NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 245

CARCINOGENESIS BIOASSAY OF MELAMINE (CAS NO. 108-78-1) IN F344/N RATS AND B6C3F$_1$ MICE (FEED STUDY)

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 chemically induced disease. By bringing together the relevant programs, staff, and resources from the U.S. Public Health Service, DHHS, the National Toxicology Program has centralized and strengthened activities relating to toxicology research, testing and test development/validation efforts, and the dissemination of toxicological information to the public and scientific communities and to the research and regulatory agencies.

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

NTP TECHNICAL REPORT
ON THE

CARCINOGENESIS BIOASSAY OF MELAMINE

(CAS NO. 108-78-1)

IN F344/N RATS AND B6C3F$_1$ MICE
(FEED STUDY)

NATIONAL TOXICOLOGY PROGRAM
Box 12233
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Public Health Service
National Institutes of Health

NOTE TO THE READER

This is one in a series of experiments designed to determine whether selected chemicals produce cancer in animals. Chemicals selected for testing in the NTP carcinogenesis bioassay program 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 test animals do not have a greater incidence of cancer than control animals, do not necessarily mean that a test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical has the potential for hazard to humans. The determination of the risk to humans from chemicals found to be carcinogenic in animals requires a wider analysis which extends beyond the purview of this study.

This study was initiated by the National Cancer Institute's Carcinogenesis Testing Program, now part of the National Institute of Environmental Health Sciences, National Toxicology Program.

Comments and questions about the National Toxicology Program Technical Reports on Carcinogenesis Bioassays should be directed to the National Toxicology Program, located at Room A-306, Landow Building, Bethesda, MD 20205 (301-496-1152) or at Research Triangle Park, NC 27709 (919-541-3991).

Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to communicate any mistakes to the Deputy Director, NTP (P.O. Box 12233, Research Triangle Park, NC 27709), 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.

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650).

Single copies of this carcinogenesis bioassay technical report are available without charge (and while supplies last) from the NTP Public Information Office, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709.

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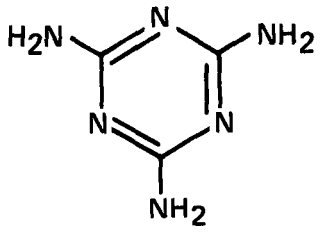

MELAMINE

CAS NO. 108-78-1

$C_3H_6N_6$ Mol. Wt. 126.13

ABSTRACT

A carcinogenesis bioassay of melamine (>95% pure), a chemical intermediate in the manufacture of amino resins and plastics, was conducted by feeding diets containing 2,250 or 4,500 ppm melamine to groups of 50 male F344/N rats and 50 B6C3F$_1$ mice of each sex for 103 weeks. Groups of 50 female rats were fed diets containing 4,500 or 9,000 ppm melamine. Groups of 49 male rats, 50 female rats, 49 male mice, and 50 female mice served as controls.

Mean body weights of dosed rats of each sex were lower than those of the controls after week 20. Survival of high-dose male rats was significantly lower ($P<0.05$) than that of the controls. Survival of all other dosed rat groups was comparable with that of the respective controls.

Transitional-cell carcinomas in the urinary bladder of male rats occurred with a statistically significant positive trend ($P\leq0.002$; controls, 0/45; low-dose, 0/50; high-dose, 8/49, 16%) and the incidence in the high-dose group was significantly higher ($P\leq0.016$) than that in the controls. A transitional-cell papilloma was observed in the urinary bladder of an additional high-dose male rat. These tumors were not observed in statistically significant proportions in female rats. Seven of the eight high-dose male rats with the transitional-cell carcinomas also had bladder stones. An association ($P\leq0.001$) was found between bladder stones and bladder tumors in male rats.

Chronic inflammation, distinguishable from the nephropathy observed in aging F344/N rats, was significantly increased ($P\leq0.01$) in the kidney of dosed female rats (controls, 4/50, 8%; low-dose, 17/50, 34%; high-dose, 41/50, 82%) and is attributed to the administration of melamine.

The mean body weight of high-dose male mice was lower than that of controls after week 50 of the study. The mean body weights of dosed and control female mice were comparable throughout the study. Survival of high-dose male mice was significantly less ($P<0.02$) than that of the controls. Survival of all other dosed groups was similar to that of the respective controls.

Acute and chronic inflammation and epithelial hyperplasia of the urinary bladder were found in increased incidence in dosed male mice. The incidence of bladder stones in dosed male mice was increased relative to controls (control, 2/45, 4%; low-dose, 40/47, 85%; high-dose, 41/44, 93%); however, there was no evidence of bladder tumor development in this species. Also, four high-dose female mice had bladder stones without any tumors.

Under the conditions of this bioassay, melamine was carcinogenic for male F344/N rats, causing transitional-cell carcinomas in the urinary bladder. With one exception, urinary bladder stones were observed in male rats that had transitional-cell carcinomas. Melamine was not carcinogenic for female F344/N rats or for B6C3F$_1$ mice of either sex.

CONTRIBUTORS

The bioassay of melamine was conducted at Litton Bionetics, Inc., under a subcontract to Tracor Jitco, Inc., the prime contractor for the Carcinogenesis Testing Program. The two-year study was begun in August 1978 and completed in September 1980.

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The pathology report and selected slides were evaluated on March 31, 1981 by the NTP Pathology Working Group, which included Drs. G. Boorman (NTP), R. Kovatch (Tracor Jitco), W. Macklin (Burroughs-Wellcome), and E. McConnell (NTP).

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*Unable to attend June 16, 1982 meeting

SUMMARY OF PEER REVIEW COMMENTS ON THE BIOASSAY OF MELAMINE

On June 16, 1982 this report underwent peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting began at 9:00 a.m. in Conference Center Building 101, South Campus, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. R. Melnick, NTP chemical manager for the melamine studies, reported that, at the request of American Cyanamid Company, meetings were held between representatives of that company and NTP staff to discuss the draft report. The NTP incorporated some of the information received into the introduction and discussion sections, and these were given to the Panel. Further, slides used to make the diagnoses of the transitional-cell carcinomas, as well as recuts (newly prepared slides), were re-reviewed by 13 pathologists from the Washington, D.C. and Research Triangle Park areas. The consensus opinion of these reviews confirmed the original diagnoses in the high dose group. Further experiments are planned, some by American Cyanamid and some by NTP, to examine the relationship between bladder stones and bladder tumors in male rats resulting from ingestion of melamine.

Dr. Highland, a principal reviewer for the report on the bioassay of melamine, agreed with the conclusions. He expressed concern, however, that the discussion was biased toward the possible role of bladder stones in the etiology of the carcinomas, and requested that some rewriting should reflect a more balanced presentation, including discussion of a possible biochemical mechanism. Dr. Highland noted that stones were found in rats without tumors, and vice versa; also, mice had stones but no tumors. He also objected to inclusion of references to American Cyanamid studies since some of the work is still in progress and others are company reports with limited availability. He asked for an explanation as to why female rats were dosed at twice the levels of male rats. [Prechronic results indicated these were appropriate doses.]

As a second principal reviewer, Dr. Scala said that evidence for association of bladder stones with the bladder tumors was strong in this study, in the cited literature, and in other work, specifically the Chemical Industry Institute of Toxicology (CIIT) studies of terephthalic acid. Thus, he suggested insertion of a sentence in the conclusion to the effect that the transitional-cell carcinomas may have been secondary to the production of bladder stones. He expressed concern that a more integrated discussion of urinary tract pathology was not given.

As a third principal reviewer, Dr. Schwetz agreed with the stated conclusions of the bioassay. He agreed with Dr. Highland regarding further remarks in the discussion about the association between bladder stones and tumors, and stated that the comments that bladder stones in male rats may contribute to the development of urinary bladder tumors were too strong. At most, the results suggest a correlation between the two, but indicate little about cause and effect. He stressed one important point that should not be ignored: that is whether the sex difference in sensitivity is related to a sex difference in metabolism or kinetics.

In further discussion, the Panel Members agreed that there should be a separate sentence in the conclusion that bladder stones were seen in 7 of 8 high-dose male rats that had transitional-cell carcinomas of the urinary bladder.

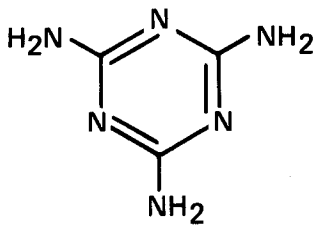
In discussion from the public audience, Dr. C. Frith, consultant for American Cyanamid, gave his personal opinion that there was a strong correlation between melamine stones and urinary bladder tumors in the NTP study, disputed the diagnoses of some of the transitional-cell carcinomas in the NTP bioassay, and stated that in an ongoing melamine study sponsored by American Cyanamid there were no compound-related bladder tumors. Dr. L. Golberg, also a consultant for American Cyanamid, talked about the historical background of the relationship between bladder stones and bladder neoplasia. Dr. R. Mast, American Cyanamid, commented on specific portions of the NTP melamine report, and made suggestions for additional changes.

Dr. Boorman, NTP, responded by summarizing the recent reviews of slides of the urinary bladder, including recuts for additional sections in some cases, that confirmed the original diagnoses of transitional-cell carcinomas. The 13 pathologists involved were from industry and private laboratories as well as from NTP, and the studies were done in a coded or blind fashion. Dr. Swenberg said that he and other pathologists from CIIT had examined the slides, including the recuts, and agreed with Dr. Boorman's assessment.

Dr. Highland moved that the report on the bioassay of melamine be accepted with the inclusion of a separate sentence in the conclusion concerning the observation of bladder stones in male rats having transitional-cell carcinomas, as well as other modifications requested by the reviewers. These should include a more balanced discussion about possible mechanisms. Dr. Breslow seconded the motion and the report was approved unanimously by the Peer Review Panel.

I. INTRODUCTION

I. INTRODUCTION



MELAMINE

CAS NO. 108-78-1

$C_3H_6N_6$ Mol. Wt. 126.13

Melamine (2,4,6-triamino-*s*-triazine; cyanurotriamide) is an important starting material in the manufacture of polymeric amino resins and thermosetting plastics used in electrical equipment and housewares (buttons, table tops, wall coverings, and dinnerware) (Simonds and Church, 1967). Some amino resins (polymers) containing melamine are used in laminates, adhesives, and paints, and in anti-crease agents applied to permanent-press fabrics. Others are used to improve the wet strength of paper. Melamine pyrophosphate is used to enhance the wash durability of flame-retardant textile finishes (Kirk-Othmer, 1979).

Melamine may be found in silver tarnish cleaners, and melamine derivatives (perhydrates) may be found in neutralizer solutions for permanent wave preparations (Bann and Miller, 1958; Balsam and Sagarin, 1971). Melamine-formaldehyde polymer is approved by the U.S. Food and Drug Administration for use in food-contact applications (USCFR, 1977). In 1978, 112 million pounds of melamine were produced in the United States (USITC, 1979), practically all (99%) of which was used in the manufacture of melamine resins and melamine-based amino resins.

In both rats and humans, melamine is a metabolite of the antineoplastic agent hexamethylmelamine (Worzalla et al., 1974). Melamine was ineffective as an antitumor compound in male BD2F1 mice bearing Sarcoma 180 or Lewis lung carcinoma; methylated melamine (adding 1 to 6 methyl groups) did exhibit antitumor activity (Lake et al., 1975).

The amino groups of melamine (pK_b=9.0) confer basic properties on this chemical. The reactivity of melamine resembles that of an amide. In contrast to aromatic amines, melamine does not react with alkyl halides, and it reacts slowly with acid chloride (Simonds and Church, 1967; Bann and Miller, 1958).

The oral LD_{50} value of melamine was reported to be 4.55 g/kg for mice (Clayton and Clayton, 1981). Lake et al. (1975) determined an LD_{10} of 762 mg/kg/day for male $BD2F_1$ mice given intraperitoneal injections once daily for 5 days.

Recovery of urinary metabolites following administration of hexamethylmelamine to two human patients and to rats indicated that the *s*-triazine ring is very stable and does not undergo cleavage *in vivo* (Worzalla et al., 1974). Melamine has a diuretic effect in rats (Lipschitz and Hadidian, 1944) and dogs (Lipschitz and Stokey, 1945). After a single oral dose of 250 mg/kg to rats, 50% to 60% of unmodified melamine was excreted in the urine in 6 hours (Lipschitz and Stokey, 1945). Nearly 20% of the melamine excreted by the rats was recovered as the crystalline dimelamine—monophosphate.

Melamine, administered intraperitoneally at 70 mg/kg to pregnant Wistar rats, had no significant effect on rat litters or growing fetuses (Thiersch, 1957). Melamine was not mutagenic for *Drosophila melanogaster* (Rohrborn, 1962); for *Salmonella typhimurium* G46, TA 1530, TA 1531, TA 1532, and TA 1534 (Seiler, 1973); or for TA 98, TA 100, TA 1535, and TA 1538, with

or without metabolic activation (Lusby et al., 1979). Short-term mutagenicity assays conducted by the American Cyanamid Co. and the National Toxicology Program indicate that melamine is not mutagenic for *Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537, or TA 1538 in the presence or absence of a rat liver S-9 metabolic activation system (American Cyanamid Co., 1981a; Appendix I, Tables I1-I4).

Melamine is not mutagenic for the hypoxanthine-guanine phosphoribosyl transferase locus in Chinese hamster ovary cells in the presence or absence of metabolic activation (American Cyanamid Co., 1981b). In addition, melamine was apparently negative in tests for induction of chromosomal abberations (NTP, unpublished results) or sister chromatid exchanges in Chinese hamster ovary cells (NTP, unpublished results; American Cyanamid Co., 1982a), and for unscheduled DNA synthesis in a rat hepatocyte primary culture (American Cyanamid Co., 1982b). Oral administration of melamine to mice did not produce a significant increase in the number of micronuclei in polychromatic erythrocytes (American Cyanamid Co., 1981c).

No compound-related effects were observed in groups of 10 Carworth Farm albino rats fed diets containing 1,000 ppm melamine for 2 years (American Cyanamid Co., 1953). Four of 10 male rats and 2 of 10 female rats fed 10,000 ppm melamine for 2 years had bladder stones associated with the development of benign papillomas. There were no papillomas observed in either the male or female control groups.

Melamine was tested by the Carcinogenesis Bioassay Program because of the large amount produced and the potential for human exposure and because small numbers of animals were used in previous chronic studies.

II. MATERIALS AND METHODS

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TWO-YEAR STUDIES

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Clinical Examinations and Pathology

Data Recording and Statistical Methods

CHEMICAL ANALYSIS

Technical-grade melamine was obtained in two batches from American Cyanamid Company (Bound Brook, NJ). Lot No. A7-11-75 was used for the single-dose and prechronic studies and for the first 14 months of the chronic study. Lot No. A13179 was used for the remainder of the chronic studies. (Methods used for all chemical analyses are given in Appendix E.) Results of purity and identity analyses conducted at Midwest Research Institute (MRI) indicated that both lots were similar in purity in all respects. Results of elemental analyses for both lots agreed with the theoretical values. Titration of one amino group indicated that both lots were approximately 100%±1% pure. For both lots, only one spot was detected by thin-layer chromatography. Several minor impurities were detected in both lots by high-performance liquid chromatography (HPLC) (Appendix E). The impurities were not further characterized, but 6-amino-*s*-triazine-2,4-diol and 4,6-diamino-*s*-triazine-2-ol are reported to be common impurities in melamine (Hamprecht and Schwarzmann, 1968). The differences in purity determined by HPLC and titration could be due to impurities with titratable amine groups, such as the impurities mentioned above, that would result in an apparently high titration value. In addition, the detector response in HPLC is highly dependent upon the absorbance of the substance at the detector wavelength used. The values reported are absolute areas expressed as percentages of the area of the major peak and do not take into account the different values of the compound and its impurities at 254 nm. Therefore, the relative areas determined by HPLC do not necessarily reflect the actual weight percentages of the impurities in the sample.

The infrared and ultraviolet spectra of both lots were consistent with the literature spectra (Morimoto 1966a, 1966b).

The chemical was stable at 60°C for 2 weeks and therefore required no special storage temperature. The chemical was stored at 4°C throughout the study, and periodic analyses by thin-layer chromatography and infrared spectroscopy indicated that no significant degradation occurred over the lifetime of the study.

The melamine used in this bioassay was analyzed by the Midwest Research Institute, 425 Volker Blvd., Kansas City, Missouri 64110; reanalysis of the bulk chemical and analysis of the chemical/feed mixtures were performed at Litton Bionetics, Inc.

PREPARATION OF TEST DIETS

Test diets were prepared by first mixing a small amount of Purina® Lab Chow (Table 1) and the required amount of melamine with a mortar and pestle and then adding this premix to the required amount of animal meal and mixing for 10 to 30 minutes in a Patterson-Kelly® twin-shell blender equipped with an intensifier bar. Prepared diets containing 100,000 ppm melamine were analyzed at Midwest Research Institute and were found to be stable for 2 weeks at temperatures up to 45°C (Appendix F). Test diets were stored in the freezer for no longer than 3 weeks. Control animals were fed Purina® Lab Chow.

Dosed feed samples from the chronic studies were analyzed periodically by ultraviolet spectroscopy. The methods used and results obtained are tabulated in Appendix G and indicate that only one of the formulations analyzed was slightly (+10.6%) out of specifications (>±10%). Results from three separate referee analyses at MRI verified the accuracy of the formulations.

SHORT-TERM STUDIES

Single-Dose Study

Male and female F344/N rats and $B6C3F_1$ mice were obtained from Frederick Cancer Research Center (Frederick, MD) and held for approximately 6 weeks before the test began.

Groups of five male and five female rats were administered single doses of melamine (2,150 to 10,000 mg/kg body weight) in corn oil by gavage (Table 1). Groups of five male mice received doses of 1,470 to 14,700 mg/kg and groups of five female mice received doses of 3,160 to 14,700 mg/kg.

Rats were housed two or three per cage and mice were housed five per cage. Water and feed were available *ad libitum* during the observation period. Details of animal maintenance are presented in Table 1.

Animals were observed for mortality at 30-minute intervals for the first 8 hours on the day of dosing and then daily for 14 days. Necropsies were performed on all animals.

Fourteen-Day Study

Male and female F344/N rats and $B6C3F_1$ mice were obtained from Frederick Cancer Research Center and held for approximately 2 months before the study began. Animals were approximately 11 weeks old when placed on study.

Groups of five male and five female rats were fed diets containing 0, 5,000, 10,000, 15,000, 20,000, or 30,000 ppm melamine for 2 weeks. Similar groups of mice were fed diets containing 0, 5,000, 7,500, 10,000, 12,500, 15,000, or 30,000 ppm melamine.

Rats were housed two or three per cage and mice were housed five per cage. Water and control or test diets were available *ad libitum*. Details of animal maintenance are presented in Table 1. The rats and mice were observed daily for mortality and were weighed weekly. Necropsies were performed on all animals at the end of the 14-day study.

Thirteen-Week Studies

Thirteen-week studies were conducted to evaluate the cumulative toxicity of melamine, to identify the target organs of this chemical in rats and mice, and to determine the concentrations to be used in the two-year studies.

Three-to-four-week-old male and female F344/N rats and $B6C3F_1$ mice were obtained from the Frederick Cancer Research Center, observed for 2 weeks, and then randomized by weight and assigned to test groups so that average cage weights were approximately equal for all animals of the same sex and species.

Rats were housed four per cage and mice five per cage in polycarbonate cages covered with nonwoven polyester filter sheets (Table 1). Racks and filters were changed once every 2 weeks. Cages and bedding were replaced twice per week, and water bottles were replaced three times per week.

Test diets consisted of Purina® Lab Chow and the required amount of melamine. Control diets consisted of Purina® Lab Chow. Test diets, control diets, and water (acidified with hydrochloric acid to pH 2.5 for bacterial control) were available *ad libitum*.

In the first 13-week study, diets containing 0, 6,000, 9,000, 12,000, 15,000, or 18,000 ppm melamine were fed to groups of 12 male and 12 female rats and to groups of 10 male and 10 female mice for 13 weeks.

Two additional 13-week studies were conducted to find a no-effect level for urinary bladder stone formation and to determine the effect of ammonium chloride in the drinking water on stone formation.

In the second 13-week study, groups of 10 rats of either sex were fed diets containing 0, 750, 1,500, 3,000, 6,000, or 12,000 ppm melamine for 13 weeks. At day 65, five rats of either sex fed 750 ppm melamine and two control rats of each sex were placed in metabolism cages and fasted overnight. Urine samples collected from each cage were centrifuged and the sediment fractions were examined microscopically.

In a third 13-week study, groups of 10 rats of either sex were fed diets containing 0, 10,000, or 18,000 ppm melamine in the presence and absence of 1% ammonium chloride in the drinking water.

Animals were checked for mortality and signs of morbidity daily. Those animals that were judged moribund were killed and necropsied. Body weight and feed consumption data were collected weekly.

At the end of the 91-day studies, survivors were killed with carbon dioxide, and necropsies were performed on animals that survived to the end of the studies and on all animals found dead, unless precluded in whole or in part by autolysis or cannibalization. In the first 13-week study, the following tissues were examined for control and high-dose groups: gross lesions, tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, sciatic nerve, bone marrow, costochondral junction (rib), thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenals, urinary bladder, seminal vesicles/prostate/testes or ovaries/uterus, nasal cavity, brain, and pituitary gland. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Only the kidney and urinary bladder of lowest-dose animals were examined microscopically.

In the second study, all animals were killed with carbon dioxide and then necropsied. The kidneys and urinary bladders of all animals were examined microscopically. In the third 13-week study, all surviving animals were killed with carbon dioxide and necropsied.

TWO-YEAR STUDIES

Study Design

Diets containing 4,500 or 9,000 ppm melamine were fed to groups of 50 female rats for 103 weeks. Diets containing 2,250 or 4,500 ppm were fed to groups of 50 male rats and to groups of 50 male or female mice. All control groups initially consisted of 50 animals. One control rat and one control mouse from the male groups were discarded at weeks 13 and 21, respectively, when a sexing error was discovered. Rats and mice were approximately 6 weeks old when placed on study.

Source and Specifications of Test Animals

Four-week-old male and female F344/N rats and $B6C3F_1$ mice were obtained from Charles River Breeding Laboratories, Portage, MI, observed for 2 weeks, and assigned to individual cages according to a table of random numbers. The cages were then distributed to control and dosed groups according to another table of random numbers.

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

The C57BL/6 mice were homogeneous at all loci tested. Eighty-five percent of 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 random bred stocks.

Male mice from the C3H colony and female mice from the C57BL/6 colony were used as parents for the hybrid $B6C3F_1$ mice used in this bioassay. The influence of the potential genetic non-uniformity in the hybrid mice on the bioassay results is not known. However, the bioassay is valid since matched, concurrent controls were included in the study.

Animal Maintenance

Rats and mice were housed five per cage in polycarbonate cages covered with nonwoven polyester filter sheets (Table 1). Racks and filters were changed once every 2 weeks. Cages, bedding, and glass water bottles (equipped with stainless steel sipper tubes) were replaced twice per week. Test diets, control diets, and tap water

(acidified with hydrochloric acid to pH 2.5 for bacterial control) were available *ad libitum*. Stainless steel feed containers were changed once per week.

The temperature in the animal rooms was 22°-26°C and the humidity was 30%-70%. Room air was changed 12-15 times per hour. The air was prefiltered with DRICO air filters and then filtered with HEPA filters. Fluorescent lighting provided illumination 12 hours per day.

Clinical Examinations and Pathology

All animals were observed twice daily for morbidity or mortality. Clinical signs were recorded monthly. Body weights and feed consumption by cage were recorded once per week for the first 13 weeks, monthly until week 91, and then every 2 weeks. The mean body weight of each group was calculated by dividing the total weight of all surviving animals in the group by the number of surviving animals in the group. The average feed consumption per animal was calculated by dividing the total feed consumption measured for all cages in a group by the number of surviving animals in the group. Moribund animals and animals that survived to the end of the bioassay were killed with carbon dioxide and immediately necropsied.

Examinations for grossly visible lesions were performed on major tissues or organs. Tissues were preserved in 10% neutral buffered formalin embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The following were examined microscopically: gross lesions, skin with mammary gland, mandibular lymph node, salivary gland, sternum with bone marrow, larynx or anterior trachea, esophagus, thyroid, parathyroid, lungs with mainstem bronchi, heart, stomach (glandular and nonglandular), duodenum, large intestine, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenal glands, urinary bladder, entire gonads, prostate or uterus, brain, and pituitary gland.

Necropsies were performed on all animals found dead and on those killed at the end of the study, unless precluded in whole or in part by autolysis or cannibalization. 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 in each group.

The pathology report and selected slides were evaluated by the NTP Pathology Working Group as described by Maronpot and Boorman (in press). The classification of neoplastic nodules was done according to the recommendations of Squire and Levitt (1975) and the National Academy of Sciences (1980). The diagnoses represent a consensus of contracting pathologists and the NTP Pathology Working Group.

Data Recording and Statistical Methods

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, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969).

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically 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) extensions of Cox's methods for testing for a dose-related trend. All reported P values for the survival analyses are two-sided.

The incidence of neoplastic or nonneoplastic lesions has been 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 included only those animals for which that 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 numbers of animals necropsied.

For the statistical analysis of tumor incidence data, two different methods of adjusting for intercurrent mortality were employed. Each used the classical methods for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included pairwise comparisons of high- and low-dose groups with controls and tests for overall dose-response trends.

The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel method 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). In this report, interstitial-cell tumors of the testis in male F344/N rats were not subjected to the "fatal tumor analysis," since this frequently occurring lesion is not regarded as life threatening.

The second method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "incidental"; i.e., they were merely observed at autopsy in animals dying of an unrelated cause. According to this approach, the proportions of animals found to have tumors in dosed and control groups were compared in each of five time intervals: 0-52 weeks, 53-78 weeks, 79-92 weeks, week 93 to the week before the terminal kill, and the terminal kill period. The denominators of these proportions were the number of animals actually autopsied during the time interval. The individual time interval comparisons were then combined by the previously described methods to obtain a single overall result. (See Peto et al., 1980, for the computational details of both methods.)

In addition to these tests, one other set of statistical analyses was carried out and reported in the tables analyzing primary tumors: the Fisher's exact test for pairwise comparisons and the Cochran-Armitage linear trend test for dose-response trends (Armitage, 1971; Gart, 1979). These tests were based on the overall proportion of tumor-bearing animals. All reported P values for the tumor incidence analyses are one-sided.

For studies in which there is little effect of compound administration 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.

TABLE 1. MATERIALS AND METHODS AND EXPERIMENTAL DESIGN

	Single-Dose Study	Fourteen-Day Study	Thirteen-Week Studies	Two-Year Study
Animals and Animal Maintenance				
Species	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice
Animal Source	Frederick Cancer Research Center, Frederick, MD	Same as single-dose study	Same as single-dose study	Charles River Breeding Laboratories, Portage, MI.
Time Held Before Start of Test	6 weeks	2 months	2 weeks	2 weeks
Age When Placed on Study	10 weeks	11 weeks	5-6 weeks	6 weeks
Age When Killed	12 weeks	13 weeks	18-19 weeks	111 weeks
Method of Animal Distribution	—	—	Animals assigned to cages by species and sex such that the average cage weights were approximately the same	Animals assigned by species and sex to cages according to a table of random numbers; cages then assigned to control and dosed groups according to another table of random numbers
Feed	Purina® Laboratory Chow Ralston Purina Co. St. Louis, MO.	Same as single-dose study	Same as single-dose study	Same as single-dose study
Bedding	Absorb-Dri® heat-treated hardwood chips (Lab Products, Inc.)	Same as single-dose study	Same as single-dose study; changed twice per week	Absorb-Dri® hardwood chips (Lab Products, Inc.); changed twice per week
Water	Tap water (acidified with hydrochloric acid to pH 2.5) available *ad libitum*	Same as single-dose study	First and second studies: Same as single-dose study; third study (rats): ± 1% ammonium chloride in drinking water	Same as single dose study.
Cages	Polycarbonate	Polycarbonate	Polycarbonate; changed twice per week	Polycarbonate; changed twice per week

TABLE 1. MATERIALS AND METHODS AND EXPERIMENTAL DESIGN (Continued)

	Single-Dose Study	Fourteen-Day Study	Thirteen-Week Studies	Two-Year Study
Cage Filters	Non-woven polyester filter sheets	Same as single-dose study	Same as single-dose study	Same as single-dose study
Animals per Cage	Rats: two-three Mice: five	Rats: two-three Mice: five	Rats: four Mice: five	Five
Animal Room Environment	22°-26°C; 30%-70% relative humidity	Same as single-dose study	Same as single-dose study	22°-26°C; 30%-70% relative humidity; room air was changed 12-15 times per hour; 12 hours of fluorescent light per day
Other Chemicals on Test in the Same Room	Rats: toluene diisocyanate; diallyl phthalate; caprolactam; diphenylmethane diisocyanate; 2,6-dichloro-p-phenylene-diamine; Mice: bisphenol A; 11-aminoundecanoic acid; diphenylmethane diisocyanate	Rats: none Mice: 11-aminoundecanoic acid	Rats: none Mice: bisphenol A	None
Experimental Design				
Size of Test Groups	5 males and 5 females of each species	5 males and 5 females of each species	First Study: 12 male and 12 female rats; 10 male and 10 female mice. Second Study: 10 male and 10 female rats Third Study: 10 male and 10 female rats	50 males and 50 females of each species (except for only 49 control male rats and 49 control male mice)

TABLE 1. MATERIALS AND METHODS AND EXPERIMENTAL DESIGN (Continued)

	Single-Dose Study	Fourteen-Day Study	Thirteen-Week Studies	Two-Year Study
Doses	Male and female rats: 2,150, 3,160, 4,640, 6,810, or 10,000 mg/kg body weight in corn oil by gavage. Male mice: 1,470, 2,150, 3,160, 4,640, 6,810, 10,000 or 14,700 mg/kg in corn oil by gavage. Female mice: 3,160, 4,640, 6,810, 10,000, or 14,700 mg/kg in corn oil by gavage	Rats: 0, 5,000, 10,000, 15,000, 20,000, or 30,000 ppm in feed Mice: 0, 5,000, 7,500, 10,000, 12,500, 15,000, or 30,000 ppm in feed. Diets available *ad libitum*	First Study: 0, 6,000, 9,000, 12,000, 15,000, or 18,000 ppm in feed (rats and mice) *(a)* Second Study: 0, 750, 1,500, 3,000, 6,000, or 12,000 ppm in feed (rats only) *(b)* Third Study: 0, 10,000, or 18,000 ppm in feed; 0, 10,000, or 18,000 ppm in feed plus 1% ammonium chloride in drinking water (rats only). Diets available *ad libitum*	Female rats: 0, 4,500, or 9,000 ppm in feed Male rats and male and female mice: 0, 2,250, or 4,500 ppm in feed. Diets available *ad libitum*
Duration of Dosing	Single dose	2 weeks	13 weeks	103 weeks
Type and Frequency of Observation	Observed for mortality every 30 min. for first 8 hrs. and then daily for 14 days	Observed daily for mortality and weighed on days 0, 7, and 14	Observed daily for mortality and signs of morbidity. Body weight and feed consumption data collected weekly	Observed twice daily for mortality and signs of morbidity. Body weight data collected weekly for the first 13 weeks, monthly until week 91, and every 2 weeks thereafter. Feed consumption data collected every 4 weeks. Clinical signs were recorded monthly.

TABLE 1. MATERIALS AND METHODS AND EXPERIMENTAL DESIGN (Continued)

	Single-Dose Study	Fourteen-Day Study	Thirteen-Week Studies	Two-Year Study
Necropsy and Histologic Examination	All animals necropsied	All animals necropsied	First Study: necropsies performed on all animals; following tissues examined histologically in controls and animals in highest dosed groups: gross lesions, tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary glands, salivary gland, thigh muscle, sciatic nerve, bone marrow, costochondral junction (rib), thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejenum, ileum, colon, mesenteric lymph nodes, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenals, bladder, seminal vesicles/prostate/testes or ovaries/uterus, nasal cavity, brain, and pituitary. For lowest dose group, only kidney and urinary bladder examined. Second Study: necropsies performed on all animals; kidney and urinary bladder of all animals examined microscopically Third study; necropsy only	All animals necropsied and examined histologically. Tissues examined: gross lesions, skin (with mammary gland), mandibular lymph nodes, salivary gland, sternum (with bone marrow), larynx or anterior trachea, esophagus, thyroid, parathyroid, lungs with mainstream bronchi, heart, stomach (glandular and nonglandular), duodenum, large intestine, liver, gall bladder (mice), pancreas, spleen, kidneys, adrenal glands, urinary bladder, gonads, prostate or uterus, brain, and pituitary.

TABLE 1. MATERIALS AND METHODS AND EXPERIMENTAL DESIGN (Continued)

	Single-Dose Study	Fourteen-Day Study	Thirteen-Week Studies	Two-Year Study
Chemical Vehicle/Feed Mixture				
Preparation		Melamine mixed with Lab Chow in a Patterson-Kelly® twin-shell blender.	Aliquots of melamine and feed mixed in a mortar and pestle; premix transferred to 1/2 cubic foot Patterson-Kelly® twin-shell blender, equipped with an intensifier bar; and blended 15 minutes (rats) or 30 minutes (mice) with remaining feed.	Melamine and a small quantity of feed ground in a mortar and pestle. This premix mixed for 10 minutes with remaining feed in Patterson-Kelly® twin-shell blender equipped with an intensifier bar.
Maximum Storage Time	2 hours	2 weeks	2 weeks	3 weeks
Storage Conditions		4°C	4°C	-20°C

(a) Estimated melamine consumption in mg/kg/day for each animal was: 0, 560, 850, 1,100, 1,400, or 1,700 for male rats; 0, 560, 880, 1,200, 1,400 or 1,600 for female rats; 0, 1,400, 2,000, 2,800, 3,900, or 4,700 for male mice; and 0, 1,800, 2,700, 3,500, 4,800, or 5,900 for female mice.

(b) Estimated melamine consumption in mg/kg/day for each animal was: 0, 72, 150, 300, 590, or 1,300 for male rats and 0, 84, 150, 300, 600, or 1,300 for female rats.

III. RESULTS

RATS

SHORT-TERM STUDIES

Single-Dose Study

Fourteen-Day Study

Thirteen-Week Studies

TWO-YEAR STUDY

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

SHORT-TERM STUDIES

Single-Dose Study

Fourteen-Day Study

Thirteen-Week Study

TWO-YEAR STUDY

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

SHORT-TERM STUDIES

Single-Dose Study

Deaths of animals administered a single dose of melamine were dose related. All rats that received 6,810 or 10,000 mg/kg body weight died (Table 2). White crystals (not further identified) were found in the stomach of 3/5 males and 4/5 females that received 10,000 mg/kg body weight, 4/5 males and 5/5 females that received 6,810 mg/kg body weight, 1/5 males and 2/5 females that received 3,160 mg/kg body weight, and 1/5 males that received 2,150 mg/kg body weight. The LD_{50} values and 95% confidence levels were 3,161 (1,344-4,722) mg/kg and 3,828 (2,787-5,255) mg/kg for male and female (F344/N) rats, respectively. These values were determined by probit analysis (Finney, 1964) and were based on deaths occurring within 14 days of administration of melamine.

TABLE 2. MORTALITY OF RATS AFTER ADMINISTRATION OF A SINGLE DOSE OF MELAMINE IN CORN OIL BY GAVAGE

Dose (mg/kg body weight)	Mortality (Day of Death)	
	Males	Females
2,150	2/5 (3,6)	0/5
3,160	1/5 (6)	2/5 (3,4)
4,640	4/5 (2,5,5,11)	3/5 (2,8,11)
6,810	5/5 (3,3,4,4,5)	5/5 (3,3,4,7,9)
10,000	5/5 (2,3,3,4,5)	5/5 (2,4,5,8,8)

Fourteen-Day Study

All test and control animals survived to the end of the dosing period. All female rats and male rats receiving 15,000 ppm or more had mean body weight gain depressions of greater than 43% when compared with controls (Table 3). Male and female rats receiving 20,000 or 30,000 ppm melamine lost weight. A hard crystalline solid was found in the urinary bladder of 4/5 to 5/5 male rats in groups fed 10,000 ppm or more and in 4/5 female rats in groups fed 20,000 ppm or more. The kidneys of 2/5 males that received 30,000 ppm were pale and pitted. No other compound-related effects were observed at necropsy.

TABLE 3. SURVIVAL AND MEAN BODY WEIGHTS OF RATS FED DIETS CONTAINING MELAMINE FOR 14 DAYS

Dose (ppm)	Survival *(a)*	Mean Body Weights (grams)			Weight Change Relative to Controls *(b)* (Percent)
		Initial	Final	Change	
Males					
0	5/5	212	240	+28	
5,000	5/5	217	252	+35	+ 25
10,000	5/5	224	252	+28	0
15,000	5/5	230	239	+ 9	- 68
20,000	5/5	210	202	- 8	-129
30,000	5/5	227	175	-52	-286
Females					
0	5/5	144	158	+14	
5,000	5/5	140	152	+12	- 14
10,000	5/5	152	164	+12	- 14
15,000	5/5	141	149	+ 8	- 43
20,000	5/5	140	132	- 8	-157
30,000	5/5	149	129	-20	-243

(a) Number surviving/number per group

(b) Weight Change Relative to Controls =

$$\frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$$

Thirteen-Week Studies

First Thirteen-Week Study:

One male rat receiving 18,000 ppm and two males receiving 6,000 ppm died (Table 4). Mean body weight gain in males and females receiving 12,000 ppm or more was depressed by more than 8% when compared with controls.

Feed consumption by rats receiving 18,000 ppm was approximately 80%-90% that of controls. Stones were found in the urinary bladders of most dosed male rats, and the incidence was dose related (Table 5). Twenty-five percent (3/12) or more females in the two highest dosed groups had stones.

Histopathologic evaluations were performed on 10 animals of either sex from the high-dose (18,000 ppm), low-dose (6,000 ppm), and control groups. Diffuse epithelial hyperplasia of the urinary bladder was found in 8/10 males and 2/10 females receiving 18,000 ppm melamine, while in animals receiving 6,000 ppm melamine, focal epithelial hyperplasia was observed in only 1/10 males and in none of the females. The urinary bladders of animals from other dosed groups were not examined microscopically. No other compound-related histopathologic effects were observed.

TABLE 4. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF RATS FED DIETS CONTAINING MELAMINE IN THE FIRST 13-WEEK STUDY

Dose (ppm)	Survival *(a)* (Week of Death)	Mean Body Weights (grams)			Weight Change Relative to Respective Controls *(b)* (Percent)	Feed Consumption (Percent of Control)
		Initial	Final	Gain		
Males						
0	12/12	88	297	209		
6,000	10/12 (8,10)	87	287	200	- 4	96
9,000	12/12	90	288	198	- 5	92
12,000	12/12	91	276	185	-11	94
15,000	12/12	92	259	167	-20	90
18,000	11/12 (7)	87	255	168	-20	88
Females						
0	12/12	87	191	104		
6,000	12/12	79	181	102	- 2	87
9,000	12/12	83	187	104	0	94
12,000	12/12	83	179	96	- 8	94
15,000	12/12	82	174	92	-12	84
18,000	12/12	81	165	84	-19	78

(a) Number surviving/number per group

(b) Weight Change Relative to Controls =

$$\frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$$

TABLE 5. INCIDENCE OF RATS WITH URINARY BLADDER STONES OR GRANULAR MATERIAL IN THE FIRST 13-WEEK STUDY

Dose (ppm)	Number of Rats with Urinary Bladder Stones
Males	
0	0/12
6,000	6/12
9,000	8/12
12,000	12/12
15,000	10/12
18,000	12/12
Females	
0	0/12
6,000	0/12
9,000	0/12
12,000	0/12
15,000	3/12
18,000	5/12

Second Thirteen-Week Study:

None of the rats died. Mean body weight gain was depressed by more than 10% when compared with controls for male rats receiving 6,000 and 12,000 ppm, but no depression was observed in any group of dosed females (Table 6).

Feed consumption was not affected by incorporation of melamine in the feed. Other than stones in the bladder of dosed male rats, no compound-related effects were observed at necropsy. The incidence of stones in the urinary bladder of male rats was dose related (Table 7). Stones were present even in the male group receiving 750 ppm. Hyperplasia of the transitional epithelium of the bladder was present in 1/10 male rats receiving 3,000 ppm, in 3/10 receiving 6,000 ppm, and in 9/9 receiving 12,000 ppm melamine. The hyperplastic epithelial changes, which were found only in male rats that had bladder stones, were accompanied by prominent capillaries and occasional edema and scattered mast cells in the submucosa. Kidney changes in male rats were minimal. There was no evidence of urinary bladder stones or hyperplasia of the bladder epithelium in any groups of dosed female rats, but dose-related calcareous deposits were observed in the straight segments of the proximal tubules in female rats (2/10 controls, 3/10 receiving 750 ppm, 4/10 receiving 1,500 ppm, 10/10 receiving 3,000 ppm, 8/10 receiving 6,000 ppm, and 10/10 receiving 12,000 ppm melamine).

TABLE 6. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF RATS FED DIETS CONTAINING MELAMINE IN THE SECOND 13-WEEK STUDY

Dose (ppm)	Survival *(a)*	Mean Body Weights (grams)			Weight Change Relative to Respective Controls *(c)* (Percent)	Feed Consumption (Percent of Control)
		Initial	Final *(b)*	Gain		
Males						
0	10/10	120	312	192		
750	10/10	120	302	182	- 5	86
1,500	10/10	119	302	183	- 5	87
3,000	10/10	120	299	179	- 7	89
6,000	10/10	119	290	171	-11	84
12,000	10/10	119	276	157	-18	86
Females						
0	10/10	95	176	81		
750	10/10	94	179	85	+ 5	100
1,500	10/10	95	179	84	+ 4	91
3,000	10/10	93	175	82	+ 1	87
6,000	10/10	95	176	81	0	89
12,000	10/10	93	173	80	- 1	92

(a) Number surviving/number per group

(b) Weight on day 84

(c) Weight Change Relative to Controls =

$$\frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$$

TABLE 7. INCIDENCE OF RATS WITH URINARY BLADDER STONES AND HYPERPLASIA OF THE BLADDER EPITHELIUM IN THE SECOND 13-WEEK STUDY

Dose (ppm)	Numbers of Rats with Urinary Bladder Stones	Hyperplasia of the Bladder Epithelium
Males		
0	1/10	0/10
750	2/10	0/10
1,500	5/10	0/10
3,000	7/10	1/10
6,000	9/10	3/10
12,000	9/9	9/9
Females		
0	0/10	0/10
750	0/10	0/10
1,500	0/10	0/10
3,000	0/10	0/10
6,000	0/10	0/10
12,000	0/10	0/10

Urine samples were analyzed from male and female rats receiving 750 ppm melamine and compared with urine samples from control rats (Table 8). There were no differences in the urine samples that could be attributed to the presence of melamine in the feed. Microscopic examination of the urine did not provide any evidence of melamine crystalluria.

TABLE 8. ANALYSIS OF URINE FROM RATS IN THE SECOND 13-WEEK STUDY

Dose (ppm)	Sex	Clinical Chemical Analysis *(a)*					Microscopic Examination *(b)*						
										Crystals			
		Color/Appearance	Sp. Gr.	pH	Albumin	Ketones	Epithelial cells	Amorphous Sediment	Bacteria	Uric Acid	Triple Phosphate	Calcium Oxalate	Other
750	Male	Yellow/cloudy	1.045	6.0	2+	1+	Trace	Trace	Trace	2+	Trace	Trace	Unidentified. 6-starred crystal; trace of coarsely granular casts
750	Male	Straw/Slightly Cloudy	1.033	6.0	Trace	0	—	1+	1+	1+	—	—	—
750	Male	Yellow/Slightly Cloudy	1.045	6.0	2+	1+	—	Trace	—	—	—	—	Sperm
750	Male	Straw/Slightly Cloudy	1.031	7.0	Trace	Trace	Trace	Trace	Trace	Trace	Trace	—	Sperm; crystals
750	Male	Yellow/Slightly Cloudy	1.045	6.0	2+	1+	Trace	2+	Trace	3+	—	—	0-1 RBC
750	Female	Straw/Cloudy	1.016	7.0	Trace	0+	Trace	2+	4+	—	Trace	—	Leucine, trace
750	Female	Straw/Slightly Cloudy	1.035	7.0	Trace	Trace	Trace	2+	Trace	2+	2+	—	—
750	Female	Yellow/Slightly Cloudy	1.041	7.0	Trace	Trace	1+	Trace	Trace	—	1+	—	Triple phosphate
750	Female	Yellow/Slightly Cloudy	1.035	6.0	Trace	0	Trace	2+	2+	2+	Trace	Trace	Leucine, trace; 0-1 WBC
0	Male	Yellow/Cloudy	1.045	6.0	1+	1+	Trace	2+	2+	2+	Trace	Trace	Sperm, 1+
0	Female	Straw/Cloudy	1.024	6.0	0	Trace	Trace	1+	1+	—	—	—	—
0	Female	Straw/Cloudy	1.035	6.0	Trace	0	Trace	3+	2+	Trace	Trace	—	Triple phosphate crystals; 0-1 WBC

(a) No glucose, bilirubin, or occult blood was detected in any samples
(b) Microscopic examination per high power field

Third Thirteen-Week Study:

Ammonium chloride was added to the drinking water to see if such treatment might affect the incidence of stone formation in the urinary tract. Rats fed diets containing 18,000 ppm melamine plus 1% ammonium chloride in the drinking water had decreased weight gains relative to groups receiving drinking water acidified with hydrochloric acid (Table 9). The addition of ammonium chloride in the drinking water had no apparent effect on the incidence of urinary bladder stones in male or female rats. Urinary bladder stones were seen in 8/8 males and 3/9 females in the group that received 18,000 ppm melamine in feed plus 1% ammonium chloride in drinking water, compared with 10/10 males and 3/10 females in the groups administered 18,000 ppm melamine in feed without 1% ammonium chloride in the water (Table 9). No other compound-related effects were observed at necropsy.

Because of weight gain depression observed at 6,000 ppm in males (11% in the second 13-week study) and 15,000 ppm in females (12% in the first 13-week study), doses selected for the male rats in the two-year study were 2,250 and 4,500 ppm melamine in feed and those for female rats were 4,500 and 9,000 ppm. Bladder stones and epithelial hyperplasia were not considered to affect survival in a 2-year bioassay.

TABLE 9. SURVIVAL, MEAN BODY WEIGHTS, AND INCIDENCE OF URINARY BLADDER STONES IN RATS FED DIETS CONTAINING MELAMINE FOR 13 WEEKS (WITH AND WITHOUT 1% AMMONIUM CHLORIDE IN THE DRINKING WATER)

Dose (ppm)	Survival *(a)* (Week of Death)	Mean Body Weights (grams)			Weight Change Relative to Controls *(c)* (Percent)	Incidences or Urinary Bladder Stones
		Initial	Final *(b)*	Gain		
Males						
0	10/10	119	301	182		1/10
0 *(d)*	10/10	120	292	172	- 5	0/10
18,000	10/10	100	253	153	-16	10/10
18,000 *(d)*	8/10 (3,3)	120	213	93	-49	8/8
Females						
0	10/10	93	181	88		0/10
0 *(d)*	10/10	93	170	77	-13	0/10
18,000	10/10	94	161	67	-24	3/10
18,000 *(d)*	9/10 (3)	95	126	31	-65	3/9

(a) Number surviving/number per group

(b) Weight at day 84

(c) Weight Change Relative to Controls =

$$\frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$$

(d) 1% Ammonium chloride in drinking water

TWO-YEAR STUDY

Body Weights and Clinical Signs

After week 20, mean body weights of dosed rats of each sex were lower than those of the controls (Table 10 and Figure 1). The average daily feed consumption per rat by low- and high-dose rats was 97% and 99% that of the controls for males and 99% and 99% for females (Appendix H, Table H1). No compound-related clinical signs were observed.

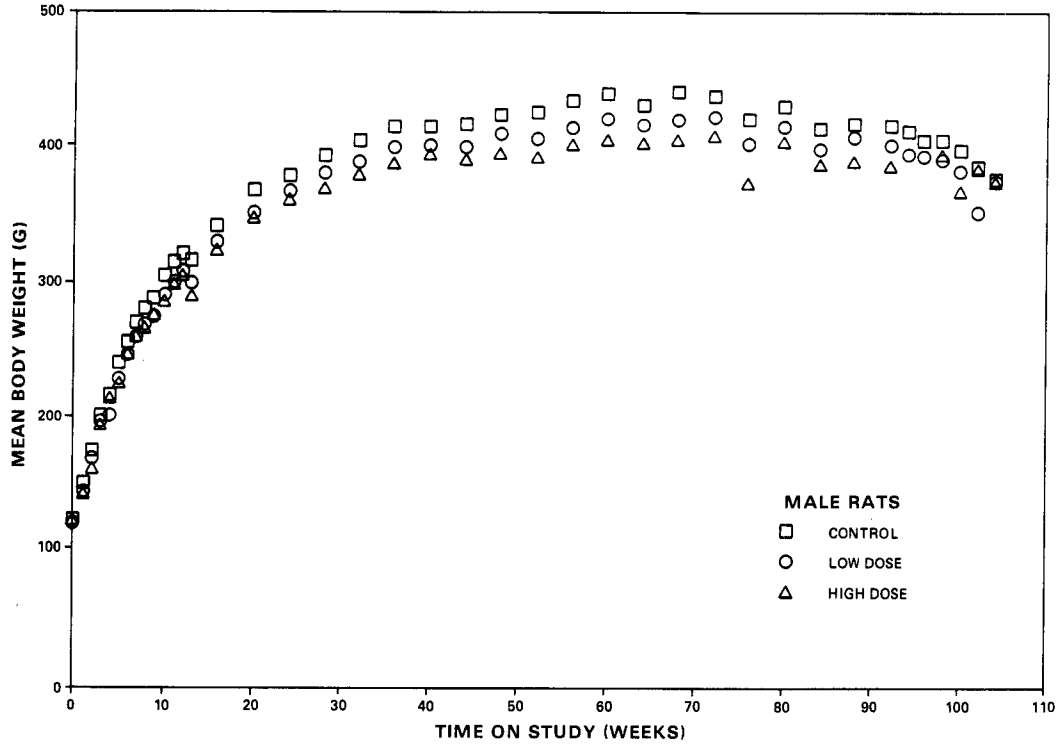
TABLE 10. CUMULATIVE MEAN BODY WEIGHT CHANGE (RELATIVE TO CONTROLS) OF RATS FED DIETS CONTAINING MELAMINE IN THE 2-YEAR STUDY

	Cumulative Mean Body Weight Change (grams)			Weight Change Relative to Controls *(a)* (Percent)	
Week No.	Control	Low Dose	High Dose	Low Dose	High Dose
Males					
0	121 *(b)*	118 *(b)*	121 *(b)*		
1	27	24	18	-11	-33
20	245	234	226	- 4	- 8
40	293	282	271	- 4	- 8
60	318	303	283	- 5	-11
80	308	296	282	- 4	- 8
100	275	262	244	- 5	-11
Females					
0	105 *(b)*	105 *(b)*	106 *(b)*		
1	14	12	9	-14	-36
20	111	109	108	- 2	- 3
40	141	135	131	- 4	- 7
60	172	164	155	- 5	-10
80	202	194	173	- 4	-14
100	185	175	177	- 5	- 4

(a) Weight Change Relative to Controls =

$$\frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$$

(b) Initial Weight



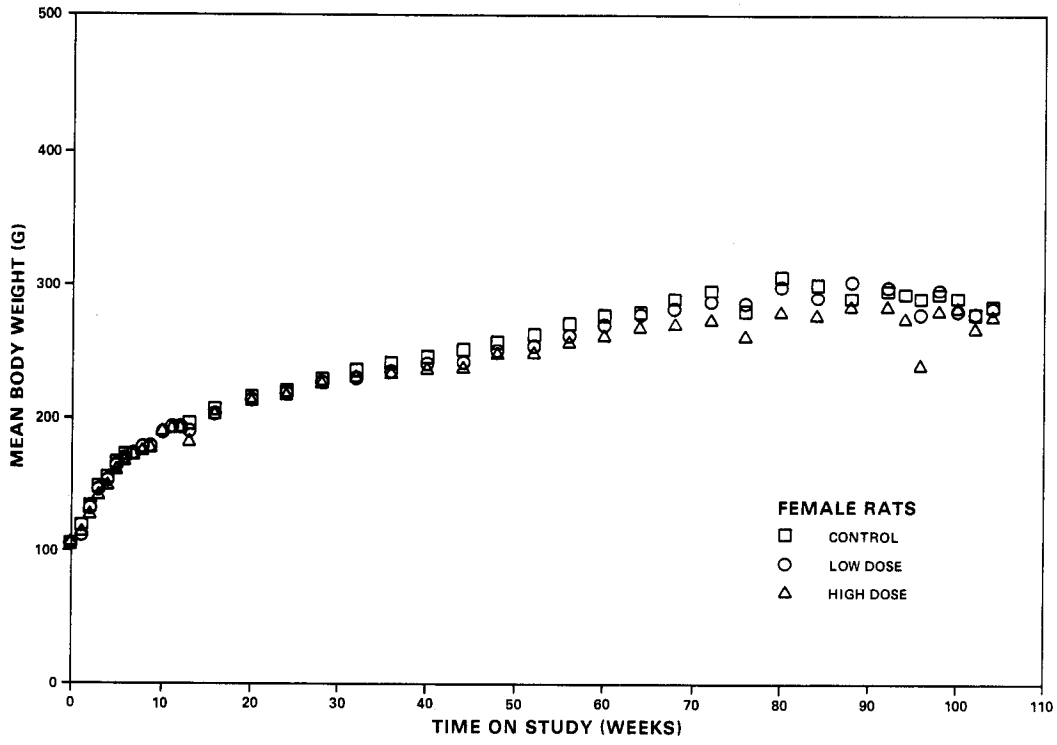


Figure 1. Growth Curves for Rats Fed Diets Containing Melamine

Survival

Estimates of the probabilities of survival of male and female rats fed diets containing melamine at the concentrations of this bioassay, together with those of the control group, are shown by the Kaplan and Meier curves in Figure 2. One control rat in the male group was missexed and removed from the study. The survival of the high-dose group of male rats was significantly reduced when compared with that of the controls (P=0.03). No significant differences were observed between any other groups of either sex.

In male rats, 30/49 (61%) of the controls, 30/50 (60%) of the low-dose, and 19/50 (38%) of the high-dose group lived to the termination period of the study at 105 weeks; 30/50 (60%) of the high-dose group of male rats survived 92 weeks of the study. In female rats, 34/50 (68%) of the controls, 30/50 (60%) of the low-dose, and 27/50 (54%) of the high-dose group lived to the termination period of the study at 105 weeks. The survival data include one low-dose and one high-dose male rat that died during the termination period of the study. For statistical purposes, these animals are considered to have been killed at the end of the study.

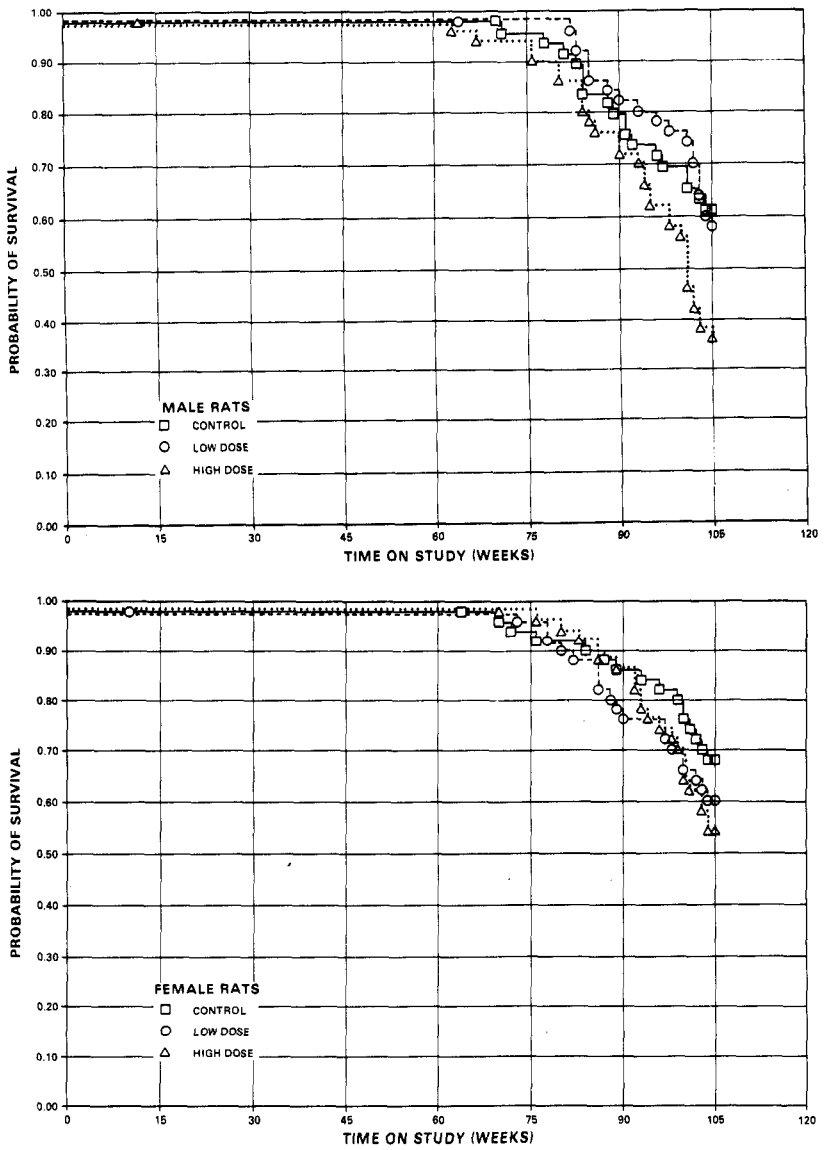


Figure 2. Survival Curves for Rats Fed Diets Containing Melamine

Pathology and Statistical Analyses of Results

Histopathologic findings on neoplasms in rats are summarized in Appendix A, Tables A1 and A2; findings on nonneoplastic lesions are summarized in Appendix C, Tables C1 and C2. Appendix Tables A3 and A4 give the survival and tumor status for each individual animal in the male rat and female rat studies, respectively.

Incidences of urinary bladder and kidney lesions are presented in Table 11. Tables 12 and 13 contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups.

Urinary Bladder: Transitional-cell carcinomas in the urinary bladder of male rats occurred with a statistically significant ($P \leq 0.002$) positive trend (controls, 0/45; low-dose, 0/50; high-dose, 8/49, 16%) and the incidence in the high-dose group was significantly higher ($P \leq 0.016$) than that in the controls (Tables 11 and 12). The combined incidence of transitional-cell carcinomas and papillomas showed a statistically significant ($P < 0.001$) positive trend (controls, 0/45; low-dose, 0/50; high-dose, 9/49, 18%) and the incidence in high-dose rats was significantly higher ($P \leq 0.008$) than that in the controls. These tumors were not observed in statistically significant proportions in female rats (0/49, 1/49, 1/47).

The transitional-cell carcinomas were visualized grossly as 1- to 1.5-cm masses attached to the mucosal surface of the urinary bladder. Seven of the eight high-dose male rats with transitional-cell carcinomas also had bladder stones (calculi). Microscopically, most of the carcinomas had transitional-like cells that formed protrusions into the bladder lumens. Some had papillary areas. The carcinomas had moderate numbers of mitoses and some nuclear pleomorphism. Discrete invasions through the bladder wall occurred in one male rat, but no metastases were evident in the lungs or other tissues.

Kidney: Chronic inflammation was observed in significantly ($P \leq 0.01$) increased incidence in dosed female rats (Table 11). The dose relationship and intensity of the increased interstitial lymphoplasmocytic infiltrates and cortical fibrosis clearly set these changes apart from the minor inflammatory component that may accompany the progressive nephropathy normally encountered in aging F344/N rats. The changes in the high-dose females were often observed grossly as pitted or roughened renal cortical surfaces. Chronic inflammation of the kidney was not significant in dosed male rats. In those animals in which this lesion was observed, there was no correlation with urinary bladder stones.

Pancreas: Pancreatic islet-cell carcinomas in male rats occurred with a statistically significant ($P=0.034$) negative trend (control, 3/44, 7%; low-dose, 0/48; high-dose, 0/45) by the Cochran-Armitage test. The incidences were not significant in pairwise comparisons between the dosed groups and the controls, and these tumors were not observed in female rats. Total pancreatic islet-cell tumors (adenomas or carcinomas) were not significantly different for either sex of rats.

Thyroid: C-cell carcinoma in the thyroid was observed in female rats with a statistically significant ($P \leq 0.038$) positive trend (controls, 0/50; low-dose, 0/49; high-dose, 3/50, 6%). Neither the pairwise comparisons of the high-dose group with the controls nor the combination of C-cell adenomas or carcinomas was statistically significant in any of the tests. These tumors were not observed in statistically significant proportions in male rats.

Uterus: Endometrial stromal polyps were observed in statistically significant ($P \leq 0.017$) negative trend (controls, 11/50, 22%; low-dose, 7/50, 14%; high-dose, 2/50, 4%) and in decreased incidence ($P \leq 0.022$) in the high-dose group in a pairwise comparison with the controls. The combined incidence of endometrial stromal polyps and sarcomas was statistically significant ($P \leq 0.017$) in the negative direction (controls, 14/50, 28%; low-dose, 7/50, 14%; high-dose, 4/50, 8%). A significantly lower ($P \leq 0.029$) incidence in the high-dose group was observed in the pairwise comparisons with the controls. The combined incidence of endometrial stromal polyps and sarcomas in the high-dose group was not significantly different from the historical rate of this tumor in untreated female F344/N rats (Appendix J, Table J3) at the same laboratory (117/759, 15.4%).

TABLE 11. INCIDENCE OF URINARY BLADDER AND KIDNEY LESIONS IN RATS IN THE 2-YEAR STUDY

	Males			Females		
	Control	Low Dose (2250 ppm)	High Dose (4500 ppm)	Control	Low Dose (4500 ppm)	High Dose (9000 ppm)
Urinary Bladder						
No. of animals with tissues examined microscopically	45	50	49	49	49	47
Transitional-cell carcinoma	0	0	8 (16%) *(a)*	0	0	0
Transitional-cell papilloma	0	0	1 (2%)	0	1 (2%)	1 (2%)
Transitional-cell hyperplasia	0	1 (2%)	2 (4%)	0	0	0
Stones (calculi) *(b)*	0	1 (2%)	10 (20%) *(c)*	0	0	0
Kidney						
No. of animals with tissues examined microscopically	49	50	49	50	50	50
Chronic inflammation	2 (4%)	3 (6%)	6 (12%)	4 (8%)	17 (34%) *(c)*	41 (82%) *(c)*
Nephropathy	32 (65%)	36 (72%)	30 (61%)	19 (38%)	23 (46%)	28 (56%)

(a) $P \leq 0.016$, relative to controls
(b) Observed at necropsy or by microscopic examination.
(c) $P \leq 0.01$, relative to controls

TABLE 12. ANALYSIS OF PRIMARY TUMORS IN MALE RATS *(a)*

	Control	Low Dose (2250 ppm)	High Dose (4500 ppm)
Hematopoietic System: Myelomonocytic Leukemia			
Tumor Rates			
Overall *(b)*	5/49(10%)	11/50(22%)	8/50(16%)
Adjusted *(c)*	13.9%	29.8%	29.9%
Terminal *(d)*	2/30(7%)	6/30(20%)	3/19(16%)
Statistical Tests *(e)*			
Life Table	P=0.097	P=0.118	P=0.138
Incidental Tumor Test	P=0.427	P=0.139	P=0.504
Cochran-Armitage Trend, Fisher Exact Tests	P=0.256	P=0.093	P=0.290
Hematopoietic System: Leukemia			
Tumor Rates			
Overall *(b)*	8/49(16%)	11/50(22%)	8/50(16%)
Adjusted *(c)*	20.7%	29.8%	29.9%
Terminal *(d)*	2/30(7%)	6/30(20%)	3/19(16%)
Statistical Tests *(e)*			
Life Table	P=0.315	P=0.364	P=0.401
Incidental Tumor Test	P=0.331N	P=0.419	P=0.341N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.539N	P=0.323	P=0.590N
Hematopoietic System: Lymphoma or Leukemia			
Tumor Rates			
Overall *(b)*	8/49(16%)	12/50(24%)	8/50(16%)
Adjusted *(c)*	20.7%	32.7%	29.9%
Terminal *(d)*	2/30(7%)	7/30(23%)	3/19(16%)
Statistical Tests *(e)*			
Life Table	P=0.304	P=0.283	P=0.401
Incidental Tumor Test	P=0.349N	P=0.324	P=0.341N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.539N	P=0.242	P=0.590N
Urinary Bladder: Transitional-Cell Carcinoma			
Tumor Rates			
Overall *(b)*	0/45(0%)	0/50(0%)	8/49(16%)
Adjusted *(c)*	0.0%	0.0%	25.0%
Terminal *(d)*	0/29(0%)	0/30(0%)	2/19(11%)
Statistical Tests *(e)*			
Life Table	P<0.001	*(g)*	P=0.003
Incidental Tumor Test	P=0.002	*(g)*	P=0.016
Cochran-Armitage Trend, Fisher Exact Tests	P<0.001	*(g)*	P=0.004
Urinary Bladder: Transitional-Cell Papilloma or Carcinoma			
Tumor Rates			
Overall *(b)*	0/45(0%)	0/50(0%)	9/49(18%)*(f)*
Adjusted *(c)*	0.0%	0.0%	25.9%
Terminal *(d)*	0/29(0%)	0/30(0%)	2/19(11%)
Statistical Tests *(e)*			
Life Table	P<0.001	*(g)*	P=0.002
Incidental Tumor Test	P<0.001	*(g)*	P=0.008
Cochran-Armitage Trend, Fisher Exact Tests	P<0.001	*(g)*	P=0.002

TABLE 12. ANALYSIS OF PRIMARY TUMORS IN MALE RATS *(a)* (Continued)

	Control	Low Dose (2250 ppm)	High Dose (4500 ppm)
Pituitary: Chromophobe Adenoma			
Tumor Rates			
Overall *(b)*	7/45(16%)	10/46(22%)	8/49(16%)
Adjusted *(c)*	21.0%	31.0%	34.9%
Terminal *(d)*	4/29(14%)	7/27(26%)	6/19(32%)
Statistical Tests *(e)*			
Life Table	P=0.193	P=0.288	P=0.234
Incidental Tumor Test	P=0.335	P=0.354	P=0.401
Cochran-Armitage Trend, Fisher Exact Tests	P=0.523	P=0.314	P=0.572
Pituitary: Chromophobe Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	9/45(20%)	11/46(24%)	8/49(16%)
Adjusted *(c)*	27.3%	32.5%	34.9%
Terminal *(d)*	6/29(21%)	7/27(26%)	6/19(32%)
Statistical Tests *(e)*			
Life Table	P=0.354	P=0.388	P=0.394
Incidental Tumor Test	P=0.529	P=0.453	P=0.580
Cochran-Armitage Trend, Fisher Exact Tests	P=0.369N	P=0.422	P=0.422N
Adrenal: Pheochromocytoma			
Tumor Rates			
Overall *(b)*	7/49(14%)	9/50(18%)	10/48(21%)
Adjusted *(c)*	21.2%	27.5%	40.9%
Terminal *(d)*	5/30(17%)	7/30(23%)	6/19(32%)
Statistical Tests *(e)*			
Life Table	P=0.066	P=0.414	P=0.092
Incidental Tumor Test	P=0.191	P=0.475	P=0.229
Cochran-Armitage Trend, Fisher Exact Tests	P=0.239	P=0.410	P=0.281
Thyroid: C-Cell Adenoma			
Tumor Rates			
Overall *(b)*	3/48(6%)	2/50(4%)	2/46(4%)
Adjusted *(c)*	10.0%	6.0%	11.8%
Terminal *(d)*	3/30(10%)	1/30(3%)	2/17(12%)
Statistical Tests *(e)*			
Life Table	P=0.584	P=0.487N	P=0.618
Incidental Tumor Test	P=0.538N	P=0.446N	P=0.618
Cochran-Armitage Trend, Fisher Exact Tests	P=0.422N	P=0.480N	P=0.520N
Thyroid: C-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	4/48(8%)	2/50(4%)	2/46(4%)
Adjusted *(c)*	13.3%	6.0%	11.8%
Terminal *(d)*	4/30(13%)	1/30(3%)	2/17(12%)
Statistical Tests *(e)*			
Life Table	P=0.455N	P=0.326N	P=0.617N
Incidental Tumor Test	P=0.377N	P=0.292N	P=0.617N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.266N	P=0.319N	P=0.359N

TABLE 12. ANALYSIS OF PRIMARY TUMORS IN MALE RATS *(a)* (Continued)

	Control	Low Dose (2250 ppm)	High Dose (4500 ppm)
Pancreatic Islets: Islet-Cell Carcinoma			
Tumor Rates			
Overall *(b)*	3/44(7%)	0/48(0%)	0/45(0%)
Adjusted *(c)*	10.3%	0.0%	0.0%
Terminal *(d)*	3/29(10%)	0/29(0%)	0/19(0%)
Statistical Tests *(e)*			
Life Table	P=0.056N	P=0.120N	P=0.203N
Incidental Tumor Test	P=0.056N	P=0.120N	P=0.203N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.034N	P=0.105N	P=0.117N
Pancreatic Islets: Islet-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	3/44(7%)	2/48(4%)	2/45(4%)
Adjusted *(c)*	10.3%	5.5%	7.6%
Terminal *(d)*	3/29(10%)	1/29(3%)	1/19(5%)
Statistical Tests *(e)*			
Life Table	P=0.532N	P=0.492N	P=0.659N
Incidental Tumor Test	P=0.529N	P=0.500N	P=0.651N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.395N	P=0.458N	P=0.489N
Preputial Gland: Adenoma, Adenocarcinoma, or Carcinoma			
Tumor Rates			
Overall *(b)*	4/49(8%)	2/50(4%)	1/50(2%)
Adjusted *(c)*	12.2%	5.7%	5.3%
Terminal *(d)*	3/30(10%)	1/30(3%)	1/19(5%)
Statistical Tests *(e)*			
Life Table	P=0.191N	P=0.325N	P=0.309N
Incidental Tumor Test	P=0.152N	P=0.310N	P=0.312N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.113N	P=0.329N	P=0.175N
Prostate: Adenoma			
Tumor Rates			
Overall *(b)*	5/49(10%)	3/48(6%)	3/46(7%)
Adjusted *(c)*	16.7%	8.8%	15.7%
Terminal *(d)*	5/30(17%)	2/29(7%)	2/16(13%)
Statistical Tests *(e)*			
Life Table	P=0.541N	P=0.367N	P=0.617
Incidental Tumor Test	P=0.482N	P=0.388N	P=0.606N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.312N	P=0.369N	P=0.393N
Testis: Interstitial-Cell Tumor			
Tumor Rates			
Overall *(b)*	42/49(86%)	44/50(88%)	42/50(84%)
Adjusted *(c)*	95.4%	100.0%	97.6%
Terminal *(d)*	28/30(93%)	30/30(100%)	18/19(95%)
Statistical Tests *(e)*			
Incidental Tumor Test	P=0.561N	P=0.555N	P=0.607N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.463N	P=0.484	P=0.517N

TABLE 12. ANALYSIS OF PRIMARY TUMORS IN MALE RATS *(a)* (Continued)

	Control	Low Dose (2250 ppm)	High Dose (4500 ppm)
Mammary Gland: Fibroadenoma			
Tumor Rates			
Overall *(b)*	0/49(0%)	3/50(6%)	0/50(0%)
Adjusted *(c)*	0.0%	8.9%	0.0%
Terminal *(d)*	0/30(0%)	1/30(3%)	0/19(0%)
Statistical Tests *(e)*			
Life Table	P=0.526	P=0.135	*(g)*
Incidental Tumor Test	P=0.514N	P=0.196	*(g)*
Cochran-Armitage Trend, Fisher Exact Tests	P=0.634N	P=0.125	*(g)*

(a) Dosed groups received doses of 2,250 or 4,500 ppm of melamine in the diet.
(b) Number of tumor bearing animals/number of animals examined at the site.
(c) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(d) Observed tumor incidence at terminal kill.
(e) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidences are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dose group is indicated by (N).
(f) One animal had a transitional-cell papilloma.
(g) Not statistically significant; no tumors observed in dosed or control groups.

TABLE 13. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS *(a)*

	Control	Low Dose (4500 ppm)	High Dose (9000 ppm)
Hematopoietic System: Myelomonocytic Leukemia			
Tumor Rates			
Overall *(b)*	6/50(12%)	6/50(12%)	6/50(12%)
Adjusted *(c)*	15.4%	16.2%	16.0%
Terminal *(d)*	3/34(9%)	2/30(7%)	2/27(7%)
Statistical Tests *(e)*			
Life Table	P=0.466	P=0.542	P=0.523
Incidental Tumor Test	P=0.378N	P=0.588N	P=0.461N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.561	P=0.620	P=0.620
Hematopoietic System: Leukemia			
Tumor Rates			
Overall *(b)*	9/50(18%)	11/50(22%)	8/50(16%)
Adjusted *(c)*	21.6%	27.1%	19.7%
Terminal *(d)*	4/34(12%)	3/30(10%)	2/27(7%)
Statistical Tests *(e)*			
Life Table	P=0.546	P=0.334	P=0.588N
Incidental Tumor Test	P=0.282N	P=0.405	P=0.280N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.449N	P=0.402	P=0.500N
Hematopoietic System: Lymphoma or Leukemia			
Tumor Rates			
Overall *(b)*	9/50(18%)	11/50(22%)	10/50(20%)
Adjusted *(c)*	21.6%	27.1%	23.8%
Terminal *(d)*	4/34(12%)	3/30(10%)	2/27(7%)
Statistical Tests *(e)*			
Life Table	P=0.363	P=0.334	P=0.410
Incidental Tumor Test	P=0.444N	P=0.405	P=0.425N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.450	P=0.402	P=0.500
Pituitary: Chromophobe Adenoma			
Tumor Rates			
Overall *(b)*	20/50(40%)	22/49(45%)	19/50(38%)
Adjusted *(c)*	50.6%	64.3%	51.3%
Terminal *(d)*	15/34(44%)	18/30(60%)	10/27(37%)
Statistical Tests *(e)*			
Life Table	P=0.325	P=0.240	P=0.390
Incidental Tumor Test	P=0.501N	P=0.238	P=0.471N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.460N	P=0.386	P=0.500N
Pituitary: Chromophobe Carcinoma			
Tumor Rates			
Overall *(b)*	2/50(4%)	4/49(8%)	1/50(2%)
Adjusted *(c)*	5.9%	10.1%	3.7%
Terminal *(d)*	2/34(6%)	1/30(3%)	1/27(4%)
Statistical Tests *(e)*			
Life Table	P=0.468N	P=0.303	P=0.581N
Incidental Tumor Test	P=0.439N	P=0.317	P=0.581N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.407N	P=0.329	P=0.500N

TABLE 13. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS *(a)* (Continued)

	Control	Low Dose (4500 ppm)	High Dose (9000 ppm)
Pituitary: Chromophobe Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	22/50(44%)	26/49(53%)	20/50(40%)
Adjusted *(c)*	55.8%	69.5%	54.2%
Terminal *(d)*	17/34(50%)	19/30(63%)	11/27(41%)
Statistical Tests *(e)*			
Life Table	P=0.377	P=0.136	P=0.438
Incidental Tumor Test	P=0.434N	P=0.128	P=0.418N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.382N	P=0.242	P=0.420N
Adrenal: Cortical Adenoma			
Tumor Rates			
Overall *(b)*	3/50(6%)	0/50(0%)	1/50(2%)
Adjusted *(c)*	8.8%	0.0%	3.7%
Terminal *(d)*	3/34(9%)	0/30(0%)	1/27(4%)
Statistical Tests *(e)*			
Life Table	P=0.228N	P=0.143N	P=0.390N
Incidental Tumor Test	P=0.228N	P=0.143N	P=0.390N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.176N	P=0.121N	P=0.309N
Thyroid: C-Cell Carcinoma			
Tumor Rates			
Overall *(b)*	0/50(0%)	0/49(0%)	3/50(6%)
Adjusted *(c)*	0.0%	0.0%	11.1%
Terminal *(d)*	0/34(0%)	0/30(0%)	3/27(11%)
Statistical Tests *(e)*			
Life Table	P=0.025	*(f)*	P=0.083
Incidental Tumor Test	P=0.025	*(f)*	P=0.083
Cochran-Armitage Trend, Fisher Exact Tests	P=0.038	*(f)*	P=0.121
Thyroid: C-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	0/50(0%)	2/49(4%)	3/50(6%)
Adjusted *(c)*	0.0%	6.7%	11.1%
Terminal *(d)*	0/34(0%)	2/30(7%)	3/27(11%)
Statistical Tests *(e)*			
Life Table	P=0.053	P=0.211	P=0.083
Incidental Tumor Test	P=0.053	P=0.211	P=0.083
Cochran-Armitage Trend, Fisher Exact Tests	P=0.083	P=0.242	P=0.121
Mammary Gland: Fibroadenoma			
Tumor Rates			
Overall *(b)*	11/50(22%)	11/50(22%)	6/50(12%)
Adjusted *(c)*	28.5%	31.4%	20.7%
Terminal *(d)*	7/34(21%)	7/30(23%)	4/27(15%)
Statistical Tests *(e)*			
Life Table	P=0.251N	P=0.474	P=0.276N
Incidental Tumor Test	P=0.129N	P=0.508	P=0.135N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.124N	P=0.595	P=0.143N

TABLE 13. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS *(a)* (Continued)

	Control	Low Dose (4500 ppm)	High Dose (9000 ppm)
Preputial Gland: Adenoma, Carcinoma, or Cystadenoma			
Tumor Rates			
Overall *(b)*	0/50(0%)	3/50(6%)	2/50(4%)
Adjusted *(c)*	0.0%	9.6%	5.9%
Terminal *(d)*	0/34(0%)	2/30(7%)	1/27(4%)
Statistical Tests *(e)*			
Life Table	P=0.164	P=0.102	P=0.215
Incidental Tumor Test	P=0.225	P=0.102	P=0.298
Cochran-Armitage Trend, Fisher Exact Tests	P=0.202	P=0.121	P=0.274
Uterus: Endometrial Stromal Polyp			
Tumor Rates			
Overall *(b)*	11/50(22%)	7/50(14%)	2/50(4%)
Adjusted *(c)*	31.2%	19.3%	7.4%
Terminal *(d)*	10/34(29%)	4/30(13%)	2/27(7%)
Statistical Tests *(e)*			
Life Table	P=0.017N	P=0.304N	P=0.022N
Incidental Tumor Test	P=0.007N	P=0.179N	P=0.018N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.006N	P=0.218N	P=0.007N
Uterus: Endometrial Stromal Sarcoma			
Tumor Rates			
Overall *(b)*	3/50(6%)	0/50(0%)	2/50(4%)
Adjusted *(c)*	8.8%	0.0%	6.1%
Terminal *(d)*	3/34(9%)	0/30(0%)	1/27(4%)
Statistical Tests *(e)*			
Life Table	P=0.461N	P=0.143N	P=0.588N
Incidental Tumor Test	P=0.423N	P=0.143N	P=0.544N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.390N	P=0.121N	P=0.500N
Uterus: Endometrial Stromal Polyp or Sarcoma			
Tumor Rates			
Overall *(b)*	14/50(28%)	7/50(14%)	4/50(8%)
Adjusted *(c)*	39.8%	19.3%	13.3%
Terminal *(d)*	13/34(38%)	4/30(13%)	3/27(11%)
Statistical Tests *(e)*			
Life Table	P=0.017N	P=0.119N	P=0.029N
Incidental Tumor Test	P=0.007N	P=0.057N	P=0.020N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.005N	P=0.070N	P=0.009N

(a) Dosed groups received doses of 4,500 or 9,000 ppm of melamine in the diet.

(b) Number of tumor bearing animals/number of animals examined at the site.

(c) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.

(d) Observed tumor incidence at terminal kill.

(e) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidences are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

(f) Not statistically significant; no tumors observed in control or dosed groups.

SHORT-TERM STUDIES

Single-Dose Study

All animals receiving 10,000 or 14,700 mg/kg body weight died (Table 14). Deaths were dose related. No compound-related toxic effects were observed at necropsy. The LD_{50} values and 95% confidence levels were 3,296 (2,335-4,722) mg/kg and 7,014 (5,798-8,486) mg/kg for male and female $B6C3F_1$ mice, respectively. These values were determined by probit analysis (Finney, 1964) and were based on deaths occurring within 14 days of compound administration.

TABLE 14. MORTALITY OF MICE AFTER ADMINISTRATION OF A SINGLE DOSE OF MELAMINE IN CORN OIL BY GAVAGE

Dose (mg/kg)	Mortality (Day of Death)	
	Males	Females
1,470	0/5	—
2,150	1/5 (4)	—
3,160	3/5 (3, 4, 4)	0/5
4,640	3/5 (4, 5, 5)	0/5
6,810	5/5 (3, 3, 3, 4, 6)	2/5 (3, 4)
10,000	5/5 (2, 2, 2, 2, 2)	5/5 (2, 2, 2, 2, 4)
14,700	5/5 (2, 2, 2, 2, 2)	5/5 (2, 2, 2, 2, 2)

Fourteen-Day Study

All animals survived to the end of the study. Weight changes were difficult to interpret because control male mice gained no weight (Table 15). A hard, crystalline solid was found in the urinary bladder of all male mice and in 2/5 female mice fed diets containing 30,000 ppm melamine. No other compound-related effects were observed at necropsy.

Thirteen-Week Study

One female mouse receiving 9,000 ppm died (Table 16). Mean body weight gain relative to controls was depressed by 9% or more in all dosed groups. Feed consumption data were not considered reliable because the mice scattered the contents of their feeders.

TABLE 15. SURVIVAL AND MEAN BODY WEIGHTS OF MICE FED DIETS CONTAINING MELAMINE FOR 14 DAYS

Dose (ppm)	Survival *(a)*	Mean Body Weights (grams)		
		Initial	Final *(b)*	Change
Males				
0	5/5	24	24	0
5,000	5/5	22	21	-1
7,500	5/5	23	24	+1
10,000	5/5	25	23	-2
12,500	5/5	26	25	-1
15,000	5/5	24	25	+1
30,000	5/5	27	24	-3
Females				
0	5/5	18	20	+2
5,000	5/5	19	19	0
7,500	5/5	18	18	0
10,000	5/5	18	20	+2
12,500	5/5	21	20	-1
15,000	5/5	19	19	0
30,000	5/5	19	19	0

(a) Number surviving/number per group
(b) Weight at day 14

TABLE 16. SURVIVAL AND MEAN BODY WEIGHTS OF MICE FED DIETS CONTAINING MELAMINE FOR 13 WEEKS

Dose (ppm)	Survival *(a)*	Mean Body Weights (grams)			Weight Change Relative to Controls *(c)* (Percent)
		Initial	Final	Gain	
Males					
0	10/10	19	30	+11	
6,000	10/10	19	29	+10	- 9
9,000	10/10	19	25	+ 6	-45
12,000	10/10	19	27	+ 8	-27
15,000	10/10	19	26	+ 7	-36
18,000	10/10	19	26	+ 7	-36
Females					
0	10/10	16	26	+10	
6,000	10/10	15	23	+ 8	-20
9,000	9/10	16	25	+ 9	-10
12,000	10/10	16	24	+ 8	-20
15,000	10/10	16	23	+ 7	-30
18,000	10/10	16	23	+ 7	-30

(a) Number surviving/number per group
(b) Weight at day 84
(c) Weight Change Relative to Controls =

$$\frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$$

The incidence of mice with bladder stones, observed at necropsy or by microscopic examination, was dose related and was greater in males than in females (Table 17). Ulceration of the urinary bladder epithelium was also dose related. Sixty percent of the mice having bladder ulcers also had urinary bladder stones; 40% did not. Bladder ulcers were multifocal or associated with inflammation (cystitis). The distribution of bladder ulcers among male and female mice, and the correspondence with bladder stones are shown in Table 17. These results do not provide evidence for an association between ulceration and bladder stones in either sex. Epithelial hyperplasia in the bladder was observed in 2/10 males fed 18,000 ppm melamine. Both animals also had bladder stones. Epithelial cell atypia was seen in 2/10 males fed 9,000 ppm melamine. Because of epithelial changes in the bladder in males fed 9,000 ppm melamine and the death of one female fed 9,000 ppm melamine, doses of 2,250 and 4,500 ppm melamine in feed were selected for mice in the two-year study.

TABLE 17. INCIDENCE OF MICE WITH BLADDER STONES AND ULCERATION OF THE URINARY BLADDER EPITHELIUM IN THE 13-WEEK STUDY

Dose (ppm)	Mice with Bladder Stones	Mice with Multifocal Ulceration	Mice with Ulcerative Cystitis
Males			
		(a)	*(a)*
0	0/10	0/10 (0)	0/10 (0)
6,000	0/10	0/10 (0)	0/10 (0)
9,000	0/10	0/10 (0)	2/10 (0)
12,000	6/10	2/10 (0)	1/10 (0)
15,000	9/10	3/10 (3)	2/10 (2)
18,000	7/10	4/10 (3)	2/10 (2)
Females			
0	0/10	0/10 (0)	0/10 (0)
6,000	0/10	0/10 (0)	0/10 (0)
9,000	0/10	1/10 (0)	0/10 (0)
12,000	1/10	0/10 (0)	0/10 (0)
15,000	3/10	2/10 (1)	1/10 (1)
18,000	7/10	1/10 (0)	2/10 (2)

(a) Number of mice with bladder ulcers that also had bladder stones.

TWO-YEAR STUDY

Body Weights and Clinical Signs

Mean body weights of high-dose male mice were slightly lower than those of the controls after week 50 of the study; mean body weights of dosed and control female mice were comparable throughout the study (Figure 3 and Table 18). The average daily feed consumption per mouse by low- and high-dose mice was 93% and 95% that of the controls for males and 88% and 87% for females (Appendix H, Table H2). No other compound-related clinical signs were observed.

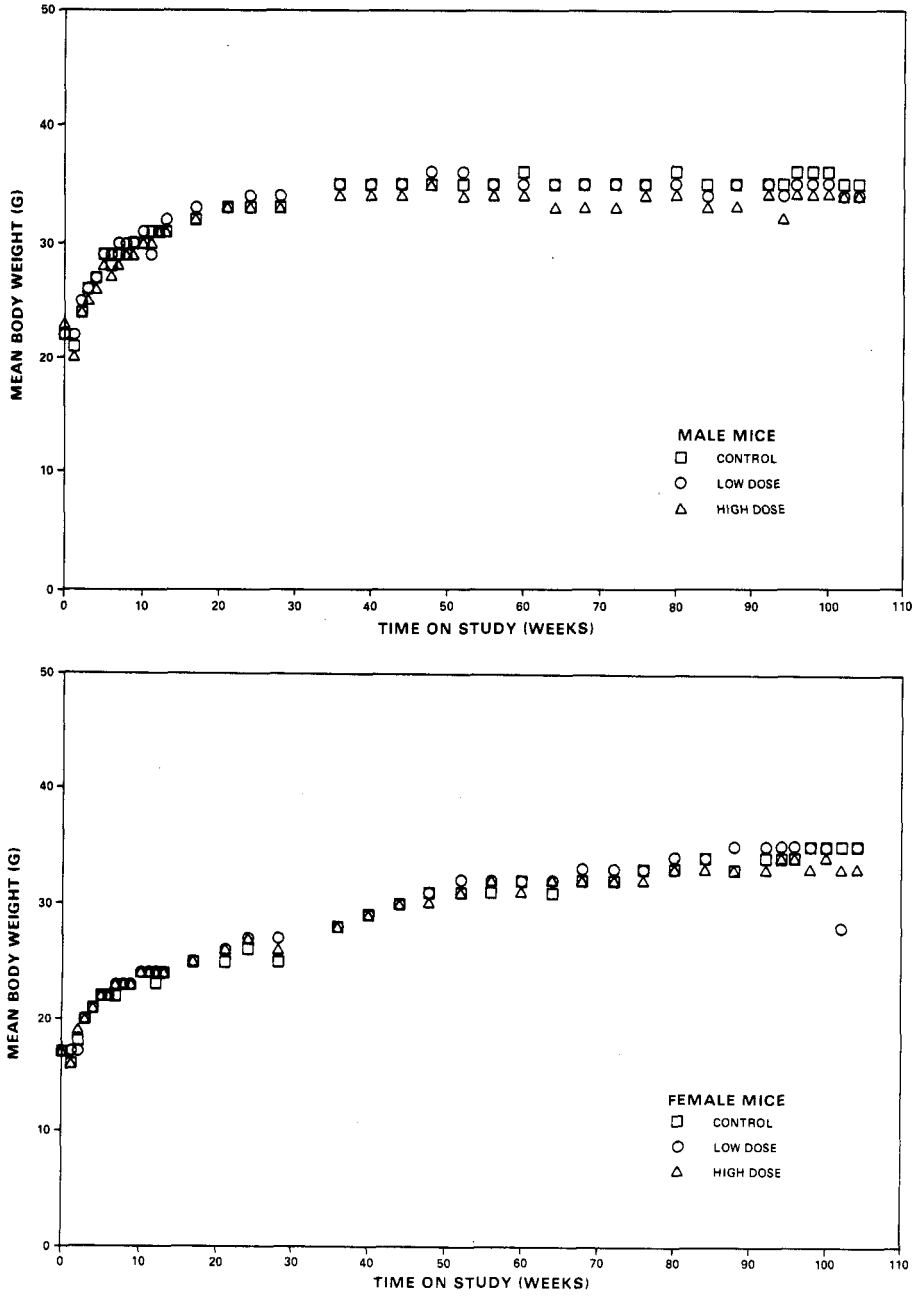


Figure 3. Growth Curves for Mice Fed Diets Containing Melamine

TABLE 18. CUMULATIVE MEAN BODY WEIGHT CHANGE (RELATIVE TO CONTROLS) OF MICE FED DIETS CONTAINING MELAMINE IN THE 2-YEAR STUDY

	Cumulative Mean Body Weight Change (grams)			Weight Change Relative to Controls *(a)* (Percent)	
Week No.	Control	Low Dose	High Dose	Low Dose	High Dose
Males					
0	22 *(b)*	22 *(b)*	23 *(b)*		
21	11	11	10	0	- 9
40	13	13	11	0	-15
60	14	13	11	- 7	-21
80	14	13	11	- 7	-21
100	14	13	11	- 7	-21
Females					
0	17 *(b)*	17 *(b)*	17 *(b)*		
21	8	9	9	+13	+13
40	12	12	12	0	0
60	15	15	14	0	- 7
80	16	17	16	+ 6	0
100	18	18	17	0	- 6

(a) Weight Change Relative to Controls =

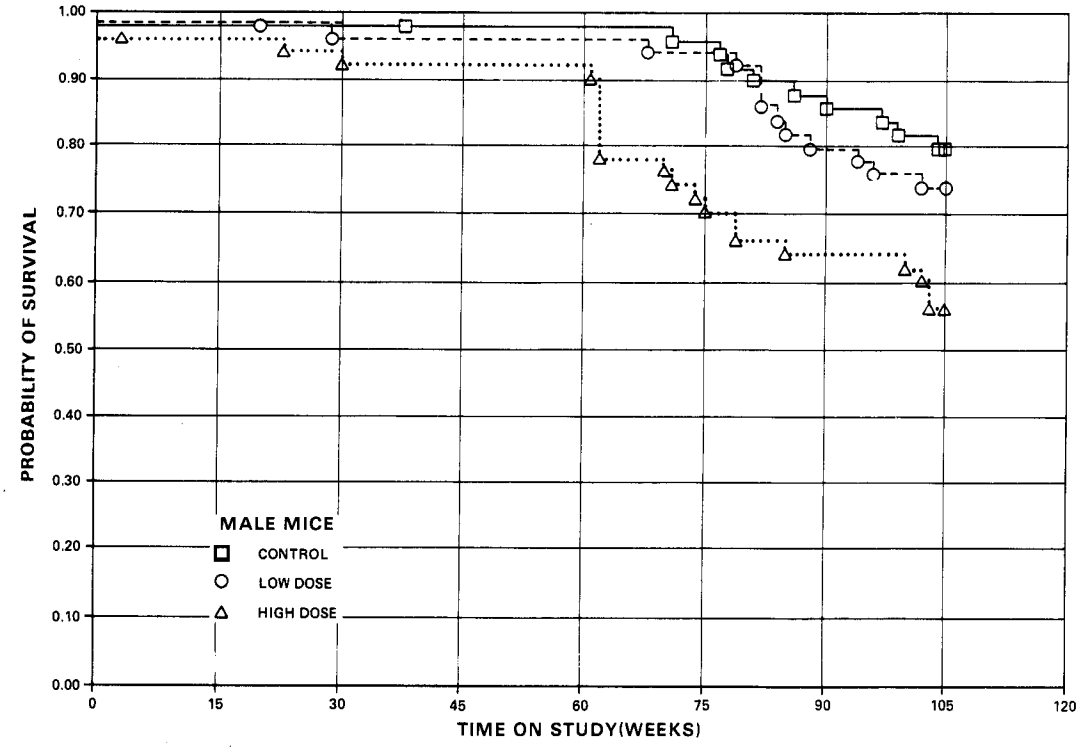
$$\frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$$

(b) Initial Weight

Survival

Estimates of the probabilities of survival of male and female mice fed diets containing melamine at the concentrations of this bioassay, together with those of the control group, are shown by the Kaplan and Meier curves in Figure 4. One control mouse in the male group was missexed and removed from the study. The survival of the high-dose group of male mice was significantly reduced when compared with that of the controls (P=0.013). No other significant differences in survival were observed between any groups of either sex.

In male mice, 39/49 (80%) of the controls, 36/50 (72%) of the low-dose, and 28/50 (56%) of the high-dose group lived to the termination period of the study at 105 weeks. In female mice, 37/50 (74%) of the controls, 43/50 (86%) of the low-dose, and 41/50 (82%) of the high-dose group lived to the termination period of the study at 105 weeks. The survival data include one control and one low-dose female mouse that died during the termination period of the study. For statistical purposes, these animals are considered to have been killed at the end of the study.



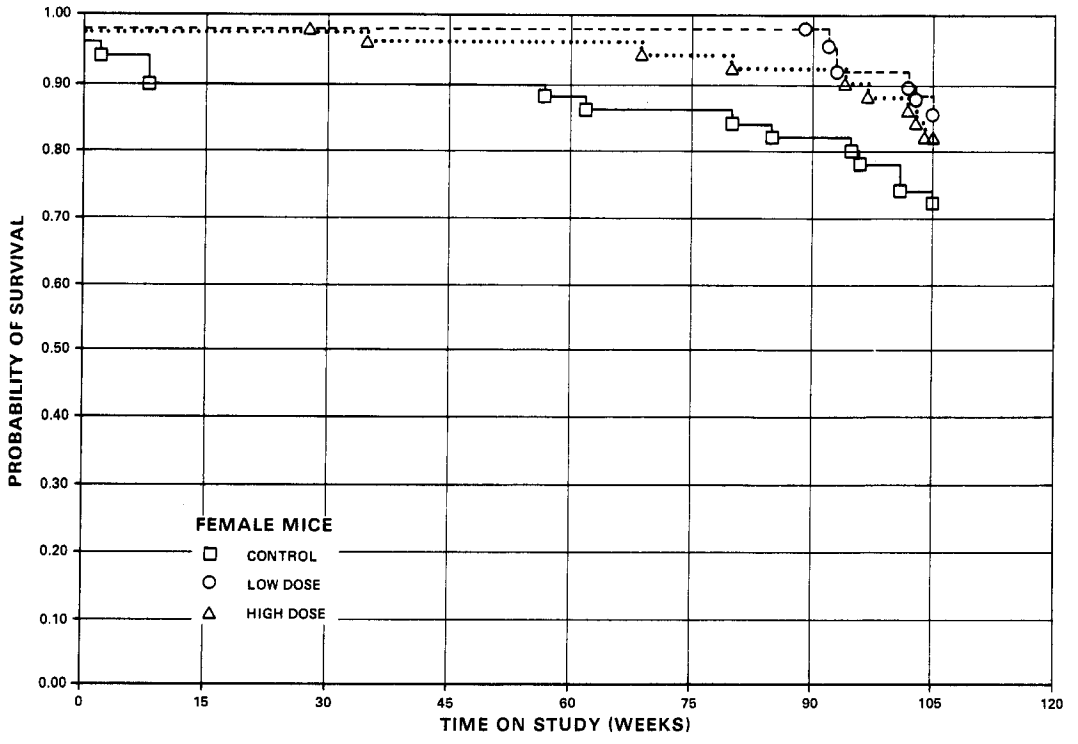


Figure 4. Survival Curves for Mice Fed Diets Containing Melamine

Pathology and Statistical Analyses of Results

Histopathologic findings on neoplasms occurring in mice are summarized in Appendix B, Tables B1 and B2; findings on nonneoplastic lesions are summarized in Table 19 and Appendix D, Tables D1 and D2. Tables B3 and B4 give the survival and tumor status for each animal in the male and female mouse studies, respectively. Tables 20 and 21 contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups.

Urinary Bladder: The incidences of stones (calculi) and inflammatory and hyperplastic changes in the urinary bladder are presented in Table 19. The incidences of stones were obtained from gross examination of the urinary bladder, while the incidences given in Appendix D, Tables D1 and D2 were obtained from microscopic examination. Most of the stones were green and multiple. Although epithelial hyperplasia occurred at higher incidences in males and females fed diets containing melamine, there was no evidence, either in histopathologic features or incidence of neoplasia in the bladder, to suggest that this change was preneoplastic. Hyperplasia was generally very mild.

Lung: The lungs of three high-dose female mice were diffusely infiltrated with structures morphologically compatible with the protozoan organism *Pneumocystis carinii* (Vavra and Kučera, 1970). Similar involvement was not present in other groups of mice. *P. carinii* can occur as a latent, inapparent infection in laboratory rodents (Sheldon, 1959). Under conditions of stress (e.g., immunosuppression), the organism is capable of being pathogenic. Two of the affected mice killed at the end of the study (104 weeks) had a neoplasm (chromophobe adenoma or malignant lymphoma). The other mouse died with no evidence of generalized systemic disease. Other than the presence of generalized neoplasia in two of the affected mice, there was no direct morphologic evidence of systemic immunosuppression in these animals.

Alveolar/bronchiolar adenomas in female mice were observed in decreased ($P \leq 0.025$) incidence in the low-dose group compared with that of the controls (controls, 5/44, 11%; low-dose, 0/48). The incidence in the high-dose group (2/50, 4%) was not significantly different from that in the controls, and the combined incidence of alveolar/bronchiolar adenomas and carcinomas was not significantly different between any groups of either sex of mice. In addition, the low-dose incidence of alveolar/bronchiolar adenomas is not significantly different from the historical rate of this tumor in untreated female $B6C3F_1$ mice (Appendix J, Table J4) at the same laboratory (25/502, 5.0%).

TABLE 19. INCIDENCE OF MICE WITH LESIONS IN THE URINARY BLADDER IN THE 2-YEAR STUDY

	Males			Females		
	Control	Low Dose (2250 ppm)	High Dose (4500 ppm)	Control	Low Dose (2250 ppm)	High Dose (4500 ppm)
No. of animals with tissues examined microscopically	45	47	44	42	49	50
Stones (calculi) *(a)*	2 (4%)	40 (85%)	41 (93%)	0	0	4 (8%)
Inflammation, acute	0	1 (2%)	0	0	0	0
Inflammation, acute and chronic	0	25 (53%)	24 (55%)	0	0	4 (8%)
Inflammation, chronic	2 (4%)	10 (21%)	14 (32%)	0	0	2 (4%)
Hyperplasia, epithelial	1 (2%)	11 (23%)	13 (30%)	0	0	4 (8%)

(a) Observed at necropsy

TABLE 20. ANALYSIS OF PRIMARY TUMORS IN MALE MICE *(a)*

	Control	Low Dose (2250 ppm)	High Dose (4500 ppm)
Subcutaneous Tissue: Sarcoma			
Tumor Rates			
Overall *(b)*	2/49(4%)	3/49(6%)	2/48(4%)
Adjusted *(c)*	4.6%	7.5%	6.5%
Terminal *(d)*	1/39(3%)	1/36(3%)	0/28(0%)
Statistical Tests *(e)*			
Life Table	P=0.473	P=0.479	P=0.590
Incidental Tumor Test	P=0.482N	P=0.466	P=0.567N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.585	P=0.500	P=0.684
Skin or Subcutaneous Tissue: Fibrosarcoma			
Tumor Rates			
Overall *(b)*	2/49(4%)	4/49(8%)	0/48(0%)
Adjusted *(c)*	5.1%	9.9%	0.0%
Terminal *(d)*	2/39(5%)	1/36(3%)	0/28(0%)
Statistical Tests *(e)*			
Life Table	P=0.322N	P=0.307	P=0.314N
Incidental Tumor Test	P=0.244N	P=0.445	P=0.314N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.228N	P=0.339	P=0.253N
Skin or Subcutaneous Tissue: Sarcoma or Fibrosarcoma			
Tumor Rates			
Overall *(b)*	4/49(8%)	7/49(14%)	2/48(4%)
Adjusted *(c)*	9.6%	16.0%	6.5%
Terminal *(d)*	3/39(8%)	2/36(6%)	0/28(0%)
Statistical Tests *(e)*			
Life Table	P=0.464N	P=0.237	P=0.480N
Incidental Tumor Test	P=0.232N	P=0.309	P=0.274N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.307N	P=0.262	P=0.349N
Lung: Alveolar/Bronchiolar Adenoma			
Tumor Rates			
Overall *(b)*	3/47(6%)	4/48(8%)	1/47(2%)
Adjusted *(c)*	7.7%	11.1%	3.6%
Terminal *(d)*	3/39(8%)	4/36(11%)	1/28(4%)
Statistical Tests *(e)*			
Life Table	P=0.390N	P=0.456	P=0.429N
Incidental Tumor Test	P=0.390N	P=0.456	P=0.429N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.257N	P=0.512	P=0.308N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	5/47(11%)	4/48(8%)	1/47(2%)
Adjusted *(c)*	12.8%	11.1%	3.6%
Terminal *(d)*	5/39(13%)	4/36(11%)	1/28(4%)
Statistical Tests *(e)*			
Life Table	P=0.159N	P=0.551N	P=0.193N
Incidental Tumor Test	P=0.159N	P=0.551N	P=0.193N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.081N	P=0.486N	P=0.102N

TABLE 20. ANALYSIS OF PRIMARY TUMORS IN MALE MICE *(a)* (Continued)

	Control	Low Dose (2250 ppm)	High Dose (4500 ppm)
Liver: Carcinoma			
Tumor Rates			
Overall *(b)*	10/45(22%)	8/48(17%)	11/47(23%)
Adjusted *(c)*	24.0%	21.1%	30.8%
Terminal *(d)*	8/39(21%)	6/36(17%)	5/28(18%)
Statistical Tests *(e)*			
Life Table	P=0.212	P=0.463N	P=0.237
Incidental Tumor Test	P=0.396N	P=0.249N	P=0.455N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.497	P=0.339N	P=0.545
Liver: Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	12/45(27%)	8/48(17%)	12/47(26%)
Adjusted *(c)*	28.9%	21.1%	33.8%
Terminal *(d)*	10/39(26%)	6/36(17%)	6/28(21%)
Statistical Tests *(e)*			
Life Table	P=0.273	P=0.289N	P=0.284
Incidental Tumor Test	P=0.331N	P=0.124N	P=0.407N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.499N	P=0.179N	P=0.545N

(a) Dosed groups received doses of 2,250 or 4,500 ppm of melamine in the diet.
(b) Number of tumor bearing animals/number of animals examined at the site.
(a) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(d) Observed tumor incidence at terminal kill.
(e) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidences are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

TABLE 21. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE *(a)*

	Control	Low Dose (2250 ppm)	High Dose (4500 ppm)
Lung: Alveolar/Bronchiolar Adenoma			
Tumor Rates			
Overall *(b)*	5/44(11%)	0/48(0%)	2/50(4%)
Adjusted *(c)*	13.0%	0.0%	4.9%
Terminal *(d)*	4/37(11%)	0/43(0%)	2/41(5%)
Statistical Tests *(e)*			
Life Table	P=0.091N	P=0.024N	P=0.178N
Incidental Tumor Test	P=0.081N	P=0.025N	P=0.158N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.088N	P=0.022N	P=0.168N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	5/44(11%)	1/48(2%)	3/50(6%)
Adjusted *(c)*	13.0%	2.3%	7.3%
Terminal *(d)*	4/37(11%)	1/43(2%)	3/41(7%)
Statistical Tests *(e)*			
Life Table	P=0.216N	P=0.076N	P=0.302N
Incidental Tumor Test	P=0.200N	P=0.079N	P=0.277N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.208N	P=0.083N	P=0.288N
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Tumor Rates			
Overall *(b)*	1/47(2%)	3/49(6%)	1/50(2%)
Adjusted *(c)*	2.7%	6.6%	2.1%
Terminal *(d)*	1/37(3%)	2/43(5%)	0/41(0%)
Statistical Tests *(e)*			
Life Table	P=0.583N	P=0.362	P=0.739N
Incidental Tumor Test	P=0.544	P=0.348	P=0.699
Cochran-Armitage Trend, Fisher Exact Tests	P=0.597N	P=0.324	P=0.737N
Hematopoietic System: Lymphoma, All Malignant			
Tumor Rates			
Overall *(b)*	15/47(32%)	19/49(39%)	11/50(22%)
Adjusted *(c)*	37.4%	39.5%	23.9%
Terminal *(d)*	12/37(32%)	14/43(33%)	7/41(17%)
Statistical Tests *(e)*			
Life Table	P=0.152N	P=0.464	P=0.173N
Incidental Tumor Test	P=0.184N	P=0.328	P=0.199N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.171N	P=0.313	P=0.192N
Hematopoietic System: Lymphoma or Leukemia			
Tumor Rates			
Overall *(b)*	15/47(32%)	19/49(39%)	12/50(24%)
Adjusted *(c)*	37.4%	39.5%	25.7%
Terminal *(d)*	12/37(32%)	14/43(33%)	7/41(17%)
Statistical Tests *(e)*			
Life Table	P=0.206N	P=0.464	P=0.235N
Incidental Tumor Test	P=0.242N	P=0.328	P=0.260N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.232N	P=0.313	P=0.260N

TABLE 21. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE *(a)* (Continued)

	Control	Low Dose (2250 ppm)	High Dose (4500 ppm)
Circulatory System: Hemangioma			
Tumor Rates			
Overall *(b)*	3/47(6%)	0/49(0%)	2/50(4%)
Adjusted *(c)*	8.1%	0.0%	4.9%
Terminal *(d)*	3/37(8%)	0/43(0%)	2/41(5%)
Statistical Tests *(e)*			
Life Table	P=0.347N	P=0.096N	P=0.453N
Incidental Tumor Test	P=0.347N	P=0.096N	P=0.453N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.363N	P=0.114N	P=0.471N
Liver: Adenoma			
Tumor Rates			
Overall *(b)*	3/46(7%)	3/48(6%)	1/50(2%)
Adjusted *(c)*	8.1%	7.0%	2.4%
Terminal *(d)*	3/37(8%)	3/43(7%)	1/41(2%)
Statistical Tests *(e)*			
Life Table	P=0.204N	P=0.592N	P=0.269N
Incidental Tumor Test	P=0.204N	P=0.592N	P=0.269N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.214N	P=0.641N	P=0.278N
Liver: Carcinoma			
Tumor Rates			
Overall *(b)*	1/46(2%)	3/48(6%)	1/50(2%)
Adjusted *(c)*	2.4%	6.8%	2.4%
Terminal *(d)*	0/37(0%)	2/43(5%)	1/41(2%)
Statistical Tests *(e)*			
Life Table	P=0.578N	P=0.361	P=0.738N
Incidental Tumor Test	P=0.564N	P=0.329	P=0.724N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.589N	P=0.325	P=0.731N
Liver: Adenoma or Carcinoma			
Tumor Rates			
Overall *(b)*	4/46(9%)	6/48(13%)	2/50(4%)
Adjusted *(c)*	10.3%	13.6%	4.9%
Terminal *(d)*	3/37(8%)	5/43(12%)	2/41(5%)
Statistical Tests *(e)*			
Life Table	P=0.244N	P=0.466	P=0.293N
Incidental Tumor Test	P=0.236N	P=0.447	P=0.284N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.256N	P=0.398	P=0.300N
Pituitary: Chromophobe Adenoma			
Tumor Rates			
Overall *(b)*	4/39(10%)	5/43(12%)	8/48(17%)
Adjusted *(c)*	11.2%	12.8%	19.5%
Terminal *(d)*	3/34(9%)	5/39(13%)	8/41(20%)
Statistical Tests *(e)*			
Life Table	P=0.217	P=0.587	P=0.278
Incidental Tumor Test	P=0.233	P=0.603	P=0.305
Cochran-Armitage Trend, Fisher Exact Tests	P=0.231	P=0.563	P=0.294

TABLE 21. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE *(a)* (Continued)

(a) Dosed groups received doses of 2,250 or 4,500 ppm of melamine in the diet
(b) Number of tumor bearing animals/number of animals examined at the site.
(c) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(d) Observed tumor incidence at terminal kill.
(e) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidences are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

IV. DISCUSSION AND CONCLUSIONS

IV. DISCUSSION AND CONCLUSIONS

A carcinogenesis bioassay of melamine was conducted in F344/N rats and $B6C3F_1$ mice; diets contained 2,250 or 4,500 ppm melamine for male rats and for male and female mice, whereas female rats received diets containing 4,500 or 9,000 ppm melamine. Compound-related lesions were observed in the urinary tract. The urinary bladder was the primary site affected in male rats and mice, and is considered to be the primary target organ for melamine.

Transitional-cell carcinoma of the urinary bladder occurred in male rats with a statistically significant ($P \leq 0.002$) positive trend, and the incidence in the high-dose group (8/49) was significantly higher ($P \leq 0.016$) than that in the controls. The incidence of urinary bladder transitional-cell carcinomas in high-dose male rats is significantly higher ($P \leq 0.001$) than the historical rate of this tumor in untreated male F344/N rats (Appendix J, Table J1) at this laboratory (0/789) and throughout the bioassay program (0/3551). A transitional-cell papilloma was observed in the urinary bladder of an additional high-dose male rat. These tumors were not observed in statistically significant proportions in either female rats or in mice of either sex.

An increased incidence of urinary bladder stones occurred in high-dose male rats: of the 49 urinary bladders of this group examined histologically, 7 had transitional-cell carcinomas with stones, 1 had transitional-cell carcinoma without stones, 3 had stones without evidence of carcinoma, and 38 had neither stones nor transitional-cell carcinomas. A significant association ($P \leq 0.001$) was found to exist (by a Fisher's exact test) between bladder stones and bladder tumors. Of the three rats with bladder stones and no transitional-cell carcinomas, one had a transitional-cell papilloma and one other had epithelial hyperplasia in the urinary bladder. Stones and papillomas have been reported in the urinary bladder of 4/10 male rats and 2/10 female rats fed diets containing 10,000 ppm melamine for 2 years (American Cyanamid Co., 1953). In that study, no carcinomas of the urinary bladder were reported.

The presence of urinary tract parasites could complicate interpretation of the results of the 2-year study. No evidence of *Trichosomoides crassicauda* was observed in this bioassay or in any other NTP study conducted to date at this laboratory.

In the 13-week studies, bladder stones were observed in male rats at doses as low as 750 ppm melamine, while in female rats no bladder stones were seen in animals receiving less than 15,000 ppm. The circumferential relationship of the prostate gland to the urethra in males may increase the tendency for obstruction of the urethra and thereby account for the apparent difference in susceptibility between male and female rats in developing bladder stones. The incidences of urinary bladder stones in male mice fed diets containing melamine were increased in the 13-week and chronic studies in comparison with those of the controls. In the chronic study, acute and chronic inflammation and epithelial hyperplasia were observed in the urinary bladders; however, there was no apparent evidence of bladder tumor development. Species variations may account for the lack of such tumors in male mice.

Hyperplasia of the transitional epithelium is a common response to mechanical irritation from a foreign body in the urinary bladder of rats or mice. When male F344 rats were fed diets containing terephthalic acid or dimethyl terephthalate, extensive hyperplasia of the transitional epithelium occurred only in the urinary bladders that contained bladder stones (Chin et al., 1981). In the 13-week studies of melamine, described in this report, hyperplastic epithelial changes were found only in male rats that had bladder stones. In weanling male F344 rats fed diets containing melamine for 4 weeks (American Cyanamid Co., 1982c), there were dose-related increases in the incidence of urinary bladder stones (at dietary levels of melamine between 4,000 and 19,000 ppm) and in the incidence of urinary bladder hyperplasia (at dietary levels of melamine between 7,000 and 19,000 ppm). There was an apparent association between bladder stones and bladder hyperplasia.

Bladder tumors have been previously associated with the presence of bladder stones (Weil et al., 1965; Clayson, 1974; Cheng, 1980). In such cases, the suggestion has been made that bladder tumors may result from mechanical irritation produced by the stones. Likewise, it is tempting to suggest that bladder stones in male rats fed diets containing melamine were involved in the development of urinary bladder tumors. In support of this view are studies which indicate that melamine does not undergo metabolic cleavage *in vivo* (Worzalla et al., 1974; American Cyanamid Co., 1982d), and studies cited in the Introduction indicate that melamine apparently lacks genotoxic activity. Nonetheless, a positive association between bladder stones and bladder tumors does not prove that a causal relationship

exists. No association between bladder stones and bladder tumors was found in male rats fed diets containing saccharin (Arnold et al., 1980). A similar lack of an association was evident from the male mouse portion of the melamine study (Table 19). Presently, there is no known mechanism of tumor induction by bladder stones. A biochemical mechanism for tumor induction is considered possible for the following reasons. First, the genotoxic potential of melamine has not been tested adequately because cytotoxic doses were not used in most of the short-term genotoxic tests. Furthermore, the metabolic activation systems used in the tests for genotoxicity were microsomal fractions derived from liver homogenates, while the *in vivo* target site is the urothelium. Bladder epithelial cells may metabolically activate melamine differently than do liver S-9 activation systems. To clarify this issue, the National Toxicology Program will test melamine for mutagenic activity using activating systems derived from bladder epithelial cells. Metabolic activation systems will include freshly isolated, intact bovine urinary bladder epithelial cells and S-9 fractions derived from these cells.

Secondly, the aromatic amines *o*-anisidine and *p*-cresidine have been tested under the protocols of the Bioassay Program and were found to induce transitional-cell carcinomas of the urinary bladder in male and female F344/N rats (NCI, 1978a; NCI, 1978b). There was no evidence of bladder stones in rats in those studies. Thirdly, male mice in the present study had bladder stones but did not develop bladder tumors. This finding is difficult to explain since a wide variety of materials, including chemically inert foreign bodies (e.g., glass beads, paraffin wax), induce bladder tumors in mice after surgical implantation into the mouse bladder lumen (Clayson and Cooper, 1970; Jull, 1979). Finally, in the 2-year study of melamine, 1/8 high-dose male rats with transitional cell carcinomas did not have bladder stones. However, the possibility exists that bladder stones developed in that animal and were passed before postmortem examination.

Although there was a significant association between urinary bladder stones and urinary bladder tumors in male rats fed diets containing 4,500 ppm melamine, the data from the carcinogenesis bioassay are not sufficient to determine whether the tumors developed as a consequence of the bladder stones. Additional experimental data on urinary bladder tumorigenesis induced by melamine or melamine stones might resolve this issue. The classical approach to this problem has involved surgical implantation. Weil et al. (1965) observed that bladder implantations with calcium oxalate stones increased the likelihood of tumor development in male and female rats. A similar study with melamine stones is feasible if the stones do not deteriorate after transplantation. However, such a study would not eliminate the possibility that melamine also induces tumors by a biochemical mechanism. The surgical trauma likewise disrupts the normal architecture and physiology of the urinary bladder. The question of whether melamine was involved in the carcinogenic response in the urinary bladder may be resolved by studying the effects of melamine in male rats, at dose levels below which stones form, in which the urothelium has been irritated by implantation with a nondegradable foreign body (e.g., glass beads).

The contribution of bladder stones to the formation of bladder carcinomas could be determined by preventing stone formation or the retention of stones in the urinary bladder of male rats fed diets containing 4,500 ppm melamine and testing for carcinogenicity under this condition. Ammonium chloride added to drinking water inhibited stone and tumor formation in urinary bladders of mice fed diets containing 4-ethylsulfonylnaphthalene-l-sulfonamide (Flaks et al., 1973), but ammonium chloride had no effect on bladder stone formation in male and female rats fed diets containing melamine for 13 weeks (Table 9). Alternative means of preventing stone formation might be devised after the physico-chemical properties of stones produced in rodents fed diets containing melamine are determined. Such treatments could be used if they do not adversely affect the health of the animals. X-ray microscopic analysis and Fourier transform infrared analysis of two urinary bladder stones obtained from male F344 rats fed diets containing 16,000 ppm and 19,000 ppm melamine indicates that the principal component of the bladder stones is melamine (American Cyanamid Co., 1982c).

The American Cyanamid Company has initiated a number of studies (in addition to the previously mentioned genotoxicity tests, metabolism studies, and bladder stone analyses) on the potential toxicity and carcinogenicity of melamine. A 30-month dosed-feed study was conducted (American Cyanamid Co., 1981d) in F344 rats at dose levels apparently below those at which bladder stones are produced. When 10 animals of each sex in the control and high-dose groups (1,000 ppm and 2,000 ppm for male and

female rats, respectively) were killed after 18 months on study, there were no macroscopic or microscopic changes that could be attributed to administration of melamine in the feed. A final report of the 30-month studies has not been issued. American Cyanamid is conducting further analyses of the composition of urinary bladder stones and the concentration of plasma and urine electrolytes in male F344 rats fed diets containing melamine.

Perhaps greater insight on the mechanism of tumor induction in male rats fed melamine may be gained from a study of the potential promoting activity of melamine and melamine bladder stones. Okajima et al. (1973) showed that foreign bodies implanted in the urinary bladders of male Wistar rats increased the incidence of proliferative epithelial lesions and promoted carcinogenesis of the bladder induced by N-butyl-N-(4-hydroxybutyl) nitrosamine. The National Toxicology Program will conduct a series of urinary bladder promotional assays with melamine in male F344/N rats.

The absolute demonstration of a causal relationship between bladder stones and bladder tumors resulting from ingestion of melamine is a difficult problem. The studies by the American Cyanamid Company and the National Toxicology Program should help explain this phenomenon and provide a better assessment of risk of bladder stone formation due to exposure to melamine.

Chronic renal inflammation, distinguishable from the nephropathy observed in aging F344/N rats, was found at an increased incidence in dosed female rats in the chronic study. This was attributed to administration of melamine.

One other lesion found to occur with a statistically significant ($P<0.05$) positive trend was C-Cell carcinoma of the thyroid gland in female rats. However, the high-dose incidence (3/50) is not significantly different from the historical rate of this tumor in untreated female F344/N rats (Appendix J, Table J2) at the same laboratory (14/689, 2.0%) or throughout the bioassay program (98/3544, 2.8%). Thus this tumor is not considered to be related to administration of melamine.

Conclusions: Under the conditions of this bioassay, melamine was carcinogenic for male F344/N rats, causing transitional-cell carcinomas in the urinary bladder. With one exception, urinary bladder stones were observed in male rats that had transitional-cell carcinomas. Melamine was not carcinogenic for female F344/N rats or for B6C3F$_1$ mice of either sex.

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V. REFERENCES

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS IN THE 2-YEAR DOSED FEED STUDY OF MELAMINE

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE 2-YEAR DOSED-FEED STUDY OF MELAMINE

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(49)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	2 (4%)	2 (4%)	
BASAL-CELL TUMOR	1 (2%)		
TRICHOEPITHELIOMA		1 (2%)	2 (4%)
FIBROMA			1 (2%)
*SUBCUT TISSUE	(49)	(50)	(50)
SARCOMA, NOS			1 (2%)
FIBROMA		1 (2%)	1 (2%)
NEUROFIBROMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(49)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)		
ADENOSQUAMOUS CARCINOMA			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(49)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
LEUKEMIA,NOS	3 (6%)		
MYELOMONOCYTIC LEUKEMIA	5 (10%)	11 (22%)	8 (16%)
#MANDIBULAR L. NODE	(49)	(49)	(47)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)
CIRCULATORY SYSTEM			
#HEART	(49)	(50)	(50)
SARCOMA, NOS			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(49)	(49)	(49)
SQUAMOUS CELL CARCINOMA			1 (2%)
#LIVER	(49)	(50)	(50)
BILE DUCT CARCINOMA		1 (2%)	
NEOPLASTIC NODULE		1 (2%)	
#STOMACH	(49)	(49)	(48)
SARCOMA, NOS		1 (2%)	
URINARY SYSTEM			
#KIDNEY/CORTEX	(49)	(50)	(49)
ADENOMA, NOS		1 (2%)	
ADENOCARCINOMA, NOS			1 (2%)
#URINARY BLADDER	(45)	(50)	(49)
TRANSITIONAL-CELL PAPILLOMA			1 (2%)
TRANSITIONAL-CELL CARCINOMA			8 (16%)
CARCINOSARCOMA, INVASIVE	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(45)	(46)	(49)
ADENOMA, NOS		2 (4%)	1 (2%)
CHROMOPHOBE ADENOMA	7 (16%)	10 (22%)	8 (16%)
CHROMOPHOBE CARCINOMA	2 (4%)	1 (2%)	
#ADRENAL	(49)	(50)	(48)
PHEOCHROMOCYTOMA	7 (14%)	9 (18%)	10 (21%)
GANGLIONEUROMA		1 (2%)	
#THYROID	(48)	(50)	(46)
NEOPLASM, NOS	1 (2%)		
C-CELL ADENOMA	3 (6%)	2 (4%)	2 (4%)
C-CELL CARCINOMA	1 (2%)		
#PARATHYROID	(39)	(41)	(36)
CHIEF-CELL ADENOMA			1 (3%)
#PANCREATIC ISLETS	(44)	(48)	(45)
ISLET-CELL ADENOMA		2 (4%)	2 (4%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ISLET-CELL CARCINOMA	3 (7%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(49)	(50)	(50)
FIBROADENOMA		3 (6%)	
*PREPUTIAL GLAND	(49)	(50)	(50)
CARCINOMA,NOS	1 (2%)		
ADENOMA, NOS	1 (2%)	1 (2%)	1 (2%)
ADENOCARCINOMA, NOS	2 (4%)	1 (2%)	
#PROSTATE	(49)	(48)	(46)
ADENOMA, NOS	5 (10%)	3 (6%)	3 (7%)
*SEMINAL VESICLE	(49)	(50)	(50)
CARCINOSARCOMA	1 (2%)		
#TESTIS	(49)	(50)	(50)
INTERSTITIAL-CELL TUMOR	42 (86%)	44 (88%)	42 (84%)
*EPIDIDYMIS	(49)	(50)	(50)
MESOTHELIOMA, NOS		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(49)	(50)	(50)
PINEALOMA			1 (2%)
ASTROCYTOMA		2 (4%)	
SPECIAL SENSE ORGANS			
*EXTERNAL EAR	(49)	(50)	(50)
NEUROFIBROSARCOMA	1 (2%)		
*ZYMBAL'S GLAND	(49)	(50)	(50)
SQUAMOUS CELL CARCINOMA			1 (2%)
MUSCULOSKELETAL SYSTEM			
*MANDIBLE	(49)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
*MUSCLE OF BACK	(49)	(50)	(50)
FIBROSARCOMA		1 (2%)	
BODY CAVITIES			
*MEDIASTINUM	(49)	(50)	(50)
SARCOMA, NOS			1 (2%)
*ABDOMINAL CAVITY	(49)	(50)	(50)
LIPOMA		1 (2%)	
*TUNICA VAGINALIS	(49)	(50)	(50)
MESOTHELIOMA, NOS	1 (2%)		
MESOTHELIOMA, MALIGNANT	1 (2%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(49)	(50)	(50)
MESOTHELIOMA, METASTATIC	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	14	11	22
MORIBUND SACRIFICE	5	10	10
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	30	29	18
ANIMAL MISSEXED	1		
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	47	48	48
TOTAL PRIMARY TUMORS	92	105	100
TOTAL ANIMALS WITH BENIGN TUMORS	45	47	46
TOTAL BENIGN TUMORS	70	83	76
TOTAL ANIMALS WITH MALIGNANT TUMORS	16	18	20
TOTAL MALIGNANT TUMORS	20	20	23
TOTAL ANIMALS WITH SECONDARY TUMORS#	2		1
TOTAL SECONDARY TUMORS	2		1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	2	2	1
TOTAL UNCERTAIN TUMORS	2	2	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE 2-YEAR DOSED-FEED STUDY OF MELAMINE

	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			
*SUBCUT TISSUE	(50)	(50)	(50)
LEIOMYOSARCOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS			2 (4%)
LEUKEMIA,NOS	2 (4%)	4 (8%)	2 (4%)
UNDIFFERENTIATED LEUKEMIA	1 (2%)		
MYELOMONOCYTIC LEUKEMIA	6 (12%)	6 (12%)	6 (12%)
GRANULOCYTIC LEUKEMIA		1 (2%)	
#MANDIBULAR L. NODE	(49)	(50)	(48)
OSTEOSARCOMA, METASTATIC	1 (2%)		
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
*TONGUE	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
#LIVER	(50)	(50)	(50)
NEOPLASTIC NODULE		2 (4%)	1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#URINARY BLADDER	(49)	(49)	(47)
PAPILLOMA, NOS	1 (2%)		
TRANSITIONAL-CELL PAPILLOMA		1 (2%)	1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(49)	(50)
CARCINOMA,NOS			1 (2%)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)	
ADENOMA, NOS	1 (2%)		
CHROMOPHOBE ADENOMA	20 (40%)	22 (45%)	19 (38%)
CHROMOPHOBE CARCINOMA	2 (4%)	4 (8%)	1 (2%)
#ADRENAL	(50)	(50)	(50)
CORTICAL ADENOMA	3 (6%)		1 (2%)
PHEOCHROMOCYTOMA	1 (2%)	1 (2%)	1 (2%)
#THYROID	(50)	(49)	(50)
FOLLICULAR-CELL CARCINOMA		1 (2%)	
C-CELL ADENOMA		2 (4%)	
C-CELL CARCINOMA			3 (6%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS			1 (2%)
CYSTADENOMA, NOS	1 (2%)		
PAPILLARY CYSTADENOMA, NOS			1 (2%)
FIBROMA	1 (2%)		
FIBROSARCOMA	1 (2%)		
FIBROADENOMA	11 (22%)	11 (22%)	6 (12%)
*PREPUTIAL GLAND	(50)	(50)	(50)
CARCINOMA,NOS		2 (4%)	1 (2%)
ADENOMA, NOS			1 (2%)
CYSTADENOMA, NOS		1 (2%)	
#UTERUS	(50)	(50)	(50)
ENDOMETRIAL STROMAL POLYP	11 (22%)	7 (14%)	2 (4%)
ENDOMETRIAL STROMAL SARCOMA	3 (6%)		2 (4%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#UTERUS/ENDOMETRIUM	(50)	(50)	(50)
ADENOCARCINOMA, NOS		1 (2%)	
#OVARY	(50)	(50)	(50)
CYSTADENOMA, NOS			1 (2%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(49)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)
#BRAIN	(49)	(50)	(50)
GRANULAR-CELL TUMOR, NOS			1 (2%)
ASTROCYTOMA	2 (4%)		
OLIGODENDROGLIOMA			1 (2%)
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*MANDIBLE	(50)	(50)	(50)
OSTEOSARCOMA	1 (2%)		
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	7	12	10
MORIBUND SACRIFICE	9	8	13
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	34	30	27
ANIMAL MISSING			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	42	43	36
TOTAL PRIMARY TUMORS	68	68	57
TOTAL ANIMALS WITH BENIGN TUMORS	35	34	27
TOTAL BENIGN TUMORS	50	45	34
TOTAL ANIMALS WITH MALIGNANT TUMORS	18	20	19
TOTAL MALIGNANT TUMORS	18	21	21
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1	1
TOTAL SECONDARY TUMORS	1	1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		2	2
TOTAL UNCERTAIN TUMORS		2	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

@ INCLUDES AUTOLYZED ANIMALS

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR DOSED FEED STUDY OF MELAMINE

CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	008	009	010	011	012	013	014	015	016	017	018	019	021	022	023	024	025	026
WEEKS ON STUDY	105	105	097	105	105	088	105	105	105	105	084	105	096	105	091	091	078	105	105	105	105	105	105	101
INTEGUMENTARY SYSTEM																								
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																				X				
BASAL-CELL TUMOR																								
RESPIRATORY SYSTEM																								
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA							X																	
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
HEMATOPOIETIC SYSTEM																								
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	–	+	+	–	+	–	+	–	–	+	–	+	–	–	+	+	+	+	+	–	+	+	–	+
CIRCULATORY SYSTEM																								
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM (CONT)																								
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
URINARY SYSTEM																								
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	–	+	+
CARCINOSARCOMA, INVASIVE																								
ENDOCRINE SYSTEM																								
PITUITARY	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+		+
CHROMOPHOBE ADENOMA							X											X						
CHROMOPHOBE CARCINOMA		X																						
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA	X								X						X	X				X			X	
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASM, NOS																								
C-CELL ADENOMA										X									X					
C-CELL CARCINOMA		X																						
PARATHYROID	–	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+
ISLET-CELL CARCINOMA																					X			
REPRODUCTIVE SYSTEM																								
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+
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	X	X
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS										X										X		X		X
SEMINAL VESICLE	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOSARCOMA																								
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
CARCINOMA,NOS						X																		
ADENOMA, NOS							X																	
ADENOCARCINOMA, NOS																							X	
NERVOUS SYSTEM																								
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																								
EAR	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N
NEUROFIBROSARCOMA																								
BODY CAVITIES																								
TUNICA VAGINALIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MESOTHELIOMA, NOS										X														
MESOTHELIOMA, MALIGNANT		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
MESOTHELIOMA, METASTATIC		X																						
LEUKEMIA,NOS															X	X								
MYELOMONOCYTIC LEUKEMIA			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 MIS-SEXED
NO TISSUE INFORMATION SUBMITTED
C NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A AUTOLYSIS
M ANIMAL MISSING
B NO NECROPSY PERFORMED

TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) CONTROL

ANIMAL NUMBER	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	105	084	103	105	111	105	105	105	083	081	089	105	090	091	071	105	070	081	051	105	041	105	105	
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49*
SQUAMOUS CELL PAPILLOMA						X																			2
BASAL-CELL TUMOR																				X					1
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ALVEOLAR/BRONCHIOLAR ADENOMA				X																					2
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYMUS	-	-	+	+	+	+	-	-	+	-	+	+	+	-	-	-	+	+	+	+	+	+	+	+	31
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
PANCREAS	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	-	+	+	+	+	+	44
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM (CONT)																									
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	-	+	+	-	+	+		42
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	-	+	+		45
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	45
CARCINOSARCOMA, INVASIVE																		X							1
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
CHROMOPHOBE ADENOMA	X			X									X						X			X			7
CHROMOPHOBE CARCINOMA					X																				2
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PHEOCHROMOCYTOMA																								X	7
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+		48
NEOPLASM, NOS										X															1
C-CELL ADENOMA																			X						3
C-CELL CARCINOMA																									1
PARATHYROID	+	+	-	+	-	-	+	-	+	-	+	+	+	+	+	+	+	-	+	+	-	+	+		39
PANCREATIC ISLETS	+	+	+	+	+	+	+	•	+	-	-	+	+	+	+	+	+	-	+	+	+	+	+		44
ISLET-CELL CARCINOMA									X										X						3
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	N	49*
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
INTERSTITIAL-CELL TUMOR		X	X		X	X	X	X	X		X	X	X	X	X		X	X		X	X	X	X	X	42
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ADENOMA, NOS																				X					5
SEMINAL VESICLE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	49*
CARCINOSARCOMA																		X							1
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
CARCINOMA,NOS																									1
ADENOMA, NOS																									1
ADENOCARCINOMA, NOS																					X				2
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																									
EAR	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
NEUROFIBROSARCOMA					X																				1
BODY CAVITIES																									
TUNICA VAGINALIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49*
MESOTHELIOMA, NOS																									1
MESOTHELIOMA, MALIGNANT																									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	49*
MESOTHELIOMA, METASTATIC													X												1
LEUKEMIA,NOS																									3
MYELOMONOCYTIC LEUKEMIA																									5

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
.: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR DOSED FEED STUDY OF MELAMINE

LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	115	085	096	090	105	105	085	105	105	105	082	098	061	105	102	105	105	083	093	105	105	105	103	105
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																									
TRICHOEPITHELIOMA	X																								
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA																									X
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	-	-	-	+	+	-	+	+	-	-	+	-	+	+	+	+	-	-	+	+	-	-	-	+	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT CARCINOMA												X													
NEOPLASTIC NODULE															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	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																						X			
SMALL INTESTINE	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																									
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	-	+	+	+	+	+
ADENOMA, NOS																									
CHROMOPHOBE ADENOMA	X	X			X					X		X					X	X							
CHROMOPHOBE CARCINOMA								X																	X
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA							X											X				X			
GANGLIONEUROMA																									
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-CELL ADENOMA										X						X									
PARATHYROID	+	+	+	-	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	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	X
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																						X			
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																				X					
ADENOCARCINOMA, NOS																									
EPIDIDYMIS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MESOTHELIOMA, NOS																									
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ASTROCYTOMA				X												X									
MUSCULOSKELETAL SYSTEM																									
BONE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA																									
MUSCLE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
FIBROSARCOMA																			X						
BODY CAVITIES																									
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
LIPOMA																									
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
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
MYELOMONOCYTIC LEUKEMIA	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 MIS-SEXED

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY; NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	105	101	051	105	105	104	105	083	105	038	105	105	105	104	103	105	102	104	105	105	105	105	086	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA							X									X										2
TRICHOEPITHELIOMA																										1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FIBROMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	49
THYMUS	-	+	-	-	-	+	+	+	-	-	+	+	+	-	+	-	+	+	-	+	+	-	-	-	+	25
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	●	+	+	-	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BILE DUCT CARCINOMA																										1
NEOPLASTIC NODULE																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
PANCREAS	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SARCOMA, NOS																										1
SMALL INTESTINE	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOMA, NOS	X																									1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	46
ADENOMA, NOS											X					X										2
CHROMOPHOBE ADENOMA		X												X												10
CHROMOPHOBE CARCINOMA																										1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA								X	X				X					X						X	X	9
GANGLIONEUROMA														X												1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-CELL ADENOMA																										2
PARATHYROID	+	+	+	+	+	-	-	+	+	+	-	+	+	+	●	-	+	+	●	-	+	+	+			41
PANCREATIC ISLETS	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			48
ISLET-CELL ADENOMA								X										X								2
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	50
FIBROADENOMA													X		X											3
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	44
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	48
ADENOMA, NOS			X					X																		3
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																										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
MESOTHELIOMA, NOS											X															1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ASTROCYTOMA																										2
MUSCULOSKELETAL SYSTEM																										
BONE	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL CARCINOMA																						X				1
MUSCLE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
FIBROSARCOMA																										1
BODY CAVITIES																										
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
LIPOMA													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
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																	X									1
MYELOMONOCYTIC LEUKEMIA								X					X			X		X						X	X	11

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
': NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR DOSED FEED STUDY OF MELAMINE

HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	095	095	051	105	084	081	012	105	085	051	011	012	063	094	067	051	063	115	011	076	084	100	102	105
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRICHOEPITHELIOMA				X																					
FIBROMA																	X								
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																									
FIBROMA																									
NEUROFIBROMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOSQUAMOUS CARCINOMA																									
TRACHEA	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	-	-	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
SQUAMOUS CELL CARCINOMA, METASTAT																									
THYMUS	+	-	-	+	-	+	-	+	+	-	-	-	+	+	-	+	+	+	+	+	-	-	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS			X																						
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA																									
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	-	-	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																	X								
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRANSITIONAL-CELL PAPILLOMA																X									
TRANSITIONAL-CELL CARCINOMA	X											X									X	X			
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS										X															
CHROMOPHOBE ADENOMA				X	X						X						X								X
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+
PHEOCHROMOCYTOMA									X		X				X							X		X	
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+
C-CELL ADENOMA																									
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	+	-	+	+	+	-	+	+
CHIEF-CELL ADENOMA																						X			
PANCREATIC ISLETS	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA										X															
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	N	+	+	N	+	+	N	N	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR	X	X	X	X		X		X	X	X	X	X			X		X	X	X	X	X	X	X	X	X
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																			X						
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																			X						
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PINEALOMA																									
SPECIAL SENSE ORGANS																									
ZYMBAL'S GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SQUAMOUS CELL CARCINOMA																									
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
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
MYELOMONOCYTIC LEUKEMIA								X						X						X					

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER / WEEKS ON STUDY	026 084	027 080	028 015	029 105	030 105	031 101	032 098	033 105	034 105	035 076	036 105	037 093	038 011	039 013	040 098	041 086	042 090	043 101	044 105	045 105	046 098	047 105	048 105	049 090	050 105	TOTAL TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRICHOEPITHELIOMA																			X							2
FIBROMA																										1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SARCOMA, NOS			X																							1
FIBROMA												X														1
NEUROFIBROMA																									X	1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOSQUAMOUS CARCINOMA									X																	1
TRACHEA	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	47
SQUAMOUS CELL CARCINOMA, METASTAT																	X									1
THYMUS	-	•	-	-	+	+	-	+	+	+	+	-	+	-	+	-	-	-	+	+	-	+	-	+	-	28
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SARCOMA, NOS																										1
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SQUAMOUS CELL CARCINOMA																	X									1
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	45
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	+	+	+	+	+	+	+	+	+	42
LARGE INTESTINE	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	44
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ADENOCARCINOMA, NOS																										1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	49
TRANSITIONAL-CELL PAPILLOMA																										1
TRANSITIONAL-CELL CARCINOMA							X	X		X			X													8
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	49
ADENOMA, NOS	X				X																					1
CHROMOPHOBE ADENOMA																X										8
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
PHEOCHROMOCYTOMA					X			X	X					X									X			10
THYROID	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	46
C-CELL ADENOMA					X																		X			2
PARATHYROID	+	+	+	+	+	+	+	-	+	-	+	-	-	+	+	+	+	-	+	+	+	-	+	+	+	36
CHIEF-CELL ADENOMA																										1
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	45
ISLET-CELL ADENOMA					X																					2
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	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	42
PROSTATE	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	-	+	+	+	46
ADENOMA, NOS						X			X																	3
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																										1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PINEALOMA					X																					1
SPECIAL SENSE ORGANS																										
ZYMBAL'S GLAND	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
SQUAMOUS CELL CARCINOMA				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
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
MYELOMONOCYTIC LEUKEMIA			X	X										X	X					X						8

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR DOSED FEED STUDY OF MELAMINE

CONTROL

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0010	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025
WEEKS ON STUDY	105	101	105	105	105	087	064	089	105	105	105	105	105	093	101	101	076	105	105	105	105	105	099	102	104
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
OSTEOSARCOMA, METASTATIC																						X			
THYMUS	+	-	-	-	-	+	-	-	+	-	-	-	+	-	-	+	+	-	-	+	-	+	+	-	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
SMALL INTESTINE	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+
LARGE INTESTINE	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
PAPILLOMA, NOS																					X				
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																					X				
CHROMOPHOBE ADENOMA	X	X					X			X				X					X	X					
CHROMOPHOBE CARCINOMA			X																						
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																X									
PHEOCHROMOCYTOMA																								X	
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+
CYSTADENOMA, NOS																									
FIBROMA			X																						
FIBROSARCOMA									X																
FIBROADENOMA	X								X			X		X								X			X
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP											X	X			X	X								X	
ENDOMETRIAL STROMAL SARCOMA																	X								
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ASTROCYTOMA								X									X								
MUSCULOSKELETAL SYSTEM																									
BONE	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
OSTEOSARCOMA																							Y		
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,NOS						X																			
UNDIFFERENTIATED LEUKEMIA																									
MYELOMONOCYTIC LEUKEMIA		X												X	X	X									

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) CONTROL

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	105	105	072	105	105	096	103	105	105	105	105	105	105	105	105	070	105	105	105	105	084	105	105	105	105	TISSUES TUMORS
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+		47
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
OSTEOSARCOMA, METASTATIC																										1
THYMUS	+	+	-	-	+	-	+	-	-	+	+	-	-	+	+	+	-	-	+	+	-	-	+	+	-	23
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	47
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	48
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SMALL INTESTINE	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	44
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PAPILLOMA, NOS																										1
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOMA, NOS																										1
CHROMOPHOBE ADENOMA		X					X			X	X	X	X		X			X	X		X		X		X	20
CHROMOPHOBE CARCINOMA					X																					2
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA														X												3
PHEOCHROMOCYTOMA											X															1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PARATHYROID	+	+	+	-	+	-	-	+	+	+	-	-	+	+	+	-	+	+	+	+	+	+	+	-	+	41
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	50*
CYSTADENOMA, NOS															X											1
FIBROMA																										1
FIBROSARCOMA																										1
FIBROADENOMA	X						X				X							X		X						11
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOMETRIAL STROMAL POLYP				X					X	X		X	X											X		11
ENDOMETRIAL STROMAL SARCOMA														X												3
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ASTROCYTOMA																										2
MUSCULOSKELETAL SYSTEM																										
BONE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
OSTEOSARCOMA																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
LEUKEMIA,NOS			X																							2
UNDIFFERENTIATED LEUKEMIA		X																								1
MYELOMONOCYTIC LEUKEMIA									X	X																6

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR DOSED FEED STUDY OF MELAMINE

LOW DOSE

ANIMAL NUMBER	0012	0023	0041	0053	0066	0078	0083	0097	0110	0111	0123	0135	0145	0156	0178	0189	0195	0221	0232	0246	0255
WEEKS ON STUDY	1104	1102	1105	0889	1105	0505	0807	0978	1105	1105	1105	1105	1100	1101	0905	1105	1105	1097	0886	0886	1105
RESPIRATORY SYSTEM																					
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	+	+	+	+	+	+	-	+	+	+	-	+	+	-	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																					
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	-	-	-	-	+	-	+	-	-	+	-	-	+	+	-	+	+	-	+
CIRCULATORY SYSTEM																					
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																					
ORAL CAVITY SQUAMOUS CELL CARCINOMA	N	N	N	N	N	N	N	N X	N	N	N	N	N	N	N	N	N	N	N	N	N
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER NEOPLASTIC NODULE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
URINARY SYSTEM																					
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER TRANSITIONAL-CELL PAPILLOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																					
PITUITARY SQUAMOUS CELL CARCINOMA, METASTAT CHROMOPHOBE ADENOMA CHROMOPHOBE CARCINOMA	+	+ X	+ X	+	+ X	+ X	+	+ X	+	+ X	+ X	+	+	+ X	+	+	+ X	+	+ X	+ X	+
ADRENAL PHEOCHROMOCYTOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+
THYROID FOLLICULAR-CELL CARCINOMA C-CELL ADENOMA	+	+	+	+	+	+ X	+	+	+	+	+	+ X	+	+	+	+ X	+	+	+	+	+
PARATHYROID	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																					
MAMMARY GLAND FIBROADENOMA	+ X	+	+	+ X	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+
PREPUTIAL/CLITORAL GLAND CARCINOMA,NOS CYSTADENOMA, NOS	N	N	N	N	N	N	N	N	N	N	N	N X	N	N	N	N	N	N	N	N	N
UTERUS ADENOCARCINOMA, NOS ENDOMETRIAL STROMAL POLYP	+	+	+	+ X	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+ X	+	+
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																					
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																					
EYE SQUAMOUS CELL CARCINOMA	N	N	N	N	N	N	+	+	+	N	+	+	+	N	+	N	+	+	N	N	N
ALL OTHER SYSTEMS																					
MULTIPLE ORGANS NOS LEUKEMIA,NOS MYELOMONOCYTIC LEUKEMIA GRANULOCYTIC LEUKEMIA	N X	N X	N	N	N	N	N X	N	N	N	N	N	N	N X	N	N X	N	N	N	N	N X

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICRDSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	0026	0027	0028	0029	0030	0031	0032	0033	0034	0035	0036	0037	0038	0039	0040	0041	0042	0043	0044	0045	0046	0047	0048	0049	0050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	0881	1000	1051	1001	1051	1001	1051	1001	0773	1051	1051	0802	1051	0781	1051	1051	1051	0991	1051	0991	1051	1051	1051	0886	1051	
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRACHEA	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	-	-	+	+	-	-	-	-	+	+	+	+	+	-	+	-	-	+	-	-	+	+	+	+	-	25
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
NEOPLASTIC NODULE											X					X										2
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	47
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+		49
TRANSITIONAL-CELL PAPILLOMA															X											1
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	49
SQUAMOUS CELL CARCINOMA, METASTAT																								X		1
CHROMOPHOBE ADENOMA		X		X		X	X			X	X		X		X		X				X		X		X	22
CHROMOPHOBE CARCINOMA	X																									4
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+		49
FOLLICULAR-CELL CARCINOMA																										1
C-CELL ADENOMA																										2
PARATHYROID	-	+	-	+	+	+	-	+	-	+	+	+	+	-	+	-	+	-	+	+	+	+	+	-	+	40
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
FIBROADENOMA					X	X	X	X			X			X		X						X			X	11
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
CARCINOMA,NOS										X						X										2
CYSTADENOMA, NOS																										1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS																										1
ENDOMETRIAL STROMAL POLYP						X													X		X			X		7
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
EYE	N	N	N	N	N	N	N	N	+	N	N	+	N	+	+	+	+	N	N	N	N	N	N	+	N	50*
SQUAMOUS CELL CARCINOMA																								X		1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
LEUKEMIA,NOS									X					X			X									4
MYELOMONOCYTIC LEUKEMIA												X														6
GRANULOCYTIC LEUKEMIA																X										1

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR DOSED FEED STUDY OF MELAMINE

HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	100	101	070	105	076	105	105	105	105	105	099	103	105	093	093	094	105	080	083	100	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LEIOMYOSARCOMA														X											
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
THYMUS	-	+	+	-	+	+	+	-	+	+	+	+	-	+	+	-	+	+	-	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE										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	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
TRANSITIONAL-CELL PAPILLOMA																									
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS																									
CHROMOPHOBE ADENOMA		X					X					X	X					X		X		X		X	
CHROMOPHOBE CARCINOMA										X															
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA														X											
PHEOCHROMOCYTOMA																							X		
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-CELL CARCINOMA		X					X							X											
PARATHYROID	+	-	+	+	+	+	+	+	+	+	-	-	+	-	+	-	+	+	+	+	-	+	+	+	-
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+
ADENOCARCINOMA, NOS														X											
PAPILLARY CYSTADENOMA, NOS																									
FIBROADENOMA								X									X					X			
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA,NOS																									
ADENOMA, NOS								X																	
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP																					X				
ENDOMETRIAL STROMAL SARCOMA															X		X								
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CYSTADENOMA, NOS									X																
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, METASTAT					X																				
GRANULAR-CELL TUMOR, NOS																								X	
OLIGODENDROGLIOMA																									
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														
LEUKEMIA,NOS																									
MYELOMONOCYTIC LEUKEMIA										X								X							

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	0262	0278	0289	0310	0319	0321	0331	0341	0355	0361	0371	0381	0390	0401	0411	0423	0435	0445	0455	0461	0471	0481	0490	0501	TOTAL
WEEKS ON STUDY	092	086	105	098	013	096	105	105	105	100	092	111	089	104	105	105	105	105	105	105	104	086	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
LEIOMYOSARCOMA																									1
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA					X																				1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
THYMUS	-	-	+	+	+	-	+	+	+	-	-	-	-	-	+	-	-	-	+	-	+	-	-	+	30
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE																									1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LARGE INTESTINE	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
TRANSITIONAL-CELL PAPILLOMA		X																							1
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA,NOS			X																						1
CHROMOPHOBE ADENOMA		X			X			X	X			X		X	X		X	X				X		X	19
CHROMOPHOBE CARCINOMA																									1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA																									1
PHEOCHROMOCYTOMA																									1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-CELL CARCINOMA																									3
PARATHYROID	-	+	+	+	+	-	-	-	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+		37
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	N	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
ADENOCARCINOMA, NOS																									1
PAPILLARY CYSTADENOMA, NOS																							X		1
FIBROADENOMA															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	50*
CARCINOMA,NOS												X													1
ADENOMA, NOS																									1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOMETRIAL STROMAL POLYP							X																		2
ENDOMETRIAL STROMAL SARCOMA																									2
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CYSTADENOMA, NOS																									1
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL CARCINOMA, METASTAT																									1
GRANULAR-CELL TUMOR, NOS																									1
OLIGODENDROGLIOMA											X														1
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MALIGNANT LYMPHOMA, NOS	X																								2
LEUKEMIA,NOS		X												X											2
MYELOMONOCYTIC LEUKEMIA				X		X		X															X		6

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

I: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE IN THE 2-YEAR DOSED FEED STUDY OF MELAMINE

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE 2-YEAR DOSED-FEED STUDY OF MELAMINE

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	49	49	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	48	49	47
INTEGUMENTARY SYSTEM			
*SKIN	(49)	(49)	(48)
FIBROMA	1 (2%)	1 (2%)	
FIBROSARCOMA	1 (2%)	2 (4%)	
*SUBCUT TISSUE	(49)	(49)	(48)
SARCOMA, NOS	2 (4%)	3 (6%)	2 (4%)
FIBROMA			1 (2%)
FIBROSARCOMA	1 (2%)	2 (4%)	
RESPIRATORY SYSTEM			
#LUNG	(47)	(48)	(47)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)	1 (2%)	2 (4%)
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (6%)	4 (8%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	2 (4%)		
FIBROSARCOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(49)	(49)	(48)
MALIGNANT LYMPHOMA, NOS		1 (2%)	1 (2%)
MYELOMONOCYTIC LEUKEMIA		1 (2%)	
#LYMPH NODE	(38)	(32)	(36)
MALIGNANT LYMPHOMA, NOS	1 (3%)		
#LIVER	(45)	(48)	(47)
KUPFFER-CELL SARCOMA	1 (2%)		
#DUODENUM	(42)	(42)	(36)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (3%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
#LIVER	(45)	(48)	(47)
HEMANGIOMA	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(45)	(48)	(47)
HEPATOCELLULAR ADENOMA	2 (4%)		1 (2%)
HEPATOCELLULAR CARCINOMA	10 (22%)	8 (17%)	11 (23%)
#JEJUNUM	(42)	(42)	(36)
ADENOCARCINOMA, NOS		1 (2%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#ADRENAL	(43)	(47)	(45)
ADENOMA, NOS		1 (2%)	
CORTICAL ADENOMA			1 (2%)
PHEOCHROMOCYTOMA			2 (4%)
#THYROID	(46)	(47)	(44)
PAPILLARY ADENOMA		1 (2%)	
FOLLICULAR-CELL ADENOMA	1 (2%)		
REPRODUCTIVE SYSTEM			
*PENIS	(49)	(49)	(48)
PAPILLOMA, NOS		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(49)	(49)	(48)
ADENOMA, NOS	2 (4%)	2 (4%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(49)	(49)	(48)
SARCOMA, NOS, METASTATIC	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	10	11	20
MORIBUND SACRIFICE		2	2
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	39	36	28
ANIMAL MISSING		1	
ANIMAL MISSEXED	1		

@ INCLUDES AUTOLYZED ANIMALS

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	23	22	20
TOTAL PRIMARY TUMORS	28	28	21
TOTAL ANIMALS WITH BENIGN TUMORS	10	8	6
TOTAL BENIGN TUMORS	10	10	6
TOTAL ANIMALS WITH MALIGNANT TUMORS	16	17	14
TOTAL MALIGNANT TUMORS	18	18	15
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	2	2
TOTAL SECONDARY TUMORS	2	2	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE 2-YEAR DOSED-FEED STUDY OF MELAMINE

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	47	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	47	49	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(44)	(48)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	5 (11%)		2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	1 (2%)
OSTEOSARCOMA, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(47)	(49)	(50)
MALIGNANT LYMPHOMA, NOS	13 (28%)	14 (29%)	9 (18%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		3 (6%)	1 (2%)
PLASMA-CELL TUMOR	1 (2%)		1 (2%)
MYELOMONOCYTIC LEUKEMIA			1 (2%)
#SPLEEN	(44)	(48)	(50)
MALIGNANT LYMPHOMA, NOS	1 (2%)	1 (2%)	1 (2%)
#HEPATIC LYMPH NODE	(38)	(42)	(45)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
#LIVER	(46)	(48)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
CIRCULATORY SYSTEM			
#LIVER	(46)	(48)	(50)
HEMANGIOSARCOMA			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#UTERUS	(46)	(49)	(50)
HEMANGIOMA	3 (7%)		1 (2%)
HEMANGIOSARCOMA		1 (2%)	1 (2%)
#OVARY	(40)	(45)	(48)
HEMANGIOMA			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(46)	(48)	(50)
NEOPLASM, NOS	1 (2%)		
HEPATOCELLULAR ADENOMA	3 (7%)	3 (6%)	1 (2%)
HEPATOCELLULAR CARCINOMA	1 (2%)	3 (6%)	1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(39)	(43)	(48)
CHROMOPHOBE ADENOMA	4 (10%)	5 (12%)	8 (17%)
#ADRENAL	(44)	(49)	(50)
ADENOMA, NOS			1 (2%)
PHEOCHROMOCYTOMA	1 (2%)		
SARCOMA, NOS			1 (2%)
#THYROID	(42)	(45)	(48)
FOLLICULAR-CELL ADENOMA		2 (4%)	1 (2%)
#PANCREATIC ISLETS	(44)	(46)	(50)
ISLET-CELL ADENOMA	1 (2%)	1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(47)	(49)	(50)
ADENOCARCINOMA, NOS	2 (4%)	1 (2%)	
*VULVA	(47)	(49)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#UTERUS	(46)	(49)	(50)
NEOPLASM, NOS	1 (2%)		
ADENOCARCINOMA, NOS			1 (2%)
MYXOMA		1 (2%)	
ENDOMETRIAL STROMAL POLYP			1 (2%)
#OVARY	(40)	(45)	(48)
CYSTADENOMA, NOS		1 (2%)	
TERATOMA, NOS			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(45)	(49)	(50)
LIPOMA			1 (2%)
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(47)	(49)	(50)
ADENOMA, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*INGUINAL REGION	(47)	(49)	(50)
MYXOSARCOMA	1 (2%)		
ALL OTHER SYSTEMS			
LEG			
OSTEOSARCOMA			1
TOE			
FIBROSARCOMA		1	
SITE UNKNOWN			
ADENOCARCINOMA, NOS			1

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATHa	14	7	9
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	36	42	41
ANIMAL MISSING		1	
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	28	33	26
TOTAL PRIMARY TUMORS	39	41	40
TOTAL ANIMALS WITH BENIGN TUMORS	14	13	13
TOTAL BENIGN TUMORS	17	14	18
TOTAL ANIMALS WITH MALIGNANT TUMORS	17	25	18
TOTAL MALIGNANT TUMORS	19	27	20
TOTAL ANIMALS WITH SECONDARY TUMORS#			1
TOTAL SECONDARY TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	2		2
TOTAL UNCERTAIN TUMORS	3		2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

a INCLUDES AUTOLYZED ANIMALS

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR DOSED FEED STUDY OF MELAMINE

CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025	026
WEEKS ON STUDY	105	105	081	105	105	105	041	105	105	099	105	105	105	097	105	105	105	105	105	105	105	071	105	105	105	105
INTEGUMENTARY SYSTEM																										
SKIN	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA									X																	
FIBROSARCOMA									X																	
SUBCUTANEOUS TISSUE	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS												X					X					X				
FIBROSARCOMA																										
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA																										
ALVEOLAR/BRONCHIOLAR ADENOMA	X											X				X										
ALVEOLAR/BRONCHIOLAR CARCINOMA																										
TRACHEA	-	+	+	-	-	-	+	+	+	-	+	+	-	-	+	+	+	+	-	+	-	+	-	+	+	-
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	-	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	-	-	+	+	+	+	+	-
MALIGNANT LYMPHOMA, NOS							X																			
THYMUS	+	+	-	+	+	+	-	+	+	-	+	+	-	+	+	+	-	+	-	+	-	+	-	+	-	+
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	-	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA						X									X											
HEPATOCELLULAR CARCINOMA			X													X	X		X							
DIGESTIVE SYSTEM (CONT)																										
HEMANGIOMA																										
KUPFFER-CELL SARCOMA																									X	
BILE DUCT	+	+	+	+	+	+	-	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	N	+	+	+	N	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
PANCREAS	+	+	+	+	+	+	-	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	-	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+			+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	-	+	+	-	+	+	-	+	+	+	+				+	+	+	+	+	+
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	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	N
ADENOMA, NOS																										
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SARCOMA, NOS, METASTATIC																						X				

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) CONTROL

ANIMAL NUMBER	0207	0289	0219	0330	0331	0321	0313	0314	0335	0336	0337	0338	0339	0401	0411	0412	0431	0443	0445	0446	0447	0448	0449	0450	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	038	105	077	078	105	105	086	105	090	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	49M
FIBROMA																									1
FIBROSARCOMA																									1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	49M
SARCOMA, NOS																									2
FIBROSARCOMA																									1
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	47
HEPATOCELLULAR CARCINOMA, METASTA												X													1
ALVEOLAR/BRONCHIOLAR ADENOMA							X																		3
ALVEOLAR/BRONCHIOLAR CARCINOMA																		X							2
TRACHEA	+	-	-	-	-	-	-	+	+	+	-	+	+	A	+	+	~	+	-	+	-	-	-	+	26
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	-	46
SPLEEN	+	+	+	+	+	+	-	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	44
LYMPH NODES	+	+	+	+	-	-	+	-	+	+	+	+	+	A	+	+	+	+	+	-	+	-	+	+	38
MALIGNANT LYMPHOMA, NOS																									1
THYMUS	+	-	+	+	+	+	-	-	+	+	-	+	+	A	+	-	+	+	-	+	-	+	+	+	33
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	46
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	47
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	45
HEPATOCELLULAR ADENOMA																									2
HEPATOCELLULAR CARCINOMA		X									X	X					X					X	X		10
HEMANGIOMA					X																				1
KUPFFER-CELL SARCOMA																									1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	45
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	N	+	+	N	+	+	N	+	N	+	+	+	+	+	+	+	+	49M
PANCREAS	+	+	+	+	+	+	-	-	+	+	-	+	+	A	+	+	+	+	+	+	+	+	+	+	42
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	45
STOMACH	+	+	+	+	+	+	+	-	+	+	+	+	+	A	+	-	+	+	+	+	+	+	+	+	43
SMALL INTESTINE	+	+	+	+	+	+	+	-	+	+	-	+	+	A	+	-	+	+	+	+	+	+	+	+	42
LARGE INTESTINE	+	+	+	+	+	+	+	-	+	+	+	+	+	A	+	-	+	+	+	+	+	+	+	+	43
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	47
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	45
ENDOCRINE SYSTEM																									
PITUITARY	+	-	+	+	+	+	+	-	+	+	+	+	+	A	+	+	-	+	+	+	+	+	+	+	41
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	43
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	46
FOLLICULAR-CELL ADENOMA																							+		1
PARATHYROID	+	+	-	+	-	+	+	+	~	-	-	-	+	A	-	-	+	+	+	+	+	-	-		22
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	49M
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	48
PROSTATE	+	+	+	+	+	+	+	+	+	+	-	+	+	A	+	-	+	+	+	+	+	+	+	+	46
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	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	49M
ADENOMA, 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	49M
SARCOMA, NOS, METASTATIC																									1

M ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
~: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR DOSED FEED STUDY OF MELAMINE

LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	105	105	105	080	105	105	105	094	105	079	105	105	082	105	105	105	105	084	088	105	085	105	105
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	M	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA																									
FIBROSARCOMA								X		X															
SUBCUTANEOUS TISSUE	+	+	+	+	+	M	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS															X										
FIBROSARCOMA																					X		X		
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA					X																				
ALVEOLAR/BRONCHIOLAR ADENOMA																									
FIBROSARCOMA, METASTATIC																							X		
TRACHEA	+	+	-	+	-	M	-	-	-	+	-	A	+	-	+	-	-	-	+	-	+	-	+	+	-
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	M	+	+	+	+	-	A	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	-	+	+	M	-	+	+	-	-	A	-	+	-	+	+	+	+	+	-	+	+	-	+
THYMUS	+	+	+	+	-	M	+	+	+	-	+	A	+	+	+	+	+	-	+	-	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	M	+	+	+	+	+	A	+	+	-	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA					X														X						
BILE DUCT	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	M	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+
PANCREAS	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	-	+	+	+	+
ADENOCARCINOMA, NOS																									
LARGE INTESTINE	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	-	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
ADRENAL	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS							X																		
THYROID	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
PAPILLARY ADENOMA														X											
PARATHYROID	-	-	-	-	-	M	+	-	-	+	-	A	-	-	-	-	-	+	+	-	+	-	-	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TESTIS	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
PROSTATE	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
PENIS	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PAPILLOMA, NOS								X																	
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS							X																		
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIGNANT LYMPHOMA, NOS																				X					
MYELOMONOCYTIC LEUKEMIA																									

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	105	105	105	105	082	105	105	102	105	105	200	105	096	105	105	105	068	105	105	105	105	082	092	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	49
FIBROMA										X																1
FIBROSARCOMA																										2
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	49
SARCOMA, NOS								X										X								3
FIBROSARCOMA																										2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEPATOCELLULAR CARCINOMA, METASTA																										1
ALVEOLAR/BRONCHIOLAR ADENOMA		X						X					X													4
FIBROSARCOMA, METASTATIC																									X	1
TRACHEA	+	+	-	+	+	-	-	-	+	-	+	+	-	+	-	-	-	+	+	-	-	-	+	+	-	23
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	45
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	47
LYMPH NODES	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	-	-	-	-	-	+	-	32
THYMUS	+	+	+	-	-	-	-	+	-	-	-	+	-	-	+	+	-	-	-	+	+	-	-	+	+	30
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEPATOCELLULAR CARCINOMA							X	X				X	X		X				X							8
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	N	+	+	+	N	N	N	+	+	+	N	+	+	+	+	+	N	+	+	49
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	47
ESOPHAGUS	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	47
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	-	+	+	+	+	-	-	+	+	42
ADENOCARCINOMA, NOS							X																			1
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
PITUITARY	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	46
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	47
ADENOMA, NOS																										1
THYROID	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
PAPILLARY ADENOMA																										1
PARATHYROID	+	-	-	+	+	-	+	-	+	-	+	-	-	-	-	-	+	-	-	+	-	+	-	+	+	18
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	49
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
PROSTATE	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
PENIS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49
PAPILLOMA, NOS																										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	49
ADENOMA, NOS												X														2
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49
MALIGNANT LYMPHOMA, NOS					X																					1
MYELOMONOCYTIC LEUKEMIA																										1

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

I: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR DOSED FEED STUDY OF MELAMINE

HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	051	062	062	095	030	062	062	062	062	062	095	095	095	095	095	095	095	079	071	090	083	095	095	095	095
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																	X								
FIBROMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA																						+			
ALVEOLAR/BRONCHIOLAR ADENOMA																								X	
TRACHEA	+	A	+	+	+	+	+	+	+	+	-	+	-	+	+	+	-	-	-	+	-	+	-	+	-
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	A	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
SPLEEN	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
LYMPH NODES	+	A	-	+	+	+	-	+	+	-	+	-	+	+	-	+	+	+	-	+	+	+	+	+	+
THYMUS	+	A	-	+	+	-	-	-	-	-	+	-	+	-	-	+	-	-	-	-	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	A	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA													X												
HEPATOCELLULAR CARCINOMA				X								X							X	X			X		
BILE DUCT	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	N	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	N	N	N	+	+	+	+	+
PANCREAS	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	A	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	-	-	-	+	+	+	+	+
MALIG.LYMPHOMA, HISTIOCYTIC TYPE						X																			
LARGE INTESTINE	+	A	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	A	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
ADRENAL	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA	X										X														
PHEOCHROMOCYTOMA																									
THYROID	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PARATHYROID	+	A	+	-	-	+	+	-	-	-	-	+	-	+	+	+	-	-	+	+	-	+	-	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TESTIS	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PROSTATE	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	A	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIGNANT LYMPHOMA, NOS																					X				

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	0212	0228	0239	0301	0311	0323	0334	0345	0356	0368	0377	0388	0390	0401	0412	0423	0434	0445	0456	0467	0478	0489	0490	TOTAL TISSUES TUMORS
WEEKS ON STUDY	1 0 9 1	0 8 5	1 0 5	1 0 5	0 5	0 5	1 0 2 3	0 5	1 0 5	0 5	1 0 5	0 2	1 0 5	0 3 1	0 3 5	1 0 5	0 7 5	1 0 5	0 5	0 7 0	0 5	0 6 1	0 7 4	0 5 1	0 7 9	
INTEGUMENTARY SYSTEM																								
SUBCUTANEOUS TISSUE	+	M	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	N	+	+	+	48*
SARCOMA, NOS	X											X														2
FIBROMA																										1
RESPIRATORY SYSTEM																								
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	47
HEPATOCELLULAR CARCINOMA, METASTA												X														2
ALVEOLAR/BRONCHIOLAR ADENOMA																										1
TRACHEA	+	-	-	+	+	+	+	-	-	+	+	+	-	A	A	+	+	-	-	-	+	+	+	+	+	31
HEMATOPOIETIC SYSTEM																								
BONE MARROW	+	-	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	-	43
SPLEEN	+	-	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	-	+	44
LYMPH NODES	+	-	+	+	+	+	+	-	+	+	+	+	+	A	A	-	+	+	+	+	+	+	+	-	+	56
THYMUS	-	-	+	+	+	+	+	-	+	+	+	+	-	A	A	-	+	+	-	-	+	+	+	-	-	24
CIRCULATORY SYSTEM																								
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	47
DIGESTIVE SYSTEM																								
SALIVARY GLAND	+	-	+	+	+	+	+	+	+	+	+	+	+	A	A	-	+	+	+	+	+	+	+	+	+	44
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	47
HEPATOCELLULAR ADENOMA		X							X			X										X	X	X			1
HEPATOCELLULAR CARCINOMA																										11
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	47
GALLBLADDER & COMMON BILE DUCT	N	N	+	+	+	+	N	+	+	+	+	+	+	A	A	N	+	N	+	N	N	+	N	N	+	48*
PANCREAS	+	-	+	+	+	+	-	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	-	+	+	44
ESOPHAGUS	+	-	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	46
STOMACH	+	-	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	-	+	+	45
SMALL INTESTINE	+	-	+	+	+	+	-	+	+	+	+	+	+	A	A	-	+	+	+	-	+	+	+	-	+	36
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										1
LARGE INTESTINE	+	-	+	+	+	+	+	-	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	-	+	43
URINARY SYSTEM																								
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	-	+	46
URINARY BLADDER	+	-	+	+	+	+	+	-	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	-	+	44
ENDOCRINE SYSTEM																								
PITUITARY	+	-	+	+	+	+	-	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	-	+	42
ADRENAL	+	-	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	-	+	43
CORTICAL ADENOMA																					X					1
PHEOCHROMOCYTOMA																										2
THYROID	+	-	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	-	+	+	+	-	+	46
PARATHYROID	-	-	-	+	+	+	-	+	+	-	-	-	-	A	A	-	+	-	+	-	+	+	-	-	-	22
REPRODUCTIVE SYSTEM																								
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	A	A	N	N	N	N	N	N	N	N	N	N	48*
TESTIS	+	-	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	46
PROSTATE	+	-	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	-	+	45
NERVOUS SYSTEM																								
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	46
ALL OTHER SYSTEMS																								
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	A	A	N	N	N	N	N	N	N	N	N	N	48*
MALIGNANT LYMPHOMA, NOS																										1

* ANIMALS NECROPSIED

+: TISSUE EXAMINED *MICROSCOPICALLY*
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO *MICROSCOPIC EXAMINATION*

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO *PROTOCOL*
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR DOSED FEED STUDY OF MELAMINE

CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	002	002	096	105	002	105	115	115	105	105	105	091	105	105	105	105	105	105	105	105	105	105	085	105	105
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	A	A	+	+	A	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA			X					X																	X
TRACHEA	A	A	+	+	A	-	+	-	-	+	+	-	-	-	-	-	-	+	+	-	-	-	-	-	-
HEMATOPOIETIC SYSTEM																									
BONE MARROW	A	A	+	+	A	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+
SPLEEN	A	A	+	+	A	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+
MALIGNANT LYMPHOMA, NOS										X															
LYMPH NODES	A	A	+	+	A	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+
THYMUS	A	A	+	+	A	-	-	+	-	+	+	-	+	+	+	+	+	-	+	+	+	+	-	+	+
CIRCULATORY SYSTEM																									
HEART	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	A	A	+	+	A	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+
LIVER	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASM, NOS																							X		
HEPATOCELLULAR ADENOMA										X															
HEPATOCELLULAR CARCINOMA												X													
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
BILE DUCT	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	A	A	+	+	A	+	+	+	+	+	+	N	+	+	+	+	+	N	+	+	N	+	N	+	+
PANCREAS	A	A	+	+	A	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+
ESOPHAGUS	A	A	+	+	A	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+
STOMACH	A	A	+	+	A	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+
SMALL INTESTINE	A	A	-	+	A	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	-	+	+
LARGE INTESTINE	A	A	-	+	A	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+
URINARY SYSTEM																									
KIDNEY	A	A	+	+	A	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+
URINARY BLADDER	A	A	+	+	A	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+
ENDOCRINE SYSTEM																									
PITUITARY	A	A	+	+	A	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+
CHROMOPHOBE ADENOMA																									
ADRENAL	A	A	+	+	A	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+
PHEOCHROMOCYTOMA																									
THYROID	A	A	+	+	A	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+
PARATHYROID	A	A	-	+	A	-	-	-	+	+	+	-	-	+	+	-	-	-	-	+	+	-	-	-	-
PANCREATIC ISLETS	A	A	+	+	A	+	+	+	+	+	+	-	+	+	+	X	+	+	+	+	+	+	-	+	+
ISLET-CELL ADENOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	A	A	N	+	A	+	+	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	N	+	+
ADENOCARCINOMA, NOS																		X							
UTERUS	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASM, NOS																X							X		
HEMANGIOMA																				X					
OVARY	A	A	-	+	A	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	-	+	+
NERVOUS SYSTEM																									
BRAIN	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
BODY CAVITIES																									
PERITONEUM	A	A	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MYXOSARCOMA																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	A	A	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIGNANT LYMPHOMA, NOS											X							X		X	X	X		X	
PLASMA-CELL TUMOR																									

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) CONTROL

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	101	105	101	105	105	105	105	080	057	105	105	105	105	105	105	105	105	105	105	062	108	105	108		
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+		44
ALVEOLAR/BRONCHIOLAR ADENOMA													X						X							5
TRACHEA	*	+	+	+	+	+	+	-	-	+	+	+	-	-	+	-	-	+	-	-	-	+	-	-		20
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-		43
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+		44
MALIGNANT LYMPHOMA, NOS																										1
LYMPH NODES	-	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	-	+		38
THYMUS	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	-	+	-	+	+	-	+		35
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+		45
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+		43
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+		46
NEOPLASM, NOS																										1
HEPATOCELLULAR ADENOMA					X																X					3
HEPATOCELLULAR CARCINOMA																										1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																	X									1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+		46
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+	+	N	+	N		47*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+		44
ESOPHAGUS	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+		42
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+		44
SMALL INTESTINE	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+		41
LARGE INTESTINE	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		43
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+		44
URINARY BLADDER	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+		42
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	-	-	-	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+		39
CHROMOPHOBE ADENOMA		X	X																X		X					4
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+		44
PHEOCHROMOCYTOMA									X																	1
THYROID	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+		42
PARATHYROID	+	-	-	-	-	+	+	+	+	+	-	-	+	-	-	+	+	-	-	-	+	-	-	-		19
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+		44
ISLET-CELL ADENOMA																										1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+		47*
ADENOCARCINOMA, NOS									X																	2
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+		46
NEOPLASM, NOS																										1
HEMANGIOMA											X															3
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	-	+	+		40
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+		45
BODY CAVITIES																										
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		47*
MYXOSARCOMA																			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		47*
MALIGNANT LYMPHOMA, NOS		X		X								X		X					X		X	X				13
PLASMA-CELL TUMOR										X																1

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
.: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR DOSED FEED STUDY OF MELAMINE

LOW DOSE

ANIMAL NUMBER	0012	0023	0041	0056	0067	0089	0090	0101	0112	0133	0141	0155	0166	0178	0189	0201	0221	0233	0241	0251
WEEKS ON STUDY	1105	1105	1105	0331	1005	1005	1105	1105	1105	1105	1105	1105	0331	1105	0931	1105	1105	1105	1105	1105
RESPIRATORY SYSTEM																				
LUNGS AND BRONCHI	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
ALVEOLAR/BRONCHIOLAR CARCINOMA		X																		
TRACHEA	–	+	–	–	M	+	+	+	–	–	–	+	+	+	–	–	–	+	–	+
HEMATOPOIETIC SYSTEM																				
BONE MARROW	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MALIGNANT LYMPHOMA, NOS	X																			
LYMPH NODES	+	+	–	–	M	+	+	+	+	+	+	+	+	–	–	+	+	+	–	+
MALIGNANT LYMPHOMA, NOS																				
THYMUS	+	+	+	–	M	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+
CIRCULATORY SYSTEM																				
HEART	+	+	+	+	M	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
DIGESTIVE SYSTEM																				
SALIVARY GLAND	+	+	+	–	M	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
LIVER	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA						X														
HEPATOCELLULAR CARCINOMA																				
BILE DUCT	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	M	+	+	+	+	+	+	N	+	+	N	+	N	+	+	+
PANCREAS	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
ESOPHAGUS	+	+	+	+	M	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+
STOMACH	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	M	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+
LARGE INTESTINE	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																				
KIDNEY	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																				
PITUITARY	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
CHROMOPHOBE ADENOMA													X				X		X	
ADRENAL	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	–	+	+	+	M	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+
FOLLICULAR-CELL ADENOMA							X													
PARATHYROID	–	+	–	+	M	–	+	+	–	+	–	+	–	+	–	–	+	–	+	–	–	–	–	+
PANCREATIC ISLETS	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
ISLET-CELL ADENOMA														X						
REPRODUCTIVE SYSTEM																				
MAMMARY GLAND	+	+	+	+	M	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																				
FEMALE EXTERNAL GENITALIA	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SQUAMOUS CELL CARCINOMA																				
UTERUS	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MYXOMA																				
HEMANGIOSARCOMA																				
OVARY	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CYSTADENOMA, NOS																X				
NERVOUS SYSTEM																				
BRAIN	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																				
HARDERIAN GLAND	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																				
ALL OTHER SYSTEMS																				
MULTIPLE ORGANS NOS	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIGNANT LYMPHOMA, NOS						X			X	X		X	X	X	X					
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																		X	X	
TOE NOS					M															
FIBROSARCOMA								X												

+: TISSUE EXAMINED MICROSCOPICALLY
–: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	026	027	028	029	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	089	102	105	105	105	105	105	092	105	105	093	105	105	105	105	105	105	105	105	105	105	105	105	105	TISSUES TUMORS
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ALVEOLAR/BRONCHIOLAR CARCINOMA																									1
TRACHEA	-	+	-	-	+	+	-	+	-	+	+	+	+	-	-	-	-	-	+	+	-	-	-	+	22
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	48
SPLEEN	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
MALIGNANT LYMPHOMA, NOS																									1
LYMPH NODES	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
MALIGNANT LYMPHOMA, NOS																		X							1
THYMUS	-	+	+	-	+	+	-	+	+	-	-	+	-	-	+	+	+	+	+	+	+	+	+	+	38
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
LIVER	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEPATOCELLULAR ADENOMA					X																				3
HEPATOCELLULAR CARCINOMA		X		X																	X		X		3
BILE DUCT	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
GALLBLADDER & COMMON BILE DUCT	N	N	+	N	+	+	+	N	+	+	+	N	+	+	+	N	+	+	N	+	+	+	+	+	49*
PANCREAS	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
STOMACH	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SMALL INTESTINE	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	45
LARGE INTESTINE	-	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																									
KIDNEY	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																									
PITUITARY	-	-	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	43
CHROMOPHOBE ADENOMA									X								X								5
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYROID	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
FOLLICULAR-CELL ADENOMA													X												2
PARATHYROID	-	+	-	-	+	+	-	-	+	-	+	-	-	-	+	-	-	-	+	+	+	+	-	-	22
PANCREATIC ISLETS	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ISLET-CELL ADENOMA																									1
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49*
ADENOCARCINOMA, NOS																								X	1
FEMALE EXTERNAL GENITALIA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
SQUAMOUS CELL CARCINOMA																					X				1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
MYXOMA																		X							1
HEMANGIOSARCOMA																				X					1
OVARY	+	+	+	-	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	-	+	+	+	45
CYSTADENOMA, NOS																									1
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
ADENOMA, NOS																								X	1
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
MALIGNANT LYMPHOMA, NOS	X					X		X				X													14
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			X				X														X				3
TOE NOS																									
FIBROSARCOMA																									1

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
.: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR DOSED-FEED STUDY OF MELAMINE

HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	069	105	105	105	105	097	105	105	105	105	105	105	105	094	105	105	105	105	105	095	105	105	080	105
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																									
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
OSTEOSARCOMA, METASTATIC																									
TRACHEA	+	+	+	-	+	-	+	-	+	-	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MALIGNANT LYMPHOMA, NOS																									
LYMPH NODES	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+
THYMUS	+	-	+	+	+	+	-	+	+	+	-	+	+	+	+	-	+	-	+	+	+	+	-	-	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA																									
HEPATOCELLULAR CARCINOMA																									X
HEMANGIOSARCOMA																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	N	+	+	+	N	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
SMALL INTESTINE	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
CHROMOPHOBE ADENOMA	X										X			X											X
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																									
SARCOMA, NOS																									
THYROID	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA				X																					
PARATHYROID	-	-	+	+	+	+	-	-	+	-	+	-	+	+	+	-	+	+	-	-	-	-	-	-	
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA	X																								
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																									
ENDOMETRIAL STROMAL POLYP																									
HEMANGIOMA										X															
HEMANGIOSARCOMA																X									
OVARY	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TERATOMA, NOS																									
HEMANGIOMA																									
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIPOMA																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIGNANT LYMPHOMA, NOS	X						X								X							X			
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																								X	
PLASMA-CELL TUMOR														X											
MYELOMONOCYTIC LEUKEMIA																									
LEG NOS																									
OSTEOSARCOMA																									
SITE UNKNOWN																									
ADENOCARCINOMA, NOS																									

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER / WEEKS ON STUDY	TOTAL TISSUES TUMORS
RESPIRATORY SYSTEM	
LUNGS AND BRONCHI	50
ALVEOLAR/BRONCHIOLAR ADENOMA	2
ALVEOLAR/BRONCHIOLAR CARCINOMA	1
OSTEOSARCOMA, METASTATIC	1
TRACHEA	32
HEMATOPOIETIC SYSTEM	
BONE MARROW	50
SPLEEN	50
MALIGNANT LYMPHOMA, NOS	1
LYMPH NODES	45
THYMUS	41
CIRCULATORY SYSTEM	
HEART	50
DIGESTIVE SYSTEM	
SALIVARY GLAND	49
LIVER	50
HEPATOCELLULAR ADENOMA	1
HEPATOCELLULAR CARCINOMA	1
HEMANGIOSARCOMA	1
BILE DUCT	50
GALLBLADDER & COMMON BILE DUCT	50M
PANCREAS	50
ESOPHAGUS	48
STOMACH	49
SMALL INTESTINE	45
LARGE INTESTINE	47
URINARY SYSTEM	
KIDNEY	50
URINARY BLADDER	50
ENDOCRINE SYSTEM	
PITUITARY	48
CHROMOPHOBE ADENOMA	8
ADRENAL	50
ADENOMA, NOS	1
SARCOMA, NOS	1
THYROID	48
FOLLICULAR-CELL ADENOMA	1
PARATHYROID	24
PANCREATIC ISLETS	50
ISLET-CELL ADENOMA	1
REPRODUCTIVE SYSTEM	
MAMMARY GLAND	50M
UTERUS	50
ADENOCARCINOMA, NOS	1
ENDOMETRIAL STROMAL POLYP	1
HEMANGIOMA	1
HEMANGIOSARCOMA	1
OVARY	48
TERATOMA, NOS	1
HEMANGIOMA	1
NERVOUS SYSTEM	
BRAIN	50
LIPOMA	1
ALL OTHER SYSTEMS	
MULTIPLE ORGANS NOS	50M
MALIGNANT LYMPHOMA, NOS	9
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1
PLASMA-CELL TUMOR	1
MYELOMONOCYTIC LEUKEMIA	1
LEG NOS	1
OSTEOSARCOMA	1
SITE UNKNOWN	1
ADENOCARCINOMA, NOS	1

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS IN THE 2-YEAR DOSED FEED STUDY OF MELAMINE

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE 2-YEAR DOSED-FEED STUDY OF MELAMINE

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(49)	(50)	(50)
EDEMA, NOS	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)		
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)		
HYPERKERATOSIS	1 (2%)		1 (2%)
RESPIRATORY SYSTEM			
*NASAL CAVITY	(49)	(50)	(50)
HEMORRHAGE		1 (2%)	
INFLAMMATION, SUPPURATIVE			1 (2%)
#TRACHEA	(48)	(49)	(45)
INFLAMMATION, SUPPURATIVE			1 (2%)
#LUNG	(49)	(50)	(50)
ATELECTASIS			1 (2%)
CONGESTION, NOS	1 (2%)	1 (2%)	2 (4%)
EDEMA, NOS			1 (2%)
HEMORRHAGE		1 (2%)	
INFLAMMATION, SUPPURATIVE			2 (4%)
BRONCHOPNEUMONIA SUPPURATIVE	3 (6%)		2 (4%)
BRONCHOPNEUMONIA, ACUTE		1 (2%)	1 (2%)
INFLAMMATION, ACUTE			1 (2%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
PNEUMONIA, CHRONIC MURINE	1 (2%)	2 (4%)	1 (2%)
INFLAMMATION, GRANULOMATOUS			1 (2%)
GRANULOMA, NOS		1 (2%)	1 (2%)
INFECTION, BACTERIAL			1 (2%)
HEMOSIDEROSIS		1 (2%)	1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(48)	(49)	(50)
INFLAMMATION, GRANULOMATOUS	1 (2%)	1 (2%)	
GRANULOMA, NOS		1 (2%)	
HYPOPLASIA, NOS		4 (8%)	
OSTEOSCLEROSIS		1 (2%)	
HYPERPLASIA, HEMATOPOIETIC		1 (2%)	
#SPLEEN	(49)	(50)	(49)
ACCESSORY SPLEEN			1 (2%)
INFLAMMATION, GRANULOMATOUS	1 (2%)		
FIBROSIS	1 (2%)	1 (2%)	
FIBROSIS, FOCAL	1 (2%)		
ATROPHY, NOS			1 (2%)
HYPERPLASIA, RETICULUM CELL		1 (2%)	
HYPERPLASIA, LYMPHOID	1 (2%)		
HEMATOPOIESIS	1 (2%)	2 (4%)	3 (6%)
#SPLENIC FOLLICLES	(49)	(50)	(49)
ATROPHY, NOS	1 (2%)	3 (6%)	4 (8%)
#LYMPH NODE	(49)	(49)	(47)
INFLAMMATION, GRANULOMATOUS	1 (2%)		
PLASMACYTOSIS			1 (2%)
HYPERPLASIA, PLASMA CELL		1 (2%)	
#MANDIBULAR L. NODE	(49)	(49)	(47)
CONGESTION, NOS	1 (2%)		
INFLAMMATION, SUPPURATIVE			1 (2%)
INFLAMMATION ACTIVE CHRONIC		1 (2%)	
INFLAMMATION, GRANULOMATOUS			2 (4%)
NECROSIS, NOS	1 (2%)		
PLASMACYTOSIS		1 (2%)	2 (4%)
#MEDIASTINAL L.NODE	(49)	(49)	(47)
HEMORRHAGE	1 (2%)		
#HEPATIC LYMPH NODE	(49)	(49)	(47)
HYPERPLASIA, LYMPHOID		1 (2%)	
#PANCREATIC L.NODE	(49)	(49)	(47)
GRANULOMA, NOS			1 (2%)
#MESENTERIC L. NODE	(49)	(49)	(47)
HEMORRHAGE	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#RENAL LYMPH NODE	(49)	(49)	(47)
HEMORRHAGE	1 (2%)		
HEMOSIDEROSIS		1 (2%)	
HISTIOCYTOSIS	1 (2%)		
#SACRAL LYMPH NODE	(49)	(49)	(47)
HISTIOCYTOSIS		1 (2%)	
*STERNUM	(49)	(50)	(50)
MYELOSCLEROSIS	1 (2%)		
CIRCULATORY SYSTEM			
#BRAIN	(49)	(50)	(50)
THROMBOSIS, NOS			1 (2%)
#MANDIBULAR L. NODE	(49)	(49)	(47)
LYMPHANGIECTASIS	7 (14%)	2 (4%)	1 (2%)
#MESENTERIC L. NODE	(49)	(49)	(47)
LYMPHANGIECTASIS	1 (2%)		
#LUNG	(49)	(50)	(50)
PERIVASCULITIS		1 (2%)	
#HEART	(49)	(50)	(50)
DEGENERATION, NOS	35 (71%)	41 (82%)	36 (72%)
#HEART/ATRIUM	(49)	(50)	(50)
THROMBOSIS, NOS		2 (4%)	
*AORTA	(49)	(50)	(50)
PERIVASCULITIS		1 (2%)	
MEDIAL CALCIFICATION	1 (2%)		
*CORONARY ARTERY	(49)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
NECROSIS, FIBRINOID		1 (2%)	
*MESENTERIC ARTERY	(49)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
*PORTAL VEIN	(49)	(50)	(50)
THROMBOSIS, NOS		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#TESTIS	(49)	(50)	(50)
PERIVASCULITIS	1 (2%)	1 (2%)	2 (4%)
#ADRENAL	(49)	(50)	(48)
THROMBOSIS, NOS		2 (4%)	3 (6%)
PERIVASCULITIS			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(49)	(49)	(49)
ABSCESS, CHRONIC			1 (2%)
ATROPHY, NOS			1 (2%)
#LIVER	(49)	(50)	(50)
HERNIA, NOS	2 (4%)	2 (4%)	
CONGESTION, NOS		1 (2%)	
HEMORRHAGE			1 (2%)
ABSCESS, NOS		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)		1 (2%)
GRANULOMA, NOS	8 (16%)	13 (26%)	6 (12%)
DEGENERATION, HYDROPIC		1 (2%)	
NECROSIS, NOS	1 (2%)	1 (2%)	1 (2%)
METAMORPHOSIS FATTY	2 (4%)	6 (12%)	2 (4%)
BASOPHILIC CYTO CHANGE	1 (2%)	2 (4%)	3 (6%)
EOSINOPHILIC CYTO CHANGE	1 (2%)	1 (2%)	
ANGIECTASIS	1 (2%)		
#PORTAL TRACT	(49)	(50)	(50)
INFLAMMATION ACTIVE CHRONIC		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
#LIVER/CENTRILOBULAR	(49)	(50)	(50)
DEGENERATION, NOS		1 (2%)	
CLOUDY SWELLING			1 (2%)
NECROSIS, NOS	1 (2%)		1 (2%)
METAMORPHOSIS FATTY		1 (2%)	
HEMOSIDEROSIS		1 (2%)	
#LIVER/MIDLOBULAR	(49)	(50)	(50)
METAMORPHOSIS FATTY			1 (2%)
#BILE DUCT	(49)	(50)	(50)
HYPERPLASIA, NOS	35 (71%)	37 (74%)	31 (62%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#PANCREAS	(44)	(48)	(45)
CYST, NOS			1 (2%)
MULTILOCULAR CYST			1 (2%)
CYSTIC DUCTS			1 (2%)
INFLAMMATION, INTERSTITIAL			1 (2%)
ATROPHY, NOS			1 (2%)
#PANCREATIC ACINUS	(44)	(48)	(45)
ATROPHY, NOS	6 (14%)	12 (25%)	10 (22%)
HYPERPLASIA, NOS			1 (2%)
#ESOPHAGUS	(49)	(50)	(49)
HYPERKERATOSIS			1 (2%)
#STOMACH	(49)	(49)	(48)
INFLAMMATION, SUPPURATIVE	1 (2%)		
ULCER, ACUTE		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
CALCIFICATION, NOS	1 (2%)		3 (6%)
HYPERPLASIA, EPITHELIAL		1 (2%)	
#GASTRIC MUCOSA	(49)	(49)	(48)
MINERALIZATION	1 (2%)		
#FORESTOMACH	(49)	(49)	(48)
TRICHOBEZOAR			1 (2%)
ULCER, NOS			1 (2%)
INFLAMMATION, SUPPURATIVE			1 (2%)
INFLAMMATION, ACUTE		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC		3 (6%)	2 (4%)
HYPERPLASIA, EPITHELIAL	1 (2%)	1 (2%)	2 (4%)
#COLON	(45)	(47)	(44)
INFLAMMATION, ACUTE	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
NEMATODIASIS			1 (2%)
#CECUM	(45)	(47)	(44)
INFLAMMATION, GRANULOMATOUS	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(49)	(50)	(49)
MINERALIZATION	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYDRONEPHROSIS	1 (2%)	1 (2%)	1 (2%)
PYELONEPHRITIS, NOS		1 (2%)	
PYELONEPHRITIS, ACUTE/CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC	2 (4%)	3 (6%)	6 (12%)
NEPHROPATHY	32 (65%)	36 (72%)	30 (61%)
CALCIFICATION, NOS			1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)	2 (4%)
#KIDNEY/TUBULE	(49)	(50)	(49)
DILATATION, NOS	1 (2%)	1 (2%)	
PIGMENTATION, NOS	2 (4%)	3 (6%)	2 (4%)
ATROPHY, NOS			2 (4%)
#KIDNEY/PELVIS	(49)	(50)	(49)
CALCULUS,UNKN GROSS OR MICRO			1 (2%)
CALCIFICATION, NOS		1 (2%)	1 (2%)
#URINARY BLADDER	(45)	(50)	(49)
CALCULUS,UNKN GROSS OR MICRO		1 (2%)	10 (20%)
CAST, NOS	1 (2%)		1 (2%)
HEMORRHAGE		1 (2%)	
INFLAMMATION ACTIVE CHRONIC		1 (2%)	
HYPERPLASIA, EPITHELIAL		1 (2%)	2 (4%)
*URETHRA	(49)	(50)	(50)
HYPERPLASIA, EPITHELIAL			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(45)	(46)	(49)
CYST, NOS	3 (7%)	3 (7%)	3 (6%)
HEMATOMA, NOS			1 (2%)
CYTOLOGIC DEGENERATION		1 (2%)	
HYPERPLASIA, CHROMOPHOBE-CELL	4 (9%)	4 (9%)	6 (12%)
ANGIECTASIS		1 (2%)	1 (2%)
#ADRENAL	(49)	(50)	(48)
NECROSIS, NOS			1 (2%)
CYTOLOGIC DEGENERATION	6 (12%)	5 (10%)	6 (13%)
ANGIECTASIS		1 (2%)	1 (2%)
#ADRENAL CORTEX	(49)	(50)	(48)
DEGENERATION, LIPOID	1 (2%)		
HYPERTROPHY, NOS			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, NOS	1 (2%)	1 (2%)	
#ADRENAL MEDULLA	(49)	(50)	(48)
HYPERPLASIA, NOS	4 (8%)	2 (4%)	2 (4%)
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)	1 (2%)
#THYROID	(48)	(50)	(46)
ULTIMOBRANCHIAL CYST			1 (2%)
HYPERPLASIA, C-CELL	2 (4%)	5 (10%)	7 (15%)
#PARATHYROID	(39)	(41)	(36)
HYPERPLASIA, NOS	1 (3%)		
#PANCREATIC ISLETS	(44)	(48)	(45)
HYPERPLASIA, NOS	1 (2%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(49)	(50)	(50)
DILATATION/DUCTS	8 (16%)	6 (12%)	6 (12%)
GALACTOCELE	1 (2%)	1 (2%)	
CALCIFICATION, NOS	1 (2%)		
HYPERPLASIA, NOS		1 (2%)	1 (2%)
*MAMMARY LOBULE	(49)	(50)	(50)
HYPERPLASIA, NOS	1 (2%)	2 (4%)	
*PREPUTIAL GLAND	(49)	(50)	(50)
ABSCESS, NOS			2 (4%)
#PROSTATE	(49)	(48)	(46)
HEMORRHAGE			1 (2%)
INFLAMMATION, SUPPURATIVE	2 (4%)	4 (8%)	1 (2%)
INFLAMMATION, ACUTE			1 (2%)
INFLAMMATION ACTIVE CHRONIC	1 (2%)	2 (4%)	
INFLAMMATION, CHRONIC	1 (2%)	1 (2%)	2 (4%)
INFLAMMATION, CHRONIC SUPPURATIV	1 (2%)	1 (2%)	
*SEMINAL VESICLE	(49)	(50)	(50)
HEMORRHAGE			1 (2%)
INFLAMMATION, ACUTE			1 (2%)
#TESTIS	(49)	(50)	(50)
MINERALIZATION		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ATROPHY, NOS	13 (27%)	8 (16%)	7 (14%)
HYPERPLASIA, INTERSTITIAL CELL	1 (2%)	1 (2%)	5 (10%)
#TESTIS/TUBULE	(49)	(50)	(50)
CALCIFICATION, NOS			1 (2%)
#SPERMATID	(49)	(50)	(50)
CYTOMEGALY		1 (2%)	1 (2%)
*EPIDIDYMIS	(49)	(50)	(50)
INFLAMMATION, GRANULOMATOUS	1 (2%)		
GRANULOMA, SPERMATIC			1 (2%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(49)	(50)	(50)
INFLAMMATION, ACUTE			1 (2%)
*CHOROID PLEXUS	(49)	(50)	(50)
CALCIFICATION, NOS		2 (4%)	
#BRAIN	(49)	(50)	(50)
HEMORRHAGE		1 (2%)	2 (4%)
ABSCESS, NOS			1 (2%)
#CEREBELLUM	(49)	(50)	(50)
HEMORRHAGE		1 (2%)	
SPECIAL SENSE ORGANS			
*EYE	(49)	(50)	(50)
HEMORRHAGE		1 (2%)	1 (2%)
INFLAMMATION, ACUTE			1 (2%)
INFLAMMATION ACTIVE CHRONIC			1 (2%)
INFLAMMATION, CHRONIC	1 (2%)		
CATARACT	18 (37%)	9 (18%)	10 (20%)
*EYEBALL TUNICA VASCU	(49)	(50)	(50)
HEMORRHAGE		1 (2%)	
*EYE/RETINA	(49)	(50)	(50)
ATROPHY, NOS	15 (31%)	8 (16%)	9 (18%)
*EAR	(49)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
*MANDIBLE	(49)	(50)	(50)
CYST, NOS		1 (2%)	
BODY CAVITIES			
*ABDOMINAL CAVITY	(49)	(50)	(50)
HEMORRHAGE		1 (2%)	
INFLAMMATION ACTIVE CHRONIC		1 (2%)	
INFLAMMATION, GRANULOMATOUS		3 (6%)	2 (4%)
*PLEURA	(49)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
*MESENTERY	(49)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)
ALL OTHER SYSTEMS			
PERIORBITAL REGION			
INFLAMMATION, ACUTE/CHRONIC			1
SPECIAL MORPHOLOGY SUMMARY			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE 2-YEAR DOSED-FEED STUDY OF MELAMINE

	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)
EPIDERMAL INCLUSION CYST	1 (2%)		
RESPIRATORY SYSTEM			
*NASAL CAVITY	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE		1 (2%)	
#LUNG	(50)	(50)	(50)
CONGESTION, NOS	1 (2%)		
EDEMA, NOS		1 (2%)	
HEMORRHAGE	2 (4%)	1 (2%)	
BRONCHOPNEUMONIA SUPPURATIVE	1 (2%)		1 (2%)
ABSCESS, NOS			2 (4%)
INFLAMMATION ACTIVE CHRONIC		1 (2%)	
PNEUMONIA, CHRONIC MURINE	3 (6%)	1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	
GRANULOMA, NOS		2 (4%)	1 (2%)
GRANULOMA, FOREIGN BODY	1 (2%)	1 (2%)	
INFLAMMATION, PYOGRANULOMATOUS			1 (2%)
HYPERPLASIA, ADENOMATOUS		1 (2%)	
HISTIOCYTOSIS	1 (2%)		1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(48)	(50)	(50)
INFLAMMATION, GRANULOMATOUS	3 (6%)	4 (8%)	4 (8%)
GRANULOMA, NOS		1 (2%)	
MYELOFIBROSIS			1 (2%)
MYELOSCLEROSIS	1 (2%)		
#SPLEEN	(50)	(50)	(50)
INFLAMMATION, ACUTE		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, GRANULOMATOUS			1 (2%)
GRANULOMA, NOS	1 (2%)		
HEMOSIDEROSIS		1 (2%)	
HYPERPLASIA, NODULAR	1 (2%)		
HYPERPLASIA, LYMPHOID	1 (2%)		
HEMATOPOIESIS	4 (8%)	2 (4%)	4 (8%)
#SPLENIC CAPSULE	(50)	(50)	(50)
FIBROSIS	1 (2%)		
CALCIFICATION, NOS	1 (2%)		
#SPLENIC FOLLICLES	(50)	(50)	(50)
ATROPHY, NOS		2 (4%)	1 (2%)
#LYMPH NODE	(49)	(50)	(48)
INFLAMMATION, SUPPURATIVE			1 (2%)
#MANDIBULAR L. NODE	(49)	(50)	(48)
HEMORRHAGE		1 (2%)	
PLASMACYTOSIS	1 (2%)		1 (2%)
#MEDIASTINAL L.NODE	(49)	(50)	(48)
HEMORRHAGE	1 (2%)	1 (2%)	
GRANULOMA, NOS	1 (2%)	1 (2%)	
HYPERPLASIA, RETICULUM CELL		1 (2%)	
#HEPATIC LYMPH NODE	(49)	(50)	(48)
INFLAMMATION, GRANULOMATOUS		1 (2%)	
#PANCREATIC L.NODE	(49)	(50)	(48)
HEMORRHAGE	1 (2%)		
INFLAMMATION, GRANULOMATOUS		1 (2%)	
#MESENTERIC L. NODE	(49)	(50)	(48)
HEMORRHAGE	1 (2%)		
#LIVER	(50)	(50)	(50)
HEMATOPOIESIS	1 (2%)		
#KIDNEY/PELVIS	(50)	(50)	(50)
HEMATOPOIESIS		1 (2%)	
CIRCULATORY SYSTEM			
#BRAIN/MENINGES	(49)	(50)	(50)
THROMBOSIS, NOS		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#LYMPH NODE	(49)	(50)	(48)
LYMPHANGIECTASIS		1 (2%)	
#MANDIBULAR L. NODE	(49)	(50)	(48)
LYMPHANGIECTASIS	1 (2%)	3 (6%)	2 (4%)
#PANCREATIC L.NODE	(49)	(50)	(48)
LYMPHANGIECTASIS	1 (2%)		
#HEART	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
DEGENERATION, NOS	24 (48%)	22 (44%)	26 (52%)
CALCIFICATION, NOS		2 (4%)	
*CORONARY ARTERY	(50)	(50)	(50)
MEDIAL CALCIFICATION		1 (2%)	
*VEIN	(50)	(50)	(50)
THROMBUS, ORGANIZED		1 (2%)	
*PORTAL VEIN	(50)	(50)	(50)
THROMBOSIS, NOS		1 (2%)	
THROMBUS, ORGANIZED	1 (2%)		
#LIVER	(50)	(50)	(50)
THROMBOSIS, NOS			2 (4%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(47)	(50)	(49)
DILATATION/DUCTS		1 (2%)	
NECROSIS, NOS		1 (2%)	
#LIVER	(50)	(50)	(50)
HERNIA, NOS	1 (2%)	1 (2%)	4 (8%)
CYST, NOS			1 (2%)
CONGESTION, NOS		1 (2%)	1 (2%)
INFLAMMATION, ACUTE NECROTIZING		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC	1 (2%)	1 (2%)	
INFLAMMATION, GRANULOMATOUS	1 (2%)	1 (2%)	1 (2%)
GRANULOMA, NOS	21 (42%)	23 (46%)	19 (38%)
NECROSIS, NOS	1 (2%)	1 (2%)	2 (4%)
NECROSIS, FOCAL	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
METAMORPHOSIS FATTY	11 (22%)	9 (18%)	4 (8%)
HEMOSIDEROSIS		1 (2%)	
BASOPHILIC CYTO CHANGE	7 (14%)	3 (6%)	6 (12%)
HYPERPLASIA, FOCAL	1 (2%)		
ANGIECTASIS		1 (2%)	
#HEPATIC CAPSULE	(50)	(50)	(50)
CONGESTION, NOS			1 (2%)
#PORTAL TRACT	(50)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)
#LIVER/CENTRILOBULAR	(50)	(50)	(50)
DEGENERATION, NOS		1 (2%)	
HYPERTROPHY, NOS	1 (2%)		
#LIVER/PERIPORTAL	(50)	(50)	(50)
INFLAMMATION, CHRONIC	2 (4%)		1 (2%)
#BILE DUCT	(50)	(50)	(50)
HYPERPLASIA, NOS	9 (18%)	10 (20%)	7 (14%)
#PANCREAS	(48)	(49)	(50)
CYST, NOS		1 (2%)	
INFLAMMATION, INTERSTITIAL		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
NECROSIS, FAT	1 (2%)		
#PANCREATIC ACINUS	(48)	(49)	(50)
ATROPHY, NOS	10 (21%)	12 (24%)	9 (18%)
#STOMACH	(48)	(50)	(49)
HEMORRHAGE			1 (2%)
ULCER, NOS	1 (2%)		1 (2%)
INFLAMMATION, ACUTE			1 (2%)
ULCER, ACUTE			1 (2%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
EROSION		1 (2%)	
CALCIFICATION, NOS		2 (4%)	
#FORESTOMACH	(48)	(50)	(49)
INFLAMMATION, ACUTE		1 (2%)	
ULCER, ACUTE		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC	1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#PEYER'S PATCH	(44)	(47)	(48)
HYPERPLASIA, NOS		1 (2%)	2 (4%)
#COLON	(47)	(49)	(49)
NEMATODIASIS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
CALCULUS, NOS	1 (2%)		
INFLAMMATION, CHRONIC	4 (8%)	17 (34%)	41 (82%)
NEPHROPATHY	19 (38%)	23 (46%)	28 (56%)
CALCIFICATION, NOS		2 (4%)	
HEMOSIDEROSIS	2 (4%)		
#KIDNEY/CORTEX	(50)	(50)	(50)
CYST, NOS			2 (4%)
#KIDNEY/TUBULE	(50)	(50)	(50)
DILATATION, NOS	1 (2%)		
PIGMENTATION, NOS	7 (14%)	6 (12%)	4 (8%)
ATROPHY, NOS			1 (2%)
#KIDNEY/PELVIS	(50)	(50)	(50)
MINERALIZATION			2 (4%)
INFLAMMATION, ACUTE	1 (2%)		
#URINARY BLADDER	(49)	(49)	(47)
HEMORRHAGE		1 (2%)	
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, ACUTE HEMORRHAGIC	1 (2%)		
INFLAMMATION, GRANULOMATOUS	1 (2%)		
NECROSIS, NOS	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(49)	(50)
CYST, NOS	18 (36%)	16 (33%)	18 (36%)
HEMOSIDEROSIS	3 (6%)		
HYPERPLASIA, CHROMOPHOBE-CELL	7 (14%)	3 (6%)	5 (10%)
ANGIECTASIS			1 (2%)
#ADRENAL	(50)	(50)	(50)
ACCESSORY STRUCTURE			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NECROSIS, NOS		1 (2%)	
CYTOLOGIC DEGENERATION	10 (20%)	7 (14%)	7 (14%)
ANGIECTASIS	1 (2%)	2 (4%)	2 (4%)
#ADRENAL CORTEX	(50)	(50)	(50)
DEGENERATION, LIPOID	3 (6%)	3 (6%)	2 (4%)
FOCAL CELLULAR CHANGE	1 (2%)	1 (2%)	
HYPERTROPHY, NOS			2 (4%)
HYPERPLASIA, NOS		2 (4%)	
#ADRENAL MEDULLA	(50)	(50)	(50)
HYPERPLASIA, NOS	2 (4%)	2 (4%)	2 (4%)
#THYROID	(50)	(49)	(50)
ULTIMOBRANCHIAL CYST	1 (2%)	1 (2%)	1 (2%)
CYSTIC FOLLICLES			1 (2%)
HYPERPLASIA, C-CELL	5 (10%)	5 (10%)	5 (10%)
#PANCREATIC ISLETS	(48)	(49)	(50)
HYPERPLASIA, NOS			2 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
DILATATION/DUCTS	17 (34%)	19 (38%)	23 (46%)
GALACTOCELE	9 (18%)	6 (12%)	
HYPERPLASIA, NOS	2 (4%)	2 (4%)	1 (2%)
*MAMMARY LOBULE	(50)	(50)	(50)
HYPERPLASIA, NOS	6 (12%)	6 (12%)	7 (14%)
*PREPUTIAL GLAND	(50)	(50)	(50)
DILATATION/DUCTS			1 (2%)
ABSCESS, NOS		1 (2%)	
#UTERUS	(50)	(50)	(50)
HYDROMETRA			1 (2%)
CYST, NOS			1 (2%)
HEMATOMA, NOS	1 (2%)		
INFLAMMATION, SUPPURATIVE		1 (2%)	
ABSCESS, NOS			1 (2%)
HEMOSIDEROSIS		1 (2%)	
#CERVIX UTERI	(50)	(50)	(50)
INFLAMMATION, ACUTE			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ABSCESS, NOS		1 (2%)	
#UTERUS/ENDOMETRIUM	(50)	(50)	(50)
CYST, NOS	6 (12%)	2 (4%)	1 (2%)
INFLAMMATION, SUPPURATIVE			1 (2%)
HEMOSIDEROSIS	1 (2%)		
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, CYSTIC	4 (8%)	5 (10%)	3 (6%)
#OVARY	(50)	(50)	(50)
CYST, NOS	3 (6%)	2 (4%)	1 (2%)
INFLAMMATION, GRANULOMATOUS			1 (2%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(49)	(50)	(50)
INFLAMMATION ACTIVE CHRONIC		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
#BRAIN	(49)	(50)	(50)
HEMORRHAGE		2 (4%)	4 (8%)
INFLAMMATION, SUPPURATIVE			1 (2%)
ABSCESS, NOS		1 (2%)	
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
HEMORRHAGE			2 (4%)
INFLAMMATION, SUPPURATIVE	1 (2%)		
INFLAMMATION, ACUTE	2 (4%)	1 (2%)	
ULCER, ACUTE			1 (2%)
INFLAMMATION ACTIVE CHRONIC	1 (2%)	1 (2%)	1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	1 (2%)
CATARACT	12 (24%)	6 (12%)	10 (20%)
ATROPHY, NOS		1 (2%)	
*EYE/CORNEA	(50)	(50)	(50)
ULCER, ACUTE		1 (2%)	
*EYE/RETINA	(50)	(50)	(50)
ATROPHY, NOS	11 (22%)	6 (12%)	11 (22%)
MUSCULOSKELETAL SYSTEM			
*BONE	(50)	(50)	(50)
FIBROUS OSTEODYSTROPHY	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
*MANDIBLE	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)	
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
INFLAMMATION, GRANULOMATOUS		1 (2%)	
NECROSIS, FAT		1 (2%)	
*MESENTERY	(50)	(50)	(50)
INFLAMMATION, GRANULOMATOUS			1 (2%)
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE IN THE 2-YEAR DOSED FEED STUDY OF MELAMINE

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE 2-YEAR DOSED-FEED STUDY OF MELAMINE

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	49	49	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	48	49	47
INTEGUMENTARY SYSTEM			
*SKIN	(49)	(49)	(48)
MINERALIZATION	1 (2%)		2 (4%)
CYST, NOS	1 (2%)		
INFLAMMATION, ACUTE			1 (2%)
INFLAMMATION ACUTE AND CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)		
*SUBCUT TISSUE	(49)	(49)	(48)
FOREIGN BODY, NOS	1 (2%)		
ABSCESS, NOS	1 (2%)	1 (2%)	3 (6%)
INFLAMMATION WITH FIBROSIS	1 (2%)		
RESPIRATORY SYSTEM			
#TRACHEA	(26)	(23)	(31)
HEMORRHAGE		1 (4%)	
ABSCESS, NOS		1 (4%)	
#LUNG	(47)	(48)	(47)
CONGESTION, NOS	2 (4%)	1 (2%)	3 (6%)
HEMORRHAGE	5 (11%)	8 (17%)	6 (13%)
LYMPHOCYTIC INFLAMMATORY INFILTR	3 (6%)	1 (2%)	2 (4%)
ABSCESS, NOS		1 (2%)	
HISTIOCYTOSIS	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(49)	(49)	(48)
LEUKEMOID REACTION		2 (4%)	2 (4%)
HYPERPLASIA, LYMPHOID	3 (6%)	3 (6%)	1 (2%)
HEMATOPOIESIS	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
*TAIL	(49)	(49)	(48)
MYELOSCLEROSIS			1 (2%)
#BONE MARROW	(46)	(45)	(43)
LEUKEMOID REACTION	1 (2%)		
HYPERPLASIA, HEMATOPOIETIC		1 (2%)	4 (9%)
#SPLEEN	(44)	(47)	(44)
CYST, NOS		1 (2%)	
CONGESTION, NOS			1 (2%)
INFLAMMATION, GRANULOMATOUS			1 (2%)
INFLAMMATION, FIBRINOID	1 (2%)		
HEMOSIDEROSIS	1 (2%)		2 (5%)
ANGIECTASIS		1 (2%)	
HYPERPLASIA, LYMPHOID	1 (2%)		
HEMATOPOIESIS	2 (5%)	4 (9%)	4 (9%)
#LYMPH NODE	(38)	(32)	(36)
HYPERPLASIA, LYMPHOID	1 (3%)		
#MANDIBULAR L. NODE	(38)	(32)	(36)
PLASMACYTOSIS	1 (3%)	2 (6%)	1 (3%)
HYPERPLASIA, LYMPHOID			1 (3%)
#MEDIASTINAL L.NODE	(38)	(32)	(36)
PLASMACYTOSIS			1 (3%)
#LUMBAR LYMPH NODE	(38)	(32)	(36)
HEMORRHAGE		1 (3%)	
HYPERPLASIA, LYMPHOID		1 (3%)	
#MESENTERIC L. NODE	(38)	(32)	(36)
HEMORRHAGE	6 (16%)	8 (25%)	5 (14%)
INFLAMMATION, NECROTIZING	1 (3%)		
SCLEROSIS	1 (3%)		
#RENAL LYMPH NODE	(38)	(32)	(36)
HYPERPLASIA, LYMPHOID		1 (3%)	
#SACRAL LYMPH NODE	(38)	(32)	(36)
HYPERPLASIA, LYMPHOID		1 (3%)	
#INGUINAL LYMPH NODE	(38)	(32)	(36)
HYPERPLASIA, LYMPHOID			1 (3%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#FEMORAL LYMPH NODE	(38)	(32)	(36)
HYPERPLASIA, LYMPHOID	2 (5%)	1 (3%)	
#LUNG	(47)	(48)	(47)
LEUKEMOID REACTION	1 (2%)	1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	
#PEYER'S PATCH	(42)	(42)	(36)
HYPERPLASIA, LYMPHOID	1 (2%)		
#THYMUS	(33)	(30)	(24)
ULTIMOBRANCHIAL CYST			1 (4%)
CYST, NOS	1 (3%)	1 (3%)	1 (4%)
CIRCULATORY SYSTEM			
#HEART	(46)	(48)	(47)
INFLAMMATION, NECROTIZING			1 (2%)
INFLAMMATION, ACUTE			1 (2%)
INFLAMMATION, FIBRINOID	1 (2%)		
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(47)	(47)	(44)
MINERALIZATION		2 (4%)	
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (4%)	2 (4%)	
INFLAMMATION, ACUTE			1 (2%)
ATROPHY, NOS		1 (2%)	1 (2%)
#LIVER	(45)	(48)	(47)
CYST, NOS			1 (2%)
CONGESTION, NOS		1 (2%)	
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, NECROTIZING		1 (2%)	
INFLAMMATION, ACUTE	1 (2%)		
INFLAMMATION, CHRONIC			1 (2%)
INFLAMMATION, FIBRINOID		1 (2%)	
NECROSIS, NOS		4 (8%)	4 (9%)
METAMORPHOSIS FATTY			1 (2%)
CYTOPLASMIC VACUOLIZATION			1 (2%)
FOCAL CELLULAR CHANGE	4 (9%)	3 (6%)	4 (9%)
*GALLBLADDER	(49)	(49)	(48)
INFLAMMATION, ACUTE		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#BILE DUCT	(45)	(48)	(47)
DILATATION, NOS			1 (2%)
#PANCREAS	(42)	(47)	(44)
INFLAMMATION, ACUTE			1 (2%)
ATROPHY, NOS	1 (2%)		1 (2%)
#PERIPANCREATIC TISSU	(42)	(47)	(44)
NECROSIS, FAT			1 (2%)
#STOMACH	(43)	(47)	(45)
HEMORRHAGE			1 (2%)
INFLAMMATION, ACUTE	2 (5%)	2 (4%)	2 (4%)
INFLAMMATION ACUTE AND CHRONIC	2 (5%)		
HYPERPLASIA, EPITHELIAL	1 (2%)		
#COLON	(43)	(46)	(43)
NEMATODIASIS	2 (5%)		1 (2%)
URINARY SYSTEM			
#KIDNEY	(47)	(48)	(46)
MINERALIZATION		4 (8%)	2 (4%)
CYST, NOS		1 (2%)	3 (7%)
GLOMERULONEPHRITIS, NOS	3 (6%)	1 (2%)	1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	5 (11%)	9 (19%)	4 (9%)
INFLAMMATION, INTERSTITIAL	1 (2%)	1 (2%)	
ABSCESS, NOS		1 (2%)	
INFLAMMATION, CHRONIC	2 (4%)	1 (2%)	1 (2%)
PYELONEPHRITIS, CHRONIC			1 (2%)
NEPHROSIS, NOS	2 (4%)	2 (4%)	
ATROPHY, NOS		1 (2%)	
#URINARY BLADDER	(45)	(47)	(44)
CALCULUS, NOS			3 (7%)
CONGESTION, NOS	1 (2%)	1 (2%)	
EDEMA, NOS	1 (2%)		1 (2%)
HEMORRHAGE	1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (4%)		
INFLAMMATION, ACUTE		1 (2%)	
INFLAMMATION ACUTE AND CHRONIC		25 (53%)	24 (55%)
INFLAMMATION, CHRONIC	2 (4%)	10 (21%)	14 (32%)
HYPERPLASIA, EPITHELIAL	1 (2%)	11 (23%)	13 (30%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
*URETHRAL GLAND	(49)	(49)	(48)
HEMORRHAGE			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(41)	(46)	(42)
CYST, NOS			2 (5%)
ABSCESS, NOS	1 (2%)		
HYPERPLASIA, CHROMOPHOBE-CELL			1 (2%)
#ADRENAL	(43)	(47)	(45)
CONGESTION, NOS		1 (2%)	
FIBROSIS			1 (2%)
AMYLOIDOSIS	1 (2%)		
HYPERPLASIA, NODULAR	2 (5%)		1 (2%)
HYPERPLASIA, NOS	9 (21%)	8 (17%)	5 (11%)
HYPERPLASIA, FOCAL			1 (2%)
#ADRENAL CORTEX	(43)	(47)	(45)
HYPERPLASIA, NOS		1 (2%)	
#ADRENAL MEDULLA	(43)	(47)	(45)
HYPERPLASIA, NOS		1 (2%)	
#THYROID	(46)	(47)	(44)
FOLLICULAR CYST, NOS	3 (7%)	4 (9%)	4 (9%)
#PARATHYROID	(22)	(18)	(22)
CYST, NOS			2 (9%)
REPRODUCTIVE SYSTEM			
*PREPUCE	(49)	(49)	(48)
IMPACTION, NOS	1 (2%)		
*PREPUTIAL GLAND	(49)	(49)	(48)
DILATATION, NOS	2 (4%)	3 (6%)	1 (2%)
ABSCESS, NOS	1 (2%)	2 (4%)	1 (2%)
INFLAMMATION, CHRONIC	1 (2%)	2 (4%)	
HYPERPLASIA, EPITHELIAL	1 (2%)	1 (2%)	
#PROSTATE	(46)	(47)	(45)
INFLAMMATION, NOS	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, ACUTE		3 (6%)	1 (2%)
*SEMINAL VESICLE	(49)	(49)	(48)
DILATATION, NOS		2 (4%)	1 (2%)
HEMORRHAGE		1 (2%)	
INFLAMMATION, ACUTE		1 (2%)	
#TESTIS	(48)	(48)	(46)
MINERALIZATION	24 (50%)	27 (56%)	31 (67%)
ATROPHY, NOS	4 (8%)	2 (4%)	2 (4%)
HYPERPLASIA, INTERSTITIAL CELL		1 (2%)	
METAPLASIA, OSSEOUS		1 (2%)	1 (2%)
*EPIDIDYMIS	(49)	(49)	(48)
CYST, NOS		1 (2%)	
NECROSIS, FAT	1 (2%)		
*VAS DEFERENS	(49)	(49)	(48)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(46)	(48)	(46)
MINERALIZATION	23 (50%)	25 (52%)	26 (57%)
EDEMA, NOS	7 (15%)	7 (15%)	5 (11%)
HEMORRHAGE	1 (2%)	1 (2%)	
ABSCESS, NOS	1 (2%)		1 (2%)
SPECIAL SENSE ORGANS			
*EYE	(49)	(49)	(48)
ABSCESS, NOS	1 (2%)		
INFLAMMATION ACUTE AND CHRONIC		1 (2%)	
*EYE/LACRIMAL GLAND	(49)	(49)	(48)
HYPERPLASIA, EPITHELIAL		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(49)	(49)	(48)
SCLEROSIS	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*ABDOMINAL CAVITY	(49)	(49)	(48)
NECROSIS, FAT			1 (2%)
*PELVIS	(49)	(49)	(48)
STEATITIS		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(49)	(49)	(48)
MINERALIZATION		1 (2%)	
CYST, NOS			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	10 (20%)	4 (8%)	5 (10%)
INFLAMMATION, FIBRINOID	1 (2%)		
LEG			
SCLEROSIS			1
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1		
ANIMAL MISSING/NO NECROPSY		1	
AUTO/NECROPSY/HISTO PERF		1	
AUTO/NECROPSY/NO HISTO	1		1
AUTOLYSIS/NO NECROPSY			2

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE 2-YEAR DOSED FEED STUDY OF MELAMINE

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	47	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	47	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(47)	(49)	(50)
ABSCESS, NOS	1 (2%)		
ACANTHOSIS	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(44)	(48)	(50)
MINERALIZATION		2 (4%)	
CONGESTION, NOS		1 (2%)	
EDEMA, NOS		1 (2%)	
HEMORRHAGE	3 (7%)	1 (2%)	1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	4 (9%)	2 (4%)	3 (6%)
INFECTION, PROTOZOAN			3 (6%)
HYPERPLASIA, ALVEOLAR EPITHELIUM		1 (2%)	2 (4%)
HISTIOCYTOSIS		1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(47)	(49)	(50)
LEUKEMOID REACTION	1 (2%)		
HYPERPLASIA, LYMPHOID	5 (11%)	9 (18%)	4 (8%)
HEMATOPOIESIS	1 (2%)		3 (6%)
#BONE MARROW	(43)	(48)	(50)
MYELOFIBROSIS	35 (81%)	44 (92%)	43 (86%)
#SPLEEN	(44)	(48)	(50)
CONGESTION, NOS		1 (2%)	
HEMOSIDEROSIS	11 (25%)	9 (19%)	6 (12%)
HYPERPLASIA, LYMPHOID	2 (5%)	2 (4%)	2 (4%)
HEMATOPOIESIS	1 (2%)	3 (6%)	2 (4%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#LYMPH NODE	(38)	(42)	(45)
HYPERPLASIA, LYMPHOID	2 (5%)		
#MANDIBULAR L. NODE	(38)	(42)	(45)
HEMORRHAGE	1 (3%)		3 (7%)
HYPERPLASIA, LYMPHOID		1 (2%)	1 (2%)
#MEDIASTINAL L.NODE	(38)	(42)	(45)
PLASMACYTOSIS	1 (3%)		
HYPERPLASIA, LYMPHOID	1 (3%)		
#LUMBAR LYMPH NODE	(38)	(42)	(45)
HYPERPLASIA, LYMPHOID		1 (2%)	
#MESENTERIC L. NODE	(38)	(42)	(45)
HEMORRHAGE	2 (5%)	3 (7%)	
INFLAMMATION, ACUTE	1 (3%)		
ABSCESS, NOS	1 (3%)		
#RENAL LYMPH NODE	(38)	(42)	(45)
EDEMA, NOS	1 (3%)		
HYPERPLASIA, LYMPHOID			2 (4%)
*STERNUM	(47)	(49)	(50)
MYELOFIBROSIS	1 (2%)	1 (2%)	2 (4%)
#LUNG	(44)	(48)	(50)
HYPERPLASIA, LYMPHOID			1 (2%)
#LIVER	(46)	(48)	(50)
HEMATOPOIESIS			1 (2%)
#STOMACH	(44)	(48)	(49)
MASTOCYTOSIS		1 (2%)	
#THYMUS	(35)	(38)	(41)
CYST, NOS	1 (3%)		
HEMORRHAGE		1 (3%)	
HYPERPLASIA, LYMPHOID	1 (3%)	1 (3%)	
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(47)	(49)	(50)
THROMBOSIS, NOS			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#MYOCARDIUM	(45)	(48)	(50)
INFLAMMATION, NOS	1 (2%)		
#UTERUS	(46)	(49)	(50)
THROMBOSIS, NOS			1 (2%)
#INFUNDIBULUM OF FALL	(46)	(49)	(50)
THROMBOSIS, NOS			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(43)	(47)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (5%)		3 (6%)
#LIVER	(46)	(48)	(50)
CYST, NOS	1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR		2 (4%)	
INFLAMMATION, ACUTE	3 (7%)	4 (8%)	2 (4%)
NECROSIS, NOS	4 (9%)	2 (4%)	
CYTOPLASMIC VACUOLIZATION	2 (4%)		
FOCAL CELLULAR CHANGE	6 (13%)	4 (8%)	6 (12%)
CELL-SIZE, ALTERATION			1 (2%)
ANGIECTASIS			1 (2%)
*GALLBLADDER	(47)	(49)	(50)
INFLAMMATION, ACUTE	1 (2%)		
#PANCREAS	(44)	(46)	(50)
CYST, NOS		2 (4%)	1 (2%)
INFLAMMATION ACUTE AND CHRONIC			1 (2%)
FIBROSIS	1 (2%)		
ATROPHY, NOS		1 (2%)	4 (8%)
#STOMACH	(44)	(48)	(49)
MINERALIZATION	1 (2%)	1 (2%)	1 (2%)
INFLAMMATION, NOS	1 (2%)		
INFLAMMATION, ACUTE	1 (2%)	4 (8%)	1 (2%)
NECROSIS, NOS	1 (2%)	1 (2%)	
#COLON	(43)	(46)	(47)
NEMATODIASIS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(44)	(48)	(50)
GLOMERULONEPHRITIS, NOS	2 (5%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)	2 (4%)	
INFLAMMATION, ACUTE			1 (2%)
NEPHROSIS, NOS			2 (4%)
AMYLOIDOSIS	1 (2%)		
METAPLASIA, OSSEOUS		1 (2%)	
#URINARY BLADDER	(42)	(49)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	3 (7%)	1 (2%)	1 (2%)
INFLAMMATION ACUTE AND CHRONIC			4 (8%)
INFLAMMATION, CHRONIC			2 (4%)
HYPERPLASIA, EPITHELIAL			4 (8%)
ENDOCRINE SYSTEM			
#PITUITARY	(39)	(43)	(48)
CYST, NOS		1 (2%)	
HYPERPLASIA, CHROMOPHOBE-CELL	3 (8%)	1 (2%)	
ANGIECTASIS			1 (2%)
#ADRENAL	(44)	(49)	(50)
CONGESTION, NOS	1 (2%)		2 (4%)
AMYLOIDOSIS	1 (2%)		
CYTOPLASMIC VACUOLIZATION		2 (4%)	1 (2%)
HYPERPLASIA, NOS	38 (86%)	47 (96%)	45 (90%)
#THYROID	(42)	(45)	(48)
CYST, NOS		1 (2%)	
FOLLICULAR CYST, NOS	4 (10%)	4 (9%)	2 (4%)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
HYPERPLASIA, EPITHELIAL	1 (2%)		
HYPERPLASIA, FOLLICULAR-CELL		2 (4%)	1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(47)	(49)	(50)
LACTATION			1 (2%)
#UTERUS	(46)	(49)	(50)
DILATATION, NOS	1 (2%)		
CONGESTION, NOS		1 (2%)	
EDEMA, NOS			1 (2%)
HEMORRHAGE	1 (2%)		
INFLAMMATION, ACUTE		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, CHRONIC			1 (2%)
HYPERPLASIA, EPITHELIAL		3 (6%)	1 (2%)
ADENOMYOSIS			1 (2%)
#UTERUS/ENDOMETRIUM	(46)	(49)	(50)
CYST, NOS	39 (85%)	48 (98%)	48 (96%)
#OVARY	(40)	(45)	(48)
MINERALIZATION	1 (3%)	1 (2%)	
CYST, NOS	9 (23%)	8 (18%)	7 (15%)
HEMORRHAGE		1 (2%)	
HEMORRHAGIC CYST			1 (2%)
ABSCESS, NOS	1 (3%)		
NERVOUS SYSTEM			
#BRAIN	(45)	(49)	(50)
MINERALIZATION	23 (51%)	26 (53%)	18 (36%)
EDEMA, NOS	26 (58%)	21 (43%)	25 (50%)
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(47)	(49)	(50)
DILATATION, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*THORACIC VERTEBRA	(47)	(49)	(50)
EXOSTOSIS	1 (2%)		
BODY CAVITIES			
*MEDIASTINUM	(47)	(49)	(50)
INFLAMMATION, GRANULOMATOUS		1 (2%)	
*MESENTERY	(47)	(49)	(50)
NECROSIS, FAT			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(47)	(49)	(50)
MINERALIZATION	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HEMORRHAGE	2 (4%)		
STEATITIS			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	14 (30%)	21 (43%)	26 (52%)
INFLAMMATION, CHRONIC	1 (2%)		
ATYPIA, NOS			1 (2%)
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1		
ANIMAL MISSING/NO NECROPSY		1	
AUTOLYSIS/NO NECROPSY	3		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX E

ANALYSIS OF MELAMINE
(MIDWEST RESEARCH INSTITUTE)

APPENDIX E

A. ELEMENTAL ANALYSIS

Element	C	H	N
Theory	28.57	4.80	66.64
Determined			
Lot No. A7-11-75	28.46	4.79	66.48
	28.59	4.80	66.62
Lot No. A13179	28.56	4.72	66.80
	28.57	4.84	66.61

B. WATER ANALYSIS (Karl Fisher)

Lot No. A7-11-75: 0.15% ± 0.05%

Lot No. A13179: 0.22% ± 0.07%

C. MELTING POINT

Determined	Literature Values
245°-300°C (Du Pont 900 DTA)	No literature value
350°-365°C (visual, capillary)	found

D. TITRATION

1. Analysis: Non-aqueous titration of one amine group. Samples were dissolved in glacial acetic acid (~50 mg/25 ml) and titrated with 0.1 N perchloric acid, monitoring the endpoint potentiometrically with a combination pH electrode.

2. Results: Lot No. A7-11-75: 100% ± 1 (s) %
   Lot No. A13179: 100.8% ± 0.5 (s) %

E. THIN-LAYER CHROMATOGRAPHY

Plates: Silica gel 60 F254 or cellulose F, 0.10 mm layer thickness
Amount Spotted: 100 and 300 μg
Ref. Standard: Pyrazinamide
Visualization: Ultraviolet 254 nm, iodine vapor, and formaldehyde-Schiff reagent

System 1: Ethylene glycol monomethyl ether, 100%; Silica gel 60 F254

Lot No. A7-11-75:	R_f: 0.86	R_{st}: 0.93
Lot No. A13179:	R_f: 0.62	R_{st}: 0.84

System 2: Methanol, 100%; Silica gel 60 F254

Lot No. A7-11-75:	R_f: 0.54	R_{st}: 0.75

System 3: n-Butanol saturated with ammonium hydroxide; cellulose F, 0.10 mm layer thickness

Lot No. A13179:	R_f: 0.16	R_{st}: 0.24

F. HIGH PERFORMANCE LIQUID CHROMATOGRAPHY (Lot No. A7-11-75)

Column: Partisil 10-SCX - 25 cm x 4.6 mm I.D.
Detector: Ultraviolet - 254 nm
Flow: 1 ml/min

System 1 - Instrument: Waters ALC - GPC 301
Solvent: pH 3 citric acid/phosphate buffer diluted 1 to 5 with H_2O, isocratic

System 2 - Instrument: Waters ALC 202
Solvent: pH 5 citric acid/phosphate buffer diluted 1 to 5 with H_2O, isocratic

Results:

Peak No.	Retention Time (min.)	Normalized Retention Time (min.)	Relative Areas
System 1			
1	4.38	0.35	0.64
2	5.47	0.44	0.94
3	11.56	0.92	0.43
4	12.50	1.00	100.00
System 2			
1	4.22	0.82	2.82 *(a)*
2	5.16	1.00	100.00
3	9.69	1.88	4.23 *(a)*

(a) pH changes affect the absorbance of at least the major peak at 254 nm and probably the impurities as well. Therefore, the relative areas of the peaks vary greatly with small changes in pH.

G. HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY (Lot No. A13179)

Instrument System:
Pump(s): Waters 6000A
Programmer: Waters 660
Detector: Waters 440
Injector: Waters U6K
Detection: Ultraviolet, 254 nm
Column: μBondapak C_{18}, 300 mm x 3.9 mm I.D.
Guard Column: CO:PELL ODS, 72 x 2.3 mm I.D.
Solvent System:
A. Water with 0.005 M heptanesulfonic acid, sodium salt, and 1% (v:v) acetic acid.
B. Methanol with 0.005 M heptanesulfonic acid, sodium salt, and 1% (v:v) acetic acid.
Program:
System 1: 100% A, isocratic
System 2: 70% A:30% B, isocratic

APPENDIX E

Flow Rate: 1 ml/min
Samples Injected:
System 1: 100 μl of a solution of 1.0 mg/ml melamine in solvent A, filtered.
System 2: 50 μl of 1.0 mg/ml and 0.5 mg/ml of melamine in solvent A, filtered.

Results:
System 1: Major peak and six impurities, five before and one after the major peak. The peak after the major peak had an an area of 1.2% of the major peak. The remaining impurities had areas totaling 1.1% of the major peak
System 2: Major peak and five impurities, three before and two after the major peak. One impurity after the major peak had an area of 1.9% of the major peak area. The remaining impurities totaled 1.2% of the major peak.

Peak No.	Retention Time (min.)	Retention Time (Relative to Major Peak)	Area (Percent of Major Peak)
System 1			
1	2.8	0.21	0.01
2	3.8	0.28	0.01
3	5.1	0.38	0.30
4	7.4	0.55	0.07
5	11.5	0.86	0.70
6	13.4	1.00	100
7	24.0	1.79	1.2
System 2			
1	2.8	0.56	0.06
2	3.6	0.72	0.32
3	4.0	0.80	0.75
4	5.0	1.00	100
5	6.6	1.32	0.06
6	9.0	1.80	1.9

Injections were made at 100%, 80%, 60%, 40%, 20%, and 10% B, with no additional impurities observed.

Lot No. A7-11-75 of melamine was chromatographed using System 2 (30% B). The chromatographic profile, peak retention times, and peak areas were very similar to those obtained for Lot No. A13179.

H. SPECTRAL DATA

1. Infrared

Instrument: Beckman IR-12

Consistent with literature spectrum (Morimoto, 1966a; and Sadtler Standard Spectra)

Lot No. A7-11-75:
Cell: 0.15% in potassium bromide pellet

Results: See Figure 5

Lot No. A13179:
Cell: 0.5% in potassium bromide pellet

Results: See Figure 6

2. Ultraviolet/Visible

Instrument: Cary 118

Determined		Literature (Morimoto, 1966b)	
λ max (nm)	$\varepsilon \times 10^{-4}$	λ max (nm)	$\varepsilon \times 10^{-4}$
Lot No. A7-11-75: 235	1.0248 ± 0.0006	236	1.08
Lot No. A13179: 235	1.011 ± 0.003		

No absorbance detected between 350 and 800 nm (visible range) at a concentration of 0.6 mg/ml

Solvent: 0.1 N HCl

Solvent: 0.1 N HCl

3. Nuclear Magnetic Resonance

Spectrum not recorded because compound is soluble only in solvents which exchange protons.

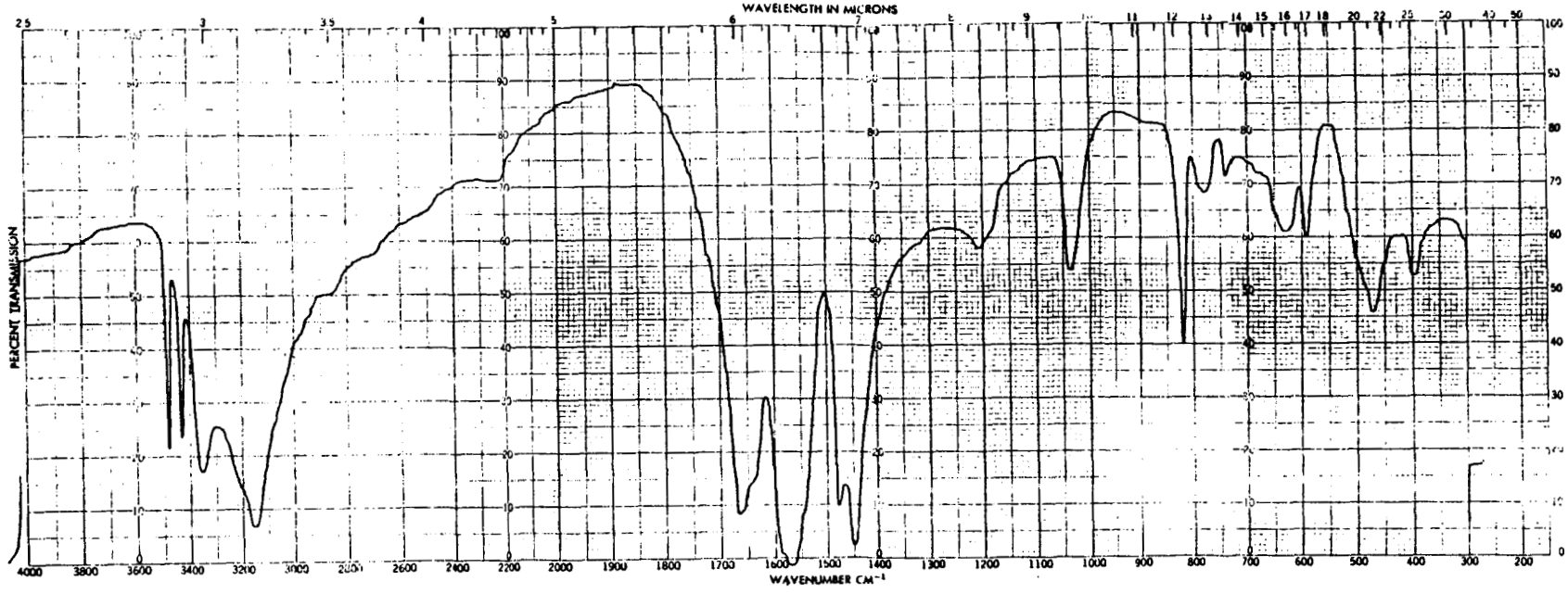

Figure 5. Infrared Absorption Spectrum of Melamine (Lot No. A7-11-75)

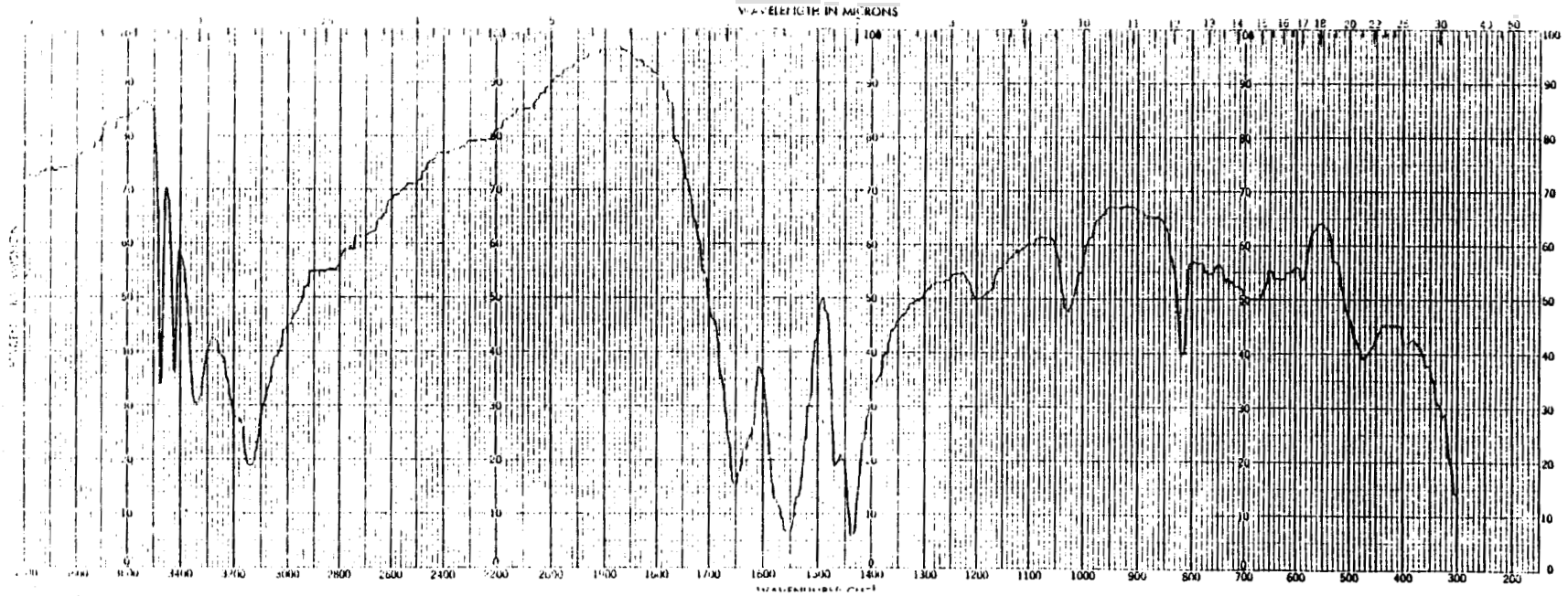

Figure 6. Infrared Absorption Spectrum of Melamine (Lot No. A13179)

APPENDIX F

ANALYSIS OF FORMULATED DIETS FOR STABILITY OF MELAMINE

APPENDIX F

A. MIXING AND STORAGE: Melamine (20 g) and Wayne Lab-Blox® Rodent Feed (180 g) were mixed for 30 minutes using a mortar and pestle. Samples of the mix were then removed and stored for 2 weeks at -20°, 5°, 25°, and 45°C, respectively.

B. EXTRACTION: The samples were mixed with boiling water in an ultrasonic vibratory bath and then were triturated with the boiling water using a Polytron® mixer. The resulting mixture was centrifuged. The supernatant solutions were combined and diluted to working volume for analysis by high-pressure liquid chromatography.

C. ANALYSIS: The samples were dissolved in boiling water and analyzed by high-pressure liquid chromatography using the following system.

Instrument: Waters ALC 202
Column: Partisil 10-SCX - 25 cm x 4.6 mm I.D.
Detector: Ultraviolet - 254 nm
Flow: 1 ml/min
Solvent system: pH3 citric acid/phosphate buffer diluted 1 to 5 with H_2O, isocratic

D. RESULTS:

Temperature (°C)	Average (Percent) *(a)*
45	9.5 ± 0.5
25	9.7 ± 0.5
5	9.9 ± 0.5
-20	9.9 ± 0.5

(a) Theoretical concentration of the mix was 10.0%

There is no significant difference between the samples stored at the various temperatures.

E. CONCLUSION: Melamine mixed with feed is stable for 2 weeks at temperatures up to 45°C.

APPENDIX G

ANALYSIS OF FORMULATED DIETS FOR CONCENTRATIONS OF MELAMINE

Duplicate 5-gram samples of appropriate dosed feed were added to two 200-ml reagent bottles. One hundred milliliters of extractant* were added to each bottle and the bottles were stoppered tightly and shaken for 1 hour. A 50-ml portion of each extract was centrifuged at 2,000 rpm for 5 minutes and then 2 ml of the clear extract was pipetted into a 100-ml volumetric flask and brought up to the volume with diluent.** Ten milliliters of the diluted extract was filtered through a HATF 0.5 micron size Millipore® filter. The absorbance of the filtrate was measured at 235 nm against 1N HCl in the reference cell, using matched 1-cm cuvettes in a Dual Beam Beckman 3600 Spectrophotometer. The average absorbance of two feed blank samples (0 ppm melamine) was subtracted from each sample absorbance value. The melamine concentration in dosed feed was calculated against a standard curve of absorbance vs ppm melamine as follows:

$$\text{ppm melamine in dosed feed} = \frac{(\text{Abs of dosed feed}) - (\text{y intercept})}{\text{Slope (Abs units/ppm)}}$$

Results of the analysis are presented in Table G1.

* Extractant = 850 ml methanol + 100 ml distilled water + 50 ml ammonium hydroxide stored in a tightly capped bottle.

** Diluent = 1 N HCl; 83 ml HCl diluted to 1,000 ml with distilled water and stored in a tightly capped bottle.

TABLE G1. ANALYSIS OF FORMULATED DIETS *(a)*

Date mixed	Date Used (Week of)	Concentration *(a)* of Melamine in Feed for Target Concentration of		
		2,250 ppm	4,500 ppm	9,000 ppm
09/27/78	09/28/78	—	—	8,540
11/08/78	11/09/78	—	4,785	—
12/05/78	12/06/78	2,275	—	—
01/17/79	01/18/79	2,324	4,933	9,820
02/15/79	02/16/79	—	4,828 *(b)*	—
02/28/79	02/29/79	—	4,722	—
03/29/79	03/30/79	2,254	4,494	9,031
05/10/79	05/11/79	2,309	4,317	8,982
06/21/79	06/22/79	—	4,518	—
07/19/79	07/20/79	2,440	4,976 *(c)*	9,076
08/02/79	08/03/79		4,065	9,006
			4,284	9,269
			4,253	8,718
08/04/79	08/13/79	2,141	—	—
		2,188	—	—
		2,093	—	—
09/13/79	09/20/79	2,373	—	—
		2,144 *(b)*		
10/25/79	11/03/79		4,907	—
12/06/79	12/13/79	—	—	8,616
01/17/80	01/24/80	2,158	4,714	9,388
02/28/80	03/06/80	2,437	4,830	8,952
			4,486 *(b)*	—
04/10/80	04/17/80	—	—	9,321
05/22/80	05/22/80	2,200	4,490	8,990
07/02/80	07/09/80	—	4,704	—
08/14/80	08/20/80	—	—	9,261
Mean (ppm)		2,266	4,599	9,069
Standard deviation		114	279	334
Coefficient of variation (%)		5.0	6.1	3.7
Range (ppm)		2,093-2,440	4,065-4,976	8,540-9,820
Number of samples		12	15	14

(a) The data presented are the average of the results of duplicate analyses.
(b) MRI referee analysis
(c) Out of specification (i.e., $> \pm 10\%$)

APPENDIX H

FEED AND MELAMINE CONSUMPTION IN RATS AND MICE IN THE 2-YEAR STUDY

TABLE H1. FEED AND COMPOUND CONSUMPTION IN RATS FED DIETS CONTAINING MELAMINE IN THE 2-YEAR STUDY

Week	Control		Low				High			
	Grams Feed/ Day *(a)*	Body Weight (grams)	Grams Feed/ Day *(a)*	Body Weight (grams)	Low/ Control *(b)*	Dose/ Day *(c)*	Grams Feed/ Day *(a)*	Body Weight (grams)	High/ Control *(b)*	Dose/ Day *(c)*
Males										
32	22.6	404	23.6	387	1.0	137	23.9	377	1.1	285
36	24.1	414	23.3	398	1.0	132	24.3	386	1.0	283
40	24.9	414	27.1	400	1.1	153	23.4	392	0.9	269
44	17.6	416	14.7	398	0.8	83	17.3	389	1.0	200
48	25.9	423	26.3	409	1.0	145	27.4	394	1.1	313
52	26.1	425	22.6	405	0.9	125	20.1	390	0.8	232
56	27.6	434	25.9	414	0.9	141	26.1	400	0.9	294
60	25.3	439	24.1	421	1.0	129	26.7	404	1.1	298
64	28.7	432	24.9	415	0.9	135	26.4	401	0.9	297
68	26.6	440	28.7	419	1.1	154	29.1	404	1.1	325
72	24.0	437	24.3	422	1.0	129	25.0	406	1.0	277
76	16.0	420	16.4	401	1.0	92	14.6	370	0.9	177
80	18.4	429	15.9	414	0.9	86	17.4	403	0.9	195
84	14.9	413	15.1	396	1.0	86	15.6	385	1.0	182
88	29.7	416	28.6	406	1.0	158	27.1	386	0.9	316
92	19.7	415	22.3	400	1.1	125	23.0	384	1.2	270
Mean	23.3	423	22.7	407	1.0	126	23.0	392	1.0	263
SD *(d)*	4.6		4.7		0.1	25	4.6		0.1	50
CV *(e)*	19.7		20.7		10.0	19.8	20.0		10.0	19.0
Females										
32	13.6	236	12.9	230	0.9	252	14.0	231	1.0	545
36	15.3	241	14.3	235	0.9	274	13.9	234	0.9	533
40	16.1	246	15.7	240	1.0	295	15.9	237	1.0	602
44	15.9	253	10.0	241	0.6	187	10.1	238	0.6	384
48	15.9	257	17.0	252	1.1	304	15.6	249	1.0	563
52	15.7	263	13.1	254	0.8	233	12.9	251	0.8	461
56	18.3	271	17.6	262	1.0	302	16.6	257	0.9	580
60	17.9	277	16.4	269	0.9	275	18.3	261	1.0	631
64	19.0	279	19.7	278	1.0	319	21.3	267	1.1	717
68	19.3	289	20.9	282	1.1	333	20.4	271	1.1	678
72	17.7	296	17.6	287	1.0	276	16.9	274	1.0	554
76	9.3	280	13.6	286	1.5	214	11.6	261	1.2	399
80	15.6	307	14.1	299	0.9	213	13.9	279	0.9	447
84	11.1	301	12.1	290	1.1	188	12.3	277	1.1	399
88	17.1	290	19.1	303	1.1	284	19.1	284	1.1	607
92	14.7	296	16.7	299	1.1	252	17.9	284	1.2	566
Mean	15.8	274	15.7	269	1.0	262	15.7	260	1.0	542
SD *(d)*	2.7		3.0		0.2	45	3.2		0.2	100
CV *(e)*	17.1		19.1		20.0	17.2	20.4		20.0	18.5

(a) Grams of feed consumed per animals per day.
(b) Grams of feed per day for the dosed group divided by that for the controls.
(c) Mg of compound consumed per day per kg of body weight.
(d) Standard Deviation
(e) Coefficient of Variation (standard deviation/mean) x 100

TABLE H2. FEED AND COMPOUND CONSUMPTION IN MICE FED DIETS CONTAINING MELAMINE IN THE 2-YEAR STUDY

Week	Control		Low				High			
	Grams Feed/ Day *(a)*	Body Weight (grams)	Grams Feed/ Day *(a)*	Body Weight (grams)	Low/ Control *(b)*	Dose/ Day *(c)*	Grams Feed/ Day *(a)*	Body Weight (grams)	High/ Control *(b)*	Dose/ Day *(c)*
Males										
40	6.0	35	6.0	35	1.0	386	5.9	34	1.0	775
44	5.9	35	5.9	35	1.0	377	5.7	34	1.0	756
48	5.7	35	5.4	36	1.0	339	5.6	35	1.0	716
52	6.0	35	5.7	36	1.0	357	5.9	34	1.0	775
56	5.7	35	5.1	35	0.9	331	5.3	34	0.9	700
60	5.9	36	5.6	35	1.0	358	5.9	34	1.0	775
64	6.1	35	5.0	35	0.8	321	4.7	33	0.8	643
68	6.1	35	5.9	35	1.0	377	6.6	33	1.1	896
72	6.0	35	5.6	35	0.9	358	5.3	33	0.9	721
76	5.6	35	4.9	35	0.9	312	5.0	34	0.9	662
80	5.1	36	4.9	35	1.0	312	4.9	34	1.0	643
84	5.1	35	5.1	34	1.0	340	4.4	33	0.9	604
88	5.3	35	4.9	35	0.9	312	5.0	33	0.9	682
92	4.1	35	4.3	35	1.0	276	4.9	34	1.2	643
96	4.7	36	3.6	35	0.8	230	3.6	34	0.8	473
100	4.7	36	3.7	35	0.8	239	4.1	34	0.9	548
Mean	5.5	35	5.1	35	0.9	327	5.2	34	0.9	688
SD *(d)*	0.6		0.7		0.1	46	0.8		0.1	101
CV *(e)*	10.9		13.7		11.1	14.1	15.4		11.1	14.7
Females										
40	8.7	29	9.3	29	1.1	720	7.9	29	0.9	1,219
44	9.4	30	7.3	30	0.8	546	6.6	30	0.7	986
48	8.0	31	7.4	31	0.9	539	7.1	30	0.9	1,071
52	9.4	31	7.9	32	0.8	552	7.3	31	0.8	1,058
56	9.0	31	8.3	32	0.9	583	6.7	32	0.7	944
60	9.7	32	8.6	32	0.9	603	8.1	31	0.8	1,182
64	10.0	31	8.0	32	0.8	563	8.4	32	0.8	1,185
68	9.7	32	8.1	33	0.8	555	7.6	32	0.8	1,065
72	10.0	32	8.4	33	0.8	575	9.0	32	0.9	1,266
76	10.9	33	8.7	33	0.8	594	9.4	32	0.9	1,326
80	8.1	33	6.9	34	0.8	454	7.6	33	0.9	1,032
84	7.9	34	7.9	34	1.0	520	8.6	33	1.1	1,169
88	6.4	33	6.7	35	1.0	432	7.0	33	1.1	955
92	5.9	34	6.1	35	1.0	395	6.1	33	1.0	838
96	8.4	34	5.7	35	0.7	367	5.9	34	0.7	775
100	6.7	35	5.7	35	0.9	367	7.3	34	1.1	964
Mean	8.6	32	7.6	33	0.9	523	7.5	32	0.9	1,065
SD *(d)*	1.4		1.1		0.1	96	1.0		0.1	153
CV *(e)*	16.3		14.5		11.1	18.4	13.3		11.1	14.4

(a) Grams of feed consumed per animal per day.
(b) Grams of feed per day for the dosed group divided by that for the controls.
(c) Milligrams of compound consumed per day per kg of body weight.
(d) Standard Deviation
(e) Coefficient of Variation (standard deviation/mean) x 100

APPENDIX I

MUTAGENESIS RESULTS FOR MELAMINE IN *SALMONELLA TYPHIMURIUM*

APPENDIX I

A. METHODS FOR SALMONELLA/MICROSOME MUTAGENICITY TEST SYSTEM

Melamine was tested and evaluated in the blind in each of four tester strains of *Salmonella typhimurium,* using a preincubation modification (Yahagi et al., 1975) of the *Salmonella* assay (Ames et al., 1975). Strains of TA 98 and TA 1537 are more sensitive to chemicals that express frameshift mutagenic activity; strains TA 100 and TA 1535 are more sensitive to chemicals that cause base-pair substitutions. Melamine was dissolved in dimethyl sulfoxide (DMSO) and added to the suspension culture. This mixture was incubated with the tester strains in suspension culture (20 min. at 37°C) prior to the addition of soft agar and plating for detection of induced mutants. Exogenous metabolic activation was provided by liver S-9 preparations from Arochlor-1254 induced rats and hamsters. Coded chemicals were tested at five doses (μg/plate) in triplicate (A, B, and C) in each strain and were retested two weeks later.

B. RESULTS

See Tables I1-I4.

TABLE I1. RESULTS OF MUTAGENICITY TESTS OF MELAMINE IN *SALMONELLA TYPHIMURIUM* TA 98

Dose (μg/plate)	Number of Revertants per Plate *(a)* Initial Test A	B	C	Mean	± SE	Dose (μg/plate)	First Retest *(b)* A	B	C	Mean	± SE	Dose (μg/plate)	Second Retest *(c)* A	B	C	Mean	± SE
A. No Activation																	
0.0 *(d)*	13	13	15	14	± 0.7	0.0 *(d)*	20	18	14	17	± 1.8	0.0 *(d)*	18	21	14	18	± 2.0
3.3	11	14	11	12	± 1.0	33.0	12	10	15	12	± 1.5	1000.0	12	15	12	13	± 1.0
10.0	10	6	7	8	± 1.2	100.0	11	16	14	14	± 1.5	3333.0	0T	0T	0T		
33.0	13	11	11	12	± 0.7	333.0	16	18	16	17	± 0.7						
100.0	10	12	10	11	± 0.7	1000.0	16	15	15	15	± 0.3						
111.0	16	11	12	13	± 1.5	1111.0	18	13	15	15	± 1.5						
B. Preincubation with Arochlor-1254 Induced Sprague-Dawley Rat Liver S-9 Preparation																	
0.0 *(d)*	18	19	24	20	± 1.9	0.0	16	25	20	20	± 2.6	0.0 *(d)*	17	18	19	18	± 0.6
3.3	20	21	17	19	± 1.2	33.0	18	14	21	18	± 2.0	3333.0	6	2	4	4	± 1.2
10.0	31	38	29	33	± 2.7	100.0	15	10	22	16	± 3.5	5550.0	4	0	3	2	± 1.2
33.0	20	24	19	21	± 1.5	333.0	24	20	18	21	± 1.8						
100.0	32	14	19	22	± 5.4	1000.0	21	14	22	19	± 2.5						
111.0	21	17	16	18	± 1.5	1111.0	18	16	20	18	± 1.2						
C. Preincubation with Arochlor-1254 Induced Syrian Hamster Liver S-9 Preparation																	
0.0 *(d)*	17	21	26	21	± 2.6	0.0	29	30	21	27	± 2.8	0.0 *(d)*	18	21	17	19	± 1.2
3.3	20	28	20	23	± 2.7	33.0	25	15	37	26	± 6.4	3333.0	1	6	3	3	± 1.5
10.0	23	14	15	17	± 2.8	100.0	15	20	25	20	± 2.9	5550.0	8	2	7	6	± 1.9
33.0	32	29	25	29	± 2.0	333.0	26	26	31	28	± 1.7						
100.0	27	16	18	20	± 3.4	1000.0	28	31	31	30	± 1.0						
111.0	27	23	21	24	± 1.8	1111.0	22	23	28	24	± 1.9						

(a) Measured in triplicate (A, B, C)
(b) Retest was done 7 weeks after initial test
(c) Retest was done 2 weeks after first retest
(d) DMSO used as solvent control
T = chemical was toxic

TABLE I2. RESULTS OF MUTAGENICITY TESTS OF MELAMINE IN *SALMONELLA TYPHIMURIUM* TA 100

Dose (μg/plate)	Number of Revertants per Plate (a) Initial Test A	B	C	Mean	± SE	Dose (μg/plate)	First Retest (b) A	B	C	Mean	± SE	Dose (μg/plate)	Second Retest (c) A	B	C	Mean	± SE
A. No Activation																	
0.0 (d)	99	81	86	89	± 5.4	0.0 (d)	99	96	89	95	± 3.0	0.0 (d)	110	60	75	82	± 14.8
3.3	91	100	94	95	± 2.6	33.0	113	91	117	107	± 8.1	1000.0	72	72	69	71	± 1.0
10.0	92	121	105	106	± 8.4	100.0	115	70	134	106	± 19.0	3333.0	0T	37T	18T		
33.0	114	108	109	110	± 1.9	333.0	83	76	137	99	± 19.3						
100.0	123	130	125	126	± 2.1	1000.0	114	102	126	114	± 6.9						
111.0	131	129	128	129	± 0.9	1111.0	91	80	136	102	± 17.1						
B. Preincubation with Arochlor-1254 Induced Sprague-Dawley Rat Liver S-9 Preparation																	
0.0 (d)	145	118	145	136	± 9.0	0.0 (d)	87	171	136	131	± 24.4	0.0 (d)	138	128	121	129	± 4.9
3.3	192	195	200	196	± 2.3	33.0	112	113	161	129	± 16.2	3333.0	3	8	5	5	± 1.5
10.0	143	184	169	165	± 12.0	100.0	101	147	166	138	± 19.3	5550.0	0	0	0	0	± 0.0
33.0	159	172	171	167	± 4.2	333.0	129	116	162	136	± 13.7						
100.0	186	155	176	172	± 9.1	1000.0	129	116	164	136	± 14.3						
111.0	172	161	172	168	± 3.7	1111.0	C	102	164	133	± 31.0						
C. Preincubation with Arochlor-1254 Induced Syrian Hamster Liver S-9 Preparation																	
0.0 (d)	142	112	142	132	± 10.0	0.0 (d)	101	162	132	132	± 17.6	0.0 (d)	122	118	84	108	± 12.1
3.3	154	195	181	177	± 12.0	33.0	C	168	198	183	± 15.0	3333.0	2	25	12	13	± 6.7
10.0	210	177	201	196	± 9.8	100.0	230	183	173	195	± 17.6	5550.0	1	0	0	0	± 0.3
33.0	206	185	203	198	± 6.6	333.0	103	155	197	152	± 27.2						
100.0	173	168	177	173	± 2.6	1000.0	126	147	198	157	± 21.4						
111.0	189	199	202	197	± 3.9	1111.0	185	120	185	163	± 21.7						

(a) Measured in triplicate (A, B, C)
(b) Retest was done 2 weeks after initial test
(c) Retest was done 38 weeks after first retest
(d) DMSO used as solvent control
T = chemical was toxic;
C = plate was contaminated

TABLE I3. RESULTS OF MUTAGENICITY TESTS OF MELAMINE IN *SALMONELLA TYPHIMURIUM* TA 1535

Dose (μg/plate)	Number of Revertants per Plate (a) Initial Test A	B	C	Mean	± SE	Dose (μg/plate)	First Retest (b) A	B	C	Mean	± SE	Dose (μg/plate)	Second Retest (c) A	B	C	Mean	± SE
A. No Activation																	
0.0 (d)	6	4	7	6	± 0.9	0.0 (d)	10	17	6	11	± 3.2	0.0 (d)	3	7	6	5	± 1.2
3.3	8	9	7	8	± 0.6	33.0	22	17	9	16	± 3.8	1000.0	0	0	0	0	± 0.0
10.0	8	7	6	7	± 0.6	100.0	22	16	9	16	± 3.8	3333.0	1	0T	1T	1	
33.0	7	3	4	5	± 1.2	333.0	11	8	13	11	± 1.5						
100.0	3	8	4	5	± 1.5	1000.0	10	21	9	13	± 3.8						
111.0	6	8	6	7	± 0.7	1111.0	18	9	11	13	± 2.7						
B. Preincubation with Arochlor-1254 Induced Sprague-Dawley Rat Liver S-9 Preparation																	
0.0 (d)	9	3	12	8	± 2.6	0.0	19	11	8	13	± 3.3	0.0 (d)	0	2	7	3	± 2.1
3.3	7	11	6	8	± 1.5	33.0	10	C	13	12	± 1.5	3333.0	2	1	2	2	± 0.3
10.0	7	12	6	8	± 1.9	100.0	18	21	16	18	± 1.5	5550.0	0	0T	0T	0	
33.0	13	5	6	8	± 2.5	333.0	16	16	8	13	± 2.7						
100.0	12	10	7	10	± 1.5	1000.0	12	14	15	14	± 0.9						
111.0	C	6	4	5	± 1.0	1111.0	16	21	12	16	± 2.6						
C. Preincubation with Arochlor-1254 Induced Syrian Hamster Liver S-9 Preparation																	
0.0 (d)	5	6	14	8	± 2.8	0.0	18	24	8	17	± 4.7	0.0 (d)	3	2	5	3	± 0.9
3.3	6	7	4	6	± 0.9	33.0	17	14	10	14	± 2.0	3333.0	1	4	3	3	± 0.9
10.0	8	7	4	6	± 1.2	100.0	14	19	19	17	± 1.7	5550.0	3	3	4	3	± 0.3
33.0	5	6	3	5	± 0.9	333.0	14	21	15	17	± 2.2						
100.0	11	9	6	9	± 1.5	1000.0	10	14	15	13	± 1.5						
111.0	9	C	5	7	± 2.0	1111.0	17	15	17	16	± 0.7						

(a) Measured in triplicate (A, B, C)
(b) Retest was done 2 weeks after initial test
(c) Retest was done 38 weeks after first retest
(d) DMSO used as solvent control
T = chemical was toxic;
C = plate was contaminated

TABLE I4. RESULTS OF MUTAGENICITY TESTS OF MELAMINE IN *SALMONELLA TYPHIMURIUM* TA 1537

Dose (μg/plate)	Number of Revertants per Plate (a) Initial Test A	B	C	Mean	± SE	Dose (μg/plate)	First Retest (b) A	B	C	Mean	± SE	Dose (μg/plate)	Second Retest (c) A	B	C	Mean	± SE
A. No Activation																	
0.0 (d)	4	3	8	5	± 1.5	0.0 (d)	2	2	5	3	± 1.0	0.0 (d)	2	5	3	3	± 0.9
3.3	6	2	3	4	± 1.2	33.0	5	4	1	3	± 1.2	1000.0	3	2	2	2	± 0.3
10.0	2	2	1	2	± 0.3	100.0	8	6	5	6	± 0.9	3333.0	0T	0T	0T		
33.0	2	4	1	2	± 0.9	333.0	5	4	1	3	± 1.2						
100.0	8	10	6	8	± 1.2	1000.0	1	2	3	2	± 0.6						
111.0	2	3	2	2	± 0.3	1111.0	4	3	3	3	± 0.3						
B. Preincubation with Arochlor-1254 Induced Sprague-Dawley Rat Liver S-9 Preparation																	
0.0 (d)	6	4	8	6	± 1.2	0.0 (d)	10	9	6	8	± 1.2	0.0 (d)	3	4	5	4	± 0.6
3.3	8	5	5	6	± 1.0	33.0	6	7	8	7	± 0.6	3333.0	C	1	1	1	± 0.0
10.0	4	6	4	5	± 0.7	100.0	6	6	4	5	± 0.7	5550.0	0	0T	0T	0	
33.0	5	8	5	6	± 1.0	333.0	3	1	4	3	± 0.9						
100.0	C	3	2	3	± 0.5	1000.0	5	5	6	5	± 0.3						
111.0	3	3	2	3	± 0.3	1111.0	9	5	4	6	± 1.5						
C. Preincubation with Arochlor-1254 Induced Syrian Hamster Liver S-9 Preparation																	
0.0 (d)	6	5	11	7	± 1.9	0.0	10	10	7	9	± 1.0	0.0 (d)	2	2	5	3	± 1.0
3.3	8	11	6	8	± 1.5	33.0	6	2	10	6	± 2.3	3333.0	4	6	8	6	± 1.2
10.0	C	8	5	6	± 1.5	100.0	6	5	10	7	± 1.5	5550.0	1	1	2	1	± 0.3
33.0	8	10	6	8	± 1.2	333.0	7	5	8	7	± 0.9						
100.0	8	9	6	8	± 0.9	1000.0	4	6	10	7	± 1.8						
111.0	7	7	5	6	± 0.7	1111.0	1	8	9	6	± 2.5						

(a) Measured in triplicate (A, B, C)
(b) Retest was done 2 weeks after initial test
(c) Retest was done 38 weeks after first retest
(d) DMSO used as solvent control
T = chemical was toxic;
C = plate was contaminated

APPENDIX J

HISTORICAL INCIDENCES OF TUMORS IN UNTREATED F344/N RATS AND B6C3F$_1$ MICE IN THE BIOASSAY PROGRAM

TABLE J1. HISTORICAL INCIDENCE OF URINARY BLADDER TRANSITIONAL-CELL TUMORS IN UNTREATED MALE F344/N RATS *(a)*

Laboratory	Papillomas	Carcinomas
Battelle	0/290	0/290
Dow	0/94	0/94
Frederick	0/450	0/450
Gulf South	0/97	0/97
Hazleton	0/198	0/198
Litton	0/789	0/789
Mason	4/997	0/997
Papanicolaou	0/50	0/50
Southern	0/586	0/586
Total	4/3551 (0.1%)	0/3551 (0.0%)
Overall Historical Range		
High	1/46 (2.2%)	
Low	0/90	

(a) Data as of June 15, 1981 for studies of at least 104 weeks. The range is presented for groups of 35 or more animals.

TABLE J2. HISTORICAL INCIDENCE OF THYROID TUMORS IN UNTREATED FEMALE F344/N RATS *(a)*

Laboratory	C-Cell Adenoma	C-Cell Carcinoma	C-Cell Adenoma or Carcinoma
Battelle	2/281 (0.7%)	10/281 (3.6%)	12/281 (4.3%)
Dow	11/98 (11.2%)	2/98 (2.0%)	13/98 (13.3%)
Frederick	41/519 (7.9%)	10/519 (1.9%)	51/519 (9.8%)
Gulf South	9/92 (9.8%)	1/92 (1.1%)	10/92 (10.9%)
Hazleton	4/196 (2.0%)	3/196 (1.5%)	7/196 (3.6%)
Litton	32/689 (4.6%)	14/689 (2.0%)	45/689 (6.5%)
Mason	28/1056 (2.7%)	35/1056 (3.3%)	63/1056 (6.0%)
Papanicolaou	2/36 (5.6%)	1/36 (2.8%)	3/36 (8.3%)
Southern	50/577 (8.7%)	22/577 (3.8%)	69/577 (12.0%)
Total	179/3544 (5.1%)	98/3544 (2.8%)	273/3544 (7.7%)
Overall Historical Range			
High	9/52	5/50	13/52
Low	0/86	0/50	0/50

(a) Data as of June 15, 1981 for studies of at least 104 weeks. The range is presented for groups of 35 or more animals.

TABLE J3. HISTORICAL INCIDENCE OF UTERINE TUMORS IN UNTREATED FEMALE F344/N RATS *(a)*

Laboratory	Endometrial Stromal Polyp	Endometrial Stromal Sarcoma
Battelle	65/286 (22.7%)	1/286 (0.3%)
Dow	11/100 (11.0%)	0/100 (0.0%)
Frederick	73/517 (14.1%)	1/517 (0.2%)
Gulf South	8/85 (9.4%)	0/85 (0.0%)
Hazleton	28/197 (14.2%)	2/197 (1.0%)
Litton	114/759 (15.0%)	3/759 (0.4%)
Mason	232/1097 (21.1%)	9/1097 (0.8%)
Papanicolaou	11/45 (24.4%)	0/45 (0.0%)
Southern	90/587 (15.3%)	8/587 (1.4%)
Total	632/3673 (17.2%)	24/3673 (0.7%)
Overall Historical Range		
High	18/49	3/50
Low	2/50	0/87

(a) Data as of June 15, 1981 for studies of at least 104 weeks. The range is presented for groups of 35 or more animals.

TABLE J4. HISTORICAL INCIDENCE OF LUNG TUMORS IN UNTREATED FEMALE B6C3F1 MICE *(a)*

Laboratory	Alveolar/Bronchiolar Adenoma	Alveolar/Bronchiolar Carcinoma	Alveolar/Bronchiolar Adenoma or Carcinoma
Battelle	13/349 (3.7%)	5/349 (1.4%)	18/349 (5.2%)
Dow	5/95 (5.3%)	1/95 (1.1%)	6/95 (6.3%)
Frederick	18/428 (4.2%)	11/428 (2.6%)	29/428 (6.8%)
Gulf South	3/64 (4.7%)	4/64 (6.3%)	7/64 (10.9%)
Hazleton	5/99 (5.1%)	1/99 (1.0%)	6/99 (6.1%)
Litton	25/502 (5.0%)	4/502 (0.8%)	29/502 (5.8%)
Mason	53/864 (6.1%)	21/864 (2.4%)	74/864 (8.6%)
Southern	29/645 (4.5%)	11/645 (1.7%)	39/645 (6.0%)
Total	151/3046 (5.0%)	58/3046 (1.9%)	208/3046 (6.8%)
Overall Historical Range			
High	7/50	4/48	8/50
Low	0/50	0/50	0/50

(a) Data as of June 15, 1981 for studies of at least 104 weeks. The range is presented for groups of 35 or more animals.