NOS	11 (23%)	15 (31%)	16 (33%)
Necrosis, NOS			1 (2%)
Pigmentation, NOS			2 (4%)
*Seminal vesicle	(50)	(50)	(50)
Dilatation, NOS	1 (2%)		1 (2%)
Inflammation, NOS	1 (2%)		1 (2%)
Atrophy, NOS	1 (2%)	3 (6%)	4 (8%)
#Testis	(50)	(50)	(50)
Mineralization			1 (2%)
Inflammation, NOS	2 (4%)		
Infarct, NOS			1 (2%)
Atrophy, NOS	5 (10%)	8 (16%)	17 (34%)
Hyperplasia, interstitial cell	24 (48%)	23 (46%)	21 (42%)
Angiectasis		1 (2%)	
#Testis/tubule	(50)	(50)	(50)
Necrosis, coagulative		1 (2%)	
*Epididymis	(50)	(50)	(50)
Inflammation, NOS		3 (6%)	2 (4%)
Fibrosis	1 (2%)		
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Hydrocephalus, NOS			1 (2%)
Cyst, NOS		1 (2%)	
Hemorrhage	2 (4%)	3 (6%)	2 (4%)
Inflammation, granulomatous focal			1 (2%)
Necrosis, ischemic			1 (2%)
#Brain/thalamus	(50)	(50)	(50)
Atrophy, pressure	1 (2%)		
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Inflammation, NOS			4 (8%)
Synechia, NOS			1 (2%)
*Eye/anterior chamber	(50)	(50)	(50)
Inflammation, chronic diffuse			1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	Low Dose	High Dose
SPECIAL SENSE ORGANS (Continued)			
*Eye/cornea	(50)	(50)	(50)
Inflammation, NOS	2 (4%)	2 (4%)	19 (38%)
Hyperplasia, epithelial			1 (2%)
*Eye/retina	(50)	(50)	(50)
Atrophy, NOS	5 (10%)	9 (18%)	24 (48%)
*Eye/crystalline lens	(50)	(50)	(50)
Cataract	4 (8%)	14 (28%)	19 (38%)
MUSCULOSKELETAL SYSTEM			
*Femur	(50)	(50)	(50)
Fibrous osteodystrophy	1 (2%)		2 (4%)
*Skeletal muscle	(50)	(50)	(50)
Degeneration, NOS			1 (2%)
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Vegetable foreign body			1 (2%)
Inflammation, granulomatous			1 (2%)
*Peritoneal cavity	(50)	(50)	(50)
Inflammation, acute fibrinous			1 (2%)
*Pleural cavity	(50)	(50)	(50)
Inflammation, acute fibrinous			1 (2%)
*Pleura	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
*Mesentery	(50)	(50)	(50)
Hemorrhage			1 (2%)
Inflammation, chronic		1 (2%)	1 (2%)
Inflammation, granulomatous		1 (2%)	
Necrosis, fat	1 (2%)	8 (16%)	2 (4%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Mineralization	1 (2%)		
Congestion, NOS	2 (4%)	3 (6%)	8 (16%)
Necrosis, coagulative		1 (2%)	
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX B

SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT

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TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell carcinoma		1 (2%)	
Basal cell tumor		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma		1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
#Trachea	(48)	(49)	(49)
Follicular cell carcinoma, invasive			1 (2%)
#Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma			1 (2%)
C-cell carcinoma, metastatic		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	5 (10%)	12 (24%)	4 (8%)
#Renal lymph node	(43)	(43)	(39)
Pheochromocytoma, metastatic	1 (2%)		
CIRCULATORY SYSTEM			
None			
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(50)
Squamous cell carcinoma	1 (2%)		
#Liver	(50)	(50)	(50)
Neoplastic nodule			1 (2%)
#Forestomach	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)		1 (2%)
#Jejunum	(50)	(48)	(44)
Leiomyoma	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Tubular cell adenoma		1 (2%)	
ENDOCRINE SYSTEM			
#Pituitary intermedia	(49)	(49)	(48)
Adenoma, NOS	1 (2%)		1 (2%)
#Anterior pituitary	(49)	(49)	(48)
Carcinoma, NOS	2 (4%)		
Adenoma, NOS	16 (33%)	10 (20%)	2 (4%)
#Adrenal	(50)	(50)	(50)
Cortical adenoma		1 (2%)	
#Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma	4 (8%)	2 (4%)	1 (2%)
Pheochromocytoma, malignant	1 (2%)		

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Thyroid	(50)	(50)	(50)
Follicular cell adenoma	2 (4%)		5 (10%)
Follicular cell carcinoma		1 (2%)	2 (4%)
C-cell adenoma	9 (18%)	6 (12%)	1 (2%)
C-cell carcinoma		1 (2%)	
#Pancreatic islets	(50)	(50)	(50)
Islet cell adenoma		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenocarcinoma, NOS	1 (2%)		
Fibroadenoma	6 (12%)	10 (20%)	1 (2%)
*Clitoral gland	(50)	(50)	(50)
Adenoma, NOS	1 (2%)		
*Vagina	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)		
Sarcoma, NOS		1 (2%)	
#Uterus	(50)	(48)	(50)
Adenocarcinoma, NOS	1 (2%)		
Endometrial stromal polyp	9 (18%)	9 (19%)	5 (10%)
#Uterus/endometrium	(50)	(48)	(50)
Papilloma, NOS	1 (2%)		
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Carcinoma, NOS, invasive	2 (4%)		
Astrocytoma	1 (2%)		
SPECIAL SENSE ORGANS			
None			
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	4	5	18
Moribund sacrifice	9	7	16
Terminal sacrifice	37	37	14
Dosing accident		1	2

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	37	37	21
Total primary tumors	64	58	26
Total animals with benign tumors	31	28	17
Total benign tumors	52	42	19
Total animals with malignant tumors	12	16	6
Total malignant tumors	12	16	6
Total animals with secondary tumors##	3	1	1
Total secondary tumors	3	1	1
Total animals with tumors uncertain--benign or malignant			1
Total uncertain tumors			1

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

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT: VEHICLE CONTROL

ANIMAL NUMBER	037	045	030	006	004	041	016	032	001	009	050	002	044	003	005	007	008	010	011	012	013	014	015	017	018
WEEKS ON STUDY	024	036	062	077	083	083	086	087	094	095	098	102	103	104	104	104	104	104	104	104	104	104	104	104	104
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	–	+	+	–	+	+	+	–	+	+	+	+	–	+	+	+	+	+
Pheochromocytoma, metastatic																	X								
Thymus	–	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma				X																					
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma					X																				
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma												X													
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS										X															
Adenoma, NOS					X						X		X										X	X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma					X									X											
Pheochromocytoma, malignant																	X								
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma													X								X				
C-cell adenoma										X				X					X				X		
Parathyroid	–	–	+	–	–	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	–	–	–
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Fibroadenoma																									
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
Vagina	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma												X													
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS																									
Adenocarcinoma, NOS																								X	
Endometrial stromal polyp							X					X						X						X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive										X															
Astrocytoma		X																							
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell			X			X	X				X														

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

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

ANIMAL NUMBER	0 1 9	0 2 0	0 2 1	0 2 2	0 2 3	0 2 4	0 2 5	0 2 6	0 2 7	0 2 8	0 2 9	0 3 1	0 3 3	0 3 4	0 3 5	0 3 6	0 3 8	0 3 9	0 4 0	0 4 2	0 4 3	0 4 6	0 4 7	0 4 8	0 4 9	TOTAL TISSUES TUMORS
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	43
Pheochromocytoma, metastatic																										1
Thymus	+	–	–	+	+	+	+	+	–	+	+	–	+	–	–	+	+	+	–	+	+	+	+	+	–	38
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma																										1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																										1
Large intestine	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS																			X							2
Adenoma, NOS	X				X	X		X	X	X	X		X				X	X			X					17
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma	X				X																					4
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																										2
C cell adenoma				X										X	X									X	X	9
Parathyroid	+	–	+	–	–	–	+	+	+	+	+	–	+	–	+	+	+	+	–	–	+	+	–	+	+	32
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	*50
Adenocarcinoma, NOS				X																						1
Fibroadenoma	X							X		X			X				X				X					6
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS	X																									1
Vagina	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma, NOS																	X									1
Adenocarcinoma, NOS																										1
Endometrial stromal polyp														X						X			X	X	X	9
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																			X							2
Astrocytoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell														X												5

* Animals necropsied

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

ANIMAL NUMBER	049	034	030	016	026	001	050	039	023	017	013	018	011	002	003	004	005	006	007	008	009	010	012	014	015
WEEKS ON STUDY	012	045	047	067	067	082	083	089	097	098	099	102	103	105	105	105	105	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Basal cell tumor																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma				X																					
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell carcinoma, metastatic																						X			
Trachea	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	−	+	+	+	+	−	+	+	+	+	−	−	+	+	+	+	+	+	+	+	−	−
Thymus	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS												X	X								X		X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma															X										
Pheochromocytoma										X	X														
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																							X		
C-cell adenoma													X							X			X		X
C-cell carcinoma																						X			
Parathyroid	+	+	−	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																			X						
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma												X									X				X
Vagina	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS		X																							
Uterus	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Endometrial stromal polyp															X				X	X			X		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell					X			X	X	X	X		X							X				X	

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

ANIMAL NUMBER	0119	0200	0201	0222	0224	0225	0227	0228	0229	0231	0232	0233	0235	0236	0237	0238	0240	0241	0242	0243	0244	0245	0246	0247	0248	TOTAL:
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell carcinoma																			X							1
Basal cell tumor																X										1
Subcutaneous tissue	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell carcinoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	43
Thymus	−	+	−	+	+	+	+	+	+	+	−	+	−	+	+	−	+	−	+	+	+	+	+	+	+	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma			X																							1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	49
Adenoma, NOS	X	X								X													X	X	X	10
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																										1
Pheochromocytoma																										2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell carcinoma																										1
C-cell adenoma	X							X																		6
C-cell carcinoma																										1
Parathyroid	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	42
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma	X								X		X	X			X		X	X								10
Vagina	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Endometrial stromal polyp					X					X									X		X					9
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell					X									X		X						X				12

* Animals necropsied

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

ANIMAL NUMBER	0006	0002	0013	0112	0221	0227	0229	0235	0117	0118	0142	0446	0448	0116	0223	0336	0008	0004	0222	0224	0114	0150	0100	0450	0193
WEEKS ON STUDY	0554	0555	0556	0559	0559	0559	0600	0602	0602	0603	0699	0699	0712	0733	0777	0788	0811	0811	0814	0844	0855	0899	0933
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma, invasive																									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	−	+	+	+	−	+	−	−	−	+	+	−	+	+	−	+	−	+	+	−	+	−	+	+	+
Thymus	−	−	−	+	+	+	+	+	+	+	+	−	−	+	−	−	+	+	−	−	−	+	+	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma							X																		
Small intestine	+	+	+	+	+	+	+	−	+	+	−	+	+	−	+	+	+	+	+	+	+	−	−	+	+
Large intestine	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																								X	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma												X													
Follicular cell carcinoma																									
C-cell adenoma																									
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	−	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	N	+	+	+	+	+	+	+
Fibroadenoma									X																
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp														X										X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell																									

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

ANIMAL NUMBER	0040	0026	0097	0033	0041	0009	0003	0001	0020	0028	0031	0005	0011	0015	0030	0032	0034	0035	0037	0038	0039	0043	0044	0047	0049	TOTAL:
WEEKS ON STUDY	093	094	095	095	095	097	098	099	099	101	101	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma											X															1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																						X				1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	49
Follicular cell carcinoma, invasive											X															1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Thymus	+	+	+	+	+	+	–	–	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	34
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule						X																				1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Large intestine	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS						X											X			X						3
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma												X	X		X	X										5
Follicular cell carcinoma					X						X															2
C-cell adenoma																					X					1
Parathyroid	+	+	+	+	+	+	–	+	–	+	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	42
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp												X							X				X			5
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell	X	X										X		X												4

* Animals necropsied

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT

	Vehicle Control	50 mg/kg	100 mg/kg
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	5/50 (10%)	12/50 (24%)	4/50 (8%)
Adjusted Rates (b)	11.2%	27.6%	21.0%
Terminal Rates (c)	1/37 (3%)	6/37 (16%)	2/14 (14%)
Week of First Observation	62	67	93
Life Table Tests (d)	P=0.202	P=0.070	P=0.397
Incidental Tumor Tests (d)	P=0.221N	P=0.034	P=0.317N
Cochran-Armitage Trend Test (d)	P=0.443N		
Fisher Exact Test (d)		P=0.054	P=0.500N
Pituitary Gland: Adenoma			
Overall Rates (a)	16/49 (33%)	10/49 (20%)	2/48 (4%)
Adjusted Rates (b)	39.8%	26.2%	14.3%
Terminal Rates (c)	13/37 (35%)	8/36 (22%)	2/14 (14%)
Week of First Observation	83	102	104
Life Table Tests (d)	P=0.032N	P=0.147N	P=0.060N
Incidental Tumor Tests (d)	P=0.005N	P=0.146N	P=0.015N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.126N	P<0.001N
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	18/49 (37%)	10/49 (20%)	2/48 (4%)
Adjusted Rates (b)	43.7%	26.2%	14.3%
Terminal Rates (c)	14/37 (38%)	8/36 (22%)	2/14 (14%)
Week of First Observation	83	102	104
Life Table Tests (d)	P=0.013N	P=0.074N	P=0.034N
Incidental Tumor Tests (d)	P=0.001N	P=0.068N	P=0.004N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.058N	P<0.001N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	10.1%	4.9%	3.7%
Terminal Rates (c)	3/37 (8%)	0/37 (0%)	0/14 (0%)
Week of First Observation	83	98	89
Life Table Tests (d)	P=0.300N	P=0.340N	P=0.457N
Incidental Tumor Tests (d)	P=0.086N	P=0.359N	P=0.275N
Cochran-Armitage Trend Test (d)	P=0.118N		
Fisher Exact Test (d)		P=0.339N	P=0.181N
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	5/50 (10%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	12.7%	4.9%	3.7%
Terminal Rates (c)	4/37 (11%)	0/37 (0%)	0/14 (0%)
Week of First Observation	83	98	89
Life Table Tests (d)	P=0.197N	P=0.222N	P=0.364N
Incidental Tumor Tests (d)	P=0.051N	P=0.235N	P=0.210N
Cochran-Armitage Trend Test (d)	P=0.060N		
Fisher Exact Test (d)		P=0.218N	P=0.102N
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	2/50 (4%)	0/50 (0%)	5/50 (10%)
Adjusted Rates (b)	5.3%	0.0%	30.4%
Terminal Rates (c)	1/37 (3%)	0/37 (0%)	4/14 (29%)
Week of First Observation	103		69
Life Table Tests (d)	P=0.015	P=0.240N	P=0.020
Incidental Tumor Tests (d)	P=0.069	P=0.240N	P=0.083
Cochran-Armitage Trend Test (d)	P=0.118		
Fisher Exact Test (d)		P=0.247N	P=0.218

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	2/50 (4%)	1/50 (2%)	7/50 (14%)
Adjusted Rates (b)	5.3%	2.7%	37.6%
Terminal Rates (c)	1/37 (3%)	1/37 (3%)	4/14 (29%)
Week of First Observation	103	105	69
Life Table Tests (d)	P=0.001	P=0.500N	P=0.003
Incidental Tumor Tests (d)	P=0.026	P=0.500N	P=0.045
Cochran-Armitage Trend Test (d)	P=0.036		
Fisher Exact Test (d)		P=0.500N	P=0.080
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	9/50 (18%)	6/50 (12%)	1/50 (2%)
Adjusted Rates (b)	23.5%	15.8%	7.1%
Terminal Rates (c)	8/37 (22%)	5/37 (14%)	1/14 (7%)
Week of First Observation	95	103	104
Life Table Tests (d)	P=0.102N	P=0.287N	P=0.156N
Incidental Tumor Tests (d)	P=0.050N	P=0.287N	P=0.100N
Cochran-Armitage Trend Test (d)	P=0.008N		
Fisher Exact Test (d)		P=0.288N	P=0.008N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	9/50 (18%)	7/50 (14%)	1/50 (2%)
Adjusted Rates (b)	23.5%	18.4%	7.1%
Terminal Rates (c)	8/37 (22%)	6/37 (16%)	1/14 (7%)
Week of First Observation	95	103	104
Life Table Tests (d)	P=0.126N	P=0.392N	P=0.156N
Incidental Tumor Tests (d)	P=0.065N	P=0.392N	P=0.100N
Cochran-Armitage Trend Test (d)	P=0.009N		
Fisher Exact Test (d)		P=0.393N	P=0.008N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	6/50 (12%)	10/50 (20%)	1/50 (2%)
Adjusted Rates (b)	16.2%	26.3%	2.4%
Terminal Rates (c)	6/37 (16%)	9/37 (24%)	0/14 (0%)
Week of First Observation	104	102	62
Life Table Tests (d)	P=0.462N	P=0.204	P=0.297N
Incidental Tumor Tests (d)	P=0.278N	P=0.204	P=0.168N
Cochran-Armitage Trend Test (d)	P=0.078N		
Fisher Exact Test (d)		P=0.207	P=0.056N
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	9/50 (18%)	9/48 (19%)	5/50 (10%)
Adjusted Rates (b)	22.8%	25.0%	26.4%
Terminal Rates (c)	7/37 (19%)	9/36 (25%)	3/14 (21%)
Week of First Observation	86	105	72
Life Table Tests (d)	P=0.358	P=0.580	P=0.431
Incidental Tumor Tests (d)	P=0.508N	P=0.566	P=0.469N
Cochran-Armitage Trend Test (d)	P=0.167N		
Fisher Exact Test (d)		P=0.565	P=0.194N
All Sites: Benign Tumors			
Overall Rates (a)	31/50 (62%)	28/50 (56%)	17/50 (34%)
Adjusted Rates (b)	72.0%	66.6%	77.8%
Terminal Rates (c)	25/37 (68%)	23/37 (62%)	10/14 (71%)
Week of First Observation	83	67	59
Life Table Tests (d)	P=0.210	P=0.352N	P=0.186
Incidental Tumor Tests (d)	P=0.085N	P=0.356N	P=0.179N
Cochran-Armitage Trend Test (d)	P=0.003N		
Fisher Exact Test (d)		P=0.342N	P=0.005N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
All Sites: Malignant Tumors			
Overall Rates (a)	12/50 (24%)	16/50 (32%)	6/50 (12%)
Adjusted Rates (b)	26.2%	35.9%	29.2%
Terminal Rates (c)	5/37 (14%)	9/37 (24%)	2/14 (14%)
Week of First Observation	36	45	93
Life Table Tests (d)	P=0.474	P=0.278	P=0.567N
Incidental Tumor Tests (d)	P=0.041N	P=0.241	P=0.048N
Cochran-Armitage Trend Test (d)	P=0.094N		
Fisher Exact Test (d)		P=0.252	P=0.097N
All Sites: All Tumors			
Overall Rates (a)	37/50 (74%)	37/50 (74%)	21/50 (42%)
Adjusted Rates (b)	78.6%	80.4%	85.3%
Terminal Rates (c)	27/37 (73%)	28/37 (76%)	11/14 (79%)
Week of First Observation	36	45	59
Life Table Tests (d)	P=0.168	P=0.568N	P=0.184
Incidental Tumor Tests (d)	P=0.018N	P=0.576	P=0.054N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.590N	P=0.002N

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

TABLE B4a. HISTORICAL INCIDENCE OF THYROID GLAND FOLLICULAR CELL TUMORS IN FEMALE F344/N RATS (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence in Water Gavage Controls at Battelle Columbus Laboratories (b)			
Chlorpheniramine maleate	0/47	0/47	0/47
Tetrakis(hydroxymethyl)phosphonium chloride	3/50	0/50	3/50
Tetrakis(hydroxymethyl)phosphonium sulfate	0/49	1/49	1/49
TOTAL	3/146 (2.1%)	1/146 (0.7%)	4/146 (2.7%)
SD (c)	3.46%	1.18%	3.05%
Range (d)			
High	3/50	1/49	3/50
Low	0/49	0/50	0/47
Overall Historical Incidence in Untreated Controls			
TOTAL	(e) 13/1,952 (0.7%)	(f) 7/1,952 (0.4%)	(e,f) 20/1,952 (1.0%)
SD (c)	1.11%	0.78%	1.34%
Range (d)			
High	2/42	1/47	2/42
Low	0/50	0/86	0/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) No other water gavage studies are included in the historical data base.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes one papillary adenoma, one cystadenoma, and one papillary cystadenoma
(f) Includes one papillary carcinoma and one papillary cystadenocarcinoma

TABLE B4b. HISTORICAL INCIDENCE OF LEUKEMIA IN FEMALE F344/N RATS (a)

Study	Incidence in Controls
Historical Incidence in Water Gavage Controls at Battelle Columbus Laboratories (b)	
Chlorpheniramine maleate	11/50
Tetrakis(hydroxymethyl)phosphonium chloride	4/50
Tetrakis(hydroxymethyl)phosphonium sulfate	23/49
TOTAL	38/149 (25.5%)
SD (c)	19.72%
Range (d)	
High	23/49
Low	4/50
Overall Historical Incidence in Untreated Controls	
TOTAL	375/2,021 (18.6%)
SD (c)	6.55%
Range (d)	
High	19/50
Low	3/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) No other water gavage studies are included in the historical data base.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE B4c. HISTORICAL INCIDENCE OF PITUITARY GLAND TUMORS IN FEMALE F344/N RATS (a)

Study	Incidence in Controls		
	Adenoma (b)	Carcinoma (c)	Adenoma or Carcinoma (b,c)
Historical Incidence in Water Gavage Controls at Battelle Columbus Laboratories (d)			
Chlorpheniramine maleate	24/48	1/48	25/48
Tetrakis(hydroxymethyl)phosphonium chloride	24/49	0/49	24/49
Tetrakis(hydroxymethyl)phosphonium sulfate	23/46	0/46	23/46
TOTAL	71/143 (49.7%)	1/143 (0.7%)	72/143 (50.3%)
SD (e)	0.59%	1.20%	1.58%
Range (f)			
High	24/48	1/48	25/48
Low	24/49	0/49	24/49
Overall Historical Incidence			
TOTAL	862/1,952 (44.2%)	71/1,952 (3.6%)	931/1,952 (47.7%)
SD (e)	11.56%	3.97%	11.02%
Range (f)			
High	33/47	8/49	33/47
Low	7/39	0/50	9/39

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Includes adenoma, NOS, chromophobe adenoma, and acidophil adenoma
(c) Includes carcinoma, NOS, and chromophobe carcinoma
(d) No other water gavage studies are included in the historical data base.
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Inflammation, NOS	1 (2%)	†2 (4%)	1 (2%)
Hyperplasia, NOS	1 (2%)		
Acanthosis	1 (2%)	1 (2%)	1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Epidermal inclusion cyst	2 (4%)		3 (6%)
Inflammation, acute/chronic			1 (2%)
Inflammation, chronic	1 (2%)		1 (2%)
RESPIRATORY SYSTEM			
#Trachea	(48)	(49)	(49)
Inflammation, acute	2 (4%)		
Inflammation, acute/chronic	1 (2%)		
#Lung	(50)	(50)	(50)
Vegetable foreign body			1 (2%)
Congestion, NOS		3 (6%)	4 (8%)
Hemorrhage			1 (2%)
Inflammation, NOS	6 (12%)	1 (2%)	7 (14%)
Pneumonia, aspiration			2 (4%)
Hyperplasia, alveolar epithelium	2 (4%)		1 (2%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(50)	(50)
Inflammation, granulomatous	1 (2%)		
Atrophy, NOS	3 (6%)		1 (2%)
Hyperplasia, hematopoietic	2 (4%)	4 (8%)	11 (22%)
Hyperplasia, granulocytic		1 (2%)	
Hyperplasia, reticulum cell	6 (12%)	19 (38%)	7 (14%)
#Spleen	(50)	(50)	(50)
Inflammation, granulomatous			1 (2%)
Hemosiderosis	7 (14%)	3 (6%)	1 (2%)
Depletion, lymphoid	2 (4%)		1 (2%)
Angiectasis		2 (4%)	
Hematopoiesis	1 (2%)	2 (4%)	9 (18%)
#Splenic capsule	(50)	(50)	(50)
Hematoma, NOS		2 (4%)	
#Mandibular lymph node	(43)	(43)	(39)
Inflammation, acute			2 (5%)
Inflammation, granulomatous		1 (2%)	
#Mediastinal lymph node	(43)	(43)	(39)
Inflammation, granulomatous		1 (2%)	
#Mesenteric lymph node	(43)	(43)	(39)
Dilatation/sinus	1 (2%)	3 (7%)	
Hemorrhage			1 (3%)
#Lung	(50)	(50)	(50)
Hematopoiesis		1 (2%)	
#Thymus	(38)	(41)	(34)
Ultimobranchial cyst	1 (3%)		
Cyst, NOS	2 (5%)	1 (2%)	
Hemorrhage		1 (2%)	
Inflammation, acute			1 (3%)
Fibrosis, focal	1 (3%)		
Depletion, lymphoid			1 (3%)
Hyperplasia, epithelial	1 (3%)		

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	Low Dose	High Dose
CIRCULATORY SYSTEM			
#Heart	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)		
Inflammation, acute/chronic	1 (2%)		
#Heart/atrium	(50)	(50)	(50)
Thrombosis, NOS			1 (2%)
#Myocardium	(50)	(50)	(50)
Degeneration, NOS	41 (82%)	38 (76%)	26 (52%)
Necrosis, coagulative		1 (2%)	
#Jejunum	(50)	(48)	(44)
Lymphangiectasis			1 (2%)
DIGESTIVE SYSTEM			
#Salivary gland	(50)	(49)	(48)
Edema, NOS			1 (2%)
Inflammation, chronic focal	2 (4%)		
Focal cellular change	4 (8%)	3 (6%)	
Atrophy, NOS	1 (2%)		2 (4%)
Atrophy, focal	3 (6%)		
Hyperplasia, NOS			1 (2%)
#Liver	(50)	(50)	(50)
Abnormal curvature	2 (4%)	1 (2%)	2 (4%)
Hemorrhage, chronic		1 (2%)	
Inflammation, acute		1 (2%)	
Inflammation, acute/chronic	1 (2%)		
Inflammation, granulomatous	3 (6%)	3 (6%)	
Degeneration, cystic			5 (10%)
Degeneration, lipoid		1 (2%)	2 (4%)
Necrosis, coagulative	2 (4%)	2 (4%)	
Cytoplasmic vacuolization	6 (12%)	6 (12%)	18 (36%)
Basophilic cyto change	36 (72%)	40 (80%)	43 (86%)
Focal cellular change	8 (16%)	7 (14%)	10 (20%)
Hyperplasia, nodular		2 (4%)	1 (2%)
Angiectasis		2 (4%)	
#Bile duct	(50)	(50)	(50)
Fibrosis	1 (2%)		1 (2%)
Hyperplasia, NOS	17 (34%)	15 (30%)	35 (70%)
#Pancreas	(50)	(50)	(50)
Dilatation/ducts	2 (4%)		
Edema, NOS			2 (4%)
Inflammation, acute focal	1 (2%)		
#Pancreatic acinus	(50)	(50)	(50)
Edema, NOS			1 (2%)
Cytoplasmic vacuolization		1 (2%)	1 (2%)
Focal cellular change			2 (4%)
Eosinophilic cyto change			1 (2%)
Atrophy, NOS	3 (6%)	1 (2%)	
Atrophy, focal	8 (16%)	14 (28%)	12 (24%)
Atrophy, diffuse	5 (10%)	27 (54%)	42 (84%)
Hyperplasia, NOS	1 (2%)	1 (2%)	
*Pharynx	(50)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
#Esophagus	(50)	(50)	(50)
Dilatation, NOS			1 (2%)
Inflammation, acute necrotizing			1 (2%)
Inflammation, acute/chronic			1 (2%)
#Gastric fundal gland	(50)	(50)	(50)
Hyperplasia, NOS		1 (2%)	5 (10%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Glandular stomach	(50)	(50)	(50)
Mineralization		1 (2%)	
Inflammation, NOS	1 (2%)	2 (4%)	3 (6%)
Ulcer, NOS	1 (2%)	2 (4%)	19 (38%)
Inflammation, necrotizing		1 (2%)	9 (18%)
#Forestomach	(50)	(50)	(50)
Inflammation, NOS			2 (4%)
Hyperplasia, epithelial	4 (8%)	5 (10%)	18 (36%)
#Duodenum	(50)	(48)	(44)
Inflammation, acute/chronic	1 (2%)		
#Jejunum	(50)	(48)	(44)
Edema, NOS			1 (2%)
Inflammation, granulomatous	1 (2%)		
#Colon	(47)	(49)	(45)
Parasitism		1 (2%)	3 (7%)
#Cecum	(47)	(49)	(45)
Edema, NOS			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Pyelonephritis, acute			1 (2%)
Nephropathy	38 (76%)	38 (76%)	48 (96%)
#Urinary bladder	(49)	(48)	(49)
Edema, NOS		1 (2%)	
Inflammation, NOS		1 (2%)	
ENDOCRINE SYSTEM			
#Pituitary intermedia	(49)	(49)	(48)
Cyst, NOS		1 (2%)	
#Anterior pituitary	(49)	(49)	(48)
Cyst, NOS	1 (2%)		
Colloid cyst	14 (29%)	7 (14%)	1 (2%)
Follicular cyst, NOS			1 (2%)
Clear cell change			1 (2%)
Hyperplasia, chromophobe cell	15 (31%)	16 (33%)	3 (6%)
Angiectasis	3 (6%)	5 (10%)	
#Adrenal	(50)	(50)	(50)
Congestion, NOS		1 (2%)	4 (8%)
Necrosis, coagulative			1 (2%)
#Adrenal cortex	(50)	(50)	(50)
Degeneration, lipoid	19 (38%)	20 (40%)	30 (60%)
Necrosis, NOS		1 (2%)	
Necrosis, coagulative		1 (2%)	3 (6%)
Cytoplasmic vacuolization	5 (10%)	2 (4%)	2 (4%)
Eosinophilic cyto change	5 (10%)	10 (20%)	
Hypertrophy, focal	5 (10%)	6 (12%)	1 (2%)
Hyperplasia, focal	12 (24%)	18 (36%)	14 (28%)
Angiectasis	1 (2%)	3 (6%)	4 (8%)
#Adrenal medulla	(50)	(50)	(50)
Hyperplasia, focal	10 (20%)	14 (28%)	4 (8%)
#Thyroid	(50)	(50)	(50)
Ultimobranchial cyst	1 (2%)		12 (24%)
Follicular cyst, NOS	4 (8%)	2 (4%)	2 (4%)
Focal cellular change			4 (8%)
Hyperplasia, C-cell	43 (86%)	44 (88%)	27 (54%)
Hyperplasia, follicular cell	10 (20%)	10 (20%)	26 (52%)
#Parathyroid	(32)	(42)	(42)
Hyperplasia, NOS		6 (14%)	1 (2%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Pancreatic islets	(50)	(50)	(50)
Hyperplasia, focal		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Dilatation/ducts	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, NOS	3 (6%)	3 (6%)	
Hyperplasia, focal	1 (2%)		
Hyperplasia, cystic	16 (32%)	24 (48%)	
*Nipple	(50)	(50)	(50)
Epidermal inclusion cyst		1 (2%)	3 (6%)
*Clitoral gland	(50)	(50)	(50)
Impaction, NOS		1 (2%)	
Inflammation, chronic		1 (2%)	
Hyperplasia, NOS		1 (2%)	
#Uterus	(50)	(48)	(50)
Dilatation, NOS	3 (6%)	6 (13%)	
#Uterus/endometrium	(50)	(48)	(50)
Cyst, NOS	4 (8%)	4 (8%)	11 (22%)
Inflammation, acute	1 (2%)	2 (4%)	
Inflammation, acute/chronic	1 (2%)		
Hyperplasia, cystic	2 (4%)		4 (8%)
#Ovary/parovarian	(50)	(50)	(50)
Inflammation, granulomatous		1 (2%)	
#Ovary	(50)	(50)	(50)
Cyst, NOS	7 (14%)	7 (14%)	5 (10%)
Inflammation, acute			1 (2%)
Fibrosis	1 (2%)		
NERVOUS SYSTEM			
#Brain/meninges	(50)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
#Brain	(50)	(50)	(50)
Hydrocephalus, NOS	1 (2%)		
Spongiosis			2 (4%)
Hemorrhage	2 (4%)	2 (4%)	
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Collapse		1 (2%)	1 (2%)
Inflammation, NOS	1 (2%)	1 (2%)	3 (6%)
*Eye/cornea	(50)	(50)	(50)
Inflammation, NOS	2 (4%)	2 (4%)	25 (50%)
*Eye/retina	(50)	(50)	(50)
Atrophy, NOS	3 (6%)	31 (62%)	30 (60%)
*Eye/crystalline lens	(50)	(50)	(50)
Cataract	4 (8%)	26 (52%)	31 (62%)
*Zymbal gland	(50)	(50)	(50)
Impaction, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Femur	(50)	(50)	(50)
Fibrous osteodystrophy			1 (2%)
*Skeletal muscle	(50)	(50)	(50)
Inflammation, chronic focal	1 (2%)		

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	Low Dose	High Dose
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic	1 (2%)		
Abscess, chronic	1 (2%)		
Granuloma, NOS			1 (2%)
*Pleural cavity	(50)	(50)	(50)
Foreign material, NOS		1 (2%)	
*Pleura	(50)	(50)	(50)
Inflammation, acute fibrinous		1 (2%)	
*Pericardium	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Inflammation, acute/chronic	1 (2%)		
Granuloma, foreign body			1 (2%)
*Mesentery	(50)	(50)	(50)
Inflammation, granulomatous			1 (2%)
Necrosis, fat	5 (10%)	5 (10%)	2 (4%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Congestion, NOS	2 (4%)	3 (6%)	4 (8%)
Hemorrhage			1 (2%)
Inflammation, fibrinous	1 (2%)		
SPECIAL MORPHOLOGY SUMMARY			
None			

* Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
† Multiple occurrence of morphology in the same organ; tissue is counted once only.
# Number of animals examined microscopically at this site

APPENDIX C

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT

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TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Fibrosarcoma	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS	2 (4%)	4 (8%)	1 (2%)
Fibroma	2 (4%)	3 (6%)	
Fibrosarcoma	8 (16%)	6 (12%)	3 (6%)
Neurofibrosarcoma	1 (2%)		1 (2%)
RESPIRATORY SYSTEM			
#Lung	(47)	(50)	(49)
Hepatocellular carcinoma, metastatic	6 (13%)	2 (4%)	2 (4%)
Alveolar/bronchiolar adenoma	7 (15%)	5 (10%)	4 (8%)
Alveolar/bronchiolar carcinoma	5 (11%)	1 (2%)	4 (8%)
Fibrosarcoma, metastatic	2 (4%)		2 (4%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS		1 (2%)	1 (2%)
Malignant lymphoma, undiffer type	1 (2%)		1 (2%)
Malignant lymphoma, histiocytic type	2 (4%)	4 (8%)	1 (2%)
Malignant lymphoma, mixed type	1 (2%)	1 (2%)	
#Kidney	(50)	(47)	(49)
Malignant lymphoma, NOS			1 (2%)
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hemangiosarcoma			1 (2%)
*Lower extremity	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)	
#Spleen	(47)	(48)	(50)
Hemangioma		1 (2%)	
Hemangiosarcoma, metastatic		1 (2%)	
#Heart	(47)	(50)	(50)
Hemangioma	1 (2%)		
#Liver	(50)	(49)	(49)
Hemangiosarcoma			1 (2%)
DIGESTIVE SYSTEM			
#Liver	(50)	(49)	(49)
Hepatocellular adenoma	4 (8%)	6 (12%)	5 (10%)
Hepatocellular carcinoma	14 (28%)	15 (31%)	14 (29%)
Mixed hepatocellular and bile duct carcinoma		1 (2%)	
Fibrosarcoma, metastatic			1 (2%)
#Pancreatic acinus	(43)	(43)	(45)
Adenocarcinoma, NOS	1 (2%)		
#Gastric fundal gland	(44)	(46)	(39)
Adenomatous polyp, NOS		1 (2%)	
#Forestomach	(44)	(46)	(39)
Squamous cell carcinoma		1 (2%)	

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Adrenal	(44)	(45)	(46)
Pheochromocytoma			1 (2%)
#Adrenal medulla	(44)	(45)	(46)
Pheochromocytoma	1 (2%)		
#Thyroid	(45)	(48)	(45)
Follicular cell adenoma		1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM			
#Prostate	(42)	(44)	(47)
Adenoma, NOS	1 (2%)		
#Testis	(45)	(44)	(44)
Interstitial cell tumor	1 (2%)		
*Epididymis	(50)	(50)	(50)
Leiomyoma	1 (2%)		
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS	3 (6%)	2 (4%)	1 (2%)
Adenocarcinoma, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Maxilla	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)		
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Fibrosarcoma, metastatic			1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Mixed hepato and bile duct carcinoma, meta		1 (2%)	
Alveolar/bronchiolar carcinoma, metastatic	1 (2%)		1 (2%)
Sarcoma, NOS		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	16	22	25
Moribund sacrifice	8	7	11
Terminal sacrifice	23	19	14
Accidentially killed, nda	3	2	

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	39	37	31
Total primary tumors	58	56	41
Total animals with benign tumors	19	16	11
Total benign tumors	21	19	12
Total animals with malignant tumors	30	31	25
Total malignant tumors	37	37	29
Total animals with secondary tumors##	9	4	5
Total secondary tumors	9	4	7

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

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT: VEHICLE CONTROL

ANIMAL NUMBER	026	030	021	038	046	020	007	012	022	042	044	003	032	047	018	017	011	023	015	037	040	006	035	008	025
WEEKS ON STUDY	011	018	039	058	062	078	079	081	081	082	082	085	085	090	092	093	095	096	098	098	098	100	100	102	103
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS								X																	
Fibroma																									
Fibrosarcoma																X	X		X			X	X		X
Neurofibrosarcoma										X															
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic						X								X											X
Alveolar/bronchiolar adenoma				X																					
Alveolar/bronchiolar carcinoma							X											X							
Fibrosarcoma, metastatic																	X						X		
Trachea	−	+	+	+	+	+	−	−	+	+	+	−	+	−	−	+	+	−	−	+	+	+	+	+	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+
Lymph nodes	−	+	−	+	+	+	−	+	−	+	+	+	+	+	−	+	−	−	−	+	+	+	+	+	−
Thymus	−	+	−	+	+	−	−	−	−	−	+	−	+	+	−	−	−	−	−	−	+	−	+	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+
Hemangioma																									
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma							X																		
Hepatocellular carcinoma					X	X						X		X			X			X	X				X
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	N	N	N	+	N	N	N	N	N	N	N	+	N	N	N	N	+	+	N	N	N
Pancreas	+	+	−	−	+	−	−	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS															X										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	−	−	+	+	−	+	−	−	+	+	+	−	+	+	+	+	+	+	+	+
Small intestine	+	+	−	+	−	−	−	−	+	−	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	−	+	+	−	−	−	+	+	−	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	−	+	+	−	+	−	−	+	−	+	−	+	+	+	+	+	+	−	+
ENDOCRINE SYSTEM																									
Pituitary	+	−	+	+	+	+	−	+	+	+	−	−	+	−	+	+	−	+	+	+	−	+	−	+	−
Adrenal	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	−	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Parathyroid	−	−	−	+	+	−	−	−	−	−	−	−	+	−	+	−	−	−	−	−	+	−	−	−	−
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	−
Interstitial cell tumor																									
Prostate	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	−
Adenoma, NOS																X									
Epididymis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leiomyoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																							X		
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS							X																		
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Alveolar/bronchiolar carcinoma, metastatic							X																		
Malignant lymphoma, undiffer type																									
Malignant lymphoma, histiocytic type																		X							
Malignant lymphoma, mixed type													X												

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

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

ANIMAL NUMBER	048	001	002	004	005	009	010	013	014	016	019	024	027	028	029	031	033	034	036	039	041	043	045	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma						X																				1
Subcutaneous tissue	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																							X			2
Fibroma					X			X																		2
Fibrosarcoma												X				X										8
Neurofibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	47
Hepatocellular carcinoma, metastatic				X	X																		X			6
Alveolar/bronchiolar adenoma								X										X	X		X	X			X	7
Alveolar/bronchiolar carcinoma				X															X						X	5
Fibrosarcoma, metastatic																										2
Trachea	–	–	–	+	–	–	–	–	+	–	–	–	–	–	+	+	+	+	–	–	+	+	+	+	+	27
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph nodes	+	+	+	+	+	+	–	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	–	+	37
Thymus	+	+	–	+	–	–	–	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	–	–	25
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	47
Hemangioma																								X		1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma			X	X				X																		4
Hepatocellular carcinoma				X	X		X								X				X				X			14
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	N	N	N	+	+	N	+	+	+	+	+	N	N	N	+	+	+	+	+	N	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Adenocarcinoma, NOS																										1
Esophagus	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Small intestine	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	39
Large intestine	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	41
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	39
Adrenal	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	–	+	+	+	–	+	+	+	+	44
Pheochromocytoma																							X			1
Thyroid	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Parathyroid	–	–	–	+	–	–	–	–	+	–	–	–	+	+	–	–	+	–	–	–	+	+	+	–	+	13
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	45
Interstitial cell tumor																	X									1
Prostate	+	–	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	42
Adenoma, NOS																										1
Epididymis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leiomyoma															X											1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS												X	X													3
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Alveolar/bronchiolar carcinoma, meta																										1
Malignant lymphoma, undiffer type										X																1
Malignant lymphoma, histiocytic type	X																									2
Malignant lymphoma, mixed type																										1

* Animals necropsied

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

ANIMAL NUMBER	0003	0005	0020	0117	0119	0004	0050	0227	0001	0037	0033	0226	0228	0231	0110	0225	0118	0445	0111	0002	0229	0449	0006	0422	0433
WEEKS ON STUDY	017	034	043	044	044	059	060	061	070	076	079	080	081	083	090	090	091	091	092	093	093	095	096	097	097
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+
Sarcoma, NOS											X			X				X							
Fibroma																		X							
Fibrosarcoma								X																X	
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic												X													
Alveolar/bronchiolar adenoma													X												
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+
Spleen	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hemangiosarcoma, metastatic																									
Lymph nodes	+	+	−	−	+	−	+	+	+	−	−	+	+	−	+	−	+	−	−	+	−	+	+	+	−
Thymus	+	+	−	−	−	+	−	+	−	−	−	−	−	−	+	+	−	−	−	−	−	+	−	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma					X						X										X				
Hepatocellular carcinoma	X						X		X			X	X	X		X		X	X	X					
Mixed hepato/cholangiocarcinoma																							X		
Bile duct	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	N	N	N	N	N	+	N	N	N	N	+	N	+	+	+	N	N	+	N	N	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	−	−	+	+	+	−	−	+	−	−	+	+	+	+	+	−
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	−	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Squamous cell carcinoma																					X				
Adenomatous polyp, NOS																									
Small intestine	+	+	+	−	−	+	−	+	+	−	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−
URINARY SYSTEM																									
Kidney	+	+	+	+	−	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	−	+	+	−	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	−	+	+	−	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	−	−	−	−	+	−	+	−	+	+	+	−	+	+	−	+	−	−	−	+	+	+	−	+	−
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N
Testis	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	−	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
Adenocarcinoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mixed hepato/cholangio carcinoma, metastatic																							X		
Sarcoma, NOS									X																
Malignant lymphoma, NOS															X										
Malignant lymphoma, histiocytic type																								X	
Malignant lymphoma, mixed type																									
Lower extremity, NOS																									
Hemangiosarcoma																									

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

ANIMAL NUMBER	044	007	032	021	012	008	009	013	014	015	016	022	023	024	030	034	035	036	038	039	040	041	046	047	048	TOTAL TISSUES TUMORS
WEEKS ON STUDY	097	100	100	102	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS		X																								4
Fibroma																		X		X						3
Fibrosarcoma												X	X					X						X		6
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic							X																			2
Alveolar/bronchiolar adenoma		X						X												X	X					5
Alveolar/bronchiolar carcinoma																					X					1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+		47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Hemangioma														X												1
Hemangiosarcoma, metastatic																	X									1
Lymph nodes	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	37
Thymus	+	–	–	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	30
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma					X	X																		X		6
Hepatocellular carcinoma							X			X					X		X					X			15
Mixed hepato/cholangiocarcinoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Squamous cell carcinoma																										1
Adenomatous polyp, NOS																									X	1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	–	–	–	+	+	+	–	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	40
Adrenal	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	45
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma								X																		1
Parathyroid	–	+	+	–	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	31
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	–	–	–	+	+	+	+	+	–	+	+	+	+	+	+	+	44
Prostate	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	44
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS												X						X								2
Adenocarcinoma, NOS																									X	1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mixed hepato/cholangio carcinoma, meta																										1
Sarcoma, NOS																										1
Malignant lymphoma, NOS																										1
Malignant lymphoma, histiocytic type											X		X			X										4
Malignant lymphoma, mixed type																									X	1
Lower extremity, NOS																										
Hemangiosarcoma																	X									1

* Animals necropsied

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

ANIMAL NUMBER	00 08	00 47	00 12	00 05	00 49	00 24	00 39	01 14	01 11	02 22	01 13	01 16	02 26	05 00	00 02	00 01	00 09	03 37	04 41	04 46	02 23	02 25	00 03	03 31	03 32
WEEKS ON STUDY	06 65	06 65	06 67	07 70	07 71	07 73	08 80	08 82	08 85	08 85	08 86	08 86	08 86	08 87	08 88	08 89	09 00	09 00	09 00	09 00	09 11	09 11	09 22	09 22	09 32
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Fibrosarcoma							X									X									
Neurofibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic						X									X										
Alveolar/bronchiolar adenoma				X																					
Alveolar/bronchiolar carcinoma																									
Fibrosarcoma, metastatic							X									X									
Trachea	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	−	+	−	−	+	+	+	+	+	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	−	+	+	+	+	+	+	+	−	+	+	+	−	−	+	+	+	+	−	−	−	+	+
Thymus	+	+	−	+	+	−	−	−	−	+	−	−	−	−	−	−	+	−	−	−	+	−	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma	X				X	X				X	X	X			X		X								
Fibrosarcoma, metastatic																X									
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	N	N	N	N	+	N	N	+	N	+	+	N	+	+	+	+	+	+	+	+	N	+
Pancreas	+	+	−	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	−
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Stomach	+	−	−	−	+	+	+	−	−	−	+	−	−	+	−	+	+	+	+	−	−	+	+	+	+
Small intestine	+	−	−	−	+	−	+	−	−	−	+	−	−	+	−	+	+	+	+	+	+	+	+	+	+
Large intestine	+	−	−	−	+	−	+	+	−	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS															X										
Urinary bladder	+	−	+	−	+	−	+	+	−	−	+	−	−	+	−	−	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	−	−	+	+	−	+	+	−	+	−	+	−	+	−	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	−	+	+	−
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	−
Follicular cell adenoma																									
Parathyroid	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	+	−	+	+	+	−
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	−	+	−	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	−	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
BODY CAVITIES																									
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma, metastatic							X																		
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Alveolar/bronchiolar carcinoma, metastatic																									
Hemangiosarcoma																									
Malignant lymphoma, NOS												X													
Malignant lymphoma, undifferentiated type																									
Malignant lymphoma, histiocytic type																									

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

ANIMAL NUMBER	0 1 0	0 3 4	0 3 5	0 3 8	0 0 6	0 2 7	0 4 4	0 4 5	0 3 6	0 2 1	0 4 0	0 0 4	0 0 7	0 1 5	0 1 7	0 1 8	0 1 9	0 2 0	0 2 8	0 2 9	0 3 0	0 3 3	0 4 2	0 4 3	0 4 8	TOTAL:
WEEKS ON STUDY	0 9 3	0 9 4	0 9 4	0 9 4	0 9 5	0 9 5	0 9 5	0 9 5	0 9 9	1 0 1	1 0 2	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	TISSUES / TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS								X																		1
Fibrosarcoma																						X				3
Neurofibrosarcoma						X																				1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic																										2
Alveolar/bronchiolar adenoma				X									X						X							4
Alveolar/bronchiolar carcinoma					X				X														X		X	4
Fibrosarcoma, metastatic																										2
Trachea	+	−	+	+	+	−	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
HEMATOPOIETIC SYSTEM																										
Bone marrow	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Thymus	−	−	−	+	−	−	+	−	+	−	+	−	+	−	−	+	+	−	−	−	+	−	+	−	+	17
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma												X					X			X				X	X	5
Hepatocellular carcinoma		X											X					X		X		X			X	14
Fibrosarcoma, metastatic																										1
Hemangiosarcoma																			X							1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	N	+	+	+	+	+	+	N	+	+	N	+	+	+	+	N	+	+	N	N	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Esophagus	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Small intestine	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	38
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	42
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, NOS																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	−	+	+	+	−	−	+	+	+	−	+	+	+	+	+	+	+	+	39
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pheochromocytoma											X															1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	45
Follicular cell adenoma																X										1
Parathyroid	−	+	+	+	−	−	+	−	+	−	+	+	+	+	−	+	−	−	−	−	+	+	+	+	+	21
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Prostate	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																									X	1
BODY CAVITIES																										
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma, metastatic																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Alveolar/bronchiolar carcinoma, metast									X																	1
Hemangiosarcoma				X																						1
Malignant lymphoma, NOS																										1
Malignant lymphoma, undiffer type														X												1
Malignant lymphoma, histiocytic type	X																									1

* Animals necropsied

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT

	Vehicle Control	60 mg/kg	120 mg/kg
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	8.3%	12.6%	0.0%
Terminal Rates (c)	2/24 (8%)	2/20 (10%)	0/14 (0%)
Week of First Observation	104	91	
Life Table Tests (d)	P=0.333N	P=0.428	P=0.362N
Incidental Tumor Tests (d)	P=0.268N	P=0.433	P=0.362N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Test (d)		P=0.500	P=0.247N
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	8/50 (16%)	6/50 (12%)	3/50 (6%)
Adjusted Rates (b)	25.0%	24.8%	11.8%
Terminal Rates (c)	2/24 (8%)	4/20 (20%)	1/14 (7%)
Week of First Observation	93	61	80
Life Table Tests (d)	P=0.260N	P=0.527N	P=0.307N
Incidental Tumor Tests (d)	P=0.096N	P=0.417N	P=0.094N
Cochran-Armitage Trend Test (d)	P=0.078N		
Fisher Exact Test (d)		P=0.387N	P=0.100N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	10/50 (20%)	8/50 (16%)	3/50 (6%)
Adjusted Rates (b)	31.9%	31.5%	11.8%
Terminal Rates (c)	4/24 (17%)	5/20 (25%)	1/14 (7%)
Week of First Observation	93	61	80
Life Table Tests (d)	P=0.160N	P=0.554N	P=0.184N
Incidental Tumor Tests (d)	P=0.044N	P=0.454N	P=0.047N
Cochran-Armitage Trend Test (d)	P=0.031N		
Fisher Exact Test (d)		P=0.398N	P=0.036N
Integumentary System: Fibrosarcoma			
Overall Rates (a)	9/50 (18%)	6/50 (12%)	3/50 (6%)
Adjusted Rates (b)	28.5%	24.8%	11.8%
Terminal Rates (c)	3/24 (13%)	4/20 (20%)	1/14 (7%)
Week of First Observation	93	61	80
Life Table Tests (d)	P=0.189N	P=0.429N	P=0.239N
Incidental Tumor Tests (d)	P=0.063N	P=0.320N	P=0.067N
Cochran-Armitage Trend Test (d)	P=0.045N		
Fisher Exact Test (d)		P=0.288N	P=0.061N
Integumentary System: Fibroma or Fibrosarcoma			
Overall Rates (a)	11/50 (22%)	8/50 (16%)	3/50 (6%)
Adjusted Rates (b)	35.3%	31.5%	11.8%
Terminal Rates (c)	5/24 (21%)	5/20 (25%)	1/14 (7%)
Week of First Observation	93	61	80
Life Table Tests (d)	P=0.113N	P=0.464N	P=0.139N
Incidental Tumor Tests (d)	P=0.028N	P=0.364N	P=0.033N
Cochran-Armitage Trend Test (d)	P=0.017N		
Fisher Exact Test (d)		P=0.306N	P=0.020N
Integumentary System: Sarcoma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (a)	12/50 (24%)	10/50 (20%)	5/50 (10%)
Adjusted Rates (b)	35.1%	34.9%	20.2%
Terminal Rates (c)	4/24 (17%)	4/20 (20%)	1/14 (7%)
Week of First Observation	81	61	80
Life Table Tests (d)	P=0.227N	P=0.569N	P=0.252N
Incidental Tumor Tests (d)	P=0.035N	P=0.449N	P=0.042N
Cochran-Armitage Trend Test (d)	P=0.045N		
Fisher Exact Test (d)		P=0.405N	P=0.054N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	60 mg/kg	120 mg/kg
Integumentary System: Fibroma, Sarcoma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (a)	14/50 (28%)	11/50 (22%)	5/50 (10%)
Adjusted Rates (b)	41.6%	38.9%	20.2%
Terminal Rates (c)	6/24 (25%)	5/20 (25%)	1/14 (7%)
Week of First Observation	81	61	80
Life Table Tests (d)	P=0.141N	P=0.504N	P=0.158N
Incidental Tumor Tests (d)	P=0.017N	P=0.385N	P=0.021N
Cochran-Armitage Trend Test (d)	P=0.017N		
Fisher Exact Test (d)		P=0.322N	P=0.020N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	7/47 (15%)	5/50 (10%)	4/49 (8%)
Adjusted Rates (b)	28.8%	20.7%	19.6%
Terminal Rates (c)	6/22 (27%)	3/20 (15%)	2/14 (14%)
Week of First Observation	58	81	70
Life Table Tests (d)	P=0.412N	P=0.451N	P=0.486N
Incidental Tumor Tests (d)	P=0.290N	P=0.393N	P=0.381N
Cochran-Armitage Trend Test (d)	P=0.187N		
Fisher Exact Test (d)		P=0.336N	P=0.238N
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	5/47 (11%)	1/50 (2%)	4/49 (8%)
Adjusted Rates (b)	18.2%	5.0%	23.4%
Terminal Rates (c)	3/22 (14%)	1/20 (5%)	2/14 (14%)
Week of First Observation	79	104	95
Life Table Tests (d)	P=0.516	P=0.131N	P=0.507
Incidental Tumor Tests (d)	P=0.514N	P=0.116N	P=0.607N
Cochran-Armitage Trend Test (d)	P=0.398N		
Fisher Exact Test (d)		P=0.088N	P=0.473N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	10/47 (21%)	5/50 (10%)	8/49 (16%)
Adjusted Rates (b)	36.8%	20.7%	40.1%
Terminal Rates (c)	7/22 (32%)	3/20 (15%)	4/14 (29%)
Week of First Observation	58	81	70
Life Table Tests (d)	P=0.465	P=0.184N	P=0.457
Incidental Tumor Tests (d)	P=0.446N	P=0.137N	P=0.546N
Cochran-Armitage Trend Test (d)	P=0.306N		
Fisher Exact Test (d)		P=0.105N	P=0.360N
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	6.8%	18.1%	4.0%
Terminal Rates (c)	0/24 (0%)	3/20 (15%)	0/14 (0%)
Week of First Observation	96	97	93
Life Table Tests (d)	P=0.553	P=0.261	P=0.681N
Incidental Tumor Tests (d)	P=0.503N	P=0.295	P=0.500N
Cochran-Armitage Trend Test (d)	P=0.406N		
Fisher Exact Test (d)		P=0.339	P=0.500N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	4/50 (8%)	6/50 (12%)	4/50 (8%)
Adjusted Rates (b)	12.9%	25.1%	15.5%
Terminal Rates (c)	1/24 (4%)	4/20 (20%)	1/14 (7%)
Week of First Observation	85	90	86
Life Table Tests (d)	P=0.338	P=0.281	P=0.464
Incidental Tumor Tests (d)	P=0.562N	P=0.315	P=0.569N
Cochran-Armitage Trend Test (d)	P=0.568		
Fisher Exact Test (d)		P=0.370	P=0.643

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	60 mg/kg	120 mg/kg
Liver: Hepatocellular Adenoma			
Overall Rates (a)	4/50 (8%)	6/49 (12%)	5/49 (10%)
Adjusted Rates (b)	14.5%	20.9%	35.7%
Terminal Rates (c)	3/24 (13%)	2/20 (10%)	5/14 (36%)
Week of First Observation	79	44	104
Life Table Tests (d)	P=0.196	P=0.287	P=0.214
Incidental Tumor Tests (d)	P=0.225	P=0.333	P=0.250
Cochran-Armitage Trend Test (d)	P=0.421		
Fisher Exact Test (d)		P=0.357	P=0.487
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	14/50 (28%)	15/49 (31%)	14/49 (29%)
Adjusted Rates (b)	40.5%	42.7%	49.5%
Terminal Rates (c)	6/24 (25%)	5/20 (25%)	5/14 (36%)
Week of First Observation	62	17	65
Life Table Tests (d)	P=0.260	P=0.350	P=0.264
Incidental Tumor Tests (d)	P=0.404N	P=0.513	P=0.490N
Cochran-Armitage Trend Test (d)	P=0.518		
Fisher Exact Test (d)		P=0.474	P=0.563
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	17/50 (34%)	21/49 (43%)	17/49 (35%)
Adjusted Rates (b)	48.3%	56.4%	66.3%
Terminal Rates (c)	8/24 (33%)	7/20 (35%)	8/14 (57%)
Week of First Observation	62	17	65
Life Table Tests (d)	P=0.194	P=0.163	P=0.195
Incidental Tumor Tests (d)	P=0.506N	P=0.263	P=0.577N
Cochran-Armitage Trend Test (d)	P=0.511		
Fisher Exact Test (d)		P=0.242	P=0.555
Harderian Gland: Adenoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	11.5%	10.0%	7.1%
Terminal Rates (c)	2/24 (8%)	2/20 (10%)	1/14 (7%)
Week of First Observation	100	104	104
Life Table Tests (d)	P=0.405N	P=0.584N	P=0.517N
Incidental Tumor Tests (d)	P=0.368N	P=0.567N	P=0.456N
Cochran-Armitage Trend Test (d)	P=0.222N		
Fisher Exact Test (d)		P=0.500N	P=0.309N
Harderian Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	11.5%	15.0%	7.1%
Terminal Rates (c)	2/24 (8%)	3/20 (15%)	1/14 (7%)
Week of First Observation	100	104	104
Life Table Tests (d)	P=0.445N	P=0.576	P=0.517N
Incidental Tumor Tests (d)	P=0.409N	P=0.592	P=0.456N
Cochran-Armitage Trend Test (d)	P=0.238N		
Fisher Exact Test (d)		P=0.661	P=0.309N
All Sites: Benign Tumors			
Overall Rates (a)	19/50 (38%)	16/50 (32%)	11/50 (22%)
Adjusted Rates (b)	66.4%	56.2%	62.5%
Terminal Rates (c)	15/24 (63%)	9/20 (45%)	8/14 (57%)
Week of First Observation	58	44	70
Life Table Tests (d)	P=0.418N	P=0.568N	P=0.491N
Incidental Tumor Tests (d)	P=0.223N	P=0.472N	P=0.303N
Cochran-Armitage Trend Test (d)	P=0.052N		
Fisher Exact Test (d)		P=0.338N	P=0.063N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	60 mg/kg	120 mg/kg
All Sites: Malignant Tumors			
Overall Rates (a)	30/50 (60%)	31/50 (62%)	25/50 (50%)
Adjusted Rates (b)	69.2%	79.6%	76.3%
Terminal Rates (c)	11/24 (46%)	13/20 (65%)	8/14 (57%)
Week of First Observation	62	17	65
Life Table Tests (d)	P=0.279	P=0.256	P=0.312
Incidental Tumor Tests (d)	P=0.094N	P=0.441	P=0.112N
Cochran-Armitage Trend Test (d)	P=0.181N		
Fisher Exact Test (d)		P=0.500	P=0.211N
All Sites: All Tumors			
Overall Rates (a)	39/50 (78%)	37/50 (74%)	31/50 (62%)
Adjusted Rates (b)	88.4%	91.8%	92.8%
Terminal Rates (c)	19/24 (79%)	17/20 (85%)	12/14 (86%)
Week of First Observation	58	17	65
Life Table Tests (d)	P=0.273	P=0.344	P=0.289
Incidental Tumor Tests (d)	P=0.061N	P=0.527N	P=0.066N
Cochran-Armitage Trend Test (d)	P=0.049N		
Fisher Exact Test (d)		P=0.408N	P=0.063N

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

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Mineralization		1 (2%)	
Dilatation, NOS		1 (2%)	
Ulcer, NOS			1 (2%)
Lymphocytic inflammatory infiltrate		1 (2%)	
Abscess, NOS	2 (4%)	1 (2%)	
Inflammation, acute/chronic	3 (6%)	3 (6%)	1 (2%)
Ulcer, chronic	1 (2%)	5 (10%)	3 (6%)
Inflammation, chronic focal			2 (4%)
Inflammation, chronic diffuse	1 (2%)		
Inflammation, chronic suppurative			2 (4%)
Abscess, chronic	1 (2%)	1 (2%)	2 (4%)
Inflammation with fibrosis		4 (8%)	
Fibrosis	1 (2%)		
Fibrosis, focal	4 (8%)	2 (4%)	1 (2%)
Fibrosis, diffuse	3 (6%)	6 (12%)	3 (6%)
Pigmentation, NOS		1 (2%)	31 (62%)
Atrophy, focal		1 (2%)	
Atrophy, diffuse			1 (2%)
Hyperplasia, focal	2 (4%)	1 (2%)	1 (2%)
Hyperplasia, adenomatous	1 (2%)		
Acanthosis	1 (2%)	2 (4%)	2 (4%)
Metaplasia, osseous	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Foreign body, NOS	1 (2%)		
Inflammation, acute suppurative		1 (2%)	
Inflammation, acute/chronic		3 (6%)	
Inflammation, chronic suppurative	1 (2%)		
RESPIRATORY SYSTEM			
#Trachea	(27)	(48)	(40)
Inflammation, acute focal	1 (4%)		
#Tracheal gland	(27)	(48)	(40)
Hyperplasia, focal			1 (3%)
Dysplasia, NOS	1 (4%)		
#Lung/bronchiole	(47)	(50)	(49)
Vegetable foreign body		1 (2%)	
#Lung	(47)	(50)	(49)
Aspiration, foreign body	1 (2%)		
Atelectasis	1 (2%)	1 (2%)	
Congestion, acute	6 (13%)	13 (26%)	9 (18%)
Hemorrhage	4 (9%)	7 (14%)	4 (8%)
Inflammation, interstitial	1 (2%)	4 (8%)	2 (4%)
Inflammation, acute focal			1 (2%)
Inflammation, acute/chronic		1 (2%)	
Fibrosis, focal			1 (2%)
Foreign material, NOS		1 (2%)	
Alveolar macrophages			1 (2%)
Hyperplasia, focal		1 (2%)	
Hyperplasia, alveolar epithelium		1 (2%)	
Histiocytosis		2 (4%)	
#Lung/alveoli	(47)	(50)	(49)
Hemorrhage	1 (2%)		
Inflammation, interstitial		1 (2%)	
Histiocytosis	1 (2%)		

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hematopoiesis		1 (2%)	
*Mediastinum	(50)	(50)	(50)
Hematopoiesis			1 (2%)
*Blood	(50)	(50)	(50)
Leukocytosis, neutrophilic		1 (2%)	1 (2%)
#Bone marrow	(48)	(47)	(45)
Congestion, NOS	1 (2%)		
Congestion, acute	4 (8%)	6 (13%)	8 (18%)
Hemorrhage			1 (2%)
Abscess, NOS			1 (2%)
Necrosis, focal	1 (2%)		
Hypoplasia, NOS	2 (4%)		1 (2%)
Hyperplasia, diffuse	7 (15%)	5 (11%)	11 (24%)
Hyperplasia, erythroid		1 (2%)	
Hyperplasia, granulocytic	5 (10%)	17 (36%)	6 (13%)
#Spleen	(47)	(48)	(50)
Depletion, lymphoid	1 (2%)	1 (2%)	1 (2%)
Hypoplasia, lymphoid			1 (2%)
#Splenic follicles	(47)	(48)	(50)
Necrosis, focal			1 (2%)
Atrophy, diffuse	7 (15%)	4 (8%)	3 (6%)
Hyperplasia, diffuse	1 (2%)		1 (2%)
Hyperplasia, lymphoid	2 (4%)	1 (2%)	2 (4%)
Hypoplasia, lymphoid	1 (2%)	1 (2%)	2 (4%)
#Splenic red pulp	(47)	(48)	(50)
Congestion, acute		1 (2%)	1 (2%)
Hematopoiesis	19 (40%)	20 (42%)	18 (36%)
#Lymph node	(37)	(37)	(41)
Congestion, acute		2 (5%)	
Hemorrhage	1 (3%)	4 (11%)	4 (10%)
Hyperplasia, reticulum cell		1 (3%)	2 (5%)
Hyperplasia, lymphoid		1 (3%)	
Hematopoiesis	1 (3%)	1 (3%)	1 (2%)
Hypoplasia, lymphoid			1 (2%)
#Mandibular lymph node	(37)	(37)	(41)
Hemorrhage	1 (3%)	1 (3%)	1 (2%)
Depletion, lymphoid			1 (2%)
Hyperplasia, reticulum cell	2 (5%)		
Mastocytosis		1 (3%)	
Hypoplasia, lymphoid		1 (3%)	
#Tracheal lymph node	(37)	(37)	(41)
Hemorrhage	1 (3%)		
#Mediastinal lymph node	(37)	(37)	(41)
Histiocytosis			1 (2%)
#Mesenteric lymph node	(37)	(37)	(41)
Edema, NOS			1 (2%)
Hemorrhage	6 (16%)	3 (8%)	7 (17%)
Necrosis, focal			1 (2%)
Histiocytosis	1 (3%)		
Hyperplasia, reticulum cell	1 (3%)		
Hyperplasia, lymphoid		1 (3%)	2 (5%)
Hematopoiesis	1 (3%)	1 (3%)	
Hypoplasia, lymphoid			1 (2%)
#Renal lymph node	(37)	(37)	(41)
Necrosis, focal			1 (2%)
Hyperplasia, lymphoid			1 (2%)
#Inguinal lymph node	(37)	(37)	(41)
Inflammation, chronic focal			1 (2%)

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Lung	(47)	(50)	(49)
Leukocytosis, NOS		2 (4%)	
#Alveolar wall	(47)	(50)	(49)
Leukocytosis, neutrophilic			1 (2%)
#Liver	(50)	(49)	(49)
Leukocytosis, neutrophilic			1 (2%)
Hematopoiesis	4 (8%)	7 (14%)	
#Hepatic sinusoid	(50)	(49)	(49)
Hematopoiesis	1 (2%)		
#Small intestine	(39)	(44)	(38)
Hyperplasia, lymphoid			1 (3%)
#Thymus	(25)	(30)	(17)
Congestion, acute		1 (3%)	
Hemorrhage	1 (4%)		
Inflammation, active chronic	1 (4%)		
Atrophy, diffuse			2 (12%)
#Thymic cortex	(25)	(30)	(17)
Necrosis, NOS		1 (3%)	
#Thymic lymphocytes	(25)	(30)	(17)
Degeneration, NOS	1 (4%)		
Necrosis, NOS		1 (3%)	
Necrosis, diffuse			1 (6%)
CIRCULATORY SYSTEM			
#Heart	(47)	(50)	(50)
Inflammation, acute/chronic		2 (4%)	
#Heart/atrium	(47)	(50)	(50)
Thrombosis, NOS	1 (2%)		
Thrombus, organized			1 (2%)
#Heart/ventricle	(47)	(50)	(50)
Mineralization		1 (2%)	
Histiocytosis		1 (2%)	
#Myocardium	(47)	(50)	(50)
Inflammation, acute/chronic			1 (2%)
Degeneration, NOS		1 (2%)	
Atrophy, focal			1 (2%)
*Renal vein	(50)	(50)	(50)
Inflammation with fibrosis	1 (2%)		
#Prostate	(42)	(44)	(47)
Thrombus, organized	1 (2%)		
DIGESTIVE SYSTEM			
#Salivary gland	(49)	(48)	(49)
Atrophy, focal		5 (10%)	1 (2%)
Atrophy, diffuse	3 (6%)		1 (2%)
#Liver	(50)	(49)	(49)
Congestion, acute		1 (2%)	
Congestion, chronic			1 (2%)
Hemorrhage		1 (2%)	
Inflammation, acute focal			1 (2%)
Inflammation, granulomatous focal			1 (2%)
Inflammation with fibrosis		2 (4%)	
Necrosis, focal	1 (2%)	2 (4%)	
Necrosis, coagulative	3 (6%)	2 (4%)	1 (2%)
Necrosis, ischemic			1 (2%)
Focal cellular change			3 (6%)
Angiectasis	1 (2%)		
#Liver/centrilobular	(50)	(49)	(49)
Degeneration, NOS			1 (2%)
Cytoplasmic vacuolization			2 (4%)

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Liver/hepatocytes	(50)	(49)	(49)
Degeneration, lipoid			1 (2%)
Necrosis, focal			1 (2%)
Focal cellular change	1 (2%)		1 (2%)
Atrophy, focal			1 (2%)
Atrophy, diffuse		1 (2%)	
Hyperplasia, focal			1 (2%)
*Gallbladder	(50)	(50)	(50)
Cyst, NOS			1 (2%)
#Bile duct	(50)	(49)	(49)
Dilatation, NOS	1 (2%)		
Hyperplasia, cystic	1 (2%)		
#Pancreas	(43)	(43)	(45)
Multiple cysts	1 (2%)		
Hemorrhage, chronic	1 (2%)		
Inflammation, suppurative	1 (2%)		
Inflammation, chronic focal	1 (2%)		
Necrosis, ischemic			1 (2%)
Necrosis, fat			1 (2%)
Histiocytosis			1 (2%)
#Pancreatic acinus	(43)	(43)	(45)
Necrosis, focal	1 (2%)		
Focal cellular change		3 (7%)	
Atrophy, focal	5 (12%)	18 (42%)	29 (64%)
Atrophy, diffuse			2 (4%)
*Esophageal lumen	(50)	(50)	(50)
Hemorrhage	1 (2%)		
#Esophagus	(48)	(50)	(48)
Lacerated wound	2 (4%)	1 (2%)	
#Periesophageal tissue	(48)	(50)	(48)
Inflammation, active chronic	1 (2%)		
#Stomach	(44)	(46)	(39)
Inflammation, suppurative		1 (2%)	
Ulcer, acute		1 (2%)	
Inflammation, acute/chronic		1 (2%)	
Inflammation, pyogranulomatous	1 (2%)		
Hyperkeratosis			1 (3%)
Acanthosis	1 (2%)		1 (3%)
#Gastric mucosa	(44)	(46)	(39)
Ulcer, acute	1 (2%)		
#Gastric fundal gland	(44)	(46)	(39)
Metaplasia, NOS			1 (3%)
Metaplasia, squamous	1 (2%)		
#Cardiac stomach	(44)	(46)	(39)
Hyperkeratosis		1 (2%)	
Acanthosis		1 (2%)	
#Small intestine	(39)	(44)	(38)
Inflammation, acute necrotizing	1 (3%)		
Histiocytosis			1 (3%)
#Small intestine/mucous membrane	(39)	(44)	(38)
Atrophy, focal		1 (2%)	1 (3%)
Atrophy, diffuse		1 (2%)	
#Intestinal villus	(39)	(44)	(38)
Atrophy, NOS		1 (2%)	
Atrophy, diffuse		2 (5%)	1 (3%)

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Colon	(43)	(47)	(42)
Parasitism	3 (7%)	4 (9%)	5 (12%)
#Colonic crypt of Lieberkuhn	(43)	(47)	(42)
Atrophy, diffuse			1 (2%)
#Cecum	(43)	(47)	(42)
Inflammation, chronic necrotizing			1 (2%)
Parasitism	1 (2%)		
URINARY SYSTEM			
#Urinary bladder/cavity	(41)	(46)	(41)
Hemorrhage	1 (2%)		
#Kidney	(50)	(47)	(49)
Mineralization	1 (2%)	1 (2%)	
Hydronephrosis		1 (2%)	
Congestion, acute			1 (2%)
Inflammation, interstitial		1 (2%)	
Pyelonephritis, acute	2 (4%)	1 (2%)	4 (8%)
Pyelonephritis, chronic		3 (6%)	2 (4%)
Nephropathy	1 (2%)		
Hyperplasia, tubular cell		1 (2%)	
#Kidney/cortex	(50)	(47)	(49)
Mineralization	2 (4%)		3 (6%)
Cyst, NOS	2 (4%)		1 (2%)
Nephropathy	21 (42%)	17 (36%)	22 (45%)
Infarct, focal	1 (2%)		
Infarct, healed	1 (2%)		
Metaplasia, osseous			1 (2%)
#Kidney/glomerulus	(50)	(47)	(49)
Atrophy, diffuse		1 (2%)	
#Kidney/tubule	(50)	(47)	(49)
Mineralization		1 (2%)	
Dilatation, NOS	1 (2%)	1 (2%)	
Inflammation, acute suppurative		1 (2%)	
Cytoplasmic vacuolization	1 (2%)	1 (2%)	1 (2%)
Atrophy, focal			2 (4%)
Atrophy, diffuse		3 (6%)	
#Kidney/pelvis	(50)	(47)	(49)
Hydronephrosis		2 (4%)	2 (4%)
Inflammation, suppurative		1 (2%)	
Inflammation, chronic focal	1 (2%)		
*Ureter	(50)	(50)	(50)
Inflammation chronic suppurative		1 (2%)	
#Urinary bladder	(41)	(46)	(41)
Lymphocytic inflammatory infiltrate			1 (2%)
Inflammation, acute diffuse	1 (2%)		
Inflammation, chronic focal		1 (2%)	2 (5%)
Inflammation, chronic diffuse		1 (2%)	
Inflammation, chronic necrotizing			2 (5%)
Hyperplasia, epithelial			1 (2%)
#Urinary bladder/mucous membrane	(41)	(46)	(41)
Necrosis, diffuse	1 (2%)		
*Prostatic urethra	(50)	(50)	(50)
Necrosis, NOS	1 (2%)		

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Pituitary	(39)	(40)	(39)
Cyst, NOS	2 (5%)	2 (5%)	1 (3%)
Multiple cysts			1 (3%)
Congestion, acute		1 (3%)	3 (8%)
Hyperplasia, focal			1 (3%)
#Anterior pituitary	(39)	(40)	(39)
Embryonal duct cyst		1 (3%)	
#Adrenal	(44)	(45)	(46)
Hypertrophy, focal		1 (2%)	
Hyperplasia, focal	2 (5%)		
#Adrenal cortex	(44)	(45)	(46)
Lymphocytic inflammatory infiltrate		1 (2%)	
Hypertrophy, focal	2 (5%)	5 (11%)	4 (9%)
#Zona fasciculata	(44)	(45)	(46)
Necrosis, focal			1 (2%)
#Adrenal medulla	(44)	(45)	(46)
Degeneration, NOS			1 (2%)
Hyperplasia, focal		1 (2%)	
#Periadrenal tissue	(44)	(45)	(46)
Hemorrhage		1 (2%)	
#Thyroid	(45)	(48)	(45)
Cyst, NOS			1 (2%)
Hyperplasia, cystic			1 (2%)
Hyperplasia, follicular cell	3 (7%)		
#Thyroid follicle	(45)	(48)	(45)
Atrophy, focal	1 (2%)		
Hyperplasia, cystic		1 (2%)	2 (4%)
#Parathyroid	(13)	(31)	(21)
Thyroglossal duct cyst	1 (8%)		
Hyperplasia, diffuse	1 (8%)		
#Pancreatic islets	(43)	(43)	(45)
Hyperplasia, focal			2 (4%)
REPRODUCTIVE SYSTEM			
*Penis	(50)	(50)	(50)
Inflammation, acute suppurative		1 (2%)	
*Prepuce	(50)	(50)	(50)
Epidermal inclusion cyst	1 (2%)		
Inflammation with fibrosis	1 (2%)		
*Preputial gland	(50)	(50)	(50)
Dilatation, NOS	1 (2%)		
Cyst, NOS	1 (2%)		1 (2%)
Inflammation, acute	1 (2%)		
Inflammation, acute/chronic	1 (2%)		
#Prostate	(42)	(44)	(47)
Mineralization		1 (2%)	
Hemorrhage	1 (2%)		
Inflammation, suppurative	1 (2%)		1 (2%)
Inflammation, acute diffuse		1 (2%)	
Inflammation, acute suppurative	1 (2%)	6 (14%)	6 (13%)
Inflammation, acute/chronic		2 (5%)	2 (4%)
Inflammation, chronic focal		1 (2%)	1 (2%)
Inflammation, chronic suppurative			1 (2%)
Atrophy, diffuse			1 (2%)
*Seminal vesicle	(50)	(50)	(50)
Dilatation, NOS	7 (14%)	2 (4%)	8 (16%)
Hemorrhage	1 (2%)		
Inflammation, chronic focal	1 (2%)		
Inflammation with fibrosis	1 (2%)		
Hyperplasia, focal	2 (4%)		1 (2%)

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM (Continued)			
#Testis	(45)	(44)	(44)
Hemorrhage		1 (2%)	
Metaplasia, osseous			1 (2%)
Dysplasia, NOS		1 (2%)	
#Testis/tubule	(45)	(44)	(44)
Mineralization	1 (2%)	5 (11%)	
Degeneration, NOS	1 (2%)	1 (2%)	1 (2%)
Atrophy, focal			1 (2%)
Atrophy, diffuse		3 (7%)	3 (7%)
*Epididymis	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate		1 (2%)	
Inflammation, acute/chronic	2 (4%)	1 (2%)	2 (4%)
Inflammation, chronic focal	1 (2%)		
Inflammation, chronic suppurative			1 (2%)
Granuloma, spermatic			4 (8%)
Inflammation with fibrosis			1 (2%)
Necrosis, focal			1 (2%)
Atrophy, diffuse			1 (2%)
Hyperplasia, focal	1 (2%)		
*Scrotum	(50)	(50)	(50)
Inflammation, chronic focal			1 (2%)
NERVOUS SYSTEM			
#Brain/meninges	(48)	(48)	(46)
Inflammation, acute/chronic	1 (2%)	1 (2%)	
#Brain/ependyma	(48)	(48)	(46)
Hemorrhage			1 (2%)
#Brain	(48)	(48)	(46)
Mineralization	14 (29%)	15 (31%)	21 (46%)
Hydrocephalus, NOS			1 (2%)
Hemorrhage	1 (2%)		1 (2%)
#Cerebral white matter	(48)	(48)	(46)
Mineralization	1 (2%)		1 (2%)
#Brain/thalamus	(48)	(48)	(46)
Mineralization		1 (2%)	1 (2%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Phthisis bulbi			1 (2%)
*Eye/cornea	(50)	(50)	(50)
Inflammation, chronic suppurative		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Joint of lower extremity	(50)	(50)	(50)
Inflammation, chronic suppurative			1 (2%)
Abscess, chronic	1 (2%)		
*Intercostal muscle	(50)	(50)	(50)
Inflammation, necrotizing granulomatous		1 (2%)	
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Foreign body, NOS	2 (4%)	1 (2%)	
Inflammation, acute suppurative	2 (4%)	1 (2%)	
Inflammation, pyogranulomatous		1 (2%)	

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	Low Dose	High Dose
BODY CAVITIES (Continued)			
*Peritoneum	(50)	(50)	(50)
Necrosis, fat			1 (2%)
*Peritoneal cavity	(50)	(50)	(50)
Abscess, chronic	1 (2%)		
*Pleural cavity	(50)	(50)	(50)
Foreign body, NOS	2 (4%)		
Hemorrhage	1 (2%)		
Inflammation, acute suppurative	2 (4%)		
*Pleura	(50)	(50)	(50)
Inflammation, pyogranulomatous		1 (2%)	
*Subpleural tissue	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate		1 (2%)	
*Mediastinal pleura	(50)	(50)	(50)
Hemorrhage	1 (2%)		
*Pericardial cavity	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Inflammation, chronic suppurative	1 (2%)		
*Pericardium	(50)	(50)	(50)
Inflammation, chronic suppurative		1 (2%)	
*Epicardium	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Inflammation, acute suppurative	1 (2%)		
Inflammation, necrotizing granulomatous		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Congestion, acute	2 (4%)	1 (2%)	1 (2%)
Periorbital region	—	—	—
Inflammation, chronic suppurative			1 ( )
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX D

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT

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TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Trichoepithelioma			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Fibrosarcoma		2 (4%)	1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(49)
Adenocarcinoma, NOS, metastatic			2 (4%)
Alveolar/bronchiolar adenoma	4 (8%)	4 (8%)	2 (4%)
Alveolar/bronchiolar carcinoma	1 (2%)	3 (6%)	2 (4%)
Fibrosarcoma, metastatic		2 (4%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS	3 (6%)	1 (2%)	2 (4%)
Malignant lymphoma, lymphocytic type	1 (2%)	4 (8%)	3 (6%)
Malignant lymphoma, histiocytic type	5 (10%)	2 (4%)	1 (2%)
Malignant lymphoma, mixed type	3 (6%)	7 (14%)	2 (4%)
#Splenic follicles	(47)	(50)	(49)
Malignant lymphoma, histiocytic type			1 (2%)
Malignant lymphoma, mixed type	1 (2%)		
#Mediastinal lymph node	(45)	(41)	(45)
Fibrosarcoma, metastatic		1 (2%)	
#Pancreatic lymph node	(45)	(41)	(45)
Malignant lymphoma, lymphocytic type			1 (2%)
#Mesenteric lymph node	(45)	(41)	(45)
Sarcoma, NOS, unclear primary or metastatic			1 (2%)
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)	
#Bone marrow	(45)	(43)	(46)
Hemangiosarcoma		1 (2%)	
#Spleen	(47)	(50)	(49)
Hemangiosarcoma		1 (2%)	
#Splenic red pulp	(47)	(50)	(49)
Hemangiosarcoma		1 (2%)	
#Ovary	(44)	(45)	(46)
Hemangioma	1 (2%)		
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Hepatocellular adenoma			2 (4%)
Hepatocellular carcinoma	2 (4%)	3 (6%)	3 (6%)
#Cardiac stomach	(46)	(47)	(48)
Squamous cell papilloma	1 (2%)		
URINARY SYSTEM			
None			

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Pituitary	(43)	(40)	(40)
Adenoma, NOS	2 (5%)	4 (10%)	
#Pituitary intermedia	(43)	(40)	(40)
Adenoma, NOS		1 (3%)	1 (3%)
#Adrenal	(48)	(45)	(45)
Pheochromocytoma	1 (2%)		1 (2%)
#Adrenal/capsule	(48)	(45)	(45)
Carcinoma, NOS	1 (2%)		
Adenoma, NOS		1 (2%)	
#Adrenal medulla	(48)	(45)	(45)
Pheochromocytoma			1 (2%)
#Thyroid	(48)	(48)	(44)
Follicular cell adenoma	3 (6%)	3 (6%)	
#Pancreatic islets	(47)	(50)	(48)
Islet cell carcinoma	1 (2%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenocarcinoma, NOS	1 (2%)	2 (4%)	2 (4%)
Fibroadenoma		1 (2%)	
#Uterus	(49)	(48)	(47)
Squamous cell carcinoma, in situ			1 (2%)
Endometrial stromal polyp	1 (2%)		1 (2%)
#Ovary	(44)	(45)	(46)
Papillary cystadenoma, NOS	1 (2%)		
Papillary cystadenocarcinoma NOS		1 (2%)	
Teratoma, NOS		1 (2%)	
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenocarcinoma, NOS			2 (4%)
MUSCULOSKELETAL SYSTEM			
*Bone/lower extremity	(50)	(50)	(50)
Osteoma	1 (2%)		
BODY CAVITIES			
*Thoracic cavity	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic		1 (2%)	
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	6	4	8
Moribund sacrifice	3	7	5
Terminal sacrifice	41	38	30
Accidentally killed, nda		1	7

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	27	31	26
Total primary tumors	35	44	31
Total animals with benign tumors	15	13	9
Total benign tumors	15	14	9
Total animals with malignant tumors	18	23	20
Total malignant tumors	20	29	21
Total animals with secondary tumors##		3	2
Total secondary tumors		4	2
Total animals with tumors uncertain--benign or malignant		1	
Total uncertain tumors		1	
Total animals with tumors uncertain--primary or metastatic			1
Total uncertain tumors			1

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

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT: VEHICLE CONTROL

ANIMAL NUMBER	04747	04744	04040	02828	03030	01010	03737	02020	03939	00101	00202	00303	00404	00505	00606	00707	00808	00909	01101	01212	01313	01414	01505	01616	01717
WEEKS ON STUDY	04646	07373	07707	08282	08899	09393	09393	09595	10303	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X					X				X										
Alveolar/bronchiolar carcinoma																									X
Trachea	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+
Spleen	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Malignant lymphoma, mixed type																									
Lymph nodes	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Thymus	+	+	−	+	−	−	−	+	−	−	+	+	+	−	+	−	+	+	+	−	+	+	−	+	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma		X																							
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	+	+	+	N	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	−	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	−	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma		X																							
Small intestine	−	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	−	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	−	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Adenoma, NOS													X												X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Pheochromocytoma																									
Thyroid	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma									X														X		
Parathyroid	−	−	−	−	−	+	−	−	+	+	+	+	+	+	+	−	−	−	+	+	+	+	−	+	−
Pancreatic islets	−	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	+
Adenocarcinoma, NOS							X																		
Uterus	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																									
Ovary	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Papillary cystadenoma, NOS																						X			
Hemangioma																								X	
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangiosarcoma									X																
Malignant lymphoma, NOS	X				X																		X		
Malignant lymphoma, lymphocytic type																									
Malignant lymphoma, histiocytic type			X					X												X					X
Malignant lymphoma, mixed type			X																						

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

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

ANIMAL NUMBER	0 1 8	0 1 9	0 2 1	0 2 2	0 2 3	0 2 4	0 2 5	0 2 6	0 2 7	0 2 9	0 3 1	0 3 2	0 3 3	0 3 4	0 3 5	0 3 6	0 3 8	0 4 1	0 4 2	0 4 3	0 4 5	0 4 6	0 4 8	0 4 9	0 5 0	TOTAL TISSUES TUMORS
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X																							4
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Malignant lymphoma, mixed type			X																							1
Lymph nodes	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	45
Thymus	+	+	+	−	+	+	+	+	+	−	−	+	+	+	+	+	+	+	−	+	+	+	+	+	−	34
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																							X			2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	46
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	45
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	43
Adenoma, NOS																										2
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS																							X			1
Pheochromocytoma																								X		1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma		X																								3
Parathyroid	+	−	+	−	+	−	−	+	−	+	−	+	−	+	+	+	−	+	+	−	+	+	+	+	+	29
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Islet cell carcinoma												X														1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	N	N	N	N	N	N	N	N	+	+	N	+	N	N	+	N	+	N	N	N	N	N	+	*50
Adenocarcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endometrial stromal polyp																									X	1
Ovary	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	−	+	44
Papillary cystadenoma, NOS																										1
Hemangioma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	49
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteoma											X															1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangiosarcoma																										1
Malignant lymphoma, NOS																										3
Malignant lymphoma, lymphocytic type					X																					1
Malignant lymphoma, histiocytic type	X																									5
Malignant lymphoma, mixed type										X											X					3

* Animals necropsied

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

ANIMAL NUMBER	042	008	025	037	018	038	015	013	026	046	049	021	001	092	003	004	005	006	007	009	010	011	012	014	016
WEEKS ON STUDY	035	065	072	078	080	080	095	097	099	100	100	103	105	105	105	105	105	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Hemangiosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X													X						
Alveolar/bronchiolar carcinoma															X					X					
Fibrosarcoma, metastatic																									
Trachea	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	−	−	+	+
Hemangiosarcoma				X																					
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X																X					
Lymph nodes	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	−	+	+	+	+	+	−
Fibrosarcoma, metastatic																									
Thymus	+	−	−	+	−	+	+	−	−	+	−	−	+	+	+	−	+	+	+	+	−	+	−	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																		X							
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	N	+	N	N	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	N	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	−	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Adenoma, NOS																				X					X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Adenoma, NOS																									
Thyroid	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																					X		X		
Parathyroid	−	+	+	−	+	−	+	−	+	+	−	+	+	+	−	−	−	+	+	+	−	+	+	+	−
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	+	N	N	N	+	N	N	N	+	+	N	N	N	N	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS								X				X													
Fibroadenoma																									
Uterus	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Ovary	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+
Papillary cystadenocarcinoma, NOS															X										
Teratoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BODY CAVITIES																									
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Alveolar/bronchiolar carcinoma, metastatic															X										
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS								X																	
Malignant lymphoma, lymphocytic type		X				X																			
Malignant lymphoma, histiocytic type							X				X													X	
Malignant lymphoma, mixed type																									

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

ANIMAL NUMBER	0 1 7	0 1 9	0 2 0	0 2 2	0 2 3	0 2 4	0 2 7	0 2 8	0 2 9	0 3 0	0 3 1	0 3 2	0 3 3	0 3 4	0 3 5	0 3 6	0 3 9	0 4 0	0 4 1	0 4 3	0 4 4	0 4 5	0 4 7	0 4 8	0 5 0	TOTAL. TISSUES TUMORS
WEEKS ON STUDY	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma							X														X					2
Hemangiosarcoma																							X			1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X										X										4
Alveolar/bronchiolar carcinoma							X																			3
Fibrosarcoma, metastatic							X														X					2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	43
Hemangiosarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										2
Lymph nodes	−	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	41
Fibrosarcoma, metastatic																					X					1
Thymus	+	+	−	+	+	+	+	−	+	+	−	−	+	−	+	+	−	+	−	+	−	+	+	+	+	32
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma									X													X				3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	−	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	−	+	−	+	−	+	+	40
Adenoma, NOS						X						X										X				5
Adrenal	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	−	+	−	+	+	45
Adenoma, NOS																			X							1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma																							X			3
Parathyroid	−	+	+	+	+	−	+	−	+	−	+	+	+	−	+	+	+	+	+	−	−	+	+	+	−	32
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	*50
Adenocarcinoma, NOS																										2
Fibroadenoma					X																					1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Ovary	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Papillary cystadenocarcinoma, NOS																										1
Teratoma, NOS											X															1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
BODY CAVITIES																										
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Alveolar/bronchiolar carcinoma, metast																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS												X														1
Malignant lymphoma, lymphocytic type													X	X											X	4
Malignant lymphoma, histiocytic type																	X		X		X			X		2
Malignant lymphoma, mixed type																										7

* Animals necropsied

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

ANIMAL NUMBER	037	009	002	030	028	034	035	026	013	011	010	014	046	047	048	049	050	016	023	039	001	004	005	006	007
WEEKS ON STUDY	052	074	077	077	081	081	081	083	084	090	092	093	094	094	094	094	094	098	099	100	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+
Trichoepithelioma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+
Fibrosarcoma																				X					
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Adenocarcinoma, NOS, metastatic				X																					
Alveolar/bronchiolar adenoma													X												
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	−	−	−	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, histiocytic type																									
Lymph nodes	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	−	+	+	+	−	+	+	+
Sarcoma, NOS, unclear primary or metastatic																									
Malignant lymphoma, lymphocytic type																									
Thymus	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	~	+	+	+	+	+	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																							X		
Hepatocellular carcinoma																		X							
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	+	N	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+
Pancreas	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Stomach	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
Urinary bladder	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	−	+	~	+	+	+	−	+	+	−
Adenoma, NOS								X																	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	~	+	+	+	+	−	+	+
Pheochromocytoma																								X	
Thyroid	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	−
Parathyroid	−	+	+	−	+	−	+	−	+	−	−	+	+	+	+	−	+	+	−	−	+	−	−	−	−
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	+	N	N	+	+	+	N	+	N	N	N	N	N	N	N	+	N	+	N	N	N	N
Adenocarcinoma, NOS				X															X						
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Squamous cell carcinoma, in situ																									
Endometrial stromal polyp																				X					
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS																									X
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS										X															
Malignant lymphoma, lymphocytic type		X									X												X		
Malignant lymphoma, histiocytic type									X																
Malignant lymphoma, mixed type								X										X							

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

ANIMAL NUMBER	0008	0009	0012	0015	0017	0018	0019	0020	0021	0022	0024	0025	0027	0029	0031	0032	0033	0036	0038	0040	0041	0042	0043	0044	0045	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Trichoepithelioma																									X	1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS, metastatic																			X							2
Alveolar/bronchiolar adenoma																X										2
Alveolar/bronchiolar carcinoma																							X		X	2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	42
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, histiocytic type					X																					1
Lymph nodes	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Sarcoma, NOS, unclear primary or meta										X																1
Malignant lymphoma, lymphocytic type									X																	1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	44
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X																									2
Hepatocellular carcinoma						X														X						3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	45
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	−	−	+	+	+	40
Adenoma, NOS																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	−	+	+	+	+	45
Pheochromocytoma															X											2
Thyroid	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	44
Parathyroid	+	+	−	+	−	+	−	+	+	+	+	−	+	+	+	−	−	+	−	+	+	−	+	+	+	29
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenocarcinoma, NOS																										2
Uterus	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	47
Squamous cell carcinoma, in situ																	X									1
Endometrial stromal polyp																										1
Ovary	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	46
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenocarcinoma, NOS																			X							2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS																							X			2
Malignant lymphoma, lymphocytic type																										3
Malignant lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type																										2

* Animals necropsied

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT

	Vehicle Control	60 mg/kg	120 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	4/50 (8%)	4/50 (8%)	2/49 (4%)
Adjusted Rates (b)	9.4%	9.9%	6.0%
Terminal Rates (c)	3/41 (7%)	3/38 (8%)	1/29 (3%)
Week of First Observation	93	80	94
Life Table Tests (d)	P=0.400N	P=0.607	P=0.470N
Incidental Tumor Tests (d)	P=0.243N	P=0.638	P=0.319N
Cochran-Armitage Trend Test (d)	P=0.282N		
Fisher Exact Test (d)		P=0.643	P=0.349N
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	2/49 (4%)
Adjusted Rates (b)	2.4%	7.9%	6.9%
Terminal Rates (c)	1/41 (2%)	3/38 (8%)	2/29 (7%)
Week of First Observation	104	105	104
Life Table Tests (d)	P=0.270	P=0.278	P=0.380
Incidental Tumor Tests (d)	P=0.270	P=0.278	P=0.380
Cochran-Armitage Trend Test (d)	P=0.391		
Fisher Exact Test (d)		P=0.309	P=0.492
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	7/50 (14%)	4/49 (8%)
Adjusted Rates (b)	11.8%	17.6%	12.7%
Terminal Rates (c)	4/41 (10%)	6/38 (16%)	3/29 (10%)
Week of First Observation	93	80	94
Life Table Tests (d)	P=0.495	P=0.335	P=0.592
Incidental Tumor Tests (d)	P=0.495N	P=0.360	P=0.561N
Cochran-Armitage Trend Test (d)	P=0.449N		
Fisher Exact Test (d)		P=0.380	P=0.513N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	1/50 (2%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	2.4%	10.0%	10.9%
Terminal Rates (c)	1/41 (2%)	3/38 (8%)	2/30 (7%)
Week of First Observation	104	97	74
Life Table Tests (d)	P=0.088	P=0.165	P=0.127
Incidental Tumor Tests (d)	P=0.167	P=0.187	P=0.210
Cochran-Armitage Trend Test (d)	P=0.146		
Fisher Exact Test (d)		P=0.181	P=0.181
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	5/50 (10%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	11.4%	4.2%	5.6%
Terminal Rates (c)	3/41 (7%)	0/38 (0%)	1/30 (3%)
Week of First Observation	77	65	84
Life Table Tests (d)	P=0.206N	P=0.238N	P=0.321N
Incidental Tumor Tests (d)	P=0.062N	P=0.161N	P=0.156N
Cochran-Armitage Trend Test (d)	P=0.146N		
Fisher Exact Test (d)		P=0.218N	P=0.218N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	4/50 (8%)	7/50 (14%)	2/50 (4%)
Adjusted Rates (b)	9.3%	17.2%	5.3%
Terminal Rates (c)	3/41 (7%)	5/38 (13%)	0/30 (0%)
Week of First Observation	82	95	83
Life Table Tests (d)	P=0.446N	P=0.233	P=0.444N
Incidental Tumor Tests (d)	P=0.192N	P=0.273	P=0.180N
Cochran-Armitage Trend Test (d)	P=0.297N		
Fisher Exact Test (d)		P=0.262	P=0.339N

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	60 mg/kg	120 mg/kg
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	13/50 (26%)	14/50 (28%)	10/50 (20%)
Adjusted Rates (b)	27.8%	31.9%	25.3%
Terminal Rates (c)	8/41 (20%)	9/38 (24%)	4/30 (13%)
Week of First Observation	46	65	74
Life Table Tests (d)	P=0.519N	P=0.442	P=0.534N
Incidental Tumor Tests (d)	P=0.102N	P=0.550	P=0.119N
Cochran-Armitage Trend Test (d)	P=0.281N		
Fisher Exact Test (d)		P=0.500	P=0.318N
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	2.4%	7.3%	0.0%
Terminal Rates (c)	0/41 (0%)	2/38 (5%)	0/30 (0%)
Week of First Observation	103	78	
Life Table Tests (d)	P=0.455N	P=0.288	P=0.567N
Incidental Tumor Tests (d)	P=0.332N	P=0.366	P=0.338N
Cochran-Armitage Trend Test (d)	P=0.378N		
Fisher Exact Test (d)		P=0.309	P=0.500N
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	4.8%	7.3%	0.0%
Terminal Rates (c)	1/41 (2%)	2/38 (5%)	0/30 (0%)
Week of First Observation	103	78	
Life Table Tests (d)	P=0.272N	P=0.473	P=0.313N
Incidental Tumor Tests (d)	P=0.184N	P=0.552	P=0.182N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Test (d)		P=0.500	P=0.247N
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	4.4%	7.9%	9.5%
Terminal Rates (c)	1/41 (2%)	3/38 (8%)	2/30 (7%)
Week of First Observation	73	105	98
Life Table Tests (d)	P=0.298	P=0.469	P=0.395
Incidental Tumor Tests (d)	P=0.373	P=0.509	P=0.522
Cochran-Armitage Trend Test (d)	P=0.412		
Fisher Exact Test (d)		P=0.500	P=0.500
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	5/50 (10%)
Adjusted Rates (b)	4.4%	7.9%	16.0%
Terminal Rates (c)	1/41 (2%)	3/38 (8%)	4/30 (13%)
Week of First Observation	73	105	98
Life Table Tests (d)	P=0.085	P=0.469	P=0.130
Incidental Tumor Tests (d)	P=0.117	P=0.509	P=0.194
Cochran-Armitage Trend Test (d)	P=0.158		
Fisher Exact Test (d)		P=0.500	P=0.218
Pituitary Gland: Adenoma			
Overall Rates (a)	2/43 (5%)	4/40 (10%)	0/40 (0%)
Adjusted Rates (b)	5.6%	12.9%	0.0%
Terminal Rates (c)	2/36 (6%)	4/31 (13%)	0/24 (0%)
Week of First Observation	104	105	
Life Table Tests (d)	P=0.355N	P=0.269	P=0.331N
Incidental Tumor Tests (d)	P=0.355N	P=0.269	P=0.331N
Cochran-Armitage Trend Test (d)	P=0.245N		
Fisher Exact Test (d)		P=0.304	P=0.265N

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT (Continued)

	Vehicle Control	60 mg/kg	120 mg/kg
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	3/48 (6%)	3/48 (6%)	0/44 (0%)
Adjusted Rates (b)	7.3%	7.9%	0.0%
Terminal Rates (c)	2/40 (5%)	3/38 (8%)	0/26 (0%)
Week of First Observation	103	105	
Life Table Tests (d)	P=0.182N	P=0.636	P=0.202N
Incidental Tumor Tests (d)	P=0.139N	P=0.651N	P=0.126N
Cochran-Armitage Trend Test (d)	P=0.115N		
Fisher Exact Test (d)		P=0.661	P=0.138N
All Sites: Benign Tumors			
Overall Rates (a)	15/50 (30%)	13/50 (26%)	9/50 (18%)
Adjusted Rates (b)	33.9%	33.1%	26.4%
Terminal Rates (c)	12/41 (29%)	12/38 (32%)	6/30 (20%)
Week of First Observation	73	80	83
Life Table Tests (d)	P=0.309N	P=0.499N	P=0.347N
Incidental Tumor Tests (d)	P=0.140N	P=0.440N	P=0.141N
Cochran-Armitage Trend Test (d)	P=0.101N		
Fisher Exact Test (d)		P=0.412N	P=0.121N
All Sites: Malignant Tumors			
Overall Rates (a)	18/50 (36%)	23/50 (46%)	20/50 (40%)
Adjusted Rates (b)	36.6%	50.7%	49.9%
Terminal Rates (c)	10/41 (24%)	16/38 (42%)	11/30 (37%)
Week of First Observation	46	65	74
Life Table Tests (d)	P=0.131	P=0.183	P=0.172
Incidental Tumor Tests (d)	P=0.472N	P=0.280	P=0.484N
Cochran-Armitage Trend Test (d)	P=0.380		
Fisher Exact Test (d)		P=0.208	P=0.418
All Sites: All Tumors			
Overall Rates (a)	27/50 (54%)	31/50 (62%)	26/50 (52%)
Adjusted Rates (b)	54.0%	68.6%	64.1%
Terminal Rates (c)	18/41 (44%)	24/38 (63%)	16/30 (53%)
Week of First Observation	46	65	74
Life Table Tests (d)	P=0.175	P=0.212	P=0.230
Incidental Tumor Tests (d)	P=0.361N	P=0.329	P=0.346N
Cochran-Armitage Trend Test (d)	P=0.460N		
Fisher Exact Test (d)		P=0.272	P=0.500N

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

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF MALONALDEHYDE, SODIUM SALT

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Abscess, NOS	1 (2%)		
Inflammation, acute/chronic		1 (2%)	
Ulcer, chronic			1 (2%)
Inflammation, chronic suppurative			1 (2%)
Fibrosis, diffuse			1 (2%)
Pigmentation, NOS	2 (4%)		27 (54%)
Acanthosis		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Metaplasia, cartilaginous	1 (2%)		
RESPIRATORY SYSTEM			
#Peritracheal tissue	(47)	(47)	(42)
Inflammation, acute focal			1 (2%)
#Lung/bronchiole	(50)	(50)	(49)
Vegetable foreign body			1 (2%)
#Lung	(50)	(50)	(49)
Congestion, acute	1 (2%)	6 (12%)	3 (6%)
Hemorrhage	6 (12%)	5 (10%)	3 (6%)
Inflammation, interstitial		1 (2%)	1 (2%)
Pneumonia, giant cell	1 (2%)		
Pneumonia, aspiration			1 (2%)
Hyperplasia, alveolar epithelium		1 (2%)	
Histiocytosis	2 (4%)	2 (4%)	2 (4%)
#Lung/alveoli	(50)	(50)	(49)
Histiocytosis			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hematopoiesis			1 (2%)
*Skin	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)		
#Bone marrow	(45)	(43)	(46)
Congestion, acute	2 (4%)	4 (9%)	2 (4%)
Necrosis, focal	1 (2%)		
Hypoplasia, NOS	2 (4%)	3 (7%)	6 (13%)
Atrophy, focal		1 (2%)	
Hyperplasia, focal		1 (2%)	
Hyperplasia, diffuse	9 (20%)	5 (12%)	1 (2%)
Myelofibrosis			1 (2%)
Hyperplasia, granulocytic	3 (7%)	6 (14%)	3 (7%)
#Splenic follicles	(47)	(50)	(49)
Atrophy, diffuse	4 (9%)	4 (8%)	3 (6%)
Hyperplasia, diffuse	2 (4%)	2 (4%)	2 (4%)
Hyperplasia, reticulum cell		1 (2%)	
Hyperplasia, lymphoid	6 (13%)	9 (18%)	13 (27%)
Hypoplasia, lymphoid		2 (4%)	3 (6%)
#Splenic red pulp	(47)	(50)	(49)
Congestion, acute	2 (4%)		1 (2%)
Pigmentation, NOS	2 (4%)		
Hyperplasia, lymphoid	1 (2%)		
Hematopoiesis	18 (38%)	20 (40%)	15 (31%)

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

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Lymph node	(45)	(41)	(45)
Congestion, acute			1 (2%)
Hemorrhage			1 (2%)
Inflammation, chronic focal			1 (2%)
Hyperplasia, reticulum cell			1 (2%)
Hyperplasia, lymphoid	1 (2%)	2 (5%)	
#Mandibular lymph node	(45)	(41)	(45)
Hyperplasia, plasma cell	1 (2%)		
Hyperplasia, reticulum cell	1 (2%)		
Hyperplasia, lymphoid		2 (5%)	1 (2%)
#Tracheal lymph node	(45)	(41)	(45)
Hyperplasia, lymphoid			1 (2%)
#Mediastinal lymph node	(45)	(41)	(45)
Hyperplasia, lymphoid		1 (2%)	
#Mesenteric lymph node	(45)	(41)	(45)
Hemorrhage			1 (2%)
Hemorrhage, chronic			1 (2%)
Inflammation, acute suppurative			1 (2%)
Inflammation, chronic suppurative			1 (2%)
Hematopoiesis			1 (2%)
#Renal lymph node	(45)	(41)	(45)
Hemorrhage			1 (2%)
Hyperplasia, lymphoid	1 (2%)		
#Lung	(50)	(50)	(49)
Leukocytosis, NOS			1 (2%)
Hyperplasia, lymphoid		2 (4%)	
#Liver	(50)	(50)	(50)
Hyperplasia, lymphoid	2 (4%)		2 (4%)
Hematopoiesis	2 (4%)	3 (6%)	2 (4%)
#Pancreas	(47)	(50)	(48)
Hyperplasia, lymphoid		1 (2%)	2 (4%)
#Pancreatic interstitial tissue	(47)	(50)	(48)
Hyperplasia, lymphoid	2 (4%)		
#Peyer's patch	(45)	(48)	(49)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	1 (2%)
#Kidney	(50)	(49)	(49)
Hyperplasia, lymphoid	2 (4%)		1 (2%)
#Kidney/cortex	(50)	(49)	(49)
Hyperplasia, lymphoid		1 (2%)	
#Kidney/pelvis	(50)	(49)	(49)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	
#Ovary	(44)	(45)	(46)
Hyperplasia, lymphoid		1 (2%)	
#Adrenal	(48)	(45)	(45)
Hematopoiesis			1 (2%)
#Thymus	(34)	(32)	(44)
Cyst, NOS		1 (3%)	
Hemorrhage	1 (3%)		
Depletion, lymphoid			1 (2%)
Histiocytosis			1 (2%)
#Thymic medulla	(34)	(32)	(44)
Hyperplasia, focal	1 (3%)		
Hyperplasia, lymphoid	1 (3%)		1 (2%)
#Thymic lymphocytes	(34)	(32)	(44)
Necrosis, diffuse			1 (2%)
CIRCULATORY SYSTEM			
#Lung	(50)	(50)	(49)
Arteriosclerosis, NOS			1 (2%)
#Heart	(50)	(50)	(49)
Periarteritis		1 (2%)	1 (2%)

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

	Vehicle Control	Low Dose	High Dose
CIRCULATORY SYSTEM (Continued)			
#Heart/atrium	(50)	(50)	(49)
Thrombus, organized			1 (2%)
#Heart/ventricle	(50)	(50)	(49)
Inflammation, acute/chronic		1 (2%)	
#Liver	(50)	(50)	(50)
Thrombus, organized	1 (2%)	1 (2%)	
#Urinary bladder	(46)	(47)	(45)
Periarteritis		1 (2%)	
#Uterus/endometrium	(49)	(48)	(47)
Thrombus, organized	1 (2%)		
#Thyroid	(48)	(48)	(44)
Periarteritis		1 (2%)	
DIGESTIVE SYSTEM			
#Salivary gland	(47)	(48)	(46)
Atrophy, focal	4 (9%)	3 (6%)	8 (17%)
Atrophy, serous	1 (2%)	3 (6%)	
#Salivary gland interstitial tissue	(47)	(48)	(46)
Inflammation, acute/chronic	1 (2%)		
#Liver	(50)	(50)	(50)
Congestion, acute			4 (8%)
Hemorrhage	2 (4%)		1 (2%)
Inflammation, acute/chronic	11 (22%)	5 (10%)	2 (4%)
Degeneration, lipoid			1 (2%)
Necrosis, focal	1 (2%)		
Infarct, focal		1 (2%)	
Pigmentation, NOS		1 (2%)	
Focal cellular change	1 (2%)		
Hyperplasia, nodular		1 (2%)	
Histiocytosis		1 (2%)	
#Liver/centrilobular	(50)	(50)	(50)
Degeneration, lipoid			1 (2%)
Necrosis, diffuse		1 (2%)	
Atrophy, diffuse			1 (2%)
#Liver/hepatocytes	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Degeneration, lipoid			1 (2%)
Necrosis, focal		1 (2%)	2 (4%)
Necrosis, coagulative	1 (2%)		
Necrosis, ischemic	2 (4%)		
Cytoplasmic vacuolization			1 (2%)
Focal cellular change		2 (4%)	
Atrophy, diffuse	1 (2%)		
Dysplasia, NOS	2 (4%)	1 (2%)	
*Gallbladder	(50)	(50)	(50)
Hyperplasia, cystic	1 (2%)		
#Bile duct	(50)	(50)	(50)
Hyperplasia, focal	1 (2%)		
#Pancreas	(47)	(50)	(48)
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic suppurative	1 (2%)		
Necrosis, fat			1 (2%)
#Pancreatic duct	(47)	(50)	(48)
Necrosis, NOS			1 (2%)
#Pancreatic acinus	(47)	(50)	(48)
Inflammation with fibrosis			1 (2%)
Atrophy, focal	7 (15%)	25 (50%)	41 (85%)
Atrophy, diffuse	1 (2%)	1 (2%)	
Hyperplasia, focal			1 (2%)

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

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Periesophageal tissue	(50)	(49)	(48)
Foreign body, NOS		1 (2%)	
Inflammation, acute suppurative		1 (2%)	
#Stomach	(46)	(47)	(48)
Mineralization	1 (2%)		
Ulcer, NOS		1 (2%)	
Inflammation, acute suppurative		1 (2%)	
Inflammation, acute/chronic			1 (2%)
Inflammation with fibrosis		1 (2%)	
Hyperkeratosis	2 (4%)		
Acanthosis	2 (4%)	1 (2%)	
Metaplasia, NOS		1 (2%)	
Metaplasia, squamous		1 (2%)	
#Gastric mucosa	(46)	(47)	(48)
Inflammation, acute/chronic		1 (2%)	
Acanthosis		1 (2%)	
#Gastric fundal gland	(46)	(47)	(48)
Dilatation, NOS			1 (2%)
Edema, NOS	1 (2%)		
Atrophy, focal	1 (2%)		
Hyperplasia, focal	1 (2%)		
#Forestomach	(46)	(47)	(48)
Hyperplasia, epithelial		1 (2%)	
#Cardiac stomach	(46)	(47)	(48)
Inflammation, acute/chronic			1 (2%)
#Small intestine	(45)	(48)	(49)
Parasitism			1 (2%)
Atrophy, focal		1 (2%)	
Atrophy, pressure		1 (2%)	
#Intestinal villus	(45)	(48)	(49)
Atrophy, focal			1 (2%)
#Colon	(45)	(48)	(48)
Parasitism	2 (4%)	1 (2%)	2 (4%)
URINARY SYSTEM			
#Kidney	(50)	(49)	(49)
Glomerulonephritis, membranous	1 (2%)		
Glomerulonephritis, chronic	2 (4%)		
#Kidney/cortex	(50)	(49)	(49)
Glomerulonephritis, membranous		1 (2%)	
Inflammation, acute/chronic	1 (2%)		
Nephropathy	11 (22%)	9 (18%)	12 (24%)
Infarct, healed	1 (2%)		
Metaplasia, osseous			1 (2%)
#Kidney/tubule	(50)	(49)	(49)
Mineralization	1 (2%)		
Degeneration, NOS	1 (2%)		
Degeneration, granular		1 (2%)	
Atrophy, focal	1 (2%)		
*Ureter	(50)	(50)	(50)
Mineralization	1 (2%)		
#Urinary bladder	(46)	(47)	(45)
Congestion, acute	1 (2%)		
ENDOCRINE SYSTEM			
#Pituitary	(43)	(40)	(40)
Cyst, NOS		3 (8%)	3 (8%)
Hemorrhage		1 (3%)	
Hemorrhagic cyst	3 (7%)		
Hemorrhage, chronic			1 (3%)

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Pituitary (Continued)	(43)	(40)	(40)
Hypertrophy, focal		1 (3%)	
Hyperplasia, focal	6 (14%)	2 (5%)	
Hyperplasia, chromophobe cell	3 (7%)		
#Anterior pituitary	(43)	(40)	(40)
Hyperplasia, focal	1 (2%)		
#Adrenal	(48)	(45)	(45)
Hemorrhage		1 (2%)	
Inflammation, acute suppurative		1 (2%)	
#Adrenal/capsule	(48)	(45)	(45)
Fibrosis, focal	1 (2%)		
#Adrenal cortex	(48)	(45)	(45)
Congestion, NOS			1 (2%)
Congestion, acute			1 (2%)
Degeneration, NOS		1 (2%)	
Hypertrophy, focal	2 (4%)	2 (4%)	1 (2%)
#Thyroid	(48)	(48)	(44)
Embryonal duct cyst		1 (2%)	
Cyst, NOS	1 (2%)	1 (2%)	
Hyperplasia, follicular cell	3 (6%)	3 (6%)	
Histiocytosis	1 (2%)		
#Thyroid follicle	(48)	(48)	(44)
Atrophy, focal		1 (2%)	
Atrophy, diffuse			1 (2%)
REPRODUCTIVE SYSTEM			
#Uterus	(49)	(48)	(47)
Dilatation, NOS		12 (25%)	16 (34%)
Hemorrhage		2 (4%)	
Inflammation, suppurative			1 (2%)
Inflammation, acute suppurative	2 (4%)		
Polypoid hyperplasia		1 (2%)	
#Uterus/endometrium	(49)	(48)	(47)
Edema, NOS			1 (2%)
Hemorrhage	1 (2%)		
Inflammation, acute suppurative	2 (4%)		
Hypoplasia, NOS		2 (4%)	2 (4%)
Atrophy, focal			1 (2%)
Hyperplasia, focal			1 (2%)
Hyperplasia, diffuse		2 (4%)	2 (4%)
Hyperplasia, cystic	45 (92%)	42 (88%)	31 (66%)
#Uterus/myometrium	(49)	(48)	(47)
Inflammation, acute/chronic	1 (2%)		
#Ovary/parovarian	(44)	(45)	(46)
Hemorrhagic cyst			1 (2%)
#Ovary	(44)	(45)	(46)
Dilatation, NOS		1 (2%)	
Cyst, NOS	10 (23%)	10 (22%)	8 (17%)
Follicular cyst, NOS			1 (2%)
Multiple cysts	2 (5%)		
Hemorrhage	1 (2%)		
Hemorrhagic cyst	2 (5%)	2 (4%)	2 (4%)
Inflammation, acute suppurative	2 (5%)		
Necrosis, fat		1 (2%)	1 (2%)
Pigmentation, NOS			3 (7%)
Atrophy, senile			1 (2%)
Hyperplasia, cystic		2 (4%)	
Histiocytosis	1 (2%)		
#Ovary/follicle	(44)	(45)	(46)
Hemorrhagic cyst	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
NERVOUS SYSTEM			
#Brain/meninges	(49)	(48)	(50)
Hemorrhage	1 (2%)		
Inflammation, acute/chronic	3 (6%)		
Fibrosis, multifocal			1 (2%)
#Brain	(49)	(48)	(50)
Mineralization	10 (20%)	18 (38%)	20 (40%)
Inflammation, acute/chronic			1 (2%)
SPECIAL SENSE ORGANS			
*Eye/cornea	(50)	(50)	(50)
Inflammation, acute diffuse			1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Foreign body, NOS			2 (4%)
Hemorrhage			1 (2%)
Inflammation, acute suppurative			2 (4%)
Inflammation, chronic focal			1 (2%)
*Peritoneum	(50)	(50)	(50)
Necrosis, fat	2 (4%)		
*Peritoneal cavity	(50)	(50)	(50)
Necrosis, fat	1 (2%)	3 (6%)	1 (2%)
*Pleural cavity	(50)	(50)	(50)
Foreign body, NOS			1 (2%)
Hematoma, organized			1 (2%)
Inflammation, acute suppurative			1 (2%)
*Pleural mesothelium	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	
*Epicardium	(50)	(50)	(50)
Inflammation, acute/chronic			1 (2%)
ALL OTHER SYSTEMS			
None			
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX E

GENETIC TOXICOLOGY OF

MALONALDEHYDE, SODIUM SALT

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TABLE E1. MUTAGENICITY OF MALONALDEHYDE, SODIUM SALT, IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/plate (b)					
		−S9		+S9 (hamster)		+S9 (rat)	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
TA100	0	141 ± 10.7	100 ± 2.3	160 ± 3.4	151 ± 20.5	161 ± 7.8	150 ± 3.8
	33	--	--	153 ± 4.3	118 ± 13.5	162 ± 13.6	125 ± 4.0
	100	117 ± 8.4	99 ± 9.7	155 ± 3.5	125 ± 7.2	164 ± 10.8	142 ± 5.8
	333	120 ± 6.0	84 ± 3.2	150 ± 5.7	138 ± 13.0	148 ± 11.2	135 ± 9.7
	1,000	113 ± 6.8	98 ± 2.7	150 ± 12.7	169 ± 10.7	157 ± 16.3	158 ± 2.7
	3,333	113 ± 7.1	95 ± 3.2	167 ± 9.1	162 ± 3.0	160 ± 13.7	182 ± 8.5
	10,000	115 ± 0.3	97 ± 2.0	--	--	--	--
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (c)	1,417 ± 76.4	1,034 ± 140.2	2,712 ± 147.0	2,550 ± 299.1	1,114 ± 45.0	1,940 ± 283.6
TA1535	0	11 ± 1.7	16 ± 1.0	13 ± 3.4	21 ± 1.5	10 ± 1.2	13 ± 2.2
	33	--	--	19 ± 3.0	18 ± 3.5	11 ± 1.5	13 ± 0.9
	100	14 ± 1.2	14 ± 0.6	12 ± 0.3	18 ± 1.2	15 ± 1.8	13 ± 0.6
	333	9 ± 2.7	17 ± 2.6	9 ± 2.4	12 ± 1.0	11 ± 0.9	17 ± 0.7
	1,000	12 ± 3.7	12 ± 1.5	12 ± 0.3	15 ± 0.3	12 ± 1.3	16 ± 1.9
	3,333	10 ± 1.5	14 ± 1.3	11 ± 2.5	17 ± 1.5	5 ± 1.0	13 ± 1.5
	10,000	5 ± 0.3	8 ± 1.7	--	--	--	--
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (c)	983 ± 64.1	571 ± 16.0	312 ± 16.8	216 ± 11.6	193 ± 10.5	220 ± 13.0
TA1537	0	13 ± 3.0	7 ± 1.7	13 ± 0.3	12 ± 4.1	17 ± 1.7	10 ± 2.9
	33	--	--	19 ± 2.0	7 ± 0.3	21 ± 2.0	8 ± 0.7
	100	14 ± 1.3	8 ± 0.7	18 ± 3.2	6 ± 1.8	16 ± 3.2	6 ± 2.3
	333	14 ± 1.5	7 ± 0.0	18 ± 3.2	11 ± 1.0	18 ± 2.1	6 ± 1.0
	1,000	16 ± 0.3	8 ± 1.2	17 ± 2.4	11 ± 2.0	21 ± 2.8	5 ± 1.2
	3,333	14 ± 1.0	6 ± 0.9	18 ± 1.9	11 ± 2.5	14 ± 4.7	6 ± 0.9
	10,000	7 ± 1.2	2 ± 0.3	--	--	--	--
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (c)	758 ± 40.5	154 ± 7.0	372 ± 30.3	231 ± 45.4	252 ± 23.2	153 ± 9.8
TA98	0	26 ± 1.8	15 ± 1.7	38 ± 7.2	25 ± 2.5	39 ± 3.1	24 ± 2.9
	33	--	--	32 ± 3.7	23 ± 2.3	29 ± 2.4	25 ± 1.0
	100	31 ± 4.2	16 ± 1.2	43 ± 3.9	22 ± 1.2	33 ± 3.4	22 ± 2.2
	333	34 ± 4.2	18 ± 0.6	42 ± 4.9	29 ± 4.7	31 ± 2.4	19 ± 1.8
	1,000	26 ± 3.2	16 ± 0.7	34 ± 3.7	31 ± 3.2	36 ± 1.5	24 ± 3.5
	3,333	26 ± 4.4	16 ± 3.8	44 ± 3.7	27 ± 1.2	36 ± 5.8	18 ± 2.3
	10,000	15 ± 0.3	17 ± 3.8	--	--	--	--
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (c)	162 ± 7.1	292 ± 14.4	942 ± 29.6	2,121 ± 390.8	463 ± 15.3	1,162 ± 175.6

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

TABLE E2. MUTAGENICITY OF MALONALDEHYDE, SODIUM SALT, IN MOUSE L5178Y LYMPHOMA CELLS (a,b)

Compound	Concentration (µg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutant Count	Mutant Fraction (c)
Trial 1					
Distilled water		72.3 ± 3.2	100.0 ± 32.0	112.0 ± 9.0	51.3 ± 2.0
Malonaldehyde, sodium salt					
	125	71.3 ± 9.2	128.7 ± 10.5	166.7 ± 11.3	(d) 79.3 ± 6.4
	250	79.3 ± 9.9	88.7 ± 5.8	157.7 ± 10.7	67.0 ± 5.0
	500	63.0 ± 12.0	59.0 ± 4.0	268.0 ± 23.0	(d) 145.5 ± 15.5
	1,000	Lethal	--	--	--
Methyl methanesulfonate					
	5	46.3 ± 10.2	46.7 ± 9.8	787.7 ± 122.0	(d) 596.7 ± 71.5
Trial 2					
Distilled water		89.5 ± 2.5	100.0 ± 2.3	106.8 ± 7.0	39.8 ± 2.3
Malonaldehyde, sodium salt					
	300	83.7 ± 3.3	69.7 ± 3.5	165.7 ± 7.5	(d) 66.0 ± 1.2
	400	74.7 ± 4.4	67.0 ± 3.1	226.7 ± 8.4	(d) 101.7 ± 3.7
	500	84.3 ± 2.4	54.0 ± 1.5	273.0 ± 24.6	(d) 107.7 ± 7.2
	600	73.3 ± 1.9	51.0 ± 7.6	222.7 ± 15.2	(d) 101.0 ± 6.1
	800	58.0 ± 4.0	35.3 ± 2.8	360.3 ± 11.3	(d) 210.3 ± 19.0
	1,000	54.3 ± 6.6	11.3 ± 0.9	442.0 ± 21.4	(d) 279.3 ± 27.4
Methyl methanesulfonate					
	5	52.0 ± 8.5	28.7 ± 3.5	610.0 ± 46.5	(d) 405.3 ± 48.0

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

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

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

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

TABLE E3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY MALONALDEHYDE, SODIUM SALT (a)

Compound	Dose (μg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
−S9 (c)								
Trial No. 1--Summary: Positive								
Medium		50	1,042	393	0.38	7.9	26.5	--
Malonaldehyde, sodium salt								
	14.9	50	1,049	394	0.38	7.9	26.5	100.0
	49.8	50	1,044	479	0.46	9.6	26.5	121.5
	149	50	1,041	596	0.57	11.9	26.5	150.6
Mitomycin C								
	0.002	50	1,045	660	0.63	13.2	26.5	167.1
	0.010	10	208	331	1.59	33.1	26.5	419.0
Trial No. 2--Summary: Positive								
Medium		50	1,040	428	0.41	8.6	26.0	--
Malonaldehyde, sodium salt								
	15	50	1,048	529	0.50	10.6	26.0	123.3
	50	50	1,036	568	0.55	11.4	26.0	132.6
	150	50	1,045	726	0.69	14.5	26.0	168.6
	300	50	1,038	1,018	0.98	20.4	26.0	237.2
Mitomycin C								
	0.002	50	1,036	496	0.48	9.9	26.0	115.1
	0.010	10	209	93	0.44	9.3	26.0	108.1
+S9 (d)								
Trial No. 1--Summary: Positive								
Medium		50	1,047	453	0.43	9.1	26.0	--
Malonaldehyde, sodium salt								
	149	50	1,043	438	0.42	8.8	26.0	96.7
	498	50	1,047	533	0.51	10.7	26.0	117.6
	1,490	50	1,042	691	0.66	13.8	26.0	151.6
Cyclophosphamide								
	0.500	50	1,034	416	0.40	8.3	26.0	91.2
	2.500	10	206	292	1.42	29.2	26.0	320.9
Trial No. 2--Summary: Positive								
Medium		50	1,047	470	0.45	9.4	26.0	--
Malonaldehyde, sodium salt								
	150	50	1,049	543	0.52	10.9	26.0	116.0
	500	50	1,042	655	0.63	13.1	26.0	139.4
	1,000	50	1,039	613	0.59	12.3	26.0	130.9
	2,000	50	1,032	818	0.79	16.4	(e) 30.0	174.5
Cyclophosphamide								
	0.500	100	2,092	2,049	0.98	20.5	26.0	218.1
	2.500	10	213	460	2.16	46.0	26.0	489.4

TABLE E3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY MALONALDEHYDE, SODIUM SALT (Continued)

(a) Study performed at Bioassay Systems Corp. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or medium as described in (c) or (d) below and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air-dried, and stained.
(b) SCEs/cell of culture exposed to study chemical relative to those of culture exposed to medium
(c) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or medium for 2 hours at 37° C. Then BrdU was added, and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and colcemid was added, and incubation was continued for 2-3 hours.
(d) In the presence of S9, cells were incubated with study compound or medium for 2 hours at 37° C. Then cells were washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with colcemid present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.
(e) Because some chemicals induce a delay in the cell division cycle, harvest times are occasionally extended to maximize the proportion of second division cells available for analysis.

TABLE E4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY MALONALDEHYDE, SODIUM SALT (a)

Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
−S9 (b)				
Trial 1--Harvest time 10.5 hours				
Medium				
	100	8	0.08	7
Malonaldehyde, sodium salt				
81.8	100	6	0.06	6
245	100	5	0.05	5
409	100	3	0.03	3
Summary: Negative				
Mitomycin C				
5	100	69	0.69	46
+S9 (d)				
Trial 1--Harvest time 12.0 hours				
Medium				
	100	2	0.02	2
Malonaldehyde, sodium salt				
409	100	3	0.03	3
1,640	100	2	0.02	2
3,270	100	5	0.05	4
Summary: Negative				
Cyclophosphamide				
50	100	38	0.38	33
−S9 (b)				
Trial 2--Harvest time 20.0 hours (c)				
Medium				
	100	5	0.05	4
Malonaldehyde, sodium salt				
42.9	100	4	0.04	4
71.5	100	6	0.06	6
143	100	5	0.05	5
215	100	4	0.04	3
Summary: Negative				
Mitomycin C				
1	10	13	1.3	50
5	10	81	8.1	90

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

TABLE E5. INDUCTION OF SEX-LINKED RECESSIVE LETHAL MUTATIONS IN DROSOPHILA BY MALONALDEHYDE, SODIUM SALT (a)

Route of Exposure	Dose (ppm)	Incidence of Deaths (percent)	Incidence of Sterility (percent)	No. of Lethals/No. of X Chromosomes Tested			Overall Total (b)
				Mating 1	Mating 2	Mating 3	
Injection	10,000	22	8	3/2,388	3/2,105	1/1,472	7/5,965 (0.12%)
	0			2/2,476	4/2,388	6/2,195	12/7,059 (0.17%)
Feeding	25,000	24	11	4/2,602	2/1,992	0/1,177	6/5,771 (0.10%)
	0			1/3,784	2/2,863	1/2,128	4/8,775 (0.05%)

(a) Study performed at Bowling Green State University. A detailed protocol of the sex-linked recessive lethal assay is presented in Zimmering et al. (1985). (Exposure by feeding was done by allowing 24-hour-old Canton-S males to feed for 3 days on a solution of the study chemical dissolved in 5% sucrose. In the injection experiments, 24-hour-old Canton-S males were treated with a solution of the chemical dissolved in 0.7% saline and allowed 24 hours to recover.) Exposed males were mated to three *Basc* females for 3 days and given fresh females at 2-day intervals to produce three broods of 3, 2, and 2 days; sample sperm from successive matings were treated as spermatozoa (mating 1), spermatids (mating 2), and spermatocytes (mating 3). F_1 heterozygous females were crossed to their siblings and placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters; no clusters were found. After 17 days, presumptive lethal mutations were identified as vials containing no wild-type males; these were retested. Results were not significant at the 5% level (Margolin et al., 1983).
(b) Combined total of number of lethal mutations/number of X chromosomes tested for three mating trials

APPENDIX F

SENTINEL ANIMAL PROGRAM

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APPENDIX F. SENTINEL ANIMAL PROGRAM

I. Methods

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

Fifteen $B6C3F_1$ mice and 15 F344/N rats of each sex are selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group are killed at 6, 12, and 18 months on study. Data from animals surviving 24 months are collected from 5/50 randomly selected vehicle control animals of each sex and species. The blood from each animal is collected and clotted, and the serum is separated. The serum is cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral antibody titers. The following tests are performed:

	Hemagglutination Inhibition	Complement Fixation	ELISA
Mice	PVM (pneumonia virus of mice) Reo 3 (reovirus type 3) GDVII (Theiler's encephalomyelitis virus) Poly (polyoma virus) MVM (minute virus of mice) Ectro (infectious ectromelia) Sendai	M. Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus) MHV (6, 12, 18 mo)	MHV (mouse hepatitis virus) (24 mo)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai	RCV (rat coronavirus)	

II. Results

Results are presented in Table F1.

TABLE F1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF MALONALDEHYDE, SODIUM SALT (a)

Interval (months)	No. of Animals	Positive Serologic Reaction for
RATS		
6	6/10	KRV
12	5/10	KRV
18	3/10	KRV
24	4/10	KRV
MICE		
6	0/10	None positive
12	2/10	MVM
18	1/7	GDVII
24	5/10	Reo 3

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

APPENDIX G

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

Pelleted Diet: December 1979 to January 1982

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

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

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

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

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

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

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

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

Nutrients	Mean ± Standard Deviation	Range	No. of Samples
Crude protein (percent by weight)	24.29 ± 0.81	22.7-26.1	24
Crude fat (percent by weight)	4.81 ± 0.38	4.1-5.5	24
Crude fiber (percent by weight)	3.31 ± 0.50	1.4-4.3	24
Ash (percent by weight)	6.76 ± 0.44	5.83-7.43	24
Amino Acids (percent of total diet)			
Arginine	1.260	1.21-1.31	2
Cystine	0.395	0.39-0.40	2
Glycine	1.175	1.15-1.20	2
Histidine	0.553	0.530-0.576	2
Isoleucine	0.908	0.881-0.934	2
Leucine	1.905	1.85-1.96	2
Lysine	1.250	1.20-1.30	2
Methionine	0.310	0.306-0.314	2
Phenylalanine	0.967	0.960-0.974	2
Threonine	0.834	0.840-0.827	2
Tryptophan	0.175	0.171-0.178	2
Tyrosine	0.587	0.566-0.607	2
Valine	1.085	1.05-1.12	2
Essential Fatty Acids (percent of total diet)			
Linoleic	2.37		1
Linolenic	0.308		1
Arachidonic	0.008		1
Vitamin			
Vitamin A (IU/kg)	10,192 ± 2,534	6,700-17,000	24
Vitamin D (IU/kg)	6,300		1
α-Tocopherol (ppm)	37.6	31.1-44.0	2
Thiamine (ppm) (b)	16.2 ± 4.5	7.4-27.0	23
Riboflavin (ppm)	6.9	6.1-7.4	2
Niacin (ppm)	75	65-85	2
Pantothenic acid (ppm)	30.2	29.8-30.5	2
Pyridoxine (ppm)	7.2	5.6-8.8	2
Folic acid (ppm)	2.1	1.8-2.4	2
Biotin (ppm)	0.24	0.21-0.27	2
Vitamin B_{12} (ppb)	12.8	10.6-15.0	2
Choline (ppm)	3,315	3,200-3,430	2
Minerals			
Calcium (percent)	1.34 ± 0.20	0.81-1.69	24
Phosphorus (percent)	1.01 ± 0.08	0.82-1.10	24
Potassium (percent)	0.809	0.772-0.846	2
Chloride (percent)	0.557	0.479-0.635	2
Sodium (percent)	0.304	0.258-0.349	2
Magnesium (percent)	0.172	0.166-0.177	2
Sulfur (percent)	0.278	0.270-0.285	2
Iron (ppm)	418	409-426	2
Manganese (ppm)	90.8	86.0-95.5	2
Zinc (ppm)	55.1	54.2-56.0	2
Copper (ppm)	12.68	9.65-15.70	2
Iodine (ppm)	2.58	1.52-3.64	2
Chromium (ppm)	1.86	1.79-1.93	2
Cobalt (ppm)	0.57	0.49-0.65	2

(a) One or two batches of feed analyzed for nutrients reported in this table were manufactured in January and/or April 1983.
(b) One batch (7/22/81) was not analyzed for thiamine.

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

Contaminants	Mean ± Standard Deviation	Range	No. of Samples
Arsenic (ppm)	0.39 ± 0.23	<0.05-1.06	24
Cadmium (ppm) (a)	0.11 ± 0.07	<0.05-0.40	24
Lead (ppm)	0.91 ± 0.51	0.50-2.65	24
Mercury (ppm) (b)	< 0.05		24
Selenium (ppm)	0.29 ± 0.09	0.10-0.52	24
Aflatoxins (ppb) (b,c)	<10	<10-<5	24
Nitrate nitrogen (ppm) (d,e)	7.00 ± 3.70	<0.1-13.0	24
Nitrite nitrogen (ppm) (d,e)	1.45 ± 1.02	<0.1-4.0	24
BHA (ppm) (f,g)	3.83 ± 3.88	<0.2-13.0	24
BHT (ppm) (f)	2.97 ± 1.74	0.8-7.6	24
Aerobic plate count (CFU/g) (h)	48,786 ± 32,701	5,500-120,000	22
Aerobic plate count (CFU/g) (i)	70,970 ± 81,410	5,500-320,000	24
Coliform (MPN/g) (j)	39 ± 57	<3-240	20
Coliform (MPN/g) (k)	270 ± 580	<3-2,400	24
E. coli (MPN/g) (l)	<3		24
Total nitrosamines (ppb) (m,n)	7.63 ± 6.67	2.2-24.5	21
Total nitrosamines (ppb) (m,o)	29.77 ± 64.59	2.2-273	24
N-Nitrosodimethylamine (ppb) (m,n)	5.81 ± 6.30	1.1-20.0	21
N-Nitrosodimethylamine (ppb) (m,o)	27.79 ± 64.31	1.1-272	24
N-Nitrosopyrrolidine (ppb)	1.44 ± 0.89	0.5-3.5	24
Pesticides (ppm)			
α-BHC (b,p)	<0.01		24
β-BHC (b)	<0.02		24
γ-BHC-Lindane (b)	<0.01		24
δ-BHC (b)	<0.01		24
Heptachlor (b)	<0.01		24
Aldrin (b)	<0.01		24
Heptachlor epoxide (b)	<0.01		24
DDE (b)	<0.01		24
DDD (b)	<0.01		24
DDT (b)	<0.01		24
HCB (b)	<0.01		24
Mirex (b)	<0.01		24
Methoxychlor (q)	<0.05	0.09 (8/26/81)	24
Dieldrin (b)	<0.01		24
Endrin (b)	<0.01		24
Telodrin (b)	<0.01		24
Chlordane (b)	<0.05		24
Toxaphene (b)	<0.1		24
Estimated PCBs (b)	<0.2		24
Ronnel (b)	<0.01		24
Ethion (b)	<0.02		24
Trithion (b)	<0.05		24
Diazinon (q)	<0.1	0.2 (4/27/81)	24
Methyl parathion (b)	<0.02		24
Ethyl parathion (b)	<0.02		24
Malathion (r)	0.10 ± 0.07	<0.05-0.27	24
Endosulfan I (b)	<0.01		24
Endosulfan II (b)	<0.01		24
Endosulfan sulfate (b)	<0.03		24

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

(a) Three batches contained more than 0.1 ppm.
(b) All values were less than the detection limit, given in the table as the mean.
(c) The detection limit was reduced from 10 ppb to 5 ppb after 7/81.
(d) Source of contamination: alfalfa, grains, and fish meal
(e) Two batches contained less than 0.1 ppm.
(f) Source of contamination: soy oil and fish meal
(g) Six batches contained less than 0.5 ppm.
(h) CFU = colony forming units; mean, standard deviation, and range exclude two extreme values (300,000 and 320,000) obtained for batches produced on 12/21/79 and 2/26/80.
(i) Mean, standard deviation, and range include the two extreme values given in footnote (h).
(j) Mean, standard deviation, and range exclude four very high values in the range of 1,100-2,400 obtained for batches produced on 2/4/80, 2/26/80, 5/29/80, and 12/16/80.
(k) Mean, standard deviation, and range include the very high values listed in footnote (j).
(l) MPN = most probable number; all values were less than 3 MPN/g.
(m) All values were corrected for percent recovery.
(n) Mean, standard deviation, and range exclude three very high values in the range of 115-280 ppb obtained for batches produced on 1/26/81, 2/23/81 and 4/27/81.
(o) Mean, standard deviation, and range include the very high values given in footnote (n).
(p) BHC = hexachlorocyclohexane or benzene hexachloride
(q) One observation was above the detection limit. The value and the date it was obtained are listed under the range.
(r) Nine batches contained more than 0.05 ppm.

APPENDIX H

AUDIT SUMMARY

APPENDIX H. AUDIT SUMMARY

The experimental data, documents, pathology materials, and draft Technical Report for the 2-year toxicology and carcinogenesis studies of malonaldehyde, sodium salt, in rats and mice were audited for accuracy, consistency, and completeness. Animal exposures for the 2-year studies began in February 1980. The laboratory experiments were conducted for the NTP by Battelle Columbus Laboratories (Columbus, Ohio) under a subcontract with Tracor Jitco, Inc. The retrospective audit was conducted at the NTP Archives in May 1986 by Program Resources, Inc., William L. Oller, Ph.D., Principal Investigator. The other individuals who conducted the audit are listed in the full report that is on file at the NIEHS.

The audit included, as minimum requirements, a review of:

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

Review of the inlife data revealed no discrepancies or problems that would influence the validity of the studies. The number of masses (10 in the rat and 9 in the mouse studies) that were observed clinically but did not correlate with necropsy findings was small. The review of analytical chemistry data revealed no discrepancies. Review of the pathology documents resulted in a change of the disposition code for one rat and eight mice from natural death or moribund kill to accidental death because of gavage trauma. Review of the pathology specimens revealed no discrepancies that would influence interpretation of the study results.

The minor discrepancies identified in this audit were adequately resolved or were considered not to affect the interpretation of these studies of malonaldehyde, sodium salt. Thus, the records and specimens examined in the audit support the data and results presented in the NTP Technical Report.

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NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS
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TR No.	CHEMICAL
201	2,3,7,8-Tetrachlorodibenzo-p-dioxin (Dermal)
206	Dibromochloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane (Inhalation)
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butylbenzyl Phthalate
214	Caprolactam
215	Bisphenol A
216	11-Aminoundecanoic Acid
217	Di(2-ethylhexyl)phthalate
219	2,6-Dichloro-*p* phenylenediamine
220	C.I. Acid Red 14
221	Locust Bean Gum
222	C I. Disperse Yellow 3
223	Eugenol
224	Tara Gum
225	D & C Red No. 9
226	C.I. Solvent Yellow 14
227	Gum Arabic
229	Guar Gum
230	Agar
231	Stannous Chloride
233	2-Biphenylamine Hydrochloride
234	Allyl Isothiocyanate
235	Zearalenone
236	D-Mannitol
238	Ziram
239	Bis(2 chloro-1-methylethyl)ether
240	Propyl Gallate
242	Diallyl Phthalate (Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
247	L-Ascorbic Acid
248	4,4'-Methylenedianiline Dihydrochloride
249	Amosite Asbestos
250	Benzyl Acetate
251	Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
267	Propylene Oxide
269	Telone II®
271	HC Blue No 1
272	Propylene
273	Trichloroethylene (Four strains of rats)
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
281	H.C. Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethy)phosphonium Sulfate and Tetrakis(hydroxymethy)phosphonium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C I Disperse Blue 1
300	3-Chloro-2-methylpropene
301	*o*-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane
307	Ephedrine Sulfate
308	Chlorinated Paraffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	*n*-Butyl Chloride
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2 methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
320	Rotenone
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
323	Dimethyl Methylphosphonate
324	Boric Acid
325	Pentachloronitrobenzene
326	Ethylene Oxide
327	Xylenes (Mixed)
328	Methyl Carbamate
329	1,2-Epoxybutane
330	4 Hexylresorcinol
332	Mercaptobenzothiazole
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol
336	Penicillin VK
337	Nitrofurazone
339	2-Amino-4-nitrophenol

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