NATIONAL TOXICOLOGY PROGRAM
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No. 266

TOXICOLOGY AND CARCINOGENESIS STUDIES OF MONURON

(CAS NO. 150-68-5)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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

NATIONAL TOXICOLOGY PROGRAM

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

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

Special Note: This Technical Report was peer reviewed in public session on June 29, 1983. Thereafter, the NTP adopted the policy that the experimental data and laboratory records for all NTP toxicology and carcinogenesis studies not yet printed would be audited. [A summary of the audit is presented in Appendix P.] Consequently, printing and distribution of this Technical Report have been delayed, and the format and definitions of levels of evidence of carcinogenicity differ from those of Technical Reports peer reviewed more recently. This final Technical Report supersedes all previous drafts of this Report which have been distributed.

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF MONURON

(CAS NO. 150-68-5)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

Dexter S. Goldman, Ph.D., Chemical Manager

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

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

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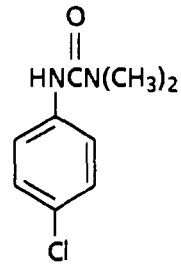


MONURON

CAS NO. 150-68-5

$C_9H_{11}ClN_2O$ Molecular weight 198.65

Synonyms and Trade Names: *N'*-(4-Chlorophenyl)-*N*,*N*-Dimethylurea; 1,1-Dimethyl-3-(*p*-Chlorophenyl)urea; CMU; Karmex Monuron Herbicide; Telvar

ABSTRACT

Carcinogenesis studies of monuron (greater than 99% pure), a substituted urea herbicide, were conducted by feeding diets containing 0, 750, or 1,500 ppm monuron to groups of 50 F344/N rats of each sex and 0, 5,000, or 10,000 ppm to groups of 50 $B6C3F_1$ mice of each sex for 103 weeks. Survivors then were fed a control diet for 1 week, killed, and examined.

Throughout most of the studies, mean body weights of dosed rats and mice of each sex were lower than those of the controls. Survival rates of low dose female rats and high dose male and female mice were increased relative to those of the controls.

In 13-week toxicity studies, the lympho/hematopoietic system of rats and mice was the primary site affected. The lymphoid depletion found in these animals was not seen in rats or mice surviving to the end of the 104-week studies.

Nonneoplastic changes associated with the long-term administration of monuron to rats included renal tubular cell cytomegaly, mainly involving the proximal convoluted tubules in male and female rats, and dose-related hepatic cytoplasmic changes in male rats.

In the 104-week study, the kidneys and liver of male rats were the primary tissues affected. Long-term administration of monuron was associated with an increase in renal tubular cell adenomas (control, 0/50; low dose, 2/50; high dose, 7/50) and renal tubular cell adenocarcinomas (0/50; 1/50; 8/50). Administration of monuron to male rats was associated with increased incidences of neoplastic nodules of the liver (1/50; 6/49; 7/50) and of neoplastic nodules or carcinomas (combined) of the liver (1/50; 6/49; 9/50).

Dosed male and female rats had decreased incidences of mononuclear cell leukemia; dosed male rats had lower incidences of pheochromocytomas of the adrenal glands and C-cell carcinomas of the thyroid gland; dosed female rats had reduced incidences of mammary gland fibroadenomas.

In male mice, dose-related decreases occurred in the incidences of hepatocellular carcinomas (6/50; 5/49; 2/50) and hepatocellular adenomas or carcinomas (12/50; 8/49; 6/50); incidences of hepatocellular tumors in low dose female mice were reduced, but the decreases were not dose related. The incidences of malignant lymphomas were reduced in dosed female mice (16/50; 8/50; 7/50).

Monuron was not mutagenic in Salmonella strains TA98, TA100, TA1535, or TA1537 in the presence or absence of Aroclor 1254-induced rat liver S9. Monuron did induce chromosomal aberrations and sister chromatid exchanges in cultured Chinese hamster ovary cells.

The data, documents, and pathology materials from the 2-year studies of monuron have been audited. The audit findings show that the conduct of the studies is documented adequately and support the data and results given in this Technical Report.

Under the conditions of these 2-year feed studies, there was *clear evidence of carcinogenicity** for male F344/N rats in that monuron caused increased incidences of tubular cell adenocarcinomas of the kidney, tubular cell adenomas of the kidney, and neoplastic nodules or carcinomas (combined) of the liver. Monuron induced cytomegaly of the renal tubular epithelial cells in both male and female F344/N rats. There was *no evidence of carcinogenicity* for female F344/N rats or for male or female $B6C3F_1$ mice.

*Categories of evidence of carcinogenicity are defined in the *Note to the Reader* on page 6. A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 9.

NOTE TO THE READER

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for testing in the NTP Carcinogenesis 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.

Five categories of interpretative conclusions were adopted for use in June 1983 in the Technical Reports series to specifically emphasize consistency and the concept of actual evidence of carcinogenicity. For each definitive study result (male rats, female rats, male mice, female mice), one of the following quintet will be selected to describe the findings. These categories refer to the strength of the experimental evidence and not to either potency or mechanism.

- **Clear Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of malignant neoplasms, studies that exhibit a substantially increased incidence of benign neoplasms, or studies that exhibit an increased incidence of a combination of malignant and benign neoplasms where each increases with dose.
- **Some Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of benign neoplasms, studies that exhibit marginal increases in neoplasms of several organs/tissues, or studies that exhibit a slight increase in uncommon malignant or benign neoplasms.
- **Equivocal Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related marginal increase of neoplasms.
- **No Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.
- **Inadequate Study of Carcinogenicity** demonstrates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as valid for showing either the presence or absence of a carcinogenic effect.

Additionally, the following concepts (as patterned from the International Agency for Research on Cancer Monographs) have been adopted by the NTP to give further clarification of these issues:

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

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

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

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

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Monuron is based on the 2-year studies that began in July 1979 and ended in August 1981 at EG&G Mason Research Institute (Worcester, Massachusetts).

National Toxicology Program
(Evaluated Experiment, Interpreted Results, and Reported Findings)

Dexter S. Goldman, Ph.D., Chemical Manager

Gary A. Boorman, D.V.M., Ph.D.
Rajendra S. Chhabra, Ph.D.
David M. DeMarini, Ph.D.
Joseph K. Haseman, Ph.D.
James Huff, Ph.D.
C.W. Jameson, Ph.D.
E.E. McConnell, D.V.M.
John A. Moore, D.V.M.
G.N. Rao, D.V.M., Ph.D.
B. A. Schwetz, D.V.M., Ph.D.
M.D. Shelby, Ph.D.
Raymond W. Tennant, Ph.D.

NTP Pathology Working Group
(Evaluated Slides and Prepared Pathology Report on 6/3/82)

Gary A. Boorman, D.V.M., Ph.D. (NTP)
Scot L. Eustis, D.V.M., Ph.D. (NTP)
Bhola N. Gupta, B.V.Sc., Ph.D. (NTP)
Frank A. Voelker, D.V.M.
Burroughs Wellcome Laboratories

Principal Contributors at EG&G Mason Research Institute
(Conducted Studies and Evaluated Tissues)

Herman S. Lilja, Ph.D.
Agnes Russfield, M.D., Ph.D.
D. Stuart Wyand, D.V.M.

Experimental Pathology Laboratories, Inc.
(Provided Pathology Quality Assurance)

Deborah Banas, D.V.M.

Principal Contributors at Carltech Associates, Inc.
(Contractor for Technical Report Preparation)

William D. Theriault, Ph.D.
Abigail C. Jacobs, Ph.D.
John Warner, M.S.

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on monuron on June 29, 1983, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee

Jerry B. Hook, Ph.D. (Chair)
Vice President, Preclinical Research and Development
Smith Kline & French Laboratories
Philadelphia, Pennsylvania

Curtis Harper, Ph.D.
Associate Professor of Pharmacology
School of Medicine
University of North Carolina
Chapel Hill, North Carolina

James Swenberg, D.V.M., Ph.D.
Chief of Pathology
Chemical Industry Institute of Toxicology
Research Triangle Park, North Carolina

Ad Hoc Subcommittee Panel of Experts

Louis S. Beliczky, M.S., M.P.H.
Director, Department of Industrial Hygiene
United Rubber Workers International Union
Akron, Ohio

Devra L. Davis, Ph.D. (Principal Reviewer)
Science Policy Director
Environmental Law Institute
Washington, D.C.

Robert M. Elashoff, Ph.D.
University of California at Los Angeles
Jonsson Comprehensive Cancer Center
Los Angeles, California

Seymour L. Friess, Ph.D.
Arlington
Virginia

J. Michael Holland, Ph.D., D.V.M.
Chevron Environmental Health Center
Richmond, California

Robert A. Scala, Ph.D.
Exxon Corporation
East Millstone, New Jersey

Tom Slaga, Ph.D. (Principal Reviewer)
University of Texas System Cancer Center
Science Park, Research Division
Smithville, Texas

John R. Van Ryzin, Ph.D. (Principal Reviewer)
Division of Biostatistics
School of Public Health
Columbia University
New York, New York

Stan D. Vesselinovitch, D.V.Sc.*
Professor, Departments of Radiology and Pathology
University of Chicago
Chicago, Illinois

Mary Vore, Ph.D.*
Assistant Professor
Pharmacology Department
University of Kentucky
College of Medicine
Lexington, Kentucky

*Unable to attend meeting

SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF MONURON

On June 29, 1983, the draft Technical Report on the toxicology and carcinogenesis studies of monuron received public 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 the Conference Center, Building 101, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. D. Goldman, NTP, introduced the studies by reviewing the experimental design, results, and proposed conclusions (clear evidence of carcinogenicity in male rats, no evidence of carcinogenicity in female rats or in male or female mice).

Dr. Davis, a principal reviewer, agreed with the conclusions. She requested that the observations on chromosomal damage in cultured Chinese hamster ovary cells and reproductive tract damage in female mice be included in the Report [p. 42]. Dr. Davis commented that the reasons given for weight loss in mice were speculations. She asked that any available information on behavior be included routinely in the Technical Reports.

As a second principal reviewer, Dr. Slaga agreed in principle with the conclusion but thought more emphasis should be given to the subcutaneous tumors in the low dose group of male mice. He said that with the two doses used, a dose response may have been missed.

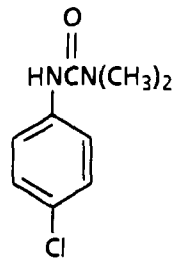
As a third principal reviewer, Dr. Van Ryzin said the evidence for liver neoplastic lesions in male rats would be strengthened by citing "neoplastic nodules or carcinomas." He said that the comparative statistical analyses were considerably more significant for the combined tumors. Dr. Goldman replied that the combined tumors would be shown in the conclusion.

Dr. Van Ryzin and Dr. Friess asked for an expanded discussion of renal tubular cell adenocarcinomas, suggesting that this may be a lesion that could be unique to the male F344/N rat. Dr. E. McConnell, NTP, responded that the lesion might be unique to male rats but not just to the Fischer strain. An NTP study has shown occurrence of these tumors in four other rat strains, albeit few in number, exposed to chlorinated aliphatic chemicals. Dr. Scala expressed concern over the fluctuations in animal room temperature and the low relative humidity. He asked the NTP to investigate the impact of these variables on overall animal stress and health using available literature. Dr. Scala commented on the negative tumor incidences.

Dr. Davis moved that the Technical Report on the carcinogenesis studies of monuron be accepted with suggested revisions. Dr. Van Ryzin seconded the motion, and the Technical Report was approved unanimously by the Peer Review Panel.

I. INTRODUCTION

I. INTRODUCTION



MONURON

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Monuron is a fine, white crystalline powder with a melting point of 170.5°-171.5° C. It has a slight odor and is stable to oxygen and moisture at neutral pH and room temperature (Merck, 1976).

Monuron is a member of a group of potent phytotoxic phenyl-substituted ureas (Bucha and Todd, 1951). Monuron was introduced commercially in 1952 and quickly gained acceptance as a broad-spectrum herbicide for control of grasses and weeds along ditches and rights-of-way. It was used in the United States on a number of food crops to control weeds. Use on food crops was banned in 1973 (Fed. Regist., 1972; USEPA, 1975). Deregistration was based on published reports of possible carcinogenicity and on the lack of toxicity testing data.

Production of monuron in the United States ceased by 1978. Approximately 230,000-400,000 kg of monuron was produced in the United States in 1973; production in previous years was probably higher (USEPA, 1975). At the time of these studies, 45,000-90,000 kg of monuron was imported annually for use as a general herbicide on nonedible crops (R. Zuccarini, Hopkins Chemical Co., Madison, WI, personal communication to D. Goldman, 1982). It is usually formulated as a wettable powder and as a granular powder containing 2%-8% monuron. Commercial monuron is usually about 98% pure; *p*-chloroaniline and dimethylamine are possible impurities (USEPA, 1975).

When applied at rates recommended for commercial crops (1-4 pounds per acre), monuron disappears from the soil in less than 1 year. When monuron is applied at higher, nonselective rates for total control of vegetation (10-60 pounds per acre), phytotoxicity persists for up to 3 years (Birk, 1955; Alexander, 1973; USEPA, 1975).

Within the wide range of chemical and physical properties of the urea herbicides, monuron is intermediate in its adsorption to organic type soils, inactivation within the soil, and persistence within the soil (Crafts, 1961; Hartley, 1964; Sheets, 1964; Audus, 1964; Geissbuhler, 1969; Crosby and Li, 1969). The water solubility and lipophilicity of pesticides may be used to predict the potential for bioaccumulation of the molecules (Ellgehausen et al., 1980). Monuron showed no biomagnification in the food chain of algae to daphnids to catfish.

As with other urea herbicides, monuron is rapidly taken up from the soil solution by the root system and translocates rapidly into stems and leaves. Studies of corn and soybeans grown in nutrient solutions showed that monuron and diuron--3-(3,4-dichlorophenyl)-1,1-dimethyl urea--were quickly transported to the leaves, where mono- and didemethylation occurred (Smith and Sheets, 1967; Onley et al., 1968). Monuron-tolerant species (e.g., cotton) are able to metabolize monuron to *p*-chloroaniline, whereas susceptible species (e.g., corn, oats, and soybeans) both

metabolize monuron and accumulate unmetabolized monuron in the leaves.

Substituted ureas inhibit photosynthesis in whole leaves and inhibit the Hill reaction (the evolution of oxygen by intact chloroplasts in the presence of a suitable hydrogen acceptor) in chloroplast preparations (Wessels and van der Veen, 1956). Monuron inhibits photophosphorylation in isolated chloroplasts; this inhibition can be reversed in the presence of ascorbate and phenazine methosulfate (Jagendorf, 1958; Jagendorf and Margulies, 1960). The phytotoxicity of monuron may be due not only to the inhibition of a site close to photochemical system II (Gingras and Lemasson, 1965) but also to the release of excited singlet oxygen that eventually leads to the breakdown of the chloroplast membrane (Pallett and Dodge, 1980).

Monuron is probably metabolized by soil microorganisms (Dalton et al., 1966) in the same way as diuron: by sequential demethylation first to the monomethyl derivative, then to *p*-chlorophenyl urea, and finally by hydrolysis to *p*-chloroaniline. The monomethyl derivative is less toxic than monuron; the desmethyl and aniline compounds are not phytotoxic (Geissbuhler et al., 1963; Dalton et al., 1966). When [^{14}C]methyl monuron was metabolized by soil organisms, the methyl carbon was oxidized and labeled carbon dioxide was recovered (Audus, 1964; Geissbuhler, 1969).

Analysis of the urinary metabolites of monuron in male albino rats (administered four 50-mg doses in corn oil by gavage over a 48-hour period) showed that free monuron was not excreted in the urine (Ernst and Bohme, 1965; Bohme and Ernst, 1965). The major metabolic processes identified were sequential demethylation to *p*-chlorophenylurea, as well as ring hydroxylation and sequential demethylation to *o*-hydroxy-*p*-chlorophenylurea and *m*-hydroxy-*p*-chlorophenylurea. All phenolic metabolites were excreted either as the glucuronides or as the ether sulfates. Small amounts of the corresponding anilines or aniline derivatives also were found as urinary metabolites (Ernst, 1969).

p-Chloroaniline is the only known metabolite of monuron that has been tested in a long-term study (NCI, 1979). In that study, *p*-chloroaniline was administered to F344/N rats and B6C3F$_1$ mice in the diet for 78 weeks; the rats were observed for an additional 24 weeks and the mice for 13 weeks. The spleen was the primary organ affected in both rats and mice; inflammatory and nonneoplastic proliferative changes were noted. Although fibromas and fibrosarcomas of the spleen were seen in exposed male rats and hemangiomas and hemangiosarcomas were observed at several sites in exposed mice, the evidence linking these lesions to administration of *p*-chloroaniline was not conclusive.

The mutagenic potential of monuron was reviewed by Sandhu and Waters (1980). Of five mutagenicity studies of monuron in Salmonella, four reported negative results in the presence or absence of Aroclor 1254-induced rat liver S9 (Andersen et al., 1972; Shirasu, 1975; Shirasu et al., 1976; Simmon et al., 1976; Simmon, 1978; NTP, 1982; Appendix G). The one positive result (Seiler, 1978) was obtained in strain TA1535 in the presence of uninduced rat liver S9; the spontaneous mutation frequency was not reported in that study. Until these results are confirmed, there is no convincing evidence for the mutagenicity of monuron in Salmonella.

Monuron was not mutagenic in other microbial systems, including *Escherichia coli* (pol A$^-$ assay), *Bacillus subtilis* (rec$^-$ assay), and yeast (mitotic recombination). Although monuron failed to induce point mutations in bacteria, it did induce chromosomal aberrations and sister chromatid exchanges in cultured Chinese hamster ovary cells (Appendix G). Although the results from the genetic toxicology tests are limited, and in one case conflicting, there is evidence that monuron can induce chromosomal damage in animal cells. The possible role of cytogenetic changes in the induction of neoplasia has been discussed (Weisburger and Williams, 1980; Miller and Miller, 1981; Klein, 1981). Monuron was tested in the Drosophila sex-linked recessive lethal assay, but it was too toxic to allow an adequate evaluation of mutagenicity (Valencia, 1977). Monuron was clastogenic in both the somatic and germ cells of barley (Wuu and Grant, 1966, 1967). Monuron induced unscheduled DNA synthesis in cultured human lung fibroblasts (WI-38) only in the presence of

S9 (Simmon, 1978). The inhibition of testicular DNA synthesis (DSI test) has been reported in rats administered monuron (Seiler, 1978). The DSI test response was so weak, however, that the investigator concluded that the effect would be significant only at "acutely toxic levels, i.e., above the LD_{50} doses."

The LD_{50} value for monuron has been estimated to be 1,480 mg/kg (oral) in rats and 1,920 mg/kg (oral) and 1,000 mg/kg (intraperitoneal) in mice (Hodge et al., 1958; Rubenchik, 1969; Rubenchik et al., 1970).

In its review of available data, the International Agency for Research on Cancer concluded that monuron is probably carcinogenic (IARC, 1976). When monuron was administered to (C57BL/6×AKR)F_1 mice, first by gavage (215 mg/kg per day for 4 weeks) and then in the diet (517 ppm for 78 weeks), a total tumor increase of questionable significance was noted (Innes et al., 1969). In this study, the incidence of lung adenomas in dosed male B6AKF_1 mice was 6/16 (38%) as compared with 9/90 (10%) in the controls (NCI, 1968). Male B6C3F_1 mice, in the identical and parallel study, showed no significant increase in the number of pulmonary adenomas.

Increased incidences of total tumors were seen in random-bred and C57BL mice that were administered monuron (6 mg per animal in milk by gavage) once per week for 15 weeks; the mice were then observed for 9 months (Rubenchik et al., 1970). Neoplastic lesions were found in the liver, lungs, and kidneys of both strains of dosed animals; few or no tumors were found in parallel control animals. Survival rates in control animals were not reported. Tumors were observed at various sites in random-bred male rats fed diets containing 450 ppm monuron for 18 months and then observed for 9 months. The reported lack of tumors in a concurrent control group of 50 rats at 27 months was considered to be unusual. When monuron at a concentration of 2,500 ppm was fed to albino rats for 2 years, tumor incidences in the dosed groups were within the range of incidences in the control groups (Hodge et al., 1958).

The number of people exposed to monuron through industrial and agricultural applications, crop residues, surface water runoff, and water system contamination is not known. The 1972 decision by the U.S. Environmental Protection Agency to prohibit monuron residues on edible crops was based on the Russian study of carcinogenicity (Rubenchik et al., 1970). The study was considered in the IARC (1976) monograph, and the data were determined to be equivocal. No epidemiologic studies have been published.

Study Rationale: Monuron was studied by the NTP because of the potential for human exposure and because earlier studies for carcinogenicity suggested but did not demonstrate carcinogenicity.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF MONURON

PREPARATION AND ANALYSES OF FORMULATED DIETS

PRELIMINARY SHORT-TERM STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Study Design

Source and Specifications of Animals

Animal Maintenance

Clinical Examinations and Pathology

Statistical Methods

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF MONURON

The monuron used in these studies was obtained from the Hopkins Chemical Co. (Madison, WI) in one lot (no. D-A330). Midwest Research Institute (MRI), the analytical chemistry laboratory, conducted purity and identity determinations (Appendix H).

The identity of the substance was confirmed by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectroscopic data were consistent with the structure and/or literature values.

The purity of the chemical was determined by elemental analysis, water analysis, thin-layer chromatography, and high-performance liquid chromatography. Results of the elemental analyses agreed with the theoretical values. The moisture content was 0.25%. A trace impurity was detected by thin-layer chromatography. High-performance liquid chromatography with three solvent systems indicated the presence of eight small impurities totaling less than 0.3% of the total peak area. According to the data obtained from these studies, the chemical was greater than 99% pure.

A heat stability study performed by the analytical chemistry laboratory indicated that the compound was stable in storage (Appendix H).

After receiving the study chemical from the analytical chemistry laboratory, the study laboratory stored it at 0° ± 5° C. Periodic characterization of the chemical at EG&G Mason Research Institute by infrared spectroscopy and thin-layer chromatography indicated that no detectable decomposition occurred during the studies (Appendix H).

PREPARATION AND ANALYSES OF FORMULATED DIETS

The analytical chemistry laboratory demonstrated the homogeneity of a formulated diet mixture. Further studies showed that monuron was stable in feed when stored for 2 weeks at 25° C or below (Appendix I).

The study laboratory prepared formulated diets by layering a dry premix between portions of feed and blending the mixture for 15 minutes. The mixture was held at 5° C until use and was used within 13 days after being mixed (Table 1; Appendix I).

Periodic analyses for monuron in feed mixtures were performed by both the study and analytical chemistry laboratories. The analytical method included a methanolic extraction followed by spectrophotometric determination of monuron concentrations (Appendix J). These analyses (summarized below) indicated that the diets were properly formulated (Appendix K).

THIRTEEN-WEEK STUDIES

Target Conc. (ppm)	Experimental Mean (ppm)	Coefficient of Variation (percent)
750	900	0.0
1,500	1,800	4.0
3,000	3,200	8.8
6,000	7,000	7.1
12,000	12,400	6.3
25,000	28,100	7.8
50,000	49,800	5.1

n=2

TWO-YEAR STUDIES

Target Conc. (ppm)	Experimental Mean (ppm)	Coefficient of Variation (percent)	Range (ppm)
750	747	6.1	675-800
1,500	1,514	3.8	1,450-1,630
5,000	4,965	3.2	4,700-5,300
10,000	10,004	4.8	9,200-10,850

n=13

PRELIMINARY SHORT-TERM STUDIES

Several preliminary short-term studies (8-13 weeks) were carried out in 1978 at Frederick Cancer Research Center (Frederick, MD) before EG&G Mason began its studies. Rats and mice (sources and strains not specified) were fed diets containing 50-6,000 ppm monuron for 8 or 13 weeks. Animals were weighed at the start and finish of the studies.

No results or reports of these studies are available (D. Cresia, Frederick Cancer Research Center, personal communication to D. Goldman, 1983). These preliminary studies will not be discussed further. The remainder of the studies reported here were carried out at EG&G Mason Research Institute.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the toxicity associated with repeated ingestion of monuron and to determine the concentrations to be used in the 2-year studies.

Groups of 10 F344/N rats of each sex were fed diets containing 0, 750, 1,500, 3,000, 6,000, or 12,000 ppm monuron. Groups of 10 $B6C3F_1$ mice of each sex were fed diets containing 0, 3,000, 6,000, 12,000, 25,000, or 50,000 ppm monuron. All diets were available ad libitum.

Formulated diets were first offered to each group on September 25, 1978. Except for mice in the 3,000-ppm groups, necropsies were performed between December 26 and December 29, 1978. Necropsies were performed on mice in the 3,000-ppm groups on January 2, 1979.

Animals were checked two times per day; moribund animals were killed, and necropsies were performed. Feed consumption was measured once per week. One day before the animals were killed, formulated diets were replaced with control feed. Individual animal weights were recorded once per week. Further experimental details are summarized in Table 1.

At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals, except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 1.

TWO-YEAR STUDIES

Study Design

Groups of 50 F344/N rats of each sex were fed diets containing 0, 750, or 1,500 ppm monuron for 103 weeks, and groups of 50 $B6C3F_1$ mice of each sex were fed diets containing 0, 5,000, or 10,000 ppm monuron for the same period of time.

Source and Specifications of Animals

The male and female F344/N rats and $B6C3F_1$ (C57BL/6N, female $\times$ C3H/HeN MTV^-, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the Carcinogenesis Program. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Rats were shipped to the study laboratory at 4-5 weeks of age and mice, at 4-6 weeks. The rats were quarantined at the study laboratory for 16 days and the mice, for 21 days. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rats were placed on study at 7 weeks of age and the mice, at 7-9 weeks of age. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix M).

Animal Maintenance

Feed and water were available ad libitum. Details of animal maintenance are summarized in Table 1. Environmental conditions are summarized in Appendix L. Because of extensive renovations to the animal room areas at EG&G Mason Research Institute, it was necessary to change the study rooms during the progress of the monuron study. For the first year of the studies, all animals were in room 541. On July 29, 1980, the study was transferred to room 528 and on January 15, 1981, to room 542, where all animals remained until study completion.

The positioning of the cages within the cage racks is shown in Appendix N. Male and female rats were placed on separate racks with sentinels on top of the rack. Male and female mice were placed on opposite sides of the same rack with sentinels on the top of the rack. Cages and racks were not rotated during the study.

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE FEED STUDIES OF MONURON

Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN	
Size of Study Groups 10 males and 10 females of each species	50 males and 50 females of each species
Doses Rats--0, 750, 1,500, 3,000, 6,000, or 12,000 ppm monuron in feed; mice--0, 3,000, 6,000, 12,000, 25,000, or 50,000 ppm monuron in feed	Rats--0, 750, or 1,500 ppm monuron in feed; mice--0, 5,000, or 10,000 ppm monuron in feed
Duration of Dosing 13 wk	103 wk
Date of First Dose 9/25/78	Rats--7/12/79; mice--7/24/79
Necropsy Dates 12/26/78-1/2/79	Rats--7/13/81-7/22/81; mice--7/22/81-7/31/81
Type and Frequency of Observation Observed 2 × d; weighed 1 × wk; feed consumption monitored 1 × wk	Observed 2 × d; weighed 1 × wk for 13 wk and then 1 × mo; feed consumption monitored 1 × mo over a 5-d period
Necropsy and Histologic Examination A necropsy performed on all animals; histologic exam performed on control, 6,000-, and 12,000-ppm groups and early-death rats and on all control, 12,000-, 25,000-, and 50,000-ppm groups and early-death mice: gross lesions and tissue masses, mandibular lymph nodes, mammary gland, salivary glands, thyroid gland, parathyroids, sternebrae, liver, colon, small intestine, prostate/testes or ovaries/uterus, urinary bladder, lungs and bronchi, heart, esophagus, stomach, brain, thymus, trachea, pancreas, spleen, kidneys, adrenal glands, pituitary gland, spinal cord and eyes; partial histologic exam on 3,000-ppm group: thymus, bone marrow, spleen, mesenteric and mandibular lymph nodes	A necropsy performed on all animals; the following tissues examined in all groups: tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, thigh muscle, sciatic nerve, bone marrow, costochondral junction, thymus, larynx, trachea, lungs and bronchi, heart, thyroid gland, parathyroids, esophagus, stomach, duodenum, jejunum, colon, mesenteric lymph nodes, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenal glands, urinary bladder, seminal vesicles/prostate/testes or ovaries/uterus, brain, pituitary gland, eyes, external and middle ear, stomach, ileum, salivary glands, nasal cavity, and spinal cord; histologic exam performed on all above tissues except eyes, external and middle ear, spinal cord, nasal cavity, thigh muscle, and sciatic nerve
ANIMALS AND ANIMAL MAINTENANCE	
Species F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice;
Animal Source Harlan Industries, Inc. (Indianapolis, IN)	Charles River Breeding Laboratories (Portage, MI)
Time Held Before Start of Study 18 d	Rats--16 d; mice--21 d
Age When Placed on Study Rats--7-8 wk; mice--8-9 wk	Rats--7 wk; mice--7-9 wk
Age When Killed Rats--20-21 wk; mice--21-22 wk	Rats--111-113 wk; mice--111-114 wk
Method of Distribution Distributed to groups so that average group weights approximately equal	Distributed to cages and then to groups according to two separate tables of random numbers
Feed Wayne Lab Blox® (Allied Mills, Inc., Chicago, IL); ad libitum	Same as 13-wk studies

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE FEED STUDIES OF MONURON (Continued)

Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)	
Bedding Aspen Bed® hardwood chips (American Excelsior Co., Baltimore, MD)	Same as 13-wk studies
Water Tap, available ad libitum via automatic watering system (Edstrom Industries, Waterford, WI)	Same as 13-wk studies
Cages Polycarbonate (Lab Products, Inc., Rochelle Park, NJ)	Same as 13-wk studies
Cage Filters Nonwoven fiber (Lab Products, Inc., Rochelle Park, NJ)	Nonwoven fiber (Lab Products, Inc., Rochelle Park, NJ, and Snow Filtration, Cincinnati, OH)
Animals per Cage 5	5
Animal Room Environment (a) 10 changes room air/h; avg temp--22° C; temp range--19°-26° C; fluorescent light 12 h/d; avg rel humidity--23.9%; range--7%-55%	10 changes room air/h; avg temp--24° C; temp range--18°-33° C; fluorescent light 12 h/d; avg rel hum--51.3% (rats), 53.6% (mice); range--8%-80%
Other Chemicals on Study in Same Room None	None
CHEMISTRY	
Lot No. Used D-A330	D-A330
Supplier Hopkins Chemical Co. (Madison, WI)	Same as 13-wk studies
Chemical/Vehicle Preparation Chemical ground in mortar with small amount of feed; additional meal added and mixed in blender for 15 min	Same as 13-wk studies
Maximum Storage Time 14 d	14 d
Storage Conditions Double plastic bags at 4° C in the dark	Double plastic bags in covered plastic bucket; 0° ± 5° C in the dark

(a) For detailed information on temperature and relative humidity values and ranges during the 2-year studies, see Appendix L, Tables L1 and L2.

II. MATERIALS AND METHODS

A quality control skin grafting program has been in effect since early 1978 to monitor the genetic integrity of the inbred mice used to produce the hybrid B6C3F$_1$ study animal. In mid-1981, data were obtained that showed incompatibility between the NIH C3H reference colony and the C3H colony from a Program supplier. In August 1981, inbred parental lines of mice were further tested for genetic integrity via isozyme and protein electrophoresis profiles that demonstrate phenotype expressions of known genetic loci.

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

Male mice from the C3H colony and female mice from the C57BL/6 colony were used as parents for the hybrid B6C3F$_1$ mice used in these studies. The influence of the potential genetic nonuniformity in the hybrid mice on these results is not known, but results of the studies are not affected because concurrent controls were included in each study.

Clinical Examinations and Pathology

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

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. Tissues examined microscopically are listed in Table 1.

When the pathology evaluation was completed, the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assessment pathologist. The quality assessment report and slides were submitted to the Pathology Working Group (PWG) Chairperson, who reviewed all target tissues and those about which there was a disagreement between the laboratory and quality assessment pathologists.

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

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

Statistical Methods

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

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

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

Analysis of Tumor Incidence: Three statistical methods are used to analyze tumor incidence data: life table tests, incidental tumor analysis, and Fisher exact/Cochran-Armitage trend analyses. Tests of significance include pairwise comparisons of each dosed group with controls and tests for overall dose-response trends. For studies in which administration of the study compound has little effect on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death. Continuity-corrected tests are used in the analysis of tumor incidence, and reported P values are one-sided.

Life Table Analyses--The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the 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 (1959) to obtain an overall P value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975). The underlying variable considered by this analysis is time to death due to tumor. If the tumor is rapidly lethal, then time to death due to tumor closely approximates time to tumor onset. In this case, the life table test also provides a comparison of the time-specific tumor incidences.

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

obtain a single overall result. (See Haseman, 1984, for the computational details of both methods.)

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

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

III. RESULTS

RATS

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

III. RESULTS: RATS

THIRTEEN-WEEK STUDIES

Eight of 10 male rats and 9/10 female rats fed diets containing 12,000 ppm monuron died during the first 2 weeks of the studies (Table 2). Five of 10 male rats and 6/10 female rats fed diets containing 6,000 ppm monuron died during the first 4 weeks of the studies. The final weights of the rats were inversely related to the concentration of monuron in the feed. Female rats fed 750-12,000 ppm ate less than did the controls (Appendix O, Table O1).

Discoloration and mottling of the lungs, smoothing and thinning of the stomach, and enlargement and discoloration of the adrenal glands were noted at necropsy and appeared to be compound related.

A generalized atrophy of lymphocytic and hematopoietic tissues was observed in male and female rats fed diets containing 12,000 ppm monuron. These changes included lymphoid depletion and congestion of the splenic white pulp, lymphoid depletion with overall reduction in size of the thymus, myeloid depletion of bone marrow, and lymphoid depletion of B- and T-cell areas of lymph nodes causing a marked reduction in the size of all examined lymph nodes. Similar but less severe changes were seen in male and female rats fed diets containing 6,000 ppm monuron; changes seen in the lymphocytic and hematopoietic tissues of rats fed monuron at lower concentrations were considered to be slight or equivocal.

Because of weight gain depression and histopathologic changes observed at higher dose levels, doses selected for the 2-year studies in rats were 750 and 1,500 ppm monuron in feed.

TABLE 2. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK FEED STUDIES OF MONURON

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final (b)	Change (b)	Final Weight Relative to Controls (percent)
MALE					
0	10/10	126.6 ± 6.8	324.0 ± 26.2	+197.4 ± 21.4	
750	10/10	127.7 ± 6.8	315.4 ± 16.1	+187.8 ± 15.3	97
1,500	10/10	127.6 ± 7.2	289.4 ± 20.7	+161.8 ± 19.5	89
3,000	10/10	126.4 ± 6.2	257.8 ± 15.1	+131.5 ± 14.5	80
6,000	(c) 5/10	125.9 ± 6.8	166.8 ± 13.8	+40.9 ± 9.3	52
12,000	(d) 2/10	126.6 ± 7.1	119.0 ± 4.2	−7.6 ± 7.9	37
FEMALE					
0	10/10	103.7 ± 4.5	192.9 ± 12.2	+89.2 ± 9.3	
750	10/10	103.8 ± 4.7	189.4 ± 6.7	+85.6 ± 9.9	98
1,500	10/10	103.4 ± 4.4	178.1 ± 11.5	+74.7 ± 10.1	92
3,000	10/10	103.5 ± 5.4	159.2 ± 9.8	+55.6 ± 7.6	83
6,000	(e) 4/10	103.7 ± 4.9	127.4 ± 6.6	+23.7 ± 7.6	66
12,000	(f) 1/10	103.6 ± 5.3	96.0	−7.6	50

(a) Number surviving/number per group
(b) Mean ± standard error of the mean. Initial weight based on all 10 animals; final weight and weight changes based on survivors.
(c) Week of death: 3,3,4,4,4
(d) Week of death: 1,2,2,2,2,2,2,2
(e) Week of death: 3,3,3,3,4,4
(f) All deaths occurred in week 2.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

The mean body weights of dosed male and female rats were lower than those of the controls throughout the study (Table 3 and Figure 1). The mean body weights were inversely related to dose. The average daily feed consumption per rat by low dose and high dose rats was 88% and 83% that by the controls for males and 87% and 72% for females (Tables O2 and O3). These daily intake amounts are actually measurements of amounts of feed removed from the feed containers; they cannot be considered as measurements of feed (and compound) intake because they have not been corrected for scattering and waste.

After 6 months on study, one male and one female sentinel rat showed positive titers to rat coronavirus (RCV); by 12 months, virtually all animals were infected (Appendix M, Table M1). An infection by pneumonia virus of mice (PVM) was detected in all male and female sentinel rats during the 18th month of the test.

Survival

Estimates of the probabilities of survival for male and female rats fed diets containing monuron at the concentrations used in these studies and for controls are shown in Figure 2.

In groups of male rats, 28/50 (56%) control, 45/50 (90%) low dose, and 41/50 (82%) high dose rats lived to the termination of the study at 105-106 weeks. The death of 11 control male rats at week 93 of the study was due to a malfunction in a thermostat, which allowed the animal room to overheat. Cages housing control animals were at the top of the racks (Appendix N) where temperatures may have been higher.

Survival of low dose female rats was significantly greater than that of the control group ($P=0.034$). In groups of female rats, 38/50 (76%) control, 44/50 (88%) low dose, and 42/50 (84%) high dose rats lived to the termination of the study at 105-106 weeks.

The survival incidences include two control males, one low dose male, and four control females that died during the termination period of the study. For statistical purposes, these animals have been pooled with those killed at the end of the study.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidence of animals with neoplastic or nonneoplastic lesions in the kidney, liver, urinary bladder, or spleen. Histopathologic findings on neoplasms in rats are summarized in Appendix A (Tables A1 and A2); Appendix A (Tables A3 and A4) also gives the survival and tumor status for individual male and female rats. Findings on nonneoplastic lesions are summarized in Appendix C (Tables C1 and C2). Appendix E (Tables E1 and E2) contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. Historical incidences of tumors in control animals are listed in Appendix F. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).

TABLE 3. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR FEED STUDIES OF MONURON

Weeks on Study	Control		750 ppm			1,500 ppm		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE								
0	134	50	133	99.3	50	129	96.3	50
1	169	50	166	98.2	50	155	91.7	50
2	198	50	195	98.5	50	182	91.9	50
3	211	50	204	96.7	50	193	91.5	50
4	232	50	225	97.0	50	210	90.5	50
5	249	50	239	96.0	50	235	94.4	50
6	264	50	256	97.0	50	244	92.4	50
7	275	50	270	98.2	49	251	91.3	50
8	281	50	276	98.2	49	257	91.5	50
9	294	50	286	97.3	49	272	92.5	50
10	303	50	295	97.4	49	276	91.1	50
11	314	50	311	99.0	49	285	90.8	50
12	317	50	308	97.2	49	288	90.9	50
16	351	50	336	95.7	49	312	88.9	50
20	364	50	352	96.7	49	326	89.6	50
24	387	50	368	95.1	49	338	87.3	50
28	398	50	380	95.5	49	349	87.7	50
32	413	50	394	95.4	49	362	87.7	50
36	420	50	401	95.5	49	369	87.9	50
40	425	50	407	95.8	49	375	88.2	50
44	433	50	414	95.6	49	379	87.5	50
48	444	50	429	96.6	49	391	88.1	50
52	439	50	426	97.0	49	384	87.5	50
56	440	50	426	96.8	49	385	87.5	50
60	438	49	424	96.8	49	387	88.4	50
64	447	49	429	96.0	49	388	86.8	49
68	455	49	434	95.4	49	394	86.6	49
72	447	49	420	94.0	49	388	86.8	49
76	466	49	443	95.1	49	399	85.6	49
80	468	47	442	94.4	49	399	85.3	49
84	472	46	443	93.9	49	402	85.2	49
88	464	44	438	94.4	49	395	85.1	49
92	466	42	434	93.1	47	394	84.5	49
96	455	31	430	94.5	47	385	84.6	46
100	454	29	417	91.9	46	380	83.7	43
104	449	28	419	93.3	45	389	86.6	41
FEMALE								
0	106	50	110	103.8	50	108	101.9	50
1	129	50	130	100.8	50	120	93.0	50
2	143	50	144	100.7	50	137	95.8	50
3	155	50	154	99.4	50	146	94.2	50
4	164	50	158	96.3	50	153	93.3	50
5	173	50	170	98.3	50	160	92.5	50
6	181	50	176	97.2	50	166	91.7	50
7	186	50	180	96.8	50	170	91.4	50
8	190	50	184	96.8	50	173	91.1	50
9	196	49	192	98.0	50	176	89.8	50
10	198	49	190	96.0	50	178	89.9	50
11	203	49	195	96.1	50	182	89.7	50
12	204	49	197	96.6	50	185	90.7	50
16	213	49	206	96.7	50	190	89.2	50
20	223	49	213	95.5	50	196	87.9	50
24	230	49	217	94.3	50	199	86.5	50
28	228	49	221	96.9	50	202	88.6	50
32	233	49	227	97.4	50	206	88.4	50
36	241	49	233	96.7	50	211	87.6	50
40	246	49	237	96.3	50	211	85.8	50
44	255	49	248	97.3	50	218	85.5	50
48	266	49	255	95.9	50	220	82.7	50
52	272	49	258	94.9	50	221	81.3	49
56	271	49	263	97.0	49	223	82.3	49
60	283	49	269	95.1	49	229	80.9	49
64	295	49	276	93.6	49	232	78.6	49
68	309	49	287	92.9	49	236	76.4	49
72	320	49	300	93.8	49	245	76.6	48
76	327	48	312	95.4	49	250	76.5	48
80	338	47	323	95.6	49	255	75.4	47
84	350	47	332	94.9	49	265	75.7	47
88	350	46	336	96.0	48	265	75.7	46
92	359	43	344	95.8	47	275	76.6	43
96	355	43	342	96.3	46	278	78.3	43
100	360	40	343	95.3	46	277	76.9	43
104	354	38	349	98.6	44	285	80.5	42

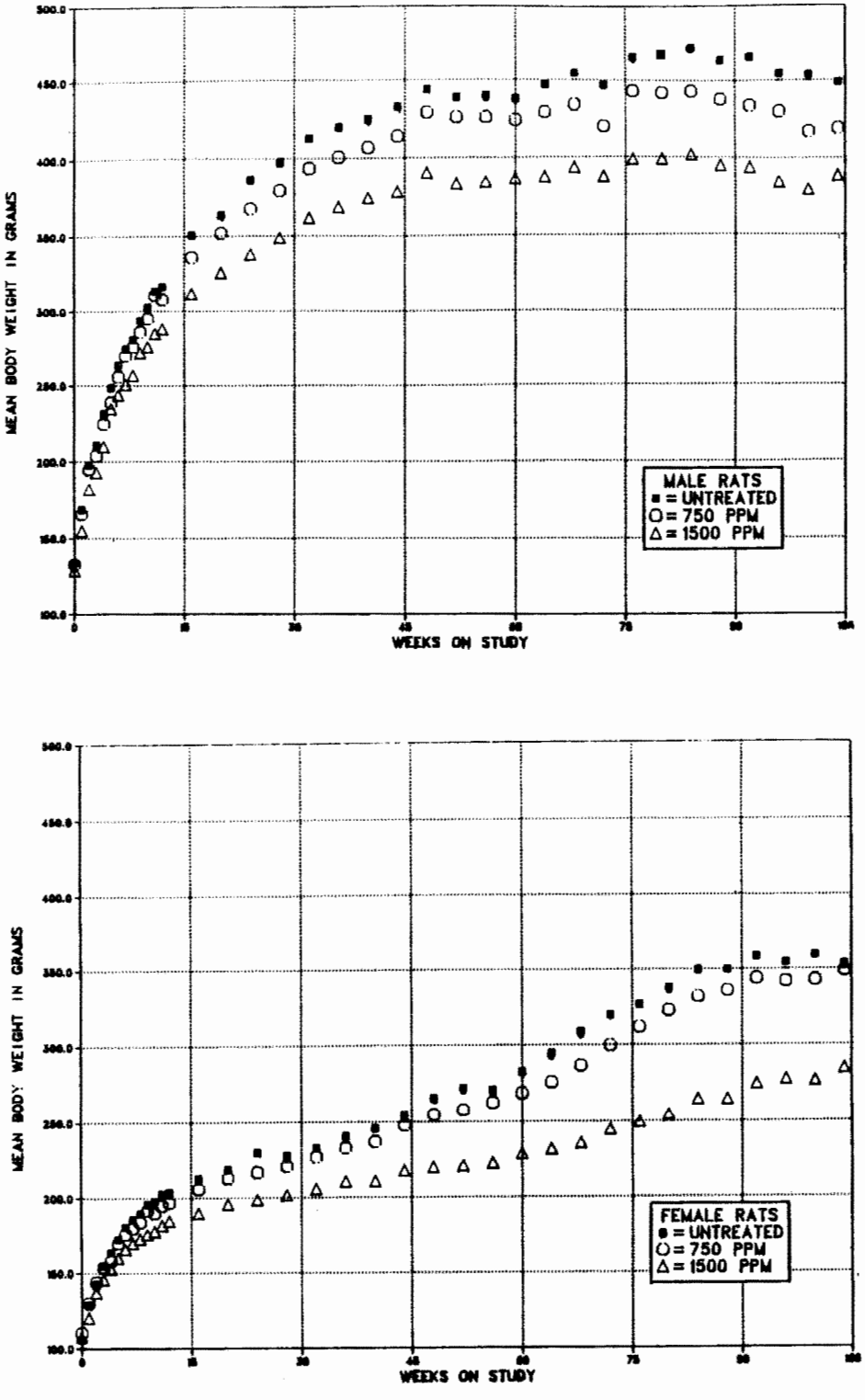


FIGURE 1. GROWTH CURVES FOR RATS FED DIETS CONTAINING MONURON FOR TWO YEARS

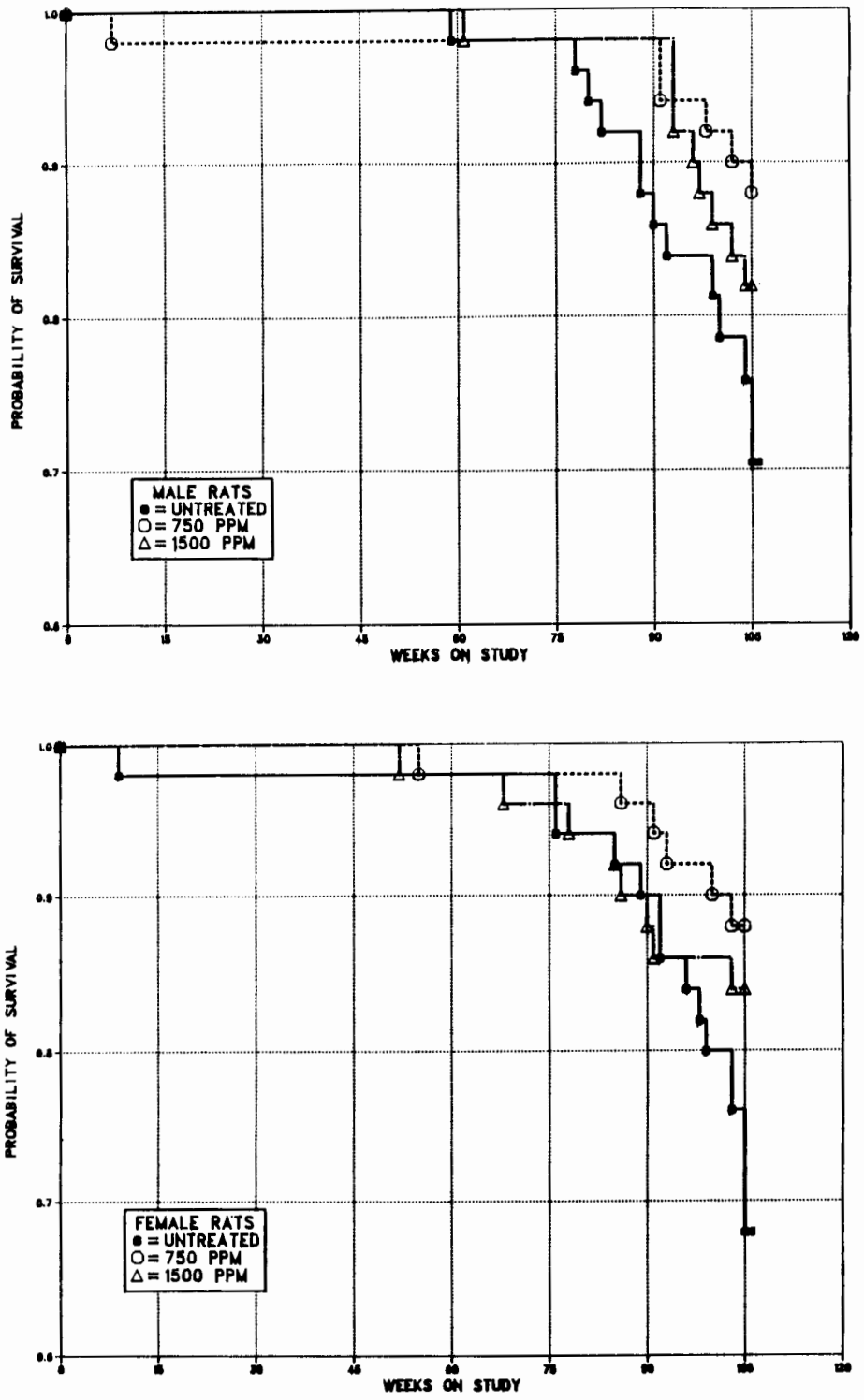


FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR RATS FED DIETS CONTAINING MONURON FOR TWO YEARS

Kidney: The most frequent nonneoplastic change observed in the kidney in dosed rats was cytomegaly of renal tubular epithelial cells, mainly involving the proximal convoluted tubules. The affected cells had a greatly increased volume of cytoplasm, and the cytoplasm was vacuolated. The nuclei were enlarged 8-10 times their normal diameter. Nucleoli were sometimes multiple. The nuclei had many anaplastic characteristics, including dispersed chromatin, parachromatin clearing, and a heavy, sometimes jagged border. Tubular cytomegaly was detected in 0/50 control, 48/50 low dose, and 50/50 high dose males and in 0/50 control, 12/50 low dose, and 49/50 high dose females.

In male rats, both tubular cell adenomas and tubular cell adenocarcinomas occurred with statistically significant positive trends, and the incidences in the high dose group of tubular cell adenomas and carcinomas, alone or combined, were significantly greater than those in the controls (Table 4). Renal tubular neoplasms were not found in the female rats.

Many of the adenomas were very small, with diameters equal to that of two or three normal tubules. The neoplasms were well-circumscribed, rounded masses of cells that resembled normal tubular cells; however, the cytoplasm was more basophilic than that of normal cells and the nuclei were somewhat enlarged with prominent nucleoli. No distinguishing characteristic other than size clearly separated the larger adenomas from the renal carcinomas. As the lesion increased in size, nuclear anaplasia increased, the tumor boundary became irregular, and capsular invasion followed.

An undifferentiated renal carcinoma that did not resemble a tubular cell adenocarcinoma was observed in the kidney of one high dose male rat, and a poorly differentiated sarcoma was observed in the kidney of another. One lipoma was found in a high dose male and another in a low dose female rat.

TABLE 4. ANALYSIS OF KIDNEY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF MONURON (a)

	Control	750 ppm	1,500 ppm
Tubular Cell Adenoma			
Overall Rates	0/50 (0%)	2/50 (4%)	7/50 (14%)
Adjusted Rates	0.0%	4.4%	17.1%
Terminal Rates	0/28 (0%)	2/45 (4%)	7/41 (17%)
Life Table Tests	P=0.007	P=0.348	P=0.030
Incidental Tumor Tests	P=0.007	P=0.348	P=0.030
Cochran-Armitage Trend Test	P=0.003		
Fisher Exact Tests		P=0.247	P=0.006
Tubular Cell Adenocarcinoma			
Overall Rates	0/50 (0%)	1/50 (2%)	8/50 (16%)
Adjusted Rates	0.0%	2.2%	18.5%
Terminal Rates	0/28 (0%)	1/45 (2%)	6/41 (15%)
Life Table Tests	P=0.002	P=0.595	P=0.021
Incidental Tumor Tests	P=0.001	P=0.595	P=0.008
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Tests		P=0.500	P=0.003
Tubular Cell Adenoma or Adenocarcinoma (b)			
Overall Rates	0/50 (0%)	3/50 (6%)	15/50 (30%)
Adjusted Rates	0.0%	6.7%	34.8%
Terminal Rates	0/28 (0%)	3/45 (7%)	13/41 (32%)
Life Table Tests	P<0.001	P=0.217	P<0.001
Incidental Tumor Tests	P<0.001	P=0.217	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Tests		P=0.121	P<0.001

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) Historical incidence of renal tubular cell neoplasms at study laboratory (mean): 1/694 (0.1%); historical incidence in NTP studies: 6/2,359 (0.3%)

Liver: Hepatic cytoplasmic changes occurred in male rats in a dose-related fashion (control, 4/50; low dose, 8/50; high dose, 17/50).

Neoplastic nodules in male rats occurred with a statistically significant positive trend; the incidence in the high dose group was significantly greater than that in the controls (Table 5). The incidence of neoplastic nodules or hepatocellular carcinomas (combined) occurred with a positive trend, and the incidence in the high dose group was greater than that in the controls. The hepatocellular carcinomas were found in one low dose and three high dose male rats. In female rats, neoplastic nodules of the liver occurred in 4/50 control, 1/50 low dose, and 2/50 high dose animals.

Urinary Bladder: Hyperplasia of the transitional cell epithelium was observed in one high dose male and one low dose female rat. One low dose and one control female rat had a transitional cell papilloma of the urinary bladder.

Spleen: A dose-related increase in the incidence of hemosiderosis was observed in female rats (control, 5/50; low dose, 36/50, high dose, 44/50).

TABLE 5. ANALYSIS OF LIVER LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF MONURON

	Control	750 ppm	1,500 ppm
Nonneoplastic Lesions			
Cytoplasmic Changes (Combined)	4/50 (8%)	8/49 (16%)	17/50 (34%)
Neoplastic Nodule			
Overall Rates	1/50 (2%)	6/49 (12%)	7/50 (14%)
Adjusted Rates	3.6%	13.6%	17.1%
Terminal Rates	1/28 (4%)	6/44 (14%)	7/41 (17%)
Life Table Tests	P=0.076	P=0.161	P=0.092
Incidental Tumor Tests	P=0.076	P=0.161	P=0.092
Cochran-Armitage Trend Test	P=0.030		
Fisher Exact Tests		P=0.053	P=0.030
Carcinoma			
Overall Rates	0/50 (0%)	1/49 (2%)	3/50 (6%)
Adjusted Rates	0.0%	2.3%	7.3%
Terminal Rates	0/28 (0%)	1/44 (2%)	3/41 (7%)
Life Table Tests	P=0.091	P=0.590	P=0.196
Incidental Tumor Tests	P=0.091	P=0.590	P=0.196
Cochran-Armitage Trend Test	P=0.061		
Fisher Exact Tests		P=0.495	P=0.121
Neoplastic Nodule or Carcinoma (a)			
Overall Rates	1/50 (2%)	6/49 (12%)	9/50 (18%)
Adjusted Rates	3.6%	13.6%	22.0%
Terminal Rates	1/28 (4%)	6/44 (14%)	9/41 (22%)
Life Table Tests	P=0.025	P=0.161	P=0.038
Incidental Tumor Tests	P=0.025	P=0.161	P=0.038
Cochran-Armitage Trend Test	P=0.008		
Fisher Exact Tests		P=0.053	P=0.008

(a) Historical incidence at study laboratory (mean): 24/643 (4%); historical incidence in NTP studies: 96/2,306 (4%)

Negative Trends: Significant negative trends were observed in the incidences of male and female rats with mononuclear cell leukemia ($P<0.02$ and $P<0.01$), of male rats with adrenal gland pheochromocytomas ($P<0.01$) and thyroid gland C-cell carcinomas ($P<0.04$), and of female rats with mammary gland fibroadenomas ($P<0.02$) (Table 6).

TABLE 6. ANALYSIS OF REDUCTIONS IN THE INCIDENCES OF NEOPLASTIC LESIONS IN RATS IN THE TWO-YEAR FEED STUDIES OF MONURON

	Control	750 ppm	1,500 ppm
MALE			
Mononuclear Cell Leukemia			
Overall Rates	5/50 (10%)	0/50 (0%)	0/50 (0%)
Adjusted Rates	14.7%	0.0%	0.0%
Terminal Rates	3/28 (11%)	0/45 (0%)	0/41 (0%)
Life Table Tests	P=0.002N	P=0.014N	P=0.016N
Incidental Tumor Tests	P=0.011N	P=0.041N	P=0.044N
Cochran-Armitage Trend Test	P=0.006N		
Fisher Exact Tests		P=0.028N	P=0.028N
Adrenal Gland: Pheochromocytoma			
Overall Rates	15/50 (30%)	13/50 (26%)	4/48 (8%)
Adjusted Rates	47.2%	27.6%	9.3%
Terminal Rates	12/28 (43%)	11/45 (24%)	2/39 (5%)
Life Table Tests	P<0.001N	P=0.061N	P<0.001N
Incidental Tumor Tests	P=0.006N	P=0.211N	P=0.005N
Cochran-Armitage Trend Test	P=0.007N		
Fisher Exact Tests		P=0.412N	P=0.006N
Thyroid Gland: C-Cell Carcinoma			
Overall Rates	6/49 (12%)	3/46 (7%)	1/50 (2%)
Adjusted Rates	19.9%	7.3%	2.0%
Terminal Rates	4/28 (14%)	3/41 (7%)	0/41 (0%)
Life Table Tests	P=0.011N	P=0.095N	P=0.022N
Incidental Tumor Tests	P=0.032N	P=0.242N	P=0.053N
Cochran-Armitage Trend Test	P=0.035N		
Fisher Exact Tests		P=0.276N	P=0.053N
FEMALE			
Mononuclear Cell Leukemia			
Overall Rates	10/50 (20%)	2/50 (4%)	2/50 (4%)
Adjusted Rates	24.5%	4.3%	4.4%
Terminal Rates	8/38 (21%)	1/44 (2%)	1/42 (2%)
Life Table Tests	P=0.004N	P=0.010N	P=0.013N
Incidental Tumor Tests	P=0.006N	P=0.020N	P=0.016N
Cochran-Armitage Trend Test	P=0.005N		
Fisher Exact Tests		P=0.014N	P=0.014N
Mammary Gland: Fibroadenoma			
Overall Rates	20/50 (40%)	15/50 (30%)	9/50 (18%)
Adjusted Rates	46.2%	32.6%	21.4%
Terminal Rates	15/38 (39%)	13/44 (30%)	9/42 (21%)
Life Table Tests	P=0.006N	P=0.105N	P=0.008N
Incidental Tumor Tests	P=0.016N	P=0.189N	P=0.019N
Cochran-Armitage Trend Test	P=0.011N		
Fisher Exact Tests		P=0.201N	P=0.014N

III. RESULTS: MICE

THIRTEEN-WEEK STUDIES

Five of 10 male and 8/10 female mice that received diets containing 50,000 ppm monuron and 5/10 females that received 25,000 ppm died (Table 7). Final weights of dosed mice were lower than those of the controls. Female mice at the higher dose levels had a moderate initial loss of body weight. Apparent increases in feed consumption by mice in the higher dosed group (Table O4) may have been due to excessive scattering.

Lymphoid depletion of the splenic white pulp, myeloid atrophy of bone marrow with marked reduction in stem cells and myeloblasts (approximately half the marrow was made up of band cells), lymphoid depletion of mandibular and mesenteric lymph nodes, and lymphoid depletion of the thymus were observed in males and females fed diets containing 50,000 ppm monuron. The incidence and severity of the lesions in the lymphoid tissues and bone marrow were lower in mice fed 25,000 ppm. Atrophy of hematopoietic tissues was not observed in the 12,000-ppm group.

Doses selected for the 2-year studies of mice (5,000 and 10,000 ppm monuron in feed) were based primarily on the depression in weight gain of male mice observed in the 13-week studies.

TABLE 7. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK FEED STUDIES OF MONURON

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final (b)	Change (b)	Final Weight Relative to Controls (percent)
MALE					
0	10/10	20.77 ± 1.35	33.91 ± 1.35	+13.14 ± 1.04	
3,000	10/10	20.47 ± 1.52	31.17 ± 2.31	+10.70 ± 1.38	92
6,000	10/10	20.67 ± 1.52	30.69 ± 1.53	+10.02 ± 1.73	91
12,000	10/10	20.67 ± 1.83	28.68 ± 1.95	+8.01 ± 1.97	85
25,000	10/10	20.78 ± 1.29	26.72 ± 1.68	+5.94 ± 1.36	79
50,000	(c) 5/10	20.82 ± 1.05	23.84 ± 1.24	+3.42 ± 0.46	70
FEMALE					
0	10/10	16.07 ± 0.80	23.62 ± 2.44	+7.55 ± 1.88	
3,000	10/10	15.96 ± 0.98	22.57 ± 2.65	+6.61 ± 1.83	96
6,000	10/10	15.57 ± 1.09	22.18 ± 0.89	+6.61 ± 1.18	94
12,000	10/10	15.77 ± 1.15	22.95 ± 1.46	+7.18 ± 0.86	97
25,000	(d) 5/10	15.42 ± 0.98	22.26 ± 0.74	+6.84 ± 1.34	94
50,000	(e) 2/10	16.50 ± 0.91	22.50 ± 1.41	+6.00 ± 1.63	95

(a) Number surviving/number per group
(b) Mean ± standard error of the mean. Initial weight based on all 10 animals; final weight and weight changes based on survivors.
(c) Week of death: 1,1,1,1,2
(d) Week of death: 1,1,1,2,2
(e) Week of death: 1,1,1,1,1,4,12,13

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed males and females were lower than those of the controls throughout most of the study (Table 8 and Figure 3). The average daily feed consumption by low dose and high dose male mice was 184% and 198% that by the controls and by low dose and high dose female mice, 175% and 173% that by the controls (Tables O5 and O6). The feed consumption data are uncorrected for scattered feed and suggest that the measurements are inadequate.

Survival

Estimates of the probabilities of survival for male and female mice fed diets containing monuron at the concentrations used in these studies and for controls are shown in Figure 4. In male mice, the survival of both the control ($P=0.011$) and the low dose ($P=0.034$) groups was significantly lower than that of the high dose group. In female mice, the survival of the high dose group was significantly greater than that of the low dose group ($P=0.005$) and of the control group ($P=0.035$).

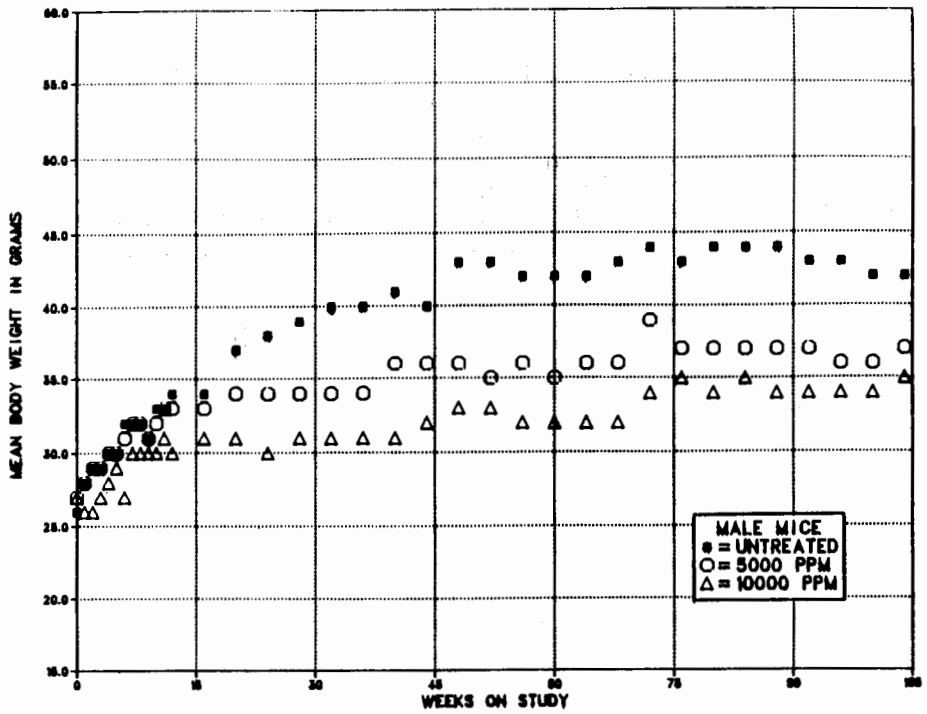
For male mice, 34/50 (68%) control, 36/50 (72%) low dose, and 46/50 (92%) high dose mice lived to the termination of the study at 104-105 weeks. For female mice, 31/50 (62%) control, 25/50 (50%) low dose, and 41/50 (82%) high dose mice lived to the termination of the study at 104-105 weeks. The survival incidences include one high dose male and one control female that died during the termination period of the study. For statistical purposes, these two animals have been pooled with those killed at the end of the study. One low dose female was accidentally killed at week 97 of the study.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy increases in the incidence of animals with neoplastic or nonneoplastic lesions of the subcutaneous tissue, liver, and reproductive tract. Histopathologic findings on neoplasms in mice are summarized in Appendix B (Tables B1 and B2); Appendix B (Tables B3 and B4) gives the survival and tumor status for individual male and female mice. Findings on nonneoplastic lesions are summarized in Appendix D (Tables D1 and D2). Appendix E (Tables E3 and E4) contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. Historical incidences of tumors in control animals are listed in Appendix F. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).

TABLE 8. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF MONURON

Weeks on Study	Control		5,000 ppm			10,000 ppm		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE								
0	28	50	27	103.8	50	27	103.8	50
1	28	50	28	100.0	50	26	92.9	50
2	29	50	29	100.0	50	26	89.7	50
3	29	50	29	100.0	50	27	93.1	50
4	30	50	30	100.0	50	28	93.3	50
5	30	50	30	100.0	50	29	96.7	50
6	32	50	31	96.9	50	27	84.4	50
7	32	50	32	100.0	50	30	93.8	49
8	32	50	32	100.0	50	30	93.8	49
9	31	49	31	100.0	50	30	96.8	49
10	33	49	32	97.0	50	30	90.9	49
11	33	49	33	100.0	50	31	93.9	49
12	34	49	33	97.1	50	30	88.2	49
16	34	49	33	97.1	50	31	91.2	49
20	37	49	34	91.9	50	31	83.8	49
24	38	49	34	89.5	50	30	78.9	49
28	39	49	34	87.2	49	31	79.5	49
32	40	47	34	85.0	49	31	77.5	49
36	40	47	34	85.0	49	31	77.5	49
40	41	47	36	87.8	49	31	75.6	49
44	40	46	36	90.0	49	32	80.0	49
48	43	44	36	83.7	49	33	76.7	49
52	43	44	35	81.4	49	33	76.7	49
56	42	43	36	85.7	48	32	76.2	49
60	42	41	35	83.3	47	32	76.2	49
64	42	41	36	85.7	47	32	76.2	49
68	43	41	36	83.7	45	32	74.4	49
72	44	39	39	88.6	44	34	77.3	49
76	43	39	37	86.0	43	35	81.4	49
80	44	38	37	84.1	42	34	77.3	49
84	44	38	37	84.1	41	35	79.5	48
88	44	38	37	84.1	40	34	77.3	48
92	43	38	37	86.0	39	34	79.1	48
96	43	36	36	83.7	39	34	79.1	47
100	42	35	36	85.7	37	34	81.0	47
104	42	34	37	88.1	36	35	83.3	46
FEMALE								
0	20	50	19	95.0	50	19	95.0	50
1	22	50	20	90.9	50	20	90.9	50
2	22	50	21	95.5	50	22	100.0	50
3	23	50	22	95.7	50	22	95.7	50
4	23	50	22	95.7	50	22	95.7	50
5	24	50	23	95.8	50	22	91.7	50
6	25	50	23	92.0	50	23	92.0	50
7	25	50	24	96.0	50	24	96.0	50
8	26	50	24	92.3	50	24	92.3	50
9	26	50	24	92.3	50	24	92.3	50
10	27	50	24	88.9	50	24	88.9	50
11	28	50	24	85.7	50	24	85.7	50
12	28	50	25	89.3	50	24	85.7	50
16	31	50	25	80.6	50	24	77.4	50
20	33	50	25	75.8	50	25	75.8	50
24	35	50	26	74.3	50	25	71.4	50
28	37	50	26	70.3	50	25	67.6	50
32	39	49	27	69.2	50	26	66.7	50
36	40	49	27	67.5	50	25	62.5	50
40	44	48	27	61.4	50	25	56.8	50
44	43	47	26	60.5	50	25	58.1	50
48	45	47	27	60.0	49	26	57.8	49
52	42	47	29	69.0	49	26	61.9	49
56	45	47	28	62.2	48	26	57.8	49
60	46	47	28	60.9	48	26	56.5	49
64	47	47	28	59.6	48	26	55.3	49
68	49	45	28	57.1	48	26	53.1	47
72	51	45	29	56.9	46	27	52.9	45
76	52	43	30	57.7	46	28	53.8	45
80	54	42	30	55.6	43	27	50.0	44
84	53	40	29	54.7	40	28	52.8	44
88	54	37	30	55.6	36	28	51.9	42
92	54	36	30	55.6	34	28	51.9	42
96	52	35	29	55.8	30	28	53.8	41
100	52	32	30	57.7	28	28	53.8	41
104	52	31	30	57.7	28	30	57.7	41



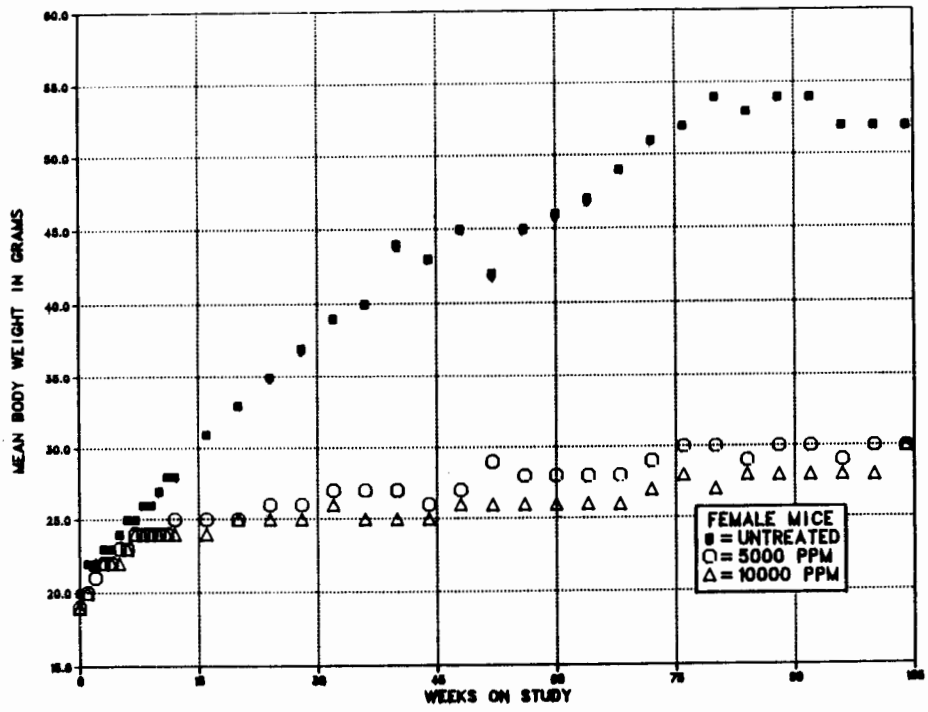


FIGURE 3. GROWTH CURVES FOR MICE FED DIETS CONTAINING MONURON FOR TWO YEARS

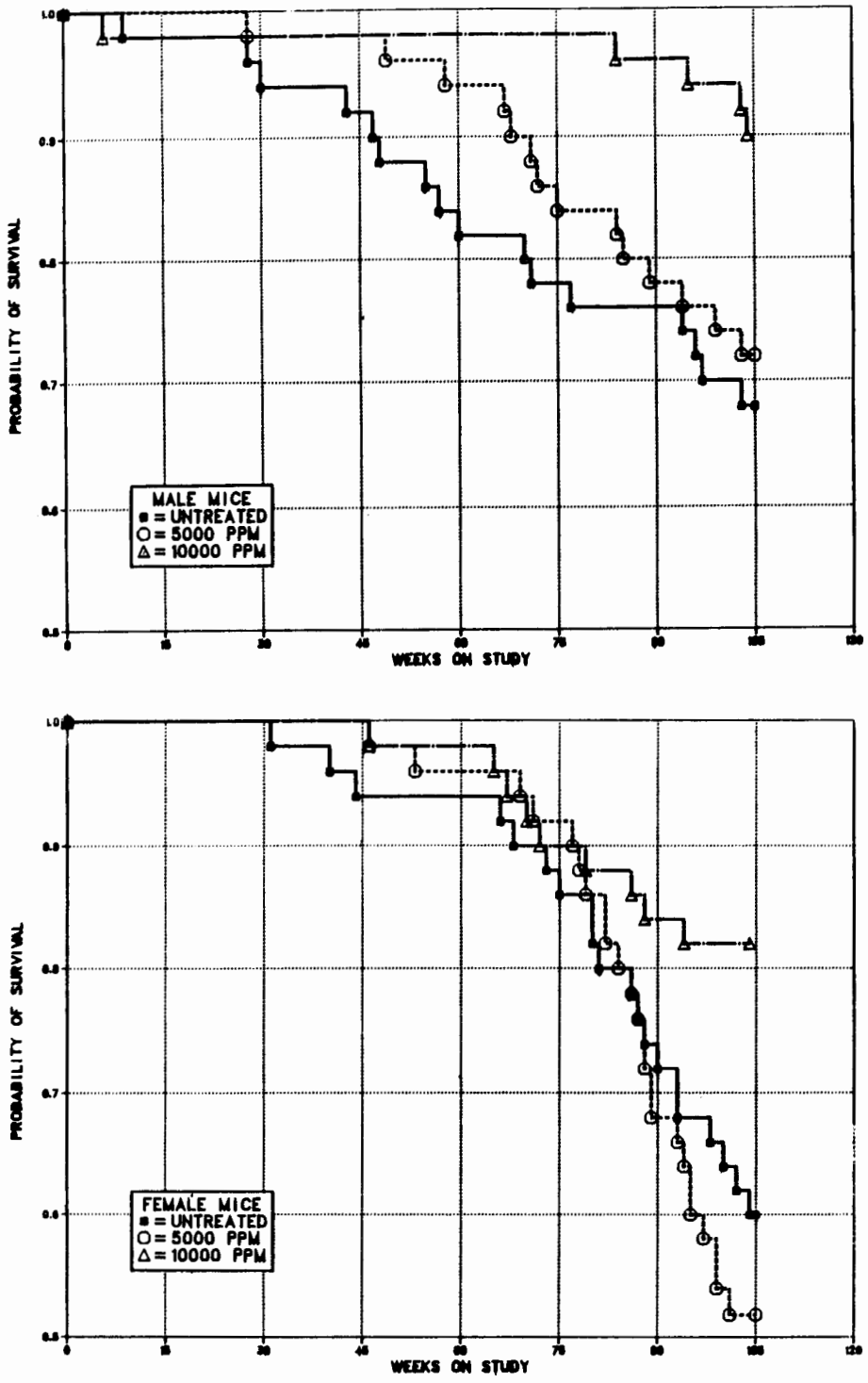


FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR MICE FED DIETS CONTAINING MONURON FOR TWO YEARS

Subcutaneous Tissue: The incidence of low dose male mice with sarcomas, fibrosarcomas, or fibromas (combined) was significantly greater than that of the controls; these lesions were found in two high dose male mice (Table 9). The incidence of these lesions is not dose related and is of questionable biologic significance.

Liver: A dose-dependent hepatocellular degeneration was found in male mice (control, 1/50; low dose, 4/49; high dose, 13/50). The lesion was primarily an eosinophilic degeneration of single or small groups of hepatocytes and was usually located in cells near the central veins. Degenerating acidophilic cells often contained granulocytes and macrophages. Free sinusoidal acidophilic bodies and hydropic degeneration with cellular enlargement and ballooning were also noted.

The incidences of neoplastic liver lesions were not affected by long-term administration of monuron to male or female $B6C3F_1$ mice.

Reproductive Tract: About week 80 of the studies, inflammatory lesions were found in the reproductive tract of female $B6C3F_1$ mice. The lesions were seen in animals that died during the study, that were killed in a moribund state, or that were killed at the end of the study. The lesions ranged from mild microscopic inflammatory infiltration of the ovaries, uterus, or oviducts to gross ovarian/uterine abscesses that may have been the cause of death. (Peritonitis, possibly resulting from the rupture of an abscess, was seen in some instances.) Suppurative inflammation was found in the ovaries, uterus, or multiple organs of 12 control, 27 low dose, and 14 high dose female mice. *Klebsiella pneumoniae* and *K. oxytoca* (two serotypes) were isolated from these lesions through the use of standard culture techniques. Attempts to isolate mycoplasma were unsuccessful.

TABLE 9. ANALYSIS OF SUBCUTANEOUS TISSUE TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF MONURON (a)

	Control	5,000 ppm	10,000 ppm
Sarcoma, Fibrosarcoma, or Fibroma			
Overall Rates	2/50 (4%)	9/50 (18%)	2/50 (4%)
Adjusted Rates	5.3%	21.6%	4.1%
Terminal Rates	1/34 (3%)	4/36 (11%)	0/46 (0%)
Life Table Tests	P=0.412N	P=0.042	P=0.601N
Incidental Tumor Tests	P=0.517N	P=0.073	P=0.725N
Cochran-Armitage Trend Test	P=0.571N		
Fisher Exact Tests		P=0.026	P=0.691N

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).

Negative Trends: The long-term administration of monuron was associated with a lowered incidence and a later onset of several kinds of tumors in male and female mice (Table 10). A dose-related reduction ($P < 0.05$) was observed in the incidences of male mice with hepatocellular carcinomas and of hepatocellular adenomas or carcinomas (combined). Male mice also had dose-related reductions in adrenal gland pheochromocytomas ($P < 0.05$). There was a dose-related reduction in hematopoietic tumors (malignant lymphomas) in female mice ($P < 0.02$).

TABLE 10. ANALYSIS OF REDUCTIONS IN THE INCIDENCES OF NEOPLASTIC LESIONS IN MICE IN THE TWO-YEAR FEED STUDIES OF MONURON

	Control	5,000 ppm	10,000 ppm
MALE			
Liver: Carcinoma			
Overall Rates	6/50 (12%)	5/49 (10%)	2/50 (4%)
Adjusted Rates	16.0%	13.5%	4.4%
Terminal Rates	3/34 (9%)	4/36 (11%)	2/46 (4%)
Life Table Tests	P=0.049N	P=0.458N	P=0.067N
Incidental Tumor Tests	P=0.117N	P=0.542N	P=0.199N
Cochran-Armitage Trend Test	P=0.107N		
Fisher Exact Tests		P=0.515N	P=0.135N
Liver: Adenoma or Carcinoma			
Overall Rates	12/50 (24%)	8/49 (16%)	6/50 (12%)
Adjusted Rates	32.3%	21.6%	12.8%
Terminal Rates	9/34 (26%)	7/36 (19%)	5/46 (11%)
Life Table Tests	P=0.018N	P=0.188N	P=0.026N
Incidental Tumor Tests	P=0.045N	P=0.227N	P=0.079N
Cochran-Armitage Trend Test	P=0.074N		
Fisher Exact Tests		P=0.242N	P=0.097N
Adrenal Gland: Pheochromocytoma			
Overall Rates	3/49 (6%)	0/48 (0%)	0/49 (0%)
Adjusted Rates	7.3%	0.0%	0.0%
Terminal Rates	1/33 (3%)	0/36 (0%)	0/45 (0%)
Life Table Tests	P=0.029N	P=0.109N	P=0.096N
Incidental Tumor Tests	P=0.113N	P=0.216N	P=0.358N
Cochran-Armitage Trend Test	P=0.038N		
Fisher Exact Tests		P=0.125N	P=0.121N
FEMALE			
Lymphoma, All Malignant			
Overall Rates	16/50 (32%)	8/50 (16%)	7/50 (14%)
Adjusted Rates	44.8%	30.2%	16.6%
Terminal Rates	12/31 (39%)	7/25 (28%)	6/41 (15%)
Life Table Tests	P=0.004N	P=0.130N	P=0.006N
Incidental Tumor Tests	P=0.008N	P=0.092N	P=0.022N
Cochran-Armitage Trend Test	P=0.018N		
Fisher Exact Tests		P=0.050N	P=0.028N

IV. DISCUSSION AND CONCLUSIONS

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Diets containing 0, 750, or 1,500 ppm monuron were fed to groups of 50 F344/N rats of each sex and 0, 5,000, or 10,000 ppm to groups of 50 $B6C3F_1$ mice of each sex for 103 weeks. Low dose male and female rats consumed about as much feed as did the controls (Appendix O, Tables O2 and O3), but they showed a moderate weight differential. The mean body weights of high dose rats were lower than those of the low dose or control rats (see Table 3). The weight gain decrements and the biologic effects noted in these studies indicate that the high doses were adequate for carcinogenesis studies.

In the 104-week studies, the weight gain decrement was established by the 8th week. This decrement was relatively steady for male rats throughout the study. The weight gain decrement increased slowly during the study for female rats (see Table 3). Similar weight gain changes were observed in the 13-week studies (see Table 2) and during the first 12 weeks of the 104-week studies.

Generalized atrophy and depletion of the lympho/hematopoietic system were the most important effects in the 13-week studies. These effects were not seen in rats dying during, or at the end of, the 104-week studies. A dose-related incidence of hemosiderosis was found in female rats at terminal kill (Appendix C, Table C2). Although hemosiderosis was also found in an apparent dose-related incidence in female rats that died during the second half of this study, the numbers are too small to permit analysis (control, 1/3; low dose, 2/2; high dose, 4/5). No information is available on possible association between the hemosiderosis found in the spleens of female rats in the 2-year study and the lymphoid changes noted in female rats in the 13-week study.

Throughout the studies, mean body weights of dosed male and dosed female mice were considerably lower than those of the corresponding controls. The decreases in weight gain occurred although feed consumption in the dosed groups was ostensibly twice as high as that in the controls (Tables O5 and O6). It is possible that mice consumed only enough dosed feed to survive and wasted the rest. Also, feed consumption data for mice are less reliable than for rats. The limited weight gains and the biologic effects noted in dosed animals suggest that the doses used were probably adequate for evaluation of potential carcinogenicity.

The weight gain decrements for male mice in the first 12 weeks of the 104-week study (see Table 8) were similar to those in the 13-week study (see Table 7); these decrements steadily increased in both dosed groups during the first year of the study. Weight gain decrements for female mice during the first 12 weeks of the 104-week study were greater than those expected from the results of the 13-week study. The relatively modest decrement in weight gain noted at the end of the 13-week study was exceeded by week 12 of the 104-week study, and this decrement increased rapidly during the rest of the first year of the study.

Generalized lymphoid depletion of the spleen, bone marrow, and lymph nodes, the principal microscopic findings in the 13-week studies, were not observed in mice surviving to the end of the 2-year studies. No exceptional microscopic changes were found in the lymphocytic and hematopoietic tissues of these animals.

The liver and kidney were the major organs affected in male F344/N rats during the 104-week study. High dose males had significantly increased incidences of neoplastic nodules of the liver (control, 1/50; low dose, 6/49; high dose, 7/50). Hepatocellular carcinomas of the liver were increased in the dosed groups, but the increases were not statistically significant (0/50; 1/49; 3/50). The incidences of neoplastic nodules in female rats were not affected by administration of monuron.

Most liver neoplasms in control F344/N rats are found in animals killed at the end of the studies (Goodman et al., 1979). Thus, the apparent increase in liver tumors in the present studies may have been influenced in part by the reduced survival of the controls relative to the dosed groups; however, the increased incidence of neoplastic nodules or hepatocellular carcinomas (combined) in high dose male rats is statistically significant ($P<0.05$) by survival-adjusted methods (see Table 5).

Dose-related increases in both tubular cell adenomas and adenocarcinomas of the kidney (see Table 4) were observed in male rats (adenomas: control, 0/50; low dose, 2/50; high dose, 7/50; adenocarcinomas: 0/50; 1/50; 8/50). The nonneoplastic changes found in the kidney of male and female F344/N rats, notably tubular cell cytomegaly, were described on page 29. Although a clear relationship exists between long-term administration of monuron and cytomegaly, no clear relationship was observed between dose-related renal tubular cell cytomegaly and dose-related renal tubular cell neoplasms.

The first adenocarcinoma was noted at week 97, and the others were found when the animals were killed at the end of the studies. No significantly increased incidences of kidney tumors in female F344/N rats were observed. The historical incidence of kidney tumors in control male F344/N rats at the study laboratory is 2/694 (0.3%) (Appendix F, Table F1).

Previous studies with randomly bred rats fed monuron (Rubenchik et al., 1970) did not report major kidney lesions. The dose administered (450 ppm for 18 months) might have been too low to produce adenomas or carcinomas, or the strain of rat used may have been less sensitive to monuron than are F344/N rats.

Innes et al. (1969) reported that $B6C3F_1$ mice did not develop pulmonary tumors when fed diets containing 517 ppm monuron for 78 weeks; pulmonary adenomas were found in $B6AKF_1$ mice fed the same diet. In the present studies, no compound-related pulmonary neoplastic changes were seen in $B6C3F_1$ mice fed diets containing 10,000 ppm monuron for 103 weeks.

Significant, dose-related reductions occurred in the incidences of adrenal gland pheochromocytomas (all types) in male rats; the incidences of these tumors were not significantly different in dosed and control female rats. Male rats also had dose-related decreased incidences of C-cell carcinomas of the thyroid gland; the incidences in females were not dose related. Administration of monuron significantly reduced the incidences of mammary gland fibroadenomas in female rats. Hodge et al. (1958) reported that mammary fibroadenomas occurred in female albino rats fed monuron for up to 2 years, but the authors did not specify if the incidence was greater or lower than the historical rates for the colony. Reductions in lifetime body weight gains in F344/N rats have been associated with decreased incidences of these previously mentioned tumors (Haseman, 1983). It is not clear if these decreases in tumor incidence are due to monuron administration or are associated with the reductions in weight gain seen in the 2-year studies.

Administration of monuron resulted in a significant reduction in the incidences of leukemia in F344/N rats. Decreased incidences of leukemia in F344/N rats have been associated with increased incidences of neoplastic nodules (Haseman, 1983). The same relationship between incidences of leukemia and neoplastic nodules of the liver is found in the present study for male rats. The mechanism responsible for this relationship is not known.

Comparison of historical tumor incidences (Tables F2 and F3) with those in the present studies indicates that the decreased incidences of leukemia in male and female rats, adrenal gland pheochromocytomas in male rats, and mammary gland fibroadenomas in female rats in the present study may be of biologic significance. In male rats, the control incidence of C-cell carcinomas of the thyroid gland was greater than that normally seen at the same laboratory, and the statistically significant reductions should be interpreted with caution.

Restriction of feed intake is associated with increased longevity in rats (Ross, 1976; Young, 1979; Yu et al., 1982). In mice, longevity is dependent on many factors, including strain, breeding history, environment (e.g., housing and handling), and unexplained laboratory differences (Abbey, 1979). Silberberg et al. (1962; cited in Abbey, 1979) reported that dietary restriction led to high juvenile mortality in several strains of mice. Tucker (1979) reported that a 20% dietary restriction led to increased longevity of SPF Alderley Park I Swiss mice.

Although several studies have reported that underfeeding inhibits tumorigenesis (Clayson, 1977), the ambiguity of the term "underfeeding"

makes interpretation of these results difficult. "Underfeeding" can be defined either as total caloric restriction or as restriction of one or more dietary components. Tucker (1979) reported that dietary restriction was associated with reduction in the incidences of several types of tumors in both rats and mice. Incidences of leukemia, lymphomas, or both were not affected significantly by dietary restriction, whereas incidences of unspecified liver tumors were reduced in male SPF Swiss albino mice, dermal tumors were reduced in male SPF Alderley Park male rats, and mammary gland tumors were reduced in female rats.

The enhanced survival of male and female $B6C3F_1$ mice fed diets containing 5,000 or 10,000 ppm may be related to their lack of weight gain during the studies. Similarly, the reductions in overall and specific tumor rates in mice receiving monuron in the diet may be the result of their remaining thin throughout the studies. This correlation may be questioned, since control female mice in this study were heavier than normal at the end of the study (see Table 8); the average terminal weights for control male and female mice in these studies were 42 g and 52 g, respectively.

The significant increase ($P=0.026$) in the combined incidence of subcutaneous sarcoma, fibromas, or fibrosarcomas in low dose male mice is not clearly associated with administration of monuron (control, 2/50; low dose, 9/50; high dose, 2/50). No other significant increases in tumor incidences were seen in dosed male mice. Incidences of tumors in female mice were not increased by administration of monuron.

Significant reductions occurred in the incidences of several types of tumors in dosed $B6C3F_1$ mice. A dose-related reduction occurred in the incidences of lymphomas of all types in female mice. Incidences of lymphomas in control male mice in the monuron study were lower than usual but within the range of historical data (Table F4). The reductions in the incidences of lymphomas in female mice are statistically significant in this study. The historical data on tumor incidence in control female mice at the study laboratory are shown in Table F5. The reduced incidence of hepatocellular adenomas or carcinomas (combined) in male mice was significant by life table analysis ($P=0.018$) but not by the Fisher exact test. Reduced incidences of hepatocellular adenomas and hepatocellular adenomas or carcinomas (combined) were seen in low dose but not high dose female mice.

The reduction in the incidence of hepatocellular carcinomas in male mice (Table F3) does not appear to have precedence. A further evaluation of the biologic significance of these reductions in tumor incidence is needed.

During the course of this study, the rats showed serologic evidence of pneumonia virus of mice (PVM) and rat coronavirus (RCV) infections; mice had titers for mouse hepatitis virus (MHV) (Appendix M, Table M1). In addition, Klebsiella infections of the female mouse urogenital system were common in this study. The infections were not dose related. Neither the viral nor the bacterial infection appeared to have influenced the incidences of tumors in rats or mice.

When this study was initiated, control of animal room environmental parameters (temperature and relative humidity) was not a strict NTP requirement. The recommended temperature and humidity range was often not met (Appendix K, Tables K1 and K2). Although these fluctuations might not be desirable, no evidence links such changes to tumor incidence. Thus, the biologic effects seen in these studies are due to the chemical (or its metabolites) or to the body weight changes already noted.

Monuron was not mutagenic in Salmonella strains TA98, TA100, TA1535, or TA1537 in the presence or absence of Aroclor 1254-induced rat liver S9 (Appendix G, Table G1). Monuron did induce chromosomal aberrations and sister chromatid exchanges in cultured Chinese hamster ovary cells (Tables G2 and G3).

IV. DISCUSSION AND CONCLUSIONS

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

Under the conditions of these 2-year feed studies, there was *clear evidence of carcinogenicity** for male F344/N rats in that monuron caused increased incidences of tubular cell adenocarcinomas of the kidney, tubular cell adenomas of the kidney, and neoplastic nodules or carcinomas (combined) of the liver. Monuron induced cytomegaly of the renal tubular epithelial cells in both male and female F344/N rats. There was *no evidence of carcinogenicity* for female F344/N rats or for male or female B6C3F$_1$ mice.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 6. A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 9.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS IN THE TWO-YEAR FEED STUDIES OF MONURON

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF MONURON

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	1 (2%)
SQUAMOUS CELL CARCINOMA	1 (2%)		1 (2%)
BASAL-CELL CARCINOMA		1 (2%)	1 (2%)
TRICHOEPITHELIOMA	1 (2%)		
KERATOACANTHOMA	1 (2%)	†4 (8%)	
*SUBCUTANEOUS TISSUE	(50)	(50)	(50)
SARCOMA, NOS		1 (2%)	
FIBROMA	1 (2%)		2 (4%)
FIBROSARCOMA		2 (4%)	
FIBROUS HISTIOCYTOMA			1 (2%)
MYXOSARCOMA		1 (2%)	
LIPOMA	1 (2%)		
NEUROFIBROMA		2 (4%)	
NEUROFIBROSARCOMA			2 (4%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(49)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)		2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		2 (4%)	
TUBULAR-CELL ADENOCARCINOMA, MET			1 (2%)
C-CELL CARCINOMA, METASTATIC	1 (2%)		1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MYELOMONOCYTIC LEUKEMIA	4 (8%)		
LEUKEMIA, MONONUCLEAR CELL	1 (2%)		
#SPLEEN	(50)	(48)	(50)
PHEOCHROMOCYTOMA, METASTATIC	1 (2%)		
SARCOMA, NOS	1 (2%)		
MALIGNANT LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
CIRCULATORY SYSTEM			
#MYOCARDIUM	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(50)	(49)	(50)
NEOPLASTIC NODULE	1 (2%)	6 (12%)	7 (14%)
HEPATOCELLULAR CARCINOMA		1 (2%)	3 (6%)
*RECTUM	(50)	(50)	(50)
ADENOCARCINOMA, NOS		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
UNDIFFERENTIATED CARCINOMA			1 (2%)
TUBULAR-CELL ADENOMA		2 (4%)	7 (14%)
TUBULAR-CELL ADENOCARCINOMA		1 (2%)	8 (16%)
SARCOMA, NOS			1 (2%)
LIPOMA			1 (2%)

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

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(47)	(47)	(44)
CARCINOMA,NOS		1 (2%)	
ADENOMA, NOS	12 (26%)	11 (23%)	10 (23%)
#ADRENAL	(50)	(50)	(48)
CORTICAL ADENOMA		3 (6%)	
PHEOCHROMOCYTOMA	14 (28%)	13 (26%)	3 (6%)
PHEOCHROMOCYTOMA, MALIGNANT	1 (2%)	1 (2%)	1 (2%)
#ADRENAL MEDULLA	(50)	(50)	(48)
PHEOCHROMOCYTOMA	1 (2%)		1 (2%)
#THYROID	(49)	(46)	(50)
FOLLICULAR-CELL ADENOMA			1 (2%)
FOLLICULAR-CELL CARCINOMA		1 (2%)	
C-CELL ADENOMA	4 (8%)	3 (7%)	2 (4%)
C-CELL CARCINOMA	6 (12%)	3 (7%)	1 (2%)
#PANCREATIC ISLETS	(48)	(49)	(49)
ISLET-CELL ADENOMA			2 (4%)
ISLET-CELL CARCINOMA	3 (6%)	2 (4%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
FIBROADENOMA		2 (4%)	
*PREPUTIAL GLAND	(50)	(50)	(50)
CARCINOMA,NOS	5 (10%)	2 (4%)	3 (6%)
ADENOMA, NOS	2 (4%)		1 (2%)
#TESTIS	(50)	(50)	(48)
INTERSTITIAL-CELL TUMOR	45 (90%)	46 (92%)	43 (90%)
MESOTHELIOMA, INVASIVE			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
ASTROCYTOMA			1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*SKULL	(50)	(50)	(50)
OSTEOSARCOMA	1 (2%)		
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
OSTEOSARCOMA		1 (2%)	
NEUROFIBROSARCOMA	1 (2%)		
*PERITONEUM	(50)	(50)	(50)
MESOTHELIOMA, MALIGNANT			1 (2%)
*PERITONEAL CAVITY	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)		
*TUNICA VAGINALIS	(50)	(50)	(50)
MESOTHELIOMA, NOS	1 (2%)		

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

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
HEPATOCELLULAR CARCINOMA, METAST			1 (2%)
MESOTHELIOMA, NOS		2 (4%)	
MESOTHELIOMA, MALIGNANT		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	12	4	6
MORIBUND SACRIFICE	1	2	3
TERMINAL SACRIFICE	26	44	41
ACCIDENTALLY KILLED, NDA	11		
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	49	49	48
TOTAL PRIMARY TUMORS	111	118	109
TOTAL ANIMALS WITH BENIGN TUMORS	47	49	47
TOTAL BENIGN TUMORS	83	88	77
TOTAL ANIMALS WITH MALIGNANT TUMORS	24	16	20
TOTAL MALIGNANT TUMORS	26	22	25
TOTAL ANIMALS WITH SECONDARY TUMORS##	2		4
TOTAL SECONDARY TUMORS	2		4
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	2	8	7
TOTAL UNCERTAIN TUMORS	2	8	7

* NUMBER OF ANIMALS RECEIVING COMPLETE NECROPSY EXAMINATION; ALL GROSS LESIONS INCLUDING MASSES EXAMINED MICROSCOPICALLY.
** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# NUMBER OF ANIMALS EXAMINED MICROSCOPICALLY AT THIS SITE
SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN
† MULTIPLE OCCURRENCE OF MORPHOLOGY IN THE SAME ORGAN; TISSUE IS COUNTED ONCE ONLY.

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF MONURON

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA			2 (4%)
*SUBCUTANEOUS TISSUE	(50)	(50)	(50)
NEOPLASM, NOS	1 (2%)		
NEOPLASM, NOS, MALIGNANT			1 (2%)
NEUROFIBROSARCOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)		1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MYELOMONOCYTIC LEUKEMIA	8 (16%)	1 (2%)	1 (2%)
LYMPHOCYTIC LEUKEMIA	1 (2%)		
LEUKEMIA, MONONUCLEAR CELL	2 (4%)	1 (2%)	1 (2%)
#SPLEEN	(50)	(50)	(50)
LIPOMA			1 (2%)
#THYMUS	(43)	(41)	(42)
THYMOMA			1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(50)	(50)	(48)
SARCOMA, NOS			1 (2%)
#LIVER	(50)	(50)	(50)
NEOPLASTIC NODULE	4 (8%)	1 (2%)	2 (4%)
#STOMACH	(49)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)		
#ILEUM	(50)	(50)	(50)
LEIOMYOSARCOMA		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
LIPOMA		1 (2%)	
#URINARY BLADDER	(50)	(50)	(50)
TRANSITIONAL-CELL PAPILLOMA		1 (2%)	
SARCOMA, NOS, INVASIVE	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(48)	(45)
CARCINOMA, NOS		1 (2%)	
ADENOMA, NOS	23 (47%)	22 (46%)	16 (36%)
#ADRENAL	(50)	(50)	(48)
CORTICAL ADENOMA	2 (4%)	1 (2%)	
PHEOCHROMOCYTOMA	3 (6%)		1 (2%)
PHEOCHROMOCYTOMA, MALIGNANT	1 (2%)		1 (2%)

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF MONURON (Continued)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#THYROID	(49)	(48)	(47)
C-CELL ADENOMA	2 (4%)	3 (6%)	1 (2%)
C-CELL CARCINOMA		2 (4%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
CARCINOMA, NOS		1 (2%)	
ADENOCARCINOMA, NOS	1 (2%)	2 (4%)	1 (2%)
PAPILLARY ADENOCARCINOMA		1 (2%)	1 (2%)
INTRADUCTAL CARCINOMA		1 (2%)	
FIBROADENOMA	20 (40%)	15 (30%)	9 (18%)
*CLITORAL GLAND	(50)	(50)	(50)
CARCINOMA, NOS	2 (4%)	3 (6%)	
ADENOMA, NOS	1 (2%)		1 (2%)
#UTERUS	(50)	(50)	(50)
LEIOMYOMA		1 (2%)	
LEIOMYOSARCOMA			1 (2%)
ENDOMETRIAL STROMAL POLYP	9 (18%)	10 (20%)	10 (20%)
ENDOMETRIAL STROMAL SARCOMA	1 (2%)		
#CERVIX UTERI	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)		
#UTERUS/ENDOMETRIUM	(50)	(50)	(50)
ADENOCARCINOMA, NOS			1 (2%)
#OVARY	(50)	(50)	(48)
GRANULOSA-CELL TUMOR		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(49)	(49)	(50)
ASTROCYTOMA		2 (4%)	
SPECIAL SENSE ORGANS			
*ZYMBAL GLAND	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA	1 (2%)		1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	8	2	5
MORIBUND SACRIFICE	8	4	3
TERMINAL SACRIFICE	34	44	42
@ INCLUDES AUTOLYZED ANIMALS			

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF MONURON (Continued)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	41	45	37
TOTAL PRIMARY TUMORS	87	72	55
TOTAL ANIMALS WITH BENIGN TUMORS	39	39	29
TOTAL BENIGN TUMORS	63	54	43
TOTAL ANIMALS WITH MALIGNANT TUMORS	16	14	9
TOTAL MALIGNANT TUMORS	19	16	10
TOTAL ANIMALS WITH SECONDARY TUMORS##	1		2
TOTAL SECONDARY TUMORS	1		2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	5	2	2
TOTAL UNCERTAIN TUMORS	5	2	2

* NUMBER OF ANIMALS RECEIVING COMPLETE NECROPSY EXAMINATION; ALL GROSS LESIONS INCLUDING MASSES EXAMINED MICROSCOPICALLY.
** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# NUMBER OF ANIMALS EXAMINED MICROSCOPICALLY AT THIS SITE
SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF MONURON: UNTREATED CONTROL

ANIMAL NUMBER	001	002	003	004	005	008	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	082	104	105	059	093	093	093	105	105	093	093	093	093	093	093	105	105	105	105	105	105	105	093	090	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Trichoepithelioma																									
Keratoacanthoma																			X						
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Lipoma																	X								
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																				X					
C-cell carcinoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma, metastatic																									
Sarcoma, NOS																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
DIGESTIVE SYSTEM																									
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	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Adenoma, NOS	X		X		X			X									X			X					
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma		X	X						X							X			X	X	X	X			
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																			X						
C-cell carcinoma		X	X														X								
Parathyroid	−	−	−	+	+	−	−	−	−	+	−	−	+	+	−	−	−	+	+	−	+	+	−	−	−
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell carcinoma							X																X		
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	+	N	N	+	N	N	N	N	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
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS				X											X										
Adenoma, NOS			X																						
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																									
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
Sarcoma, NOS																									
Neurofibrosarcoma																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, 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				
Leukemia, mononuclear cell																									

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

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: UNTREATED CONTROL (Continued)

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	106	105	105	099	105	100	105	106	105	080	105	093	088	106	078	105	106	106	092	106	106	088	106	105	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	*50
Squamous cell carcinoma						X																				1
Trichoepithelioma																								X		1
Keratoacanthoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	*50
Fibroma												X														1
Lipoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
C-cell carcinoma, metastatic					X																					1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma, metastatic											X															1
Sarcoma, NOS																									X	1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	−	−	+	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS			X																							1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule			X																							1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	−	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	44
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS									X					X					X		X	X	X			12
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma				X					X			X		X	X								X	X		15
Pheochromocytoma, malignant											X															1
Thyroid	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell adenoma			X																		X		X			4
C-cell carcinoma	X				X																	X				6
Parathyroid	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	+	+	+	−	−	−	−	+	−	−	14
Pancreatic islets	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	48
Islet cell carcinoma	X																									3
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	+	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	*50
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	45
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	48
Preputial/clitoral gland	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*50
Carcinoma, NOS			X										X						X							5
Adenoma, NOS																X										2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Osteosarcoma																X										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
Sarcoma, NOS																				X						1
Neurofibrosarcoma							X																			1
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, 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													4
Leukemia, mononuclear cell																							X			1

* Animals necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF MONURON: LOW DOSE

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	105	105	105	091	105	105	102	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma		X																							
Basal cell carcinoma																									
Keratoacanthoma								@X														X			
Subcutaneous tissue	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS					X																				
Fibrosarcoma																									
Myxosarcoma																									
Neurofibroma						X																			
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	−	−	−	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule						X				X					X								X		
Hepatocellular carcinoma															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	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−
Rectum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS																	X								
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma															X										
Tubular cell adenocarcinoma													X												
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																X									
Adenoma, NOS			X			X					X			X							X				
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma										X										X					X
Pheochromocytoma					X				X		X					X				X					
Pheochromocytoma, malignant																									
Thyroid	+	−	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Follicular cell carcinoma																									
C-cell adenoma																							X	X	
C-cell carcinoma																									
Parathyroid	+	−	+	−	−	−	+	−	−	−	−	−	−	+	−	−	−	−	−	−	+	+	−	+	−
Pancreatic islets	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell carcinoma											X		X												
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	+	N	N	+	N	N	N	+	N	N	+	N	+	N	N	N	+
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	X	X	X
Prostate	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS															X		X								
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Osteosarcoma				X																					
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS																									
Mesothelioma, malignant																									

@: Multiple occurrence of morphology

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

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	105	105	105	105	105	105	105	098	105	105	105	105	097	105	105	105	105	091	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	*50
Squamous cell papilloma																										1
Basal cell carcinoma																			X							1
Keratoacanthoma		X									X															4
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	*50
Sarcoma, NOS															X											1
Fibrosarcoma																			X							2
Myxosarcoma												X														1
Neurofibroma																		X								2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma													X					X								2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	48
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	−	+	+	+	−	−	+	+	+	+	40
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule															X	X										6
Hepatocellular carcinoma																										1
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	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	−	+	+	+	+	−	+	+	43
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Rectum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenocarcinoma, NOS																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma						X																				2
Tubular cell adenocarcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	47
Carcinoma, NOS																										1
Adenoma, NOS				X	X			X											X	X		X				11
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																										3
Pheochromocytoma								X	X	X	X	X	X										X	X		13
Pheochromocytoma, malignant				X																						1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Follicular cell carcinoma																									X	1
C-cell adenoma								X																		3
C-cell carcinoma					X								X										X			3
Parathyroid	+	+	−	−	+	+	−	−	−	−	+	−	−	−	−	−	−	+	+	+	+	+	+	−	−	18
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell carcinoma																										2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	+	*50
Fibroadenoma			X																							2
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X	X	46
Prostate	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	−	+	−	−	+	+	+	+	+	44
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																										2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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
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
Mesothelioma, NOS			X																					X		2
Mesothelioma, malignant																									X	1

* Animals necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF MONURON: 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	105	105	105	105	093	105	105	093	105	105	105	061	105	105	103	105	105	105	105	105	105	105	096	102
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Squamous cell carcinoma									X																
Basal cell carcinoma			X																						
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																							X		
Fibrous histiocytoma																									
Neurofibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X														X			
Tubular cell adenocarcinoma, metastatic																									
C-cell carcinoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, histiocytic type																									
Lymph nodes	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	−	−	+	−	+	+	−	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule								X				X		X							X				
Hepatocellular carcinoma		X						X																	
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Undifferentiated carcinoma												X													
Tubular cell adenoma											X	X						X							
Tubular cell adenocarcinoma																									
Sarcoma, NOS															X										
Lipoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+
Adenoma, NOS						X		X							X					X				X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma															X									X	
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
C-cell adenoma								X				X													
C-cell carcinoma																									
Parathyroid	−	+	+	+	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	+	−	−	+	−	+
Pancreatic islets	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma											X														
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	N	N	N	N	N	+	N	N	N	N	N	+	N	N	N	N	N	N	N	N	+	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−
Interstitial cell tumor	X	X	X	X	X		X	X		X	X	X		X	X	X	X		X	X	X	X	X		
Mesothelioma, invasive									X																
Prostate	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	−	−
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS			X	X																X					
Adenoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma																									
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
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	N
Hepatocellular carcinoma, metastatic		X																							

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

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:
WEEKS ON STUDY	1055	1055	1055	1055	1055	1055	1055	1055	1055	1055	1055	1055	1055	1055	0999	1055	1055	1055	0933	1055	0967	1055	1055	1044	1055	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	N	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																						X				1
Squamous cell carcinoma																										1
Basal cell carcinoma																										1
Subcutaneous tissue	+	N	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																							X			2
Fibroua histiocytoma									X																	1
Neurofibrosarcoma							X								X											2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										2
Tubular cell adenocarcinoma, metastatic																				X						1
C-cell carcinoma, metastatic																			X							1
Trachea	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, histiocytic type																								X		1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	–	+	–	–	+	+	+	–	–	–	+	+	+	+	–	+	–	+	+	+	+	36
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule				X						X				X												7
Hepatocellular carcinoma																						X				3
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	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Undifferentiated carcinoma																										1
Tubular cell adenoma		X									X						X								X	7
Tubular cell adenocarcinoma				X			X		X					X		X					X		X	X		8
Sarcoma, NOS																										1
Lipoma		X																								1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	44
Adenoma, NOS				X											X		X		X	X						10
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	48
Pheochromocytoma															X										X	4
Pheochromocytoma, malignant																						X				1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma					X																					1
C-cell adenoma																										2
C-cell carcinoma																			X							1
Parathyroid	+	+	+	–	–	–	–	–	–	–	–	–	–	–	+	+	–	–	–	–	+	–	–	+	–	14
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma																		X								2
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	+	N	N	N	N	N	N	N	N	+	N	N	N	+	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	43
Mesothelioma, invasive																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	45
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																										3
Adenoma, NOS						X																				1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma								X																		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
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	N	*50
Hepatocellular carcinoma, metastatic																										1

* Animals necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF MONURON: UNTREATED 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	106	106	106	106	098	106	092	105	106	106	103	106	106	106	106	106	106	106	106	106	089	092	106	106	076
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplasm, NOS																									
Neurofibrosarcoma																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																						X			
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS, invasive																					X				
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS	X	X			X	X			X	X	X	X	X			X				X			X	X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma												X													
Pheochromocytoma											X														
Pheochromocytoma, malignant														X											
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																	X							X	
Parathyroid	+	−	−	−	−	−	+	−	+	+	−	−	−	−	+	−	−	−	−	−	+	−	−	−	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	N	+	N	+	N	N	+	N	+	N	+	N	N	+	N	+	N	+	+	+	+	N
Adenocarcinoma, NOS	X																								
Fibroadenoma	X													X					X			X	X		
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																							X		
Adenoma, NOS												X													
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																					X				
Endometrial stromal polyp						X					X														
Endometrial stromal sarcoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma												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	
Lymphocytic leukemia																									
Leukemia, mononuclear cell																									

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

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: UNTREATED CONTROL (Continued)

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	106	106	106	099	106	099	085	076	106	106	105	106	098	106	106	106	106	105	106	106	106	105	103	106	106	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	*50
Neoplasm, NOS																							X			1
Neurofibrosarcoma																						X				1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X																								2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	48
Thymus	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	43
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule										X									X					X		4
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	47
Esophagus	–	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	–	–	42
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS, invasive																										1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	49
Adenoma, NOS							X	X		X	X				X	X		X	X		X	X				23
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma			X																							2
Pheochromocytoma			X																X							3
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell adenoma																										2
Parathyroid	+	+	+	–	+	–	–	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	14
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	+	+	+	N	+	N	+	+	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	*50
Adenocarcinoma, NOS																										1
Fibroadenoma			X	X	X		X		X		X	X	X			X	X			X		X	X	X	X	20
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							2
Adenoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS																										1
Endometrial stromal polyp			X						X	X							X			X	X	X				9
Endometrial stromal sarcoma					X																					1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma																										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
Lymphocytic leukemia				X																						1
Leukemia, mononuclear cell								X																X		2

* Animals necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF MONURON: 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	105	105	100	105	105	093	105	105	105	105	105	105	105	105	105	091	105	105	105	105
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
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	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma							X																		
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS	X	X	X			X		X				X			X		X	X		X				X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																								X	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
C-cell adenoma																			X						
C-cell carcinoma			X																						
Parathyroid	−	−	−	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	+	+	−
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	N	N	+	+	+	+	+	+	+	+	+	+	N	N	+	N	N	N	N	N	+	+
Carcinoma, NOS																									
Adenocarcinoma, NOS						X						X													
Papillary adenocarcinoma																									
Intraductal carcinoma						X																			
Fibroadenoma						X	X				X		X	X	X										
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS										X															X
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Endometrial stromal polyp					X								X			X				X		X	X	X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma								X																	
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Myelomonocytic leukemia																									
Leukemia, mononuclear cell																					X				

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: LOW DOSE (Continued)

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	055	105	105	105	105	105	105	105	033	105	105	105	105	088	105	105	105	105	105	105	105	105	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	−	+	+	−	+	−	+	+	−	+	−	+	−	+	+	+	−	−	+	+	+	+	+	+	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																							X			1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	42
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																								X		1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma																	X									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional cell papilloma																										1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS							X																			1
Adenoma, NOS			X					X			X		X			X	X		X	X	X		X		X	22
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																										1
Thyroid	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell adenoma																					X				X	3
C-cell carcinoma							X																			2
Parathyroid	−	−	−	−	+	−	−	+	−	−	−	−	−	−	−	−	+	−	−	−	+	−	−	+	−	10
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	N	+	+	+	N	+	+	+	+	+	N	N	+	+	+	+	+	N	+	+	+	N	*50
Carcinoma, NOS																				X						1
Adenocarcinoma, NOS																										2
Papillary adenocarcinoma													X													1
Intraductal carcinoma																										1
Fibroadenoma					X	X				X	X	X				X		X					X	X		15
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS			X																							3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma	X																									1
Endometrial stromal polyp															X			X							X	10
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor																					X					1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Astrocytoma				X																						2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Myelomonocytic leukemia																					X					1
Leukemia, mononuclear cell																										1

* Animals necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF MONURON: 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	105	105	105	105	105	105	105	105	105	105	105	105	105	103	105	868	052	090	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Skin	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+	N	+	+	+
Squamous cell papilloma					X																		X		
Subcutaneous tissue	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+	N	+	+	+
Neoplasm, NOS, malignant																		X							
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic																									
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma										X															
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	−	−	+	+	+	+	+	+
Thymoma																									X
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Sarcoma, NOS																									
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	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	−	+	−	+	+	−	+	−	+	+	+	−	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS		X	X					X		X			X				X			X	X	X			
Adrenal	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+
C-cell adenoma																									
Parathyroid	+	−	−	+	−	−	−	−	−	−	−	+	−	−	−	−	+	+	−	+	−	−	−	−	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	N	+	N	N	+	N	N	+	N	+	+	+	+	+	N	N	+	N	−	+	N	+
Adenocarcinoma, NOS																									
Papillary adenocarcinoma																X									
Fibroadenoma	X												X									X	X		
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS															•										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS															X										
Leiomyosarcoma																			X						
Endometrial stromal polyp					X				X				X												
Ovary	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS, metastatic															X										
Myelomonocytic leukemia																									
Leukemia, mononuclear cell																									

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: HIGH DOSE (Continued)

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	091	078	105	105	105	105	085	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	068	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	*50
Squamous cell papilloma																										2
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	*50
Neoplasm, NOS, malignant																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic								X																		1
Alveolar/bronchiolar adenoma																				X						1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	–	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	42
Thymoma																										1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Sarcoma, NOS																						X				1
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	–	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	–	+	+	+	+	+	–	+	+	–	+	+	+	–	+	+	+	+	–	+	+	+	+	45
Adenoma, NOS	X					X	X						X	X			X								X	16
Adrenal	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma				X																						1
Pheochromocytoma, malignant																						X				1
Thyroid	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
C-cell adenoma																		X								1
Parathyroid	+	–	–	+	–	–	–	–	–	–	+	+	–	–	+	–	–	–	+	–	–	–	–	+	–	14
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	+	N	+	+	N	N	N	+	+	+	N	+	N	N	N	+	N	+	N	N	+	*50
Adenocarcinoma, NOS								X																		1
Papillary adenocarcinoma																										1
Fibroadenoma					X							X	X									X			X	9
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
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																										1
Leiomyosarcoma																										1
Endometrial stromal polyp					X	X						X				X		X	X						X	10
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Zymbal gland	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma		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
Adenocarcinoma, NOS, metastatic																										1
Myelomonocytic leukemia										X																1
Leukemia, mononuclear cell																							X			1

* Animals necropsied

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE IN THE TWO-YEAR FEED STUDIES OF MONURON

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF MONURON

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
*SUBCUTANEOUS TISSUE	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)	1 (2%)	1 (2%)
FIBROMA		2 (4%)	
FIBROSARCOMA	1 (2%)	6 (12%)	1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(49)	(50)
HEPATOCELLULAR CARCINOMA, METAST	2 (4%)		
ALVEOLAR/BRONCHIOLAR ADENOMA	5 (10%)	4 (8%)	8 (16%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	1 (2%)	2 (4%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	2 (4%)	2 (4%)	1 (2%)
#MESENTERIC LYMPH NODE	(45)	(43)	(48)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
CIRCULATORY SYSTEM			
#SPLEEN	(50)	(48)	(50)
HEMANGIOSARCOMA	1 (2%)		
#LIVER	(50)	(49)	(50)
HEMANGIOSARCOMA	2 (4%)		
DIGESTIVE SYSTEM			
#LIVER	(50)	(49)	(50)
HEPATOCELLULAR ADENOMA	7 (14%)	3 (6%)	4 (8%)
HEPATOCELLULAR CARCINOMA	6 (12%)	5 (10%)	2 (4%)
#FORESTOMACH	(50)	(48)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)		
#JEJUNUM	(50)	(47)	(49)
ADENOCARCINOMA, NOS	1 (2%)		
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(35)	(42)	(42)
ADENOMA, NOS	2 (6%)		
#ADRENAL	(49)	(48)	(49)
CORTICAL ADENOMA	1 (2%)		
PHEOCHROMOCYTOMA	3 (6%)		
#ADRENAL/CAPSULE	(49)	(48)	(49)
ADENOMA, NOS		1 (2%)	
#THYROID	(46)	(41)	(45)
FOLLICULAR-CELL ADENOMA	2 (4%)		
REPRODUCTIVE SYSTEM			
NONE			

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF MONURON (Continued)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
ADENOMA, NOS	4 (8%)	1 (2%)	2 (4%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	
LEG			
FIBROSARCOMA	2		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	13	11	5
MORIBUND SACRIFICE	3	3	
TERMINAL SACRIFICE	34	36	45
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	30	22	19
TOTAL PRIMARY TUMORS	43	27	21
TOTAL ANIMALS WITH BENIGN TUMORS	21	9	12
TOTAL BENIGN TUMORS	25	11	14
TOTAL ANIMALS WITH MALIGNANT TUMORS	17	16	7
TOTAL MALIGNANT TUMORS	18	16	7
TOTAL ANIMALS WITH SECONDARY TUMORS##	2	1	
TOTAL SECONDARY TUMORS	2	1	

* NUMBER OF ANIMALS RECEIVING COMPLETE NECROPSY EXAMINATION; ALL GROSS LESIONS INCLUDING MASSES EXAMINED MICROSCOPICALLY.
** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# NUMBER OF ANIMALS EXAMINED MICROSCOPICALLY AT THIS SITE
SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF MONURON

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SUBCUTANEOUS TISSUE	(50)	(50)	(50)
SARCOMA, NOS		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(48)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	4 (8%)	4 (8%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	2 (4%)	3 (6%)	1 (2%)
PHEOCHROMOCYTOMA, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	15 (30%)	8 (16%)	6 (12%)
MALIGNANT LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
#LIVER	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
CIRCULATORY SYSTEM			
*SUBCUTANEOUS TISSUE	(50)	(50)	(50)
HEMANGIOSARCOMA	1 (2%)		
#SPLEEN	(50)	(50)	(49)
HEMANGIOSARCOMA			1 (2%)
#LIVER	(50)	(50)	(50)
HEMANGIOSARCOMA		1 (2%)	
#UTERUS	(49)	(48)	(49)
HEMANGIOMA	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
HEPATOCELLULAR ADENOMA	5 (10%)		3 (6%)
HEPATOCELLULAR CARCINOMA	2 (4%)		
URINARY SYSTEM			
#KIDNEY/TUBULE	(50)	(49)	(50)
PAPILLARY ADENOMA		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(40)	(35)	(40)
ADENOMA, NOS	2 (5%)	2 (6%)	
#ADRENAL	(50)	(45)	(49)
PHEOCHROMOCYTOMA		1 (2%)	1 (2%)
PHEOCHROMOCYTOMA, MALIGNANT			1 (2%)
#THYROID	(42)	(39)	(39)
FOLLICULAR-CELL ADENOMA		1 (3%)	
#PANCREATIC ISLETS	(46)	(45)	(49)
ISLET-CELL ADENOMA	1 (2%)		

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF MONURON (Continued)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS		1 (2%)	1 (2%)
*VAGINA	(50)	(50)	(50)
SARCOMA, NOS		1 (2%)	
#OVARY	(44)	(48)	(47)
PAPILLARY CYSTADENOMA, NOS	2 (5%)		
MIXED TUMOR, BENIGN		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
FOOT			
RHABDOMYOSARCOMA	1		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	15	23	8
MORIBUND SACRIFICE	5	1	1
TERMINAL SACRIFICE	30	25	41
ACCIDENTALLY KILLED, NDA		1	
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	30	21	14
TOTAL PRIMARY TUMORS	38	25	17
TOTAL ANIMALS WITH BENIGN TUMORS	13	8	6
TOTAL BENIGN TUMORS	16	10	6
TOTAL ANIMALS WITH MALIGNANT TUMORS	21	15	10
TOTAL MALIGNANT TUMORS	22	15	11
TOTAL ANIMALS WITH SECONDARY TUMORS##			1
TOTAL SECONDARY TUMORS			1

* NUMBER OF ANIMALS RECEIVING COMPLETE NECROPSY EXAMINATION; ALL GROSS LESIONS INCLUDING MASSES EXAMINED MICROSCOPICALLY.
** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# NUMBER OF ANIMALS EXAMINED MICROSCOPICALLY AT THIS SITE
SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF MONURON: UNTREATED 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	043	105	060	105	047	105	096	105	105	105	105	105	103	105	105	105	105	105	105	030	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Fibrosarcoma						X																			
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic													X												
Alveolar/bronchiolar adenoma		X													X		X								X
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph nodes	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS																								X	
Thymus	−	+	−	−	−	−	−	+	−	+	−	−	−	+	+	+	−	+	+	−	+	−	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma				X				X						X		X	X							X	
Hepatocellular carcinoma													X	X	X										
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	N	N	N	+	+	N	+	+	+	+	+	N	N	+	+	+	N	+	N	+	+
Pancreas	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	−	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																						X			
Large intestine	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	−	−	−	+	+	+	−	−	−	+	+	+	+	+	+	+	−	+	+	−
Adenoma, NOS											X														
Adrenal	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma												X													
Pheochromocytoma																									
Thyroid	+	+	+	−	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	−	+	−	−	−	−	−	−	−	+	+	+	−	−	+	+	+	−	+	−	+	−	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																			X						
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS		X																							
Leg, NOS																									
Fibrosarcoma												X													

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

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: UNTREATED CONTROL (Continued)

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	105	105	105	048	028	055	105	105	094	105	105	105	105	077	057	009	105	097	105	105	070	105	071	105	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	*50
Sarcoma, NOS																						X				1
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic									X																	2
Alveolar/bronchiolar adenoma																			X							5
Alveolar/bronchiolar carcinoma		X																								1
Trachea	+	+	+	+	+	+.	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma								X																		1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	–	+	+	+	+	+	+	45
Malignant lymphoma, NOS																										1
Thymus	+	+	+	–	–	–	–	–	–	–	+	+	–	–	–	–	–	+	–	–	–	–	+	–	+	20
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma											X															7
Hepatocellular carcinoma									X											X				X		6
Hemangiosarcoma								X							X											2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	N	+	+	N	+	N	+	N	+	+	+	+	+	N	N	+	N	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	48
Esophagus	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma									X																	1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																										1
Large intestine	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	–	+	+	+	+	+	+	–	–	+	+	+	–	+	+	–	+	–	+	+	–	+	+	+	35
Adenoma, NOS	X																									2
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma																										1
Pheochromocytoma				X	X		X																			3
Thyroid	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Follicular cell adenoma					X		X																			2
Parathyroid	–	+	+	+	+	–	–	–	–	+	+	–	+	+	–	–	–	+	+	+	–	+	+	–	+	26
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	48
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS									X	X															X	4
ALL OTHER SYSTEMS																										*
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS																									X	2
Leg, NOS																										
Fibrosarcoma														X												2

* Animals necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF MONURON: 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	104	104	104	104	104	104	104	104	058	099	028	089	104	071	103	105	105	105	085	105	105	105	105	075	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma													X												
Subcutaneous tissue	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS														X											
Fibroma																									
Fibrosarcoma										X		X							X						
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																			X		X				
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Thymus	+	−	−	−	−	+	+	+	A	−	A	−	−	−	−	−	+	+	+	+	−	−	−	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																						X			
Hepatocellular carcinoma					X										X										
Bile duct	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	N	+	+
Pancreas	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	−	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS				X																					
Thyroid	+	+	+	+	+	+	+	−	A	+	A	+	−	+	−	−	+	+	+	−	+	+	+	+	+
Parathyroid	+	−	+	+	+	−	+	−	A	+	A	+	−	+	−	−	+	+	−	−	−	+	−	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																					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
Hepatocellular carcinoma, metastatic															X										
Malignant lymphoma, NOS								X																	

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

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	105	105	067	068	105	105	105	084	105	105	105	105	105	105	105	105	105	105	105	049	105	072	094	105	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell carcinoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibroma													X			X										2
Fibrosarcoma		X																	X					X		6
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																			X					X		4
Alveolar/bronchiolar carcinoma														X												1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph nodes	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	–	+	+	43
Thymus	+	–	+	–	–	+	+	–	–	–	+	+	–	+	+	+	+	+	+	–	+	–	+	–	–	22
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma											X					X										3
Hepatocellular carcinoma								X												X					X	3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	N	+	+	N	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	N	N	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	48
Stomach	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	47
Large intestine	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	+	42
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	–	–	+	–	+	+	–	42
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	41
Parathyroid	–	–	+	–	–	–	–	–	+	–	–	–	+	–	+	+	+	+	+	+	–	–	+	–	+	24
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																										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
Hepatocellular carcinoma, metastatic																										1
Malignant lymphoma, NOS									X																	2

* Animals necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF MONURON: 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	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Fibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X								X					X			X			
Alveolar/bronchiolar carcinoma										X															
Trachea	+	+	+	+	+	−	−	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	−	+	−	−	+	+	+	−	+	−	−	+	+	+	+	+	+	−	+	−	+	+	+	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma												X													
Hepatocellular carcinoma					X		X																		
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	N	+	+	N	N	N	N	N	+	+	+	+	N	+	+	+	+	N	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	−	+	+	−	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	−	+	+	+	+	+	−	+	+	−	+	+	+	+	−	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Thyroid	+	−	+	+	+	−	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	−	−	−	+	−	+	−	+	−	+	+	−	−	−	+	+	−	+	−	+	−	−	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS								X					X												
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS																									

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

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	103	084	095	104	104	104	104	104	104	006	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS			X																							1
Fibrosarcoma		X																								1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X												X							X	X					8
Alveolar/bronchiolar carcinoma														X												2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+		48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymph nodes	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Thymus	−	−	−	+	−	−	+	+	+	−	+	+	+	−	−	+	+	+	+	−	−	+	−	−	+	28
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hepatocellular adenoma	X								X												X					4
Hepatocellular carcinoma																										2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	+	N	N	N	N	+	N	N	+	N	N	+	+	+	N	+	+	+	+	N	N	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	44
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	−	+	+	−	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	42
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Parathyroid	+	−	+	+	−	+	−	−	+	−	+	+	+	+	−	+	+	−	+	+	−	+	−	−	+	27
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																										2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS							X																			1

* Animals necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF MONURON: UNTREATED 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	093	081	102	105	086	105	105	105	105	105	104	105	105	090	105	105	031	044	105	105	080	088	105	105	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma	X																								
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X	X	X									
Alveolar/bronchiolar carcinoma																						X			
Trachea	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	−	−	+	+	+
Thymus	−	−	−	+	−	+	−	+	+	+	+	+	+	−	+	+	−	−	+	+	−	−	+	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma				X						X													X		
Hepatocellular carcinoma				X				X																	
Malignant lymphoma, NOS																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	N	N	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	−	−	+	−	+	+	−	+
Adenoma, NOS						X																			
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	−	+	+	+	−	−	−	+	+	−	−	+	+	+	+	+	+	+	+	+	+	−	+	+
Parathyroid	−	−	+	+	−	+	−	−	+	+	−	−	−	+	−	−	+	−	−	+	+	+	−	−	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Hemangioma																				X					
Ovary	+	+	−	+	+	+	+	+	+	−	+	−	−	+	+	+	+	−	+	+	+	+	+	+	+
Papillary cystadenoma, NOS						X																			
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS			X				X						X				X								
Foot, NOS																									
Rhabdomyosarcoma																									

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

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: UNTREATED CONTROL (Continued)

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	075	105	105	100	098	105	087	105	093	105	105	040	105	086	105	068	105	105	073	080	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Hemangiosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																									X	4
Alveolar/bronchiolar carcinoma		X																								2
Trachea	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	–	+	+	+	+	+	+	+	+	+	44
Thymus	–	+	–	+	+	–	–	+	+	+	+	+	+	+	+	–	+	–	+	–	–	–	+	+	+	29
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma		X													X											5
Hepatocellular carcinoma																										2
Malignant lymphoma, NOS						X																				1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	+	+	+	N	+	+	+	N	N	+	+	+	N	+	+	+	+	+	N	+	+	N	+	*50
Pancreas	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	46
Esophagus	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	49
Large intestine	+	+	–	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	–	+	–	+	+	+	+	+	40
Adenoma, NOS																									X	2
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Parathyroid	–	–	+	–	–	+	–	–	–	+	–	–	–	–	–	+	–	–	+	–	–	+	–	–	–	17
Pancreatic islets	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	46
Islet cell adenoma									X																	1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	*50	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma																										1
Ovary	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Papillary cystadenoma, NOS				X																						2
NERVOUS SYSTEM																										
Brain	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS		X																								1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS		X		X	X					X			X		X			X	X	X			X	X		15
Foot, NOS																										
Rhabdomyosarcoma											X															1

* Animals necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF MONURON: LOW DOSE

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	105	105	088	105	078	105	105	105	105	105	086	105	089	079	077	099	095	099	105	046	105	095	082	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																	X								
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X																			X		
Alveolar/bronchiolar carcinoma																						X			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	–	+	+	+	–	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	+	+	+	–	+
Thymus	+	–	–	–	+	–	+	+	+	–	–	+	+	–	–	+	–	–	–	+	–	–	–	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	+	+	+	+	–	–	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	+	+	+	+	+	+	+	+	+	N	N	+	+	+	N	N	+	+	+	+	+	+	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	+	+	–	+	+	+	+
Esophagus	+	+	+	+	+	+	–	+	–	+	+	–	+	+	+	+	–	–	+	+	+	–	–	+	+
Stomach	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Papillary adenoma		X																							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	–	–	+	+	–	+	+	+	+
Adenoma, NOS																				X					
Adrenal	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+
Pheochromocytoma																									
Thyroid	–	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	–	–	–	+	+	+	–	–	+
Follicular cell adenoma																									
Parathyroid	–	+	–	–	+	–	–	+	+	+	–	+	+	+	–	+	–	–	–	+	–	–	–	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	+	N	N	+	N	N	N	N	N	N	N	N	N	N	N	+	N	N
Adenocarcinoma, NOS																									
Vagina	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS							X																		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+
Mixed tumor, benign																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS	X								X	X															

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

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	084	105	105	101	097	089	105	093	105	105	105	105	097	105	087	105	105	094	088	071	089	105	053	082	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar adenoma					X												X									4
Alveolar/bronchiolar carcinoma								X								X										3
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	−	−	+	+	+	−	+	−	+	+	+	+	−	+	+	+	+	39
Thymus	+	−	+	−	−	+	−	−	−	+	−	+	−	−	−	−	−	+	−	−	−	−	+	−	−	16
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma				X																						1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	N	+	N	+	+	+	N	N	+	+	N	+	+	+	+	+	N	N	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	−	+	+	+	+	−	+		43
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papillary adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	−	−	+	−	−	−	+	−	−	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	−	35
Adenoma, NOS																								X		2
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	45
Pheochromocytoma																								X		1
Thyroid	+	+	+	+	+	+	+	+	−	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	39
Follicular cell adenoma																								X		1
Parathyroid	−	−	+	+	−	−	+	+	−	−	+	+	−	+	−	+	+	+	−	+	+	+	−	−	+	26
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	+	N	N	+	+	N	N	N	N	N	N	N	+	+	N	*50
Adenocarcinoma, NOS																								X		1
Vagina	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS																										1
Uterus	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mixed tumor, benign	X																									1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS	X									X		X							X				X			8

* Animals necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF MONURON: 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	104	104	104	104	104	079	104	086	104	104	104	104	104	046	104	104	104	104	104	104	104	067	104	104	094
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma		X																							
Alveolar/bronchiolar carcinoma																									
Pheochromocytoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	–
Thymus	+	+	+	+	+	–	–	–	+	+	+	+	–	+	+	–	+	+	–	–	+	–	+	+	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																								X	
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	N	+	N	+	N	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	–	+	+	+	+	–	–	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Pheochromocytoma														X											
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	–	–	–	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+
Parathyroid	–	–	–	–	–	+	+	–	–	–	–	–	+	–	+	–	–	–	–	–	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	+	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS													X					X		X					
Malignant lymphoma, histiocytic type								X																	

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

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	104	104	104	104	104	104	104	104	104	065	104	104	104	070	104	104	104	104	088	104	104	104	104	072	104	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X							X									2
Alveolar/bronchiolar carcinoma																										1
Pheochromocytoma, metastatic														X												1
Trachea	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma															X											1
Lymph nodes	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	44
Thymus	+	−	+	−	+	+	+	+	−	−	+	+	+	−	+	+	+	−	−	+	+	+	+	−	+	33
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma															X								X			3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	−	+	+	+	44
Stomach	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	−	+	+	+	−	−	+	+	+	+	+	+	+	+	−	+	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	−	−	+	−	+	−	+	+	+	+	+	+	+	−	+	40
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma																										1
Pheochromocytoma, malignant														X												1
Thyroid	+	+	−	+	+	+	−	−	+	+	+	−	+	−	−	+	+	+	+	+	+	+	+	+	+	39
Parathyroid	−	+	−	−	+	+	−	−	+	+	+	−	−	−	−	−	−	+	+	+	+	+	+	−	−	21
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	N	+	N	N	N	N	N	N	+	N	N	+	N	N	N	N	N	N	+	N	N	N	N	*50
Adenocarcinoma, NOS														X												1
Uterus	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ovary	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS				X													X			X						6
Malignant lymphoma, histiocytic type																										1

* Animals necropsied

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS IN THE TWO-YEAR FEED STUDIES OF MONURON

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF MONURON

	UNTREATED 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%)	
POLYPOID HYPERPLASIA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(50)	(49)	(50)
INFLAMMATION, NOS		1 (2%)	
#LUNG/BRONCHIOLE	(50)	(49)	(50)
METAPLASIA, NOS	1 (2%)		
#LUNG	(50)	(49)	(50)
CONGESTION, NOS	2 (4%)		
BRONCHOPNEUMONIA, NOS	1 (2%)		
GRANULOMA, FOREIGN BODY	2 (4%)	3 (6%)	3 (6%)
HYPERPLASIA, ALVEOLAR EPITHELIUM		2 (4%)	
BRONCHIOLIZATION	1 (2%)		
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(49)	(50)	(50)
HYPERPLASIA, NOS	2 (4%)	3 (6%)	1 (2%)
HYPERPLASIA, HEMATOPOIETIC			2 (4%)
#SPLEEN	(50)	(48)	(50)
CONGESTION, NOS	3 (6%)		
FIBROSIS, FOCAL		2 (4%)	1 (2%)
HEMOSIDEROSIS	1 (2%)	3 (6%)	6 (12%)
VASCULARIZATION			1 (2%)
HEMATOPOIESIS	3 (6%)	3 (6%)	1 (2%)
#SPLENIC CAPSULE	(50)	(48)	(50)
FIBROSIS			1 (2%)
FIBROSIS, FOCAL			2 (4%)
#LYMPH NODE	(50)	(50)	(49)
CONGESTION, NOS	1 (2%)		
#MANDIBULAR LYMPH NODE	(50)	(50)	(49)
CONGESTION, NOS	2 (4%)		
HYPERPLASIA, NOS			1 (2%)
#MEDIASTINAL LYMPH NODE	(50)	(50)	(49)
CONGESTION, NOS	1 (2%)	1 (2%)	
#MESENTERIC LYMPH NODE	(50)	(50)	(49)
CONGESTION, NOS		1 (2%)	1 (2%)
#JEJUNUM	(50)	(49)	(50)
HYPERPLASIA, LYMPHOID		1 (2%)	
CIRCULATORY SYSTEM			
*PERITONEAL CAVITY	(50)	(50)	(50)
THROMBUS, ORGANIZED	1 (2%)		
#LYMPH NODE	(50)	(50)	(49)
LYMPHANGIECTASIS		1 (2%)	
#MANDIBULAR LYMPH NODE	(50)	(50)	(49)
LYMPHANGIECTASIS	1 (2%)	1 (2%)	
#MEDIASTINAL LYMPH NODE	(50)	(50)	(49)
LYMPHANGIECTASIS	1 (2%)		
#ABDOMINAL LYMPH NODE	(50)	(50)	(49)
LYMPHANGIECTASIS		1 (2%)	
#MESENTERIC LYMPH NODE	(50)	(50)	(49)
LYMPHANGIECTASIS	1 (2%)		

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF MONURON (Continued)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM (Continued)			
#HEART/ATRIUM	(50)	(50)	(50)
THROMBUS, MURAL	1 (2%)		
#MYOCARDIUM	(50)	(50)	(50)
DEGENERATION, NOS	46 (92%)	47 (94%)	40 (80%)
*PULMONARY ARTERY	(50)	(50)	(50)
CALCIFICATION, NOS			1 (2%)
*URETER	(50)	(50)	(50)
THROMBOSIS, NOS			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(49)	(50)
HERNIA, NOS	2 (4%)	4 (8%)	4 (8%)
CONGESTION, NOS			1 (2%)
INFLAMMATION, FOCAL		1 (2%)	
CHOLANGIOFIBROSIS	5 (10%)	3 (6%)	
NECROSIS, FOCAL	1 (2%)		1 (2%)
METAMORPHOSIS FATTY	18 (36%)	15 (31%)	10 (20%)
CYTOPLASMIC CHANGE, NOS		2 (4%)	
BASOPHILIC CYTO CHANGE	4 (8%)	2 (4%)	
FOCAL CELLULAR CHANGE			10 (20%)
CLEAR-CELL CHANGE		4 (8%)	7 (14%)
#BILE DUCT	(50)	(49)	(50)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)
HYPERPLASIA, NOS	23 (46%)	30 (61%)	27 (54%)
#PANCREAS	(48)	(49)	(49)
FIBROSIS, FOCAL	6 (13%)	14 (29%)	5 (10%)
#STOMACH	(50)	(49)	(50)
ULCER, NOS	1 (2%)		
INFLAMMATION, CHRONIC FOCAL			1 (2%)
EROSION	2 (4%)		
ATYPIA, NOS		1 (2%)	
HYPERPLASIA, BASAL CELL		1 (2%)	1 (2%)
HYPERKERATOSIS			1 (2%)
ACANTHOSIS			1 (2%)
#GASTRIC SUBMUCOSA	(50)	(49)	(50)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
#COLON	(48)	(47)	(48)
PARASITISM	8 (17%)	5 (11%)	5 (10%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
CYST, NOS		1 (2%)	
INFLAMMATION, CHRONIC			2 (4%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		2 (4%)
NEPHROPATHY	43 (86%)	47 (94%)	35 (70%)
NEPHROSIS, NOS	1 (2%)	1 (2%)	4 (8%)
NEPHROSIS, CHOLEMIC			1 (2%)
CALCIFICATION, FOCAL	1 (2%)		
CYTOMEGALY		48 (96%)	50 (100%)
HYPERPLASIA, TUBULAR CELL			1 (2%)
#KIDNEY/TUBULE	(50)	(50)	(50)
PIGMENTATION, NOS		1 (2%)	
HYPERPLASIA, FOCAL		1 (2%)	1 (2%)
#KIDNEY/PELVIS	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL			3 (6%)
#URINARY BLADDER	(49)	(50)	(49)
CALCULUS, UNKNOWN GROSS OR MICRO	2 (4%)	2 (4%)	
HYPERPLASIA, EPITHELIAL			1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF MONURON (Continued)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
URINARY SYSTEM (Continued)			
#URINARY BLADDER/SUBMUCOSA	(49)	(50)	(49)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(47)	(47)	(44)
CYST, NOS			2 (5%)
HEMORRHAGE			1 (2%)
HEMORRHAGIC CYST			2 (5%)
HYPERPLASIA, FOCAL	6 (13%)	5 (11%)	3 (7%)
VASCULARIZATION	2 (4%)	1 (2%)	
#ADRENAL CORTEX	(50)	(50)	(48)
CYTOPLASMIC VACUOLIZATION	1 (2%)	1 (2%)	
HYPERPLASIA, NODULAR	2 (4%)		
#ADRENAL MEDULLA	(50)	(50)	(48)
HEMORRHAGIC CYST	1 (2%)		
HYPERPLASIA, NOS	10 (20%)	12 (24%)	7 (15%)
#THYROID	(49)	(46)	(50)
CYSTIC FOLLICLES			1 (2%)
HYPERPLASIA, C-CELL		1 (2%)	1 (2%)
#PARATHYROID	(14)	(18)	(14)
HYPERPLASIA, NOS		1 (6%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
GALACTOCELE		2 (4%)	
LACTATION	1 (2%)		
*PREPUTIAL GLAND	(50)	(50)	(50)
HYPERPLASIA, NOS	1 (2%)	1 (2%)	
#PROSTATE	(48)	(44)	(45)
INFLAMMATION, NOS	1 (2%)	10 (23%)	4 (9%)
INFLAMMATION, FOCAL	3 (6%)		1 (2%)
INFLAMMATION, ACUTE	4 (8%)		2 (4%)
INFLAMMATION, ACUTE FOCAL	2 (4%)	1 (2%)	1 (2%)
ABSCESS, NOS	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC	1 (2%)	1 (2%)	1 (2%)
INFLAMMATION, CHRONIC		2 (5%)	4 (9%)
INFLAMMATION, CHRONIC FOCAL	5 (10%)	1 (2%)	1 (2%)
HYPERPLASIA, FOCAL		4 (9%)	
*SEMINAL VESICLE	(50)	(50)	(50)
ATROPHY, NOS	1 (2%)	1 (2%)	
#TESTIS	(50)	(50)	(48)
ATROPHY, NOS	5 (10%)	1 (2%)	2 (4%)
HYPERPLASIA, INTERSTITIAL CELL	3 (6%)	2 (4%)	1 (2%)
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
HYDROCEPHALUS, NOS	1 (2%)		
HEMORRHAGE	1 (2%)		1 (2%)
NECROSIS, FOCAL			1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF MONURON (Continued)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
STEATITIS		1 (2%)	
*PELVIS	(50)	(50)	(50)
HEMATOMA, NOS	1 (2%)		
*MESENTERY	(50)	(50)	(50)
NECROSIS, FAT	1 (2%)	3 (6%)	2 (4%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
CONGESTION, NOS	7 (14%)		1 (2%)
ADIPOSE TISSUE			
CONGESTION, NOS	1		
OMENTUM			
NECROSIS, FAT		1	
SPECIAL MORPHOLOGY SUMMARY			
NONE			

* NUMBER OF ANIMALS RECEIVING COMPLETE NECROPSY EXAMINATION; ALL GROSS LESIONS INCLUDING MASSES EXAMINED MICROSCOPICALLY.
# NUMBER OF ANIMALS EXAMINED MICROSCOPICALLY AT THIS SITE

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF MONURON

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
ULCER, HEALED		1 (2%)	
FIBROSIS		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
HEMORRHAGE			1 (2%)
INFLAMMATION, FOCAL		1 (2%)	7 (14%)
GRANULOMA, FOREIGN BODY		2 (4%)	4 (8%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(50)	(50)	(50)
FIBROSIS			1 (2%)
HYPOPLASIA, NOS		1 (2%)	1 (2%)
HYPEROSTOSIS		1 (2%)	
HYPERPLASIA, NOS	1 (2%)	2 (4%)	2 (4%)
#SPLEEN	(50)	(50)	(50)
LACERATED WOUND		1 (2%)	
CONGESTION, NOS	1 (2%)		
HEMATOMA, NOS		1 (2%)	
HEMOSIDEROSIS	5 (10%)	36 (72%)	44 (88%)
HEMATOPOIESIS	3 (6%)	1 (2%)	1 (2%)
#MANDIBULAR LYMPH NODE	(48)	(50)	(49)
CONGESTION, NOS	1 (2%)		
HYPERPLASIA, NOS	1 (2%)	1 (2%)	
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
PERIARTERITIS			1 (2%)
#LUNG	(50)	(50)	(50)
PERIVASCULITIS	1 (2%)	4 (8%)	
#HEART/ATRIUM	(50)	(50)	(50)
THROMBUS, MURAL	1 (2%)		
#MYOCARDIUM	(50)	(50)	(50)
DEGENERATION, NOS	26 (52%)	34 (68%)	32 (64%)
#UTERUS	(50)	(50)	(50)
THROMBOSIS, NOS	1 (2%)		
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(50)	(50)	(48)
DILATATION/DUCTS		1 (2%)	
INFLAMMATION, CHRONIC FOCAL			2 (4%)
FIBROSIS, FOCAL			1 (2%)
#LIVER	(50)	(50)	(50)
HERNIA, NOS	1 (2%)		
INFLAMMATION, FOCAL	1 (2%)	1 (2%)	1 (2%)
INFLAMMATION, ACUTE FOCAL	1 (2%)	1 (2%)	1 (2%)
CHOLANGIOFIBROSIS	1 (2%)	2 (4%)	
CIRRHOSIS, NOS	1 (2%)		
NECROSIS, FOCAL	4 (8%)		
METAMORPHOSIS FATTY	18 (36%)	9 (18%)	4 (8%)

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF MONURON (Continued)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER (Continued)	(50)	(50)	(50)
LIPOIDOSIS		1 (2%)	
CYTOPLASMIC CHANGE, NOS	2 (4%)	3 (6%)	1 (2%)
BASOPHILIC CYTO CHANGE	28 (56%)	36 (72%)	31 (62%)
CLEAR-CELL CHANGE			1 (2%)
#LIVER/CENTRILOBULAR	(50)	(50)	(50)
NECROSIS, NOS	1 (2%)	1 (2%)	
#BILE DUCT	(50)	(50)	(50)
HYPERPLASIA, NOS	5 (10%)	4 (8%)	5 (10%)
HYPERPLASIA, FOCAL		1 (2%)	
#PANCREAS	(47)	(50)	(50)
FIBROSIS, FOCAL	7 (15%)	10 (20%)	10 (20%)
#STOMACH	(49)	(50)	(50)
CONGESTION, NOS			1 (2%)
ULCER, NOS	1 (2%)	1 (2%)	1 (2%)
HYPERPLASIA, BASAL CELL	1 (2%)	1 (2%)	
#GASTRIC SUBMUCOSA	(49)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		
#COLON	(50)	(50)	(48)
PARASITISM	4 (8%)	3 (6%)	1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
HYDRONEPHROSIS	2 (4%)	1 (2%)	1 (2%)
CYST, NOS		1 (2%)	1 (2%)
INFLAMMATION, CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
NEPHROPATHY	20 (40%)	24 (48%)	21 (42%)
NEPHROSIS, NOS	4 (8%)	1 (2%)	1 (2%)
NEPHROSIS, CHOLEMIC		1 (2%)	
CALCIFICATION, FOCAL	13 (26%)	18 (36%)	17 (34%)
CYTOMEGALY		12 (24%)	48 (96%)
#KIDNEY/CORTEX	(50)	(50)	(50)
FIBROSIS	1 (2%)		
#KIDNEY/TUBULE	(50)	(50)	(50)
CYST, NOS			1 (2%)
NEPHROSIS, NOS	1 (2%)		
NECROSIS, FOCAL	1 (2%)		
PIGMENTATION, NOS	2 (4%)		2 (4%)
CYTOMEGALY			1 (2%)
*URETER	(50)	(50)	(50)
INFLAMMATION, ACUTE	1 (2%)		
#URINARY BLADDER	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL		1 (2%)	
#URINARY BLADDER/MUCOSA	(50)	(50)	(50)
HYPERPLASIA, DIFFUSE	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(48)	(45)
CYST, NOS	10 (20%)	5 (10%)	8 (18%)
HEMORRHAGIC CYST		2 (4%)	
HYPERPLASIA, FOCAL	4 (8%)	5 (10%)	1 (2%)
VASCULARIZATION	1 (2%)	2 (4%)	3 (7%)
#ADRENAL	(50)	(50)	(48)
CONGESTION, NOS			1 (2%)
#ADRENAL CORTEX	(50)	(50)	(48)
INFLAMMATION, FOCAL	1 (2%)		
CYTOPLASMIC VACUOLIZATION	7 (14%)		4 (8%)
FOCAL CELLULAR CHANGE			1 (2%)

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF MONURON (Continued)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#ADRENAL CORTEX (Continued)	(50)	(50)	(48)
HYPERPLASIA, NODULAR	6 (12%)	2 (4%)	
HYPERPLASIA, FOCAL		2 (4%)	
#ADRENAL MEDULLA	(50)	(50)	(48)
HYPERPLASIA, NOS	7 (14%)	4 (8%)	4 (8%)
#THYROID	(49)	(48)	(47)
HYPERPLASIA, C-CELL	3 (6%)	6 (13%)	3 (6%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
GALACTOCELE	12 (24%)	11 (22%)	9 (18%)
#UTERUS	(50)	(50)	(50)
DILATATION, NOS	1 (2%)		4 (8%)
HYDROMETRA			1 (2%)
#UTERUS/ENDOMETRIUM	(50)	(50)	(50)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, CYSTIC	4 (8%)	7 (14%)	3 (6%)
POLYPOID HYPERPLASIA			1 (2%)
#OVARY	(50)	(50)	(48)
CYST, NOS	4 (8%)	3 (6%)	2 (4%)
NERVOUS SYSTEM			
#BRAIN	(49)	(49)	(50)
HYDROCEPHALUS, NOS	2 (4%)	3 (6%)	4 (8%)
GLIOSIS			1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PLEURA	(50)	(50)	(50)
CALCIFICATION, FOCAL	1 (2%)		
*MESENTERY	(50)	(50)	(50)
NECROSIS, FAT	7 (14%)	3 (6%)	2 (4%)
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NONE			

* NUMBER OF ANIMALS RECEIVING COMPLETE NECROPSY EXAMINATION; ALL GROSS LESIONS INCLUDING MASSES EXAMINED MICROSCOPICALLY.
# NUMBER OF ANIMALS EXAMINED MICROSCOPICALLY AT THIS SITE

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE IN THE TWO-YEAR FEED STUDIES OF MONURON

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF MONURON

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*SUBCUTANEOUS TISSUE	(50)	(50)	(50)
ABSCESS, NOS	1 (2%)	2 (4%)	
INFLAMMATION, CHRONIC	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(49)	(50)
INFLAMMATION, INTERSTITIAL	2 (4%)	1 (2%)	
PNEUMONIA INTERSTITIAL CHRONIC	1 (2%)		
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(50)	(48)	(50)
HEMORRHAGE			1 (2%)
HEMOSIDEROSIS		1 (2%)	
HYPERPLASIA, LYMPHOID	1 (2%)		1 (2%)
HEMATOPOIESIS	5 (10%)	4 (8%)	3 (6%)
#LYMPH NODE	(45)	(43)	(48)
CYST, NOS		1 (2%)	
HYPERPLASIA, NOS	1 (2%)		
#MANDIBULAR LYMPH NODE	(45)	(43)	(48)
HYPERPLASIA, PLASMA CELL			1 (2%)
#MEDIASTINAL LYMPH NODE	(45)	(43)	(48)
NECROSIS, NOS	1 (2%)		
#LUMBAR LYMPH NODE	(45)	(43)	(48)
HYPERPLASIA, LYMPHOID	1 (2%)		
#MESENTERIC LYMPH NODE	(45)	(43)	(48)
CONGESTION, NOS	1 (2%)	1 (2%)	1 (2%)
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, LYMPHOID	6 (13%)	1 (2%)	
#MIDCOLIC LYMPH NODE	(45)	(43)	(48)
HYPERPLASIA, NOS	1 (2%)		
#PEYER'S PATCH	(50)	(47)	(49)
HYPERPLASIA, LYMPHOID		1 (2%)	
#KIDNEY/TUBULE	(50)	(49)	(50)
BASOPHILIC STIPPLING			1 (2%)
CIRCULATORY SYSTEM			
#MYOCARDIUM	(50)	(49)	(50)
INFLAMMATION, ACUTE			1 (2%)
INFLAMMATION, ACUTE FOCAL			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
NECROSIS, FOCAL	1 (2%)		
#CARDIAC VALVE	(50)	(49)	(50)
ENDOCARDITIS, BACTERIAL		3 (6%)	
*PORTAL VEIN	(50)	(50)	(50)
THROMBOSIS, NOS	1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF MONURON (Continued)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(50)	(49)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
DEGENERATION, NOS	1 (2%)	4 (8%)	13 (26%)
NECROSIS, NOS	1 (2%)		
NECROSIS, FOCAL	1 (2%)		
INFARCT, NOS	1 (2%)		
METAMORPHOSIS FATTY	2 (4%)		
CYTOPLASMIC VACUOLIZATION	1 (2%)		
BASOPHILIC CYTO CHANGE	1 (2%)	1 (2%)	
HEPATOCYTOMEGALY	1 (2%)	3 (6%)	4 (8%)
#LIVER/CENTRILOBULAR	(50)	(49)	(50)
NECROSIS, NOS		1 (2%)	1 (2%)
METAMORPHOSIS FATTY	7 (14%)		1 (2%)
*GALLBLADDER	(50)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
#BILE DUCT	(50)	(49)	(50)
HYPERPLASIA, NOS	1 (2%)		
#PANCREAS	(48)	(48)	(49)
INFLAMMATION, ACUTE	1 (2%)		
#GASTRIC MUCOSA	(50)	(48)	(50)
NECROSIS, FOCAL			1 (2%)
#GASTRIC FUNDAL GLAND	(50)	(48)	(50)
INFLAMMATION, ACUTE FOCAL	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(50)	(49)	(50)
CALCULUS,UNKNOWN GROSS OR MICRO		1 (2%)	
INFLAMMATION, INTERSTITIAL	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)	4 (8%)	1 (2%)
PYELONEPHRITIS, CHRONIC		1 (2%)	1 (2%)
INFLAMMATION, CHRONIC FOCAL	3 (6%)		
FIBROSIS, FOCAL	2 (4%)		
SCAR	1 (2%)		
FIBROSIS, DIFFUSE		1 (2%)	
GLOMERULOSCLEROSIS, NOS	3 (6%)		
#KIDNEY/CORTEX	(50)	(49)	(50)
INFLAMMATION, CHRONIC		1 (2%)	1 (2%)
INFLAMMATION, CHRONIC FOCAL		4 (8%)	
FIBROSIS, FOCAL		1 (2%)	
SCAR		4 (8%)	3 (6%)
METAPLASIA, OSSEOUS	1 (2%)		
#KIDNEY/TUBULE	(50)	(49)	(50)
DILATATION, NOS		1 (2%)	
NEPHROSIS, NOS		1 (2%)	
ENDOCRINE SYSTEM			
#THYROID	(46)	(41)	(45)
CYSTIC FOLLICLES	1 (2%)		
FOLLICULAR CYST, NOS			1 (2%)
#PANCREATIC ISLETS	(48)	(48)	(49)
HYPERPLASIA, NOS	3 (6%)		
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)		1 (2%)
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, EPITHELIAL	1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF MONURON (Continued)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)			
#PROSTATE	(49)	(47)	(49)
INFLAMMATION, SUPPURATIVE	1 (2%)		
INFLAMMATION, ACUTE	2 (4%)		
#TESTIS	(50)	(49)	(50)
HYPERPLASIA, INTERSTITIAL CELL		1 (2%)	
#TESTIS/TUBULE	(50)	(49)	(50)
DEGENERATION, NOS		4 (8%)	
CALCIFICATION, NOS		2 (4%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EAR	(50)	(50)	(50)
ACANTHOSIS			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
*PERITONEUM	(50)	(50)	(50)
NECROSIS, FAT	1 (2%)		
*MESENTERY	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
NECROSIS, FAT	1 (2%)	1 (2%)	
ALL OTHER SYSTEMS			
OMENTUM			
NECROSIS, FAT			1
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	5	7	15
AUTO/NECROPSY/HISTO PERF		1	
AUTO/NECROPSY/NO HISTO		1	

* NUMBER OF ANIMALS RECEIVING COMPLETE NECROPSY EXAMINATION; ALL GROSS LESIONS INCLUDING MASSES EXAMINED MICROSCOPICALLY.
# NUMBER OF ANIMALS EXAMINED MICROSCOPICALLY AT THIS SITE

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF MONURON

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SUBCUTANEOUS TISSUE	(50)	(50)	(50)
INFLAMMATION, ACUTE		1 (2%)	
ABSCESS, NOS		1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
#LUNG/BRONCHIOLE	(50)	(48)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
#LUNG	(50)	(48)	(50)
INFLAMMATION, INTERSTITIAL		1 (2%)	
INFLAMMATION, ACUTE		1 (2%)	
INFLAMMATION, ACUTE DIFFUSE		1 (2%)	
PNEUMONIA INTERSTITIAL CHRONIC	1 (2%)		
#LUNG/ALVEOLI	(50)	(48)	(50)
HISTIOCYTOSIS	1 (2%)	4 (8%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(50)	(48)	(48)
HEMATOPOIESIS			1 (2%)
#SPLEEN	(50)	(50)	(49)
HEMORRHAGE	1 (2%)		
INFLAMMATION, GRANULOMATOUS		1 (2%)	
HEMOSIDEROSIS			1 (2%)
HYPERPLASIA, LYMPHOID	1 (2%)		
HEMATOPOIESIS	12 (24%)	13 (26%)	10 (20%)
ERYTHROPOIESIS			1 (2%)
#SPLENIC SEROSA	(50)	(50)	(49)
INFLAMMATION, ACUTE		1 (2%)	
#LYMPH NODE	(44)	(39)	(44)
CYST, NOS	1 (2%)		
HYPERPLASIA, NOS		1 (3%)	
HYPERPLASIA, PLASMA CELL	1 (2%)	1 (3%)	1 (2%)
HYPERPLASIA, LYMPHOID			1 (2%)
#MANDIBULAR LYMPH NODE	(44)	(39)	(44)
HYPERPLASIA, NOS		1 (3%)	
#MEDIASTINAL LYMPH NODE	(44)	(39)	(44)
INFLAMMATION, ACUTE	1 (2%)		
HYPERPLASIA, PLASMA CELL	1 (2%)		
HYPERPLASIA, LYMPHOID			1 (2%)
#LUMBAR LYMPH NODE	(44)	(39)	(44)
HYPERPLASIA, PLASMA CELL			1 (2%)
#MESENTERIC LYMPH NODE	(44)	(39)	(44)
CONGESTION, NOS		1 (3%)	
HYPERPLASIA, LYMPHOID	3 (7%)		
#RENAL LYMPH NODE	(44)	(39)	(44)
HYPERPLASIA, PLASMA CELL		3 (8%)	
#ILIAC LYMPH NODE	(44)	(39)	(44)
HYPERPLASIA, PLASMA CELL		1 (3%)	
#LIVER	(50)	(50)	(50)
HEMATOPOIESIS	2 (4%)	3 (6%)	3 (6%)
#OMENTUM	(50)	(49)	(49)
LYMPHOCYTOSIS	1 (2%)		

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF MONURON (Continued)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
#LUNG	(50)	(48)	(50)
PERIVASCULITIS		1 (2%)	1 (2%)
#HEART	(50)	(48)	(50)
INFLAMMATION, ACUTE FOCAL			1 (2%)
PERIARTERITIS	1 (2%)		
CALCIFICATION, FOCAL		1 (2%)	1 (2%)
#MYOCARDIUM	(50)	(48)	(50)
INFLAMMATION, ACUTE	1 (2%)		
INFLAMMATION, ACUTE FOCAL		2 (4%)	
NECROSIS, FOCAL	1 (2%)		
#CARDIAC VALVE	(50)	(48)	(50)
ENDOCARDITIS, BACTERIAL	1 (2%)		
#UTERUS	(49)	(48)	(49)
THROMBOSIS, NOS			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (2%)		2 (4%)
NECROSIS, FOCAL	1 (2%)	1 (2%)	
METAMORPHOSIS FATTY	8 (16%)		
FOCAL CELLULAR CHANGE	1 (2%)		
HEPATOCYTOMEGALY	1 (2%)		
ANGIECTASIS		1 (2%)	
#HEPATIC SEROSA	(50)	(50)	(50)
INFLAMMATION, FIBRINOUS		1 (2%)	
INFLAMMATION, ACUTE	7 (14%)	8 (16%)	1 (2%)
#LIVER/CENTRILOBULAR	(50)	(50)	(50)
METAMORPHOSIS FATTY	1 (2%)		
ATROPHY, NOS	1 (2%)		
*GALLBLADDER/SEROSA	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		
INFLAMMATION, ACUTE			1 (2%)
#BILE DUCT	(50)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	1 (2%)
#PANCREAS	(46)	(45)	(49)
INFLAMMATION, SUPPURATIVE		1 (2%)	
INFLAMMATION, ACUTE	1 (2%)		
INFLAMMATION, ACUTE FOCAL	1 (2%)		
INFLAMMATION, CHRONIC	2 (4%)	1 (2%)	
NECROSIS, FAT	1 (2%)		
#PANCREATIC ACINUS	(46)	(45)	(49)
ATROPHY, NOS	1 (2%)		
#GASTRIC SUBMUCOSA	(50)	(49)	(49)
INFLAMMATION, ACUTE FOCAL		1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	
#GASTRIC SEROSA	(50)	(49)	(49)
INFLAMMATION, ACUTE			1 (2%)
#FORESTOMACH	(50)	(49)	(49)
INFLAMMATION, ACUTE		1 (2%)	
ACANTHOSIS	1 (2%)		1 (2%)
#DUODENAL SEROSA	(49)	(49)	(49)
INFLAMMATION, ACUTE	1 (2%)		
#ILEUM	(49)	(49)	(49)
AMYLOIDOSIS	1 (2%)		

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF MONURON (Continued)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#KIDNEY	(50)	(49)	(50)
PYELONEPHRITIS, NOS			1 (2%)
PYELONEPHRITIS, ACUTE		1 (2%)	
INFLAMMATION, CHRONIC	2 (4%)		
INFLAMMATION, CHRONIC FOCAL		1 (2%)	1 (2%)
INFLAMMATION, GRANULOMATOUS		1 (2%)	
SCAR		1 (2%)	
GLOMERULOSCLEROSIS, NOS		3 (6%)	1 (2%)
#PERIRENAL TISSUE	(50)	(49)	(50)
INFLAMMATION, ACUTE		1 (2%)	
ABSCESS, NOS			1 (2%)
INFLAMMATION, CHRONIC	1 (2%)		
#URINARY BLADDER/SEROSA	(50)	(49)	(49)
INFLAMMATION, ACUTE		2 (4%)	1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(40)	(35)	(40)
ANGIECTASIS		1 (3%)	
#ADRENAL	(50)	(45)	(49)
METAMORPHOSIS FATTY	1 (2%)		
ANGIECTASIS		1 (2%)	
#ADRENAL SEROSA	(50)	(45)	(49)
INFLAMMATION, ACUTE		2 (4%)	
#PERIADRENAL TISSUE	(50)	(45)	(49)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
#THYROID	(42)	(39)	(39)
CYSTIC FOLLICLES			1 (3%)
FOLLICULAR CYST, NOS			1 (3%)
HYPERPLASIA, FOLLICULAR-CELL	2 (5%)		
REPRODUCTIVE SYSTEM			
#UTERUS	(49)	(48)	(49)
DILATATION, NOS			1 (2%)
HYDROMETRA		2 (4%)	5 (10%)
INFLAMMATION, SUPPURATIVE			1 (2%)
INFLAMMATION, ACUTE			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
HYPERPLASIA, ADENOMATOUS			1 (2%)
#UTERUS/ENDOMETRIUM	(49)	(48)	(49)
INFLAMMATION, SUPPURATIVE	3 (6%)	12 (25%)	11 (22%)
HYPERPLASIA, CYSTIC	30 (61%)	31 (65%)	26 (53%)
#FALLOPIAN TUBE	(49)	(48)	(49)
HYPERPLASIA, ADENOMATOUS	3 (6%)		
#OVARY/PAROVARIAN	(44)	(48)	(47)
INFLAMMATION, ACUTE		1 (2%)	
#OVARY	(44)	(48)	(47)
CYST, NOS	6 (14%)	5 (10%)	9 (19%)
FOLLICULAR CYST, NOS		1 (2%)	1 (2%)
HEMORRHAGIC CYST	2 (5%)		1 (2%)
INFLAMMATION, SUPPURATIVE	12 (27%)	23 (48%)	5 (11%)
INFLAMMATION, ACUTE			1 (2%)
ABSCESS, NOS			1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	
NERVOUS SYSTEM			
NONE			

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF MONURON (Continued)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(50)	(50)	(50)
INFLAMMATION, ACUTE		2 (4%)	
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
*ABDOMINAL CAVITY	(50)	(50)	(50)
ABSCESS, NOS			1 (2%)
*ABDOMINAL SEROSA	(50)	(50)	(50)
INFLAMMATION, ACUTE		2 (4%)	1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	
*ABDOMINAL WALL	(50)	(50)	(50)
ABSCESS, NOS		2 (4%)	
*PERITONEUM	(50)	(50)	(50)
INFLAMMATION, ACUTE	1 (2%)	1 (2%)	1 (2%)
ABSCESS, NOS		1 (2%)	
*INGUINAL REGION	(50)	(50)	(50)
ABSCESS, NOS		1 (2%)	
*PERICARDIUM	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL			1 (2%)
*MESENTERY	(50)	(50)	(50)
INFLAMMATION, ACUTE		2 (4%)	
INFLAMMATION, CHRONIC	2 (4%)		
NECROSIS, FAT	6 (12%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
INFLAMMATION, ACUTE		1 (2%)	
ADIPOSE TISSUE			
INFLAMMATION, ACUTE			1
OMENTUM			
INFLAMMATION, ACUTE	2	1	1
INFLAMMATION, CHRONIC		1	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED			2

* NUMBER OF ANIMALS RECEIVING COMPLETE NECROPSY EXAMINATION; ALL GROSS LESIONS INCLUDING MASSES EXAMINED MICROSCOPICALLY.
# NUMBER OF ANIMALS EXAMINED MICROSCOPICALLY AT THIS SITE

APPENDIX E

ANALYSES OF PRIMARY TUMORS IN RATS AND MICE IN THE TWO-YEAR FEED STUDIES OF MONURON

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF MONURON

	Control	750 ppm	1,500 ppm
Skin: Keratoacanthoma			
Overall Rates (a)	1/50 (2%)	4/50 (8%)	0/50 (0%)
Adjusted Rates (b)	3.6%	8.7%	0.0%
Terminal Rates (c)	1/28 (4%)	3/45 (7%)	0/41 (0%)
Life Table Tests (d)	P=0.264N	P=0.347	P=0.424N
Incidental Tumor Tests (d)	P=0.346N	P=0.183	P=0.424N
Cochran-Armitage Trend Test (d)	P=0.390N		
Fisher Exact Tests		P=0.181	P=0.500N
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	5/50 (10%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	14.7%	0.0%	0.0%
Terminal Rates (c)	3/28 (11%)	0/45 (0%)	0/41 (0%)
Life Table Tests (d)	P=0.002N	P=0.014N	P=0.016N
Incidental Tumor Tests (d)	P=0.011N	P=0.041N	P=0.044N
Cochran-Armitage Trend Test (d)	P=0.006N		
Fisher Exact Tests		P=0.028N	P=0.028N
Liver: Neoplastic Nodule			
Overall Rates (a)	1/50 (2%)	6/49 (12%)	7/50 (14%)
Adjusted Rates (b)	3.6%	13.6%	17.1%
Terminal Rates (c)	1/28 (4%)	6/44 (14%)	7/41 (17%)
Life Table Tests (d)	P=0.076	P=0.161	P=0.092
Incidental Tumor Tests (d)	P=0.076	P=0.161	P=0.092
Cochran-Armitage Trend Test (d)	P=0.030		
Fisher Exact Tests		P=0.053	P=0.030
Liver: Carcinoma			
Overall Rates (a)	0/50 (0%)	1/49 (2%)	3/50 (6%)
Adjusted Rates (b)	0.0%	2.3%	7.3%
Terminal Rates (c)	0/28 (0%)	1/44 (2%)	3/41 (7%)
Life Table Tests (d)	P=0.091	P=0.590	P=0.196
Incidental Tumor Tests (d)	P=0.091	P=0.590	P=0.196
Cochran-Armitage Trend Test (d)	P=0.061		
Fisher Exact Tests		P=0.495	P=0.121
Liver: Neoplastic Nodule or Carcinoma			
Overall Rates (a)	1/50 (2%)	6/49 (12%)	9/50 (18%)
Adjusted Rates (b)	3.6%	13.6%	22.0%
Terminal Rates (c)	1/28 (4%)	6/44 (14%)	9/41 (22%)
Life Table Tests (d)	P=0.025	P=0.161	P=0.038
Incidental Tumor Tests (d)	P=0.025	P=0.161	P=0.038
Cochran-Armitage Trend Test (d)	P=0.008		
Fisher Exact Tests		P=0.053	P=0.008
Kidney: Tubular Cell Adenoma			
Overall Rates (a)	0/50 (0%)	2/50 (4%)	7/50 (14%)
Adjusted Rates (b)	0.0%	4.4%	17.1%
Terminal Rates (c)	0/28 (0%)	2/45 (4%)	7/41 (17%)
Life Table Tests (d)	P=0.007	P=0.348	P=0.030
Incidental Tumor Tests (d)	P=0.007	P=0.348	P=0.030
Cochran-Armitage Trend Test (d)	P=0.003		
Fisher Exact Tests		P=0.247	P=0.006
Kidney: Tubular Cell Adenocarcinoma			
Overall Rates (a)	0/50 (0%)	1/50 (2%)	8/50 (16%)
Adjusted Rates (b)	0.0%	2.2%	18.5%
Terminal Rates (c)	0/28 (0%)	1/45 (2%)	6/41 (15%)
Life Table Tests (d)	P=0.002	P=0.595	P=0.021
Incidental Tumor Tests (d)	P=0.001	P=0.595	P=0.008
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Tests		P=0.500	P=0.003

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF MONURON (Continued)

	Control	750 ppm	1,500 ppm
Kidney: Tubular Cell Adenoma or Adenocarcinoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	15/50 (30%)
Adjusted Rates (b)	0.0%	6.7%	34.8%
Terminal Rates (c)	0/28 (0%)	3/45 (7%)	13/41 (32%)
Life Table Tests (d)	P<0.001	P=0.217	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.217	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Tests		P=0.121	P<0.001
Pituitary: Adenoma			
Overall Rates (a)	12/47 (26%)	11/47 (23%)	10/44 (23%)
Adjusted Rates (b)	36.8%	24.3%	24.0%
Terminal Rates (c)	8/26 (31%)	10/44 (23%)	6/35 (17%)
Life Table Tests (d)	P=0.159N	P=0.124N	P=0.190N
Incidental Tumor Tests (d)	P=0.543	P=0.322N	P=0.591
Cochran-Armitage Trend Test (d)	P=0.424N		
Fisher Exact Tests		P=0.500N	P=0.474N
Pituitary: Adenoma or Carcinoma			
Overall Rates (a)	12/47 (26%)	12/47 (26%)	10/44 (23%)
Adjusted Rates (b)	36.8%	26.5%	24.0%
Terminal Rates (c)	8/26 (31%)	11/44 (25%)	6/35 (17%)
Life Table Tests (d)	P=0.156N	P=0.167N	P=0.190N
Incidental Tumor Tests (d)	P=0.551N	P=0.396N	P=0.591
Cochran-Armitage Trend Test (d)	P=0.427N		
Fisher Exact Tests		P=0.593N	P=0.474N
Adrenal: Cortical Adenoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	0/48 (0%)
Adjusted Rates (b)	0.0%	6.7%	0.0%
Terminal Rates (c)	0/28 (0%)	3/45 (7%)	0/39 (0%)
Life Table Tests (d)	P=0.562N	P=0.217	(e)
Incidental Tumor Tests (d)	P=0.562N	P=0.217	(e)
Cochran-Armitage Trend Test (d)	P=0.629		
Fisher Exact Tests		P=0.121	(e)
Adrenal: Pheochromocytoma			
Overall Rates (a)	15/50 (30%)	13/50 (26%)	4/48 (8%)
Adjusted Rates (b)	47.2%	27.6%	9.3%
Terminal Rates (c)	12/28 (43%)	11/45 (24%)	2/39 (5%)
Life Table Tests (d)	P<0.001N	P=0.061N	P<0.001N
Incidental Tumor Tests (d)	P=0.006N	P=0.211N	P=0.005N
Cochran-Armitage Trend Test (d)	P=0.007N		
Fisher Exact Tests		P=0.412N	P=0.006N
Adrenal: Pheochromocytoma or Pheochromocytoma Malignant			
Overall Rates (a)	16/50 (32%)	14/50 (28%)	5/48 (10%)
Adjusted Rates (b)	48.3%	29.7%	11.8%
Terminal Rates (c)	12/28 (43%)	12/45 (27%)	3/39 (8%)
Life Table Tests (d)	P<0.001N	P=0.061N	P<0.001N
Incidental Tumor Tests (d)	P=0.010N	P=0.233N	P=0.010N
Cochran-Armitage Trend Test (d)	P=0.009N		
Fisher Exact Tests		P=0.414N	P=0.008N
Thyroid: C-Cell Adenoma			
Overall Rates (a)	4/49 (8%)	3/46 (7%)	2/50 (4%)
Adjusted Rates (b)	12.7%	7.3%	4.9%
Terminal Rates (c)	3/28 (11%)	3/41 (7%)	2/41 (5%)
Life Table Tests (d)	P=0.141N	P=0.322N	P=0.201N
Incidental Tumor Tests (d)	P=0.219N	P=0.399N	P=0.329N
Cochran-Armitage Trend Test (d)	P=0.258N		
Fisher Exact Tests		P=0.536N	P=0.330N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF MONURON (Continued)

	Control	750 ppm	1,500 ppm
Thyroid: C-Cell Carcinoma			
Overall Rates (a)	6/49 (12%)	3/46 (7%)	1/50 (2%)
Adjusted Rates (b)	19.9%	7.3%	2.0%
Terminal Rates (c)	4/28 (14%)	3/41 (7%)	0/41 (0%)
Life Table Tests (d)	P=0.011N	P=0.095N	P=0.022N
Incidental Tumor Tests (d)	P=0.032N	P=0.242N	P=0.053N
Cochran-Armitage Trend Test (d)	P=0.035N		
Fisher Exact Tests		P=0.276N	P=0.053N
Thyroid: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	10/49 (20%)	6/46 (13%)	3/50 (6%)
Adjusted Rates (b)	31.4%	14.6%	6.8%
Terminal Rates (c)	7/28 (25%)	6/41 (15%)	2/41 (5%)
Life Table Tests (d)	P=0.004N	P=0.053N	P=0.008N
Incidental Tumor Tests (d)	P=0.017N	P=0.157N	P=0.031N
Cochran-Armitage Trend Test, (d)	P=0.024N		
Fisher Exact Tests		P=0.248N	P=0.033N
Pancreatic Islets: Islet Cell Carcinoma			
Overall Rates (a)	3/48 (6%)	2/49 (4%)	0/49 (0%)
Adjusted Rates (b)	8.3%	4.5%	0.0%
Terminal Rates (c)	1/27 (4%)	2/44 (5%)	0/41 (0%)
Life Table Tests (d)	P=0.045N	P=0.351N	P=0.086N
Incidental Tumor Tests (d)	P=0.101N	P=0.653N	P=0.163N
Cochran-Armitage Trend Test, (d)	P=0.079N		
Fisher Exact Tests		P=0.490N	P=0.117N
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Overall Rates (a)	3/48 (6%)	2/49 (4%)	2/49 (4%)
Adjusted Rates (b)	8.3%	4.5%	4.9%
Terminal Rates (c)	1/27 (4%)	2/44 (5%)	2/41 (5%)
Life Table Tests (d)	P=0.276N	P=0.351N	P=0.365N
Incidental Tumor Tests (d)	P=0.392N	P=0.653N	P=0.497N
Cochran-Armitage Trend Test, (d)	P=0.397N		
Fisher Exact Tests		P=0.490N	P=0.490N
Preputial Gland: Carcinoma			
Overall Rates (a)	5/50 (10%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	13.1%	4.4%	7.3%
Terminal Rates (c)	2/28 (7%)	2/45 (4%)	3/41 (7%)
Life Table Tests (d)	P=0.165N	P=0.121N	P=0.227N
Incidental Tumor Tests (d)	P=0.345N	P=0.378N	P=0.447N
Cochran-Armitage Trend Test, (d)	P=0.274N		
Fisher Exact Tests		P=0.218N	P=0.357N
Preputial Gland: Adenoma or Carcinoma			
Overall Rates (a)	7/50 (14%)	2/50 (4%)	4/50 (8%)
Adjusted Rates (b)	18.1%	4.4%	9.8%
Terminal Rates (c)	3/28 (11%)	2/45 (4%)	4/41 (10%)
Life Table Tests (d)	P=0.096N	P=0.036N	P=0.141N
Incidental Tumor Tests (d)	P=0.239N	P=0.210N	P=0.313N
Cochran-Armitage Trend Test, (d)	P=0.187N		
Fisher Exact Tests		P=0.080N	P=0.262N
Testis: Interstitial Cell Tumor			
Overall Rates (a)	45/50 (90%)	46/50 (92%)	43/48 (90%)
Adjusted Rates (b)	100.0%	95.8%	95.5%
Terminal Rates (c)	28/28 (100%)	43/45 (96%)	39/41 (95%)
Life Table Tests (d)	P<0.001N	P<0.001N	P<0.001N
Incidental Tumor Tests (d)	P=0.086N	P=0.398N	P=0.111N
Cochran-Armitage Trend Test, (d)	P=0.543N		
Fisher Exact Tests		P=0.500	P=0.604N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF MONURON (Continued)

	Control	750 ppm	1,500 ppm
All Sites: Mesothelioma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	3.6%	6.7%	2.0%
Terminal Rates (c)	1/28 (4%)	3/45 (7%)	0/41 (0%)
Life Table Tests (d)	P=0.498N	P=0.486	P=0.700N
Incidental Tumor Tests (d)	P=0.566N	P=0.486	P=0.747
Cochran-Armitage Trend Test, (d)	P=0.610		
Fisher Exact Tests		P=0.309	P=0.753

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the 1,500-ppm and control groups.

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF MONURON

	Control	750 ppm	1,500 ppm
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	10/50 (20%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	24.5%	4.3%	4.4%
Terminal Rates (c)	8/38 (21%)	1/44 (2%)	1/42 (2%)
Life Table Tests (d)	P=0.004N	P=0.010N	P=0.013N
Incidental Tumor Tests (d)	P=0.006N	P=0.020N	P=0.016N
Cochran-Armitage Trend Test (d)	P=0.005N		
Fisher Exact Tests		P=0.014N	P=0.014N
Hematopoietic System: Leukemia			
Overall Rates (a)	11/50 (22%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	26.3%	4.3%	4.4%
Terminal Rates (c)	8/38 (21%)	1/44 (2%)	1/42 (2%)
Life Table Tests (d)	P=0.002N	P=0.006N	P=0.007N
Incidental Tumor Tests (d)	P=0.004N	P=0.013N	P=0.013N
Cochran-Armitage Trend Test (d)	P=0.002N		
Fisher Exact Tests		P=0.007N	P=0.007N
Liver: Neoplastic Nodule			
Overall Rates (a)	4/50 (8%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	10.5%	2.3%	4.6%
Terminal Rates (c)	4/38 (11%)	1/44 (2%)	1/42 (2%)
Life Table Tests (d)	P=0.210N	P=0.138N	P=0.302N
Incidental Tumor Tests (d)	P=0.212N	P=0.138N	P=0.301N
Cochran-Armitage Trend Test (d)	P=0.238N		
Fisher Exact Tests		P=0.181N	P=0.339N
Pituitary: Adenoma			
Overall Rates (a)	23/49 (47%)	22/48 (46%)	16/45 (36%)
Adjusted Rates (b)	54.4%	49.8%	39.3%
Terminal Rates (c)	19/38 (50%)	20/42 (48%)	13/37 (35%)
Life Table Tests (d)	P=0.109N	P=0.334N	P=0.133N
Incidental Tumor Tests (d)	P=0.151N	P=0.458N	P=0.180N
Cochran-Armitage Trend Test (d)	P=0.159N		
Fisher Exact Tests		P=0.538N	P=0.182N
Pituitary: Adenoma or Carcinoma			
Overall Rates (a)	23/49 (47%)	23/48 (48%)	16/45 (36%)
Adjusted Rates (b)	54.4%	52.1%	39.3%
Terminal Rates (c)	19/38 (50%)	21/42 (50%)	13/37 (35%)
Life Table Tests (d)	P=0.110N	P=0.404N	P=0.133N
Incidental Tumor Tests (d)	P=0.151N	P=0.534N	P=0.180N
Cochran-Armitage Trend Test (d)	P=0.161N		
Fisher Exact Tests		P=0.542	P=0.182N
Adrenal: Pheochromocytoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	1/48 (2%)
Adjusted Rates (b)	7.6%	0.0%	2.5%
Terminal Rates (c)	2/38 (5%)	0/44 (0%)	1/40 (3%)
Life Table Tests (d)	P=0.162N	P=0.100N	P=0.287N
Incidental Tumor Tests (d)	P=0.236N	P=0.133N	P=0.413N
Cochran-Armitage Trend Test (d)	P=0.184N		
Fisher Exact Tests		P=0.121N	P=0.324N
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant			
Overall Rates (a)	4/50 (8%)	0/50 (0%)	2/48 (4%)
Adjusted Rates (b)	10.2%	0.0%	5.0%
Terminal Rates (c)	3/38 (8%)	0/44 (0%)	2/40 (5%)
Life Table Tests (d)	P=0.203N	P=0.049N	P=0.313N
Incidental Tumor Tests (d)	P=0.273N	P=0.065N	P=0.420N
Cochran-Armitage Trend Test (d)	P=0.234N		
Fisher Exact Tests		P=0.059N	P=0.359N

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS (IN THE TWO-YEAR FEED STUDY OF MONURON (Continued)

	Control	750 ppm	1,500 ppm
Thyroid: C-Cell Adenoma			
Overall Rates (a)	2/49 (4%)	3/48 (6%)	1/47 (2%)
Adjusted Rates (b)	5.3%	7.1%	2.6%
Terminal Rates (c)	2/38 (5%)	3/42 (7%)	1/39 (3%)
Life Table Tests (d)	P=0.388N	P=0.546	P=0.491N
Incidental Tumor Tests (d)	P=0.388N	P=0.546	P=0.491N
Cochran-Armitage Trend Test (d)	P=0.416N		
Fisher Exact Tests		P=0.490	P=0.516N
Thyroid: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	2/49 (4%)	5/48 (10%)	1/47 (2%)
Adjusted Rates (b)	5.3%	11.9%	2.6%
Terminal Rates (c)	2/38 (5%)	5/42 (12%)	1/39 (3%)
Life Table Tests (d)	P=0.399N	P=0.258	P=0.491N
Incidental Tumor Tests (d)	P=0.399N	P=0.258	P=0.491N
Cochran-Armitage Trend Test (d)	P=0.431N		
Fisher Exact Tests		P=0.209	P=0.516N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	20/50 (40%)	15/50 (30%)	9/50 (18%)
Adjusted Rates (b)	46.2%	32.6%	21.4%
Terminal Rates (c)	15/38 (39%)	13/44 (30%)	9/42 (21%)
Life Table Tests (d)	P=0.006N	P=0.105N	P=0.008N
Incidental Tumor Tests (d)	P=0.016N	P=0.189N	P=0.019N
Cochran-Armitage Trend Test (d)	P=0.011N		
Fisher Exact Tests		P=0.201N	P=0.014N
Mammary Gland: All Carcinoma or Adenocarcinoma			
Overall Rates (a)	1/50 (2%)	4/50 (8%)	2/50 (4%)
Adjusted Rates (b)	2.6%	9.1%	4.8%
Terminal Rates (c)	1/38 (3%)	4/44 (9%)	2/42 (5%)
Life Table Tests (d)	P=0.447	P=0.226	P=0.535
Incidental Tumor Tests (d)	P=0.447	P=0.226	P=0.535
Cochran-Armitage Trend Test (d)	P=0.406		
Fisher Exact Tests		P=0.181	P=0.500
Clitoral Gland: Carcinoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	5.3%	6.8%	0.0%
Terminal Rates (c)	2/38 (5%)	3/44 (7%)	0/42 (0%)
Life Table Tests (d)	P=0.173N	P=0.567	P=0.217N
Incidental Tumor Tests (d)	P=0.173N	P=0.567	P=0.217N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Tests		P=0.500	P=0.247N
Clitoral Gland: Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	7.9%	6.8%	2.4%
Terminal Rates (c)	3/38 (8%)	3/44 (7%)	1/42 (2%)
Life Table Tests (d)	P=0.202N	P=0.594N	P=0.270N
Incidental Tumor Tests (d)	P=0.202N	P=0.594N	P=0.270N
Cochran-Armitage Trend Test (d)	P=0.238N		
Fisher Exact Tests		P=0.661	P=0.309N
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	9/50 (18%)	10/50 (20%)	10/50 (20%)
Adjusted Rates (b)	23.0%	22.7%	23.8%
Terminal Rates (c)	8/38 (21%)	10/44 (23%)	10/42 (24%)
Life Table Tests (d)	P=0.544	P=0.564N	P=0.595
Incidental Tumor Tests (d)	P=0.496	P=0.595N	P=0.524
Cochran-Armitage Trend Test (d)	P=0.450		
Fisher Exact Tests		P=0.500	P=0.500

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF MONURON (Continued)

	Control	750 ppm	1,500 ppm
Uterus: Endometrial Stromal Polyp or Sarcoma			
Overall Rates (a)	10/50 (20%)	10/50 (20%)	10/50 (20%)
Adjusted Rates (b)	25.6%	22.7%	23.8%
Terminal Rates (c)	9/38 (24%)	10/44 (23%)	10/42 (24%)
Life Table Tests (d)	P=0.453N	P=0.455N	P=0.501N
Incidental Tumor Tests (d)	P=0.501N	P=0.486N	P=0.573N
Cochran-Armitage Trend Test (d)	P=0.550		
Fisher Exact Tests		P=0.598	P=0.598

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

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF MONURON

	Control	5,000 ppm	10,000 ppm
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	1/50 (2%)	6/50 (12%)	1/50 (2%)
Adjusted Rates (b)	2.9%	14.8%	2.0%
Terminal Rates (c)	1/34 (3%)	2/36 (6%)	0/46 (0%)
Life Table Tests (d)	P=0.460N	P=0.074	P=0.697N
Incidental Tumor Tests (d)	P=0.474N	P=0.151	P=0.440N
Cochran-Armitage Trend Test (d)	P=0.588N		
Fisher Exact Tests		P=0.056	P=0.753N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	1/50 (2%)	8/50 (16%)	1/50 (2%)
Adjusted Rates (b)	2.9%	19.8%	2.0%
Terminal Rates (c)	1/34 (3%)	4/36 (11%)	0/46 (0%)
Life Table Tests (d)	P=0.432N	P=0.026	P=0.697N
Incidental Tumor Tests (d)	P=0.440N	P=0.050	P=0.440N
Cochran-Armitage Trend Test (d)	P=0.579N		
Fisher Exact Tests		P=0.015	P=0.753N
Subcutaneous Tissue: Sarcoma, Fibrosarcoma, or Fibroma			
Overall Rates (a)	2/50 (4%)	9/50 (18%)	2/50 (4%)
Adjusted Rates (b)	5.3%	21.6%	4.1%
Terminal Rates (c)	1/34 (3%)	4/36 (11%)	0/46 (0%)
Life Table Tests (d)	P=0.412N	P=0.042	P=0.601N
Incidental Tumor Tests (d)	P=0.517N	P=0.073	P=0.725N
Cochran-Armitage Trend Test (d)	P=0.571N		
Fisher Exact Tests		P=0.026	P=0.691N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	5/50 (10%)	4/49 (8%)	8/50 (16%)
Adjusted Rates (b)	14.2%	10.2%	17.0%
Terminal Rates (c)	4/34 (12%)	2/36 (6%)	7/46 (15%)
Life Table Tests (d)	P=0.402	P=0.466N	P=0.492
Incidental Tumor Tests (d)	P=0.305	P=0.371N	P=0.379
Cochran-Armitage Trend Test (d)	P=0.216		
Fisher Exact Tests		P=0.513N	P=0.277
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	6/50 (12%)	5/49 (10%)	10/50 (20%)
Adjusted Rates (b)	17.1%	12.9%	21.3%
Terminal Rates (c)	5/34 (15%)	3/36 (8%)	9/46 (20%)
Life Table Tests (d)	P=0.348	P=0.462N	P=0.433
Incidental Tumor Tests (d)	P=0.262	P=0.375N	P=0.331
Cochran-Armitage Trend Test (d)	P=0.157		
Fisher Exact Tests		P=0.514N	P=0.207
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	8.8%	5.1%	2.2%
Terminal Rates (c)	3/34 (9%)	1/36 (3%)	1/46 (2%)
Life Table Tests (d)	P=0.145N	P=0.470N	P=0.205N
Incidental Tumor Tests (d)	P=0.113N	P=0.284N	P=0.205N
Cochran-Armitage Trend Test (d)	P=0.223N		
Fisher Exact Tests		P=0.500N	P=0.309N
Liver: Adenoma			
Overall Rates (a)	7/50 (14%)	3/49 (6%)	4/50 (8%)
Adjusted Rates (b)	20.6%	8.3%	8.5%
Terminal Rates (c)	7/34 (21%)	3/36 (8%)	3/46 (7%)
Life Table Tests (d)	P=0.090N	P=0.132N	P=0.120N
Incidental Tumor Tests (d)	P=0.107N	P=0.132N	P=0.153N
Cochran-Armitage Trend Test (d)	P=0.196N		
Fisher Exact Tests		P=0.167N	P=0.263N

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF MONURON (Continued)

	Control	5,000 ppm	10,000 ppm
Liver: Carcinoma			
Overall Rates (a)	6/50 (12%)	5/49 (10%)	2/50 (4%)
Adjusted Rates (b)	16.0%	13.5%	4.4%
Terminal Rates (c)	3/34 (9%)	4/36 (11%)	2/46 (4%)
Life Table Tests (d)	P=0.049N	P=0.458N	P=0.067N
Incidental Tumor Tests (d)	P=0.117N	P=0.542N	P=0.199N
Cochran-Armitage Trend Test (d)	P=0.107N		
Fisher Exact Tests		P=0.515N	P=0.135N
Liver: Adenoma or Carcinoma			
Overall Rates (a)	12/50 (24%)	8/49 (16%)	6/50 (12%)
Adjusted Rates (b)	32.3%	21.6%	12.8%
Terminal Rates (c)	9/34 (26%)	7/36 (19%)	5/46 (11%)
Life Table Tests (d)	P=0.018N	P=0.188N	P=0.026N
Incidental Tumor Tests (d)	P=0.045N	P=0.227N	P=0.079N
Cochran-Armitage Trend Test (d)	P=0.074N		
Fisher Exact Tests		P=0.242N	P=0.097N
Adrenal: Pheochromocytoma			
Overall Rates (a)	3/49 (6%)	0/48 (0%)	0/49 (0%)
Adjusted Rates (b)	7.3%	0.0%	0.0%
Terminal Rates (c)	1/33 (3%)	0/36 (0%)	0/45 (0%)
Life Table Tests (d)	P=0.029N	P=0.109N	P=0.096N
Incidental Tumor Tests (d)	P=0.113N	P=0.216N	P=0.358N
Cochran-Armitage Trend Test (d)	P=0.038N		
Fisher Exact Tests		P=0.125N	P=0.121N
Harderian Gland: Adenoma			
Overall Rates (a)	4/50 (8%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	11.2%	2.8%	4.3%
Terminal Rates (c)	3/34 (9%)	1/36 (3%)	2/46 (4%)
Life Table Tests (d)	P=0.152N	P=0.166N	P=0.216N
Incidental Tumor Tests (d)	P=0.186N	P=0.184N	P=0.273N
Cochran-Armitage Trend Test (d)	P=0.238N		
Fisher Exact Tests		P=0.181N	P=0.339N

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

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF MONURON

	Control	5,000 ppm	10,000 ppm
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	4/50 (8%)	4/48 (8%)	2/50 (4%)
Adjusted Rates (b)	12.1%	13.0%	4.4%
Terminal Rates (c)	3/31 (10%)	1/25 (4%)	1/41 (2%)
Life Table Tests (d)	P=0.195N	P=0.554	P=0.247N
Incidental Tumor Tests (d)	P=0.337N	P=0.608N	P=0.313N
Cochran-Armitage Trend Test (d)	P=0.275N		
Fisher Exact Tests		P=0.619	P=0.339N
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	2/50 (4%)	3/48 (6%)	1/50 (2%)
Adjusted Rates (b)	5.8%	10.4%	2.4%
Terminal Rates (c)	1/31 (3%)	2/25 (8%)	1/41 (2%)
Life Table Tests (d)	P=0.315N	P=0.442	P=0.421N
Incidental Tumor Tests (d)	P=0.395N	P=0.506	P=0.529N
Cochran-Armitage Trend Test (d)	P=0.400N		
Fisher Exact Tests		P=0.480	P=0.500N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	6/50 (12%)	7/48 (15%)	3/50 (6%)
Adjusted Rates (b)	17.5%	22.3%	6.8%
Terminal Rates (c)	4/31 (13%)	3/25 (12%)	2/41 (5%)
Life Table Tests (d)	P=0.127N	P=0.393	P=0.153N
Incidental Tumor Tests (d)	P=0.250N	P=0.535	P=0.236N
Cochran-Armitage Trend Test (d)	P=0.210N		
Fisher Exact Tests		P=0.468	P=0.243N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	16/50 (32%)	8/50 (16%)	7/50 (14%)
Adjusted Rates (b)	44.8%	30.2%	16.6%
Terminal Rates (c)	12/31 (39%)	7/25 (28%)	6/41 (15%)
Life Table Tests (d)	P=0.004N	P=0.130N	P=0.006N
Incidental Tumor Tests (d)	P=0.008N	P=0.092N	P=0.022N
Cochran-Armitage Trend Test (d)	P=0.018N		
Fisher Exact Tests		P=0.050N	P=0.028N
Liver: Adenoma			
Overall Rates (a)	5/50 (10%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	16.1%	0.0%	7.3%
Terminal Rates (c)	5/31 (16%)	0/25 (0%)	3/41 (7%)
Life Table Tests (d)	P=0.159N	P=0.053N	P=0.214N
Incidental Tumor Tests (d)	P=0.159N	P=0.053N	P=0.214N
Cochran-Armitage Trend Test (d)	P=0.252N		
Fisher Exact Tests		P=0.028N	P=0.357N
Liver: Adenoma or Carcinoma			
Overall Rates (a)	6/50 (12%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	19.4%	0.0%	7.3%
Terminal Rates (c)	6/31 (19%)	0/25 (0%)	3/41 (7%)
Life Table Tests (d)	P=0.081N	P=0.030N	P=0.123N
Incidental Tumor Tests (d)	P=0.081N	P=0.030N	P=0.123N
Cochran-Armitage Trend Test (d)	P=0.146N		
Fisher Exact Tests		P=0.013N	P=0.243N

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

APPENDIX F

HISTORICAL INCIDENCES OF TUMORS IN F344/N RATS AND B6C3F$_1$ MICE RECEIVING NO TREATMENT

TABLE F1. HISTORICAL INCIDENCE OF KIDNEY TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

	At Risk	No. of Tumors	Site	Diagnosis
Incidence at EG&G Mason Research Institute				
2-Biphenylamine · HCl	49	1	Kidney, NOS	Carcinoma, NOS, unclear primary or metastatic
8-Hydroxyquinoline	50	1	Kidney, NOS	Tubular cell adenoma
All other chemicals	595	0		
Total at risk	694			
Overall Historical Incidence at All Laboratories				
	2,359	4	Kidney, NOS	Tubular cell adenoma
		2	Kidney, NOS	Tubular cell adenocarcinoma
		1	Kidney, NOS	Nephroblastoma
		1	Kidney, NOS	Carcinoma, NOS, unclear primary or metastatic
		1	Kidney/cortex	Adenoma, NOS
		1	Kidney/cortex	Carcinoma, NOS

(a) Data as of March 16, 1983, for NTP carcinogenesis studies of at least 104 weeks. No more than one of the tumors described in this table was present in any untreated control group.

TABLE F2. HISTORICAL INCIDENCE OF SELECTED TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT

Study	Kill Date	Incidence in Controls (a) Thyroid C-Cell Carcinoma	Adrenal Pheochromocytoma	Leukemia
Incidence at EG&G Mason Research Institute				
Cinnamyl anthranilate	12/76	0/42 (0%)	6/47 (13%)	(b) 0/50 (0%)
2,6-Toluenediamine · 2HCl	7/78	2/44 (5%)	10/50 (20%)	9/50 (18%)
4,4'-Oxydianiline	10/78	2/46 (4%)	4/50 (8%)	23/50 (46%)
Di(2-ethylhexyl)adipate	5/79	2/49 (4%)	3/48 (6%)	9/49 (18%)
Di(2-ethylhexyl)phthalate	6/79	4/48 (8%)	2/50 (4%)	13/50 (26%)
Locust bean gum	7/79	4/49 (8%)	4/50 (8%)	21/50 (42%)
Gum arabic	7/79	0/47 (0%)	13/47 (28%)	10/50 (20%)
Guar gum	8/79	1/50 (2%)	18/50 (36%)	13/50 (26%)
Tara gum	11/79	1/45 (2%)	9/48 (18%)	14/50 (28%)
Agar	11/79	2/49 (4%)	5/50 (10%)	9/50 (18%)
2-Biphenylamine · HCl	3/80	1/47 (2%)	12/48 (24%)	15/50 (30%)
4,4'-Methylenedianiline · 2HCl	9/80	2/49 (4%)	7/50 (14%)	12/50 (24%)
8-Hydroxyquinoline	1/82	0/50 (0%)	12/50 (24%)	17/50 (34%)
Total		21/615 (3%)	105/638 (16%)	165/649 (25%)
Range		0%-8%	4%-36%	18%-46%
Incidences in Monuron Studies				
Control	8/81	6/49 (12%)	14/50 (28%)	5/50 (10%)
Low dose	8/81	3/46 (7%)	13/50 (26%)	0/50 (0%)
High dose	8/81	1/50 (2%)	3/48 (6%)	0/50 (0%)
Overall Historical Incidence at All Laboratories				
Total		84/2,282 (4%)	389/2,332 (17%)	650/2,372 (27%)
Range		0%-12%	2%-40%	(c) 0%-46%

(a) Number of tumor-bearing animals per number of study animals (percent of animals affected)
(b) This study reported 7/50 (14%) lymphomas; this may represent a difference in nomenclature.
(c) Includes the study referred to in footnote (b)

TABLE F3. HISTORICAL INCIDENCE OF LIVER TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT

Study	Kill Date	Incidence in Controls (a) Neoplastic Nodule	Hepatocellular Carcinoma	Neoplastic Nodule or Hepatocellular Carcinoma
Incidence at EG&G Mason Research Institute				
Cinnamyl anthranilate	12/76	1/48 (2%)	0/48 (0%)	1/48 (0%)
2,6-Toluenediamine · 2HCl	7/78	0/50 (0%)	0/50 (0%)	0/50 (0%)
4,4'-Oxydianiline	10/78	1/50 (2%)	0/50 (0%)	1/50 (2%)
Di(2-ethylhexyl)adipate	5/79	2/49 (4%)	0/49 (0%)	2/49 (0%)
Di(2-ethylhexyl)phthalate	6/79	2/50 (4%)	1/50 (2%)	3/50 (6%)
Locust bean gum	7/79	0/50 (0%)	1/50 (2%)	1/50 (2%)
Gum arabic	7/79	3/49 (6%)	1/49 (2%)	4/49 (8%)
Guar gum	8/79	2/50 (4%)	1/50 (2%)	3/50 (6%)
Tara gum	11/79	1/49 (2%)	0/49 (2%)	1/49 (2%)
Agar	11/79	0/50 (0%)	0/50 (0%)	0/50 (0%)
2-Biphenylamine · HCl	3/80	0/49 (0%)	0/49 (0%)	0/49 (0%)
4,4'-Methylenedianiline · HCl	9/80	1/50 (2%)	0/50 (0%)	1/50 (2%)
8-Hydroxyquinoline	1/82	6/49 (12%)	1/49 (2%)	7/49 (14%)
Total		19/643 (3%)	5/643 (1%)	24/643 (4%)
Range		0%-12%	0%-2%	0%-14%
Incidences in Monuron Studies				
Control	8/81	1/50 (2%)	0/50 (0%)	1/50 (2%)
Low dose	8/81	6/49 (12%)	1/49 (2%)	6/49 (12%)
High dose	8/81	7/50 (14%)	3/50 (6%)	9/50 (18%)
Overall Historical Incidence at All Laboratories				
Total		78/2,306 (3%)	18/2,306 (1%)	96/2,306 (4%)
Range		0%-12%	0%-4%	0%-14%

(a) Number of tumor-bearing animals per number of study animals (percent of animals affected)

TABLE F4. HISTORICAL INCIDENCE OF SELECTED TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT

Study	Kill Date	Incidence in Controls (a) Mammary Gland Fibroadenoma	Leukemia
Incidence at EG&G Mason Research Institute			
Cinnamyl anthranilate	12/76	8/48 (17%)	(b) 0/48 (0%)
2,6-Toluenediamine · 2HCl	7/78	11/50 (22%)	4/50 (8%)
4,4'-Oxydianiline	10/78	16/50 (32%)	3/50 (6%)
Di(2-ethylhexyl)adipate	5/79	13/50 (26%)	12/50 (24%)
Butyl benzyl phthalate	5/79	20/49 (41%)	7/49 (14%)
Di(2-ethylhexyl)phthalate	6/79	10/50 (20%)	11/50 (22%)
Locust bean gum	7/79	16/50 (32%)	9/50 (18%)
Gum arabic	7/79	14/50 (28%)	10/50 (20%)
Guar gum	8/79	20/50 (40%)	12/50 (24%)
Tara gum	11/79	13/50 (26%)	6/50 (12%)
Agar	11/79	14/50 (28%)	10/50 (20%)
2-Biphenylamine · HCl	3/80	22/50 (44%)	5/50 (10%)
4,4'-Methylenedianiline · 2HCl	9/80	10/50 (20%)	3/50 (6%)
8-Hydroxyquinoline	1/82	19/50 (38%)	6/50 (12%)
Total		206/697 (30%)	98/697 (14%)
Range		17%-44%	6%-24%
Incidences in Monuron Studies			
Control	8/81	20/50 (40%)	11/50 (22%)
Low dose	8/81	15/50 (30%)	2/50 (4%)
High dose	8/81	9/50 (18%)	2/50 (4%)
Overall Historical Incidence at All Laboratories			
Total		549/2,422 (23%)	415/2,422 (17%)
Range		0%-44%	0%-38%

(a) Number of tumor-bearing animals per number of study animals (percent of animals affected)
(b) This study reported 5/48 (20%) lymphomas; this may represent a difference in nomenclature.

TABLE F5. HISTORICAL INCIDENCE OF SELECTED TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT

Study	Kill Date	Incidence in Controls (a) Malignant Lymphoma	Hepatocellular Adenoma	Hepatocellular Carcinoma
Incidence at EG&G Mason Research Institute				
Cinnamyl anthranilate	12/76	4/48 (8%)	8/48 (17%)	6/48 (12%)
2,6-Toluenediamine · 2HCl	7/78	2/50 (4%)	7/50 (14%)	14/50 (28%)
4,4'-Oxydianiline	10/78	9/50 (18%)	11/50 (22%)	18/50 (36%)
Di(2-ethylhexyl)adipate	5/79	16/50 (32%)	6/50 (12%)	7/50 (14%)
Butyl benzyl phthalate	5/79	13/50 (26%)	4/50 (8%)	9/50 (18%)
Di(2-ethylhexyl)phthalate	6/79	8/50 (16%)	6/50 (12%)	9/50 (18%)
Locust bean gum	7/79	12/50 (24%)	6/50 (12%)	15/50 (30%)
Gum arabic	7/79	9/49 (18%)	4/49 (8%)	13/49 (27%)
Guar gum	8/79	7/50 (14%)	1/50 (2%)	15/50 (30%)
Tara gum	11/79	6/50 (12%)	8/50 (16%)	9/50 (18%)
Agar	11/79	2/49 (4%)	0/49 (0%)	9/49 (18%)
2-Biphenylamine · HCl	3/80	6/50 (12%)	5/50 (10%)	9/50 (18%)
4,4'-Methylenedianiline · 2HCl	9/80	10/49 (20%)	7/49 (14%)	10/49 (20%)
8-Hydroxyquinoline	1/82	12/50 (24%)	9/50 (18%)	5/50 (10%)
Total		116/695 (17%)	82/695 (12%)	148/695 (21%)
Range		4%-32%	0%-22%	10%-36%
Incidences in Monuron Studies				
Control	8/81	3/50 (6%)	7/50 (14%)	6/50 (12%)
Low dose	8/81	2/50 (4%)	3/49 (6%)	5/49 (10%)
High dose	8/81	1/50 (2%)	4/50 (8%)	2/50 (4%)
Overall Historical Incidence at All Laboratories				
Total		281/2,395 (11.7%)	242/2,386 (10%)	501/2,386 (21%)
Range		2%-32%	0%-22%	6%-36%

(a) Number of tumor-bearing animals per number of study animals (percent of animals affected)

TABLE F6. HISTORICAL INCIDENCE OF SELECTED TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT

Study	Kill Date	Incidence in Controls (a) Malignant Lymphoma	Hepatocellular Adenoma	Hepatocellular Carcinoma
Incidence at EG&G Mason Research Institute				
Cinnamyl anthranilate	12/76	18/50 (36%)	2/50 (4%)	1/50 (2%)
2,6-Toluenediamine · 2HCl	7/78	4/50 (8%)	4/50 (8%)	0/50 (0%)
4,4'-Oxydianiline	10/78	15/50 (30%)	4/50 (8%)	4/50 (8%)
Di(2-ethylhexyl)adipate	5/79	23/50 (46%)	2/50 (4%)	1/50 (2%)
Butyl benzyl phthalate	5/79	17/50 (34%)	0/50 (0%)	2/50 (4%)
Di(2-ethylhexyl)phthalate	6/79	10/50 (20%)	1/50 (2%)	0/50 (0%)
Locust bean gum	7/79	31/50 (62%)	1/49 (2%)	2/49 (4%)
Gum arabic	7/79	18/49 (37%)	2/49 (4%)	1/49 (2%)
Guar gum	8/79	19/50 (38%)	2/50 (4%)	4/50 (8%)
Tara gum	11/79	16/50 (32%)	9/49 (18%)	1/49 (2%)
Agar	11/79	9/50 (18%)	1/50 (2%)	3/50 (6%)
2-Biphenylamine · HCl	3/80	10/49 (20%)	3/49 (6%)	4/49 (8%)
4,4'-Methylenedianiline · 2HCl	9/80	13/50 (26%)	3/50 (6%)	1/50 (2%)
8-Hydroxyquinoline	1/82	13/50 (26%)	2/49 (4%)	3/49 (6%)
Total		216/698 (31%)	36/695 (5%)	27/695 (4%)
Range		8%-62%	0%-18%	0%-8%
Incidences in Monuron Studies				
Control	8/81	16/50 (32%)	5/50 (10%)	2/50 (4%)
Low dose	8/81	8/50 (16%)	0/50 (0%)	0/50 (0%)
High dose	8/81	7/50 (14%)	3/50 (6%)	0/50 (0%)
Overall Historical Incidence at All Laboratories				
Total		637/2,537 (25%)	102/2,519 (4%)	106/2,519 (4%)
Range		8%-62%	0%-18%	0%-14%

(a) Number of tumor-bearing animals per number of study animals (percent of animals affected)

APPENDIX G

GENETIC TOXICOLOGY OF MONURON

TABLE G1. MUTAGENICITY OF MONURON IN SALMONELLA

Strain	Dose (μg/plate)	Revertants/plate (a,b) −S9	+S9 (rat)	+S9 (hamster)
TA100	0	155 ± 8.7	153 ± 10.5	155 ± 7.3
	10	143 ± 10.7		
	33	141 ± 6.4		
	100	156 ± 9.2	157 ± 0.3	139 ± 2.0
	333	126 ± 2.3	142 ± 5.6	141 ± 3.5
	1,000	Toxic	144 ± 7.8	135 ± 4.5
	3,333		125 ± 5.5	117 ± 7.7
	5,000		118 ± 4.3	87 ± 4.3
TA1535	0	36 ± 1.5	18 ± 1.9	15 ± 1.0
	10	27 ± 1.2		
	33	28 ± 2.1		
	100	28 ± 1.5	17 ± 0.6	15 ± 1.2
	333	21 ± 2.9	14 ± 1.9	15 ± 2.9
	1,000	Toxic	12 ± 1.8	16 ± 1.2
	3,333		8 ± 1.9	10 ± 1.3
	5,000		10 ± 0.9	10 ± 0.9
TA1537	0	9 ± 0.7	10 ± 1.0	18 ± 3.2
	10	8 ± 2.0		
	33	10 ± 1.8		
	100	12 ± 4.9	13 ± 1.5	17 ± 3.5
	333	8 ± 1.9	12 ± 0.9	15 ± 3.2
	1,000	7 ± 1.5	11 ± 3.8	13 ± 1.5
	3,333		10 ± 3.0	7 ± 2.3
	5,000		7 ± 2.0	9 ± 1.5
TA98	0	20 ± 3.3	30 ± 2.8	41 ± 2.5
	10	18 ± 2.9		
	33	20 ± 1.9		
	100	21 ± 0.6	32 ± 2.2	32 ± 1.5
	333	18 ± 3.2	28 ± 2.1	37 ± 0.9
	1,000	17 ± 3.2	27 ± 4.9	31 ± 0.6
	3,333		14 ± 2.2	17 ± 2.1
	5,000		22 ± 1.9	18 ± 2.9

(a) The S9 fractions were prepared from the liver of Aroclor 1254-induced male Sprague-Dawley rats and male Syrian hamsters. Cells and study compound or solvent (DMSO) were incubated for 20 minutes at 37° C in the presence of either S9 or buffer (Yahagi et al., 1975). After the addition of soft agar, the contents of each tube were poured onto minimal medium, and the plates were incubated at 37° C for 48 hours (Ames et al., 1975). The experiment was performed twice, each in triplicate; because the results were similar, data from only one experiment are shown.
(b) Revertants are presented as mean ± standard error from three plates.

TABLE G2. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY MONURON (a)

−S9 (b)		+S9 (c)	
Dose (μg/ml)	SCE/Cell	Dose (μg/ml)	SCE/Cell
DMSO (10 μl)	10.1 ± 0.44	DMSO (10 μl)	9.9 ± 0.44
50	11.4 ± 0.47	1,200	12.6 ± 0.49
100	12.6 ± 0.49	1,400	13.2 ± 0.50
200	12.5 ± 0.49	1,500	12.9 ± 0.50
Mitomycin C (0.005)	33.1	Cyclophosphamide (1.5)	34.8

(a) SCE = sister chromatid exchange
(b) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then BrdU was added, and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU (10 μM) and colcemid (0.1 μg/ml) was added, and incubation was continued for 2-3 hours. Cells were then collected by mitotic shake-off, treated for 3 minutes with potassium chloride (75 mM), washed twice with fixative, and dropped onto slides and air-dried. Staining was by a modified technique (Galloway et al., 1985).
(c) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Then cells were washed, and medium containing 10 μM BrdU was added. Cells were incubated for a further 26 hours, with colcemid (0.1 μg/ml) present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

TABLE G3. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY MONURON (a)

−S9 (b)		+S9 (c)	
Dose (μg/ml)	Abs/100 Cells (percent cells with abs)	Dose (μg/ml)	Abs/100 Cells (percent cells with abs)
DMSO (10 μl)	2 (2)	DMSO (10 μl)	1 (1)
800	7 (6)	1,300	37 (19)
900	0 (0)	1,400	17 (10)
1,000	5 (5)	1,500	4 (4)
Mitomycin C (0.01)	10 (8)	Cyclophosphamide (2.0)	2 (2)

(a) Abs = aberrations
(b) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid (0.1 μg/ml) was added. After a further 2-3 hours of incubation, cells were harvested by mitotic shake-off, fixed, and stained *in 6% Giemsa*.
(c) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8-10 hours. Colcemid (0.1 μg/ml) was added for the last 2-3 hours of incubation; then cells were harvested and fixed as above. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

APPENDIX H

CHEMICAL CHARACTERIZATION OF MONURON

APPENDIX H. CHEMICAL CHARACTERIZATION

I. Identity and Purity Determinations Performed by the Analytical Chemistry Laboratory

A. Lot no. D-A330

1. Physical properties

a. Appearance: Fine, white microcrystalline powder

b. Melting point:

Determined	Literature Values
171°-173° C	170.5°-171.5° C (Weast et al., 1975)

2. Spectral data

a. Infrared

Instrument: Beckman IR-12
Cell: 1.5% in a potassium bromide pellet

Results: See Figure 5

No literature spectrum found. Spectrum consistent with structure.

b. Ultraviolet/visible

Instrument: Cary 118
Solvent: Methanol

Results:

λ_{max} (nm)	$\varepsilon \times 10^{-3}$	λ_{max} (nm)
247	21.33 ± 0.32 (δ)	~245 (solvent and concentration not given) (Pribyl and Herzel, 1976)
285 (shoulder)	1.01 ± 0.04 (δ)	

No maxima observed between 800 nm and 350 nm but gradual increase in absorbance toward 350 nm at a concentration of 10 mg/ml

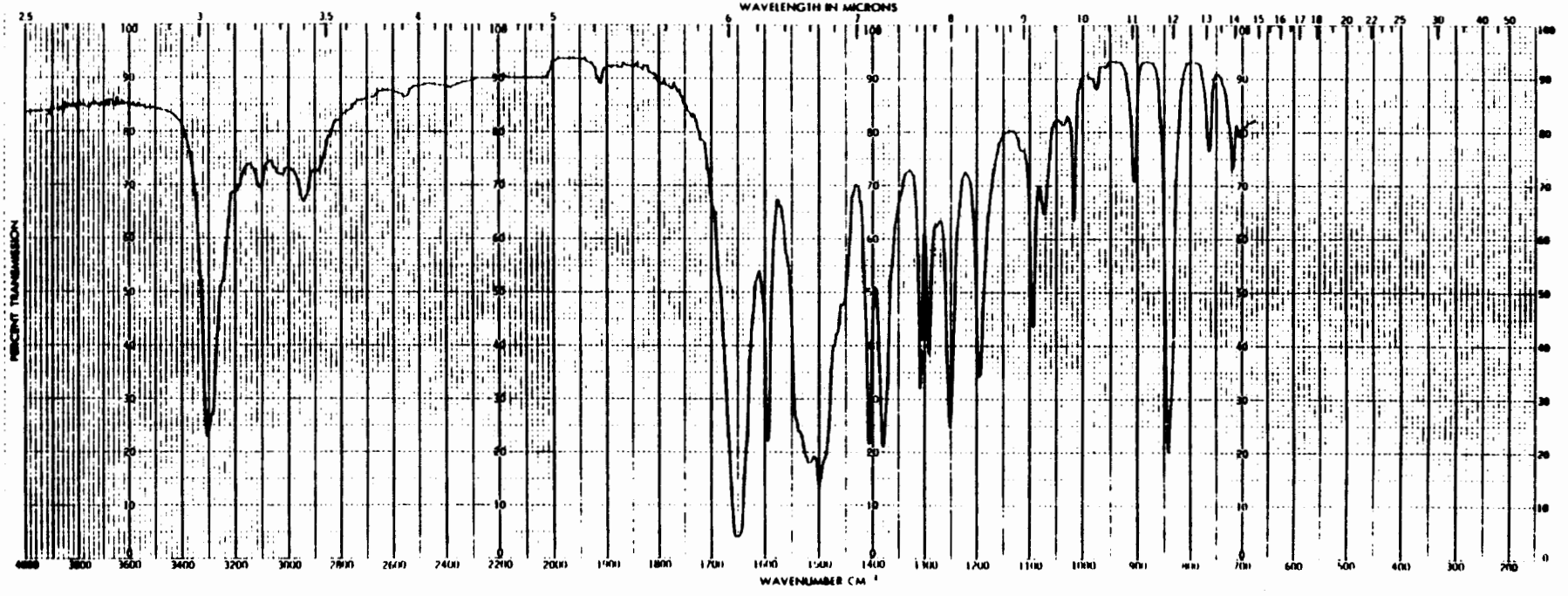

FIGURE 5. INFRARED ABSORPTION SPECTRUM OF MONURON (LOT NO. D-A330)

c. **Nuclear magnetic resonance**

	Determined	Literature Values
Instrument:	Varian EM-360A	
Solvent:	Deuterated dimethyl sulfoxide with internal tetramethylsilane	
Assignments:	See Figure 6	No literature reference found. Spectrum is consistent with that expected for structure.
Chemical shift (δ):	a s, 2.90 ppm b d, 7.26 ppm c d, 7.50 ppm d s, 8.40 ppm	
Coupling constant:	$J_{b\text{-}c}$ = 9 Hz	
Integration ratios	a 5.90 b, c 4.05 d 1.06	

3. **Water analysis (Karl Fischer):** 0.25% ± 0.04(δ)%

4. **Elemental analysis**

Element	C	H	N	Cl
Theory (T) (percent)	54.41	5.58	14.10	17.85
Determined (D) (percent)	54.73	5.58	14.07	17.65
	54.53	5.77	14.08	17.87
Percent (D/T)	100.40	101.70	99.82	99.50

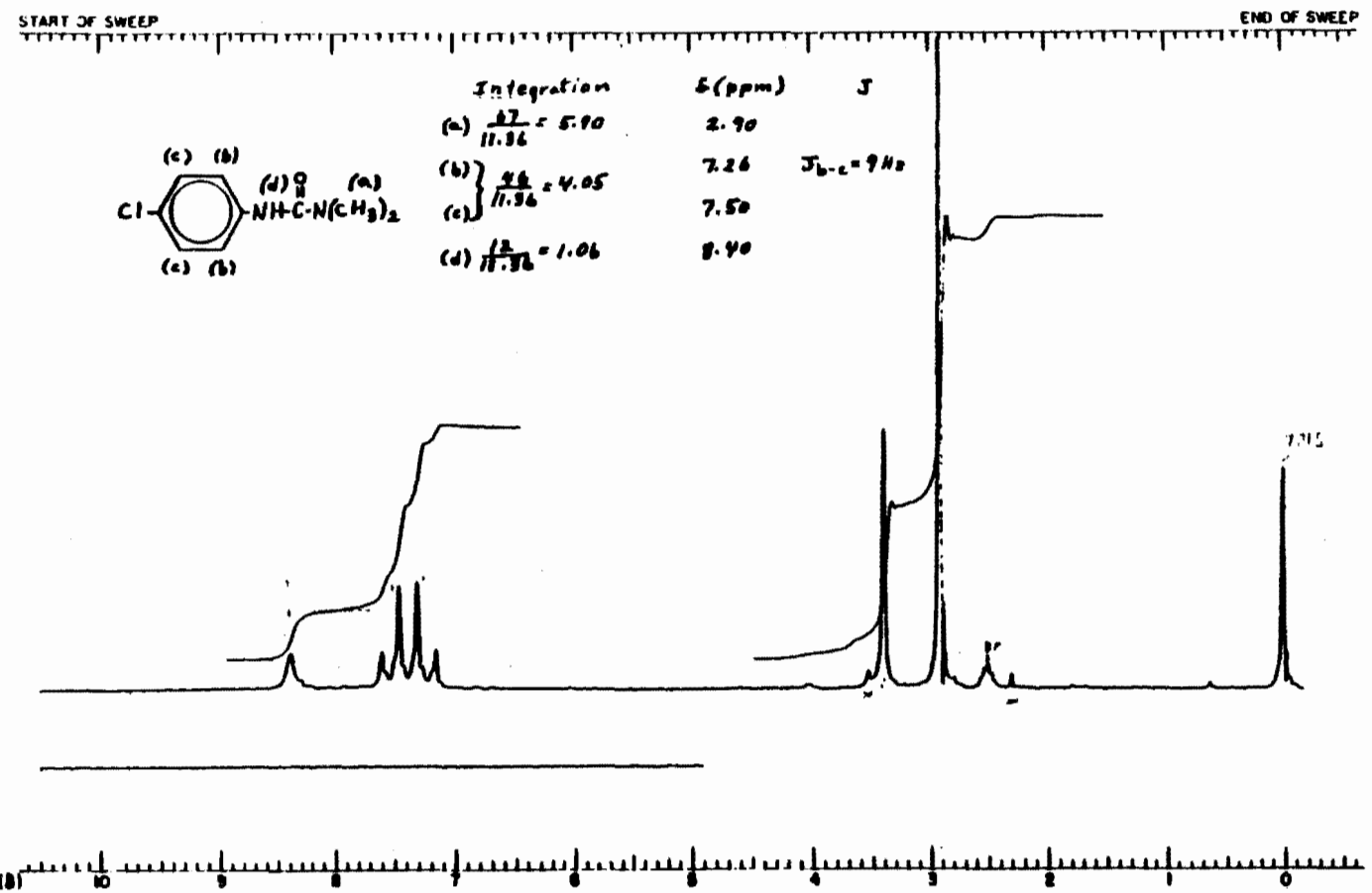

FIGURE 6. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF MONURON (LOT NO. D-A330)

5. **Chromatographic analysis**

a. **Thin-layer chromatography**

Plates: Silica Gel 60 F-254
Reference Standard: Acetanilide, 10 µg/µl in tetrahydrofuran
Amount Spotted: 100 µg and 300 µg (10 µg/µl in tetrahydrofuran)
Visualization: 254 nm ultraviolet light and 0.5% $KMnO_4$ in 1N NaOH

System 1: Isopropyl alcohol:toluene:tetrahydrofuran (5:15:1)

R_f: 0.54 (major)

R_{st}: 1.0

System 2: Diethyl ether:methanol (95:5)

R_f: 0.27 (major); 0.90 (slight trace)

R_{st}: 0.67, 2.17

b. **Gas chromatography:** The major component did not chromatograph well on a 3% OV-17 column, even at high isothermal temperatures. Therefore, it was decided that high-performance liquid chromatography would be used to detect impurities.

c. **High-performance liquid chromatography**

Instrument: Waters programmable component system
Column: µ Bondapak-C_{18}, 30 cm × 4 mm ID
Detector: Ultraviolet, 254 nm
Flow rate: 1.0 ml/min

System 1

Solvent program: 70% water; 30% acetonitrile, isocratic

Results: Major peak and six impurities, three before and three after the major peak, with a total combined area of 0.16% of the major peak area.

Peak No.	Retention Time (min)	Retention Time (relative to monuron)	Area (percent of monuron)
1	6.9	0.51	0.03
2	10.8	0.81	0.01
3	11.6	0.87	0.07
4	13.4	1.00	100
5	19.9	1.48	0.03
6	27.6	2.06	0.01
7	34.9	2.60	0.01

System 2

Solvent program: 60% water, 40% acetonitrile, isocratic

Results: Major peak and eight impurities, three before and five after the major peak, with total combined areas of 0.21% of the major peak area.

Peak No.	Retention Time (min)	Retention Time (relative to monuron)	Area (percent of monuron)
1	5.3	0.64	0.01
2	6.9	0.83	<0.01
3	7.7	0.93	0.01 (a)
4	8.3	1.00	100
5	11.2	1.36	0.01 (a)
6	12.6	1.52	0.01 (a)
7	13.2	1.60	0.04
8	15.8	1.90	0.02
9	55.6	6.71	0.11

(a) Not resolved from major peak

System 3

Solvent program: 50% water, 50% acetonitrile, isocratic

Results: Major peak and seven impurities, two before and five after the major peak, with total combined areas of 0.12% of the major peak area.

Peak No.	Retention Time (min)	Retention Time (relative to monuron)	Area (percent of monuron)
1	4.3	0.76	<0.01
2	5.0	0.88	<0.01
3	5.7	1.00	100
4	7.3 (shoulder)	1.28	0.01 (a)
5	7.9 (shoulder)	1.38	0.01 (a)
6	8.9 (shoulder)	1.55	0.01 (a)
7	18.7 (unresolved)	3.28	0.07 (two peaks)
8	19.5 (unresolved)	3.41	

(a) Not resolved from major peak

Summary of the data from the three systems

	Areas (percent of monuron)		
Peak No.	System 1 (70% water: 30% acetonitrile)	System 2 (60% water: 40% acetonitrile)	System 3 (50% water: 50% acetonitrile)
1	0.03	0.01	<0.01
2	0.01	<0.01	<0.01
3	0.07	0.01 (a)	---
4	100	100	100
5	0.03	0.01 (a)	---
6	0.01	0.01 (a)	0.01 (a)
7	0.01	0.04	0.01 (a)
8	--	0.02	0.01 (a)
9	--	0.11	0.07 (two peaks unresolved)

(a) Not resolved from major peak

6. **Conclusions:** Results of elemental analysis for carbon, hydrogen, nitrogen and chlorine were in agreement with the theoretical values. Thin-layer chromatography by one system indicated one slight trace impurity. A second system indicated the major spot only. High-performance liquid chromatography with three systems indicated eight small impurities totaling approximately 0.3% of the major peak area. The infrared, ultraviolet/visible, and nuclear magnetic resonance spectra were consistent with those expected for the structure of monuron.

II. Chemical Stability Study Performed by the Analytical Chemistry Laboratory

Heat stability

A. **Sample preparation and storage:** Samples were stored in glass tubes with Teflon®-lined lids at −20°, 5°, 25°, or 60° C for 2 weeks.

B. **Analytical method:** Samples were dissolved in methanol at a concentration of 0.03% for analysis by high-performance liquid chromatography (a). The major peak heights of all samples were compared to the major peak height of the −20° C samples.

C. **Results**

Storage Temperature (degrees centigrade)	Percent Purity
−20	100.0 ± 2.3
5	98.8 ± 2.3
25	101.7 ± 2.3
60	96.5 ± 2.3

D. **Conclusion:** Monuron is stable as the bulk chemical for 2 weeks at temperatures of up to 60° C. The 60° C sample showed some slight decomposition.

III. Chemical Stability at the Study Laboratory

A. **Storage conditions:** The chemical was stored at 0° ± 5° C.

B. **Analytical method**

Purity determination: The chemical (in tetrahydrofuran) was spotted on Whatman LK5DF or Quantum LQDF silca gel thin-layer chromatography plates. The plates were developed in diethyl ether (95%): methanol (5%); the reference standard was acetanilide.

Identity determination: The infrared absorption spectrum of the sample in potassium bromide was obtained with a Perkin-Elmer Infracord #137.

C. **Conclusion:** The purity and identity determinations were made three times per year and showed that the chemical maintained its identity and purity throughout the studies.

(a) Conditions given in section I.A.5.c. (system 3)

APPENDIX I

PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

APPENDIX I. PREPARATION AND CHARACTERIZATION

I. Studies Conducted at the Analytical Chemistry Laboratory

A. Preparation procedure

1. **Premix:** Monuron (7.54 g ± 0.01 g) was added directly to 100 g of Wayne Lab Blox® rodent feed. This premixture was homogenized in a 1-qt large-mouth glass jar rotated for 15 minutes on a ball-mill type tumbler apparatus, with manual end-over-end tumbling every 5 minutes.

2. **Bulk mixing:** The above premix and 1,400 g more feed were mixed in a Patterson-Kelly Twin-Shell® blender for 15 minutes. The blender was loaded from the top of the shells as follows: 700 g of feed was poured in and allowed to settle and level at the bottom (vertex of the "V"); then the dried premix was poured in on top of the feed from each side; this layer was covered with the remaining 700 g of feed poured in from each side. After 10- and 15-minute mixing times, duplicate 5-g samples were removed from the top of each shell and the bottom trap of blender for subsequent analysis.

3. **Extraction and analysis:** Each sample was placed in a 200-ml centrifuge bottle (quantitative transfer) and triturated with 60 ml of absolute methanol for 30 seconds with a Brinkman Polytron® high-speed blender. The mixture was then placed in an ultrasonic vibratory bath for 30 seconds and centrifuged for 10 minutes. The supernatant solution (50 ml) was removed by pipette; the feed residue was mixed with an additional 50 ml of methanol and extracted again as described above. The combined supernatant solutions (100 ml) were analyzed by ultraviolet absorption spectroscopy at 246 nm on a Cary 118 spectrophotometer.

4. **Quality control:** Blank (undosed) feed samples and individual spiked (0.5% concentration) mixtures were extracted and prepared for analysis in the same manner described for the samples above. Standard solutions of monuron in methanol (1.65, 4.96, and 8.27 µg/ml) were used to determine the extinction coefficient for the compound at the analytical wavelength and to test the applicability of the Beer-Lambert relationship. The system was found to be effectively linear with concentration, having a least-squares correlation coefficient of greater than 0.999. Blank sample absorbance was 0.148 ± 0.023 absorbance units (or 23% ± 3% of sample absorbance) and was subtracted from the absorbance values of samples containing monuron.

B. Homogeneity

1. Results

Sample Location	Average Percent Found in Chemical/Vehicle Mixture (a)
Right, 10	0.57 ± 0.01
Right, 15	0.54 ± 0.01
Left, 10	0.53 ± 0.01
Left, 15	0.51 ± 0.01
Bottom, 10	0.49 ± 0.01
Bottom, 15	0.47 ± 0.01

(a) Mean ± standard deviation corrected for a spiked recovery yield of 82.1% (extraction efficiency 84.6% volume correction, 97%). The target concentration of chemical in feed is 0.498% ± 0.002%.

2. **Conclusion:** The mixture of monuron in stock rodent feed at the 0.5% (5,000 ppm) concentration was more homogenous after 15 minutes than after 10 minutes mixing in a 4-qt Patterson-Kelly Twin-Shell® blender with intensifier bar. The variations in the samples of the 15-minute mixture are within 10% of the target concentration of chemical in the feed.

C. Heat stability of 5,000 ppm monuron in feed

1. **Sample mixing and storage:** Samples were prepared by weighing 5 g of Wayne Lab Blox® rodent feed into 200-ml centrifuge bottles. Monuron (25 mg, individual samples accurately weighed to ± 0.1 mg) was added to each feed sample, and the contents of the bottles were mixed on a vortex mixer for 15 seconds. Duplicate samples were used as spikes for recovery determinations and for 2-weeks' storage at −20°, 5°, 25°, or 45° C. No attempt was made to protect the samples from light.

2. **Extraction and analysis:** Each sample was equilibrated at room temperature and triturated with 50 ml of methanol for 30 seconds in a Brinkman Polytron® high-speed blender. The mixture was then placed in an ultrasonic vibratory bath for 60 seconds and centrifuged for 10 minutes. A portion of the supernatant solution (40 ml) was pipetted into a separate flask. The feed residue was mixed with an additional 50 ml of methanol and extracted again as described above. A 5-ml aliquot of the combined supernatant solutions (80 ml total) was transferred to a 100-ml volumetric flask, and 4 ml of a 0.536 mg/ml ± 0.001 mg/ml solution of acetanilide in methanol was added (as internal reference standard for chromatographic analysis). This solution was brought to 100-ml volume with additional methanol, and 3 ml of the dilute solution was filtered through a Millipore 0.5-μ organic filter before being used for high-performance liquid chromatographic analysis.

Instrument: Water Programmable Component System
Column: E. Merck Hibar II, Lichrosorb RP-18, 10 µ, 250 mm × 4.6 mm ID
Detector: Ultraviolet, 254 nm
Solvent: Water:methanol (40:60), isocratic
Solvent flow rate: 1.0 ml/min
Retention time of compound: 0.5 min
Retention time of internal standard: 4.5 min

3. **Quality control:** Analyses were performed in duplicate for each storage temperature. Acetanilide was used as an internal reference standard. Room temperature recovery studies were performed in duplicate at a concentration of 5,000 ppm. Blank (undosed) feed samples were extracted and prepared for analysis in the manner described above for the study samples. Blanks showed no interference from feed at the retention time of the major component. Detector linearity was established by methanolic standard solutions of 23.3, 16.7, and 10.0 µg/ml for monuron and 20.2, 14.4 and 8.7µg/ml for the acetanilide internal reference. Least-squares correlation coefficients for both compounds were greater than 0.999 (effectively linear).

4. **Results**

Storage Temperature	Target Percent Chemical in Chemical/ Vehicle Mixture (a)	Average Percent Chemical in Chemical/ Vehicle Mixture (a)	Average Percent Recovery
−20° C	0.545 ± 0.002	0.55 ± 0.03	100.9 ± 0.8
5° C	0.504 ± 0.002	0.50 ± 0.03	98.2 ± 0.8
25° C	0.555 ± 0.002	0.54 ± 0.03	98.9 ± 0.8
45° C	0.545 ± 0.002	0.48 ± 0.03	88.5 ± 0.8

(a) Mean ± standard deviation corrected for a spiked recovery yield of 81.2% ± 0.5% (extraction efficiency, 86.9%; volume correction 93%).

5. **Conclusions:** Monuron mixed with stock rodent feed at a concentration of 5,000 ppm was stable when stored for 2 weeks at temperatures of 25° C and below. Samples stored at 45° C for the 2-week period showed a small but significant loss of the study chemical upon analysis.

APPENDIX J

METHODS OF ANALYSIS OF FORMULATED DIETS FOR CONCENTRATION OF MONURON

APPENDIX J. METHODS OF ANALYSIS

I. Studies Conducted at the Study Laboratory

A. Preparation of formulated diets: The study laboratory prepared the diets for the studies by layering a dry premix between portions of the feed and blending the mixture for 15 minutes. The diet mixtures were held at 5° C until use, within 13 days after mixing. The analytical procedure used by the study laboratory employed a methanolic extraction procedure and a spectrophotometric quantitation step. The analytical chemistry laboratory also employed a methanolic extraction procedure. The monuron content of the filtered extract was determined by high-performance liquid chromatography.

B. Analysis of formulated diets: Feed samples of 2 g each were extracted with 50 ml of methanol in 100-ml graduated cylinders by repeated inversions of the cylinders. The feed particles were allowed to settle overnight, and the absorbance of the supernatant solution were determined at 247 nm with a Perkin-Elmer Lambda 3 or equivalent spectrophotometer after appropriate dilutions with methanol. Blank feed samples and spiked controls were analyzed in the same manner. The recovery values were adjusted for blank and spiked feed extract absorbance readings.

II. Studies Conducted at the Analytical Chemistry Laboratory

A. Preparation of spiked feed standards: Two standard solutions of monuron were prepared independently in methanol at concentrations of 4.54 and 3.01 mg/ml. These solutions were diluted with methanol to make four additional standards at concentrations of 2.27, 1.51, 1.13, and 0.75 mg/ml. Aliquots (20 ml) of the six standard solutions were pipetted into individual 200-ml centrifuge bottles containing 10 g of undosed feed to make spiked feed standards bracketing the specified dose range of the referee sample. One 200-ml centrifuge bottle containing 10 g of undosed feed was treated with 20 ml of methanol for use as a blank. The spiked feeds and the feed blank were sealed and allowed to stand overnight at room temperature before being used in the analysis procedure.

B. Preparation of the referee sample: Triplicate weights of the referee feed sample (~10 g weighed to the nearest 0.001 g) were transferred to individual 200-ml centrifuge bottles. Methanol (20 ml) was pipetted into each sample; the bottles were sealed and allowed to stand overnight at room temperature before analysis by the procedure below.

C. Analysis procedure: Methanol (80 ml) was pipetted into each blank, standard, and referee sample bottle, and the bottles were shaken at maximum stroke for 30 minutes on a Burrell Model 75 Wrist-Action® shaker. After 5 minutes of centrifugation, a 3-ml aliquot of each extract was combined with 8 ml of internal-standard solution (acetanilide in methanol, 0.05 mg/ml) and diluted to 100 ml with methanol. Aliquots (2 ml) of the diluted samples were mixed with 1 ml of internal standard solution (a); then they were filtered through a 0.5-μ Millipore® filter. The monuron content of the filtrates was determined by the high-performance liquid chromatographic system below.

Instrument: Waters Liquid Chromatography System consisting of Model 6000 Pumps; Model 660 Solvent Programmer; Model U6K Injector
Column: Waters μBondapak C_{18}, 300 mm × 3.9 mm ID
Detector: Waters Model 440 at 254 nm, 0.05 AUFS
Solvent program: Water:methanol (Fisher HPLC Grade) (65:35), isocratic
Solvent flow rate: 2.0 ml/min
Volume injected: 20 μl
Retention time of compound: Monuron: 3.7 min
Acetanilide internal standard: 2.5 min

The total amount of monuron in the referee feed samples was determined from the linear regression equation obtained by dividing the peak height of each spiked feed standard by the peak height of the internal standard, to the amount of chemical in the respective spiked feed standard. The line defined by the regression equation exhibited a slope of 0.01019 and a y-intercept of −0.001946.

(a) After the sample dilution was prepared, the concentration of the internal standard was too low; therefore, the additional dilution was made with internal-standard solution.

APPENDIX K

RESULTS OF ANALYSIS OF FORMULATED DIETS FOR CONCENTRATION OF MONURON

TABLE K1. CONCENTRATIONS OF MONURON IN THE THIRTEEN-WEEK FEED STUDIES (a)

Target concentration (ppm)	750	1,500	3,000	6,000	12,000	25,000	50,000
Determined concentration (ppm) (b)	900	1,800	3,200	7,000	12,400	28,100	49,800
Coefficient of variation (percent)	0.0	4.0	8.8	7.1	6.3	7.8	5.1

(a) The formulated diets were analyzed twice during the 13-week studies. The results ranged from 96% to 122% of the target concentrations.
(b) N = 2

TABLE K2. CONCENTRATIONS OF MONURON IN THE TWO-YEAR FEED STUDIES

Date Mixed	Concentration for Target Concentration of			
	750 ppm	1,500 ppm	5,000 ppm	10,000 ppm
07/26/79	675	1,450	5,300	10,250
09/13/79	775	1,500	4,850	10,850
11/01/79	730	1,630	5,100	9,800
02/07/80	740	1,450	4,850	10,250
03/20/80	800	1,550	5,050	9,200
04/24/80	700	1,500	4,700	9,500
07/02/80	800	1,530	5,100	10,300
09/10/80	700	1,500	5,100	9,800
10/29/80	760	1,600	4,900	9,800
01/14/81	770	1,500	5,000	10,600
01/28/81	780	1,550	4,850	9,400
04/01/81	800	1,450	4,850	10,300
05/13/81	685	1,470	4,900	10,000
Mean (ppm)	747	1,514	4,965	10,004
Standard deviation	45	57	160	479
Coefficent of variation (percent)	6.1	3.8	3.2	4.8
Range (ppm)	675-800	1,450-1,630	4,700-5,300	9,200-10,850
No. of samples	13	13	13	13

TABLE K3. RESULTS OF REFEREE ANALYSIS OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF MONURON

Date Mixed	Target Concentration (ppm)	Concentration Found (ppm)	
		Study Laboratory	Referee Laboratory
09/13/79	750	775	720
02/07/80	1,500	1,450	1,500
10/29/80	10,000	9,800	10,000
05/13/81	5,000	4,900	5,000

APPENDIX L

ANIMAL ROOM ENVIRONMENTAL CONDITIONS DURING THE TWO-YEAR FEED STUDIES OF MONURON

TABLE L1. TEMPERATURE RECORD FOR ANIMAL ROOMS USED DURING THE TWO-YEAR FEED STUDIES OF MONURON

Room No.	Month/ Year	Tav (a) (° F)	n (b)	Tmax (° F)	Tmin (° F)	n in Specification	Percent of Readings in Specification	Hours Out of Specification (c)
541	07/79	75.2	31	80	73	26	84	120
	08/79	74.0	31	80	71	26	84	120
	09/79	74.7	29	77	71	25	86	96
	10/79	74.5	34	78	72	32	94	48
	11/79	74.7	60	80	73	59	98	24
	12/79	75.5	62	80	74	56	90	72
	01/80	75.8	62	80	73	47	76	180
	02/80	78.6	58	83	74	17	29	492
	03/80	81.3	62	83	79	0	0	744
	04/80	81.0	60	83	79	0	0	720
	05/80	79.7	62	83	77	0	0	744
	06/80	78.7	57	86	76	3	5	648
	07/80	78.1	55	81	75	14	26	492
528	08/80	70.2	62	74	66	23	37	468
	09/80	70.3	58	78	65	23	40	420
	10/80	70.9	60	73	68	20	33	480
	11/80	71.3	59	74	67	23	39	432
	12/80	70.3	61	74	68	10	16	612
	01/81	70.4	30	73	66	7	23	276
542	01/81	78.1	32	80	76	1	3	372
	02/81	76.6	56	79	73	23	41	396
	03/81	74.0	61	78	71	59	97	24
	04/81	73.4	59	(d) 92	70	49	83	120
	05/81	73.0	62	79	70	58	94	48
	06/81	72.7	60	75	71	57	95	36
	07/81	72.7	59	74	70	57	97	24

(a) Temperature (T) average; recommended temperature for animal rooms was 74° ± 2° F.
(b) n = number of readings
(c) Approximation
(d) During study week 93, a thermostat malfunction allowed a gradual increase in the room temperature. Over an 18-hour period, the temperature rose to 92° F, after which corrective action was taken.

TABLE L2. RELATIVE HUMIDITY RECORD FOR ANIMAL ROOMS USED DURING THE TWO-YEAR FEED STUDIES OF MONURON

Room No.	Month/ Year	RHav (a) (percent)	n (b)	RHmax (percent)	RHmin (percent)	n in Specification	Percent of Readings in Specification	Hours Out of Specification (c)
541	07/79	55.5	31	75	28	17	55	336
	08/79	53.0	31	72	33	20	65	264
	09/79	43.4	29	66	23	16	55	312
	10/79	36.0	34	56	18	11	32	480
	11/79	32.2	60	55	9	13	22	564
	12/79	21.9	62	39	10	0	0	744
	01/80	18.6	62	36	10	0	0	744
	02/80	30.5	58	50	8	25	43	396
	03/80	44.2	62	55	30	50	81	144
	04/80	48.4	60	61	41	59	98	12
	05/80	54.0	62	68	42	45	73	204
	06/80	61.1	57	75	47	30	53	324
	07/80	65.4	54	78	53	16	30	456
528	08/80	76.4	62	80	71	0	0	744
	09/80	74.1	58	79	61	0	0	696
	10/80	64.7	58	78	45	24	41	408
	11/80	53.2	59	69	45	50	85	108
	12/80	49.7	61	61	29	55	90	72
	01/81	46.6	30	60	37	28	93	24
542	01/81	34.5	32	44	24	4	13	336
	02/81	42.2	56	60	28	33	59	276
	03/81	38.9	61	59	28	15	25	552
	04/81	45.2	59	72	28	36	61	276
	05/81	48.6	62	69	25	41	66	252
	06/81	55.8	60	65	45	49	82	132
	07/81	58.7	59	73	49	37	63	264

(a) Relative humidity (RH) average; recommended relative humidity for animal rooms was 50% ± 10%.
(b) n = number of readings
(c) Approximation

APPENDIX M

SENTINEL ANIMAL PROGRAM

APPENDIX M. SENTINEL ANIMAL PROGRAM

I. Methods

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

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

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

II. Results

Results are presented in Table M1.

TABLE M1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR FEED STUDIES OF MONURON

Interval (months)	Number	Positive Serologic Reaction for
RATS		
6	2/10	RCV
12	7/10	RCV
18	10/10	PVM
	10/10	RCV
24	10/10	PVM
	10/10	RCV
MICE		
12	2/10	MHV
24	1/10	MHV

APPENDIX N

RACK POSITIONS OF RATS AND MICE IN THE TWO-YEAR FEED STUDIES OF MONURON

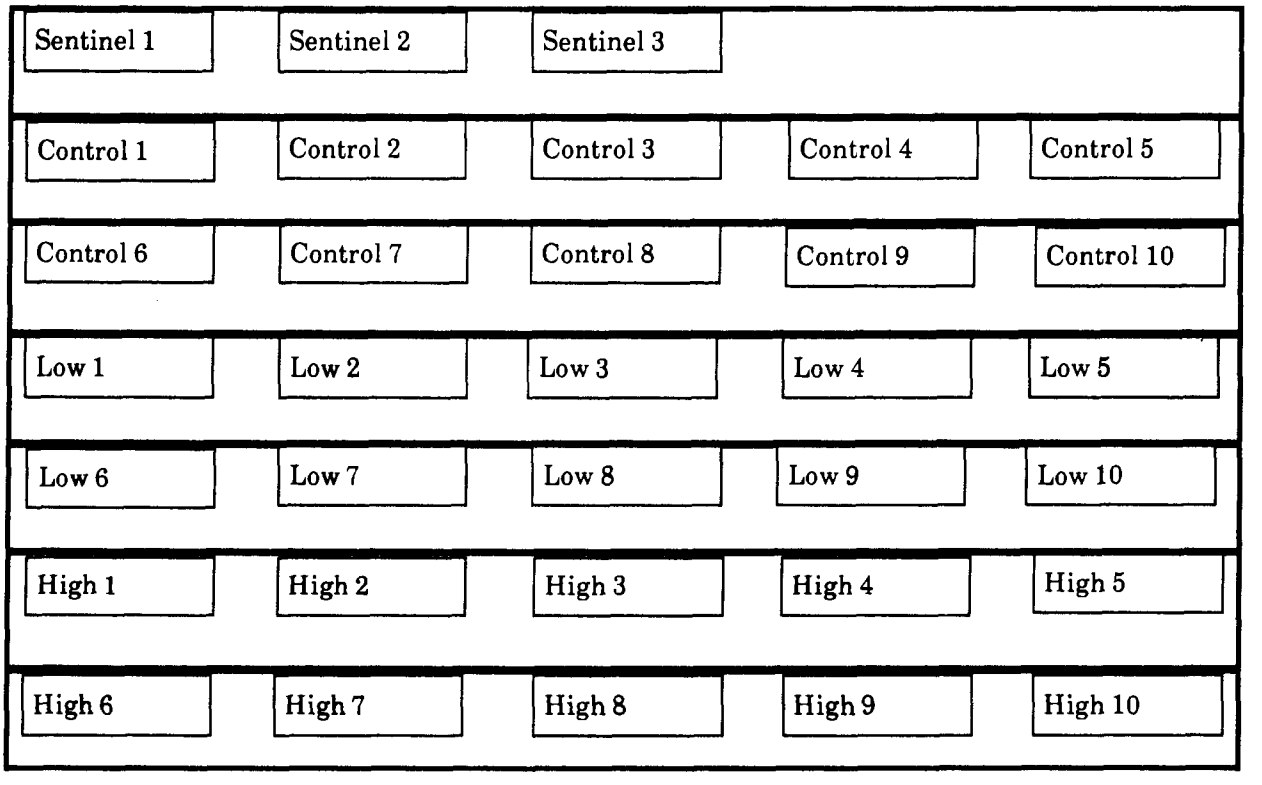

FIGURE 7. RACK POSITIONS OF RATS AND MICE IN THE TWO-YEAR FEED STUDIES OF MONURON

APPENDIX O

FEED AND COMPOUND CONSUMPTION BY RATS AND MICE IN THE THIRTEEN-WEEK AND TWO-YEAR FEED STUDIES OF MONURON

TABLE O1. FEED AND COMPOUND CONSUMPTION BY RATS IN THE THIRTEEN-WEEK FEED STUDIES OF MONURON

Dose (ppm)	Male			Female		
	Survivors	Body Weight (a)	Feed Consumed (b)	Survivors	Body Weight	Feed Consumed
Week 4						
0	10/10	229.3	19	10/10	148.2	17
750	10/10	224.2	18	10/10	148.9	14
1,500	10/10	199.7	18	10/10	137.0	14
3,000	10/10	194.6	13	10/10	127.1	10
6,000	5/10	92.0	10	4/10	81.1	14
12,000	2/10	110.1	22	1/10	94.8	15
Week 8						
0	10/10	284.5	18	10/10	175.0	18
750	10/10	277.5	17	10/10	175.6	12
1,500	10/10	252.6	15	10/10	164.4	11
3,000	10/10	223.5	14	10/10	144.6	12
6,000	5/10	133.9	11	4/10	109.9	10
12,000	2/10	101.7	19	1/10	84.8	15
Week 12						
0	10/10	321.1	19	10/10	192.6	20
750	10/10	309.8	19	10/10	187.7	16
1,500	10/10	283.6	16	10/10	176.0	12
3,000	10/10	248.0	15	10/10	152.3	10
6,000	5/10	154.8	15	4/10	117.6	11
12,000	2/10	108.0	20	1/10	86.2	15

(a) Group average in grams
(b) Grams of feed removed from the feed hopper per animal per day; not corrected for scatter.

TABLE O2. FEED AND COMPOUND CONSUMPTION BY MALE RATS IN THE TWO-YEAR FEED STUDY OF MONURON

	Control		Low Dose			High Dose		
Week	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Low/ Control (b)	Grams Feed/ Day (a)	Body Weight (grams)	High/ Control (b)
4	19	232	18	225	0.9	17	210	0.9
8	19	281	18	276	0.9	17	257	0.9
12	19	317	16	308	0.8	15	288	0.8
16	20	351	17	336	0.8	17	312	0.8
20	22	364	19	352	0.9	17	326	0.8
24	21	387	18	368	0.9	16	338	0.8
28	20	398	18	380	0.9	16	349	0.8
32	24	413	21	394	0.9	18	362	0.8
36	19	420	18	401	0.9	17	369	0.9
40	21	425	18	407	0.9	17	375	0.8
44	21	433	18	414	0.9	16	379	0.8
48	22	444	21	429	1.0	19	391	0.9
52	21	439	19	426	0.9	17	384	0.8
56	25	440	23	426	0.9	21	385	0.8
60	25	438	21	424	0.8	20	387	0.8
64	23	447	19	429	0.8	19	388	0.8
68	26	455	22	434	0.8	20	394	0.8
72	27	447	19	420	0.7	18	388	0.7
76	22	466	19	443	0.9	18	399	0.8
80	20	468	20	442	1.0	22	399	1.1
84	19	472	17	443	0.9	16	402	0.8
88	19	464	17	438	0.9	16	395	0.8
92	21	466	17	434	0.8	16	394	0.8
96	18	455	17	430	0.9	17	385	0.9
100	23	454	18	417	0.8	18	380	0.8
Mean	21	415	19	396	0.9	18	361	0.8
SD (c)	2.5		1.7		0.1	1.7		0.1
CV (d)	11.9		8.9		11.1	9.4		12.5

(a) Grams of feed removed from the feeder; not corrected for scatter.
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Standard deviation
(d) Coefficient of variation = (standard deviation/mean) × 100

TABLE O3. FEED AND COMPOUND CONSUMPTION BY FEMALE RATS IN THE TWO-YEAR FEED STUDY OF MONURON

Week	Control		Low Dose			High Dose		
	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Low/ Control (b)	Grams Feed/ Day (a)	Body Weight (grams)	High/ Control (b)
4	14	164	11	158	0.8	12	153	0.9
8	14	190	13	184	0.9	12	173	0.9
12	14	204	12	197	0.9	11	185	0.8
16	18	213	13	206	0.7	12	190	0.7
20	19	219	15	213	0.8	13	196	0.7
24	17	230	14	217	0.8	11	199	0.6
28	18	228	15	221	0.8	12	202	0.7
32	23	233	20	227	0.9	14	206	0.6
36	18	241	15	233	0.8	15	211	0.8
40	19	246	15	237	0.8	11	211	0.6
44	18	255	15	248	0.8	12	218	0.7
48	19	266	17	255	0.9	12	220	0.6
52	17	272	15	258	0.9	12	221	0.7
56	18	271	16	263	0.9	13	223	0.7
60	20	283	18	269	0.9	14	229	0.7
64	18	295	15	276	0.8	14	232	0.8
68	22	309	20	287	0.9	15	236	0.7
72	26	320	16	300	0.6	14	245	0.5
76	20	327	18	312	0.9	15	250	0.8
80	17	338	17	323	1.0	16	255	0.9
84	16	350	16	332	1.0	13	265	0.8
88	17	350	16	336	0.9	13	265	0.8
92	20	359	17	344	0.8	15	275	0.8
96	15	355	16	342	1.1	14	278	0.9
100	19	360	17	343	0.9	13	277	0.7
Mean	18	275	16	263	0.9	13	225	0.7
SD (c)	2.8		2.2		0.1	1.4		0.1
CV (d)	15.6		13.8		11.1	10.8		14.3

(a) Grams of feed removed from the feeder; not corrected for scatter.
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Standard deviation
(d) Coefficient of variation = (standard deviation/mean) × 100

TABLE O4. FEED AND COMPOUND CONSUMPTION BY MICE IN THE THIRTEEN-WEEK FEED STUDIES OF MONURON

Dose (ppm)	Male			Female		
	Survivors	Body Weight (a)	Feed Consumed (b)	Survivors	Body Weight	Feed Consumed
Week 4						
0	10/10	27.9	9	10/10	19.7	11
3,000	10/10	26.8	10	10/10	19.1	9
6,000	10/10	25.7	11	10/10	18.5	10
12,000	10/10	24.5	11	10/10	19.1	12
25,000	10/10	21.4	12	5/10	18.5	20
50,000	5/10	18.4	19	4/10	17.4	24
Week 8						
0	10/10	31.1	9	10/10	22.4	12
3,000	10/10	28.5	10	10/10	21.2	11
6,000	10/10	27.7	14	10/10	20.4	13
12,000	10/10	26.7	9	10/10	20.6	14
25,000	10/10	23.1	14	5/10	19.6	24
50,000	5/10	20.8	20	4/10	18.2	28
Week 12						
0	10/10	33.8	8	10/10	23.7	9
3,000	10/10	31.2	8	10/10	22.8	8
6,000	10/10	30.0	8	10/10	22.7	8
12,000	10/10	29.0	7	10/10	22.4	8
25,000	10/10	25.3	9	5/10	20.9	14
50,000	5/10	22.5	14	3/10	19.5	17

(a) Group average in grams
(b) Grams of feed removed from the feed hopper per animal per day; not corrected for scatter.

TABLE O5. FEED AND COMPOUND CONSUMPTION BY MALE MICE IN THE TWO-YEAR FEED STUDY OF MONURON

	Control		Low Dose			High Dose		
Week	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Low/ Control (b)	Grams Feed/ Day (a)	Body Weight (grams)	High/ Control (b)
4	6	30	10	30	1.7	14	28	2.3
8	6	32	11	32	1.8	14	30	2.3
12	6	34	12	33	2.0	13	30	2.2
16	6	34	11	33	1.8	13	31	2.2
20	6	37	10	34	1.7	12	31	2.0
24	6	38	10	34	1.7	13	30	2.2
28	6	39	9	34	1.5	10	31	1.7
32	9	40	11	34	1.2	9	31	1.0
36	5	40	9	34	1.8	10	31	2.0
40	6	41	8	36	1.3	11	31	1.8
44	6	40	10	36	1.7	13	32	2.2
48	4	43	11	36	2.8	13	33	3.3
52	5	43	10	35	2.0	14	33	2.8
56	6	42	8	36	1.3	12	32	2.0
60	6	42	9	35	1.5	11	32	1.8
64	6	42	10	36	1.7	11	32	1.8
68	6	43	9	36	1.5	12	32	2.0
72	7	44	17	39	2.4	16	34	2.3
76	6	43	18	37	3.0	17	35	2.8
80	6	44	12	37	2.0	12	34	2.0
84	7	44	15	37	2.1	14	35	2.0
88	6	44	13	37	2.2	14	34	2.3
92	8	43	14	37	1.8	11	34	1.4
96	7	43	17	36	2.4	10	34	1.4
100	7	42	14	36	2.0	14	34	2.0
Mean	6	40	12	35	1.9	13	32	2.1
SD (c)	1.0		2.8		0.4	1.9		0.5
CV (d)	16.7		23.3		21.1	14.6		23.8

(a) Grams of feed removed from the feeder; not corrected for scatter.
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Standard deviation
(d) Coefficient of variation = (standard deviation/mean) × 100

TABLE O6. FEED AND COMPOUND CONSUMPTION BY FEMALE MICE IN THE TWO-YEAR FEED STUDY OF MONURON

	Control		Low Dose			High Dose		
Week	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Low/ Control (b)	Grams Feed/ Day (a)	Body Weight (grams)	High/ Control (b)
4	8	23	12	22	1.5	14	22	1.8
8	8	26	11	24	1.4	13	24	1.6
12	8	28	12	25	1.5	13	24	1.6
16	7	31	14	25	2.0	13	24	1.9
20	7	33	11	25	1.6	12	25	1.7
24	7	35	14	26	2.0	14	25	2.0
28	6	37	11	26	1.8	12	25	2.0
32	7	39	6	27	0.9	11	26	1.6
36	7	40	12	27	1.7	13	25	1.9
40	7	44	11	27	1.6	12	25	1.7
44	7	43	12	26	1.7	13	25	1.9
48	6	45	11	27	1.8	13	26	2.2
52	6	42	14	29	2.3	14	26	2.3
56	7	45	11	28	1.6	12	26	1.7
60	7	46	11	28	1.6	12	26	1.7
64	7	47	13	28	1.9	12	26	1.7
68	7	49	12	28	1.7	12	26	1.7
72	9	51	15	29	1.7	14	27	1.6
76	8	52	17	30	2.1	14	28	1.8
80	7	54	15	30	2.1	15	27	2.1
84	7	53	16	29	2.3	14	28	2.0
88	8	54	15	30	1.9	14	28	1.8
92	9	54	16	30	1.8	13	28	1.4
96	8	52	16	29	2.0	13	28	1.6
100	10	52	19	30	1.9	13	28	1.3
Mean	7	43	13	27	1.8	13	26	1.8
SD (c)	1.0		2.7		0.3	1.0		0.2
CV (d)	14.3		20.8		16.7	7.7		11.1

(a) Grams of feed removed from the feeder; not corrected for scatter.
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Standard deviation
(d) Coefficient of variation = (standard deviation/mean) × 100

APPENDIX P

AUDIT SUMMARY

APPENDIX P. AUDIT SUMMARY

The experimental data, documents, pathology materials, and draft Technical Report for the 2-year toxicology and carcinogenesis studies of monuron in F344/N rats and B6C3F$_1$ mice were audited for accuracy, consistency, and completeness. The laboratory experiments were conducted for the NTP by the EG&G Mason Research Institute, Worcester, Massachusetts. Animal exposure to monuron began in July 1979 and ended in July 1981. The studies were completed before October 1, 1981, the date when the NTP implemented its requirement that studies be conducted in compliance with the Good Laboratory Practice (GLP) regulations of the Food and Drug Administration. The retrospective audit was conducted for the NIEHS at the NTP Archives and at Dynamac Corporation from June to December 1985 by ImmuQuest Laboratories, Pamela H. Errico, Audit Coordinator. The other individuals who conducted the audit are listed in the full audit report that is on file at the NTP Archives, Research Triangle Park, North Carolina. The audit included a review of:

(1) All records concerning animal receipt, quarantine, randomization, and disposition prior to study start.
(2) All chemistry records.
(3) Body weight and clinical observation data for a random 10% sample of the study animals.
(4) Feed consumption data (by cage) for approximately 20% of the animals.
(5) Inlife records concerning environmental conditions, palpable masses, and mortality.
(6) All postmortem records for individual animals concerning identification, disposition and condition codes, and correlations between gross observations and microscopic diagnoses.
(7) Wet tissues from a random 10% sample of the study animals to verify animal identification and to examine for untrimmed lesions.
(8) Blocks and slides of tissues from all control and high dose animals to examine for inventory and correspondence.

Problems with the automatic watering system resulted in weight fluctuations for both rats and mice. Clinical observations were inconsistent and incomplete. Bulk chemical reanalysis confirmed that there was no degradation of the compound during the course of study. Chemical/vehicle analysis verified the dietary concentrations. Pathology data were generally complete and consistent, although there were many tissues for which accountability was poor. Very few discrepancies between gross observations and microscropic diagnoses were noted.

In conclusion, the audit findings support the data and results presented in the Technical Report.

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TR No.	CHEMICAL
201	2,3,7,8-Tetrachlorodibenzo-p-dioxin (Dermal)
206	Dibromochloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane (Inhalation)
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butylbenzyl Phthalate
214	Caprolactam
215	Bisphenol A
216	11-Aminoundecanoic Acid
217	Di(2-ethylhexyl)phthalate
219	2,6-Dichloro-p-phenylenediamine
220	C.I. Acid Red 14
221	Locust Bean Gum
222	C.I. Disperse Yellow 3
223	Eugenol
224	Tara Gum
225	D & C Red No. 9
226	C.I. Solvent Yellow 14
227	Gum Arabic
228	Vinylidene Chloride
229	Guar Gum
230	Agar
231	Stannous Chloride
232	Pentachloroethane
233	2-Biphenylamine Hydrochloride
234	Allyl Isothiocyanate
235	Zearalenone
236	D-Mannitol
237	1,1,1,2-Tetrachloroethane
238	Ziram
239	Bis(2-chloro-1-methylethyl)ether
240	Propyl Gallate
242	Diallyl Phthalate (Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
247	L-Ascorbic Acid
248	4,4'-Methylenedianiline Dihydrochloride
249	Amosite Asbestos
250	Benzyl Acetate
251	Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
267	Propylene Oxide
269	Telone II®
271	HC Blue No. 1
272	Propylene
273	Trichloroethylene (Four strains of rats)
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
281	H.C. Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No. 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethy)phosphonium Sulfate and Tetrakis(hydroxymethy)phosphonium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	*o*-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane
307	Ephedrine Sulfate
308	Chlorinated Paraffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	*n*-Butyl Chloride
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
320	Rotenone
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
323	Dimethyl Methylphosphonate
324	Boric Acid
325	Pentachloronitrobenzene
326	Ethylene Oxide
327	Xylenes (Mixed)
328	Methyl Carbamate
329	1,2-Epoxybutane
330	4-Hexylresorcinol
332	Mercaptobenzothiazole
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol
336	Penicillin VK
337	Nitrofurazone
339	2-Amino-4-nitrophenol

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